Efficacy of Qigong/Tai Chi for Depression and Cognition in Middle and Older Age Bipolar Patients During COVID-19: A Pilot Randomized Controlled Trial

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Abstract

Background: Older adults with bipolar disorder (BD) are expected to exceed over 50% of the BD population, and is associated with depression, persistent sub-syndromal depressive symptoms, and poor cognition. Current pharmacotherapies are limited in efficacy for depression, not effective in cognition, and often poorly-tolerated. Mind-body interventions have been found to be effective in treating several psychiatric conditions including BD. It is unknown whether qigong/Tai Chi, forms of moving mindfulness, will be efficacious in improving depression, cognition, and other mental health outcomes in any BD patient population.

Methods: We conducted a 12-week online randomized controlled trial comparing qigong/Tai Chi vs. an active control light exercise in 23 patients with BD aged ≥40 years. The primary outcome was change in depressive symptoms, with a secondary analysis examining patients with at least sub-syndromal baseline depressive symptom severity. The secondary outcome was verbal fluency and exploratory outcomes included mania, anxiety, quality of life, daily functioning, mindfulness, self-compassion, self-reported depression, and self-reported mania.

Results: There were no significant differences between trial arms in study outcomes. However, for the subgroup of patients with subsyndromal or acute depressive symptoms at baseline, there was a clinically significant change in depressive symptoms at 12-weeks (qigong/Tai Chi vs. active control, 15.43 (±6.08) to 9.42 (±11.41) vs. 17.25 (±6.92) to 15.25 (±8.48), p=0.069).

Conclusion: Qigong/Tai Chi may be efficacious in reducing depressive symptoms for middle to older age BD patients with at least subsyndromal or more severe depressive symptoms. More research is needed to further determine the efficacy of qigong/Tai Chi in the BD population.

Résumé

Contexte: Les personnes âgées atteintes de trouble bipolaire (TB) devraient excéder 50% de la population atteinte de TB. Celle-çi est également associée à la dépression, à des symptômes dépressifs sous-syndromiques persistants et à une mauvaise cognition. Les pharmacothérapies actuelles ont une efficacité satisfaisante pour combattre la dépression, aucunement efficace pour la cognition, puis sont généralement mal tolérées. Les interventions corps-esprit se sont avérées efficaces afin de traiter plusieurs troubles psychiatriques dont le TB. Il y a peu d'informations sur le qigong/tai chi et les différentes formes de mouvement de pleine conscience et leur efficacité afin d'améliorer la dépression, la cognition et d'autres effets de santé mentale dans toute population de patients atteints de TB.

Méthodes: Nous avons réalisé une étude contrôlée aléatoire de douze semaines en ligne, comparant le qigong/tai chi à un léger exercice de contrôle actif chez 23 patients.es atteints de TB âgé.es de 40 ans et plus. Le critère principal était le changement des symptômes dépressifs, avec une analyse secondaire examinant les patients.es présentant au moins des symptômes dépressifs sous-syndromiques de base. Le critère secondaire était la fluidité verbale et les effets exploratoires comprenant la manie, l'anxiété, la qualité de vie, le fonctionnement quotidien, la pleine conscience, l'auto-compassion, la dépression autodéclarée et la manie autodéclarée.

Résultats: Pas de différences significatives entre les bras d'étude ont pu être observées. Cependant, pour le sous-groupe de patients présentant au départ des symptômes dépressifs

sous-syndromique ou augus, un changement cliniquement significatif des symptômes dépressifs à 12 semaines (qigong/tai chi vs contrôle actif; 15,43 (± 6,08) à 9,42 (± 11,41) vs 17,25 (± 6,92) à 15,25 (± 8,48), p = 0,069).

Conclusion: Le qigong/tai chi peut être efficace pour réduire les symptômes dépressifs chez les patients avec TB d'âge moyen à plus âgées présentant au moins des symptômes dépressifs subsyndromiques ou plus sévères. Plus de recherche sera nécessaire afin de déterminer davantage l'efficacité du qigong/tai chi chez la population atteinte de TB.

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Author Contributions

Haley Park wrote, and Dr. Soham Rej, Dr. Serge Beaulieu, Dr. Lisa Eyler, Dr. Chen-Lin Su, and Gabriella Buck revised Chapters 1-3 of this thesis.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction

Bipolar disorder (BD) is a debilitating and costly disease affecting over 550 000 people in Canada (McDonald et al., 2015). By 2030, older adults with bipolar disorder over sixty years are expected to comprise more than 50% of the BD population (Sajatovic et al., 2015). Older-age bipolar disorder (OABD) thus constitute an important group with projected costs on patients, caregivers, and the healthcare system, and despite this, there is a lack of research specific to their needs and recommendations.

Persistent, treatment-resistant sub-syndromal depressive symptoms are particularly common in this population (Nivoli et al., 2014), account for a significant proportion of weeks unwell (Judd et al., 2002), and are associated with impaired functioning (Gitlin et al., 1995; Marangell et al., 2009), reduced quality of life (Bauer et al., 2010; MacQueen et al., 2003), and increased risk of mood relapse (De Dios et al., 2012; Perlis et al., 2006). Cognitive dysfunction – independent of mood status (Tsitsipa & Fountoulakis, 2015) – is similarly common, with 40-60% of euthymic patients experiencing neurocognitive impairment (Bourne et al., 2013; Robinson et al., 2006) and subsequent difficulty in daily functioning (Gildengers et al., 2007; Martino et al., 2009).

Current pharmacotherapy for these illness burdens is limited by high rates of medical co-morbidity in OABD affecting drug tolerability, drug-drug interactions, and drug metabolism (Ghose, 1991; Ng et al., 2009; Sajatovic et al., 2015). Even in lieu of tolerability and adverse

side-effects, treatment efficacy is limited, with up to 40% of patients experiencing depressive treatment non-response (De Fruyt et al., 2012; Sienaert et al., 2013).

Psychosocial interventions have been evaluated in younger or mixed-aged studies, with findings supporting their efficacy as adjunctive therapy in reducing illness severity, and relapse rates by about 15% (Yatham et al., 2018). Mindfulness-based or mind-body interventions, of which a primary feature is the cultivation of non-judgmental awareness of the present moment (Kabat-Zinn, 2003), have in the last twenty years been found to be effective in treating a number of psychological symptoms and psychiatric illnesses including BD (Goldberg et al., 2018; Ives-Deliperi et al., 2013; Williams et al., 2008). Qigong and Tai Chi, practices of moving mindfulness, present accessible forms of exercise for older populations with the potential to facilitate greater ease in engagement with mindfulness. They have been found to be beneficial for physical and mental health (Abbott & Lavretsky, 2013; Chong-Wen et al., 2013; Rogers et al., 2009; Wang et al., 2004). However, their efficacies have not been examined in any bipolar population.

Our intent was to conduct a 12-week pilot randomized controlled trial examining the efficacy of online qigong/Tai Chi vs. a light exercise active control in improving symptoms of depression, cognition, anxiety, quality of life, daily functioning, mindfulness, self-compassion, and self-rated depression. We also aimed to examine that qigong/Tai Chi will not be associated with elevated mania in comparison to light exercise.

This thesis is a manuscript-based thesis. Following this introduction will be a literature review of relevant background material, then a manuscript of a journal article based on our pilot study.

Chapter 2: Literature Review

2.1 Bipolar Disorder

2.1.1 Clinical characteristics and epidemiology

Bipolar disorder, formerly known as manic-depressive illness, is a life-long condition characterized by recurring episodes of mania and/or depression. In the DSM-5, a manic episode is period of seven or more days wherein there is an "abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy" (American Psychiatric, 2013). Three of more of the following symptoms must be present reflecting a significant change from usual behaviour, without attribution to physiological effects of a substance or another medical condition: increased self-esteem or grandiosity, decreased need for sleep, increased talkativeness or pressure to keep talking, flight of ideas or racing thoughts, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in activities with high potential for painful consequences. Typical symptoms of mania are shown in Table 1.

The depressive polarity of bipolar disorder is characterized by a depressed mood or loss of interest or pleasure in life. The DSM-5 states at least five of the following markers depression should be present for a minimum period of two weeks to warrant classification as a depressive episode: depressed mood most of the day for nearly every day, loss of interest or pleasure in all or almost all activities nearly every day, significant weight loss when not dieting or weight gain,

insomnia or hypersomnia nearly every day, psychomotor agitation or retardation nearly every day, fatigue or loss of energy nearly every day, feelings of worthlessness or excessive and inappropriate guilt nearly every day, diminished ability to think or concentrate or indecisiveness nearly every day, and recurrent thoughts of death or suicidal ideation, or a suicide attempt or a specific plan for committing suicide. Typical symptoms of depression are shown in Table 2. Both manic and depressive periods should also be sufficiently severe enough to cause marked impairment in social or occupational functioning or necessitate hospitalization.

