USING MOTIVATION TO UNDERSTAND TREATMENT AND DECISION-MAKING

USING MOTIVATION TO UNDERSTAND TREATMENT AND DECISION-MAKING IN PSYCHIATRIC ILLNESS

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LAY ABSTRACT

Mental health challenges continue to impact Canadians, with major depression, bipolar disorder and substance use among the leading causes of disability. Depression and bipolar disorders are often associated with diminished motivation. Substance use, however, has been described as a "motivated behaviour", where the use of drugs is associated with specific goals, such as motivations to reduce negative feelings, achieve pleasure, and perhaps most importantly, avoid withdrawal. By assessing potential treatments for patients who lack motivation, and characterizing patient motives for health decisions like vaping, the following thesis aims to study motivation and mental illness from several perspectives. Study findings suggest that behavioural approaches can produce meaningful improvements for patients with diminished motivation, and identify several motivators for engagement with vaping behaviours, both of which have implications for mental illness treatment and policy building. Taken together, this work aims to generate evidence to improve treatment and enhance harm reduction approaches.

ABSTRACT

Background: Mental health challenges continue to impact Canadians, with major depression, bipolar disorder and substance use among the leading causes of disability. Depressive disorders are often associated with diminished motivation. In contrast, substance use has been described as a "motivated behaviour", where use of drugs is associated with specific goals; motivation may therefore help explain health behaviours like vaping. This thesis studies motivation and mental illness, by assessing treatments for patients who lack motivation, and characterizing motives for behaviour.

Methods: A pilot trial (RCT) was conducted to determine the feasibility of a trial to test the effects of behavioural activation (BA) in patients with major depressive disorder (MDD) (n=20). The full RCT was conducted to test the effectiveness of BA (n=169). Next, a protocol for a systematic review is described which explores outcomes used in trials for bipolar disorder type 1. Finally, a mixed-methods study was undertaken to identify vaping perceptions in patients with opioid use disorder (OUD) who vape (n=41).

Results: The pilot RCT demonstrated the feasibility for a full trial. The full RCT revealed that behavioural approaches may produce improvements in depression and quality of life (QoL) for patients with diminished motivation. Finally, the mixed-methods study identified 14 themes, revealing that vaping is convenient, common among youth, and a tool for smoking cessation.

Discussion: The pilot and full RCT trials reveal that BA has positive effects on depression and QoL in patients with depression, specifically showing significant improvements compared to waitlist. The mixed-methods study of vaping provides a lens through which vaping behaviours in the OUD population can be understood, generating evidence which can inform cessation efforts.

Conclusions: These works highlight how motivation can be intervened upon through treatment, and harnessed to better understand health decisions, with the overall objective of improving care within psychiatric populations.

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List of abbreviations and symbols

MDD: Major Depressive Disorder
OUD: Opioid Use Disorder
RCT: Randomized Controlled Trial
BA: Behavioural Activation
CBT: Cognitive Behavioral Therapy (CBT)
BRAVE: BehaviouRal ActiVation for reducing dEpressive symptoms and improving quality of life in patients with depression
HIREB: Hamilton Integrated Research Ethics Board
CONSORT: CONsolidated Standards Of Reporting Trials
SCID-I: Structured Clinical Interview for Diagnostic and Statistical Manual - Fifth Edition
DSM-5: Diagnostic and Statistical Manual - Fifth Edition
CRF: Case Report Form
BDI: Beck Depression Inventory II
BADS: Behavioural Activation for Depression Scale
Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form
SF-12: Short-Form 12 Health Survey
PCS: Physical Component Score
MCS: Mental Component Score
WSAS: Work and Social Adjustment Scale
LMS: Leisure Motivation Scale
EQ-5D-5L: EuroQol 5-Dimension
RSQ-RRS: Response Style Questionnaire – Ruminative Response Scale
REDCap: Research Electronic Data Capture
SD: Standard Deviation
BMI: Body-mass Index
REML: restricted maximum likelihood
BD: Bipolar Disorder I
CAT: Cognitive Analytical Therapy
IPT: Interpersonal Psychotherapy
QoL: Quality of life
PCS: Physical component score
MCS: Mental component score
SARIs: Serotonin antagonist and reuptake inhibitors
SNRIs: Serotonin and norepinephrine reuptake
SSRI: Selective serotonin reuptake inhibitors
TCA: Tetracyclic antidepressants
MAOI: Monoamine oxidase inhibitors
NASSA: Noradrenergic and specific serotonergic antidepressants
LOCF: Last observation carried forward
PIO: Patient-important outcomes
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analyses

Protocols
ICTRP: International Clinical Trials Registry Platform
MOUD: Medication for Opioid Use Disorder
EVALI: E-cigarette and vaping associated lung injuries urine toxicology screens (UTS)
COVID-19: Coronavirus 2019
HCP: health care provider
COREQ: Consolidated Criteria for Reporting Qualitative Research
IWLE: individuals with lived experience
UTS: Urine Toxicology Screens
QVC: Questionnaire of Vaping Cravings

Declaration of academic achievement

I, Alessia D'Elia, am the primary author of the presented manuscripts. I have contributed to these works through formulation of the study questions, completion of analyses, and development of the manuscripts. Co-authors contributing to the studies are listed on the first page of each study, with declarations of their contributions following the conclusion section of each study.

CHAPTER 1: Introduction

1.1 BACKGROUND AND SIGNIFICANCE

Mental health challenges continue to impact Canadians, with as many as 20% experiencing a mental health concern within a single year[1]. Among the leading causes of disability in Canada are mental illness and substance use disorders[2]. Such conditions have important, often devastating, impacts on quality of life and life expectancy[3,4]. Despite treatment options being available, many individuals relapse, and find existing interventions to be insufficient in sustaining remission[5–8]. Advances in treatment and harm reduction are especially necessary to respond to known risks for co-morbid physical and mental health conditions in psychiatric populations[9,10]. Research is needed to help improve quality of life in patients with mental health disorders, achieved by focusing on both treatment development and harm reduction[11,12].

Major depressive disorder (MDD) and bipolar disorders are often associated with diminished motivation[13]. Behavioural therapies like cognitive behavioural therapy (CBT) and behavioural activation (BA) have shown promise as therapeutics for depressive disorders which can be applied both individually and as an adjunct to other forms of treatment[14–18], such as medications like antidepressants. BA is a time-efficient format that mobilizes psychological strategies and activity tracking to eliminate reinforcers of depressive behaviours and connect with positive reinforcers[16,19–21]. BA is used to help interrupt cycles of depression by promoting engagement with activities that are personally rewarding and motivate other fulfilling behaviours, and has been shown to lead to similar outcomes as anti-depressants and improved outcomes compared to other cognitive therapies[22]. Despite possible benefits, the evidence regarding BA is limited by methodological gaps, such as small sample sizes, poor generalizability to clinical populations, and limited testing of different intervention formats, such as group BA[23,24]. Such limitations preclude the potential widespread offering of BA treatment to clinical populations, particularly those for which existing pharmacological behavioural approaches are insufficient in producing lasting remission and preventing relapse. Indeed, evidence is needed for treatment options which allow patients to avoid potentially unpleasant side effects of existing treatment, while supporting behaviour modifications that increase motivation to engage with daily activity and achieve positive effects. Additionally, current BA research requires further investigation to explore differences in the therapeutic effects of BA by sex, as there are known sex differences in motivation, treatment response and course. These shortcomings highlight the need for testing of BA treatment in MDD and mood disorders, and for sex-based analyses to support efforts for patient-centred care. This evidence is needed to arm healthcare providers and present additional options to bolster mental health services.

Individuals with BD type 1 (BAD) experience low mood and low motivation during periods of depression, similar to those with MDD. These individuals also experience periods of mania, episodes which have been correlated with heightened approach motivation[25], defined as an impulse toward positive stimuli[26]. Within both types of episodes, motivation is altered, and accordingly presents a potential target for treatment

which may be important to patients and should be tested within trials of treatment for BAD. The alteration of motivation and the impairment of behavioural inhibition is pervasive within the course of BAD[27], suggesting that motivation should be present within core outcome sets, that detail which outcomes must be included in trials evaluating treatment. Exploration of outcomes within trials for BD and patient-important outcomes presents an opportunity to ensure that trial outcomes are congruent with participant perspectives, and therefore align with key consequences and symptoms of BAD.

While MDD and BAD are associated with impaired motivation that results in negative social and personal consequences, opioid use disorder (OUD) is associated with problematic consumption of illicit opioids that is motivated or driven by desires to ease or improve physical or psychological needs. OUD is a chronic, relapsing disorder where dependence on opioids leads to a number of social, economic, and legal consequences[28]. Substance use has generally been described as a "motivated behaviour", where the use of drugs is associated with and reinforced by motivations to reduce negative affect, achieve pleasure, and perhaps most importantly, avoid withdrawal[29]. As the majority of patients with OUD suffer from co-morbid mental health concerns[30] that may lead to or occur as a result of drug use, OUD is often cyclical and relapsing, with continued opioid use being driven by desires to escape short-term physical or psychological consequences[29]. Individuals with OUD often demonstrate greater stress while having less use of adaptive coping strategies compared to controls[31]. While acting on short-term cravings, individuals with OUD fail to activate or motivate themselves toward behaviour modification and demonstrate impulsivity[32], often requiring cognitive and behavioural approaches to building coping strategies and change their behaviour[33].

Some literature suggests that substance abuse is driven by stress, with individuals being motivated to "self-medicate" as a coping strategy for managing stress or past trauma[34], alongside strong tendencies toward impulsivity[35] and poor behaviour inhibition[36]. Given the role of motivation within addiction and health behaviour, motivation may present an important framework for examining other behaviours within patients with addiction, such as vaping. Vaping is a novel and prevalent behaviour among patients with OUD[37]. Given its novelty, there has been limited exploration of motivations for vaping in patients with OUD, and little characterization of perceptions of vaping within this population. The absence of adequate research in this field has important consequences for patients with OUD who have proven susceptibility to poly-substance use[38] and other health comorbidities[39,40], as it precludes appropriate harm reduction planning and meaningful clinical interactions regarding vaping. Understanding of population-specific motives and perceptions is critical to developing nuanced and effective strategies for managing vaping, which respond to the barriers and enforcers experienced by patients with OUD.

Motivation is an important framework through which treatment and harm reduction within mental health can be understood and acted upon. Motivation is regarded as an internal or external processes or conditions which drive behaviour. Within the context of depressive disorders, motivation is impaired; patients with MDD or BAD experience extended periods of diminished motivation[41] and negative affect[42] which lead to poor engagement with daily activities and their interpersonal networks. Individuals with BAD may also see periods of impaired and heightened motivation and fluctuating mood[43] that

impact impulse control[44,45] and may lead to poor consequences[46–48]. Substance use is a motivated behaviour, resulting from internal desires to sate physical and psychological needs, and manage experiences of withdrawal[29].

Studying motivation helps to answer questions like "what causes behaviour" and "what causes behaviour to vary?" Answers to such questions within mental health populations provide a launching point for treatment and harm reduction strategies, both of which must be addressed in order to support appropriate care for individuals who experience, often overlapping, mental health challenges. Further, a nuanced understanding of motivation within mental health and motivators that underlie certain behaviours can generate important lessons for health promotion within specific mental health populations faced by population-specific risks, such as informing harm reduction planning and resources.

Through a motivation-based lens, this thesis has implications for understanding treatment and decision-making in psychiatric disorders, adding to the literature on motivation and mental illness. This work studies this connection in three ways, by studying how specific treatment modalities address diseases which impact motivation (within the context of depressive disorders like MDD and BAD), evaluating which outcomes are used in trials of treatment for BAD and the extent to which motivation-based outcome domains are explored, and finally, characterizing patients' motivations for engaging in specific risky behaviours (vaping within the OUD population).

Despite important distinctions between different mood disorders and substance use disorders, many of such conditions are characterized by similar challenges with motivating positive behaviours and behavioural inhibition of actions associated with negative consequences. Accordingly, lessons learned about individuals within each patient population have consequences for that specific population, but also have transferable applications due to important phenotypic similarities and comorbidities within psychiatric populations.

Therefore, to explore different aspects of motivation within psychiatric illnesses, this thesis employs various methodological approaches through the context of select psychiatric conditions. This work explored the ways in which motivation can be targeted in the treatment of pervasive mood symptoms, appraises the trial literature for outcomes of effectiveness and outcomes valued by patient populations, and finally, explored the motivations underlying health decisions. The studies detailed within this thesis suggest the extent to which motivation can be addressed through treatment, comprises outcome sets used to test prospective treatment, and can be used to better understand behaviour. Given the strong, shared genetic and environmental underpinnings among different psychiatric diagnoses, the prevalence of co-morbid psychiatric conditions, and phenotypic transdiagnostic similarities in traits, the findings of these studies have important implications for treatment and risk management in psychiatric populations. This thesis provides tactful and specific directions for treatment and policy, providing insight into future investigation for each condition, but also more broadly, to the field of psychiatrics.

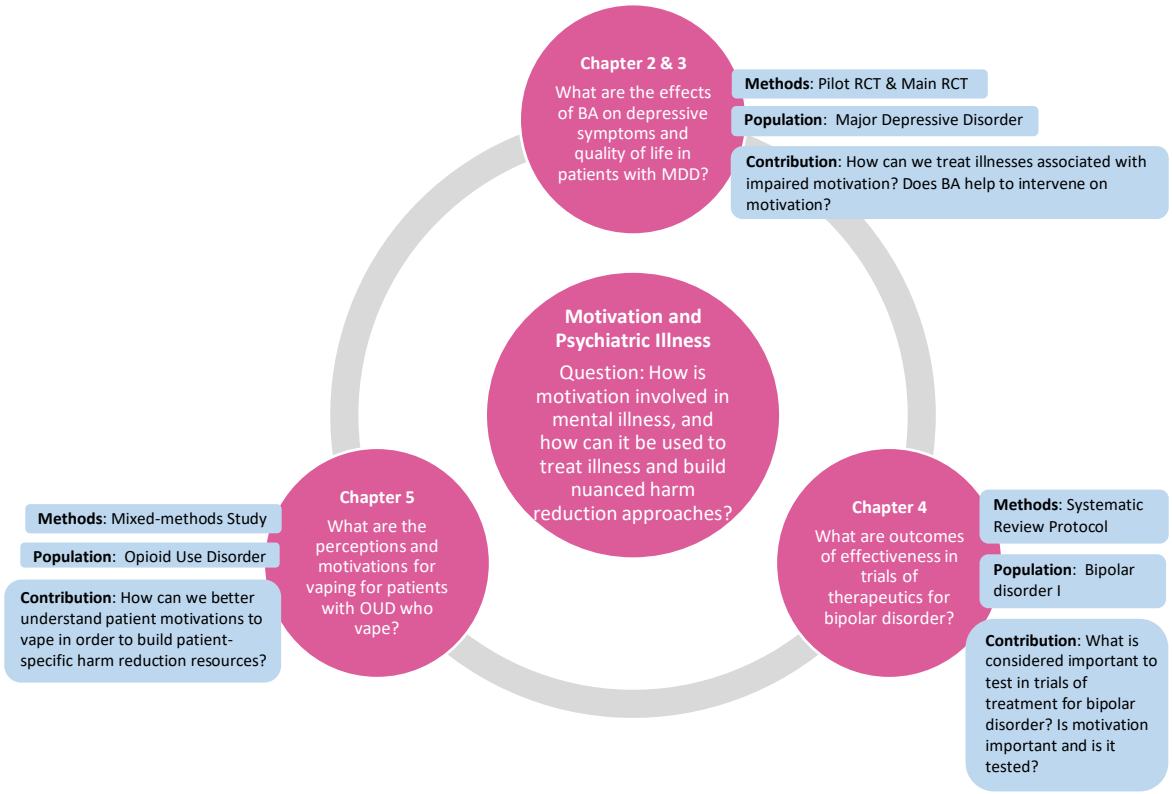
1.2 OBJECTIVES

The following research objectives are addressed through the four manuscripts that comprise this thesis:

1. To test the feasibility of a pragmatic randomized controlled trial to test the effects of behavioural activation group therapy on improving mood symptoms and quality of life in patients with MDD.
2. To test the effectiveness of behavioural activation using a randomized controlled trial design (piloted through objective 1), a potential treatment format underscored by principles of motivation and activation, on mood symptoms and quality of life in patients with MDD.
3. To develop a strategy to systematically appraise the literature to determine which outcomes are used to establish effectiveness within trials of treatment for bipolar disorder, and examine any literature reporting patient-important outcomes.
4. To explore the perspectives and motivations for vaping in patients with OUD currently on medication for opioid use disorder (MOUD) treatment.

In order to adequately explore motivation within mental illness, it is essential to assess how impaired motivation can be treated, empirically studied, and understood, within the context of more than one psychiatric condition. Using various methodological approaches, these separate objectives access different facets of motivation, namely, the way that motivation is an active part of the disorder and is inherent to decision-making with psychiatric populations. Figure 1.1 summarizes the ways in which each paper contributes to an overall understanding of motivation in psychiatric illness, to support a better understanding of treatment and harm reduction.

Figure 1.1 Table Summary of Chapter Objectives



1.3 COHERENCE OF THESIS CHAPTERS

To understand the ways in which motivation can be used to understand and inform intervention within psychiatric populations, three core methodologies were used in three distinct psychiatric populations described below. These papers contribute evidence surrounding treating and characterizing motivation within psychiatric populations, specifically commenting on motivation as an avenue for treatment, proposing its relevance as a trial outcome and/or patient-important outcome, and as a tool through which we may examine decision-making. This thesis focused on three different psychiatric populations: major depressive disorder (Chapter 2 and 3), bipolar disorder (Chapter 4) and opioid use disorder (Chapter 5). Motivation was explored using various methodologies, ultimately testing behavioural activation as a form of treatment, appraising the literature for trial outcomes and patient important outcomes, and gathering perspectives on vaping behaviours. Through randomized control trial methodology (Chapter 2 and 3), the effectiveness of treatment underscored by motivation and activation principles was investigated. This work ultimately drew conclusions about how effective behavioural activation group treatment is for patients with depression, through a pilot and full RCT. Next, a multi-pronged, systematic review protocol (Chapter 4) is presented for a systematic review of outcomes in the trial literature for bipolar disorder treatment. This study provides

a strategy for appraising the outcomes used to measure treatment success and to explore patients' goals for treatment within the scope of BD. This work will provide insight into the outcomes that are used to establish treatment success and patient-important outcomes. Finally, this thesis aimed to generate an understanding of patients' motivations and explored patient-decision making, through a mixed-methods, observational approach that studied perceptions and motivations for vaping, an emerging and important behaviour impacting mental and physical health within patients with opioid use disorder (Chapter 5). Using a variety of approaches, and through the scope of both mood and substance use disorders, this thesis contributes evidence to specific research fields, and when taken together, accesses and provides insight into the ways that motivation can be understood and used to improve health within psychiatric populations.

CHAPTER 2: Feasibility of behavioral activation group therapy in reducing depressive symptoms and improving quality of life in patients with depression: the BRAVE pilot trial

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2.1 COPYRIGHT STATEMENT

D'Elia, A., Bawor, M., Dennis, B.B., Bhatt, M., Litke, K., McCabe, K., Whattam, J., Garrick, L., O'Neill, L., Simons, S., Chalmers, S., Key, B., Goyert, S., Laplante, P., Vanstone, M., Xie, F., Guyatt, G., Thabane, L., and Samaan, Z. Feasibility of behavioral activation group therapy in reducing depressive symptoms and improving quality of life in patients with depression: the BRAVE pilot trial. Pilot Feasibility Stud 6, 61 (2020). https://doi.org/10.1186/s40814-020-00596-z

2.2 ABSTRACT

Background: Depression impacts the lives of millions of people worldwide. Behavioral activation (BA), derived from cognitive behavioral therapy, has the potential for improving depressive symptoms in patients with depression. Studies evaluating the effectiveness of BA specifically in the context of group therapy program in a hospital setting for patients with depression are limited. In this study we report findings from a pilot trial evaluating group BA for major depressive disorder.

Objective: The objectives of this pilot trial are to assess the potential of a full trial of BA group therapy in a large-scale tertiary care setting, and to provide preliminary information about possible results regarding mood symptoms and quality of life in adults with depression.

Methods: Using a parallel single-cohort pragmatic pilot randomized controlled trial design, we evaluated the potential of conducting a large trial of BA effectiveness among adults with depression. Participants were randomized to the intervention (BA in addition to usual care) or control (support group in addition to usual care) groups, and were assessed weekly for 18 consecutive weeks. Participants randomized to intervention underwent 28 two-hour group BA therapy visits administered by trained therapists and completed assessments to examine treatment outcomes. Feasibility was measured in terms of enrollment rates (min. 20%), completion rates of study (min. 80%), and completion rates of weekly measurement scales (min. 80%). The reporting of this pilot trial is in accordance with the CONSORT extension for randomized pilot and feasibility trials.

Results: We randomized 20 individuals of mean age of 48.8 years (standard deviation=9.7) with a DSM-5 diagnosis of major depressive disorder to intervention (n=10) or control (n=10) groups. Based on our feasibility criteria, our recruitment rate was excellent (20/27; 74%), study completion was found to be a moderate (80% of the total participants in both arms completed the study; BA=100%, control=60%), and completeness of measurements on a weekly basis was adequate overall (82%; BA=86%, control=79%).

Conclusions: The study has demonstrated the potential feasibility to perform a larger scale trial upon modifications to the control group to avoid the low rate of study completion (60%) in this group.

Trial Registration: ClinicalTrials NCT02045771, Registered January 22, 2014 https://clinicaltrials.gov/ct2/show/NCT02045771

Keywords: behavioral activation, behavioral group therapy, depression, quality of life, pilot randomized trial

2.3 BACKGROUND

Depression, a complex chronic disorder affecting over 350 million people globally[1], has become the second leading cause of disability worldwide[2] and is associated with increased risk of medical comorbidity, suicide, and all-cause mortality[3,4]. Although pharmacological treatment with antidepressant medication, the most common approach to treat depression, has shown promise for improving mood in adults[5], nearly half of patients continue to show depressive symptoms over the long-term[6-8]. Given the limitations of pharmacology antidepressant treatment, it is necessary to evaluate alternate and additional treatment strategies. Further, psychotropic medications as well as depression itself are known to be associated with risk of increased body weight and other metabolic changes[9], suggesting the need for treatments for depression that do not precipitate poorer physical health outcomes or are protective against metabolic changes involved in the course of depression[10].

Psychotherapy, including psychological interventions such as cognitive behavioral therapy (CBT), has been successful in the management of depression both as a single therapy or in combination with antidepressants[11], improving the overall quality of life and coping skills and producing positive long-term results[12,13]. CBT requires, however, extensive training and resources, as well as patients' thorough understanding of their core beliefs and behaviors.

Behavioural activation (BA), originally a component of CBT, addresses behaviours and encourages individuals to eliminate reinforcers of depressive behaviours and connect with positive reinforcers in their environment[14]. The emergence of behavioural therapy for depression has opened opportunities for the development of simplified time-efficient treatment strategies that can have lasting positive effects on depressive symptoms and quality of life.

The evidence for BA is limited in comparison to CBT, however it has reported advantages in the form of individual therapy for adult out-patients with depression[14]. BA is reportedly just as effective in treating symptoms of depression and reducing the risk of relapse as CBT in community samples of adults with depression[12,15,16]. Interestingly, a study comparing BA, cognitive therapy and anti-depressant medication in adults with depression found BA to lead to similar outcomes as anti-depressant treatment, and better outcomes than cognitive therapies[17]. A systematic review identified sixteen studies investigating behavioural activation treatment and demonstrated that changes between end of study and follow-up are not significant, suggesting that the benefits of BA are retained in follow-up[13].

While BA appears helpful in treating depressive symptoms, many studies addressing BA in treating depression tend to have small sample sizes, and some biased methodology[19]. A systematic review of BA treatment for older patients with depression found significant reductions in depressive symptoms but maintained that many of these studies should be considered cautiously, suggesting the need for studies with larger sample sizes and well-developed methodology[18]. Further, many of these studies did not assess efficacy of BA as a group intervention in a hospital setting.

Based on the available evidence, BA has the potential for success as a cost-effective treatment intervention that requires minimal guidance from clinical staff, allowing reduced

wait times and increasing the number of patients that can utilize this program[13]. In this study we report findings from a pilot trial evaluating group BA for major depressive disorder, and highlight the importance of implementing such therapies to determine their effectiveness in real-life clinical settings. While we previously reported the acceptability of group BA therapy among patients with depression[19], this paper details results of the pilot trial.

The objectives of the **B**ehaviou**R**al **A**cti**V**ation for reducing d**E**pressive symptoms and improving quality of life in patients with depression (BRAVE) pilot trial are to test the feasibility of implementing a pragmatic randomized trial to evaluate the overall efficacy of group BA, assess participants' satisfaction with the program, and receive feedback to modify future treatment program. We aimed to (1) evaluate the feasibility of the study process, including recruitment rate, completion of study, group size, and data completion; (2) assess resources needed for successful completion of the study (i.e. interview rooms, computers, time investment, clinical staffing); (3) explore the change in treatment outcomes including depressive symptoms severity and quality of life between and within intervention and control groups by presenting preliminary data and (4) provide description of participants' scores on any of the assessments conducted during the study as well as a description of patients clinical and demographic characteristics.

2.4 METHODS

This trial has been registered with ClinicalTrials.gov (Identifier #NCT02045771) and was approved by the Hamilton Integrated Research Ethics Board (HIREB: 14-042). The protocol for this trial is published in *Pilot and Feasibility Studies*[20]. The reporting of this pilot trial is in accordance with the CONSORT extension for randomized pilot and feasibility trials[21,22]. See checklist appendix 8.2.

2.4.1 Study setting

This single-site study took place within the Mood Disorders Program at St. Joseph's Healthcare Hamilton, an outpatient specialized mood disorders clinic. This is a tertiary care center receiving referrals from the Greater Hamilton and surrounding area for the consultation and management of patients who have lack of response or inadequate response to treatment in the community and therefore, were referred to the tertiary mood disorders clinic. Hence, the clinic often caters to patients with the most severe and complex depressive disorders.

2.4.2 Recruitment of participants

Clinicians approached patients at the Mood Disorders Program who were aged 18 years or older with major depressive disorders currently receiving treatment for depression at the clinic. Patients were eligible for the study if they were undergoing treatment for depression as per usual care (including antidepressants, psychotherapy, CBT, or other treatment modalities if any). Patients unable to provide written informed consent, communicate in English, or had a primary diagnosis other than depression were excluded. Details about the screening process and reasons for study incompletion were recorded (Fig.

1). Participants were allowed to discontinue participation in the study at any time. Recruitment for the pilot trial began December 2013 and ended in March 2014 when the sample size of 20 was reached. Participants were followed up at 3 months, and the pilot study ended in July 2015. Written informed consent was obtained from each participant prior to initiating any study procedures. Participants were told that the purpose of the study was to determine if the intervention is helpful, and that behavioural activation was not known to be more effective than the support group. They were told that by consenting to the study, they could be randomized to receive either the intervention or the control condition, and were encouraged to consult with family, friends and clinical teams about their participation. The consent form was discussed, and participants were given sufficient time to review the material and ask questions. Participants were provided a copy of the consent form for their own records.

2.4.3 Study design

This is a pragmatic randomized controlled trial comparing group behavioural activation (group BA) in addition to usual care to support (control) group in addition to usual care. Eligible participants were randomly allocated to the intervention or control arms using a parallel group design with a 1:1 allocation ratio. A block randomization system with block sizes of 2, 4, and 6 randomly assigned allocations; the randomization schedule was computer-generated. Full details of the randomization assignment, concealment and other trial-related methods are described in the protocol[20]. Ten participants were recruited to each arm of the study, which was decided based on the recommended therapy group size of 6-12[20].

Following the completion of informed consent and baseline assessments including mood scales, lifestyle questionnaires, and biometric measurements, participants were randomized in blocks. A research assistant not involved in the recruitment of potential participants or the study intervention procedures allocated the participants to the trial arms using the randomization system provided and informed the participants and the therapists/study clinicians of the group allocation. Twenty participants were allocated at a time, and each was assigned a unique participant ID. Pieces of paper with participant IDs were mixed and drawn from an envelope, then assigned according to the randomization schedule. Following randomization, participants were asked to attend their respective groups and given a schedule for the group dates. Blinding to the intervention during treatment was not possible for participants or clinical staff. We selected names for the two groups to be similar, the intervention group was called the "Out of the Blues" group and the control group was called the "Blues Breakers" to avoid calling the groups intervention and control. The staff was then given a list of participants in their group.

2.4.4 Intervention Condition

The detailed methods of BA administration are described elsewhere[20]. Briefly, the intervention consisted of 28 visits across 18 weeks; twice weekly until Week 10 and once weekly thereafter. Trained clinicians administered the intervention at each visit, which included study-related assessments, as described in the study protocol[20]. These clinicians were recreation therapists and social workers who provide services in the Mood Disorders

clinic, trained to administer BA by completing a workshop in April 2013 and reading three BA workbooks (Michael Addis and Christopher Martell. Overcoming Depression One Step At A time, the new behavioural activation approach to getting your life back 2004; Jonathan Kanter, Andrew Busch and Laura Rusch. Behavioural Activation 2009; and Christopher Martell, Sona Dimidjian and Ruth Herman-Dunn. Behavioural Activation for Depression, a clinician guide 2010).

2.4.5 Control Condition

The control group participated in a support group for 28 sessions across 18 weeks that was led by clinicians not trained in BA. Support group for the control group was unstructured and included topics for discussions selected by the group members with a facilitator present in the room (clinician); these sessions occurred over the same period of time as that of the intervention group. A nurse trained in data collection was present for each visit and collected information pertaining to suicide risk in order to ensure patient safety, as well as answer any questions pertaining to the completion of study-related instruments.

2.4.6 Data collection and instruments

An initial case report form (CRF) was designed to collect details at baseline about demographic data (i.e., age, sex, ethnicity, religious background, marital status, housing, education, employment, and income), suicidal behavior, and history of previous treatments. Physical measurements were also obtained at baseline and at the end of study using the SC-3315 Body Composition Analyzer (Tanita Corporation of America, Inc., Illinois, USA) for body composition data (i.e., weight, fat, muscle, bone mass, and metabolic age). Height and blood pressure were also measured.

We administered a number of instruments throughout the course of the study to monitor participants' progress including the Beck Depression Inventory (BDI)[23], Behavioural Activation for Depression Scale (BADS)[24], Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)[25], Short-Form 12 Health Survey (SF-12)[26], Work and Social Adjustment Scale (WSAS)[27], Leisure Motivation Scale (LMS)[28], EuroQol 5-Dimension (EQ-5D-5L)[29], Response Style Questionnaire – Ruminative Response Scale (RSQ-RRS)[30]. The BDI is a tool used to measure the severity of depression that is comprised of 21 questions assigned a score between 0 and 3, with a maximum score of 63. Scores between 19-29 are indicative of moderate depression while those greater than 30 are associated with severe depression. The BADS is a self-administered 25-item tool used to measure activation and avoidance of activities, such as staying in bed or thinking about one's problems, over the last seven days, rated on a scale of "not at all" (0) to "completely" (7). The Q-LES-Q-SF is a 14-item self-report instrument measuring general quality of life (QOL) with the final score expressed as a percentage between 0% and 100%, where higher percentages are indicative of a higher QOL. WSAS is a self-report instrument with 5-items scored between 0 (indicating no impairment) and 8 (indicating severe impairment); total scores greater than 20 indicate severe psychopathology and symptomology. The LMS is a 28-item questionnaire measuring motivation for participating in leisure activities; this tool uses a 5-point scale for each item.

The LMS generates four motivation scores: intellectual motivation, social motivation, competency or mastery motivation and a stimulus avoidance scores, where higher scores are indicative of greater endorsement of each domain.

The SF-12 is a 12-item survey to evaluate general health that generates two summary scores, the physical component score (PCS) and the mental component score (MCS). For the final question on the SF-12 instrument, an additional option of "a good bit of the time" was added. To complete scoring, reports of a "a good bit of the time" for item 12 were scored as "some of the time", so as to not overestimate the effect of physical health on engagement in social activity.

Full details on when each data collection instrument was completed during the trial can be found in the protocol[20]. We also interviewed participants during the pilot trial using a qualitative study component to gather feedback on the study interventions. These results were reported previously[19]. Participants were followed-up at 3 months post-study.

Study questionnaires and assessments were entered into a confidential electronic database (Research Electronic Data Capture, REDCap; http://project-redcap.org/). Physical forms with collected data were stored securely on-site at the Mood Disorders Program according to privacy regulations.

2.4.7 Criteria for assessing trial feasibility

The following criteria were used to assess feasibility of the current study: (1) minimum 20% recruitment rate; (2) study completion rate of 80% (i.e. 80% of data available for final visit, consistent with other psychotherapy trials[31-34]; and (3) 80% completion of measurement instruments (i.e. the percentage of all scales completed across all participants throughout 18 weeks).