Table 1. Typical symptoms of mania

Elevated mood	Mood lability
Irritability	Outbursts of anger
Hyperactivity	Increased energy
Subjective experience of physical well-being	Sense of communion with nature
Inflated self-esteem	Decreased need for sleep
Over-talkativeness	Flight of ideas
Racing thoughts	Crowded thoughts
Disorganization of speech	Distractibility
Delusions	Increased intensity of perceptions
Hallucinations	Increased sociability
Increased sexual drive	Psychomotor agitations
Impulsivity	Excessive involvement in risky activities
Change in appetite or weight	Poor judgment
Loss of insight	

Table 2. Typical symptoms of depression

Depressed mood	**Loss of interest**
Anhedonia	Anxiety
Emotional emptiness	Loss of appetite and/or weight
Increased appetite and/or weight	Initial, middle, or late insomnia
Hypersomnia	Psychomotor retardation
Psychomotor agitation	Fatigue
Loss of energy	Lack of initiative
Avolition	Loss of libido
Feelings of worthlessness	Feelings of guilt
Hopelessness about the future	Thinking difficulty
Slowed speech	Problems with memory
Problems with concentration	Difficulty with decision making
Suicidal ideation	Suicidal behaviour
Delusions	Hallucinations
Illusions	Bodily symptoms (headaches, other aches and pains, palpitations, gastrointestinal problems)
Diurnal variation	Depersonalization or derealization
Panic attacks	

Bipolar I illness is characterized by at least one manic episode and typically also involves depressive episodes, and bipolar II illness is characterized by at least one major depressive episode and one hypomanic (a period of mania lasting at least four but not more than seven consecutive days) (American Psychiatric, 2013). Depressive symptoms tend to be the predominant mood symptom, as opposed to mania (Colom et al., 2006; Judd et al., 2008; Kupka et al., 2007). Both bipolar I and II are marked by psychosocial impairment and disability, and bipolar II is not necessarily a milder form of the disorder, often showing similar or greater chronicity of illness, a more depressive phase, and lethality of suicide (American Psychiatric, 2013). The illness affects about 1% of the world population and is prevalent equally among the genders, and more prevalent in lower socioeconomic status individuals (Grant et al., 2005; Merikangas et al., 2007). From the initial episode, which more than half the time is in the depressive polarity peaking at approximately age 18-20 years (Tsuang et al., 2011), cycling can occur in a stochastic manner with numerous possible patterns, frequencies, or regularity. Approximately half of patients experience a recurring episode, likely a depressive episode, within two years of their initial episode (Perlis et al., 2006).

Late-life or older age bipolar disorder affects those diagnosed with bipolar disorder aged 60 years or older. By 2030, older adults with bipolar disorder over sixty years are expected to comprise more than 50% of the BD population (Sajatovic et al., 2015), comprising a considerable subgroup with projected costs on patients, caregivers, and the healthcare system. The clinical course of bipolar disorder does not attenuate or remit over time and older patients will continue to experience recurrent mood episodes as frequent as younger populations (Angst

et al., 2005). Studies suggest there are few minor differences between younger and older patients, although older age bipolar disorder is associated with a greater polarity of depression, female to male ratio, cognitive impairment, and medical comorbidity (Depp & Jeste, 2004). OABD can be further divided into two types with varying courses: early-onset and late-onset bipolar disorder, the early-onset group having an illness onset before the age of 50 and late-onset after 50 (Sajatovic et al., 2015). Late-onset bipolar disorder is associated with greater neurological illness, likely corresponding to secondary neurovascular causes for mania (Krauthammer & Klerman, 1978; Wylie et al., 1999).

2.1.2 Pharmacotherapy and limitations

There is no comprehensive neurobiological account of bipolar disorder, although there are several molecular and cellular, neurochemical, neuroendocrine, and neuroimaging corelates. Treatment consists of maintenance therapy for the prevention of future episode in conjunction with the treatment of currently active episodes (Yatham et al., 2018). Pharmacotherapy is a backbone of treatment. There is most evidence for the support of lithium and its use for both relapse prevention of manic and depressive episodes and the treatment of acute episodes. Other first-line treatments include lamotrigine, aripiprazole, quetiapine, risperidone. Second-line treatments include divalproex, olanzapine, ziprasidone, and asenapine (Yatham et al., 2018). Responses usually occur within 3-6 weeks and slightly longer for bipolar depression with rates of about 50% (Goodwin et al., 2007; Strakowski, 2014; Zornberg & Pope, 1993). Different pharmacotherapies have varying efficacies on relapse prevention of either manic or depressive

episodes and phases, and treatment is typically closely monitored and adjusted with respect to dosage and combinations.

A limitation of pharmacotherapy is their limited efficacy on depression. As previously mentioned, treatment response rates hover around 50%. Quetiapine, the first-line recommendation from CANMAT and the only monotherapy treatment approved by the FDA and EMEA for acute bipolar depression, has shown 53-58% and response rates compared to 28-36% in placebo conditions (Calabrese et al., 2005; Thase et al., 2006). Lithium and lamotrigine, are among the second-line treatments in CANMAT guidelines, with lithium augmentation having a 41.2% response rate (Crossley & Bauer, 2007) and lamotrigine, 23.8% (Nierenberg et al., 2006), although both have also been found to be equivalent to placebo (Geddes et al., 2004; Goldsmith et al., 2003; Young et al., 2010). Antidepressants, while effective in unipolar depression, is contended as to its usefulness and the possibility of increasing the risk of mood cycling and inducing a switch into mania or hypomania in the bipolar disorder; they are recommended with some caution only as adjunctive therapy (Pacchiarotti et al., 2013).

Despite treatment, depression symptom remission rates are low and persistent treatment-resistant subsyndromal depressive symptoms are common (Pacchiarotti et al., 2013; Vieta et al., 2008). Approximately 20-50% of patients experience subsyndromal depressive symptoms in the intervals between mood episodes (Henry et al., 2015; Judd et al., 1998; Serafini et al., 2018). Periods of subsyndromal symptoms are also two to three times more frequent than periods of acute illness (Judd et al., 2003). They are associated with greater time to mood

relapse, number of illness episodes, duration of illness episode, psychosocial and cognitive impairment, quality of life, and well-being (Fagiolini et al., 2005; Fava, 1999; Gutiérrez-Rojas et al., 2008; Serafini et al., 2018). Several longitudinal studies indicate that depression is associated with poorer global outcome and work disability than mania (Goldberg & Harrow, 2011), and periods of depression, whether subsyndromal or acute, account for the majority of time ill (about 75% of a total of 54% of weeks ill) (Vázquez et al., 2013). The frequency and disability of depression in bipolar disorder and the limitations of pharmacotherapy present a cause for concern.

Another limitation of pharmacotherapy is unwanted side effects of medication. Side effects include weight gain, gastrointestinal problems such as nausea, vomiting, and diarrhea, renal toxicity, hypothyroidism, sedation, sexual dysfunction, impaired processing speed and memory, tremors, haematological and cardiovascular effects, and increased risk for metabolic syndrome (Fung et al., 2019; Kemp, 2014; Zarate, 2000). The burden of side effects can be compounded with polypharmacy, and up to 85% of patients are prescribed two or more concurrent psychiatric medications, and 36%, four or more (Fornaro et al., 2016). Medication non-adherence is also increased by the experience of side effects, and rates of non-adherence has been estimated to be nearly 50% with first-line therapies (Bates et al., 2010). Older adults with bipolar disorder are particularly at a disadvantage with medication as increased polypharmacy and altered drug metabolism affects tolerability and drug-drug interactions (Katz et al., 2017; Sajatovic et al., 2015).

2.1.3 Cognition

Most patients with bipolar disorder experience significant cognitive dysfunction, including domains of cognition such as attention, executive functioning, memory, verbal learning, psychomotor speed, and social cognition (Cardenas et al., 2016; Samamé et al., 2015; Tavares et al., 2003; Torres et al., 2007). Cognitive dysfunction persists independent of mood status (Tsitsipa & Fountoulakis, 2015), with 40-60% of euthymic patients experiencing neurocognitive impairment (Bourne et al., 2013; Robinson & Nicol Ferrier, 2006), and subsequent difficulty in daily functioning (Gildengers et al., 2007; Martino et al., 2009). While early studies suggested cognitive impairments may be compounded and accelerated in OABD by disease and age (Gildengers et al., 2014; Weisenbach et al., 2014), more recent studies contest this hypothesis (Cardoso et al., 2015; Gildengers et al., 2013; Martino et al., 2018; Santos et al., 2014). However, a number of patients with bipolar disorder will go on to develop dementia, with a calculated odds ratio of 2.36 (95% CI 1.36-4.0) compared to healthy adults (Diniz et al., 2017). Studies suggest lithium to have negative effects on psychomotor speed and verbal memory, and some anticonvulsants such as lamotrigine has a better cognitive profile than carbamazepine, valproate, topiramate, and zonisamide (Dias et al., 2012). There does not exist any unequivocal medication to improve cognition, although cognitive remediation has been found to improve composite scores of cognition as well as processing speed, visual learning and memory, and verbal fluency in the bipolar population (Demant et al., 2015; Lewandowski et al., 2017).

2.1.4 Psychosocial Treatments

Psychosocial therapies incorporating education and self-management skills and techniques support the limitations of pharmacotherapy when used as adjunctive treatment. They are evidenced to reduce depressive symptom burden and reduce relapse rates by approximately 15% (Yatham et al., 2018).

Psychoeducation is most supported by evidence leading it to be a first-line maintenance therapy generally recommended to all patients, particularly at illness onset (Yatham et al., 2018). Topics covered may include information on the illness, treatments, key coping strategies and detecting prodromes of depression and mania, problem solving, diminishing stigma, medication adherence, and healthy lifestyles. 120 euthymic patients participated in a study comparing 21 sessions of group psychoeducation as adjunct to pharmacotherapy to controls, and those receiving psychoeducation experienced fewer relapses, increased time to relapse, and lower rates and lengths of hospitalization (Colom et al., 2003). Another study found lower rates of re-hospitalization and increased use of mood stabilizers and antipsychotics in those who received group psychoeducation and optional cognitive behavioral strategies compared to standard psychiatric treatment and pharmacotherapy (Kessing et al., 2014).