2.4.8 Statistical analysis

All statistical analysis was done using R version 3.1.0 (http://www.r-project.org/) and were exploratory, therefore not intended to test the effectiveness of the intervention. Descriptive statistics are provided as mean and standard deviation (SD) or number (percent) and were used to characterize participants enrolled in the pilot study. Between-groups differences were presented as mean differences and SD. Group trajectories were plotted for each outcome to enhance visualization of group differences.

2.5 RESULTS

2.5.1 Sample demographics

We recruited 20 individuals over a period of 4.5 months (18 weeks); with a DSM-5 diagnosis of major depressive disorder, with a mean age of 48.8 (SD = 9.7). Our sample consisted of 8 (40%) men and 12 (60%) women. Eighteen (90%) participants reported physical health issues, including medical comorbidity or symptoms (e.g. arthritis, chronic pain, hypertension, insomnia, migraines, obesity, etc.) and 12 reported current alcohol use. Nineteen (95%) participants reported to be financially independent and receiving family and friends social support (e.g. from spouse, family, or friends). Less than half of participants have completed previous psychotherapy interventions for treatment of

depression. Six (30%) had previously received CBT, five (25%) participated in an emotion regulation skills group, four (20%) received occupational therapy, and five (25%) participated in a self-help group. Nearly half (45%) reported participating in general supportive counseling. Details of baseline demographics are described in Table 2.1.

2.5.2 Feasibility results

Based on our pre-defined criteria, we assessed feasibility of the main BRAVE trial. Of the 27 individuals approached, we successfully recruited 20 people over 4.5 months (18 weeks) to yield a recruitment rate of 74%, which fulfills our first feasibility recruitment criterion. Loss to follow-up at Week 18 was moderate, with four individuals not completing the study and failing to complete the final visit; therefore, we had an overall study completion rate of 80% (second feasibility criterion). However, all four patients who dropped out were from the control group, yielding a 100% completion rate for the treatment arm and 60% for the control group. Completeness of study measurements was also adequate; intervention versus control study measurements completion rates were 85% versus 61% for the BDI, 74% versus 85% for the BADS, 87% versus 80% for the Q-LES-Q-SF, 90% versus 77% for the WSAS, 90% versus 80% for the LMS, 85% versus 80% for the EQ-5D-5L, 90% versus 80% for the RSQ-RRS instrument, and 90% versus 85% for the SF-12, respectively. The average completion rate for study instruments was 86% for the intervention group and 79% for the control group; the overall completeness of measurements for all participants throughout the study was 82%, thus fulfilling our third feasibility criterion.

Therapists providing the intervention stated that a group size between 8 and 12 participants is ideal for them to manage the group at each session. This was based on the therapists' experience in the group setting, the size of meeting rooms available and time allocated for each session (2 hours). The therapists also provided feedback that two clinicians are needed per group (one therapist runs the group and one therapist cofacilitates). No other resources were identified as necessary to complete the intervention in a group format.

2.5.3 Intervention outcomes

We evaluated seven study measures over the course of the 18-week study period. We provide the mean and SD of these measures for both groups at baseline and end of study (Table 2.2). Scores on the BDI were higher among the control group, but decreased gradually for both groups across the study period (Figure 2.2). No harms were reported for either group.

2.5.4 Follow-up at 3 months

We also conducted follow-up interviews with both control and intervention groups at 3 months following the study. Completion rates for follow-up interviews were 50% for both the control and treatment groups. Mean BDI scores were 30 (SD=14.40) and 36.40 (SD=15.45) for the intervention and control groups, respectively, thus increasing slightly for both groups compared to the final study visit.

2.5.5 Anthropometry and body composition

We obtained an extensive record of participants' physical measurements and body composition using the SC-3315 Body Composition Analyzer (Tanita Corporation of America, Inc., Illinois, USA) to assess changes in overall metabolic and physical health during the study (Table 2.3). Changes in these measures (computed as the value at the end of study minus the baseline value) were explored in order to report if any differences exist between the change observed in the intervention group versus the control group on biometric variables such as BMI, weight, blood pressure. It is possible that BA may impact physical measures, perhaps mediated through mood or other factors, therefore we report whether preliminary data demonstrate any difference between groups on these variables. Generally, measurements for the intervention group demonstrated positive changes; weight, waist circumference, and fat mass decreased from study baseline to Week 18. Many of the measurements for the control group either increased slightly or remained constant throughout the study.

2.6 DISCUSSION

The study sought to evaluate the feasibility of conducting a full randomized controlled trial to investigate the effectiveness of BA in the treatment of depression. The pilot study showed it is feasible to conduct a large BA trial based on meeting relevant feasibility criteria including recruitment rate, study completion rate, and completion of study measurement scales, though the loss to follow up of the control group was high. This, however, is not inconsistent with other pilot trials investigating BA in the treatment of depression, which report completion rates such as 67% in the wait-list condition[33]. In order to limit the risk of loss to follow-up, participants recruited for the full trial will be compensated with parking vouchers or bus tickets. Rates of follow-up interviews at 3 months post-study were found to be low but equal between the intervention and control groups, demonstrating that further effort should be made to follow-up with participants following the end of the program. Participants will be provided the option of completing interviews over the phone or in person in order to improve adherence, accommodate participant availability, and decrease patient burden.

The BRAVE pilot trial also sought to explore the effectiveness of BA on depression symptoms and quality of life measures in adults with depression; preliminary data demonstrate no noticeable difference between intervention and control groups on all study measures. A full trial powered to detect clinically significant changes is needed in order to determine the effect of BA.

Behavioural activation used for the treatment of depression in a group format is practical, simple, and easy to administer; however, further research is required to understand the feasibility of this approach in a clinical setting, therefore necessitating a full trial. There are few existing trials on behavioural activation as a group therapy specifically, and further well-designed trials are needed to determine whether the use of this intervention as a therapy for patients with depression is effective in our setting or other avenues of clinical practice. This study has been designed to address these issues with proper study

design and relevant methodology. RCTs effectively demonstrate differences between groups while considering relevant known confounding factors, thus making them the gold standard for clinical evidence. We had the opportunity to monitor the progress of a specific cohort of patients with depression throughout the treatment intervention and evaluate differences between groups. We were also able to observe this cohort from study initiation to completion to evaluate the feasibility of a full trial to test the effectiveness of behavioural activation in the treatment of depression.

2.6.1 Key learning points

Based on our experiences with this pilot trial, we observed relatively high attrition rates, where all four individuals who did not complete the study participated in the control arm. These attrition rates are consistent with literature on psychotherapy trials, although the pattern of higher drop-out among control participants has not been previously apparent[31]. It is challenging to ascertain the true effect of this intervention relative to the control condition, as the nature of this control group is influenced by group effects, social interactions among participants, and possible attention received from group facilitators above and beyond usual care. This may indicate the need for potential modifications to the control arm of this trial in order to avoid these problems within the larger investigation. After exploring potential reasons for high attrition in the control arm, we concluded that the therapy provided in this arm of the trial (i.e. support group in addition to usual care) was not sufficient to retain participants in the study. Given these observations, it is possible that these participants are not benefitting from the study in any way and therefore lose interest over time. The time involved in conducting weekly visits and administering multiple questionnaires was considerable, and therefore may have also influenced attrition rates or completeness of assessments. We asked participants for their feedback on the pilot trial and they reported that they wanted the intervention to be offered to all participants at the end of the study period[35]. Feedback received from participants in the control group stated that the group was not helpful for them[19]. Offering the intervention for the control group at the end of the trial may enhance motivation to complete the study period and improve the retention of control group in the study. Given this feedback, we changed our plans for the control group for the main trial to use a wait-list group as a comparator, where participants in this group will be offered the intervention after the waiting period (approximately 18 weeks).

Participants in the intervention group were more eager to complete the study and all associated assessments, suggesting that these participants may have found it helpful in dealing with their depressive disorder, hence showing the intervention is acceptable and feasible to administer in a larger trial. This strengthens the rationale for performing the larger study, where this intervention can be explored in depth.

Unfortunately, we also observed low response rates in both groups for follow-up interviews at 3 months after study completion. An important concern in this study was loss to follow-up of the control sample where 40% of control participants initially recruited dropped out from the study prior to completion. In the future, greater efforts should be made to maintain contact with participants following completion of the study. It may also be useful to provide the option of online completion and telephone interviews in addition

to in person interviews to minimize burden to participants and encourage uptake of the follow up. This will help to determine whether the beneficial effects of BA can be maintained following treatment completion.

The long-term goals of this program are to guide the decision-making process through evaluation of the best treatment options, with the collective efforts of primary care providers, health care specialists, as well as patients themselves and their families. We also intend for our study findings to be used in the development of guidelines for BA group therapy for depression.

Following the pilot trial, we have amended the study design such that participants randomized to the control condition were later given access to BA treatment. This change was made in keeping with patient feedback about the study collected through qualitative interviews post-study. Given that the study length is 18 weeks, it is possible that participants randomized to the control/wait-list condition will be lost to follow-up before the end of the wait-list period. In order to mediate this challenge, participants will be in contact with a research staff on a weekly basis for 18 weeks, during which time they will complete weekly study instruments. Weekly contact will mitigate the effect that a loss of contact may have on participant retention. No changes were made to the eligibility criteria or study intervention length, though the follow-up duration was extended. We increased the post-study follow-up to 3, 6 and 12 months in order to understand the sustainability of changes to mood and quality of life measures up until a year after the program is completed, given the chronicity of depressive disorders.

2.6.2 Study strengths and limitations

This study included a comprehensive set of outcomes including depression severity, quality of life, behavioural activation, motivation, and physical health. We also collected detailed physical measurements using the Body Composition Analyzer to examine changes in body composition as an overall picture of the participants' health.

The current pilot study design did not allow for statistical conclusions and thus we cannot comment on the effectiveness of the intervention based on the current pilot data, however we were able to test the intervention feasibility. A limitation of the current pilot study is that we are unable to comment on or report whether the planned changes to the control group condition will be effective in mediating the issue of loss to follow-up and increasing retention. Furthermore, despite making use of validated instruments to assess outcomes of this intervention, these self-reported measures are at risk for recall bias as well as potentially social desirability bias.

A further limitation of the current study design is that since participants were not excluded if they were in CBT or other programs at the time of participation, and since there was no restriction for when previous programs were completed, the effects of CBT and other programs may impact mood symptoms and quality of life reported in this study. Due to the randomized design of this pilot trial, it is expected that this effect would be balanced between both groups. While a possible confounder, the purpose of this trial is to investigate the effectiveness of group BA in addition to care as usual, therefore participation in co-intervention does not obscure the study objectives.

2.7 CONCLUSIONS

This pilot study assessed the feasibility of conducting the full BRAVE randomized trial in a tertiary care mood disorders hospital-based clinic setting. We are able to conclude that based on our feasibility criteria as well as our study design, methodology, and comprehensive assessment of outcomes, the full investigation is likely to be conducted to evaluate the effectiveness of BA group therapy as a potential therapeutic approach to the treatment of major depression in adults. The caveat is the loss to follow-up of the control group. We will keep in mind the loss to follow-up challenge and have made changes in the plans regarding the selection of the comparator group. We will change the control condition to a wait-list followed by receiving the intervention and will compare the groups based on intervention versus wait-list conditions. We will also increase the post-intervention follow-up duration and have developed strategies to facilitate more successful follow-up in the main trial.

2.8 LIST OF ABBREVIATIONS

CBT: cognitive behavioural therapy; BA: behavioural activation; BRAVE: BehaviouRal ActiVation for reducing dEpressive symptoms and improving quality of life in patients with depression; HIREB: Hamilton Integrated Research Ethics Board; CRF: case report form; BDI: Beck Depression Inventory; BADS: Behavioural Activation for Depression Scale; Q-LES-Q-SF: Quality of Life, Enjoyment, and Satisfaction Questionnaire – Short Form; WSAS: Work and Social Adjustment Scale; LMS: Leisure Motivation Scale; EQ-5D-5L: EuroQol 5-Dimension; RSQ-RRS: Response Style Questionnaire, Ruminative Response Scale; RedCap: Research Electronic Data Capture; REML: restricted maximum likelihood

2.9 DECLARATIONS

2.9.1 Ethics approval and consent to participate

This trial was approved by the Hamilton Integrated Research Ethics Board (HIREB: 14-042).

2.9.2 Consent for publication

Not applicable.

2.9.3 Availability of data and materials

Raw data and materials for the study are available upon request.

2.9.4 Competing Interests

The authors declare that they have no competing interests.

2.9.5 Funding

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2.9.6 Author's Contributions

AD drafted the pilot manuscript. ZS conceived the study in addition to drafting the pilot manuscript. MB and BBD were responsible for addressing data queries, organizing and analysing data, and drafting the manuscript. MB assisted in analyzing data and drafting the manuscript. KL, KM, JW contributed to the design of the intervention and selection of assessment tools, wrote the intervention manual, and assisted with writing the manuscript. PL assisted with establishing the study design, developed and facilitated pharmacotherapy education, selected the questionnaires pertaining to pharmacotherapy, and contributed to the writing of the manuscript. SS and SC were responsible for designing the control arm of the study. LO and MV were responsible for the qualitative component of this study and its design, as well as revising the manuscript. LG coordinated the study and assisted with study design development, as well as contributing to the writing of the manuscript. BK assisted in study design and data collection. SC, SS, and SG assisted in running the intervention as well as contributing to the writing of the manuscript. FX assisted in the economic objective design and methods of the study, and contributed to the manuscript writing. GG contributed to developing trial design components including comparator selection and randomization, as well as writing and drafting the manuscript. LT contributed to trial design, selection of study aims, and statistical analyses. All authors read and approved the final manuscript.

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2.11 TABLES & FIGURES

Figure 2.1 Flow diagram for participants included in study

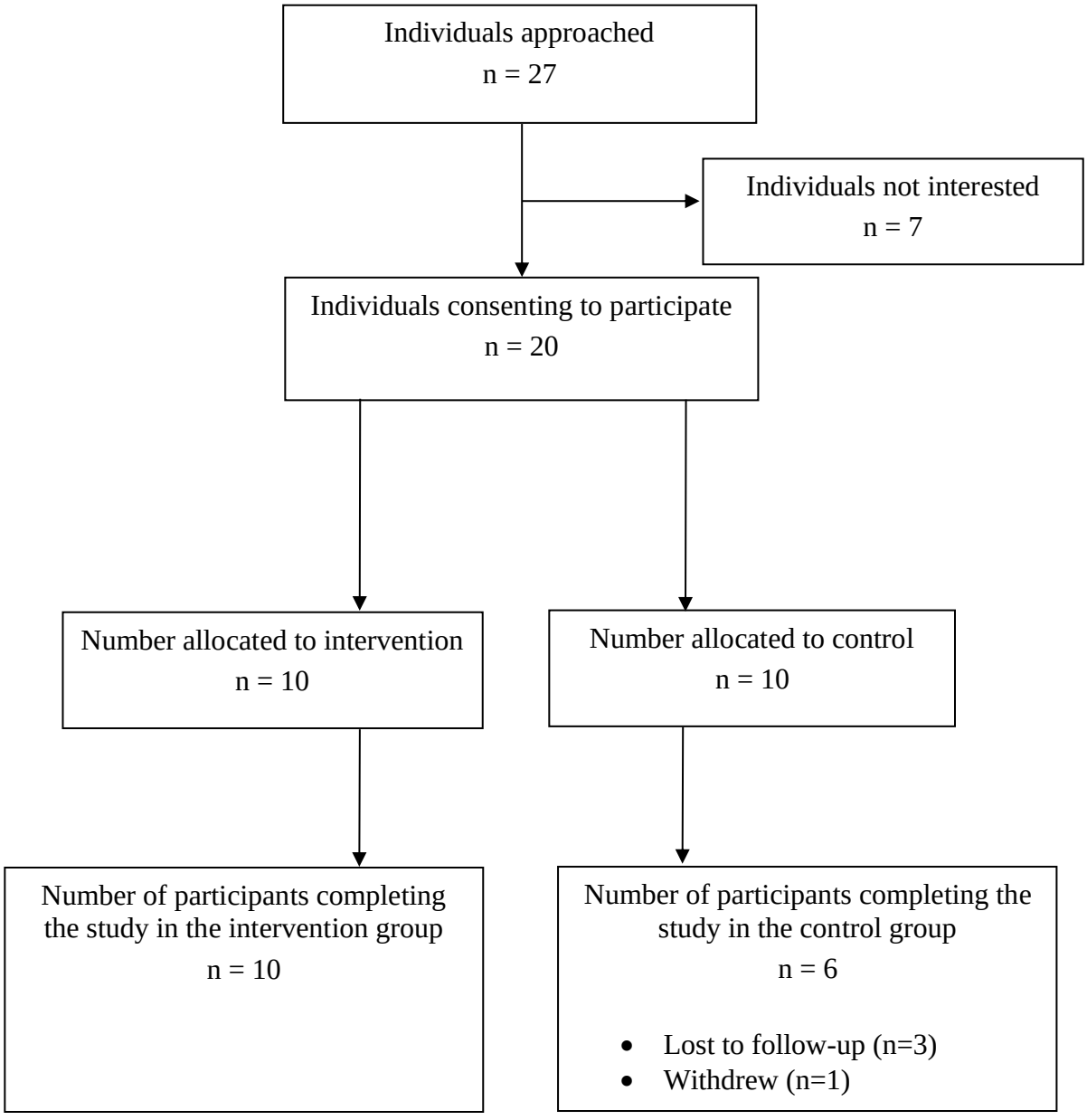


Table 2.1 Baseline demographics

Characteristic	Total (n=20)	Intervention (n=10)	Control (n=10)
Men; n (%)	8 (40.0)	4 (40.0)	4 (40.0)
Age in years; mean (SD)	48.2 (9.6)	49.5 (9.9)	46.9 (9.6)
BMI[a]; mean (SD)	34.4 (8.9)	35.8 (10.9)	33.1 (6.8)
Married/common law; n (%)	10 (50.0)	5 (50.0)	5 (50.0)
Completed post-secondary	8 (40.0)	3 (30.0)	5 (50.0)
Christian religion; n (%)	14 (70.0)	7 (70.0)	7 (70.0)
Have dependent children; n (%)	8 (40.0)	3 (30.0)	5 (50.0)
Own a house; n (%)	15 (75.0)	7 (70.0)	8 (80.0)
Financially independent; n (%)	19 (95.0)	9 (90.0)	10 (100.0)
Receiving long-term disability	8 (40.0)	3 (30.0)	5 (50.0)
Receiving social support (any)[b]; n	19 (95.0)	9 (90.0)	10 (100.0)
Currently using alcohol; n (%)	12 (60.0)	6 (60.0)	6 (60.0)
History of suicide attempt; n (%)	3 (15.0)	2 (20.0)	1 (10.0)
Physical health issues[c]; n (%)	18 (90.0)	8 (80.0)	10 (100.0)
Participated in CBT[d]; n (%)	6 (30.0)	2 (20.0)	4 (40.0)
Participated in emotion regulation skills group; n (%)	5 (25.0)	3 (30.0)	2 (20.0)
Participated in occupational	4 (20.0)	2 (20.0)	2 (20.0)
Participated in self-help group; n	5 (25.0)	2 (20.0)	3 (30.0)
Participated in general supportive counselling; n (%)	9 (45.0)	5 (50.0)	4 (40.0)

[a] BMI = Body Mass Index
[b] Social support is defined as support provided by a spouse, family members, or friends
[c] Health issues include any physical or mental comorbidity or symptoms (e.g. arthritis, chronic pain, hypertension, insomnia, migraines, obesity, etc.)
[d] CBT = Cognitive Behavioural Therapy

Table 2.2 Mean and standard deviation (SD) for intervention and control groups at baseline and end of the pilot study

	Scores; mean (SD)	
Assessments	Baseline (Screening)	End of Study (Week 18)
TREATMENT		
BDI	29.66 (3.29)	27.23 (3.99)
BADS	64.99 (5.92)	67.10 (7.49)
Q-LES-Q-SF	35.32 (3.66)	31.10 (4.27)
WSAS	26.37 (1.71)	29.55 (1.95)
LMS: Intellectual Score	39.03 (3.45)	37.77 (3.57)
LMS: Social Score	28.63 (3.37)	31.51 (2.67)
LMS: Competency Score	29.85 (3.32)	35.14 (3.05)
LMS: Stimulus Avoidance Score	42.88 (3.01)	39.98 (3.30)
EQ-5D-5L	43.19 (4.61)	43.45 (8.92)
RSQ-RRS	62.04 (3.13)	63.58 (3.39)
SF-12: PCS	33.64 (12.36)	35.17 (13.02)
SF-12: MCS	28.70 (5.94)	27.56 (10.35)
CONTROL		
BDI	34.69 (3.32)	33.41 (4.10)
BADS	52.26 (7.34)	61.72 (9.62)
Q-LES-Q-SF	31.30 (3.68)	33.95 (4.60)
WSAS	30.48 (1.73)	31.44 (2.04)
LMS: Intellectual Score	36.67 (3.47)	38.51 (3.70)
LMS: Social Score	28.86 (3.39)	31.32 (2.75)
LMS: Competency Score	35.73 (3.36)	35.64 (3.19)
LMS: Stimulus Avoidance Score	29.39 (3.03)	32.69 (3.50)
EQ-5D-5L	50.51 (4.73)	60.51 (8.97)
RSQ-RRS	67.43 (3.32)	68.00 (3.68)
SF-12: PCS	40.35 (6.87)	36.93 (6.34)
SF-12: MCS	24.63 (7.82)	30.48 (5.79)

BDI: Beck Depression Inventory; BADS: Behavioral Activation in Depression Scale; Q-LES-Q-SF: Quality of Life, Enjoyment, and Satisfaction Questionnaire – Short Form; WSAS: Work and Social Adjustment Scale; LMS: Leisure Motivation Scale; EQ-5D-5L: EuroQol 5-Dimension; RSQ-RRS: Response Style Questionnaire, Ruminative Response Scale; SF-12: Health Survey Short-Form 12

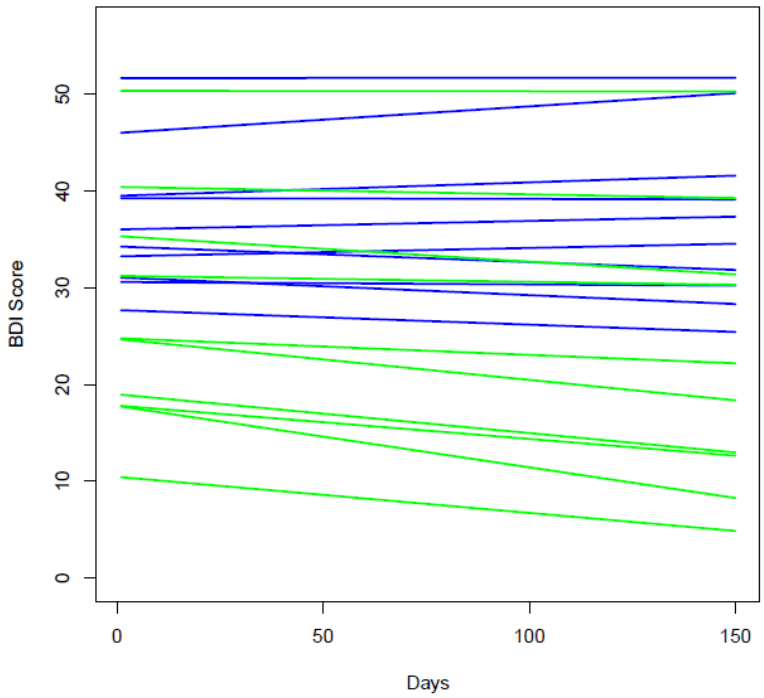
*Baseline vs. Week 18

Table 2.3 Descriptive summary of participants' physiology and body composition

	Intervention		Control	
Assessment, Mean (Standard Deviation)	**Baseline (Week 1)**	**End of Study (Week 18)**	**Baseline (Week 1)**	**End of Study (Week 18)**
Height, cm (SD)	168.0 (9.8)	168.9 (9.8)	172.2 (12.3)	172.2 (12.3)
Weight, kg (SD)	93.1 (19.6)	90.4 (16.2)	100.7 (30.0)	100.4 (32.0)
BMI, kg/m^2 (SD)	33.8 (10.9)	33.6 (7.5)	33.6 (6.8)	32.8 (5.5)
Waist circumference, cm (SD)	105.7 (12.8)	102.7 (11.9)	107.8 (19.3)	111.9 (13.4)
Hip circumference, cm (SD)	115.1 (13.0)	115.6 (14.9)	111.7 (19.0)	115.6 (14.2)
Blood pressure, systolic, mm Hg (SD)	125.7 (15.6)	126.9 (12.0)	127.9 (17.5)	132.3 (16.8)
Blood pressure, diastolic, mm Hg (SD)	77.3 (7.7)	81.9 (7.1)	81.5 (7.7)	80.4 (5.1)
Heart rate, bpm (SD)	82.5 (11.3)	82.8 (19.4)	79.3 (15.5)	77.0 (13.9)
Total fat,% (SD)	37.9 (11.9)	37.5 (11.7)	37.0 (10.6)	37.0 (8.2)
Fat mass, kg (SD)	36.2 (16.8)	34.3 (15.7)	38.7 (19.7)	37.9 (18.1)
Fat free mass, kg (SD)	56.3 (10.6)	54.3 (9.0)	61.1 (15.3)	61.1 (17.3)
Total body water, % (SD)	44. 1 (6.9)	43.7 (6.9)	45.5 (6.7)	44.9 (4.2)
Total body water mass, kg (SD)	40.2 (8.6)	38.1 (6.0)	42.0 (10.7)	44.1 (13.8)
Muscle mass, kg (SD)	53.4 (10.1)	51.5 (8.6)	58.1 (14.6)	58.1 (16.5)
Bone mass, kg (SD)	2.8 (0.5)	2.7 (0.4)	3.0 (0.7)	3.0 (0.8)
BMR, kJ (SD)	7163.4 (1320.0)	6875.6 (1011.1)	7820.4 (2011.3)	7807.9 (2280.4)
Metabolic age, years (SD)	55.6 (12.3)	57.6 (10.5)	53.5 (14.3)	56.9 (7.2)

BMI: body mass index; BMR: basal metabolic rate

Figure 2.2 Beck Depression Inventory (BDI) scores among participant groups over study period (*n*=20)



Note: Control = blue; BA = green. For four participants missing the final BDI scores, the last observations were carried forward in this figure.

CHAPTER 3: Effectiveness of behavioural activation group therapy in reducing depressive symptoms and improving quality of life in patients with depression (BRAVE Study): a randomized controlled trial

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3.1 ABSTRACT

Background:
Depression is a prevalent condition associated with extended periods of persistent low mood and low engagement with formerly enjoyable activities. Despite common management with anti-depressant medications, there is a need to assess behavioural therapies for those individuals who prefer nonpharmacological intervention or find that anti-depressants alone are insufficient in managing their symptoms.

Objective:
The objective of this trial is to assess the effectiveness of behavioral activation (BA) in improving mood symptoms and quality of life for patients with Major Depression Disorder (MDD).

Methods:
Using a pragmatic parallel randomized controlled trial design, we tested the effectiveness of BA group therapy in a tertiary care setting. Participants (n=169) were randomized (1:1 allocation) to receive either BA group therapy in addition to usual care (intervention) or participate in a waitlist condition (control) in which they would receive usual care before being offered BA therapy at the end of the waiting period. The intervention condition involved two-hour group therapy twice weekly for 10 weeks, followed by once weekly for the subsequent 8 weeks, for a total of 18 weeks (28 sessions). Treatment outcomes were measured at baseline, week 10 and session 28, with depressive symptom measures being collected once per week. The reporting of this trial (NCT02297282) is in accordance with the CONSORT statement for randomized trials.

Results:
Eighty-eight participants were randomized to receive the intervention and 81 to the waitlist condition. Participants were individuals with a confirmed DSM-5 diagnosis of major depressive disorder aged 18 years or older. Group BA was associated with positive changes in depression symptoms and some quality of life scales when compared to the waitlist group. Similar changes in clinical variables were shown among female and male participants through analysis by sex.

Conclusions:
Group BA is an effective form of treatment that is associated with positive changes in patient outcomes compared to a waitlist comparator. Changes in depression and quality of life suggest that this cost-effective treatment approach can be helpful for individuals with depressive disorders as an addition to usual care, with benefits appearing irrespective of biological sex.

Trial Registration: Clinical Trials NCT02297282, November 21, 2014
https://clinicaltrials.gov/ct2/show/NCT02297282

3.2 BACKGROUND

Depression is a chronic and recurring condition often associated with episodes of low mood and energy, changes in sleep patterns, and decreased interest in activities previously found to be enjoyable[1]. Individuals with Major Depressive Disorder (MDD) often experience remarkable changes in emotion and affect, as well as significant neurocognitive changes, that persist for at least two weeks, but typically last longer. Patients with MDD are typically prescribed anti-depressant medications, however many find pharmacological interventions ineffective or insufficient for preventing relapse or recurrence[2]. Indeed, medications demonstrate low rates of remission and high rates of discontinuation, with a number of unpleasant side effects including weight gain and sexual problems[3,4].

While pharmacological intervention is effective for some, it is imperative that other forms of treatment be tested to provide alternatives, additional treatment and further support for patients whose depressive disorders are not managed effectively or adequately through medications alone. Both individual and group therapies have been shown to improve symptoms in patients with depression[5]. Systematic reviews of studies investigating differences between individual and group therapies indicate no significant differences in outcomes, suggesting that group therapy programs are useful and cost-effective treatment option[5,6].

Specifically, Behavioural Activation (BA) is a therapeutic option that can be delivered in a group format[6]. BA is a component of Cognitive Behavioural Therapy (CBT), and involves activity tracking in order to improve engagement with behaviours that reinforce better mood and allow an individual to get more out of life[7]. The BA approach premises on the idea that "what you do effects how you feel," providing strategies for structuring behaviours to indirectly impact mood. By planning activities which are associated with better mood states, patients reinforce remissive cycles and prevent relapse into maladaptive activities which perpetuate depressive symptoms. Recent evidence suggests that effective BA programs can be implemented by general mental health workers[8], making this treatment a feasible option from a service delivery perspective as it reduces the need for specially trained therapists thereby alleviating stress on mental health services. While current evidence points to the promise of BA, many trials have focused on individual BA, suggesting the need for large trials with sound methodology to test the effects of BA in a group format[9]. Further, many published trials have evaluated community-based programs which serve a patient population with mild to moderate symptom severity, and therefore have limited applicability to clinical settings whose patients often experience more severe depressive disorders[10,11]. Our previous pilot investigation provided the feasibility of a full trial, on the basis of objectives of recruitment, retention, and data completeness, to investigate the effect of group BA on depressive symptoms and quality of life within this specific population[12].

3.2.1 Rationale

Currently, few studies assess group BA in a clinical population with major depressive disorder. Previous findings are characterized by small numbers of participants, individual-based treatment formats, and community samples with mild to moderate

symptom severity, limiting the impact and generalizability of these data to clinical populations[10,13]. This paucity of studies is also limited with respect to sex and gender-based analyses; few studies have reported important clinical outcomes by sex to explore differences in treatment effectiveness, limiting the potential for precision-medicine within case management of MDD. Therefore, the following study responds to a need for rigorous trials which are powered to detect significant differences in important outcomes, and report data in a manner that will aid clinical interpretation and decision-making. In particular, this study provides evidence for the impact of behavioural programs, which is critical given the limited effectiveness of anti-depressant medications for some patients. Therefore, we report the results of a pragmatic randomized controlled trial assessing the effectiveness of BA in a sample of patients with major depressive disorder attending a tertiary care mood disorders clinic.

3.2.2 Objectives

The primary objective of this study is to determine the effectiveness of a group BA program in addition to care as usual in patients with depression. The effectiveness of group BA treatment will be assessed by investigating the effect of BA on depressive symptoms.

The secondary objectives of this study will be to assess the effects of group BA on quality of life domains, and to explore changes in biometric variables such as body weight, body-mass index, and fat percentage.

3.2.3 Hypotheses

We hypothesize that health outcomes of depression and quality of life will improve to a greater extent in the behavioural activation (intervention) group when compared to a waitlist comparator (control) group. We aim to explore changes in biometric variables, and predict that changes in these variables will be greater in the intervention condition, with these changes reflecting an improved physical health state given the physical activity tracking component of the study.

3.3 METHODS

This trial has been registered with ClinicalTrials.gov (Identifier # NCT02297282) and was approved by the Hamilton Integrated Research Ethics Board (HIREB: 014-616). The pilot trial for this study was published in *Pilot and Feasibility Studies*[12,14]. The reporting of this trial is in accordance with the CONSORT statement[15]. See checklist in Appendix 8.3.

3.3.1 Study setting

This study was conducted at the Mood Disorders Program at St. Joseph's Healthcare Hamilton. The Mood Disorders program is a tertiary care clinic that specializes in outpatient services for patients with mood disorders and receives referrals from healthcare providers within the City of Hamilton and surrounding areas. Patients are referred to this clinic as a result of inadequate response to previous treatment, chronic illness course or

comorbidities; therefore, patients treated at this clinic often constitute a population with severe and complex depressive disorders.