Cognitive behavioral therapy (CBT) is recommended as a second-line psychological treatment by CANMAT for bipolar depression and maintenance, although evidence for its support has been mixed. Treatment typically begins with psychoeducation then skills for problem-solving, behavioral activation for inactivity and overstimulation, and cognitive restructuring for negative

or overly optimistic cognitions. An RCT with 103 euthymic bipolar I disorder patients found individual cognitive therapy to effect fewer and shorter depressive episodes, fewer hospitalizations, and better social functioning compared to controls at 12-month and 30-month follow-up (Lam et al., 2005; Lam et al., 2003). CBT was also found to improve depression and overall functioning at comparable levels to supportive therapy involving "nonspecific" features such as general empathy, support, and provision of illness related information (Meyer & Hautzinger, 2012). Another RCT found no differences between 22 sessions of individual CBT and controls in recurrence rates or overall symptom severity (Scott et al., 2006). Meta-analyses report inconclusive results on relapse prevention or depressive symptoms due to methodological problems and study selection factors, although several trials incorporating CBT with additional psychosocial strategies such as emotive techniques or psychoeducation have reported reduction in mood symptoms, greater time to relapse, better global functioning, and fewer hospitalizations (Ball et al., 2006; Isasi et al., 2010).

Family focused therapy (FFT) is another second-line therapy that addresses interpersonal communication and problem-solving strategies based on the finding that family attributes such as expressed emotion attitudes and negative interactional behaviours predicted worse clinical outcomes. A 2 year follow up study reported a 28% relapse rate in those receiving FFT compared to 60% in those receiving intensive individual treatment (support, education, and problem-solving training) (Rea et al., 2003), and another RCT found greater reduction in depression and manic symptoms, fewer relapses, longer time to remission, and improved

medication adherence over a 2-year period compared to psychoeducation with crisis management (Miklowitz et al., 2003).

Interpersonal and Social Rhythm Therapy (IPSRT) is recommended as a third-line psychosocial therapy. It was developed for bipolar disorder on the premise of irregular circadian rhythms and social rhythm disruptions and stressors triggering mood symptoms and episodes. A 2-year RCT found IPSRT to lower time to recurrence, lengthen time well, and improve occupational functioning compared to intensive clinical management (psychoeducation, illness management strategies, and general support) (Frank et al., 2005). Another trial comparing psychosocial interventions which included IPSRT (others including CBT and FFT) found acutely depressed patients in the treatment condition to improve on measures of relationship, satisfaction with activities, work/role functioning, and recreational activities compared to controls (Thase, 2007). Two small studies did not show benefits of IPSRT compared to controls (Inder et al., 2015; Swartz et al., 2012).

Studies have generally been mix-aged and there is little research on psychosocial interventions specifically for the OABD population. Only two studies investigating psychosocial interventions have focused specifically on older-aged patients with bipolar disorder. One study found feasibility and acceptability of a 12-week group intervention combining educational and motivational medication and symptom management training in 21 older outpatients with BD, as well as improvements in medication adherence, medication management ability, depressive symptoms, and indices of health-related quality of life compared to TAU (Depp et al., 2007).

Another study examined a four-session program on sessions on symptom control strategies, promotion of provider engagement, and education and promotion of behavioral change related to cardiovascular disease risk factors and found slower decline in physical-health but not mental-health related improvements in quality of life in those who received treatment compared to controls (Kilbourne et al., 2008).

2.2 Mindfulness

2.2.1 Background

Contemporary mindfulness as practiced today in a wide range of settings has roots in Buddhist teachings and associated practices from the Buddha c. 500BC and as followed as a religion in parts of Asia throughout millennia. “Mindfulness” is an English translation of the Pali word *sati*, which primarily denotes “recollection” or “memory” (Levman, 2017; Peacock, 2014). Its reference to memory implies employing the right kind of attention in a way in which phenomenal events are registered with awareness, accuracy, and clarity. It can also reference memory of the relevant teachings of the Buddha as it relates to attending to phenomena in one’s unfolding consciousness, such as the impermanence and interdependence of all things, and relatedly, the insubstantiality of an existing self in itself (Garfield, 1995). Mindfulness has been popularly described as “the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment by moment” (Kabat-Zinn, 2003a), and most other definitions follow suit in their emphasis on the awareness of the present experience as it arises as sense perceptions or thoughts, with an

open, curious, and accepting attitude (Brown et al., 2007; Hofmann et al., 2010; Shapiro et al., 2006). It is an awareness free from further mental elaboration upon the contents of awareness, which are often accompanied by valanced evaluations which can distort clear perception and cause suffering, especially when tied to conceptions of one's self or identity (Ekman et al., 2005).

Buddhism, as "the most psychological of the world's religions, and the most spiritual of the world's psychologies" (Hirst, 2003) with its extensive discourse on the nature of the mind and the absence of religious features from its central elements, combined with its concern with the predicament, causes, and cessation of suffering, found adaptability in secular contexts, especially in mental health. Mindfulness was first popularized in the West by professor Jon Kabbat-Zinn and the development of his 8-week Mindfulness Based Stress Reduction (MBSR) program at the University of Massachusetts Medical Center in the late 1970s, originally for patients with chronic pain refractory to multiple medical treatments (Kabat-Zinn, 2003b). MBSR was then followed by Mindfulness Based Cognitive Therapy (MBCT) in the United Kingdom in 1992 by Zindel Segal, Mark Williams, and John Teasdale, originally targeted for relapse prevention for those with major depressive disorder (Segal et al., 2018). Mindfulness is also a large component of other "third-wave" cognitive therapies including Acceptance and Commitment Therapy (Hayes et al., 2009) and Dialectical Behaviour Therapy (Robins & Chapman, 2004).

In the practice of mindfulness, mind and body become more apparently interdependent and no clear division between the psychological and physiological become tenable (Langer, 1992). MBSR and MBCT include practices that integrate mind and body in practices focusing on somatic experience and movement, such as meditation on the breath, body scanning, yoga, walking meditation, and mindful stretching. Mindfulness is a key element in a number of mind-body practices such as yoga, tai chi, or qigong, and these practices have been increasingly used as therapeutic modalities for improving well-being in secular contexts (Bodeker & Ong, 2005). Putative mechanisms of mindfulness involve not only cognitive reappraisal but also physiological pathways including lowered heart rate variability, and reduction of inflammation biomarkers (Black et al., 2013; Krygier et al., 2013).

2.1.2 Mindfulness in bipolar disorder

Mindfulness-based interventions and especially MBSR and MBCT have been found to be efficacious in measures of depression, depression relapse, anxiety, sleep, and stress in patients with major depressive disorder or physical health conditions (Atanes et al., 2015; Piet & Hougaard, 2011; Rodrigues et al., 2017; Rusch et al., 2019). In a study of 145 recovered recurrently depressive patients, MBCT was shown to reduce risk of relapse/recurrence by approximately half compared to treatment as usual (Teasdale et al., 2000), and results have been replicated in a follow-up study of 75 patients (Ma & Teasdale, 2004). An RCT of 76 self-referred participants with anxiety comparing MBSR and a waiting-list control found MBSR to significantly reduce levels of state and trait anxiety as well as depression, with effect sizes in the

completer sample (as opposed to intention-to-treat) in the moderate to large range (Vøllestad et al., 2011).

The evidence is yet insufficient to determine the efficacy of mindfulness-based interventions for bipolar disorder. Most studies on mindfulness in this population have focused on MBCT, on which three underpowered RCTs have been conducted. Perich et. al. (2013) found no significant differences between MBCT and treatment as usual (TAU) in time to first recurrence of mood episode or number of recurrences over a 12-month period, or in depressive symptoms, although MBCT significantly lowered state anxiety scores. Williams et al. (2008) similarly found no significant difference in depressive scores between MBCT vs. controls and a significant difference in favour of MBCT for anxiety. Ives-Deliperi et al. (2013) reported no significant improvement in depressive scores between MBCT and a control group, which may not be surprising given baseline depressive scores not meeting sub-syndromal levels. They also found significant improvements in the MBCT group in anxiety, emotion regulation, working memory, spatial memory, and verbal fluency as well as increased activation in the medial PFC, an area associated with cognitive flexibility and a potential area of pathophysiology in the disorder. However, pre-post studies have found positive effects of mindfulness on depression and anxiety in patients with bipolar disorder (Deckersbach et al., 2012; Miklowitz et al., 2009; Weber et al., 2010), and meta-analyses including both controlled and uncontrolled trials found significant pooled effects of mindfulness on depression and anxiety (Bojic et al., 2017; Xuan et al., 2020).

2.3 Qigong and Tai Chi

2.3.1 Qigong: Background

Qi is Chinese for "life energy". The older ideogram for qi in Chinese includes a picture of a forest of trees cut down, or of a man clearing trees in the upper portion, symbolizing "no" or a negation, and in the lower portion, four sparks that represent a flame, the two pictures together suggesting a meaning like "no sparks for flame". This could mean an absence of moderacy that excludes the extreme hot of fire, or, if the clearing of trees is taken to mean "without form", and fire as the fire of life, the "formless fire of life" (Cohen, 2018). Another Chinese character for qi involves steam rising from cooking rice. This image suggests life energy coming from rice, or nutrition, and the steamy breath, or more simply breath. It can also suggest the reconciliation of opposites through water and fire, or heaven (steam, air) and earth (rice) (Cohen, 2018). Similar concepts to qi are found across many ancient civilizations; it can be likened to ruach ha kodesh in Hebrew, spiritus sancti in Latin, or nafas in Islam, for breath of God, pneuma in Greek for vital breath, num among the Kung San indigenous people of the Kalahari Desert for life energy, nilch'I in the Navajo Native American tribe for the Winds that gave life to all of nature, and prana in India for life energy. It is the energy that permeates and sustains all of life, including humans (Cohen, 2018).