3.3.2 Recruitment

Participants were recruited from the Mood Disorders Program from October 2014 to April 2018. Patients with a primary diagnosis of MDD currently using clinic services for management of depression were approached. Eligible patients were aged 18 years and older, communicated in English, and could provide written informed consent. In keeping with a pragmatic approach, nonrestrictive inclusion criteria were selected for this study. Participants were not excluded if they were using anti-depressants or participating in other psychotherapies in keeping with usual care for MDD. Participants were excluded if they had a primary diagnosis for a psychiatric condition other than MDD but were not excluded for having other physical or psychiatric co-morbidities. Eligible participants were informed that by participating in the study, they could be assigned to receive BA in addition to care as usual, or to receive BA after a wait-list period.

Once referred to the study, research staff explained the study and encouraged participants to discuss their participation with their health care providers and family. Once informed consent was provided, participants were given a copy of the consent form for their records, and participants were screened to assess whether they met diagnostic criteria for major depressive disorder. The Structured Clinical Interview for Diagnostic and Statistical Manual - fourth edition (DSM-IV) (SCID-I) was used by a trained clinician to ascertain a primary diagnosis of MDD. Participants who did not meet DSM MDD criteria were then informed they were not eligible to participate in the study.

As pre-specified in the study protocol, the study team aimed to recruit 80 participants per study arm. The sample size calculation used data from previous randomized trials of behavioural activation randomized to determine the adequate sample size for a clinical superiority design. A minimum of 46 subjects per arm were required; assuming an attrition rate of 30%, 160 participants (80 subjects per arm) was selected as the target sample size.

3.3.3 Data Collection

Participants completed questionnaires throughout the study period. At baseline, participants completed an intake survey and structured clinical assessments using instruments to assess depressive symptoms, and quality of life. A full description of the study timeline and corresponding instruments has been described elsewhere[14]. Depressive symptoms were measured using the Beck Depression Inventory II (BDI)[16] at baseline, weekly and at end of study. BDI scores between 21 and 30 are associated with moderate depression, and scores above 31 are associated with severe depression[16]. Quality of life instruments included the Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF)[17], the Health Survey Short Form – 12 (SF-12)[18] and Work and Social Adjustment Scale (WSAS)[19]; these questionnaires were administered at baseline, session 10, and end of study. The Q-LES-Q-SF[17] is a self-report instrument scored by subtracting the raw score from the minimum possible score, divided by the sum of the maximum score minus the minimum score. The final score is expressed as a percentage between 0% and

100%, where higher percentages are associated with a higher quality of life (QoL). The SF-12 survey[18] is a 12-item survey that provides two summary scores, the physical component score (PCS) and the mental component score (MCS); these scores range between 0 and 100, where 100 is associated with the highest level of health state. For the final question (item 12) of the SF-12 instrument, an additional option of "a good bit of the time" was added, matching the options provided for items 9 through 11. Where participants selected this option, the scoring for the option "some of the time" was applied as this was the closest to the reported option. The final QoL measure used was the WSAS, an instrument measuring level of impairment with 5-items; individual items were scored between 0 (indicating no impairment) and 8 (indicating severe impairment)[19]. Higher scores are associated with higher impairment, with scores over 20 indicating severe psychopathology and symptomology[19]. Missing items for the WSAS scale were handled by substituting the missing item with the average of the non-missing values for that participant; the data were disregarded if more than one item was left incomplete, as the final score could not be reliably estimated using this method with high levels of missingness[19].

Finally, participants completed physical assessments at baseline, session 10 and end of study. Biometric characteristics such as body mass, body mass index (BMI), fat percentage, total body water (TBW), basal metabolic rate, fat mass and fat free mass, and metabolic age were measured using a TANITA scale (www.tanita.com). Systolic and diastolic blood pressure, pulse, and grip strength were measured by trained research assistants and clinicians. Such physical measures were collected to investigate possible effects of BA on physical outcomes.

Demographic and contact information were captured using case report forms (CRFs). These forms were generated using an online data collection tool called Research Electronic Data Capture (REDCap) (http://project-redcap.org/). REDCap was used to collect measures administered weekly and at follow-up. This online database is password-protected and accessible online by research assistants to collect data and generate reports. Records were hosted in the local institution server in accordance with the policy and privacy terms of the institution.

3.3.4 Intervention Condition

The intervention group received BA group therapy in addition to treatment as usual (this included treatment for depression as clinically indicated for each patient and may include pharmacotherapy, cognitive behavioral therapy, recreational therapy, and outpatient psychiatric follow up). The BA program consists of 10 weeks of treatment twice-weekly, followed by 8 weeks of sessions once-weekly, in a group format, for a total of 18 weeks (28 sessions). The intervention program, called "Out of the Blues" focused on activities and skill building designed to help participants re-engage with their personal and professional life. The specific program tested in this trial was designed by trained clinicians, and in keeping with BA guide developed by Christopher Martell, Sonia Dimijian and Ruth Herman-Dunn[20]. The program incorporated activity tracking, group therapy guided by discussion of the trends identified in activity records, as well as homework and worksheets designed to build and improve skills to ultimately improve depression and quality of life.

Participants were given FitBit[21] technology to help with tracking of sleep, activity and steps count; participants were asked to wear the FitBits throughout the day and evening throughout the duration of the intervention period in order to capture this information. During weekly group sessions, participants were asked to provide their FitBits to the research team; during this time, FitBit data were exported and a report of activity trends for sleep, activity and steps were generated, to be discussed with the participant and the group facilitator. Trends shared with the participants included total steps per week, number of hours of sleep, and total number of minutes of exercise; activity for any given week was compared to the week prior, with increases from the preceding week being denoted by an "up" arrow and decreases indicated by a "down" arrow. Fitbits were also charged during this time to discourage noncompliance and data missingness that may result from uncharged devices. Group session content and associated homework focused on developing strategies for coping with common experiences and depressive symptoms. The goals of the program included to (1) reduce depressive symptoms to achieve remission of mood disorder, (2) build and improve strengths and skills to fulfill personal goals, (3) improve physical health by reducing unhealthy behaviours, (4) encourage the building of social networks and community activities.

3.3.5 Waitlist Condition

Participants who were not randomized to the intervention participated in a wait-list condition in addition to treatment as usual, lasting 18 weeks serving as a comparator to the intervention condition. After the 18-week period, participants in the waitlist were offered the "Out of the Blues" group BA intervention. This comparator format was selected in response to participant feedback collected in the pilot phase, during which the control comparator consisted of unstructured group meeting "placebo" condition. Qualitative interviews from the pilot phase indicated that participants in the control condition did not feel that unstructured group meeting was helpful, and wanted the option to participate in the intervention program after participating in the control condition[12]. Qualitative feedback from participants[22] and results from the pilot phase are reported elsewhere[12].

In the current study, the waitlist condition completed study instruments weekly and had contact with a study clinician either by phone or email once per week if desired, according to the participant's preference, therefore the control group condition is an active comparator.

3.3.7 Randomization

Participants were randomly assigned in a 1:1 ratio to a treatment condition using block randomization. Participants were assigned a participant ID, and these IDs were placed in opaque, sealed envelopes. IDs were drawn from the envelopes and assignment was based on a computer-generated randomization schedule with permutated block sizes of 2, 4, and 6. Eighty-eight participants were assigned to the intervention condition and 81 were assigned to the waitlist condition. Participants and clinicians administrating the intervention and wait list conditions were aware of the allocation; statistician and researcher completing the analysis were blind to allocation. The unequal allocation to each group

resulted from randomization of odd numbers of participants which occurred due to recruitment rate and groups start dates.

3.3.8 Outcomes

The primary outcome of the current study was to assess changes in depressive symptoms, which is defined as the mean change from baseline to end of study in BDI score between the intervention and waitlist groups. Interpretation of the primary outcome was guided by the criteria pre-specified in the study protocol, which stipulates that a minimum change of 10 points on the BDI will be indicative of clinically significant improvement[14].

The secondary outcomes assessed in this study include both clinical and physical measures. First, this study aimed to assess changes in quality of life on the Q-LES-Q-SF, SF-12, and WSAS scales from baseline to end of study between the intervention and waitlist groups. Second, the current study assessed changes in biometric measurements at baseline and at session 28 in both groups; means and standard deviations for biometric measures are provided at both time points to visualize changes from baseline. These variables include body mass, body mass index, fat mass, fat free mass, total fat percentage, waist and hip measurements, blood pressure, pulse and hand grip strength. These measures were selected to approximate general measurements of physical health to allow the exploration of the effects of BA on physical health.

3.3.9 Statistical Analysis

Data for the waitlist group from the waitlist period were compared to participants in the intervention group. Demographic differences present between the study arms were assessed using Chi-squared tests for categorical variables, and T-tests for continuous variables. Variables for which there were significant baseline differences are discussed. Continuous variables were reported using mean and standard deviations (SD), and numbers and percent were reported for categorical variables. For medication, the numbers and percent of individuals prescribed medication for their mental health is presented, in addition to medication category. This study aimed to compare the primary outcome of change in depression and secondary outcomes of changes in quality of life between the intervention and waitlist condition. Mean change scores from baseline to end of study were compared for the intervention and waitlist groups. Relevant tests of normality (Shapiro-Wilk) and homogeneity of variance (Levene's test) were conducted for change scores of clinical outcomes. Therefore, Mann-Whitney U-tests were conducted, which are most appropriate for analyzing data which is not normally distributed, and does not have equal variances between groups.

For participants who did not complete the study or did not have end of study (session 28 data), the last observation for each outcome in accordance with the Last Observation Carried Forward (LOCF) principle was used to compute a change value[23]. For individuals who remained enrolled and had only baseline data for a particular outcome, no change was assumed at session 28, and these participants were assigned a change score of "0" for that variable. For participants of the control group, if no data were available at session 28, and no last observation after baseline was available, the data from their first session of the intervention were used to approximate their status at the end of the control

period, rather than assuming no change from baseline. Missing data items for clinical sales were addressed using best practices for each specific scale. Multiple imputation for the primary outcome of BDI was conducted using R Version 3.6.3[24] according to published methods for imputing missing data in the BDI, and all other analyses were conducted using SPSS Version 28[25]. BDI scores for participants who did not fully complete their questionnaires were approximated using multiple imputation according to methods described elsewhere[26]. Five imputations were generated using the Multiple Imputation by Chained Equations (MICE) package[27], and the imputation selected was based on the imputation column which yielded a mean closest to the pre-imputation mean for the item for which there was the greatest missingness (specifically, the baseline sleep item). Imputed values were then rounded to the nearest whole number within R. If more than 25% of the BDI instrument data were missing within a specific time point, the entry for that timepoint was excluded. For the Q-LES-Q-SF scale, the total score was adjusted according to the number of items missing, up to a maximum of 4 missing items. Missing items for the SF-12 were substituted with the mean weight for the corresponding population item, up to a maximum of 3 missing items[28]. Missing items for the WSAS scale were handled by substituting the missing item with the average of the non-missing values for that participant; the data were disregarded if more than one item was left incomplete, as the final score cannot be reliably estimated using this method with high levels of missingness[19].

A significance level of $p<0.05$ was used for all outcomes. An exploratory analysis by sex was conducted for both primary and secondary clinical outcome variables, in keeping with previous literature indicating asymmetries in clinical effectiveness by sex.

3.4 RESULTS

One hundred and seventy-seven potential participants were referred to the study and contacted by the study coordinator about possible inclusion. 169 participants met the eligibility criteria and were enrolled in the study, with 81 participants allocated to the waitlist condition, and 88 assigned to the intervention. Reasons for not participating included not meeting diagnostic criteria, work or school obligations which conflicted with participation, or lack of interest. One SAE occurred in the waitlist group; the participant died after enrollment for reasons unrelated to study participation. The participant flowchart can be found in Figure 1. Participants who did not complete the entire study but had sufficient data to tabulate study outcomes are included in our analysis. Baseline demographic information and clinical scores were collected and can be found in Table 3.1.

Participants predominantly reported being White/Caucasian (58.27%) and female (64.7%). The average age of participants was 49.59 (SD=11.17) for the treatment group and 46.62 (SD=13.50) for the waitlist. The mean BDI score at baseline for the intervention group was 33.81 (SD=10.44) and 35.37 (SD=11.05) for the waitlist group. Both groups were taking a number of medications, including those for physical and mental health conditions. Medications for mental health included antidepressants, mood stabilizers, and antipsychotics. Antidepressants included serotonin antagonist and reuptake inhibitors (SARIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRI). Participants also reported prescriptions for tricyclic

antidepressants (TCAs), monoamine oxidase inhibitors (MAOI), and noradrenergic and specific serotonergic antidepressants (NaSSA). Mood stabilizers medications included anticonvulsants, antipsychotics, and lithium. Participants reported prescriptions for benzodiazepine medications, stimulants and hypno-sedatives. The waitlist and intervention groups did not differ significantly at baseline on any demographic or clinical variables, with the exception of medication status (prescribed medication for psychiatric illness or not) in which a greater proportion of participants in the intervention condition were prescribed medication at baseline than the waitlist group. Though there was no significant difference in marital status, a greater proportion of participants were unmarried in the waitlist group compared to the intervention group.

3.4.1 Primary Outcome

The intervention and waitlist group showed reduced depressive symptoms scores at session 28 compared to baseline. Mean depression score (BDI) at baseline was 35.81 (10.44) for the intervention group, compared to 26.72 (SD=13.77) at session 28. For the waitlist, the mean depression score was 35.37 (SD=11.05) at baseline and 31.25 (SD=12.53) at session 28.

A Mann-Whitney U test was conducted, revealing a statistically significant difference between BDI change scores between the different treatments, $\chi 2(1)=4.069$, p=0.044, with a mean rank BDI change score of 60.04 for waitlist, and 72.90 for intervention. These results are shown in Table 3.2.

Changes over time by sex were conducted to explore possible differences in the effect of the intervention on depression (Figure 3).

3.4.2 Secondary Outcomes

Mean change scores were computed for the Q-LES-Q-SF, SF-12 PCS and MCS, and WSAS. A Mann-Whitney U test was conducted, revealing a statistically significant difference in Q-LES-Q-SF change scores between the different treatments, $\chi 2(1)=3.989$, p=0.046, with a mean rank Q-LES-Q-SF change score of 60.04 for waitlist, and 72.90 for intervention.

Mann-Whitney U tests showed a statistically significant difference in SF-12 PCS score between groups, $\chi 2(1)=0.011$, p=0.916, with a mean rank PCS change score of 65.13 for waitlist, and 65.81 for intervention. For the MCS, Mann-Whitney U tests showed a statistically significant difference in change scores between the intervention and control, $\chi 2(1)=7.746$, p=0.005, with a mean rank MCS change score of 55.70 for waitlist, and 73.64 for intervention.

Finally, for the WSAS, no significant difference was detected between groups; $\chi 2(1)=2.715$, p=0.099. Mean rank WSAS change scores were 72.03 for the intervention and 61.60 for the waitlist.

An exploration of the differences in secondary physical outcomes by sex are shown in Table 3.3. Scores at baseline and session 28 are provided for each group.

3.5 DISCUSSION

It was hypothesized that the improvement in depressive scores in the intervention condition would be larger than the change in the waitlist, resulting in a greater reduction in depression in the intervention condition than the waitlist. The change in the intervention, with respect to depression, was significantly greater than the waitlist, with results showing greater reductions in the BA group. However, our pre-specified criteria indicated that a difference of 10 points would be considered a clinically important difference. The mean decrease in symptoms of approximately 7 points in the intervention group indicates that the intervention did not, on average, produce a clinically significant decrease in symptoms, despite a significant difference between groups.

An improvement from baseline was also observed in the waitlist group, likely resulting from the waitlist condition being an active comparator. Participants allocated to waitlist were told that they were to serve a waiting period of 18 weeks, after which they would be enrolled in the BA program. These participants were also offered contact with a clinician weekly and were asked to complete weekly questionnaires. It is possible that the consistent clinical interaction involved in the waitlist condition, coupled with perceived interaction through the completion of study questionnaires, and finally, promised future access to the group BA intervention, may have had an effect on depressive symptoms. Therefore, the improvement from baseline observed in the waitlist group was expected. There did not appear to be significant differences in the changes in BDI score between men or women in either group, suggesting that the treatment effects are not likely to be associated with sex. Accordingly, the effects of BA are expected to be similar for all patients regardless of biological sex. While systematic reviews have identified sex differences in biological measures of depression[30] and the likelihood for diagnosis is nearly doubled for women[31], little consensus exists on sex or gender differences in the effects of BA treatment, to our knowledge. Therefore, our findings contribute to our understanding of the effects of BA in clinical populations; the absence of apparent sex-differences in treatment outcomes suggest no expected differences in effectiveness for BA programs, providing evidence and direction for patient-centered care and case management decisions.

Secondary outcomes of QoL, as measured by the Q-LES-Q-SF, SF-12 and WSAS, indicate that group BA can result in improvements in QoL. Significant differences between groups for the mean change from baseline to session 28 was found for the mental component score of the SF-12 instrument, and the Q-LES-Q-SF. While group adjunct BA was not found to differ from the waitlist on the change in PCS of the SF-12 QoL tool, groups differed significantly on the MCS, suggesting benefits to QoL within the mental domain. Consistent with our initial hypothesis, the intervention group had a greater mean improvement in QOL compared to the waitlist. These improvements in QoL are consistent with previous trials investigating the effect of psychotherapies on QoL in patients with depression[32]. While significant, these results should be interpreted cautiously given that there were few participants who provided final scores on the Q-LES-Q-SF, SF-12, and WSAS. As "no change" from baseline was assumed for participants who remained in the study but were noncompliant with data collection, the mean change scores generated for the intervention and waitlist groups were likely impacted. Therefore, changes in these variables are likely more modest than the actual changes sustained by participants, as the mean values may not account for changes that were sustained but not captured due to

noncompliance. Similar trends in secondary clinical measures were observed between male and female participants over the duration of observation (Figure 3), also indicating that any effects on QoL sustained through group BA are not expected to differ between the sexes.

An exploratory analysis of the effect of the intervention versus waitlist on physical measures was conducted (Table 3). While the 18-week intervention program did include FitBit technology and participants were provided with weekly reports of steps, minutes of activity and sleep to support activity scheduling and group reflection, physical composition remained fairly constant. This corresponds to survey data from the SF-12 PCS, where there were no differences between groups, indicating that group BA is unlikely to produce changes on physical health or the physical component of QoL.

These findings suggest that combined effect of BA, FitBit technology, and weekly reports of the levels of physical activity sustained by participants in this study was not sufficient to produce changes in the biometric variables measured in this study. Comparatively, interventions with more structured physical activity regimens are able to produce biometric changes in populations with MDD[33], suggesting that if BA programs are to generate changes in such variables, a more structured exercise approach would be needed. While improvements in physical measures were not observed in this study, these findings suggest that the intervention did not precipitate the poor physical outcomes that can be experienced when initiating or persisting with pharmacological treatment, such as weight gain[3,34]. These findings suggest that the BA intervention tested within this study can have important impacts on clinical mental health outcomes, despite lack of response in physical measures; this contributes to our understanding of the associations between physical and mental health outcomes in depression. While physical and mental health outcomes can be linked, it appears that participants may still experience benefits to their mental health even when the life style changes sustained do not produce changes in physical health as measured by biometric measures.

3.5.1 Strengths and Limitations

The current study is supported by strong methodology through the randomized control trial design. The inclusion of a waitlist comparator ensures the comparison of a group-based BA intervention in comparison to care as usual, and therefore appropriately explores the effects of adjunct group BA. Another strength of this study is the specific study population. Previous literature addressing BA focuses on individual BA, and often describes patients recruited from a community-based setting[6,10]. Community-based settings typically treat populations with low to moderate depression, therefore limiting the translation and scalability of their findings to clinical settings which serve those with more severe and complex depressive disorders, such as the population studied here. Our study provides evidence for group BA for participants which experience severe depressive symptoms and use services from specialized tertiary care settings. Further, our study has a large sample size in comparison to similar studies, therefore supporting the strength of our findings. Indeed, recent systematic reviews find that the median sample size reported in clinical trials of behavioural activation are 11 and 16 for treatment and comparator groups, respectively[6].

This study has several limitations. Firstly, there were high levels of attrition in both groups, but particularly in the waitlist group. This suggests that perhaps treatment length and method of delivery, including the setting and time commitment of the intervention program, may require further evaluation. Future investigations may consider investigating the ideal program length and the potential for a blended delivery method to reduce the commitment of an 18-week program and increase compliance to thereby improve symptoms and quality of life. It is worth noting, however, that attrition in the waitlist group condition indicates that a program involving care as usual with an opportunity to have weekly contact with a clinician is insufficient to retain participants, despite changes in symptoms that were experienced by some participants. The greater adherence in the intervention group suggests that group BA in addition to usual care leads to greater compliance in patients with MDD.

Another limitation of this study is the lack of diversity of the study sample. As the sample is primarily Caucasian, the generalizability of the study findings to other ethnicities or marginalized communities with severe depression is limited. While individuals belonging to marginalized groups are present in the study sample, their proportion was not representative enough to test the effect of BA on these groups. It is possible that the effect of BA may differ in such communities due to differences in cultural practices and values, which are known to impact diagnosis and treatment[35]. Future studies involving BA may consider testing its effectiveness in marginalized, underserved groups to explore and highlight possible differences in clinical effectiveness. This information would provide insight into the uptake of BA programs and provide options for remote care platforms in marginalized groups whose face poor health outcomes and are at high risk for co-morbidities and higher risk behaviours, while experiencing larger barriers to access to healthcare and mental health resources[36,37].

Participants in this study were not asked to discontinue usual care, or prohibited from initiating new treatment options during the study period. Therefore, changes sustained in both groups must be interpreted in light of possible conflations with concurrent treatment, and possible dilution of treatment effect due to continued care as usual.

Finally, this study focused on measures of depression and quality of life; future work must address the impacts of BA on measures including depression-related cognition, and consider measures of motivation, including performance-based and self-report instruments. Future work must investigate the extent to which the observed changes in clinical outcomes are lasting, and address possible effects on course of disorder.

3.6 CONCLUSIONS

This paper highlights the promise of group BA as an option for patients with depression. Participants who were allocated to the BA group experienced significant decreases in depressive symptoms compared to the comparator group. Group BA led to improvements in quality of life greater than that which was experienced by the waitlist group, suggesting that group BA was more effective in improving quality of life than care as usual and individual weekly contact with a mental health professional. This indicates that group BA programs are able to engage and support the treatment of a large number of patients,

providing a solution to current healthcare restraints which have led to limited mental health treatment access. Further, changes in depressive symptoms and quality of life for patients in the group BA condition did not appear to differ between male and female participants, suggesting similar effectiveness regardless of biological sex, a finding that will inform clinical management of complex depressive disorders. The possible adaptation and scalability of group BA programs to an electronic format will also support more remote treatment access options necessitated by vulnerable rural communities, as well as the COVID-19 pandemic whose measures have required remote access options in order to reduce risk of transmission of the virus. Treatment options such as BA which can provide care to a large number of patients at the same time and can be facilitated effectively by individuals with little psychotherapy training; this will allow for continued support for patients in the face of economical and resource constraints and unforeseen healthcare crises.

3.7 DECLARATIONS

3.7.1 Ethics approval and consent to participate

This trial was approved by the Hamilton Integrated Research Ethics Board (HIREB: 14-616).

3.7.2 Consent for publication

Not applicable.

3.7.3 Availability of data and materials

Raw data and materials for the study are available upon request.

3.7.4 Competing Interests

The authors declare that they have no competing interests.

3.7.5 Funding

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3.7.6 Author's contributions

AD was responsible for addressing data queries, organizing and analysing data, and drafted the main manuscript. ZS conceived the study in addition to drafting and critical revision of the manuscript. NS was responsible for addressing data queries, statistical analysis and critical revision of the manuscript. AH contributed to data collection, statistical analysis and critical revision of the manuscript. MB and BBD were responsible for data collection, and revision of the manuscript. MB assisted in analyzing data and drafting the manuscript. KL, KM, JW contributed to the design of the intervention and selection of assessment tools,

wrote the intervention manual, and assisted with writing the manuscript. PL assisted with establishing the study design, developed and facilitated pharmacotherapy education, selected the questionnaires pertaining to pharmacotherapy, and contributed to the writing of the manuscript. SS and SC were responsible for designing the waitlist arm of the study. LO and MV were responsible for the qualitative component of this study and its design, as well as revising the manuscript. LG coordinated the study and assisted with study design development, as well as contributing to the writing of the manuscript. BK assisted in study design and data collection. SC, SS, and SG assisted in running the intervention as well as contributing to the writing of the manuscript. FX assisted in the economic objective design and methods of the study and contributed to the manuscript writing. GG contributed to developing trial design components including comparator selection and randomization, funding acquisition, as well as writing and drafting the manuscript. LT contributed to funding acquisition, trial design, selection of study aims, and statistical analyses. All authors read and approved the final manuscript.

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3.11 TABLES & FIGURES

Figure 3.1 CONSORT Diagram Flow-chart

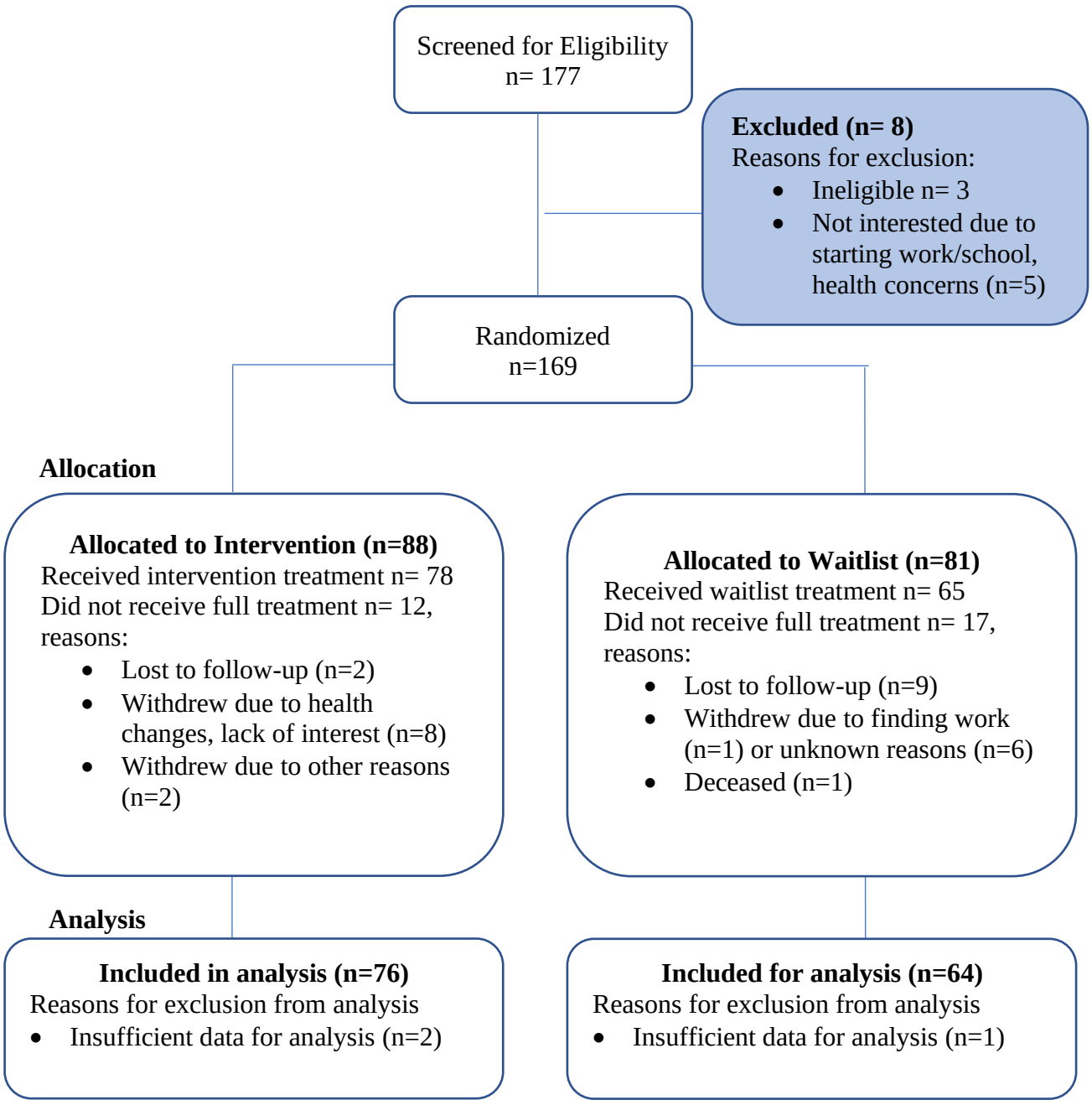


Table 3.1 Demographics & Baseline Characteristics

Characteristics	Intervention (n=76)	Wait-list (n=64)
Age, mean (SD)	49.14 (13.26)	46.71 (13.50)[a]
Sex, n (%) female	50 (65.7)	41 (64.1)
Ethnicity, n (%)		
White/European	46 (60.5)	35 (54.7)
Native North American	0 (0)	1 (1.6)
Asian	2 (2.6)	1 (1.6)
Black	1 (1.3)	0 (0)
Other	5 (6.6)	2 (3.1)
None/not reported	22 (28.9)	25 (29.1)
Marital Status, n (%)		
Single	18 (23.7)	29 (45.3)
Married/Common Law	35 (46.1)	16 (21.1)
Separated/Divorced/Widowed	21 (27.6)	18 (23.7)
Other/none/not reported	2 (2.6)	1 (1.6)
Medications, n (%)[b]	53 (69.7)	33 (51.6)
Antidepressants (SSRIs, SNRIs, NDRIs, NaSSAs, TCAs, SARIs, MAOIs)	50 (65.8)	24 (37.5)
Mood stabilizers (anticonvulsants, atypical anticonvulsants, lithium)	13 (17.1)	5 (7.8)
Antipsychotics (typical and atypical)	14 (18.4)	7 (10.9)
Benzodiazepines	19 (29.7)	11 (17.2)
Stimulants	2 (2.6)	1 (1.6)
Hypno-sedative	13 (20.3%)	6 (9.4)
Clinical Scores [Mean (SD)]		
BDI Score	33.81 (10.44)	35.38 (11.05)
Q-LES-Q-SF Score; %	38.44 (15.30)	36.22 (15.34)
SF-12, PCS	41.18 (10.70)	39.24 (10.63)
SF-12, MCS	27.74 (8.86)	28.35 (8.77)
WSAS Score	27.33 (8.46)	26.94 (8.43)

[a] n=63

[b] Counts for each category of medications refer to the number of participants who report use of at least one type of drug from that category. In the waitlist, n=33 provided information on medication, and in the intervention, n=56.

SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin and norepinephrine reuptake inhibitors; NDRI: Norepinephrine and Dopamine Reuptake Inhibitors; NaSSA: Noradrenergic and specific serotonergic antidepressants; TCA: Tetracyclic Antidepressants; SARI: Serotonin Antagonist and Reuptake Inhibitors; MAOI: Monoamine oxidase inhibitors.