Gong means "skill achieved through committed effort" or "mastery" (it is the same as the "kung" found in kung fu, "fu" for "war"). Together, qigong means working with life energy to

enhance its control and distributed flow, with its abundance, clarity, and flow throughout the body to facilitate health and improved performance in sport or martial arts (Cohen, 2018). It involves the art and science of skillful exercise using posture, movement, breathing, and meditation to refine, gather, and circulate qi in an integrative manner where the adjustments of body, breath, and mind operate in a oneness or unity (Liu & Chen, 2010). The term in these sense as the cultivation of qi and the medical sense as all Chinese self-healing exercise and meditation disciplines from ancient times to present did not come into use until the twentieth century, when in 1955 it was adopted by the "Tangshan Qigong Sanatorium" in Heibei Province (Liu & Chen, 2010). Previously, it was commonly called dao-yin, "leading and guiding energy", with references to dao-yin or qi seen as early as the first and second centuries B.C. in the “The Yellow Emperor’s Classic of Internal Medicine", and later Daoist works such as the Dao de Ching by Lao Zi and the Daoist Canon (Liu & Chen, 2010). Daoist practices has roots in shamanism and many sages developed practices to harmonize body, mind, and nature, incorporating movements and postures from shamanistic ritual dances (Liu & Chen, 2010).

Qi or the common life energy that make up a person is further divided into the "three treasures": jing, qi, and shen (Mayor & Micozzi, 2011). Jing is the subtle energy of the essence of materiality, sexuality, bodily growth, tissues, gray matter, bone marrow, and overall yin (passive) energy. Qi is a neutral (neither yin nor yang) energy that is derived from nutrition and air, and can further be classified into various types such as original qi, postnatal qi, protective qi, internal qi, or external qi. Shen is associated with the spirit, brightness of the eyes, and faculties of the mind such as awareness, thoughts, and emotions, and yang (active) energy. To

know the transformations of nature and the unfathomability of ying and yang is to know shen (Cohen, 2018). Jing transforms to qi, which transforms to shen. Jing is transformed into qi in the lower dan tien or energy field or elixir (dan) field (tien) (as opposed to the middle or upper dan tien), located about two fingers below the navel. It is the primary dan tien of focus in most of qigong (Mayor & Micozzi, 2011).

One of the most introductory qigong positions is the Tree Pose (Cohen, 2018). It begins with the basic qigong stance wherein the feet are shoulder-width apart, the whole body is relaxed, joints are relaxed open, the neck is "emptied", allowing the energy to reach crown, the head is suspended, the tongue touches the roof of the mouth, the shoulders are sunk and the elbows dropped, the spine is central and erect, the chest is sunk, the back is lifted, the creases at the junction of the hips and thighs are relaxed, the breath is slow, quiet, and deep in the abdomen. From this position, the arms are held in a rounded position at the height of either the abdomen or the chest as if holding a large beach ball. The mind is to be free from distractions and intent on the lower dan tien. Qi, guided by the adjustments of mind and breath, is sunk into the lower dan tien. The postures of qigong support principles of warmth and rootedness, relaxed alertness, sensitivity, and ease flow of qi throughout the body.

From this basic pose, or with other stances with similar supportive principles in sitting or supine positions, various other kinds of exercises can be performed. For example, slow physical movement can be introduced such as walking or movements of the whole body in the Five Animal Frolics. Qi, following the mind and breath, can be guided through meridian channels

(energy channels), such as the “Governing Channel” and “Conception Channel”, from the base of the spine, to the crown of the head, to the perinium, and again to the base of the spine (Cohen, 2018). Visualizations are also often utilized, as exemplified by a “Sunset Meditation”, wherein one visualizes golden light pouring from the sun and silver light pouring from the moon coalescing to create a clear light at the crown of the head, filling up the body from the feet up, then cascading outside the body like a waterfall.

The late 1970's saw the widespread popularity of qigong in China known as "the Qigong Fever", and with the open-door policy in China after the 1980's, research and international expansion on the practice flourished to create the medical, scientific and international disciplines seen today (Palmer, 2007). Medical qigong, one of several major practices of qigong (e.g., external qi practice, meditative or spiritual qigong, Confucian qigong, or martial qigong), is one of the five branches of Chinese medicine (the other being acupuncture, herbs, massage or tuina, and Chinese dietary medicine), and the main referent of "qigong" in this text, although all branches of qigong have healing properties and qigong at its core is a spiritual system (Liu & Chen, 2010). Qigong, in its integration of breath, body, and mind, can be thought of as a form of moving mindfulness, allowing its placement within the category of a mindfulness-based or mind-body therapy.

2.3.2 Tai Chi: Background

Tai Chi is an abbreviation of *Tai Chi Chuan*, also written as t’ai chi ch’uan, taijiquan, tai ji quan, or tai ji chuan depending on the transcription (Kaptchuk & Tomalin, 2000). *Tai* translates into

"great" or "large", and *Chi* denotes a superlative, to give rise to the meaning "biggest", "most ultimate", or "the grand ultimate" (Wayne & Fuerst, 2013). Figuratively it refers to 'the cosmos', originating from the I Ching Book of Changes, and characterizes the philosophical concept of the "Supreme Ultimate" ying-yang principle which encompasses all things (Wong, 2001). The beginning of the classic Treatise on Tai Chi Chuan, master Wang Zong Yue says "Tai Chi is born from the void. It generates movement and stillness, and is the mother of yin and yang. When moved, it separates; when still, it unites.' (Davis, 2004). Chuan is generally translated as "fist" or "boxing", sometimes described as a manifestation as the closing fist expresses a sense of practical materialization (Wayne & Fuerst, 2013). Together, Tai Chi Chuan is translated variously as Supreme Ultimate Boxing, Great Extremes Boxing, and Grand Ultimate Fist. It describes a form of martial art or exercise based on the principles of yin and yang and the integration of opposites into a dynamic whole, to strengthen, relax, and integrate the physical body and mind, enhance the flow of Qi, and improve health, personal development, and self-defence (Wayne & Fuerst, 2013).

It is popularly told that the origins of Tai Chi involved a Shaolin monk in the 13th century, Chang San-feng, who decided to leave the monastery upon graduation and become a Taoist hermit. Chang one day observed a fight between a crane (or sparrow, by some accounts) and a snake, whereby each animal would yield, evade, then attack the opponent. This sight inspired him to develop a softer style of Shaolin Kung-fu which then developed into Tai Chi Chuan, emphasizing yielding and mindful or intrinsic strength, or Jin, using methods such as breath control, Qi channeling, and visualization (Seidel & DeBary, 1970).This is in contrast to other martial arts

such as forms of karate and Kung Fu that emphasize muscular strength and speed (Davis, 2004). Tai Chi movements are generally graceful, gentle, and performed slowly to facilitate ease in development of flow of internal energy and the integration of mind and body, although once skilfulness is obtained, fast and forceful execution is possible (Wong, 2001). Although how early principles and movements attributed to characters such as Chang San-feng became codified into the formalized Tai Chi forms seen today is unknown, many distinctive postures and names seem to be able to be attributed to general Ch'I Chi-kuang of the Ming dynasty who wrote "Boxing Classic" (Wayne & Fuerst, 2013). Many of the movements of this text are in the oldest style of formal Tai Chi systems, Chen-style Tai Chi of the Chen family. Subsequent styles and lineages of tai chi include Yang, Wu, Wu/Hao and Sun styles.

While one needs to be healthy to be a martial arts artist and martial artist practitioners appreciated its health benefits, Tai Chi was not widely adopted for health promotion and self-development until Yang Chang Fu began teaching tai chi more widely in the early to mid 1900s (Wayne & Fuerst, 2013). This led to the Chinese government adopting a national "self-strengthening" movement, which included the development of a 24-posture simplified form in 1956 named the Beijing Form as a part of a national fitness program (J. Li et al., 2001). Tai Chi's healing arts influence is also seen by the continuation of the tradition of observing and imitating nature, as seen in early texts in Chinese medicine such as "The Internal Canon of the Yellow Emperor" and practices of physicians such as Hua Tuo and his Five Animal Frolics (Dharmananda, 2002; Veith, 2015), similar to the origins of Qigong. Tai Chi invariably involves qigong, for it without some form of internal direction of Qi is mere artful dance (Wong, 2001).

Even without an active martial component to Tai Chi, it can offer benefits in daily life such as lifting heavy objects, maintaining balance in a fast-paced crowded marketplace, or staying cantered during an emotionally challenging experience (Wayne & Fuerst, 2013).

Tai Chi also has philosophical and spiritual influences, primarily under the precepts of Taoism. The influence of Taoism can be seen in the emphasis on principles such as not struggling, not initiating an attack, non-aggression, of the soft overcoming the hard, as well as the development of self-awareness and the responsibility for one's self which applies to health, relationships, and martial arts (Wong, 2001). Taoism also provides a framework for practice within a larger cosmology, where practitioners can be mindful of and be nourished by the organic forces of nature and ultimate unchanging reality of the Tao (or the "way" or "path") (Wayne & Fuerst, 2013). Resting in or glimpsing into the ultimate reality or void, one can develop qualities as mentioned by Lao Tzu: "When you realize where you come from, you naturally become tolerant, disinterested, amused, kindhearted as a grandmother, dignified as a king. Immersed in the wonder of the Tao, you can deal with whatever life brings you" (Laozi et al., 2007).