BDI: Beck Depression Inventory II; Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SF-12: Short Form – 12; PCS: Physical Component Score of SF-12; MCS: Mental Component Score of SF-12; WSAS: Work and Social Adjustment Scale

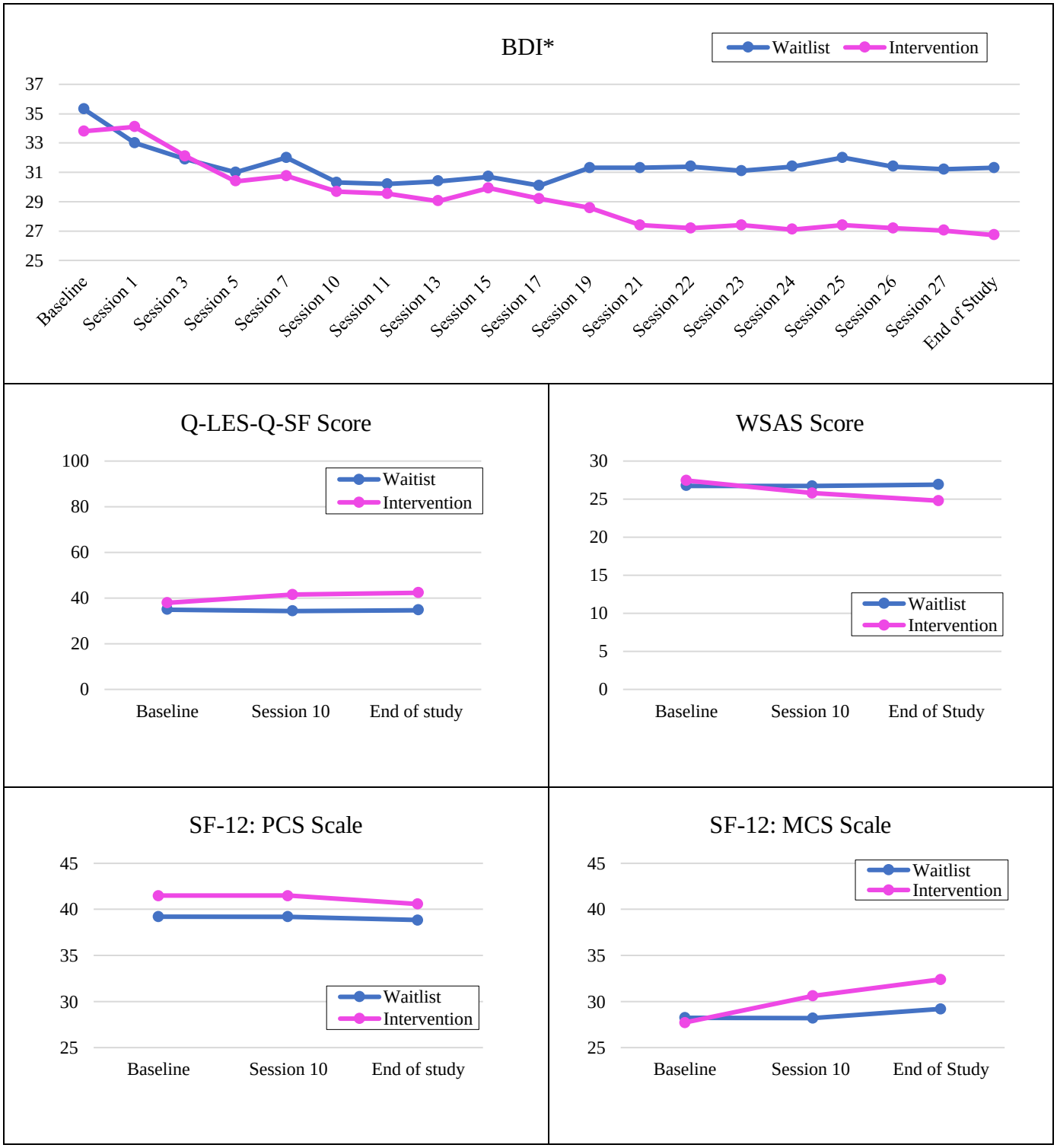
Table 3.2 One-way ANOVA for change in clinical outcomes; mean (standard deviation) [Confidence Interval (CI)]

Clinical Outcomes	Intervention (n=72) (Mean ranks)	Wait-list (n=64) (Mean ranks)	Mann-Whitney U-statistic	p-value
BDI[a] change score (end of study-baseline)	62.09	75.71	4.069	**0.044**
Q-LES-Q-SF[b] change score (end of study-baseline)	72.90	60.04	3.989	**0.046**
SF-12[c] PCS change score (end of study-baseline)	65.81	65.13	0.00	0.916
MCS change score (end of study-baseline)	73.64	55.70	5.39	**0.005**
WSAS change score[d] (end of study-baseline)	61.60	72.03	2.715	0.099

Change scores are computed based on change from baseline to post-study. Post-study scores are taken from either session 28 (end of study), or last observation was carried forward (LOCF principle) and used as the post-study score. P-values in bold type indicate significant differences in mean change scores ($p<0.05$).

[a] BDI: Beck Depression Inventory II; range: 0-63, highest values indicating more severe symptoms. Intervention, n=72; Waitlist, n =64.
[b] Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; range: 0-100%, highest percentages indicating greater quality of life. Intervention, n=72; Waitlist, n =61.
[c] SF-12: Short Form – 12. Physical Component Score (PCS) and Mental Component Scores (MCS) are generated from the SF-12; range: 0 and 100, where 100 is the highest-level health state. Intervention, n=71; Waitlist, n =59.
[d] WSAS: Work and Social Adjustment Scale; 0-45; highest values indicating greater pathology and level of impairment. Intervention, n=70; Waitlist, n =62.

Figure 3.2 Depressive (BDI) and quality of life (Q-LES-Q-SF, WSAS, SF-12) scores over the study period



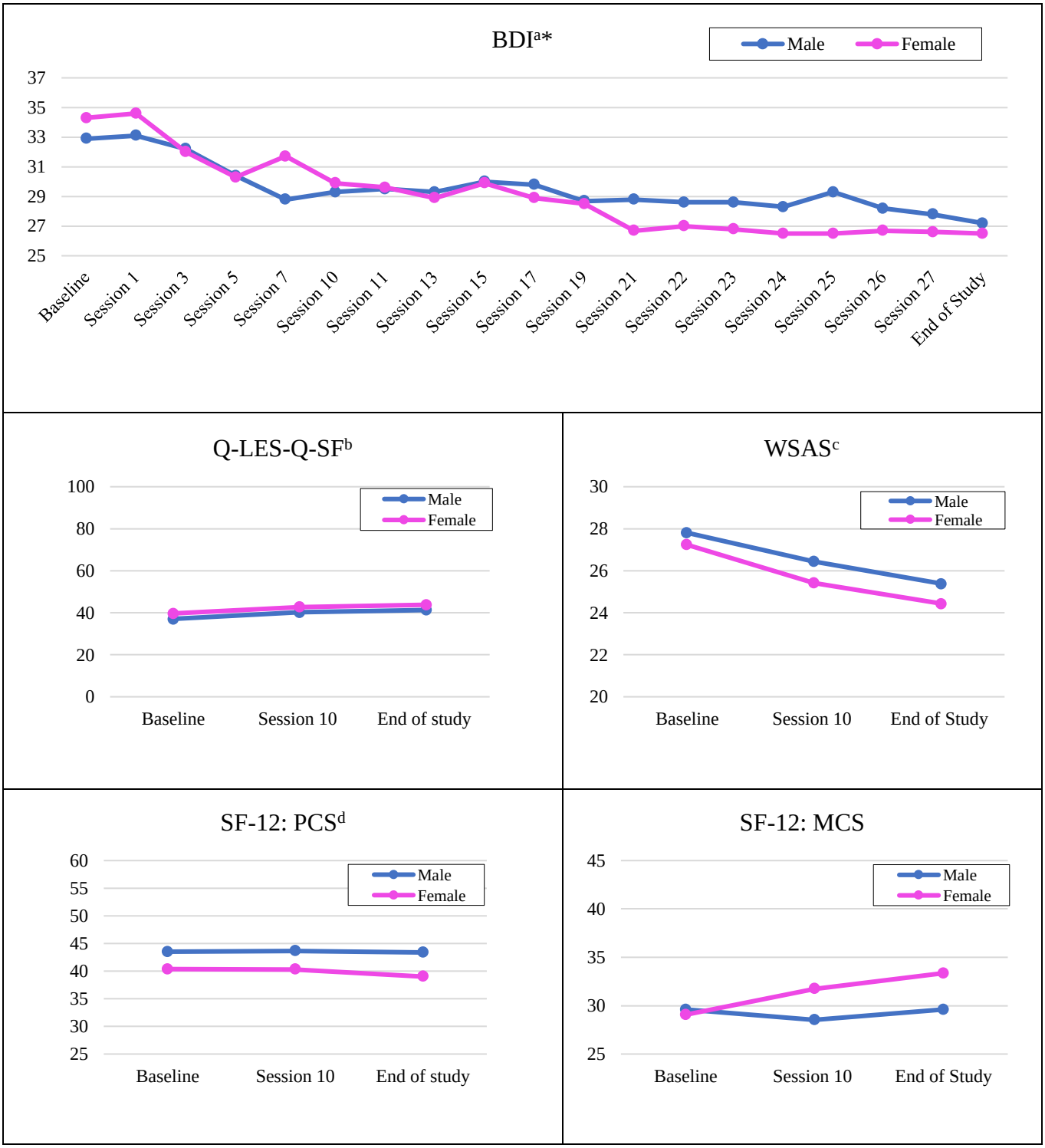
BDI: Beck Depression Inventory II; range: 0-63, highest values indicate more severe symptoms.

Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; range: 0-100%, highest percentages indicate greater quality of life. Baseline: Intervention, Waitlist. Session 10: Intervention, Waitlist. Session 28: Intervention, waitlist.

WSAS: Work and Social Adjustment Scale; 0-; highest values indicate greater level of impairment. Baseline: 72 Intervention, 63 Waitlist. Session 10: 77 Intervention, 63 Waitlist. Session 28: 78 Intervention, 63 Waitlist.

SF-12: Short Form – 12. Physical Component Score (PCS) and Mental Component Scores (MCS) are generated from the SF-12; range: 0 and 100, where 100 is the highest-level health state. Baseline: Intervention, n = 73; Waitlist, n= 62. Session 10: Intervention, n = 77; Waitlist, n= 62. Session 28: Intervention, n = 78; Waitlist, n= 63.

Figure 3.3 Changes in clinical outcomes (BDI, Q-LES-Q-SF, WSAS, SF-12) within intervention condition (n=78), reported by biological sex



[a]BDI: Beck Depression Inventory II; range: 0-63, highest values indicate more severe symptoms. Baseline: male = 27, female = 47. Session 10: women: 49. Session 28: women: 50.

[b] Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; range: 0-100%, highest percentages indicate greater quality of life. Baseline: 27 male, 47 female. Session 10: 27 male, 49 female. End of study: 27 male, 50 female.

[c]WSAS: Work and Social Adjustment Scale; 0-; highest values indicate greater level of impairment. Baseline: 27 male, 46 female. Session 10: 27 male, 50 female. Session 28: 28 male, 50 female.

[d]SF-12: Short Form – 12. Physical Component Score (PCS) and Mental Component Scores (MCS) are generated from the SF-12; range: 0 and 100, where 100 is the highest-level health state. Baseline: 27 male, 47 female. Session 10: 27 male, 50 female. Session 28: 28 male, 50 female.

Table 3.3 Biometric Characteristics at Baseline and End of Study

Biometric Outcomes	**Intervention**		**Wait-list**	
	Baseline	**End of Study**	**Baseline**	**End of Study**
Weight, kg [mean (SD)]	83.07 (18.16)	84.73 (18.32)	92.61 (24.87)	92.27 (24.56)
BMI, kg/m^2 [mean (SD)]	29.50 (6.38)	29.51 (6.37)	31.79 (8.24)	31.72 (8.13)
Total body water, % [mean (SD)]	37.98 (7.59)	37.68(7.85)	43.39 (16.31)	40.90 (18.22)
Basal Metabolic Rate, kJ [mean (SD)]	6833.21 (1268.41)	6829.59 (1276.19)	7244.84 (1829.32)	7153.99 (1687.18)
Pulse, beats per minute [mean (SD)]	78.68 (12.55)	79.40 (15.75)	77.97 (11.75)	78.54 (11.63)
Blood pressure, systolic, mm Hg [mean (SD)]	128.91 (14.54)	125.95 (15.22)	128.32 (15.64)	128.29 (16.08)
Blood pressure, diastolic, mm Hg [mean (SD)]	80.49 (8.04)	78.92 (8.24)	78.81 (8.78)	78.94 (8.92)
Total fat, % [mean (SD)]	34.65 (10.94)	35.23 (10.93)	35.44(12.37)	35.83 (12.46)
Fat mass, kg [mean (SD)]	30.19 (13.71)	30.48(13.80)	35.44 (18.64)	35.84 (19.00)
Fat free mass, kg [mean (SD)	53.98 (10.71)	53.59 (10.61)	60.57 (21.08)	59.83 (20.45)
Metabolic age [mean (SD)]	52.91 (16.70)	53.63 (16.37)	52.28 (18.81)	52.57 (19.05)
Average left-hand grip strength [mean (SD)]	26.50 (17.03)	24.43 (10.87)	27.88 (14.31)	26.80 (11.56)
Average right-hand grip strength [mean (SD)]	28.22 (17.52)	25.64 (10.73)	30.62 (15.25)	29.09 (12.53)
Waist circumference, cm [mean (SD)]	96.78 (20.12)	98.25 (18.47)	99.97 (21.52)	99.07 (23.08)
Hip circumference, cm [mean (SD)]	103.73 (21.95)	105.37 (19.15)	109.37 (21.76)	108.51 (24.08)

CHAPTER 4: Identifying patient-important outcomes for treatment of bipolar disorder: a systematic review protocol

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4.1 COPYRIGHT STATEMENT

The published manuscript is available in Appendix 8.5. The citation for this publication is shown below.

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4.2 ABSTRACT

Introduction: Treatment of bipolar disorder is the focus of several clinical trials, however the understanding of the outcomes for establishing treatment effectiveness within these trials is limited. Further, there is limited literature which reports upon the outcomes considered to be important to patients, indicating that patient perspectives are often not considered when selecting outcomes of effectiveness within trials. This protocol describes a systematic review which aims to describe the outcomes being used within trials to measure treatment effectiveness, commenting upon the inclusion of patient-important outcomes within previous trials.

Methods and analysis: This protocol is reported using the PRISMA-P statement. OVID MEDLINE, OVID Embase, OVID APA PsycINFO, Web of Science, the Wiley Cochrane Library, Clinicaltrials.gov, and the International Clinical Trials Registry Platform (ICTRP) databases will be searched for eligible studies. Screening, full-text, and data extraction stages will be completed in duplicate using the Covidence platform for systematic reviews. Eligible studies will include clinical trials of interventions in bipolar disorder, in order to identify outcomes used to assess treatment effectiveness, and qualitative studies, to determine which outcomes have been reported as important by patients.

Ethics and dissemination: This review will involve dissemination to key stakeholders, including primary end users such as patients, clinicians and trialists. Knowledge translation tools will be generated to share the relevant conclusions of this review. Results will be communicated to the scientific community through peer-reviewed publications, conferences and workshops. No ethics approval will be sought as this study is based on literature.

PROSPERO registration number: CRD42021214435
Keywords: bipolar disorder; patient-important; outcomes; protocol; systematic review.
Conflict of interest statement: Competing interests: None declared.

4.3 ARTICLE SUMMARY

Strengths and limitations of this study

- The proposed review employs a two-pronged approach to appraise outcomes used by trialists to assess treatment effectiveness in clinical trials of bipolar disorder I and describe patient-important outcomes.
- Strong methodological design developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol guidelines for transparent reporting.
- The planned analysis for reporting trials outcomes includes stratification of outcomes according to population, intervention type and mood state.
- Later analysis, including ability to conduct thematic analysis, may be impacted by large variability in the types of outcomes being used in trials of bipolar disorder I.

- Restriction to include studies published in English may lead to language bias.

4.4 INTRODUCTION

Bipolar disorder type 1 (BD) is a chronic mood disorder associated with severe depressive and manic episodes[1]. Though among the top eight most prevalent conditions worldwide[2], BD is very difficult to diagnose as a result of heterogeneous illness presentation which often leads to misdiagnosis as major depressive disorder[3,4]. Wide variability in symptom presentation, often impacted by age of diagnosis and other sociodemographic factors[5–7], presents challenges not only to diagnosis, but also to the selection of an appropriate course of treatment[8]. BD has significant impact on patients' lives including recurrence of psychiatric symptoms[9], comorbid psychiatric and medical disorders[10,11], loss of function[12,13], increased risk of mortality[14,15], poor quality of life[16,17], cognitive difficulties[18] among others. These pervasive and diverse impacts highlight the importance of determining which treatments most effectively manage specific outcomes, and for whom specific outcomes are of particular concern.

Current treatment of BD is medication paired with adjunct psychotherapy and is typically indicated by whether depressive or manic symptoms are more dominant within a particular individual. Though medications can be effective in managing mood symptoms, such symptoms and others such as cognitive and metabolic changes are often persistent, requiring adjunct psychotherapy and other interventions[19]. Indeed, current guidelines recommend the combination of psychotherapy and medication in order to obtain successful symptom management and remission[19]. Several reviews and guidelines have been published which provide evidence for such treatments, however, there is little consensus on which interventions are most effective and for what outcomes.

Further, little research investigates which treatment outcomes are most important to patients with BD. There is great variety among trials in the outcomes selected to indicate treatment success, with some studies considering treatments to be effective if patients achieve reductions in number of episodes or hospitalizations[20], some looking for reductions in mood symptom severity or burden[21], and others using measures such as the number of days without mood symptoms as an indicator of success[22]. Even in trials which use the same type of outcome or even the same type of instrument to measure effectiveness, timepoints, thresholds and definitions of effectiveness can differ greatly. While variability in outcomes is expected, this raises questions on whether these outcomes, and the way they are measured, reflect patient perspectives or can appropriately approximate the outcomes considered to be important to patients.

Some research has identified the weight or relative importance of existing outcomes often examined in trials, such as depressive and manic symptoms, social functioning, and quality of life, in addition to collecting important outcomes through focus groups[23]. However, such studies are often small convenience samples, potentially not reflecting the full range of outcomes deemed important by patients, and failing to represent the perspectives of patients at various phases of the disorder, such as those in active and acute phases[23]. The exclusion of patients' specific perspectives on what they need out of treatment of bipolar disorder emphasizes the need to evaluate the extent to which trial outcomes are in agreement with patient perspectives. In order to do so, it is essential to not

only appraise the available literature related to outcome measurements, but also the literature pertaining to patient important outcomes (PIO) in BD.

4.4.1. Rationale

Reviews which aim to systematically examine and describe the outcomes used within clinical trials of treatments for type 1 bipolar disorder to establish treatment effectiveness are needed. Such reviews are essential in order to facilitate an understanding of the inclusion of PIOs in trials. Therefore, it is important to examine the level of agreement between trialists, and moreover between trialists and patients, in order to determine whether measures of effectiveness truly reflect the needs of patient populations. This review will aim to appraise the outcomes used as a means to support future investigation of the need for a core outcome set for trials of bipolar disorder.

4.4.2. Objectives

The purpose of this systematic review is to investigate the outcomes used to measure treatment effectiveness within trials for treatment of bipolar disorder. Specifically, the aims of this review are:

(1) Summarize the outcomes (clinical scales, biological or social markers, etc.) used within clinical trials to measure treatment effectiveness, and report how these outcomes are assessed.
(2) Review the observational and qualitative research related to patient-important outcomes for bipolar disorder (i.e., goals and markers of treatment success identified as important by patients).

4.5 METHODS AND ANALYSIS

This reporting of this protocol reflects the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) statement[24].

4.5.1. Eligibility criteria

Two search strategies will be used in order to investigate our two objectives of interest. The specific inclusion and exclusion criteria are described for each objective.

The inclusion criteria for objective one is randomized controlled trials (RCTs) testing the effectiveness of treatment interventions in bipolar disorder (type 1) that report intervention outcomes of BD. No restriction on the type of intervention will be applied; trials investigating psychotherapy and pharmacotherapy. Psychotherapies included in this review will include any psychotherapeutic intervention specifically intended to treat bipolar disorder, such as cognitive behavioural therapy (CBT), behavioural activation (BA), cognitive analytical therapy (CAT), interpersonal psychotherapy (IPT), psychodynamic psychotherapies, interpersonal and social rhythm therapy, and family-focused therapy. Pharmacotherapeutic interventions will include medications being tested for effectiveness in treating bipolar disorder. Trials meeting inclusion will include an intervention, a comparator and at least one outcome measure or end point. Trials which include both group

and individual-based interventions will be eligible for this review. Interventions which include combination therapies (i.e., medication and a form of psychotherapy) will be included. Only complete studies in humans and written in the English language will be eligible, with no restrictions on age. No restrictions on country, income status, or type of recruitment (i.e., clinic or community-based settings) will be applied. Clinical trial registries will be searched; in the case of registration numbers with multiple associated publications, the most recent publication will be selected for inclusion.

Exclusion criteria for objective one will include the following: animal studies, preliminary reports, pilot studies, and trials which investigate interventions other than those outlined above. Interventions designed to address challenges within families, or couples that are explicitly not intended to treat bipolar disorder will not be included. Trials testing the effects of discontinuing treatment will not be eligible for inclusion.

The inclusion criteria for objective two are observational and qualitative studies. Qualitative studies meeting the inclusion criteria will be those involving focus groups and interviews to determine what outcomes are reported by patients with BD to be important for measuring treatment success. Again, no restrictions on country, income status or recruitment type will be applied. The exclusion criteria for objective two are studies for which the aims are unrelated to identifying patient-important outcomes.

4.5.2. Outcomes and prioritisation

The first objective of this systematic review will be to report the outcomes used to measure the effectiveness of the treatment being tested. These outcomes will be extracted from RCTs, and may include depressive or manic symptoms, quality of life measurements, or outcomes related to social adversity, such as employment. Given that the population of interest for this review is patients with BD, only outcomes explored within these patients will qualify for extraction.

The second objective will be to examine the literature pertaining to patient-important outcomes for BD. Observational and qualitative studies will be examined to determine which outcomes are reported by patients to be important measures of treatment success.

4.5.3. Information sources

The selection of databases and the corresponding search strategies were developed through partnership with a Clinical Services Librarian from the Health Sciences Library at McMaster University. Eligible studies will be identified through searches of the following databases: OVID MEDLINE (1946-Current), OVID Embase (1974-Current), OVID APA PsycINFO (1987-Current), Web of Science (1976-Current), the Wiley Cochrane Library (1999-Current), Clinicaltrials.gov, and the International Clinical Trials Registry Platform (ICTRP). Databases will be searched for all sources of literature, including gray literature, from inception to the date of search, which will be reported in the final systematic review. The search strategy for each objective for one database is described in Table 4.1.

4.5.4. Data management

Articles identified through the search strategy will be imported to Zotero, and then the Covidence platform[25]. Title and abstract, full-text and data extraction phases will be managed through this platform. Members of the research team who have not used Covidence before will be trained through online tutorials and an additional training session will be conducted with all reviewers to ensure familiarity and consistency with use at all stages. A calibration phase will be completed where reviewers will be asked to screen 25 articles on the platform, and responses will be reviewed to ensure understanding of the protocol and criteria.

4.5.5. Selection process

Each citation identified will be reviewed by two reviewers independently at title and abstract and then full-text stages, using the eligibility criteria described above. Those citations meeting eligibility during these phases will be included for data extraction. Disagreements between reviewers will be resolved by another reviewer to reach consensus. Level of agreement between reviewers will be assessed and the kappa statistic will be reported.

A flow diagram (Figure 4.1) summarizing the screening of all studies will be included in the final review. Studies included in the data extraction phase will be described in a table, which will be structured in keeping with the guidelines specified by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[26]. Reasons for exclusion or inclusion will be reported.

4.5.6. Data collection process

Data extraction forms will be built on Covidence and completed blindly, in duplicate. Separate data extraction forms will be constructed for objective one and two, and the forms will be pilot tested by all reviewers to ensure the quality of the extraction and the comprehensiveness of the forms. The data collection forms will include the following items: author, year, country, title of journal, number of participants, name of intervention, diagnosis, diagnostic criteria, mood state, phase of disorder, inclusion criteria, exclusion criteria, type of population (for example, in-patient, out-patient, or community), ethnicity, cultural factors, mean age, details on special populations (low income, pregnant, veteran, etc) and study design. Where data are missing, authors will be contacted, and all correspondence will be noted.

For objective one, the data collection form will also include details on form of treatment (i.e., cognitive-behavioural therapy, support group, behavioural activation, etc). Study outcomes used to assess effectiveness in each study will be recorded, and the following information about these outcomes will be extracted: the type of outcome, the definition of the outcome, how often it is measured, and how it is measured. For objective two, the following additional information will be extracted from the observational and qualitative literature: the outcomes reported by patients to be important as markers of treatment success and the themes of patient-important outcomes reported.

The anticipated date for data collection for objective one is October 2021, and objective two is January 2022.

4.5.7. Risk of bias assessment

In duplicate, individual studies will be examined to assess the quality of studies included in the review. For trials assessed through objective one, the Cochrane Risk of Bias Tool will be used. The standard cut offs reported for this tool in the literature is a score of 6 or higher; studies meeting this cut off will be included in subgroup analysis which will be conducted based on risk scores. For studies with an observational design in objective two, the Newcastle-Ottawa Scale will be used. Studies scoring five or lower on this tool will be included in subgroup analysis.

4.5.8. Data synthesis

The outcomes extracted for the first objective of this systematic review will be qualitatively reported. Descriptions (type of outcome, definition, method and timing of outcome data collection) of outcomes will be provided for each eligible study. Reporting of outcomes will also be stratified by type of intervention (psychotherapy, pharmacotherapy, or a combination). The rationality for the selection of outcomes will be summarized for each study.

For the second research objective, thematic analysis will be conducted to group outcomes reported by patients to be important. Thematic analysis will be sensitive to the types of outcomes reported by patients, and therefore grouping will be selected based on the themes that appear. Results of qualitative and observational studies will be summarized.

Within both objectives, stratification according to sociodemographic and clinical variables will be conducted to explore the relevance of these characteristics to patient-important outcomes. For objective one, reported outcomes will be stratified by sociodemographic characteristics including ethnicity, age, sex and gender, and clinical characteristics like phase of disorder, disorder onset, and additional treatment, where data is sufficient and available. For objective two, analysis of patient-important outcomes based on sociodemographic details such as ethnicity, age, sex and gender can be explored to identify differences in outcomes based on important identity factors. A qualitative summary of differences in outcomes reported will be presented. Where sufficient clinical data is available related to phase of disorder, disorder onset, and additional treatment, differences in patient-important outcomes can be explored.

4.6 IMPLICATIONS

Through objectives one and two, this review aims to systematically appraise the literature in order to determine the current outcomes being used within trials and how these outcomes were measured and to whom they apply to establish treatment success. Through this study, we will draw conclusions on what outcome and endpoints exist within trials, determine how these outcomes were measured, and examine the extent to which patient-important outcomes are included. Finally, these findings will inform future development of core outcome sets to measure treatment success within trials of treatment for bipolar disorder.

4.6.1. Patient and public involvement

There was no patient or public involvement in the conception of this systematic review protocol.

4.7 ETHICS AND DISSEMINATION

The findings of this systematic review will be disseminated with important stakeholders and relevant communities. The conclusions of this review will have implications for the development of a core outcomes set for trials which test treatment effectiveness for bipolar disorder. Through ongoing collaborations and partnerships with tertiary care centres, we aim to circulate findings to clinicians and patients. Tools such as summary reports and guidelines will be constructed in order to translate the results of this study to these primary end users. Findings will also be shared with researchers, knowledge users, learners and clinicians through conference presentations, workshops, and scientific publications.

4.7.1. AUTHOR CONTRIBUTIONS

AD: contributed to the conception and design of the study and study protocol, the writing and final review of the manuscript, and developed search strategy and the data collection tool within Covidence. OO: contributed to the writing and final review of the manuscript. SS: contributed critically to the development of the search strategy and final review of the manuscript. AH, NS, BP, MR, FK, LT: provided critical revision and review of the final manuscript. ZS: contributed to the conception and design of the study, provided critical revision and provided approval of the final manuscript. All authors read and approved the final manuscript.

4.7.2. Data Statement

Once the review has been completed, any additional data can be made available on request.

4.7.3. Funding

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4.7.4. Competing interests

None to declare.

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4.9 TABLES & FIGURES

Table 4.1 Search Strategy

Database	Search Strategy
OVID MEDLINE	**Search Strategy for Objective One** 1. exp "Bipolar and Related Disorders"/ 2. bipolar.mp. 3. (manic adj3 (disorder* or state*)).mp. 4. or/1-3 5. clinical trial/ or clinical trial, phase iii/ or clinical trial, phase iv/ or exp controlled clinical trial/ 6. clinical trials as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or exp controlled clinical trials as topic/ 7. clinical trial*.mp. 8. random*.mp. 9. Random Allocation/ 10. double-blind method/ or single-blind method/ 11. ((single or double or triple or treble) adj3 (blind* or mask* or method*)).mp. 12. or/5-11 13. 4 and 12 **Search Strategy for Objective Two** 1. exp "Bipolar and Related Disorders"/ 2. bipolar.mp. 3. (manic adj3 (disorder* or state*)).mp. 4. or/1-3 5. observational study/ 6. (observational adj3 (stud* or design*)).mp. 7. qualitative research/ 8. empirical research/ 9. personal narrative/ 10. interview/ 11. Interviews as Topic/ 12. "Surveys and Questionnaires"/ 13. Self Report/ 14. (qualitative or empirical research or narrative* or interview* or survey* or questionnaire* or self-report).mp. 15. or/5-14 16. 4 and 15

CHAPTER 5: Vaping in at-risk populations: Effects on physical and Mental Health (VAPE) – a mixed-methods study of motivations and perspectives for vaping in patients with opioid use disorder

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5.1 ABSTRACT

Introduction:
Vaping has become prevalent within the patients with opioid use disorder (OUD), with preliminary data suggesting more than 20% of OUD patients vape nicotine, cannabis, and water-flavours. Given the prevalence of vaping, and the co-occurrence of mental health challenges and polysubstance use with vaping, it is critical to understand perspectives on vaping within this population.

Objective:
This convergent mixed-methods study aimed to describe perceptions and motivations of vaping among patients with OUD.

Methods:
Individual, virtual semi-structured interviews were conducted with 41 individuals with OUD receiving medication for opioid use disorder (MOUD) who vape. An inductive data-driven approach was employed to characterize perspectives of vaping, engaging individuals with lived experience in the research process.

Results:
The sample was aged 39.54 (standard deviation [SD] 37.29) years (58.5% female). Participants were predominantly receiving methadone MOUD (85.4%). Qualitative analysis revealed the mean age when introduced to vaping and initiating regular vaping to be 33.95 years (SD 12.70) and 34.85 years (SD 12.38), respectively. Thirty-five participants reported daily vaping, using nicotine, flavoured nicotine, THC, and CBD; 11 participants reported vaping both nicotine and cannabis. Qualitative analysis identified 14 themes describing motivations for vaping, including viewing vaping as a smoking cessation tool, convenience, and popularity among young people.

Discussion:
Mixed-methods findings indicate that patients with OUD who vape perceive vaping to be a healthier, cleaner, and more convenient alternative to cigarette and cannabis smoking. Patient perspectives reflect the importance of guidelines and screening tools for vaping, and provide takeaways for healthcare providers concerning treatment, case management, and direction for future vaping cessation programs.

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5.2 INTRODUCTION

Vaping has gained popularity over the last several years with great expansion of product offerings. New generations of vaporizers have departed from conventional models both in appearance and substance,[1] likely following evolving Canadian marijuana legislation[2]. A 2019 survey indicated that over a third of Canadians who used cannabis in the last 12 months used a vaporizer, e-cigarette or vape pen[3], up 29% from 2017[4].

Despite expanded product offerings, the impacts of vaping remain unknown. Some camps view vapes as smoking cessation tools, while others raise alarms over the inspiration of substance use in never smokers, particularly in youth. A recent systematic review, however, shows moderate confidence around improved cessation using nicotine e-cigarettes compared to alternative cessation tools[5]. Research has found more individuals substituting some of their daily cigarettes for e-cigarettes rather than alternative, Food and Drug Administration (FDA)-approved tools, with many transitioning to dual use rather than discontinuing cigarettes entirely[6].

Despite the absence of trials, studies found that vaping is significantly associated with the same harms[7] and respiratory conditions as cigarette smoking[8]. Cases of e-cigarette and vaping associated lung injuries (EVALI) have been reported, though the true incidence is obscured by limited vaping screening within primary care and emergency settings and, most recently, overlap with coronavirus 2019 (COVID-19) presentation[9]. Patients with opioid use disorder (OUD) are at risk for vaping given their risk for polysubstance use and health comorbidities; estimates suggest over 20% of patients on medication for opioid use disorder (MOUD) currently vape[10].

Termed the "tripartite" of epidemics, it is incumbent to study the interplay between OUD, vaping, and COVID-19[11], the need for which is compounded by aggressive vaping marketing campaigns during the pandemic[12] and rising fentanyl-related deaths[11,13]. Recent work shows the social and health implications of the COVID-19 pandemic on individuals with OUD[14]. Studies have shown geographical associations between vaping and COVID-19, and strong associations between COVID-19 diagnosis and past e-cigarette use in youth[15,16]. Additionally, aerosolization in vaping has been shown to generate new compounds not present in the original solutions[17,18]. Taken together, this generates concern for individuals on MOUD, whose exposure to opioids make them vulnerable to respiratory illness[19], depression or toxicity[20], immunosuppression,[20,21], and possible drug interactions with evolving COVID-19 treatment[20,22]. Socioeconomic challenges exacerbate risks, specifically in the context of drug procurement and use[23], and residential mobility[24–26].

The lack of guidelines and the absence of screening tools disempower discussions between health care providers (HCPs) and patients, leaving patients at risk for vaping-related harms[27,28]. Understanding patient perspectives is critical to responding to the multi-faceted risks facing the OUD population, within the context of various health epidemics and a dynamic regulatory environment. This study employed convergent mixed-methods to explore perceptions of vaping among patients with OUD.

5.3 METHODS

This study is reported according to the Consolidated Criteria for Reporting Qualitative Research (COREQ)[29] (Appendix 8.6), and approved by the Hamilton Integrated Research Ethics Board (HIREB) (No. 12602). Appendix 8.7 provides additional methods, including research team characteristics, and data collection and analysis.

5.3.1 Interviews

Semi-structured, open-ended interviews were conducted with individual patients with OUD to explore perspectives on vaping. The qualitative interview guide was constructed in partnership with a qualitative methodologist and individuals with lived experience (Appendix 8.8).