2.3.3 Qigong for mental health

Studies have shown that qigong practice may improve cardiopulmonary health, arthritis, fibromyalgia, risk for falls, hypertension, lung capacity, white blood cell count, and diabetes, among other physical health outcomes (Freire & Alves, 2013; Jahnke et al., 2010; Lynch et al., 2012; Marks, 2017; Ng & Tsang, 2009; Stahl et al., 2020). As for mental health, a number of

RCTs have investigated the effects of qigong practice in improving symptoms of depression in various populations including patients with clinical depression (Guo et al., 2019), depressed elders with chronic illnesses (Tsang et al., 2002), women with perimenopausal syndrome and depression (Shorey et al., 2020), and patients with depressive symptoms secondary to chronic conditions (Lu et al., 2020). Control conditions included traditional remedial rehabilitation activities (Tsang et al., 2003), education support (Astin et al., 2003), exercise (Cheung et al., 2005), newspaper reading (Tsang et al., 2006; Tsang et al., 2013), CBT (Chan et al., 2011), and standard care (Kim et al., 2004; Oh et al., 2010; Stenlund et al., 2009). A systematic review and meta-analysis reports that nine of twelve RCTs in the review suggested a favorable effect of qigong on depressive symptoms (Chong-Wen et al., 2013). Pooled SMD by comparison groups have ranged from 0.56 (comparison to CBT), to -0.52 (comparison to exercise), -0.75 (comparison to usual care), and -1.24 (comparison to newspaper reading) (Chong-Wen et al., 2013). Research also suggests positive effects of qigong on anxiety, stress, and quality of life (Chow et al., 2012; Griffith et al., 2008; Rodrigues et al., 2021; Wang et al., 2013).

2.3.4 Tai Chi for Mental Health

Research has shown positive effects of Tai Chi on physical health conditions such as falls, arthritis, and hypertension (Hartman et al., 2000; Taylor et al., 2012; Voukelatos et al., 2007; Young et al., 1999). For mental health, RCTs have found greater reduction of depressive symptoms of Tai Chi training compared to wellness education (Chou et al., 2004; Irwin et al., 2007), stretching and wellness education (Wang et al., 2009; Wang et al., 2010), and waitlist control (Cho, 2008; Chou et al., 2004). One RCT found Tai Chi training not to be better than

health education for depressive symptoms although significant reductions were observed in both groups (Irwin et al., 2007), and another RCT found no significant benefits of Tai Chi on depressive symptoms (Fransen et al., 2007). Meta-analyses suggests Tai Chi to be beneficial for depression in patients with chronic health conditions with SMD of -0.42, -0.27, and -0.37 (Chi et al., 2013; Choo et al., 2020). Another meta-analysis reports no significant improvement in depressive symptoms in a pre-post analysis of 16 studies (Liu et al., 2015). Other studies have found positive effects of Tai Chi on outcomes such as anxiety, stress, quality of life, and positive mood (Lee et al., 2007; F. Li et al., 2001; Liang et al., 2020; Robins et al., 2006; Taj & Manoj, 2015; Tajik et al., 2018).

2.4 Summary and Goals/Aims

Older adults with bipolar disorder (BD) are expected to exceed over 50% of the BD population by 2030, yet there is a lack of research specific to this population. Persistent sub-syndromal depressive symptoms, a depressive polarity, and poor cognition is particularly common in this population. Current pharmacotherapies are limited in efficacy for depression, not effective in cognition, and often poorly-tolerated. Mind-body interventions have been found to be effective in treating several psychiatric conditions including BD. Qigong and Tai Chi, forms of moving mindfulness, been found to be beneficial for physical and mental health conditions as well as cognition. With their emphasis on attending to gentle, slow movements of the body and breath, present accessible and tolerable forms of exercise for older populations and those with cognitive impairment. Qigong and Tai Chi have not been studied in any BD population.

Our intent was to conduct a 12-week pilot randomized controlled trial examining the efficacy of online qigong/Tai Chi vs. a light exercise active control in improving symptoms of depression, cognition, anxiety, quality of life, daily functioning, mindfulness, self-compassion, and self-rated depression for middle to older age adults with bipolar disorder. We also aimed to examine that qigong/Tai Chi will not be associated with elevated mania in comparison to light exercise.

Chapter 3: Manuscript

Efficacy of Qigong/Tai Chi for Depression and Cognition in Middle and Older Age Bipolar Patients During COVID-19: A Pilot Randomized Controlled trial

3.1 Introduction

It is expected that by 2030, the percentage of patients with bipolar disorder (BD) over 60 years of age will exceed 50% (Sajatovic et al., 2005). Despite this, there is a lack of research specific to older-age bipolar disorder (OABD). In this population, depression, persistent sub-syndromal depressive symptoms, and poor cognition are particularly common, difficult to treat, associated with mood relapse, and poor daily functioning (Sajatovic et al., 2015). As current pharmacotherapies are limited in efficacy for depression, not effective in cognition, and often poorly-tolerated (Dias et al., 2012; Fung et al., 2019; Goodwin et al., 2007; Katz et al., 2017; Strakowski, 2014; Zornberg & Pope, 1993). There is thus an urgent need to find alternative interventions for this growing demographic (Martino et al., 2018).

Mind-body interventions have increasingly been found to be effective in treating several psychiatric conditions including BD (Goldberg et al., 2018; Ives-Deliperi et al., 2013; Williams et al., 2008). Qigong and Tai Chi, practices of moving mindfulness, present accessible forms of exercise for older populations with the potential to facilitate greater ease in engagement with mindfulness. They have been found to be beneficial for physical and mental health (Abbott &

Lavretsky, 2013; Chong-Wen et al., 2013; Rogers et al., 2009; Wang et al., 2004), although their efficacies have not been examined in any bipolar population.

We aimed to evaluate whether 12-weeks of online-delivered qigong/Tai Chi training during the COVID-19 pandemic would be effective in reducing and preventing increase in symptoms of depression, and improving cognition, as well as exploratory outcomes including anxiety, quality of life, daily functioning, mindfulness, and self-compassion, in comparison to a light exercise active control in older age bipolar patients as well as middle-age bipolar patients who may progress into the older age bipolar population. We hypothesized that qigong/Tai Chi will be associated with greater improvement in all outcomes and not be associated with a greater increase in mania in comparison to light exercise.

3.2 Methods

3.2.1 Study design

We conducted a 12-week assessor-blinded parallel pilot RCT comparing online qigong vs. light exercise for depressive symptoms in older adults with bipolar disorder. Prior to recruitment, the trial had been registered (ClinicalTrials.gov Identifier: NCT04450147). The study was approved by the research ethics boards at all participating hospitals.

3.2.2 Participants and study recruitment

Participants were recruited and enrolled between September 2019 and September 2020 from an outpatient bipolar clinic at Douglas Mental Health University Institute and the Jewish General Hospital psychiatric outpatient clinic in Montreal, Canada. Adult participants aged ≥40 years were included if they had a diagnosis of bipolar I or II, spoke English or French, and had access to a computer with a functioning camera, microphone, and the ability to run Zoom videoconferencing software. Patients were excluded if they had a rating >5 on the Young Mania Rating Scale (YMRS) (Young et al., 1978), current clinician diagnosis of substance abuse unless completely in remission, risk of suicide as assessed by a score above 3 on item 10 of the Montgomery Asberg Depression Rating Scale (MADRS) (Davidson et al., 1986), concurrent participation in other psychosocial group program, or unstable psychiatric medication started less than 4 weeks from the beginning of the program. All participants gave informed verbal consent.

3.2.3 Randomization and methods to reduce bias

Participants were allocated in a 1:1 ratio to qigong or light exercise using stratified randomization. A research team member uninvolved in participant recruitment or assessment performed randomization using a computerized random number generator. Randomization was stratified by baseline MADRS score (euthymic, ≤ 10; or sub-syndromal, 11-20 inclusive). Stratification based on euthymic or sub-syndromal depressive status was used to mitigate floor-effects in the analysis of change in depressive symptoms. The research team member who performed randomization directly transmitted participant group information to the

interventionists. Assessors of outcomes were blinded to participant group assignment and the study was advertised as the investigation of two alternative movement therapy interventions.

3.2.4 Sample Size

The aim was to recruit 15-30 participants in each arm for this pilot trial, standard for an initial RCT comparing the intervention with an active control, to generate a sample size estimate for a definitive RCT.[33]

3.2.5 Intervention: Online Qigong

The treatment program consisted of 12 weekly 1 hour classes of stretching and warm-up, qigong exercises, breathing techniques, and meditation/affirmations. Classes were delivered in a group format online over video-conferencing to adapt to COVID-19 social distancing measures. Breathing techniques included abdominal and spinal breathing, and qigong exercises involved 14 slow, gentle movements of the body with visualizations of energy and moving such energies in harmony with the body and mind. Qigong movements included “the connection with the universe”, “sharing the energy with the universe”, “fill and share the ball of energy”, “exchange & harmonize the universal energy”, “harmonization front-back”, “sow, harvest, and share luminous flowers with nature”, “dance with the energy of the luminous ball”, “carry the moon”, “meditate with the ball of luminous energy”, “move hands like clouds”, “scoop from the sea”, and “spread your wings”. Tai Chi movements included “repulse the monkey”, “brush the knee”, “part the horse’s mane”, “wave hands like clouds”, “golden rooster standing on one leg”, “kick heel”, “grasp sparrow’s tail”, and “cross hands”. Meditation exercises included

bringing attention to the breath and focusing on positive thoughts including acceptance, healing, balance, success, harmony, gratitude, peace, and love. 10-minute daily home practice was encouraged. Reference materials for home practice were given on the first session.

3.2.6 Active control: online light exercise

The active control program consisted of 12 weekly 1-hour classes of warm up and light exercise. Classes were delivered in a group format online over Zoom videoconferencing to adapt to COVID-19 social distancing measures. Exercises focused on flexibility and strength training and involved no props except for chairs and was adapted to be suitable to the elderly population. A 10-minute daily home practice was encouraged. Reference materials for home practice were given on the first session.

3.2.7 Feasibility outcomes

We aimed for a recruitment goal of 15-30 participants in each trial arm within 12 months, a study drop-out rate of less than 30% (completion of the 8-week post-intervention assessment), an intervention drop-out rate of less than 30% (% of people who stop attending prior to the final zoom intervention session), and a non-attendance (intervention non-completion) rate of less than 30% of participants failing to attend 75% of their assigned intervention (excluding dropouts).

3.2.8 Primary Efficacy Outcome

The primary outcome was the between group difference in the 12-week change in depressive symptoms as measured by the Montgomery Asberg Depression Rating Scale (MADRS), with a primary analysis in all randomized participants, and a secondary analysis in the subgroup of patients with a baseline MADRS score ≥10. MADRS is a widely used rater/clinician-administered 10-item questionnaire to measure the severity of depression in patients with mood disorders, with each item rated from 0-6. The total score can range from 0-60, with scores 0-10 indicating euthymia, 11-20 indicating sub-syndromal symptoms, and 20+ indicating definite or acute depression. The scale has high internal consistency (Cronbach's α=0.89) (Agrell & Dehlin, 1989). The primary outcome was measured within two-weeks of the first and last intervention sessions.

3.2.9 Secondary Outcome

The secondary outcome was verbal fluency as a measure of cognition using the Animal Fluency Test (Tombaugh et al., 1999), involving the naming of as many animals as possible within 60 seconds. The secondary outcome was measured within two weeks of the first and last intervention sessions.

3.2.10 Exploratory Outcomes

Exploratory outcome measures were between group difference in 12-week change in mania measured by the Young Mania Rating Scale (YMRS), anxiety measured by the Generalized Anxiety Disorder-7 (GAD-7) (Spitzer et al., 2006), quality of life measured by the Quality of Life Bipolar Questionnaire (QoL.BD) (Michalak et al., 2010), daily functioning measured by the

Functional Assessment Short Test (FAST) (Rosa et al., 2007), mindfulness measured by the Five Facet Mindfulness Questionnaire – Short Form (FFMQ-SF) (Bohlmeijer et al., 2011), self-compassion measured by the Self Compassion Scale – Short Form (SCS-SF) (Raes et al., 2011), self-reported depression measured by the Quick Inventory of Depressive Symptomatology- Self Report (QIDS-SR) (Rush et al., 2003), and self-reported mania measured by the Altman Self-Rating Mania Scale (ASRM) (Altman et al., 1997). All exploratory outcomes were measured within two weeks of the first and last intervention sessions.

3.2.11 Analyses

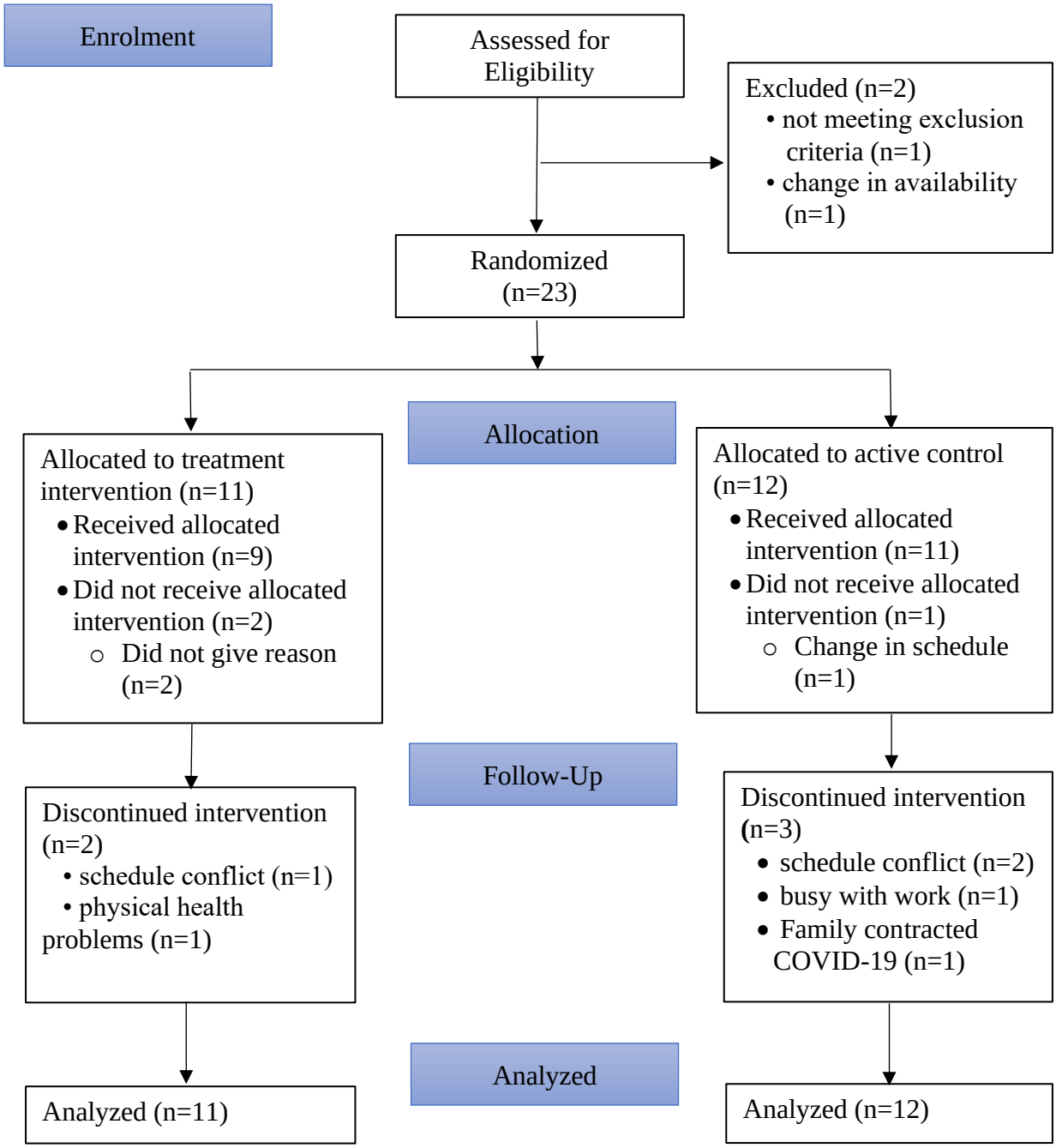
Normality of the data was assessed with the Shapiro-Wilk test. Homogeneity of variances was assessed with the Levene's test. Outliers with standardized residuals greater than 3 absolute value were identified for removal from analyses. Baseline characteristics were compared between arms using independent *t*, Mann-Whitney *U*, or a chi-square tests. Outcome measures on difference scores from baseline to 12-weeks between trial arms were analyzed using a regression analysis (Analysis of Covariance, or ANCOVA) corrected for baseline levels. A two-tailed p-value of 0.05 was used to determine significance. Measures of effect size at 95% confidence intervals were conducted using Cohen's *f* statistic or *r* ($Z/\sqrt{N}$). Effect sizes were interpreted as follows; *f*: small effect = 0.2, medium effect = 0.5, large effect = 0.8; r: small effect =0.1, medium affect = 0.3, large effect = 0.5. All analyses were completed using R. Participants with missing data in some secondary and exploratory outcome measures were reported but excluded from the outcome analyses.

3.3 Results

3.3.1 Participant flow

25 patients were screened with the MADRS, YMRS, and for eligibility, and 24 met eligibility criteria (Figure 1). Of these, 1 refused and 23 were randomized. 2 participants in the intervention arm and 1 in the intervention arm did not attend any of the sessions and did not receive the allocated intervention. 2 participants in the intervention arm and 3 participants in the active control arm discontinued the allocated intervention. The most common reason for participant drop-out was a conflict with work, especially in scheduling. All randomized participants completed follow-up assessments (n=23), leading to a total of 11 in the intervention arm and 12 in the active control arm whose data were analyzed.

Figure 1. Participant flow diagram



3.3.2 Baseline Characteristics

Baseline clinical and demographic characteristics between the intervention and control groups are presented in Table 1. Baseline characteristics did not significantly differ between the two arms. Sixty five percent of participants were female with a mean age of 58 years (±9.37). Participants had a similar age of onset of first psychiatric symptoms (43.48% between ages 10-17), type of first psychiatric symptom (78.26% with depression as first symptom type), and number of psychiatric medications (3.0 (IQR 2.0 – 4.0)). Sixty-nine percent of participants had a first-degree relative with a past or present psychiatric diagnosis, and seventeen percent were receiving mental health follow-up other than from a psychiatrist.