5.3.2 Study Design

A convergent mixed-methods approach was used; qualitative and quantitative data were compared and integrated to permit a thorough understanding of the research problem[30]. Collection, analysis, and integration of data is summarized in Figure 5.1. The virtual, contact-free format was selected to minimize risk and resist COVID-19 related research disruptions.

The qualitative component was underpinned by qualitative description methodology. The qualitative research statement[31] describes the aim of this study:

> To identify and describe the perceptions and motivations for vaping in individuals on MOUD who vape, enrolled in CATC in Ontario, Canada.

An inductive thematic analysis with a data-driven approach was used to yield "straight" descriptions of themes related to the phenomenon of interest, most appropriate for the selected study design. The concurrent quantitative analysis describes vaping patterns and perceptions, with results expressed as mean (SD) for continuous variables and count (%) for categorical. NVivo Qualitative Data Analysis Software[32] was used for data analysis.

5.3.3 Participant Selection

Participants were 16 years of age or older, had a diagnosis of OUD (Diagnostic and Statistical Manual – Fifth Edition DSM-5)[33], were enrolled in a CATC, communicated in English, and currently vaped.

5.3.4 Recruitment and Sample

Purposeful recruitment was conducted per study protocol (Appendix 8.9). Approval was obtained from HIREB to contact new and previously enrolled, eligible participants from the ongoing parent cohort study[34]. Participants received a $10 gift card and provided phone access and a private space for the interview if needed.

Fifty was selected as the target sample size, the upper limit of the range recommended for qualitative studies[35]. It was pre-specified that recruitment would terminate when saturation was reached, defined as consensus that interviews were yielding redundancy and continued enrolment was unlikely to generate new themes.

5.4 INTERPRETATION

5.4.1 Sample Description

Participants were recruited from February 2021 to April 2022. Forty-one individuals consented to participate in the study (Figure 5.2). Individuals chose not to participate due to lack of interest (n=12), or loss of contact prior to the interview (n=16). Demographic and vaping characteristics are provided in Tables 1 and 2, respectively.

Most of the sample was female (58.5%), and of European descent (78%). Methadone (mean dose 84.36 mg/day, SD 48.76)) was more common than buprenorphine (mean dose 17.83 mg/day (SD 8.64) treatment (85.4% vs 14.6%).

5.4.2 Results

Manual analysis yielded 14 themes, and NVivo statistical analysis yielded 12; comparison of analyses strengthened identified themes and codes. Table 5.3 shows 14 themes; integrations with corresponding quantitative data are visualized in a joint display table (Appendix 8.10). Figure 5.1 summarizes the integration of results. Appendix 8.11 contains the qualitative codebook.

This study collected the perspectives from 41 individuals on MOUD treatment who vape. This analysis indicated that vaping is perceived as convenient and pleasurable, permits agency, supports smoking reduction or cessation, supports changes in drug use, has both positive and negative health effects, and neutral to small effects on MOUD. Participants believed vaping remains under-investigated, but prevalent among youth. Vaping was motivated by perceived social benefits and described as a method for getting "high". Below, we outline the qualitative themes, and validate those themes with quantitative results.

5.5.1 Personal benefits

Personal benefits, including cost, were found to be important among nicotine and cannabis vapers. Participants found vaping allowed them to spend less on cigarettes, through reduction or cessation. Participants highlighted the convenience of vaping, suggesting that vaping is easier and cleaner, and positively associated with enjoyment and comfort. This is consistent with 56% of participants' reporting vaping "for pleasure". On average, participants disagreed with the statement "vaping would make me feel happier now", suggesting vaping may be associated with pleasure rather than "happiness," supported by evidence distinguishing the two[36,37]. Vaping was associated with agency and independence, matching participants' disagreement with statements like "I will vape as soon as possible" and "nothing would be better than vaping right now".

5.5.2 Vaping and smoking

Participants viewed vaping as a smoking cessation tool, with some regarding it as harmful and listing negative effects, echoing other qualitative findings[38]. Vaping was described as driven by desires to quit or reduce smoking cigarettes, later becoming an alternative, often supplementary means to consumption of nicotine or cannabis, and

supporting the ease of continued polysubstance use. Indeed, current smoking was common (67%, mean of 10 cigarettes daily) similar to estimates in non-vaping patients with OUD (an average of 14-15 cigarettes/day)[34]. Little difference in daily consumption was found between those who reported being motivated to reduce consumption and those who did not (10.4 vs 11 cigarettes/day). This raises concerns for continued nicotine consumption and possible dual use rather than smoking cessation, especially given that individuals reported vaping for approximately 4.5 years.

5.5.3 Vaping and substance use

Participants perceived vaping to be conducive to abstaining from illicit drugs and reported that vaping helped curb cravings (81%) or served as a substitute (74%) for illicit drugs. Yet, urine toxicology screens (UTS) showed 50% positivity for methamphetamine, 33.3% for cannabis, 27.3% for amphetamines, showing 24.2% positivity for cocaine, 16.2% positivity for opioids, and 16.2% positivity for benzodiazepines. This suggests that vaping may be perceived to manage cravings while not producing cessation. Coupled with mixed evidence surrounding tobacco consumption for coping with urges for other drugs[38–40], it remains unclear whether vaping reduces drug use. This perspective also appears to contradict both quantitative and qualitative data, which identify "getting high" as a common reason for vaping. While cannabis is legal in Canada and is perceived as "less harmful"[41] than illicit substances, vaping appears a convenient means to solicit and control one's "high," and may become an entry point through which individuals may initiate or remain within cycles of substance use.

5.5.4 Vaping is socially motivated

Vaping appears to have a social component, describing initiating through social settings and positive social interactions, corresponding with 20% of participants reporting vaping because others around them were, and 15% reporting that they typically vape around others. Associations between smoking, social identity[42], and peer influence[43] have been reported, suggesting that the choice to vape is linked to social identity and belonging, and may impact how, what and why individuals vape.

5.5.5 Vaping and MOUD

Perceptions were divided on the effect of vaping on MOUD treatment. UTS data for opioids showed 16% positivity, suggesting modest effects if any. Those reporting positive effects of vaping on MOUD tended to vape cannabis. While this suggests that vaping cannabis may influence MOUD, comparison of UTS in cannabis vapers and non-cannabis vapers shows higher positivity for opioids and other drugs in those who vape cannabis (20% in cannabis vapers vs 13.6% in nicotine/water-flavour only).

Perceived positive effects on MOUD may result from psychoactive properties of cannabis, which may modulate cravings for some, or produce analgesic effects, the evidence for which is mixed[44]. Further, past month cannabis use has not been associated with more or less opioid use in OUD patients on treatment[45], indicating the need for research on the effects of vaping on MOUD.

5.5.6 Vaping and health

Lack of knowledge of vaping within this sample suggests that many patients who vape are unaware of health effects and possible harms associated with vaping. Participants perceived vaping to be associated with benefits to stress and anxiety and improved respiratory symptoms. Yet, over half of the sample reported mental health concerns, including mood disorders, therefore aligning with associations between smoking and coping with psychiatric conditions[46], and studies associating e-cigarette use with psychiatric diagnoses, and greater depression and stress scores[47]. The impact of vaping on mental health remains unknown.

Perceived positive physical effects of vaping were rarely discussed independently from cigarettes, likely due to past or current smoking. A few participants perceived vaping to be associated with negative respiratory symptoms (i.e., lung infection). Most patients reported symptoms eased when adjusting strength or inhalation. While harms and addictive potential of vaping was noted, few mentioned desires to quit, implying harms were not important enough to change their behaviours. Neutral responses to the statement "I am missing vaping right now" and moderate craving scores align with contrasting opinions on vaping being addictive, though prevalent daily vaping (85%) supports possible dependence.

It is important to consider whether symptoms of vaping are regarded as less serious because of the more immediate and serious risks of opioid use, like overdose and death. Research reports greatest perceived harms among nonusers[48], with poly-tobacco use being negatively associated with perceived harm[49]. Low risk perception and continued vaping may be explained by poly-tobacco and polysubstance use[50].

The intersection of vaping initiation and smoking reduction must also be acknowledged, potentially leading patients to attribute positive effects to vaping rather than smoking cessation. Without knowledge of risks, individuals who vape to stop smoking may continue to vape. Decision-making aids must dispel misconceptions that vaping is nonaddictive or resistant to substance-related effects, and address vaping-specific health concerns, such as describing harms related to devices and aerosolization[17,18]. With new devices coming to market and experimentation with new materials, users must remain vigilant when selecting brands, products and substances[17,18], and guidelines must empower low-risk product selection.

5.5.7 Vaping and Youth

Vaping in youth was perceived; however, the mean age for trying and initiating vaping within this sample were 34 and 35 years, respectively, suggesting that vaping remains common in adults. As well, the mean age of this sample was 40 years, which aligns with the average age of patients on MOUD reported elsewhere[10]. Perceptions suggested that flavours attract youth; however, flavoured substances were common amongst older (>30 years) participants. It is possible that increases in youth vaping[51], greater media attention and regulatory changes to flavours are shaping participant perspectives on youth vaping.

5.5.8 Synthesis

Participants described little understanding of vaping, yet positively acknowledged it as an important tool for "cessation". Vaping is unsupported as a smoking cessation tool[52], and lacks adequate testing as a cessation method[5]. Minimal definitive evidence, direct messaging or government action surrounding vaping[53] may be leading individuals to reconcile personal and external perceptions of vaping, leading to possible biased decision-making. Decision-making aids are needed to provide information on the risks of vaping given strong motivators. Through the removal of barriers such as smell, taste and cost, and the introduction of flavours delivered through a convenient, "futuristic" product design, vaping appeals to patients with OUD. Coupled with the overwhelming, though unfounded perception that "vaping is healthier than cigarettes", and the largely uncharacterized risks of vaping devices, our results substantiate concerns that vaping may beget continued substance use, and intrigue those deterred by the unpleasant effects of smoking.

5.5.9 Limitations

The qualitative descriptive design used within this study is data-driven, lacking the formality of alternative, theory-based approaches. Findings must be understood considering lifetime smoking. As treatment for OUD is most common amongst adults (> 16 years), perspectives captured here may be biased to exclude youths with OUD. Results are likely shaped by participation, social desirability and recall bias.

5.6 CONCLUSIONS

These findings provide insight into reasons for vaping in individuals with OUD. This study disseminates the perspectives of a population at risk of worsening health due to comorbidities and polysubstance use, exacerbated in the context of compounding health crises. Despite views that vaping supports smoking cessation, individuals often continue to smoke and lack of understanding of the possible effects of vaping. Vaping is viewed as distinct from smoking, despite continued consumption of a particular substance. Research must address whether vaping supports cessation, or if vaping is making it easier and cheaper for individuals with OUD to continue consuming substances with known health risks, using devices for which sufficient risk assessment has yet to resolve.

Effects and patterns of vaping must be studied to empower future decision-making. Findings emphasize the importance of guidelines for clinical decision-making on vaping, the absence of which challenges HCPs and may be life-threatening for both general and psychiatric populations[27,54]. Population-specific motivators provide lessons to stakeholders to consider when developing cessation initiatives.

5.7 AUTHORS CONTRIBUTIONS

AD: Data curation, formal analysis, funding acquisition, investigation, methodology, project administration, data visualization, and drafting of the final manuscript. BP: Data curation, formal analysis, investigation, project administration; as well as critical review and revision of the manuscript. NS: Data curation, funding acquisition, investigation,

methodology, project administration, as well as critical review and revision of the manuscript. LO: methodology, resources. KP: funding acquisition, methodology, resources, and approval of the final manuscript. TR, CdO, FK, LR, DM, PM, CP, TB: Funding acquisition, methodology, critical review, and revision of the manuscript. AH: critical review and revision of the manuscript. ZS: Conceptualization of the research project, funding acquisition, methodology, project administration, resources, supervision and oversight, and critical review and revision of the manuscript.

5.8 OTHER INFORMATION

5.8.1 Funding

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5.8.2 Declaration of Interests

The authors have no conflicts of interest to declare.

5.8.3 Data Availability

The data for this study can be made available upon reasonable request.

5.8.4 Supplementary Material

Appendix 8.6 details the reporting of items in keeping with the COREQ. Appendix 8.7 and 8.8 include the study protocol and additional methodological details, respectively. Appendix 8.9 includes the Qualitative Interview Guide. Appendix 8.10 includes the full qualitative codebook. Appendix 8.11 includes a joint display table of qualitative and quantitative findings.

5.8.5 Acknowledgements

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5.9 TABLES & FIGURES

Figure 5.1 Summary of Quantitative and Qualitative Data Collection, Analysis and Integration

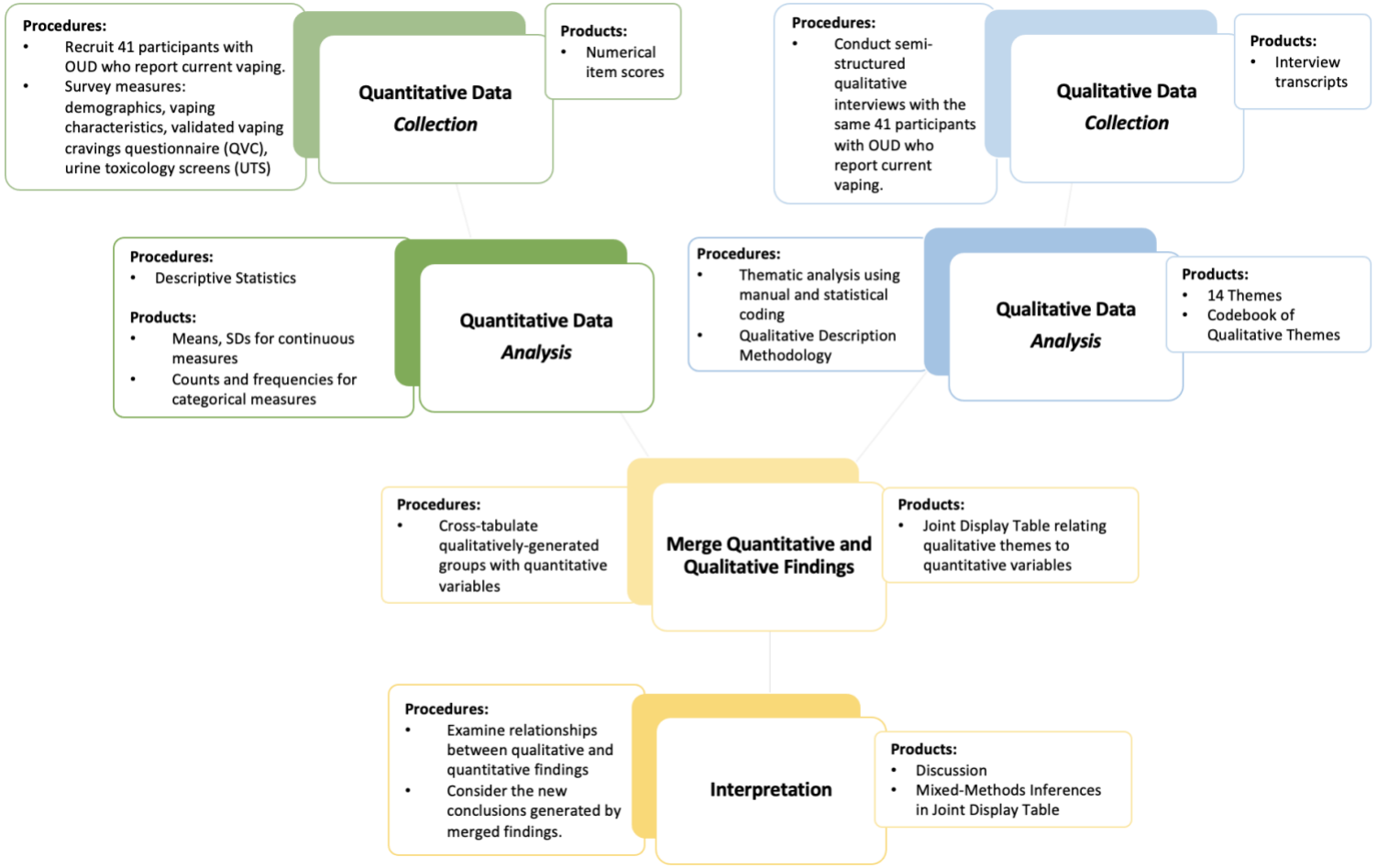
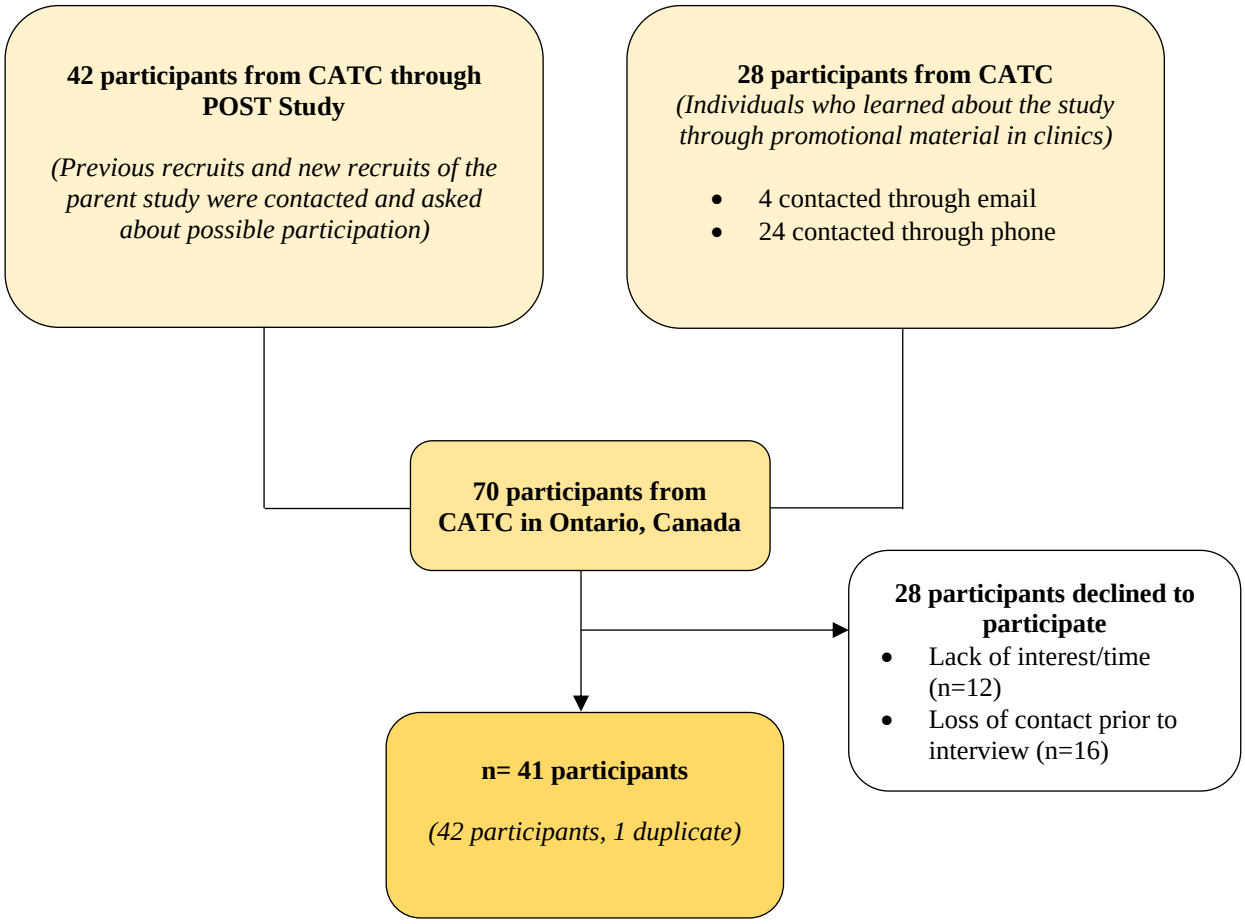


Figure 5.2 Participant Flow Diagram



The study team discussed possible participation with 70 participants in total. Participants were recruited using promotional material for the VAPE study (n=28) or were contacted by the study team after participating in the parent POST study. In all, 41 participants were enrolled; 33 enrolled participants participated in both the POST and VAPE study.

POST: Pharmacogenetics of Opioid Substitution Treatment; parent cohort study

Table 5.1 Demographic Characteristics

Characteristics	n=41
Age (years); mean (SD)	39.54 (37.29)
Females; n (%)	24 (58.5%)
Males; n (%)	17 (41.4%)
Cisgender female; n (%)	23 (56.1%)
Cisgender male; n (%)	17 (41.4%)
Nonbinary; n (%)	1 (2.4%)
Ethnicity; n (%)	
European	32 (78.0%)
Native North American	3 (7.3%)
Mixed	5 (12.2%)
Other	1 (2.4%)
Marital; n (%)	
Single, never married	24 (58.5%)
Married	3 (7.3%)
Common law/living with a partner	7 (17.0%)
Widowed/Separated/Divorced	7 (17.0%)
Education; n (%)	
Grade 1-8	7 (17.0%)
Grade 9-12	22 (52.7%)
College/University/Master's/PhD	11 (26.8%)
Other (Trade school/None)	1 (2.4%)
Medication Opioid Use Disorder (MOUD)	
Methadone; n (%)	35 (85.4%)
Buprenorphine; n (%)	6 (14.6%)
Current Methadone dose (mg); mean (SD)	84.36 (48.76)
Current Buprenorphine (mg); mean (SD)	17.83 (8.64)
Age when first introduced to vaping (years); mean (SD)	33.95 (12.70)
Age of initiating vaping regularly (years); mean (SD)	34.85 (12.38)
Number of years vaping; mean (SD)	4.58 (4.31)
Current Cigarette Use; n (%)	27 (65.9%)
Cigarettes per day; mean (SD)	10.65 (6.11)
Body-Mass Index (BMI); mean (SD)	30.67 (35.87)
Comorbid Conditions	
Autoimmune	3 (7.3%)
Cardiovascular	5 (12.2%)
Gastrointestinal	2 (4.9%)
Respiratory	5 (12.2%)
Mental health (anxiety, mood disorders, stress disorders)	21 (51.2%)

Table 5.2 Vaping Characteristics

Age when first introduced to vaping (years); mean (SD)	33.95 (12.70)
Age of initiating vaping regularly (years); mean (SD)	34.85 (12.38)
Number of years vaping; mean (SD)	4.58 (4.31)
Vaping frequency; n (%)	
Everyday	35 (85.4%)
Every other day	2 (4.9%)
2-3 times per week	3 (7.3%)
2-3 times per month	1 (2.4%)
Dollars per spent on vaping per week (CAD***/week); mean (SD) (n=38)	25.41 (29.32)
Range in dollars spent on vaping per week (CAD)	0-100
Substances vaped; n (%)	
Nicotine	26 (63.4%)
Flavoured nicotine	13 (31.7%)
Water-flavour only	1 (2.4%)
Cannabis (Tetrahydrocannabinol (THC)/Cannabidiol (CBD))	18 (43.9%)
Nicotine and THC/CBD	11 (26.8%)
Most common setting for vaping; n (%)	
Alone	35 (85.4%%)
With one person	3 (7.3%)
With two or three people	2 (4.9%)
Other (equally with others and alone)	1 (2.4%)
Reasons for vaping; n (%)	
To get high	13 (31.7%)
Calmness/Relaxation	34 (82.9%)
Others around me are using it	9 (23.1%)
For pleasure	21 (53.8%)
Stress relief	30 (76.9%)
Boredom	22 (56.4%)
Social anxiety relief	19 (48.7%)
Use a vape instead of other substances	29 (74.4%)
Substance Use withdrawal/craving symptoms relief	32 (82.1%)
Craving or withdrawal relief from Opioids (i.e., fentanyl)	8 (20.5%)
Craving or withdrawal relief from cigarettes (i.e., nicotine, tobacco)	24 (61.5%)
Craving or withdrawal relief from Cocaine (i.e., crack, cocaine)	5 (12.8%)
Craving or withdrawal relief from Marijuana	3 (7.7%)
Craving or withdrawal relief from Methadone	2 (5.1%)
Craving or withdrawal relief from Methamphetamine	1 (2.6%)
Urine Toxicology Screens (% positive; positive screens/total screens)	
Opioids	16.2% (6/37)
Benzodiazepines	16.2% (6/37)
Amphetamines	27.3% (3/11)
Cannabis	33.3% (1/3)

Cocaine Methamphetamine	24.2% (8/33) 50% (2/4)
Questionnaire of Vaping Craving (QVC) Score; mean (SD)	36.18 (15.88)

Table 5.3 Data-derived themes of participants' perceptions and motivations for vaping

Themes	Examples
1. Perceived convenience	• "Um.. cause… cause like I buy a cart- like I'll buy a cartridge and then I'll buy a pack of cigarettes, and if I don't have the money, then I just use the vape." (Case 1, F/36) • "Um, the convenience of it, and that it doesn't smell like cigarettes and stink up the house?" (Case 3, F/33) • "And sometimes it's just having a couple of inhales of the vape- the vaporizer is quicker than trying to smoke a half cigarette." (Case 5, M/25) • "I like it because it's um you don't have to do anything you know what I mean? … Like it.. no.. there's no mess it's just you just open the package up and you start puffing." (Case 31, F/52) • "Uh, just, she was like, trying to quit smoking, and she was like, hey, "you should try this". It- it made her feel healthier, it was cheaper, and so, she kind of, she actually gave me my first vape." (Case 27; F/39).
2. Perceived pleasure	• "Yeah. Like, my hands didn't smell afterwards. And stuff…" (Case 1, F/36) • "Yup, um, so I had smoked for probably like, 25 years, when I started, or when I first got it, and had no intentions on quitting. But um, but I ended up quitting. I just, I really liked -- the flavour is much better, I enjoyed the 'pull' over a cigarette 'pull' " (Case 18, F/41) • "Um, it looked like a cleaner alternative to cigarettes. Made you smell good." (Case 11, M/43) • "Sometimes it helps with relaxation when I'm at home and I don't wanna move, and I can just relax and I have my e-cigarette with me and uh, veg on the couch." (Case 3, F/33) • "Uh the smell, uh I say that I work in restaurants right, so it's not like you go outside smoke come back in and not stink so, for certain reasons yes." (Case 17, M/41)
3. Perceived Agency	• "Yeah. So like, I mean, I just like the ability to, um, begin, and and stop whenever I choose." (Case 4, F/41) • "Um, I really, don't do much research into that kinda stuff, like I just kinda go with my day and go with the flow, and um, for me, not to have to smoke a full cigarette or not to – like I just find that it, it fixes my craving, um, within one puff. Which, as I say, one puff is like 5 times a day, that's like a cigarette in a day." (Case 4, F/41)
4. Perceived smoking reduction	• "Yeah, I ran out of cigarettes and he was like "here try this", so I tried it and it, um, helped with um, the cravings, and then – I still smoked, but you know I would try once in a while. Or do it with him." (Case 3, F/33) • "Like I don't see, it's – but then again I'd have to smoke cigarettes so." (Case 9, M/31) • "I'm more addicted to cigarettes, like I've smoked cigarettes since I was 14 years old. And with vaping, I usually just uh, I usually just do it to try and see if I can go a day or – a couple days without smoking cigarettes." (Case 5, M/25) • "It was usually a matter of going back to cigarettes, or going down on the cigarettes and choosing the vape more." (Case 11, M/43)

5. Vaping is perceived to be a smoking cessation tool	• "So, um, like I'd say the first month I was still smoking, like cigarettes, strongly. But after that, and I, um, I almost went three months straight without, no cigarettes." (Case 7, M/33) • "Sure. Uh, uh I vape, um, I vape as a tool to- to- to- quit cigarettes, to quit cigarettes. So, basically I vape to- to- to- um, yeah, to help the void from cigarettes." (Case 9, M/31) • "I just, I don't know, I use it as a replacement for cigarettes, and um I guess I'm addicted to it now." (Case 16, M/45) • "Um, yeah because I had heard of it as an alternative to cigarettes. It was all because I wanted to quit cigarettes so I was looking for options, and there hasn't ever been many options other than like, you know, nicotine gum and stuff, and that stuff just doesn't work." (Case 9, M/31) • "No, I would never, I wouldn't even see vaping as something that I'd need to quit. Like wouldn't be a problem." (Case 11, M/43)
6. Perceived changes in substance use	• "Um, yeah it like just keeps me from, like, being bored, stuff like… Takes my mind off of things." (Case 1, F/36) • "Uh, the one reason is because I had been trying to get off of the fentanyl. And, if I couldn't get it, it would take away the physical ummm, withdrawal symptoms that I was - uh – going through. Like the stomach aches, the bone aches. The, the, the overall creepy feeling that you get. The vaping would take that away." (Case 29, F/53) • "Not at all, it's not a social thing at all right now, it's more so, yeah like boredom stress release, especially since I quit smoking other things which were kinda my coping mechanism." (Case 14, F/18)
7. Perceived lack of information about vaping	• "Um, I am weary of vaping because there's not that much – I'm not sure about the statistics on it? I know cigarettes cause cancer and stuff like that, but, I feel like vaping has gotta be – there's gotta be some, some sort of medical downfall to vaping. Um, it's just another toxin that we're putting into our bodies. So, I figure there's gotta be something bad about it, we just haven't found out yet." (Case 3, F/33) • [Interviewer: Okay. And who told you, um, just out of curiousity, who, uh, mentioned – or where did you hear that it was bad?] Participant: "On youtube". (Case 2, F/46) • "Um, I just, a question mark on negative health effects [unintelligible], but uh, I haven't done too much research into it myself so." (Case 13, M/36)
8. Perceived social benefits motivate vaping behaviours	• "Um, he doesn't like me smoking so he suggested I started to vape." (Case 14, F/18) • "…I-I like the way it doesn't make my clothes smell, it doesn't make my hair smell. Um, it looks a lot more friendlier around my kids." (Case 24; F/33) • "Oh okay, uh, um, it's – really it's been – it's actually positive. Uh, one because, at this age, you're sick and tired of the, of the smoke, like you-your just trying to just s–s- like um, discreetly, use. You know, like you're not trying to tell the world, you know, banners all over the place – I'm not an activist, so I try to keep – I'm very low key." (Case 42; M/65) • "It's a little cleaner. Um, in, in society now, it seems to be more accepted." (Case 37; F/52)
9. Perceived	• "It [coughing and breathing] got hugely better, cause like I'm not smoking a

positive health effects of vaping	half and a pack a day." (Case 6, F/29). • "Less phlegm, less phlegm in my throat, for coughing. Like, there's, smoking causes me to cough more." (Case 11, M/43) • "So, for me, it's been a positive, its helped my health because I am not smoking a lot of cigarettes." (Case 9, M/31) • "It's just something that calms the, you know what I mean? Calms the stress, calms the, yeah." (Case 4, F/41) • "So, when I realized that I could get my daily THCs for cheaper and easier and less - health – like- harm reduction wise." (Case 8, M/36)
10. Perceived negative health effects of vaping	• "I coughed and uh didn't care for it very much." (Case 15, F/59) • "Yes, I do get short of breath when I vape." (Case 15, F/59) • "I found at first, it uh, if I was smoking it too much, I felt nauseous, and I would get headaches." (Case 6, F/29) • "Yeah, the more you vape, the more it burns." (Case 29, F/53) • "It definitely could be addictive, especially for people who, 1 haven't smoked anything before and they're just picking up vaping just because they want to um […] um also for um people who are um cigarette smokers, it would be addictive in the sense that you are already kind of addicted to that in the nicotine so yeah." (Case 14, F/18)
11. No perceived impact of vaping on MOUD	• "Uh, no. I, uh – if it does, I haven't noticed it…" (Case 5, M/25) • "Uh, never really thought of it, I smoked before I ever started any kind of opiates and I continued smoking through, so…" (Case 13, M/36) • "N-n-no, no, no, no interaction. It's a totally – apples and oranges. For uh – […] Or fruits and vegetables, no-no-no, no bearing, one doesn't have any bearing on the other." (Case 19, M/64)
12. Vaping has some perceived effects on MOUD	• "I find that it makes the methadone seem to last longer." (Case 29, F/53) • "If I um, end up missing my drink or end up throwing it up or something, then the metha-or the weed can help subside some of that stuff. Cause I'll start to feel sick and my legs'll start to hurt –" (Case 23, M/28) • "Um I think it's helped me decrease my methadone." (Case 32, F/51) • "…a lot of people find the same thing as me that it's really complimentary. And um, weed fills in the cracks where methadone is not perfect cause no medication can be perfect, right?" (Case 36, N/24)
13. Perception that vaping is for the youth	• "Like a little younger, youths, and even uh, students, and I find, uh, their, uh, like a lot of younger people are using it rather than older people, right?" (Case 5, M/25) • "The only thing I've heard is that the young kids, the teenagers, they, they get into the, they vape around with no nicotine in it, or something, I don't know." (Case 12, F/46) • "That kind of high school group. Is doing that. Where, they're not even smoking cigarettes, they're just buying these things to smoke 'em, which – that I can kinda understand, where the government's coming from, with all the flavours and everything" (Case 28, M/30)
14. Vaping to get high	• "Well I felt that I could control my high more through vaping." (case 34; F/69) • "Um, they just said that I um, tend to like weed, I should give shatter a try. Um, and they said I could use less of it and get more high. So I tried his pen and then

	I liked it so I went out and grabbed one of mine and I've been smoking it ever since." (Case 23, M/28) • "So, I'll just vape it, like just to get high. And it will be like a hit here and there." (Case 7, M/33)

CHAPTER 6: Conclusion

6.1 OVERVIEW OF FINDINGS

This thesis aimed to identify and characterize motivations underlying health behaviour. Generating evidence within this topic precipitated conclusions on how to intervene on motivation to address and treat psychiatric conditions, but also lead to lessons that may support improved decision-making through population-specific resource building and health promotion. The papers presented within this thesis highlight the connection between motivation and mental illness. The effects of mental illness, and correspondingly, potential treatment, can be understood in terms of motivation, as can behaviours occurring within illness, including engagement with risky behaviours.