Table 3. Baseline Demographic and Clinical Characteristics

Participant Data	Total Sample (n=23)	Tai Chi Intervention (n=11)	Light Exercise Active Control (n=12)
Demographic information			
Female	65.22% (n=15)	81.81% (n=9)	50.00% (n=6)
Age, yr	58.13 (±9.37)	55.00 (±11.25)	61.00 (±6.45)
Married / common law	43.48% (n=10)	45.45% (n=5)	41.67% (n=5)
Highest Level of education			
High school	13.04% (n=3)	18.18% (n=2)	8.33% (n=1)
CEGEP (pre-university in Quebec)	21.73% (n=5)	9.11% (n=1)	33.33% (n=4)
University	65.22% (n=15)	72.73% (n=8)	58.33% (n=7)
Currently living alone	34.78% (n=8)	36.36% (n=4)	33.33% (n=4)
Medical History			
Age first psychiatric symptom (unspecific)			
0 < 10 years	17.39% (n=4)	18.18% (n=2)	16.67% (n=2)
10 < 18 years	43.48% (n=10)	63.64% (n=7)	25.00% (n=3)
18 < 30 years	21.74% (n=5)	9.11% (n=1)	33.33% (n=4)
30 < 40 years	8.70% (n=2)	0% (n=0)	16.67% (n=2)
40 < 50 years	0% (n=0)	0% (n=0)	8.33% (n=1)
50 and + years	4.34% (n=1)	9.11% (n=1)	0% (n=0)
First psychiatric symptom type			
Anxiety	17.39% (n=4)	9.11% (n=1)	25.00% (n=3)

Mood lability	13.04% (n=3)	0% (n=0)	25.00% (n=3)
Depressive symptoms	78.26% (n=18)	72.73% (n=8)	83.33% (n=10)
Manic symptoms	8.70% (n=2)	0% (n=0)	16.67% (n=2)
Psychosis	8.70% (n=2)	9.11% (n=1)	8.33% (n=1)
Suicidality	4.34% (n=1)	0% (n=0)	8.33% (n=1)
Other	17.39% (n=4)	36.36% (n=4)	0% (n=0)
Age first depressive episode			
0 < 10 years	4.34% (n=1)	9.11% (n=1)	0% (n=0)
10 < 18 years	13.04% (n=3)	18.18% (n=2)	8.33% (n=1)
18 < 30 years	39.13% (n=9)	18.18% (n=2)	58.33% (n=7)
30 < 40 years	30.43% (n=7)	36.36% (n=4)	25.00% (n=3)
40 < 50 years	13.04% (n=3)	18.18% (n=2)	8.33% (n=1)
Age first (hypo)manic episode			
0 < 10 years	4.34% (n=1)	0% (n=0)	8.33% (n=1)
10 < 18 years	8.70% (n=2)	18.18% (n=2)	0% (n=0)
18 < 30 years	13.04% (n=3)	0% (n=0)	25.00% (n=3)
30 < 40 years	26.09% (n=6)	36.36% (n=4)	16.67% (n=2)
40 < 50 years	21.73% (n=5)	9.11% (n=1)	33.33% (n=4)
50 and + years	8.70% (n=2)	18.18% (n=2)	0% (n=0)
Unknown	13.04% (n=3)	18.18% (n=2)	8.33% (n=1)
Age first treatment			
0 < 10 years	4.34% (n=1)	0% (n=0)	8.33% (n=1)
10 < 18 years	4.34% (n=1)	9.11% (n=1)	0% (n=0)
18 < 30 years	26.09% (n=6)	27.27% (n=3)	25.00% (n=3)
30 < 40 years	34.83% (n=8)	45.45% (n=5)	25.00% (n=3)

40 < 50 years	21.73% (n=5)	9.11% (n=1)	33.33% (n=4)
50 and + years	4.34% (n=1)	9.11% (n=1)	0% (n=0)
Unknown	4.34% (n=1)	0% (n=0)	8.33% (n=1)
Number of current psychiatric medications	3.0 (IQR 2.0-4.0)	3.0 (IQR 2.0-4.0)	2.0 (IQR 2.0-3.0)
Mood stabilizer	69.57% (n=16)	81.82% (n=9)	58.33% (n=7)
Anti-depressant	26.09% (n=6)	27.27% (n=3)	25.00% (n=3)
Anti-anxiety	17.39% (n=4)	18.18% (n=2)	16.67% (n=2)
Anti-psychotic	65.21% (n=15)	81.82% (n=9)	50.00% (n=6)
First degree relative diagnosed with psychiatric condition	69.57% (n=16)	72.73% (n=8)	66.67% (n=8)
Consumes alcohol	47.82% (n=11)	54.55% (n=6)	41.67% (n=5)
Smoker	30.43% (n=7)	54.55% (n=6)	16.67% (n=2)
Participated in psychoeducation in the last 5 years	34.78% (n=8)	36.36% (n=4)	33.33% (n=4)
Current non-pharmacological treatment for BD	17.39% (n=4)	18.18% (n=2)	16.67% (n=2)
Other			
Ever practiced mind-body technique	86.96% (n=20)	81.82% (n=9)	91.67% (n=11)

3.3.3 Feasibility

23 participants were recruited for the study within 12 months, with a pause within the first few months of COVID-19 and resumption thereafter. Eight participants did not attend their allocated intervention or dropped out (4 intervention, 4 control) and, leading to an intervention drop-out rate of 34.8% (36.4% intervention, 33.3% control). 5 participants failed to attend 75% of the intervention (2 intervention, 3 control), leading to a non-attendance (non-completion) rate of 21.7% (18.1% treatment, 25.0% control). All randomized participants completed follow-up assessments, leading to a study retention rate of 100% (0% dropout).

3.3.4 Efficacy outcomes

Primary analysis of the primary outcome (MADRS depression scores) included all randomized participants, and secondary analysis of the primary outcome included a sub-group of participants with a baseline MADRS score of 10 or greater (Table 2). There was no significant difference in the primary analysis of adjusted 12-week MADRS scores between groups (Intervention 12.80 (±3.48), 95% CI [5.55-20.00] vs. Control 15.30 (± 3.33) 95% CI [8.33-22.20]), $F(1,20)=0.26$, $p=0.610$, $f=0.11$. There was no significant difference in the secondary analysis of adjusted 12-week MADRS scores between groups (Intervention 10.20 (±3.39), 95% CI [2.79-17.60] vs. Control 14.60 (± 3.17) 95% CI [7.69-21.50]), $F(1,12)=0.90$, $p=0.069$, $f=0.27$.

Table 4. Primary and secondary analyses of primary outcome: 12-week MADRS Scores adjusted for baseline

Measure	Group	Baseline Mean (SD)	12-Weeks Mean (SD)	12-Weeks Adjusted Mean (SD) [95% CI]	F, p	Cohen's f
MADRS (Depression)	**Intervention** (n=11) **Control** (n-12)	11.00 (±7.86) 12.67 (±8.92)	12.72 (±11.81) 15.33 (±10.70)	12.80 (±3.48) [5.55-20.00] 15.30 (±3.33) [8.33-22.20]	F(1,20)=0.26 p=0.610	0.11
MADRS (Baseline≥10)	**Intervention** (n=7) **Control** (n=8)	15.43 (±6.08) 17.25 (±6.92)	9.42 (±11.41) 15.25 (±8.48)	10.20 (±3.39) [2.79-17.60] 14.60 (±3.17) [7.69-21.50]	F(1,12)=0.90 p=0.069	0.27

MADRS – Montgomery Asberg Depression Rating Scale

Analysis of the secondary outcome, AF verbal fluency scores as a measure of cognition also revealed no significant difference of 12-week AF scores between groups (Intervention 19.10 (±1.15), 95% CI [16.70-21.50] vs. Control 21.70 (± 1.09) 95% CI [19.40-24.00]), $F(1,16)=0.27$, $p=0.118$, $f=0.41$ (Table 3).

Table 5. Secondary outcome: 12-week AF Scores adjusted for baseline

Measure	Group	Baseline Mean (SD)	12-Weeks Mean (SD)	12-Weeks Adjusted Mean (SD) [95% CI]	F, p	Cohen's f
AF (Verbal Fluency)	**Intervention** (n=11) **Control** (n-12)	18.89 (±5.97) 19.7.0 (±6.09)	18.1 (±5.49) 21.9 (±3.70)	19.10 (±1.15) [16.70 – 21.5] 21.70 (±1.09) [19.40-24.0]	F(1, 16)=2.7 p=0.118	0.41

AF – Animal Fluency Test

Analyses of the exploratory outcomes, 12-weeks adjusted YMRS mania scores, GAD-7 anxiety scores, QoL.BD quality of life scores, FAST daily functioning scores, FFMQ-SF mindfulness scores, SCS-SF self-compassion scores, QIDS self-rated depression scores, and ASRM self-reated mania scores, as well revealed no significant differences between groups (see Table 4 for details).

Table 6. Exploratory outcomes: 12-Week YMRS, GAD-7, QoL.BD, FAST, FFMQ-SF, SCS-SF, QIDS, and ASRM scores adjusted for baseline.