The results of the pilot (Chapter 2) and full RCT (Chapter 3) highlight the possible benefits of BA for major depressive disorder, suggesting that BA may have impacts on quality of life. These possible benefits appear irrespective of sex, proposing the use of BA for both men and women experiencing MDD. Overall, these findings provide a possible pathway for acting upon low motivation and negative affect caused by MDD, by motivating activity and engagement with personally rewarding behaviours. Given the overlap in symptomology between MDD and depressive disorders, these findings justify further exploration of BA as a therapeutic in other disorders, such as BAD, to explore whether similar benefits may be conferred to other psychiatric disorders, particularly those with shared symptomology.

The results of the mixed-methods observational study provide an important understanding of perceptions and motivations for vaping in patients with OUD (Chapter 5). This study generates evidence that is critical for developing smoking and vaping cessation material. As this study reflects the perspectives of the OUD population, these findings provide direction for more nuanced, population-specific smoking cessation intervention, which considers the unique barriers and motivators for vaping within this group. These findings testify to the importance of patient education on vaping, which must not only be addressed through more concerted and coordinated research within this area, but also through evidence-based guidelines and screening protocols to embolden and encourage health care providers (HCPs) to discuss vaping with their patients.

6.2 OVERALL IMPLICATIONS

The results presented in each chapter provide an important contribution to treatment in mood disorders and harm reduction within OUD. The specific findings of each chapter of this thesis apply to the respective patient populations studied, but may also provide insight and targets for future treatment and harm reduction strategies within the broader context of psychiatric populations, particularly due to the shared heritability between psychiatric conditions and the prevalence of comorbidity.

Taken together, the findings of each chapter highlight approaches to treatment and lessons for harm reduction that exploit the important role of motivation across psychiatric conditions. This work emphasizes that therapeutics for psychiatric disorders and harm

reduction approaches must be informed by motivation and respond to the way motivation is altered within that disorder, in order to improve disease management.

This thesis aims to supplement the available literature concerning treatment of MDD. This work suggests that group-based treatment within tertiary care may have some significant effects on specific aspects of quality of life, in a manner that does not appear to be sex-specific, providing a possible treatment option for both men and women with MDD, especially among those who have found previous treatment unacceptable or insufficient. Given the possible dangers and adverse effects of polypharmacy in patients with MDD, this research provides an alternative, behavioural approach for patients and HCPs to consider. This work also provides insight into the ways in which individuals with OUD make decisions, and motivators underlying vaping behaviours, but may broadly apply to other risky-behaviours, therefore having implications for understanding risk-taking and strategizing for risk mitigation.

The findings and conclusions presented here provide evidence for researchers, policy advisors, and clinicians within mental health and addiction spaces. The results of the pilot trial suggest the feasibility of the study protocol, supporting replicability and transparency within the trial literature. The findings of the pilot also detail lessons for the design of RCTs within the MDD population, including suggestions for the selection of comparator arms. The full RCT informs the research community of the potential benefits of BA within the MDD population, discussing possible benefits for mood symptoms and quality of life outcome domains. The systematic review protocol presented within this thesis provides detailed methods for a large, upcoming review studying trial and patient-important outcomes in BAD. This planned review supports efforts toward precision-treatment by appraising and studying the congruency between trial outcomes and participant perspectives. Finally, the mixed-methods observational study within patients with OUD provides an understanding of patient perspectives on vaping. Stakeholders such as policy advisors may consider these findings when building policy, especially within the evolving regulatory environment regarding vaping and other substances.

Studying three patient populations using varied methodologies highlights the ways that motivation can be mobilized as a target for treatment and a method through which patient decision-making can be understood and progressed within psychiatric illness. This work highlights lessons and evidence which will improve service provision and contribute to health promotion.

6.3 FUTURE DIRECTIONS

While the results of the RCT conducted to test BA in MDD did not support the clinical effectiveness of BA in treating mood symptoms for depression given that changes did not meet thresholds for clinical improvement in depression, this study did support its effectiveness in possible benefits to depression and quality of life within this population, compared to treatment as usual. Further study must address how BA programs can be shaped (structure, duration) to maximize benefits and to further supplement the literature surrounding group BA treatment effectiveness. Future work must continue to support the ongoing systematic investigation of BA as a treatment for depression. These findings

provide evidence for appraisal and inclusion in future systematic reviews and meta-analyses, which will be crucial for HCPs and patients. Promise within the MDD population also highlights the importance of testing BA for individuals with BAD who also experience depressive episodes.

The published systematic review protocol details an important appraisal of outcomes in trials and patient important outcomes in patients with BAD. Once completed, this review will identify the outcomes used to establish treatment effectiveness in trials of patients with BAD. As this review will contribute to the literature on trial outcome sets in bipolar disorder, and communicate the outcomes most important to patients, review findings will demonstrate the relevance of motivation when testing treatment effects. It is expected that these findings will inform future research on core outcome sets within BAD, and reflect the extent to which motivation should be considered.

The results of the mixed-methods study on vaping strongly advocate for improved screening and formal guidelines to empower clinical interactions around vaping between patients and their care teams. The themes of vaping identified in this study inspire many possible avenues for vaping behaviour modification that will help mitigate risks within the OUD population. As evidence suggests that BA can be helpful in behaviour change, perhaps BA programs can be adapted to treatment for substance use and common health behaviours, as previous work has confirmed best treatment outcomes are achieved through a combination of pharmacological and psychotherapeutic intervention[49]. Consideration of the strong role of motivation within addiction not only suggests the candidacy of motivation-based treatment as an adjunct to pharmacological treatment; it also testifies to the importance of education and cessation campaigns which reflect and respond to intrinsic and extrinsic motivators characteristic of patients with OUD which shape decisions and health behaviour.

The study into motivations and perspectives for vaping within the OUD population has identified several themes, some of which are related to addiction and addiction treatment outcomes. The emergence of patient population-specific themes suggests that unique themes may be identified in other patient populations. This encourages the application of similar, mixed-methods investigations in other populations in which vaping is an important health concern, such as various psychiatric populations which are at great risk for substance use and risk-taking behaviour.

Lessons learned about individuals within each patient population have consequences for that specific population, but may have transferable applications to other psychiatric populations, and therefore have powerful, multiplicative implications for individuals with comorbid psychiatric disorders.

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CHAPTER 8: Appendices

8.1 CHAPTER 2, Additional file 1. CONSORT Checklist.

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	6
	2b	Specific objectives or research questions for pilot trial	6
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	8, 9
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	9
	4b	Settings and locations where the data were collected	7
	4c	How participants were identified and consented	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	11
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A

Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Table 1 & 3
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	N/A
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	13, 14, and Tables 1, 2, 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	14
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	18, 19
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	16, 17, 18
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	15,16
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	16, 18
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	4
Protocol	24	Where the pilot trial protocol can be accessed, if available	7
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	20
	26	Ethical approval or approval by research review committee, confirmed with reference number	7, 19

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	11
Sample size	7a	Rationale for numbers in the pilot trial	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	11, 12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	13 and 27 (Figure 1)
	13b	For each group, losses and exclusions after randomisation, together with reasons	27 (Figure 1)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the pilot trial ended or was stopped	8
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	28 (Table 1)

8.2 CHAPTER 2, Published Article

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Pilot and Feasibility Studies

RESEARCH Open Access

Feasibility of behavioral activation group therapy in reducing depressive symptoms and improving quality of life in patients with depression: the BRAVE pilot trial

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Abstract

Background: Depression impacts the lives of millions of people worldwide. Behavioral activation (BA), derived from cognitive behavioral therapy, has the potential for improving depressive symptoms in patients with depression. Studies evaluating the effectiveness of BA specifically in the context of group therapy programs in a hospital setting for patients with depression are limited. In this study, we report findings from a pilot trial evaluating group BA for major depressive disorder.

Objective: The objectives of this pilot trial are to assess the potential of a full trial of BA group therapy in a large-scale tertiary care setting and to provide preliminary information about possible results regarding mood symptoms and quality of life in adults with depression.

Methods: Using a parallel single-cohort pragmatic pilot randomized controlled trial design, we evaluated the potential of conducting a large trial of BA effectiveness among adults with depression. Participants were randomized to the intervention (BA in addition to usual care) or control (support group in addition to usual care) groups and were assessed weekly for 18 consecutive weeks. Participants randomized to intervention underwent 28 2-h group BA therapy visits administered by trained therapists and completed assessments to examine treatment outcomes. Feasibility was measured in terms of enrollment rates (min. 20%), completion rates of study (min. 80%), and completion rates of weekly measurement scales (min. 80%). The reporting of this pilot trial is in accordance with the CONSORT extension for randomized pilot and feasibility trials.

(Continued on next page)

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(Continued from previous page)

Results: We randomized 20 individuals of mean age of 48.8 years (standard deviation = 9.7) with a DSM-5 diagnosis of major depressive disorder to intervention ($n = 10$) or control ($n = 10$) groups. Based on our feasibility criteria, our recruitment rate was excellent (20/27; 74%), study completion was found to be a moderate (80% of the total participants in both arms completed the study; BA = 100%, control = 60%), and completeness of measurements on a weekly basis was adequate overall (82%; BA = 86%, control = 79%).

Conclusions: The study has demonstrated the potential feasibility to perform a larger scale trial upon modifications to the control group to avoid the low rate of study completion (60%) in this group.

Trial registration: ClinicalTrials NCT02045771, Registered January 22, 2014

Keywords: Behavioral activation, Behavioral group therapy, Depression, Quality of life, Pilot randomized trial

Background

Depression, a complex chronic disorder affecting over 350 million people globally [1], has become the second leading cause of disability worldwide [2] and is associated with increased risk of medical comorbidity, suicide, and all-cause mortality [3, 4]. Although pharmacological treatment with antidepressant medication, the most common approach to treat depression, has shown promise for improving mood in adults [5], nearly half of patients continue to show depressive symptoms over the long term [6–8]. Given the limitations of pharmacology antidepressant treatment, it is necessary to evaluate alternate and additional treatment strategies. Further, psychotropic medications as well as depression itself are known to be associated with risk of increased body weight and other metabolic changes [9], suggesting the need for treatments for depression that do not precipitate poorer physical health outcomes or are protective against metabolic changes involved in the course of depression [10].

Psychotherapy, including psychological interventions such as cognitive behavioral therapy (CBT), has been successful in the management of depression both as a single therapy or in combination with antidepressants [11], improving the overall quality of life and coping skills and producing positive long-term results [12, 13]. CBT requires, however, extensive training and resources, as well as patients' thorough understanding of their core beliefs and behaviors.

Behavioral activation (BA), originally a component of CBT, addresses behaviors and encourages individuals to eliminate reinforcers of depressive behaviors and connect with positive reinforcers in their environment [14]. The emergence of behavioral therapy for depression has opened opportunities for the development of simplified time-efficient treatment strategies that can have lasting positive effects on depressive symptoms and quality of life.

The evidence for BA is limited in comparison with CBT; however, it has reported advantages in the form of individual therapy for adult out-patients with depression [14]. BA is reportedly just as effective in treating symptoms of depression and reducing the risk of relapse as CBT in community samples of adults with depression [12, 15, 16]. Interestingly, a study comparing BA, cognitive therapy, and anti-depressant medication in adults with depression found BA to lead to similar outcomes as anti-depressant treatment and better outcomes than cognitive therapies [17]. A systematic review identified sixteen studies investigating behavioral activation treatment and demonstrated that changes between end of study and follow-up are not significant, suggesting that the benefits of BA are retained in follow-up [13].

While BA appears helpful in treating depressive symptoms, many studies addressing BA in treating depression tend to have small sample sizes and some biased methodology [18]. A systematic review of BA treatment for older patients with depression found significant reductions in depressive symptoms but maintained that many of these studies should be considered cautiously, suggesting the need for studies with larger sample sizes and well-developed methodology [18]. Further, many of these studies did not assess the effectiveness of BA as a group intervention in a hospital setting.

Based on the available evidence, BA has the potential for success as a cost-effective treatment intervention that requires minimal guidance from clinical staff, allowing reduced wait times and increasing the number of patients that can utilize this program [13]. In this study, we report findings from a pilot trial evaluating group BA for major depressive disorder, highlight the importance of implementing such therapies to determine their effectiveness in real-life clinical settings, and discuss planned changes for the main trial. While we previously reported the acceptability of group BA therapy among patients with depression [19], this paper details results of the pilot trial.

The objectives of the BehavioRal ActiVation for reducing dEpressive symptoms and improving quality of life in patients with depression (BRAVE) pilot trial are to test the feasibility of implementing a pragmatic randomized trial to evaluate the overall efficacy of group BA in a hospital-based setting, assess participants' satisfaction

with the program, and receive feedback to modify future treatment programs. We aimed to (1) evaluate the feasibility of the study process, including recruitment rate, completion of study, group size, and data completion; (2) assess resources needed for successful completion of the study (i.e., interview rooms, computers, time investment, clinical staffing); (3) explore the change in treatment outcomes including depressive symptoms severity and quality of life between and within intervention and control groups by presenting preliminary data; and (4) provide description of participants' scores on any of the assessments conducted during the study as well as a description of patients' clinical and demographic characteristics.

Methods

This trial has been registered with ClinicalTrials.gov (identifier #NCT02045771) and was approved by the Hamilton Integrated Research Ethics Board (HIREB: 14-042). The protocol for this trial is published in *Pilot and Feasibility Studies* [20]. The reporting of this pilot trial is in accordance with the CONSORT extension for randomized pilot and feasibility trials [21, 22]. See checklist in Additional file 1.

Study setting

This single-site study took place within the Mood Disorders Program at St. Joseph's Healthcare Hamilton, an outpatient specialized mood disorders clinic. This is a tertiary care center receiving referrals from the Greater Hamilton and surrounding area for the consultation and management of patients who have lack of response or inadequate response to treatment in the community and therefore were referred to the tertiary mood disorders clinic. Hence, the clinic often caters to patients with the most severe and complex depressive disorders.

Recruitment of participants

Clinicians approached patients at the Mood Disorders Program who were aged 18 years or older with major depressive disorders currently receiving treatment for depression at the clinic. Patients were eligible for the study if they were undergoing treatment for depression as per usual care (including antidepressants, psychotherapy, CBT, or other treatment modalities if any). Patients unable to provide written informed consent, communicate in English, or had a primary diagnosis other than depression were excluded. Details about the screening process and reasons for study incompletion were recorded

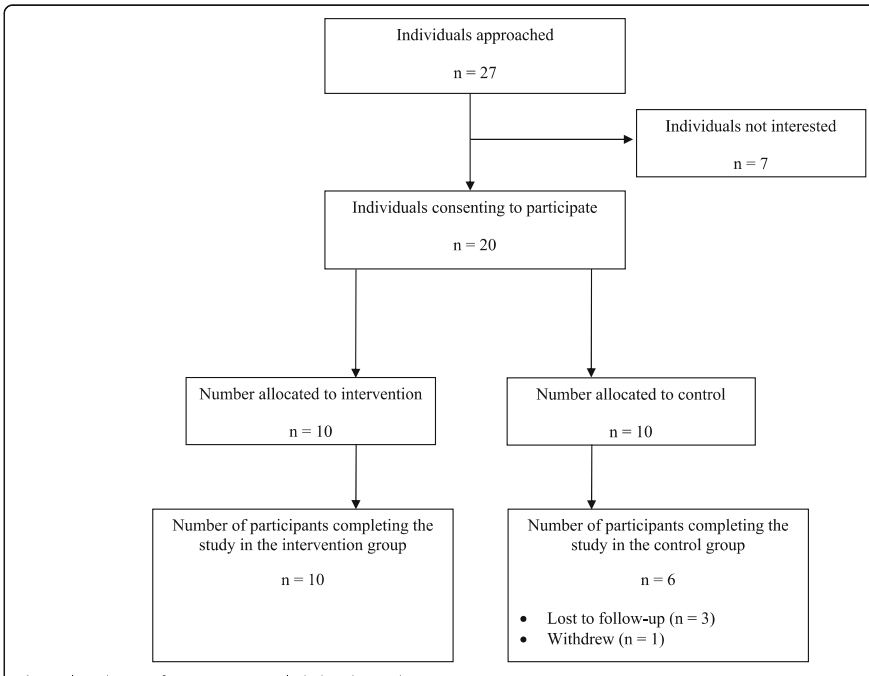

Fig. 1 Flow diagram for participants included in the study

(Fig. 1). Participants were allowed to discontinue participation in the study at any time. Recruitment for the pilot trial began December 2013 and ended in March 2014 when the sample size of 20 was reached. Participants were followed up at 3 months, and the pilot study ended in July 2015. Written informed consent was obtained from each participant prior to initiating any study procedures. Participants were told that the purpose of the study was to determine if the intervention is helpful and that behavioral activation was not known to be more effective than the support group. They were told that by consenting to the study, they could be randomized to receive either the intervention or the control condition and were encouraged to consult with family, friends, and clinical teams about their participation. The consent form was discussed, and the participants were given sufficient time to review the material and ask questions. Participants were provided a copy of the consent form for their own records.

Study design

This is a pragmatic randomized controlled trial comparing group behavioral activation (group BA) in addition to usual care to support (control) group in addition to usual care. Eligible participants were randomly allocated to the intervention or control arms using a parallel group design with a 1:1 allocation ratio. A block randomization system with block sizes of 2, 4, and 6 randomly assigned allocations; the randomization schedule was computer-generated. Full details of the randomization assignment, concealment, and other trial-related methods are described in the protocol [20]. Ten participants were recruited to each arm of the study, which was decided based on the recommended therapy group size of 6–12 [20].

Following the completion of informed consent and baseline assessments including mood scales, lifestyle questionnaires, and biometric measurements, participants were randomized in blocks. A research assistant not involved in the recruitment of potential participants or the study intervention procedures allocated the participants to the trial arms using the randomization system provided and informed the participants and the therapists/study clinicians of the group allocation. All twenty participants were assigned a unique participant ID and were randomly allocated to one of the two conditions. Pieces of paper with participant IDs were mixed and drawn from an envelope, then assigned according to the randomization schedule. Following randomization, participants were asked to attend their respective groups and given a schedule for the group dates. Blinding to the intervention during treatment was not possible for participants or clinical staff. We selected names for the two groups to be similar; the intervention group was called the "Out of the Blues" group and the control group was called the "Blues Breakers" to avoid calling the groups intervention and control. The staff was then given a list of participants in their group.

Intervention condition

The detailed methods of BA administration are described elsewhere [20]. Briefly, the intervention consisted of 28 visits across 18 weeks: twice weekly until week 10 and once weekly thereafter. Trained clinicians administered the intervention at each visit, which included study-related assessments, as described in the study protocol [20]. These clinicians were recreation therapists and social workers who provide services in the Mood Disorders clinic, trained to administer BA by completing a workshop in April 2013 and reading three BA workbooks (Michael Addis and Christopher Martell. *Overcoming Depression One Step At A time, the new behavioural activation approach to getting your life back* 2004; Jonathan Kanter, Andrew Busch and Laura Rusch. *Behavioural Activation* 2009; and Christopher Martell, Sona Dimidjian and Ruth Herman-Dunn. *Behavioural Activation for Depression, a clinician guide* 2010).

Control condition

The control group participated in a support group for 28 sessions across 18 weeks that was led by clinicians not trained in BA. Support group for the control group was unstructured and included topics for discussions selected by the group members with a facilitator present in the room (clinician); these sessions occurred over the same period of time as that of the intervention group. A nurse trained in data collection was present for each visit and collected information pertaining to suicide risk in order to ensure patient safety, as well as answer any questions pertaining to the completion of study-related instruments.

Data collection and instruments

An initial case report form (CRF) was designed to collect details at baseline about demographic data (i.e., age, sex, ethnicity, religious background, marital status, housing, education, employment, and income), suicidal behavior, and history of previous treatments. Physical measurements were also obtained at baseline and at the end of study using the SC-3315 Body Composition Analyzer (Tanita Corporation of America, Inc., IL, USA) for body composition data (i.e., weight, fat, muscle, bone mass, and metabolic age). Height and blood pressure were also measured.

We administered a number of instruments throughout the course of the study to monitor participants' progress including the Beck Depression Inventory (BDI) [23], Behavioral Activation for Depression Scale (BADS) [24], Quality of Life Enjoyment and Satisfaction Questionnaire—short form (Q-LES-Q-SF) [25], Short-Form 12

Health Survey (SF-12) [26], Work and Social Adjustment Scale (WSAS) [27], Leisure Motivation Scale (LMS) [28], EuroQol 5-Dimension 5-Level (EQ-5D-5L) [29], and Response Style Questionnaire – Ruminative Response Scale (RSQ-RRS) [30]. The BDI is a tool used to measure the severity of depression that is comprised of 21 questions assigned a score between 0 and 3, with a maximum score of 63. Scores between 19 and 29 are indicative of moderate depression while those greater than 30 are associated with severe depression. The BADS is a self-administered 25-item tool used to measure activation and avoidance of activities, such as staying in bed or thinking about one's problems, over the last 7 days, rated on a scale of "not at all" (0) to "completely" (6); higher total scores are indicative of increased activation. The Q-LES-Q-SF is a 14-item self-report instrument measuring the general quality of life (QOL) with the final score expressed as a percentage between 0 and 100%, where higher percentages are indicative of a higher QOL. WSAS is a self-report instrument measuring the level of impairment with 5 items scored between 0 (indicating no impairment) and 8 (indicating severe impairment); total scores greater than 20 indicate severe psychopathology and symptomology. The LMS is a 28-item questionnaire measuring the motivation for participating in leisure activities; this tool uses a 5-point scale for each item. The LMS generates four motivation scores: intellectual motivation, social motivation, competency or mastery motivation, and a stimulus avoidance scores, where higher scores are indicative of greater endorsement of each domain. The EQ-5D-5L questionnaire has 5 items scored from 0 to 4 and measures health state, such that higher scores are associated with poorer health. The ruminative response scale (RSS) component of the RSQ is a 22-item scale which determines an individual's tendency to participate in ruminative coping behaviors; high scores on this scale are reflective of a high frequency of ruminative behavior.

The SF-12 is a 12-item survey to evaluate general health that generates two summary scores, the physical component score (PCS) and the mental component score (MCS); these scores range between 0 and 100, where 100 is associated with the highest level of health state. For the final question on the SF-12 instrument, an additional option of "a good bit of the time" was added. To complete scoring, reports of a "a good bit of the time" for item 12 were scored as "some of the time," so as to not overestimate the effect of physical health on engagement in social activity.

Full details on when each data collection instrument was completed during the trial can be found in the protocol [20]. We also interviewed participants during the pilot trial using a qualitative study component to gather feedback on the study interventions. These results were reported previously [19]. Participants were followed up at 3 months post-study.

Study questionnaires and assessments were entered into a confidential electronic database (Research Electronic Data Capture, REDCap; http://project-redcap.org/). Physical forms with collected data were stored securely on-site at the Mood Disorders Program according to privacy regulations.

Criteria for assessing trial feasibility

The following criteria were used to assess the feasibility of the current study: (1) minimum 20% recruitment rate, (2) study completion rate of 80% (i.e., 80% of data available for the final visit, consistent with other psychotherapy trials) [31–34], and (3) 80% completion of measurement instruments (i.e., the percentage of all scales completed across all participants throughout 18 weeks).

Statistical analysis

All statistical analysis was done using R version 3.1.0 (http://www.r-project.org/) and were exploratory, therefore not intended to test the effectiveness of the intervention. Descriptive statistics are provided as mean and standard deviation (SD) or number (percent) and were used to characterize participants enrolled in the pilot study. Between-groups differences were presented as mean differences and SD. Group trajectories were plotted for each outcome to enhance visualization of group differences.

Results

Sample demographics

We recruited 20 individuals over a period of 4.5 months (18 weeks), with a DSM-5 diagnosis of major depressive disorder, with a mean age of 48.8 (SD = 9.7). Our sample consisted of 8 (40%) men and 12 (60%) women. Eighteen (90%) participants reported physical health issues, including medical comorbidity or symptoms (e.g., arthritis, chronic pain, hypertension, insomnia, migraines, and obesity) and 12 reported current alcohol use. Nineteen (95%) participants reported to be financially independent and receiving family and friend social support (e.g., from spouse, family, or friends). Less than half of participants have completed previous psychotherapy interventions for the treatment of depression. Six (30%) had previously received CBT, five (25%) participated in an emotion regulation skills group, four (20%) received occupational therapy, and five (25%) participated in a self-help group. Nearly half (45%) reported participating in general supportive counseling. Details of baseline demographics are described in Table 1.

Table 1 Baseline demographics

Characteristic	Total (***n*** = 20)	Intervention (***n*** = 10)	Control (***n*** = 10)
Men; *n* (%)	8 (40.0)	4 (40.0)	4 (40.0)
Age in years; mean (SD)	48.2 (9.6)	49.5 (9.9)	46.9 (9.6)
BMI; mean (SD)	34.4 (8.9)	35.8 (10.9)	33.1 (6.8)
Married/common law; *n* (%)	10 (50.0)	5 (50.0)	5 (50.0)
Completed post-secondary education; *n* (%)	8 (40.0)	3 (30.0)	5 (50.0)
Christian religion; *n* (%)	14 (70.0)	7 (70.0)	7 (70.0)
Have dependent children; *n* (%)	8 (40.0)	3 (30.0)	5 (50.0)
Own a house; *n* (%)	15 (75.0)	7 (70.0)	8 (80.0)
Financially independent; *n* (%)	19 (95.0)	9 (90.0)	10 (100.0)
Receiving long-term disability income; *n* (%)	8 (40.0)	3 (30.0)	5 (50.0)
Receiving social support (any)[a]; *n* (%)	19 (95.0)	9 (90.0)	10 (100.0)
Currently using alcohol; *n* (%)	12 (60.0)	6 (60.0)	6 (60.0)
History of suicide attempt; *n* (%)	3 (15.0)	2 (20.0)	1 (10.0)
Physical health issues[b]; *n* (%)	18 (90.0)	8 (80.0)	10 (100.0)
Participated in CBT; *n* (%)	6 (30.0)	2 (20.0)	4 (40.0)
Participated in emotion regulation skills group; *n* (%)	5 (25.0)	3 (30.0)	2 (20.0)
Participated in occupational therapy; *n* (%)	4 (20.0)	2 (20.0)	2 (20.0)
Participated in self-help group; *n* (%)	5 (25.0)	2 (20.0)	3 (30.0)
Participated in general supportive counseling; *n* (%)	9 (45.0)	5 (50.0)	4 (40.0)

BMI body mass index, *CBT* Cognitive Behavioral Therapy
[a]Social support is defined as support provided by a spouse, family members, or friends
[b]Health issues include any physical or mental comorbidity or symptoms (e.g., arthritis, chronic pain, hypertension, insomnia, migraines, and obesity)

Feasibility results

Based on our pre-defined criteria, we assessed the feasibility of the main BRAVE trial. Of the 27 individuals approached, we successfully recruited 20 people over 4.5 months (18 weeks) to yield a recruitment rate of 74%, which fulfills our first feasibility recruitment criterion. Loss to follow-up at week 18 was moderate, with four individuals not completing the study and failing to complete the final visit; therefore, we had an overall study completion rate of 80% (second feasibility criterion). However, all four patients who dropped out were from the control group, yielding a 100% completion rate for the treatment arm and 60% for the control group. Completeness of study measurements was also adequate; intervention versus control study measurement completion rates were 85% versus 61% for the BDI, 74% versus 85% for the BADS, 87% versus 80% for the Q-LES-Q-SF, 90% versus 77% for the WSAS, 90% versus 80% for the LMS, 85% versus 80% for the EQ-5D-5L, 90% versus 80% for the RSQ-RRS instrument, and 90% versus 85% for the SF-12, respectively. The average completion rate for study instruments was 86% for the intervention group and 79% for the control group; the overall completeness of measurements for all participants throughout the study was 82%, thus fulfilling our third feasibility criterion.

Therapists providing the intervention stated that a group size between 8 and 12 participants is ideal for them to manage the group at each session. This was based on the therapists' experience in the group setting, the size of meeting rooms available, and the time allocated for each session (2 h). The therapists also provided feedback that two clinicians are needed per group (one therapist runs the group and one therapist cofacilitates). No other resources were identified as necessary to complete the intervention in a group format.

Intervention outcomes

We evaluated seven study measures over the course of the 18-week study period. We provide the mean and SD of these measures for both groups at baseline and end of study (Table 2). Scores on the BDI were higher among the control group, but decreased gradually for both groups across the study period (Fig. 2). No harms were reported for either group.

Follow-up at 3 months

We also conducted follow-up interviews with both control and intervention groups at 3 months following the study. Completion rates for follow-up interviews were 50% for both the control and treatment groups. Mean

Table 2 Mean and standard deviation (SD) for intervention and control groups at baseline and end of the pilot study

Assessments	Scores; mean (SD)	
	Baseline (screening)	End of study (week 18)
Treatment		
BDI	29.66 (3.29)	27.23 (3.99)
BADS	64.99 (5.92)	67.10 (7.49)
Q-LES-Q-SF	35.32 (3.66)	31.10 (4.27)
WSAS	26.37 (1.71)	29.55 (1.95)
LMS: intellectual score	39.03 (3.45)	37.77 (3.57)
LMS: social score	28.63 (3.37)	31.51 (2.67)
LMS: competency score	29.85 (3.32)	35.14 (3.05)
LMS: stimulus avoidance score	42.88 (3.01)	39.98 (3.30)
EQ-5D-5 L (health state index score)	43.19 (4.61)	43.45 (8.92)
RSQ-RRS	62.04 (3.13)	63.58 (3.39)
SF-12: PCS	33.64 (12.36)	35.17 (13.02)
SF-12: MCS	28.70 (5.94)	27.56 (10.35)
Control		
BDI	34.69 (3.32)	33.41 (4.10)
BADS	52.26 (7.34)	61.72 (9.62)
Q-LES-Q-SF	31.30 (3.68)	33.95 (4.60)
WSAS	30.48 (1.73)	31.44 (2.04)
LMS: intellectual score	36.67 (3.47)	38.51 (3.70)
LMS: social score	28.86 (3.39)	31.32 (2.75)
LMS: competency score	35.73 (3.36)	35.64 (3.19)
LMS: stimulus avoidance score	29.39 (3.03)	32.69 (3.50)
EQ-5D-5 L (health state index score)	50.51 (4.73)	60.51 (8.97)
RSQ-RRS	67.43 (3.32)	68.00 (3.68)
SF-12: PCS	40.35 (6.87)	36.93 (6.34)
SF-12: MCS	24.63 (7.82)	30.48 (5.79)

BDI Beck Depression Inventory (21 items, score range 0–63, high scores associated with greater depression); *BADS* Behavioral Activation in Depression Scale (25 items, items scored 0–6, higher score means greater activation); *Q-LES-Q-SF* Quality of Life, Enjoyment, and Satisfaction Questionnaire—Short Form (score ranges from 0–100%; maximum score associated with higher quality of life); *WSAS* Work and Social Adjustment Scale (score range 0–40, maximum score is indicative of greater impairment); *LMS* Leisure Motivation Scale (28-item, items scored 0 to 5, maximum score for each of four domains is associated with greater endorsement of each domain); *EQ-5D-5L* EuroQol 5-Dimension 5-Level (5-item, scored 0 to 5, maximum score indicating poor health state); *RSQ-RRS* Response Style Questionnaire, Ruminative Response Scale (22 items, 4-point Likert scale, high scores indicative of ruminative tendencies); *SF-12* Health Survey Short-Form 12 (score range 0–100, maximum score associated with highest health state)

BDI scores were 30 (SD = 14.40) and 36.40 (SD = 15.45) for the intervention and control groups, respectively, thus increasing slightly for both groups compared to the final study visit.