Measure	Group	Baseline Mean (SD)	12-Weeks Mean (SD)	12-Weeks Adjusted Mean (SD) [95% CI]	F, p	Cohen's f
YMRS (Mania)	**Intervention** (n=11) **Control** (n-12)	1.27 (±1.56) 1.92 (±1.93)	1.36 (±1.69) 2.41 (±2.75)	1.53 (±0.67) [0.13-2.92] 2.27 (±0.64) [0.94-3.60]	F(1,20)=0.63 P=0.435	0.18
GAD-7 (Anxiety)	**Intervention** (n=11) **Control** (n-12)	8.91 (±4.21) 7.83 (±5.39)	8.91 (±5.00) 9.00 (±6.77)	8.59 (±1.64) [5.16-12.00] 9.30 (±1.57) [6.02-12.60]	F(1,20)=0.10 P=0.759	0.07
QoL.BD (Quality of Life)	**Intervention** (n=11) **Control** (n-12)	40.72 (±8.30) 39.67 (±6.98)	39.10 (±8.71) 39.83 (±7.44)	39.00 (±2.4) [34.00-44.00] 39.90 (±2.3) [35.10-44.70]	F(1,20)=0.08 p=0.786	0.06
FAST (Daily Functioning)	**Intervention** (n=10) **Control** (n-12)	29.50 (±11.33) 24.58 (±12.55)	29.9 (±14.39) 24.25 (±13.04)	27.80 (±3.29) [20.90-34.70] 26.00 (±3.00) [19.70-32.30]	F(1, 19)=0.17 P=0.686	0.09
FFMQ-SF (Mindfulness)	**Intervention** (n=11) **Control** (n-12)	80.36 (±16.49) 79.08 (±12.18)	80.63 (±6.65) 84.75 (±11.32)	80.50 (±2.76) [74.7-86.3] 84.9 (±2.65) [79.4-90.4]	F(1, 20)=1.30 P=0.267	0.26
SCS-SF (Self-Compassion)	**Intervention** (n=11) **Control** (n-12)	34.36 (±9.97) 36.00 (±12.08)	35.36 (±7.05) 37.92 (±8.51)	35.70 (±1.87) [31.90-39.60] 37.60 (±1.79) [33.80-41.30]	F(1,20)=0.492 P=0.491	0.16
QIDS (Self-Rated Depression)	**Intervention** (n=11) **Control** (n-12)	13.27 (±4.63) 10.92 (±3.58)	8.18 (±4.78) 8.17 (±5.18)	7.61 (±1.46) [4.57-10.60] 8.69 (±1.39) [5.79-11.60]	F(1,20)=0.28 p=0.604	0.12
ASRM (Self-Rated Mania)	**Intervention** (n=11) **Control** (n-12)	1.91 (±2.02) 2.75 (±3.93)	2.18 (±2.32) 1.58 (±2.23)	2.30 (±-0.65) [-0.94-3.66] 1.47 (±0.62) [0.172.78]	F(1,20)=0.84 p=0.372	0.20

YMRS – Young Mania Rating Scale, GAD-7 – Generalized Anxiety Disorder 7-item Scale, QoL.BD – Quality of Life in Bipolar Scale, FAST – Functioning Assessment Short Test, FFMQ-SF – Five Facets Mindfulness Questionnaire Short Form, SCS-SF – Self-Compassion Scale Short Form, QIDS – Quick Inventory of Depressive Symptomatology, ASRM – Altman Self Rated Mania Scale

An exploratory analysis of a repeated measures ANOVA for MADRS depression scores in the intervention group showed no significant differences between baseline and 12-week MADRS scores (15.43 (±6.08) vs. 9.42 (±11.41), $F(1,6)=3.78$, $p=0.10$, $f=0.36$.

3.4 Discussion

In this pilot trial, compared to a 12-week online light exercise active control condition, a 12-week online qigong/Tai Chi intervention delivered by Zoom video-conferencing did not significantly reduce depressive symptoms in middle to older-age adults with bipolar disorder, who at baseline were either euthymic, or had either subsyndromal or major depressive symptoms.. However, for the subgroup of patients with baseline subsyndromal depression (MADRS scores >=10), there was a clinically important reduction (approximately 5 points) in mean depressive levels from the mid-subsyndromal range (15.43 (±6.08)) to just below the MADRS=10 cut-off for euthymia (9.42 (±11.41)) in those who received the qigong/Tai Chi intervention. No such reduction was present in those who received light exercise. There was also a trend toward significance in the analysis of the difference in 12-weeks depressive scores adjusted for baseline between the two conditions in this subgroup ($p=0.067$). Thus, our study suggests that qigong/Tai Chi may be effective in reducing depressive symptoms for patients who experience at least sub-syndromal or acute depressive symptom levels.

Although results of existing literature is inconclusive, the results of our primary depressive outcome is somewhat inconsistent with most previous studies examining qigong and Tai Chi.

Studies have found significant decrease in depressive symptoms in qigong in comparison to active controls including newspaper reading, traditional rehabilitation activities, education support, exercise, and usual care, and no significant improvement in comparison to CBT. RCTs have found greater reduction of depressive symptoms of Tai Chi training compared to wellness education (Chou et al., 2004; Irwin et al., 2007), stretching and wellness education (Wang et al., 2009; Wang et al., 2010), and waitlist control (Cho, 2008; Chou et al., 2004), although one RCT found Tai Chi training not to be better than health education for depressive symptoms although significant reductions were observed in both groups (Irwin et al., 2007), and another RCT found no significant benefits of Tai Chi on depressive symptoms (Fransen et al., 2007). Meta-analyses seem to support the efficacy of qigong and Tai Chi on depressive symptoms, with one analysis on qigong reporting a pre-post Cohen's d effect size of -0.48, and other meta-analyses suggesting Tai Chi to be beneficial for depression in patients with chronic health conditions with SMD of -0.42, -0.27, and -0.37 (Chi et al., 2013; Choo et al., 2020). However, another meta-analyses reports no significant improvement in depressive symptoms in a pre-post analysis of 16 studies (Liu et al., 2015). Research is limited by heterogeneous interventions of various qigong and Tai Chi styles and duration/frequencies, and small sample sizes. The result of our primary outcome is more consistent with studies examining pharmacological anti-depressant interventions in comparison to mood stabilizers and placebo control, which have found no significant benefits on depressive symptoms or time to recovery (Kohler-Forsberg et al., 2021; Parikh et al., 2010; Sachs et al., 2007).

There are a number of explanations for our findings, including: the negative impact of COVID-19, the use of an active control group, floor effects, and the use of Zoom video-conferencing to deliver the intervention. The negative impact of COVID-19 on the mental health of the general population, especially for individuals already at increased risk, may have influenced the outcomes observed in our study (Gobbi et al., 2020; McGinty et al., 2020; Vindegaard & Benros, 2020; Yarrington et al., 2021). One study has found that depressive symptom prevalence was more than 3-fold higher in US adults during than before the pandemic (Ettman et al., 2020), and another has reported that psychological distress was heightened in patients with bipolar disorder than those with MDD or no mental disorder (Van Rheenen et al., 2020). The lack of benefits seen in the study, either for the qigong/Tai Chi or for our active control condition of exercise may be due to the groups mitigating a worsening of symptoms during the pandemic rather than to a lack of efficacy. This is especially in consideration of exercise being seen to have therapeutic benefits for mental health in previous literature. Furthermore, floor effects may have influenced the results of the study, as several participants with no to little symptoms of depression were enrolled in the study to increase recruitment. That results trended toward significance in the subgroup analysis of participants with a baseline MADRS score >=10 supports this possibility. The use of an online vs. in-person delivered intervention may have reduced the efficacy of interventions by mitigating effects of group psychosocial support and presenting possible difficulties in following the exercises via video.

Our study did not find 12 weeks of qigong/Tai Chi, compared to the light exercise active control, to be associated any significant improvement in verbal fluency as a measure of cognition,

although one study found improvements in verbal fluency in older adults following Tai Chi training in comparison to walking, social interaction, or no intervention (Mortimer et al., 2012) as well as another study in the same population examining Tai Chi in comparison to endurance, resistance/strength, and flexibility exercise (Taylor-Piliae et al., 2010). Meta-analyses have reported significant benefits of Tai Chi in global cognition on measurements of the Mini Mental State Exam (Hedges' g = 0.346 and MD = 3.69) and the Montreal Cognitive Assessment Scale (MD = 3.23) (Liu et al., 2021; Wayne et al., 2014). Qigong practice has also shown improvement in processing speed in breast cancer survivors with decreased cognitive function (Myers et al., 2019) and middle-aged subjects (Ladawan et al., 2017). More research is needed to determine the efficacy of qigong and Tai Chi on cognition in the middle and older-aged bipolar population, in line with depressive symptoms and other outcomes included in our exploratory outcomes such as anxiety and quality of life. Although no significant results were found in our exploratory outcomes, a few other studies have reported positive effects of qigong and Tai Chi on anxiety and quality of life (Chow et al., 2012; F. Li et al., 2001; Taj & Manoj, 2015; Tajik et al., 2018; Wang et al., 2013).

Although our study did not meet our recruitment goals, likely due to the interruption of the COVID-19 pandemic, and intervention drop-out rates were greater than 30% in both trial arms largely due to scheduling conflicts in participants with work, our 100% study completion rate (completing 8-week follow-up assessment) speaks to high feasibility of the study in the middle to older-age bipolar population, even in a completely online delivery by Zoom including outcome assessments and intervention delivery.

3.4.1 Strengths and Limitations

Strengths of the present study include a randomized controlled design with an active control group, as well as an intention-to-treat analysis. Limitations include a limited sample size, and a lack of enrolment limited to those with at least sub-syndromal depressive symptoms, for whom the intervention is of most relevance. Future studies should include at least 30 participants in each trial arm in a RCT, and those with a minimum of sub-syndromal depressive symptoms (MADRS>=10) at screening. It is likely that with enough statistical power, some of the our outcomes may have reached significance.

3.4.2 Conclusions

Our 12-week online qigong/Tai Chi intervention delivered by Zoom video-conferencing did not significantly reduce depressive symptoms compared to than a 12-week online light exercise active control condition in middle to older-age adults with bipolar disorder who were euthymic or had depressive symptoms at baseline. However, a clinically important reduction in depressive symptoms with qigong/Tai Chi was found in a subgroup analysis of participants with at least subsyndromal depression symptom severity at baseline (MADRS>=10). We propose that Qigong/Tai Chi may be effective in reducing depressive symptoms for bipolar patients with sub-syndromal to acute depressive symptoms, which could be further examined. Our study found no significant effect of qigong/Tai Chi on verbal fluency as a measure of cognition in this population in comparison to light exercise. In the context of COVID-19, both qigong/Tai Chi and light exercise may have mitigated further decline in depressive symptoms and other health

outcomes rather than effecting improvement. More research is needed in the examination of moving mindfulness movement exercises such as qigong as potentially effective, feasible, and acceptable for sub-syndromal and acute depression, particularly for the growing older age bipolar population for whom pharmacotherapy present greater challenges.

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