Anthropometry and body composition

We obtained an extensive record of participants' physical measurements and body composition using the SC-3315 Body Composition Analyzer (Tanita Corporation of America, Inc., IL, USA) to assess changes in overall metabolic and physical health during the study (Table 3). Changes in these measures (computed as the value at the end of study minus the baseline value) were explored in order to report if any differences exist between the change observed in the intervention group versus the control group on biometric variables such as BMI, weight, and blood pressure. It is possible that BA may impact physical measures, perhaps mediated through mood or other factors; therefore, we report whether preliminary data demonstrate any difference between groups on these variables. Generally, measurements for the intervention group demonstrated positive changes; weight, waist circumference, and fat mass decreased from study baseline to week 18. Many of the measurements for the control group either increased slightly or remained constant throughout the study.

Discussion

The study sought to evaluate the feasibility of conducting a full randomized controlled trial to investigate the effectiveness of BA in the treatment of depression. The pilot study showed it is feasible to conduct a large BA trial based on meeting relevant feasibility criteria including recruitment rate, study completion rate, and completion of study measurement scales, though the loss to follow-up of the control group was high. This, however, is not inconsistent with other pilot trials investigating BA in the treatment of depression, which report completion rates such as 67% in the wait-list condition [33]. In order to limit the risk of loss to follow-up, participants recruited for the full trial will be compensated with parking vouchers or bus tickets. Rates of follow-up interviews at 3 months post-study were found to be low but equal between the intervention and control groups, demonstrating that further effort should be made to follow-up with participants following the end of the program. Participants will be provided the option of completing interviews over the phone or in person in order to improve adherence, accommodate participant availability, and decrease patient burden.

The BRAVE pilot trial also sought to explore the potential effectiveness of BA on depression symptoms and quality of life measures in adults with depression; preliminary data demonstrate no noticeable difference between intervention and control groups on all study measures. A full trial powered to detect clinically significant changes is needed in order to determine the effect of BA.

Behavioral activation used for the treatment of depression in a group format is practical, simple, and easy to administer; however, further research is required to understand the feasibility of this approach in a clinical

setting, therefore necessitating a full trial. There are few existing trials on behavioral activation as a group therapy specifically, and further well-designed trials are needed to determine whether the use of this intervention as a therapy for patients with depression is effective in our setting or other avenues of clinical practice. This study has been designed to address these issues with proper study design and relevant methodology. RCTs effectively demonstrate differences between groups while considering relevant known confounding factors, thus making them the gold standard for clinical evidence. We had the opportunity to monitor the progress of a specific cohort of patients with depression throughout the treatment intervention and evaluate differences between groups. We were also able to observe this cohort from study initiation to completion to evaluate the feasibility of a full trial to test the effectiveness of behavioral activation in the treatment of depression.

Key learning points

Based on our experiences with this pilot trial, we observed relatively high attrition rates, where all four individuals who did not complete the study participated in the control arm. These attrition rates are consistent with literature on psychotherapy trials, although the pattern of higher drop-out among control participants has not been previously apparent [31]. It is challenging to ascertain the true effect of this intervention relative to the control condition, as the nature of this control group is influenced by group effects, social interactions among participants, and possible attention received from group facilitators above and beyond usual care. This may indicate the need for potential modifications to the control arm of this trial in order to avoid these problems within the larger investigation. After exploring potential reasons for high attrition in the control arm, we concluded that the therapy provided in this arm of the trial (i.e., support group in addition to usual care) was not sufficient to retain participants in the study. Given these observations, it is possible that these participants are not benefitting from the study in any way and therefore lose interest over time. The time involved in conducting weekly visits and administering multiple questionnaires was considerable, and therefore may have also influenced attrition rates or completeness of assessments. We asked participants for their feedback on the pilot trial, and they reported that they wanted the intervention to be offered to all participants at the end of the study period [35]. Feedback received from participants in the control group stated that the group was not helpful for them [19]. Offering the intervention for the control group at the end of the trial may enhance motivation to complete the study period and improve the retention of the control group in the study. Given this feedback, we changed our plans for the control group for the main trial to use a wait-list group as a comparator, where participants in this group will be offered the intervention after the waiting period (approximately 18 weeks).

Participants in the intervention group were more eager to complete the study and all associated assessments, suggesting that these participants may have found it helpful in dealing with their depressive disorder, hence showing the intervention is acceptable and feasible to administer in a larger trial. This strengthens the rationale for performing the larger study, where this intervention can be explored in depth.

Unfortunately, we also observed low response rates in both groups for follow-up interviews at 3 months after study completion. An important concern in this study was loss to follow-up of the control sample where 40% of the control participants initially recruited dropped out from the study prior to completion. In the future, greater efforts should be made to maintain contact with participants following completion of the study. It may also be useful to provide the option of online completion and telephone interviews in addition to in person interviews to minimize burden to participants and encourage uptake of the follow-up. This will help to determine whether the beneficial effects of BA can be maintained following treatment completion.

The long-term goals of this program are to guide the decision-making process through evaluation of the best treatment options, with the collective efforts of primary care providers, health care specialists, and patients themselves and their families. We also intend for our study findings to be used in the development of guidelines for BA group therapy for depression.

Following the pilot trial, we have amended the study design such that participants randomized to the control condition were later given access to BA treatment. This change was made in keeping with patient feedback about the study collected through qualitative interviews post-study. Given that the study length is 18 weeks, it is possible that participants randomized to the control/wait-list condition will be lost to follow-up before the end of the wait-list period. In order to mediate this challenge, participants will be in contact with a research staff on a weekly basis for 18 weeks, during which time they will complete weekly study instruments. Weekly contact will mitigate the effect that a loss of contact may have on participant retention. No changes were made to the eligibility criteria or study intervention length, though the follow-up duration was extended. We increased the post-study follow-up to 3, 6, and 12 months in order to understand the sustainability of changes to mood and quality of life measures up until a year after the program is completed, given the chronicity of depressive disorders.

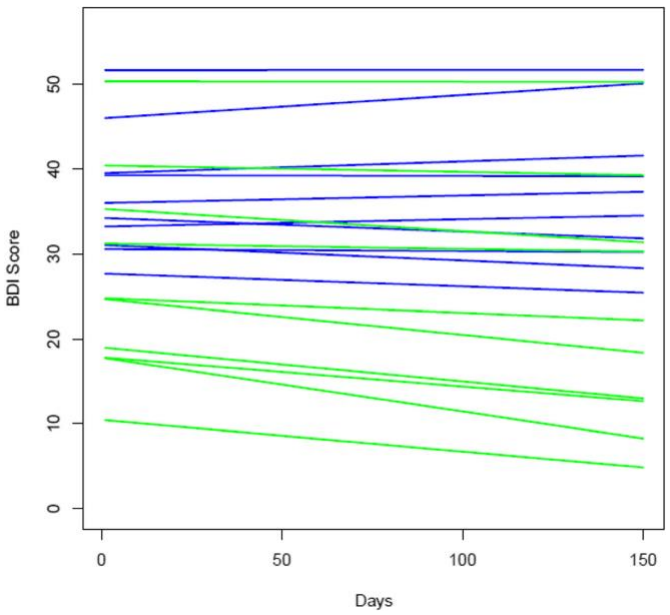

Fig. 2 Beck Depression Inventory (BDI) scores among participant groups over the study period ($n = 20$). Note: Control = blue; BA = green. For four participants missing the final BDI scores, the last observations were carried forward in this figure

Table 3 Descriptive summary of participants' physiology and body composition

	Intervention		Control	
Assessment, mean (standard deviation)	Baseline (week 1)	End of study (week 18)	Baseline (week 1)	End of study (week 18)
Height, cm (SD)	168.0 (9.8)	168.9 (9.8)	172.2 (12.3)	172.2 (12.3)
Weight, kg (SD)	93.1 (19.6)	90.4 (16.2)	100.7 (30.0)	100.4 (32.0)
BMI, kg/m^2 (SD)	33.8 (10.9)	33.6 (7.5)	33.6 (6.8)	32.8 (5.5)
Waist circumference, cm (SD)	105.7 (12.8)	102.7 (11.9)	107.8 (19.3)	111.9 (13.4)
Hip circumference, cm (SD)	115.1 (13.0)	115.6 (14.9)	111.7 (19.0)	115.6 (14.2)
Blood pressure, systolic, mm Hg (SD)	125.7 (15.6)	126.9 (12.0)	127.9 (17.5)	132.3 (16.8)
Blood pressure, diastolic, mm Hg (SD)	77.3 (7.7)	81.9 (7.1)	81.5 (7.7)	80.4 (5.1)
Heart rate, bpm (SD)	82.5 (11.3)	82.8 (19.4)	79.3 (15.5)	77.0 (13.9)
Total fat, % (SD)	37.9 (11.9)	37.5 (11.7)	37.0 (10.6)	37.0 (8.2)
Fat mass, kg (SD)	36.2 (16.8)	34.3 (15.7)	38.7 (19.7)	37.9 (18.1)
Fat free mass, kg (SD)	56.3 (10.6)	54.3 (9.0)	61.1 (15.3)	61.1 (17.3)
Total body water, % (SD)	44. 1 (6.9)	43.7 (6.9)	45.5 (6.7)	44.9 (4.2)
Total body water mass, kg (SD)	40.2 (8.6)	38.1 (6.0)	42.0 (10.7)	44.1 (13.8)
Muscle mass, kg (SD)	53.4 (10.1)	51.5 (8.6)	58.1 (14.6)	58.1 (16.5)
Bone mass, kg (SD)	2.8 (0.5)	2.7 (0.4)	3.0 (0.7)	3.0 (0.8)
BMR, kJ (SD)	7163.4 (1320.0)	6875.6 (1011.1)	7820.4 (2011.3)	7807.9 (2280.4)
Metabolic age, years (SD)	55.6 (12.3)	57.6 (10.5)	53.5 (14.3)	56.9 (7.2)

BMI body mass index, *BMR* basal metabolic rate

Study strengths and limitations

This study included a comprehensive set of outcomes including depression severity, quality of life, behavioral activation, motivation, and physical health. We also collected detailed physical measurements using the Body Composition Analyzer to examine changes in body composition as an overall picture of the participants' health.

The current pilot study design did not allow for statistical conclusions, and thus, we cannot comment on the effectiveness of the intervention based on the current pilot data; however, we were able to test the intervention feasibility. A limitation of the current pilot study is that we are unable to comment on or report whether the planned changes to the control group condition will be effective in mediating the issue of loss to follow-up and increasing retention. Furthermore, despite making use of validated instruments to assess outcomes of this intervention, these self-reported measures are at risk for recall bias as well as potentially social desirability bias.

A further limitation of the current study design is that since participants were not excluded if they were in CBT or other programs at the time of participation, and since there was no restriction for when previous programs were completed, the effects of CBT and other programs may impact mood symptoms and quality of life reported in this study. Due to the randomized design of this pilot trial, it is expected that this effect would be balanced between both groups. While a possible confounder, the purpose of this trial is to investigate the potential effectiveness of group BA in addition to care as usual; therefore, participation in co-intervention does not obscure the study objectives.

Conclusions

This pilot study assessed the feasibility of conducting the full BRAVE randomized trial in a tertiary care mood disorders hospital-based clinic setting. We are able to conclude that based on our feasibility criteria as well as our study design, methodology, and comprehensive assessment of outcomes, the full investigation is likely to be conducted to evaluate the effectiveness of BA group therapy as a potential therapeutic approach to the treatment of major depression in adults. The caveat is the loss to follow-up of the control group. We will keep in mind the loss to follow-up challenge and have made changes in the plans regarding the selection of the comparator group. We will change the control condition to a wait-list followed by receiving the intervention and will compare the groups based on intervention versus wait-list conditions. We will also increase the post-intervention follow-up duration and have developed strategies to facilitate more successful follow-up in the main trial.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s40814-020-00596-z.

Additional file 1. CONSORT checklist.

Abbreviations

CBT: Cognitive behavioral therapy; BA: Behavioral activation; BRAVE: BehavioRal ActiVation for reducing dEpressive symptoms and improving quality of life in patients with depression; HIREB: Hamilton Integrated Research Ethics Board; CRF: Case report form; BDI: Beck Depression Inventory; BADS: Behavioral Activation for Depression Scale; Q-LES-Q-SF: Quality of Life, Enjoyment, and Satisfaction Questionnaire—short form; WSAS: Work and Social Adjustment Scale; LMS: Leisure Motivation Scale; EQ-5D-5L: EuroQol 5-Dimension; RSQ-RRS: Response Style Questionnaire, Ruminative Response Scale; RedCap: Research Electronic Data Capture; REML: Restricted maximum likelihood

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Authors' contributions

AD drafted the pilot manuscript. ZS conceived the study in addition to drafting the pilot manuscript. MB and BBD were responsible for addressing data queries, organizing and analyzing data, and drafting the manuscript. MB assisted in analyzing data and drafting the manuscript. KL, KM, and JW contributed to the design of the intervention and selection of assessment tools, wrote the intervention manual, and assisted with writing the manuscript. PL assisted with establishing the study design, developed and facilitated pharmacotherapy education, selected the questionnaires pertaining to pharmacotherapy, and contributed to the writing of the manuscript. SS and SC were responsible for designing the control arm of the study. LO and MV were responsible for the qualitative component of this study and its design, as well as revising the manuscript. LG coordinated the study and assisted with study design development, as well as contributing to the writing of the manuscript. BK assisted in study design and data collection. SC, SS, and SG assisted in running the intervention as well as contributing to the writing of the manuscript. FX assisted in the economic objective design and methods of the study and contributed to the manuscript writing. GG contributed to developing trial design components including comparator selection and randomization, as well as writing and drafting the manuscript. LT contributed to trial design, selection of study aims, and statistical analyses. The authors read and approved the final manuscript.

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Availability of data and materials

Raw data and materials for the study are available upon request.

Ethics approval and consent to participate

This trial was approved by the Hamilton Integrated Research Ethics Board (HIREB: 14-042).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

8.3 CHAPTER 3: Additional file 1. CONSORT checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Ch 3, p. 30
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Ch 3, p. 32
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Ch 3, p. 33-34
	2b	Specific objectives or hypotheses	Ch 3, p. 34
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Ch 3, p. 37
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Ch 3, p. 37
Participants	4a	Eligibility criteria for participants	Ch 3, p. 35
	4b	Settings and locations where the data were collected	Ch 3, p. 34-35
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Ch 3, p. 36-37
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Ch 3, p. 37-38
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	Ch 3, p. 35
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Ch 3, p. 37
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Ch 3, p. 37
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Ch 3, p. 37
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Ch 3, p. 37
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Ch 3, p. 37

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	Ch 3, p. 37
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Ch 3, p. 38-39
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Ch 3, p. 38-39
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Ch 3, p. 39; Figure 1 (p. 49)
	13b	For each group, losses and exclusions after randomisation, together with reasons	Ch 3, p. 39
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Ch 3, p.35
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Ch 3, p. 36
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1 (p. 49)
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Ch 3, p. 39-41
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Ch 3, p. 41
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Ch 3, p. 39
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Ch 3, p. 43
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Ch 3, p. 43
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Ch 3, p.42
Other information			
Registration	23	Registration number and name of trial registry	Ch 3, p.34
Protocol	24	Where the full trial protocol can be accessed, if available	Unpublished, n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Ch 3, p.44

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

8.4 CHAPTER 4, Supplementary File 1, PRISMA-P Checklist

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Corresponding Page/Line Number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1, Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1, Line 7-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8, Line 310-317
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 8, Line 322-325
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 4, Line 156-165
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4, Line 168-175
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 4-6, Line 178-257
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 6, Line 271-280
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 5, Table 1, Line 282
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 7, Line 286-293

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 7, Line 296-305
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 8, Line 307-326
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 8, Line 307-326
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 6, Line 259-269
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 8, Line 328-334
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 8-9, Line 336-359
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 8-9, Line 336-359
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Open access Protocol

BMJ Open

Identifying patient-important outcomes for treatment of bipolar disorder: a systematic review protocol

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ABSTRACT

Introduction Treatment of bipolar disorder is the focus of several clinical trials, however the understanding of the outcomes for establishing treatment effectiveness within these trials is limited. Further, there is limited literature which reports on the outcomes considered to be important to patients, indicating that patient perspectives are often not considered when selecting outcomes of effectiveness within trials. This protocol describes a systematic review which aims to describe the outcomes being used within trials to measure treatment effectiveness, commenting on the inclusion of patient-important outcomes within previous trials.

Methods and analysis This protocol is reported using the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols statement. OVID MEDLINE, OVID Embase, OVID APA PsycINFO, Web of Science, the Wiley Cochrane Library, ClinicalTrials.gov and the International Clinical Trials Registry Platform databases will be searched for eligible studies. Screening, full-text and data extraction stages will be completed in duplicate using the Covidence platform for systematic reviews. Eligible studies will include clinical trials of interventions in bipolar disorder, in order to identify outcomes used to assess treatment effectiveness, and qualitative studies, to determine which outcomes have been reported as important by patients. Risk of bias for included studies will be assessed using the Cochrane Risk of Bias Tool for randomised controlled trials, and the Newcastle-Ottawa Scale for observational research.

Ethics and dissemination This review will involve dissemination to key stakeholders, including primary end users such as patients, clinicians and trialists. Knowledge translation tools will be generated to share the relevant conclusions of this review. Results will be communicated to the scientific community through peer-reviewed publications, conferences and workshops. No ethics approval will be sought as this study is based on literature.

PROSPERO registration number CRD42021214435.

Strengths and limitations of this study

- ► The proposed review employs a two-pronged approach to appraise outcomes used by trialists to assess treatment effectiveness in clinical trials of bipolar disorder I and describe patient-important outcomes.
- ► Strong methodological design developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol guidelines for transparent reporting.
- ► The planned analysis for reporting trials outcomes includes stratification of outcomes according to population, intervention type and mood state.
- ► Later analysis, including ability to conduct thematic analysis, may be impacted by large variability in the types of outcomes being used in trials of bipolar disorder I.
- ► Restriction to include studies published in English may lead to language bias.

INTRODUCTION

Bipolar disorder type 1 (BD-I) is a chronic mood disorder associated with severe depressive and manic episodes.[1] Though among the top eight most prevalent conditions worldwide,[2] BD-I is very difficult to diagnose as a result of heterogeneous illness presentation which often leads to misdiagnosis as major depressive disorder.[3 4] Wide variability in symptom presentation, often impacted by age of diagnosis and other sociodemographic factors,[5–7] presents challenges not only to diagnosis, but also to the selection of an appropriate course of treatment.[8] BD-I has significant impact on patients' lives including recurrence of psychiatric symptoms,[9] comorbid psychiatric and medical disorders,[10 11] loss of function,[12 13] increased risk of mortality,[14 15] poor quality of life,[16 17] cognitive difficulties[18] among others. These pervasive and diverse impacts highlight the importance of determining which treatments most effectively manage specific outcomes, and for whom specific outcomes are of particular concern.

Current treatment of BD-I is medication paired with adjunct psychotherapy and is typically indicated by whether depressive or manic symptoms are more dominant within

a particular individual. Though medications can be effective in managing mood symptoms, these symptoms and others, such as cognitive and metabolic changes, are often persistent and require adjunct psychotherapy and other interventions.[19] Indeed, current guidelines recommend the combination of psychotherapy and medication in order to obtain successful symptom management and remission.[19] Several reviews and guidelines have been published which provide evidence for such treatments, however, there is little consensus on which interventions are most effective and for what outcomes.

Further, little research investigates which treatment outcomes are most important to patients with BD-I. There is great variety among trials in the outcomes selected to indicate treatment success, with some studies considering treatments to be effective if patients achieve reductions in number of episodes or hospitalisations,[20] some looking for reductions in mood symptom severity or burden,[21] and others using measures such as the number of days without mood symptoms as an indicator of success.[22] Even in trials which measure effectiveness using the same type of outcome or instrument, time points, thresholds and definitions of effectiveness can differ greatly. While variability in outcomes is expected, this raises questions on whether these outcomes, and the way they are measured, reflect patient perspectives or can appropriately approximate the outcomes considered to be important to patients.

Some research has identified the weight or relative importance of existing outcomes often examined in trials, such as depressive and manic symptoms, social functioning, and quality of life, in addition to collecting important outcomes through focus groups.[23] However, such studies are often small convenience samples, potentially failing to reflect the full range of outcomes deemed important by patients, or represent the perspectives of patients at varied phases of the disorder, such as those in active and acute phases.[23] The exclusion of patients' specific perspectives on what they need out of treatment for bipolar disorder emphasizes the need to evaluate the extent to which trial outcomes are in agreement with patient perspectives. Further, it is essential that this assessment is disorder-specific, given that experiences of BD-I are distinct and relevant outcomes may differ importantly from those of other similar disorders. In order to do so, it is essential to not only appraise the available literature related to outcome measurements, but also the literature pertaining to patient-important outcomes (PIO) in BD-I.

Rationale

Reviews which aim to systematically examine and describe the outcomes used within clinical trials of treatments for BD-I to establish treatment effectiveness are needed. Given that BD-I is distinct from other bipolar spectrum disorders, it is essential to conduct this review within BD-I patients specifically. Such reviews are essential in order to facilitate an understanding of the inclusion of PIOs in trials of BD-I. Therefore, it is important to examine the level of agreement between trialists, and moreover between trialists and patients, in order to determine whether measures of effectiveness truly reflect the needs of patient populations. This review will aim to appraise the outcomes used as a means to support future investigation of the need for a core outcome set for trials of BD-I.

Objectives

The purpose of this systematic review is to investigate the outcomes used to measure treatment effectiveness within trials for treatment of BD-I. Specifically, the aims of this review are:

1. Summarise the outcomes (clinical scales, biological or social markers, etc) used within clinical trials to measure treatment effectiveness, and report how these outcomes are assessed.
2. Review the observational and qualitative research related to PIO for bipolar disorder (ie, goals and markers of treatment success identified as important by patients).

METHODS AND ANALYSIS

We will conduct a systematic review of outcomes reported in published trials and observational/qualitative research. The reporting of this protocol reflects the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Protocols statement.[24]

Two search strategies will be used in order to investigate our two objectives of interest. The specific inclusion and exclusion criteria are described for each objective. Further, the population, intervention, comparators, outcomes, timing and setting for studies meeting inclusion are specifically outlined.

Eligibility criteria for objective 1

The inclusion criteria for objective 1 is randomised controlled trials (RCTs) testing the effectiveness of treatment interventions in BD-I that report intervention outcomes.

Participant population

Trials testing treatments within (1) patients with BD-I and (2) a mixed sample of participants BD-I and II, will meet inclusion. While objective 1 endeavours to report on outcomes used in trials of BD-I specifically, trials with mixed BD-I and II samples will be included since a large proportion of trials evaluating treatment for BD-I involve mixed samples, and exclusion of these studies would preclude rigorous appraisal of trial outcomes.

Intervention

Trials investigating psychotherapy and pharmacotherapy interventions will meet inclusion. Psychotherapies included in this review will include any psychotherapeutic intervention specifically intended to treat bipolar disorder, such as cognitive–behavioural therapy (CBT), behavioural activation (BA), interpersonal psychotherapy, interpersonal and social rhythm therapy (IPSRT), family-focused therapy (FFT) and psychoeducation. Psychotherapy interventions were selected for inclusion based

on their classification as a (1) form of psychotherapy and (2) previous evidence of effectiveness in treatment of bipolar disorder. Pharmacotherapeutic interventions will include medications being tested for effectiveness in treating symptoms of bipolar disorder. Trials meeting inclusion will include an intervention, a comparator and at least one outcome measure or end point. Trials which include both group and individual-based interventions will be eligible for this review. Interventions which include combination therapies (ie, medication and a form of psychotherapy) will be included.

Comparators

No restrictions will be placed on comparators.

Outcomes

All outcomes pertaining to effectiveness of interventions will be included (ie, clinical scales, biological or social markers).

Studies

RCTs will be included with no restrictions on study setting (ie, clinic or community-based settings). No restrictions on age, country, income status or type of recruitment will be applied. Only complete studies in humans and written in the English language will be eligible. In addition to the identified databases, clinical trial registries will be searched; in the case of registration numbers with multiple associated publications, the most recent publication will be selected for inclusion if not already identified in the search.

Time

No restrictions on time will be applied.

Exclusion criteria

Animal studies, preliminary reports, pilot/feasibility studies, abstracts, presentations, interim-analyses and trials which investigate interventions other than those outlined above will be excluded. Interventions designed to address challenges within families, or couples that are explicitly not intended to treat bipolar disorder will not be included. Trials testing the effects of discontinuing treatment will not be eligible for inclusion. Studies investigating pharmacotherapeutics and psychotherapeutics not intended for treating bipolar disorder (ie, treating obesity or medication-related side effects), will be excluded.

Eligibility criteria for objective 2

Participant population

Studies with a BD-I population.

Outcomes

PIO (ie, any outcome, marker or measure) reported by participants by BD-I.

Studies

The inclusion criteria for objective 2 are observational and qualitative studies. Qualitative studies meeting the inclusion criteria will be those involving focus groups and interviews to determine what outcomes are reported by patients with BD-I to be important for measuring treatment success. There will be no restrictions on age, country, income status, type of recruitment or study setting.

Time

There will be no restrictions based on time.

Exclusion criteria

The exclusion criteria for objective 2 are studies for which the aims are unrelated to identifying PIO, and studies whose population is not patients with BD-I.

Outcomes and prioritisation

The first objective of this systematic review will be to report the outcomes used to measure the effectiveness of the treatment being tested. These outcomes will be extracted from RCTs, and may include depressive or manic symptoms, quality of life measurements, or outcomes related to social adversity, such as employment. Given that the population of interest for this review is patients with BD-I, outcomes explored within these patients will qualify for extraction. Therefore, extracted outcomes will be stratified based on population, with outcomes in studies of BDI only being reported separately from outcomes in studies with mixed BDI and II samples.

The second objective will be to examine the literature pertaining to PIO for BD-I. Observational and qualitative studies will be examined to determine which outcomes are reported by patients to be important measures of treatment success.

Information sources

The selection of databases and the corresponding search strategies were developed through partnership with a Clinical Services Librarian from the Health Sciences Library at McMaster University. Eligible studies will be identified through searches of the following databases: OVID MEDLINE (1946-Current), OVID Embase (1974-Current), OVID APA PsycINFO (1987-Current), Web of Science (1976-Current), the Wiley Cochrane Library (1999-Current), ClinicalTrials.gov and the International Clinical Trials Registry Platform. Databases will be searched for all sources of literature, including grey literature, from inception to the date of search, which will be reported in the final systematic review. The search strategy for each objective for one database is described in table 1.

Data management

Articles identified through the search strategy will be imported to Zotero, and then the Covidence platform.[25] Title and abstract, full-text and data extraction phases will be managed through this platform. Members of the research team who have not used Covidence before will be trained through online tutorials and an additional training session will be

Table 1 Search strategy

Database	Search strategy
OVID MEDLINE	Search Strategy for Objective One 1. exp "Bipolar and Related Disorders"/ 2. bipolar.mp. 3. (manic adj3 (disorder* or state*)).mp. 4. or/1–3 5. clinical trial/ or clinical trial, phase iii/ or clinical trial, phase iv/ or exp controlled clinical trial/ 6. clinical trials as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or exp controlled clinical trials as topic/ 7. clinical trial*.mp. 8. random*.mp. 9. Random Allocation/ 10. double-blind method/ or single-blind method/ 11. ((single or double or triple or treble) adj3 (blind* or mask* or method*)).mp. 12. or/5–11 13. 4 and 12 Search Strategy for Objective Two 1. exp "Bipolar and Related Disorders"/ 2. bipolar.mp. 3. (manic adj3 (disorder* or state*)).mp. 4. or/1–3 5. observational study/ 6. (observational adj3 (stud* or design*)).mp. 7. qualitative research/ 8. empirical research/ 9. personal narrative/ 10. interview/ 11. Interviews as Topic/ 12. "Surveys and Questionnaires"/ 13. Self Report/ 14. (qualitative or empirical research or narrative* or interview* or survey* or questionnaire* or self-report).mp. 15. or/5–14 16. 4 and 15

conducted with all reviewers to ensure familiarity and consistency of use at all stages. A calibration phase will be completed where reviewers will be asked to screen 25 articles on the platform, and responses will be reviewed to ensure understanding of the protocol and criteria.

Selection process

Each citation identified will be reviewed by two reviewers independently at title and abstract and then full-text stages, using the eligibility criteria described above. Those citations meeting eligibility during these phases will be included for data extraction. Disagreements between reviewers will be resolved by another reviewer to reach consensus. Level of agreement between reviewers will be assessed and the kappa statistic will be reported.

A flow diagram (figure 1) summarising the screening of all studies will be included in the final review. Studies included in the data extraction phase will be described in a table, which will be structured in keeping with the guidelines specified by the PRISMA guidelines.[26] Reasons for exclusion or inclusion will be reported.

Data collection process

Data extraction forms will be built on Covidence and completed blindly, in duplicate. Separate data extraction forms will be constructed for objective 1 and 2, and the forms will be pilot tested by all reviewers to ensure the quality of the extraction and the comprehensiveness of the forms. The data collection forms will include the following items: author, year, country, title of journal, number of participants, name of intervention, diagnosis, diagnostic criteria, mood state, phase of disorder, inclusion criteria, exclusion criteria, type of population (ie, inpatient, outpatient or community), ethnicity, cultural factors, mean age, details on special populations (low income, pregnant, veteran, etc) and study design. Where data are missing, authors will be contacted, and all correspondence will be noted.

For objective 1, the data collection form will also include details on form of treatment (ie, CBT, BA,

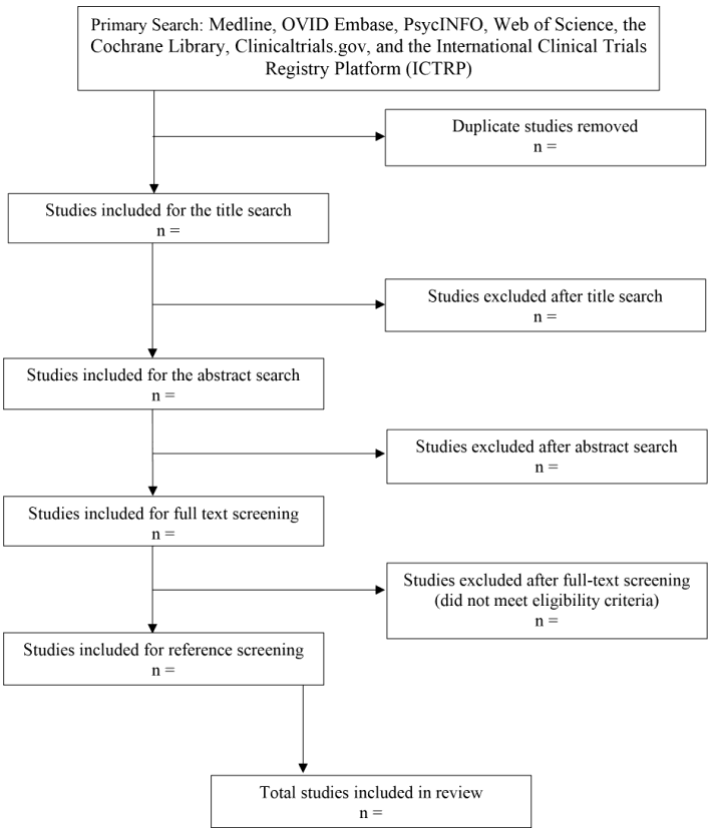

Figure 1 Flow diagram of included studies. The following flow diagram will be used in the final review to describe each phase of review, and the final number of included studies.

etc). Study outcomes used to assess effectiveness in each study will be recorded, and the following information about these outcomes will be extracted: the type of outcome, the definition of the outcome, how often it is measured, and how it is measured. For objective 2, the following additional information will be extracted from the observational and qualitative literature: the outcomes reported by patients to be important as markers of treatment success and the themes of PIO reported.

The anticipated date for data collection for objective 1 is December 2021, and objective 2 is February 2022.

Risk of bias assessment

In duplicate, individual studies will be examined to assess the quality of the included studies. For trials assessed through objective 1, the Cochrane Risk of Bias Tool[27] will be used. The standard cut offs reported for this tool in the literature is a score of 6 or higher; studies meeting this cut-off will be included in subgroup analysis. For studies with an observational or qualitative design in objective 2, the Newcastle-Ottawa Scale[28] will be used. Studies scoring 5 or lower on this tool will be included in subgroup analysis.

Data synthesis

The outcomes extracted for the first objective of this systematic review will be qualitatively reported. Descriptions (type of outcome, definition, method and timing of outcome data collection) of outcomes will be provided for each eligible study. Reporting of outcomes will also be stratified by population (BD-I, or BD-I and II mixed populations), then by type of intervention (psychotherapy, pharmacotherapy or a combination) and by mood state, for studies where this information is provided. The rationality for the selection of outcomes will be summarised for each study.

For the second research objective, thematic analysis will be conducted to group outcomes reported by patients to be important. Thematic analysis will be sensitive to the types of outcomes reported by patients, and therefore, grouping will be selected based on the themes that appear. Results of qualitative and observational studies will be summarised.

Within both objectives, stratification according to sociodemographic and clinical variables will be conducted to explore the relevance of these characteristics to PIO. For objective 1, reported outcomes will be stratified by sociodemographic characteristics including ethnicity, age, sex and gender, and clinical characteristics like phase of disorder, disorder onset and additional treatment, where data is sufficient and available. For objective 2, analysis of PIO based on sociodemographic details such as ethnicity, age, sex and gender can be explored to identify differences in outcomes based on important identity factors. A qualitative summary of differences in outcomes reported will be presented. Where sufficient clinical data is available related to phase of disorder, disorder onset, and additional treatment, differences in PIO can be explored.

Implications

Through objectives one and two, this review aims to systematically appraise the literature in order to determine the current outcomes being used within trials, how these outcomes were measured and to whom they apply to establish treatment success. Through this study, we will draw conclusions on what outcome and endpoints exist within trials, determine how these outcomes were measured, and examine the extent to which PIO are included. Guided by the review findings, insight on relevant factors (mood state, phase of disorder, social factors, etc) will precipitate a more precise approach for the possible development of a core outcome set for BD-I. Planned stratification by intervention type, phase of disorder, and other important social factors will contribute to an understanding of the specific types of outcomes used for establishing the effectiveness of certain interventions, and uncover which outcomes are important given relevant social factors. The focus on the BD-I population will precipitate appropriate comparison of the outcomes of effectiveness used in trials to those reported as important by patients, in keeping with a precision-medicine approach.

Limitations

The planned review has limitations. The first objective of this review will include only a subset of the possible medications or therapies that have been previously tested in patients with BD-I, meaning that trials of medications or treatment for conditions or symptoms distinct from their BD-I diagnosis (ie, drugs targeting obesity, medication-related side effects) will not be included. This review will be limited to studies in English, which may lead to language bias.

Patient and public involvement

There was no patient or public involvement in the conception of this systematic review protocol.

ETHICS AND DISSEMINATION

The findings of this systematic review will be disseminated with important stakeholders and relevant communities. This review will provide a systematic appraisal of the outcomes used in trials to demonstrate effectiveness, as well as those that are reported by patients to be important. Through ongoing collaborations and partnerships with tertiary care centres, we aim to circulate findings to clinicians and patients. Tools such as summary reports and guidelines will be constructed in order to translate the results of this study to these primary end users. Findings will also be shared with researchers, knowledge users, learners and clinicians through conference presentations, workshops and scientific publications.

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Contributors AD'E: contributed to the conception and design of the study and study protocol, the writing and final review of the manuscript, and developed search strategy and the data collection tool within Covidence. OO: contributed to the writing and final review of the manuscript. SS: contributed critically to the development of the search strategy and final review of the manuscript. AH, NS, BP, MR, FK and LT: provided critical revision and review of the final manuscript. ZS: contributed to the conception and design of the study, provided critical revision and provided approval of the final manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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8.6 CHAPTER 5: COREQ Checklist

No.	Item	Guide questions/description	Page; line numbers
Domain 1: Research team and reflexivity			
Personal Characteristics			
1	Interviewer/facilitator	Which author/s conducted the interview or focus group?	Appendix 8.7
2	Credentials	What were the researcher's credentials? E.g. PhD, MD	Appendix 8.7
3	Occupation	What was their occupation at the time of the study?	Appendix 8.7
4	Gender	Was the researcher male or female?	Appendix 8.7
5	Experience and training	What experience or training did the researcher have?	Appendix 8.7
Relationship with participants			
6	Relationship established	Was a relationship established prior to study commencement?	Appendix 8.7
7	Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Appendix 8.7
8	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Appendix 8.7
Domain 2: Study design			
Theoretical framework			
9	Methodological orientation and theory	What methodological orientation was stated to underpin the study? e.g. grounded theory	Chapter 5, page 74
Participant selection			
10	Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Chapter 5, page 74
11	Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Chapter 5, page 74; Figure 5.2
12	Sample size	How many participants were in the study?	Chapter 5, page 75
13	Non-participation	How many people refused to participate or dropped out? Reasons?	Appendix 8.7
Setting			

14	Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Appendix 8.7
15	Presence of non-participants	Was anyone else present besides the participants and researchers?	Appendix 8.7
16	Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Chapter 5, page 75
Data collection			
17	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Appendix 8.8
18	Repeat interviews	Were repeat interviews carried out? If yes, how many?	Appendix 8.7
19	Audio/visual recording	Did the research use audio or visual recording to collect the data?	Appendix 8.7
20	Field notes	Were field notes made during and/or after the interview or focus group?	Appendix 8.7
21	Duration	What was the duration of the interviews or focus group?	
22	Data saturation	Was data saturation discussed?	Chapter 5, page 75; Appendix 8.7
23	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	Appendix 8.7
Domain 3: Analysis and Findings			
Data analysis			
24	Number of data coders	How many data coders coded the data?	Appendix 8.7
25	Description of the coding tree	Did authors provide a description of the coding tree?	
26	Derivation of themes	Were themes identified in advance or derived from the data?	Chapter 5, page 74
27	Software	What software, if applicable, was used to manage the data?	Chapter 5, page 74
28	Participant checking	Did participants provide feedback on the findings?	Appendix 8.7
Reporting			
29	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number	Chapter 5, Table 5.3
30	Data and findings consistent	Was there consistency between the data presented and the findings?	Appendix 8.10
31	Clarity of major themes	Were major themes clearly presented in the findings?	Chapter 5, 76-79; Table 5.3

32	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Chapter 5, 75-78; Table 5.3

8.7, CHAPTER 5: Study Protocol

Vaping in At-risk Populations: Effects on Mental and Physical Health (VAPE) Study: A Patient Perspective

Study Protocol

Dr. Zainab Samaan, Dr. Lehana Thabane, Dr. Leonora Regenstreif, Dr. Tea Rosic, Dr. Claire de Oliveira, Dr. Parameswaran Nair, Dr. David Marsh, Dr. Laura O'Neill, Nitika Sanger, Alessia D'Elia, Kevin Park

MCMASTER UNIVERSITY

Table of Contents

Study PROTOCOL

ADMINISTRATIVE INFORMATION

1.0 Title

Vaping in At-risk Populations: Effects on Mental and Physical Health (VAPE) Study: A Patient Perspective

2.0 Protocol version

Date and version: Version 1, September 30, 2020

3.0 Sources of funding,

This study is funded by Canadian Institutes for Health Research, HEV-172884 .

4.0 Study Team Roles and Responsibilities

Table 1 below shows the study team members and their specific roles in the study.

Table 1 Study Investigators and Contributors

Individual	Expertise
Scientific team	
Zainab Samaan, MBChB, MRCPsych, PhD	Extensive background in clinical psychiatry and research design; primary investigator for CIHR funded RCT of behavioural intervention for depression, trial methodologist with focus in mental health, clinical professor and collaborator on over 100 publications.
Lehana Thabane, PhD	Internationally renowned epidemiologist and biostatistician with decades of experience in >100 national and international RCTs, leading > 700 peer-reviewed publications published in topic clinical journals that include JAMA, Lancet, BMJ, and Annals of Internal Medicine.
David Marsh, MD	Extensive background in addictions research, chief medical director for Canadian Addiction Treatment Centres and professor of clinical sciences at the Northern Ontario School of Medicine (NOSM).
Parameswaran Nair, MD, PhD, FRCP, FRCPC	Trained and practicing respirologist with extensive research in respiratory health, specifically investigating types of bronchitis and possible novel targeted therapies; Frederick E. Hargreave Teva Innovation Chair in Airway Diseases. Professor of medicine and collaborator on over 100 publications in journals including the NEJM and Lancet.
Leonora Regenstreif, MSc MD, CCFP(AM) FCFP ,MScCH (AMH)	Expertise in primary mental health care, addiction medicine and hospitalized patients with OUD and medical comorbidities related to drug use. Research collaborator in the management of OUD in incarcerated populations.
Tea Rosic, MD, $PhD_{(c)}$	Senior Psychiatry resident and Clinician Investigator Program trainee; PhD student in Health Research Methods with clinical and research experience in substance use disorders.
Laura O'Neill MSW, PhD, RSW, RP	Actively involved in teaching, training and supervising healthcare professionals at McMaster University. BSc (Psychology), a BSW, MSW and a PhD (Social Work). Registered Social Worker with the OCSWSSW, a

	Registered Psychotherapist with CRPO and a certified CBT therapist with the Canadian Association of Cognitive and Behavioural Therapies.
Nitika Sanger, PhD(c)	PhD. Candidate in Medical Science Graduate Program with extensive background in addiction and mental health research.
Alessia D'Elia PhD(c)	PhD. Candidate in Neuroscience Graduate Program with extensive background in mental health research.
Kevin Park	Lived experience with vaping behaviour who will contribute to the study design, the development of relevant study questions and support the dissemination of study results.

5.0 INTRODUCTION

5.1 Background and Rationale

Vaping has gained popularity in Canadians, particularly in youth and young adults. Accordingly, many questions have been raised about the short- and long-term health outcomes given the scarcity of current evidence. Regarded by some as an alternative to combustible cigarettes[1], evidence suggests that vaping and e-cigarettes are not as innocuous as this perspective may imply. The use of these products results in the release of harmful toxins that pose important risks to the user, as well as to the recipients of second- and third-hand smoking.[2,3] However, little research has investigated the short- and long-term effects that vaping may have on mental and physical health vulnerabilities. This lack of data is met with an even greater uncertainty of the effects of vaping cannabis products, the investigation of which is made especially important by the recent legalization of cannabis. Research is needed to investigate short and long-term health outcomes of vaping in vulnerable populations, specifically in those receiving out-patient treatment for opioid use disorders (OUD) who commonly use multiple substances[4,5], which may complicate or influence opioid treatment outcomes in these patients.

The number of individuals between the ages of 16 and 19 who report ever having vaped increased from 29.3% to 37.0% between 2017 and 2018, with a corresponding increase in number of days vaped in the same time.[6] While proponents of vaping might suggest increases can be explained by increased uptake of vaping as a substitution for cigarettes in an attempt to quit smoking, evidence indicates that the upward trend in vaping is observed most strongly among those who identify as "never" or "experimental" smokers.[6] As vaping substances such as nicotine or cannabis retains their addictive properties, this behaviour presents a concern for at-risk populations, including those with OUD.

OUD is a serious, chronic, relapsing and remitting characterised, at times, by compulsive use of opioids, and sustained behavioural changes affecting the individual's life and functioning.[7] OUD leads to deleterious consequences to individuals and society, including increased likelihood for infections such as hepatitis and HIV, psychiatric comorbidities, social adverse consequences, and increased mortality.[8–15] Canada is the world's second largest opioid consumer globally[16] and the increased availability of prescribed opioids has contributed to diversion and, in turn, the current opioid epidemic.[17] Patients with OUD are at greater risk of polysubstance use, as well as physical and mental health co-morbidities.[18,19] Both cigarette smoking[20,21] and cannabis use[22] are highly prevalent in this population and it remains important to examine the impact of vaping on these patients. OUD may also pose a respiratory risk due to the depressive effects of opioids on the respiratory system and additional substance use through insufflation and inhalation, potentially putting these individuals at higher risk of infection and death from the novel COVID-

19. Research has suggested that vaping may be associated with respiratory health conditions including chronic obstructive pulmonary disease (COPD) and wheezing.[23,24] The CDC has termed any respiratory condition related to vaping as e-cigarette or vaping product-use associated lung injury (EVALI). EVALI includes any shortness of breath, lung infection, fever, etc. related to vaping. As of January 2020, over 2,700 cases of EVALI have presented in the United States.[25]

Recent research suggests that those who vape may be at increased risk for COVID-19 infection and its more severe consequences. The symptomology associated with COVID-19 includes shortness of breath, fever, and cough, which can lead to pneumonia and acute hypoxemic respiratory failure.[26] There are concerns that smokers, which include those who vape, may develop serious complications if they contract COVID-19.[27] Individuals may also contract COVID-19 through the sharing of vape devices as the coronavirus may remain active on aerosols (and associated surfaces) from several hours to days.[28,29] Additionally, individuals with OUD are also at higher risk of deleterious consequences of COVID-19.[30]

Vaping has also been associated with psychological and mental health concerns. In a study of university students, the use of e-cigarettes (devices that turns liquid containing nicotine into vapor) was found to be associated with multi-drug use, including alcohol and opioids, low self-esteem, symptoms of attention-deficit/hyperactivity disorder, post-traumatic stress disorder, gambling disorder, and anxiety.[31] E-cigarette use was associated with traits of impulsivity[31] and internalizing and externalizing problems.[32] There is likely a bidirectional association between vaping and mental health. Studies showed higher depression and stress scores were predictive of e-cigarette use in college students.[33] These findings highlight the co-occurrence of vaping with mental health challenges and problematic substance use in non-psychiatric populations. Further, these studies highlight the need for investigating vaping behaviour in a high-risk population, and specifically in the context of the opioid epidemic within the current COVID-19 pandemic where vulnerable groups are expected to bear the brunt of the epidemic within the pandemic.

We completed a systematic review of vaping within OUD population and found that some research has suggested that vaping may be associated with adverse outcomes including increased psychiatric distress[34] and physical health symptoms such as coughing and headaches.[35] However, there is no research examining vaping and COVID-19 related symptoms in the OUD population.

Preliminary data from our study investigating pharmacogenetics of OUD in patients receiving medication-assisted treatment (MAT) (POST study, a CIHR funded cohort study, n=2,360, individuals 16 years and older, 56% men) showed 19.2% of individuals with OUD use vaping, with 74% of participants vaping nicotine, 33% vaping cannabis (THC, CBD, Marijuana and shatter), 11% vaping of both cannabis and nicotine, and 5.5% reporting vaping water or "flavour".[36] The POST Study collected information pertaining to initiation of opioid use, opioid addiction treatment history, cannabis use, illicit drug use, and physical and mental health symptoms, using a set of questions and validated clinical questionnaires. Specific information pertaining to vaping behaviour has also been collected. Participants were asked about vaping status (binary variable), and the type of substance that they vape (free-text response). Table 1 describes demographic characteristics and vaping behaviours in a subset of the POST study who reported "yes" to vaping (n=453), stratified by sex.

Further data are needed to understand individuals' perceptions and motivations for vaping in the OUD population. Additionally, given the variability of substance use outcomes in those receiving treatment, it is also important to explore is other substance use (i.e., cocaine,

opioids, cannabis, amphetamines and benzodiazepine use) also differ in those that vape and have OUD.

6.1 Study Objectives

The primary objective of this qualitative study is to understand the perceptions and motivations for vaping in the OUD population receiving medication assisted treatment. The secondary objective is to collect specific information pertaining to frequency of use, amount, and vaping substance as well as co-substance use information.

7.0 Study Methods

We will conduct qualitative interviews on the phone to obtain information on the perceptions of vaping and vaping behaviour patterns (i.e., reasons for vaping, type of substance, effect of vaping on health) in the OUD population. With the expertise of a qualitative expert, we have designed an unstructured interview guide (see attached interview guide) that have 8 broad, open-ended questions that will allow the interviews flexibility of asking more tailored questions as the participant shares their thoughts and experiences. The qualitative interviews will be audio recorded and transcribed without any identifying information.

In addition to the qualitative interview, we will also administer a Questionnaire of Vaping Craving (QVC), a short validated questionnaire for assessing vaping beliefs and behaviours[37], and collect demographic details. We will also be collecting urine drug screen results for opioids, cocaine, amphetamines, cannabis and benzodiazepines from medical records for a period of 12 months after study enrolment.

Participants will be provided with a $10.00 Tim Hortons gift card for their participation.

8.0 Study Setting

We will recruit 50 participants attending medication assisted treatment clinics through the Canadian Addiction Treatment Centre (CATC).

9.1 Eligibility Criteria

1. People aged 16 years or older
2. Fulfil DSM-5 criteria for OUD
3. Receiving medication assisted treatment for OUD
4. Currently vape
5. Able to provide informed consent

9.2 Research Personnel conducting qualitative interviews

All research assistants involved in conducting the qualitative interviews will be trained by Laura O'Neill.

10.0 Outcomes

Primary Outcome Measures

As the primary aim is to collect information on perceptions of vaping and will be collected through a qualitative interview, there is no structural outcome. This information will be open ended and collected through the interview guide developed.

Secondary Outcome Measures

Our **secondary outcome** is Questionnaire of Vaping Craving (QVC). This will be administered to participants electronically after the qualitative interview. We will also get information relating to co-substance use for a period of 12 months after study enrolment using their medical records at CATC.

11.0 Sample size

Based on the qualitative literature, it has been suggested that one should only conduct qualitative interviews to the point of saturation, that is until no longer obtaining different perspectives. It has been suggested that for observational studies, between 30-50 participants is the recommendation.[38] The sample size for this study is 50 participants.

12.0 Recruitment

We will recruit from Canadian Addiction Treatment Centres. We will provide the centers with a poster announcement to place in the clinic with the study details and contact information. The Director of Operations will be giving us a list of 3 sites that we will recruit from. Once a site has reached saturation, we will be provided with another site. At any given time, the maximum number of sites that will have ongoing recruiting will be 3. We have provided a template for this poster under recruitment material.

13.0 Blinding

This study is qualitative interview therefore is not possible for participants to be blinded.

14.0 Data Collection Methods

A specifically designed case report forms (CRF) will be used to collect the data using electronic research data capture, REDCap. We will be using REDCap to electronically store the surveys containing the outcome instruments. We will be using the phone to conduct the qualitative interviews. The recorded phone interviews will also be stored on REDCap. The recorded interviews will be kept for 10 years and then safely destroyed.

15.0 Data Management

Data will be entered into research Electronic Data Capture (REDCap) (http://project-redcap.org/). Electronic data will be hosted in the local institution server at McMaster Mac or Joes? with passcode protection and electronic security measures in keeping with institutional policy and privacy regulations. Reports will be generated weekly to check data quality and recruitment progress.

16.0 Statistical analyses

Data for this aim will be analyzed using Nvivo 12 qualitative data analysis software (QSR International).[39] The free-text data will be run through a word frequency query to logically arrange the information and determine the most common words. The word count query will help identify initial patterns in the data; there is evidence that this function improves analytic accuracy when compared to manual qualitative word frequency analyses.

In order to avoid decontextualization of the free-text answers, the minimum number of letters permissible in the word frequency query will be set to four. Any word with a frequency weighting of greater than 0.5% will be coded as a node. A node is a collection of references found in the free-text data that corresponds to a particular theme or word. Words with a word frequency percentage above 0.5% that are related to a similar theme will be grouped in the same node. From this output, we will employ matrix coding queries.[41] The output of a matrix coding query is a chart that displays the number of references coded at each node and the corresponding demographic attributes for each participant.

The thematic data will be presented for the overall population, by sex, gender, type of MAT, age, and ethnicity.

Additionally, with the urine drug screen results from the medical records, we will conduct linear and logistic regressions to see if there are any differences between socio-demographic variables and substance use outcomes in this population. We will need to see the distribution of the outcomes to decide on whether a linear or logistic model will be appropriate.

17.0 Data Monitoring

The main concern for this study data is the non-physical risks associated with a loss of privacy or confidentiality. Procedures have been put into place that are designed to keep your information confidential. The consent form and any study identifiers will be stored securely and separately from the collected information. This study does not require data and safety monitoring board due to the reasons described above in a social/behavioral research type of study.

18.0 Harms

This study is a minimal risk non-pharmaceutical study; however, there may be risks involved. The participant may feel upset or distressed when asked about when asked about vaping behavior. The research assistant will attend to the participant needs and remove them for the study or skip over certain questions if needed.

19.0 Auditing

The study team will virtually meet regularly to discuss the study progress and review the weekly report of study recruitment, data quality and monitoring.

20.0 Research Ethics Approval

Approval from the Hamilton Integrated Research Ethics Board (HIREB) will be sought prior to commencement of study.

21.0 Protocol Amendments

Any changes to the study protocol will be reported to the HIREB prior to implementation. In addition, any protocol deviations/violations will be reported promptly and a note to file will be kept in the study file.

22.0 Consent

Informed consent will be obtained in two ways. The first will be informed verbal consent that will be recorded on the phone in which the research assistant will thoroughly go through the consent form and the study objectives. This verbal consent will be stored separate from the qualitative interview. Once the participant has completed study, they will go to their CATC clinic, sign the written consent form, and pick up their gift card. This 2 stage consent was done to ensure timely interviews are done when participants call the research office then attend the clinic as they would normally do for clinical care for the written consent to be signed and copy is provided to the participant at that time as well as a token of appreciation for their time.

Participants will be informed that they can request additional time to consider participation when they call on the phone, and can be sent a copy of the consent form to review at their leisure before making a decision on enrolling in the study. If they have any questions, the participant can contact the research assistant and principal investigator through the details provided on the consent form.

23.0 Confidentiality

All study personnel will be trained and monitored regularly in the requirement of participants' confidentiality according to hospital and research ethics board regulations and following good clinical practice guidelines. All research related procedures including data collection and storage will be carried out in secure electronic platform of REDCap. No information about any participants will be shared outside the research team without prior consent unless there are concerns regarding participant health and safety.

24.0 Declaration of Interests

The investigators declare no conflict of interests.

25.0 Access to data

Study investigators will have access to the study data.

26.0 Dissemination

We have taken measures to ensure our study is rapidly made widely available. First, we involved respirologist, addiction medicine specialists, the medical director of CATC and a

person with lived experience. This team will aid in disseminating through communication, workshops and presentations with target patient populations.

Results and conclusions will be shared with key populations and healthcare personnel through publications in scientific journals and e-conferences, websites, university newsletters, hospital bulletins, grand rounds, educational events and seminars, physical and virtual information tools, and through collaborations with community partners.

27.0 Appendices

1. Qualitative Interview Guide

2. Questionnaire of Vaping Craving (QVC).

3. Informed Consent Form

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8.8, CHAPTER 5: Additional Methods

Research team characteristics and reflexivity

Senior, female graduate students (AD, BP, NS) who were enrolled in or had completed PhD level studies performed the interviews. All interviewers had completed qualitative interview training, had previous experience with leading qualitative interviews prior to the current study and completed practice interviews. As interviews were conducted remotely within Ontario, no professional or therapeutic relationships existed between interviewing researchers or participants. Participant perceptions of the researcher's goals were limited to those discussed during the consenting procedure, and were not collected by the researchers.

Setting of data collection

As interviews were completed over the phone, the setting of participation differed widely. For participants with their own phone access, participants were able to freely select their location, therefore, it is expected that participants selected a location in which they were comfortable participating. As some participants live in multi-tenant housing situations, it is possible that some participation occurred within shared spaces which may have impacted the way they answered questions or which topics they chose to discuss. Participants who completed interviews within the clinic setting were able to participate in a private space, in a clinic in which they regularly receive addiction services and discuss sensitive health and personal topics with clinic staff and their physician. Due to the virtual nature of the interviews, it possible that the setting or the presence of nonparticipants in their surroundings may have impacted participant's responses.

Qualitative Data Collection

Interviewers were provided a qualitative interview guide to generate discussion around participant experiences, and to probe participants with open-ended questions to incite further elaboration. The interview guide was constructed through partnership with a qualitative interview expert, then discussed amongst the research team. A person with lived experience was then consulted to provide input on content, structure, and phrasing on the qualitative interview, as well as the quantitative data items. The qualitative interview guide was piloted on the first participant; all interviewers listened to the audio recording and provided feedback to note for future interviews. After 13 interviews were completed and transcribed, an assessment for saturation was undertaken. During this assessment, the current themes were discussed, identifying additional questions and lack of comprehension around certain topics; considerations and suggestions for prompts and follow-up questions were discussed for future interviews (additional prompts are detailed within the Qualitative Interview Guide in Appendix B). During interviews, interviewers reworded and clarified questions to ascertain participant comprehension and ensure sufficient exploration of the topics presented by participants. Interviews were only conducted in the English language, by English-speaking research staff.

Researchers used audio recordings to collect the data due to the virtual, phone-based interview format. As the remote telephone interview format largely precludes data

generation from visual or audio cues, interview transcripts were the sole source data for coding and analysis. No limit was placed on interview duration, however, the mean length was nearly 8 minutes.

Accordingly, field notes of contextual or non-verbal expressions were not taken or used for analysis. Each participant was interviewed once, with no repeat interviews. Transcripts of interviews were not returned to participants for comment or correction. As mentioned previously, the OUD population often face unstable housing[1], transience[2], and potential challenges to accessing and using technology. Previous challenges to follow-up with this participant population post-interview further indicated that repeat interviews and returned transcripts would likely be infeasible and subject to rates of high missingness. Therefore, the research team did not incorporate these steps in the study protocol. Any disagreements on transcription or content were discussed between at least two interviewers (AD, BP, NS) to reach consensus.

Quantitative Data Collection

During participant interviews, quantitative data on demographic and vaping characteristics were collected. Self-reported clinical characteristics including type of MOUD treatment, current MOUD dosage, current cigarette use, average cigarette consumption per day, and body-mass index were collected. As an objective measure of drug use, urine toxicology screens (UTSs) were obtained from participants electronic medical records at their respective clinics using FaStep Assay (Trimedic Supply Network Ltd, Concord, Ontario, Canada)[3]. UTSs were ordered by the participant's physician as indicated by the participant's history, varying by outcome and clinic; counts are provided alongside UTS data to provide context for these outcomes. UTS data was presented for the following drugs: opioids (excluding methadone and buprenorphine), benzodiazepines, amphetamines, cannabis, cocaine, and methamphetamine.

Patterns and vaping behaviours were explored by collecting the following characteristics: age when first introduced to vaping, age of initiating vaping regularly, and number of years vaping. Participants were also asked to classify their vaping frequency as "everyday", "every other day", "2-3 times per week", "once per week" and "2-3 times per month." The average amount spent on vaping per week was reported in Canadian dollars (CAD). Data on the substances vaped were extracted from free-text responses, where participants were asked to report all the substances that they regularly vaped. Participants were asked to report the most common setting for vaping, with response options of "alone", "with one other person", "with two or three other people" or "with four or five other people." Participants were asked to report reasons for vaping; additional information on substances was collected for those who reported using vaping as a means of managing substance cravings.

Data Analysis

Qualitative Data Analysis

Themes were derived directly from the data. The transcript data was coded independently by 2 authors (AD and BP), and then together to discuss initial patterns and themes. Manual, partially-coded data was analyzed through Nvivo 12 qualitative data

analysis software (QSR International)[39]. Text searches were conducted, then word frequency queries were generated with those terms, arranging the information according to frequency. Manual qualitative analysis and initial patterns identified through word count queries were then analyzed together to refine themes and codes. Manual and software analyses were conducted to improve the validity of the developed themes. Results were shared with the research team for feedback, including experts in opioid addiction and mental health (NS and ZS), supporting the description of themes.

Full details on the qualitative statistical analysis are detailed in the protocol (Appendix B). Participants were not asked for feedback on the study findings, however, IWLE with vaping were consulted for feedback on identified themes. This paper reports the thematic analysis for the overall study population.

Quantitative Data Analysis

For demographic, clinical, and vaping characteristics, means and standard deviations (SD) were presented for continuous variables, while counts and percentages were provided for categorical variables. Substances vaped were presented as counts and percentage of individuals reporting vaping the substance; the number of individuals reporting both nicotine and marijuana is also reported. As several individuals reported more than one substance, counts exceed the total sample size. UTS data was presented as the percent positive screens (number of positive screens divided by the number of total screens performed, multiplied by 100%) for each drug.

Convergent Mixed-Methods Analysis

A convergent analysis approach was selected to integrate and more comprehensively understand vaping behaviour in patients with OUD who vape[4]. Qualitative and quantitative data were combined to assess how each the results generated from dataset converged or diverged[5,6]. The convergent mixed-methods analysis was conducted by comparing qualitative themes to statistical analysis of quantitative data, presented in a joint display table. For each qualitative theme, a demographic description of the participants contributing to that theme is provided, alongside analysis of related, complementary quantitative variables.

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8.9, CHAPTER 5: Qualitative Interview Guide

As you know, we are doing this interview in the hopes of getting your perspective on vaping as a whole, along with some questions about vaping while receiving medication assisted treatment for opioid use disorder.

1. How were you first introduced to vaping?
2. Can you tell me a bit about your experience of vaping?
3. What do you vape?
4. Why do you vape?
5. Have you ever tried to quit vaping? Why did you try to quit? What was quitting like for you? Or What is it about vaping that leads you to continue with it?
6. Do you find vaping to have any effect (positive or negative) on your physical health (e.g., EVALI, COVID-19, smoking cessation tool)?
7. Do you find vaping to have any effect (positive or negative) on your medication assisted treatment?
8. Is there anything else that you would like to tell me about your experience with vaping that you think is important for me to know?

Additional prompts:

Question 6:

- *If they say there are benefits to vaping,* ask: What are all the benefits of vaping?
- *If the participant indicates vaping minimizes cravings,* ask: Does vaping impact your other drug use?
- *If the participant indicates that vaping is helping them to quit smoking*, ask: Have your nicotine levels changed while vaping versus smoking?

Question 7:

- *If participant says there is no effect of vaping on treatment*, ask: Do you think this is a positive thing?

8.10, CHAPTER 5: Joint Display Table

Major Domains	Quantitative measures	Qualitative findings		Mixed-methods inference
		Sample description	Qualitative subcategories	
Personal benefits	**Average amount spent per week (CAD/week)** Mean $25.41 per week (SD 29.32)	N= 20 10 female, 10 male **Substances vaped:** Cannabis only, n=5 Nicotine & Cannabis, n=6 Nicotine only, n=9	Cost • Comments discussing or initiating because it is cheaper or because others have recommended it as a method for cost savings. Autonomy • Comments related to regaining independence over the time spent in acquiring nicotine and managing cravings.	*Congruence* • Participants perceived vaping to help with cost and agency, reported among both those vaping cannabis and nicotine. • Quantitative reports of the average amount spent on vaping products per week is over $25 CAD. • Considering the average cost of a 25 pack of cigarettes in Ontario ($14 CAD), at a mean of 10 cigarettes per day reported by this sample at the time of interview, weekly cost would be approximately $39.20. • It appears that the cost of purchasing cigarettes is much greater than vaping products, suggesting that vaping is permitting cost-savings, corresponding with participant perceptions.
Personal Benefits	**QVC item: "Vaping would make me feel happier now" (on a scale of 1 to 7, which denote strongly disagree and strongly agree, respectively, and 4 denotes "neither agree nor disagree).** Range 1-7 Mean response = 3.48.	n=27 16 female, 11 male **Substances vaped:** Cannabis only, n=5 Nicotine only, n=13 Nicotine & Cannabis, n=8 Water-flavour only, n=1	Enjoyment • Comments pertaining to enjoying vaping due to qualities such as flavour, and responses stating how the flavours of vaping were the only thing preventing them from using cigarettes again.	*Expansion* • Participants descriptions of enjoyment and pleasure resulting from vaping disagree with the average ratings of disagreement or neutrality toward the idea that "vaping would make them feel happier". • This suggests that motivations to vape involve seeking pleasure, and may be unrelated to happiness.

Personal benefits	**"Why do you vape?" (Multiple-response options)** 23/41 reported "for pleasure"		Enjoyment • Comments pertaining to enjoying vaping due to qualities such as flavour, and responses stating how the flavours of vaping were the only thing preventing them from using cigarettes again.	*Expansion* • Participants describe feelings of enjoyment and comfort when vaping, which corresponds with reports of vaping "for pleasure" endorsed by 56% of participants. • This evidence suggests that vaping is eliciting pleasure, and may be explanatory of vaping behaviour (type of substance, flavour, frequency of vaping).
Personal benefits	**QVC item: "I will vape as soon as possible" (on a scale of 1 to 7, which denote strongly disagree and strongly agree, respectively, and 4 denotes "neither agree nor disagree).** Range: 1-7 Average response: 3.76	n=13 7 female, 6 male **Substances vaped:** Cannabis only, n=5 Nicotine only, n=5 Nicotine & Cannabis, n=3	Independence • Comments related to regaining independence over the time spent in acquiring nicotine and managing cravings. Control • Comments related greater control over their consumption	*Congruence* • Participants describe how vaping allows them to have greater control over their consumption of nicotine and independence in choosing when to vape. This corresponds with average neutral responses to needing to vape as soon as possible. • Taken together, this evidence suggests that vaping may be associated with cravings that do not limit a user's independence.
Personal benefits	**QVC item: "Nothing would be better than vaping right now" (on a scale of 1 to 7, which denote strongly disagree and strongly agree, respectively, and 4 denotes "neither agree nor disagree).** Range: 1-7 Average response: 3		Independence • Comments related to regaining independence over the time spent in acquiring nicotine and managing cravings.	*Congruence* • Participants describe vaping permitting greater independence over their time and ability to engage with other activities, which corresponds with general disagreement that vaping would be better than partaking in other activities.

Vaping and Smoking Reduction	**Number of cigarettes per day** Mean 10.11 per day (SD 6.11)	N=20 13 female, 7 male **Substances vaped:** Cannabis only, n=2 Nicotine only, n=10 Nicotine & Cannabis, n=7 Water-flavour only, n=1	Reduce smoking • Comments specifically describing the motivation to vape in order to reduce the number of combustible cigarettes consumed.	*Discordance* • Participants describe vaping supporting them in reducing the number of cigarettes they consume per day. • Estimates of daily smoking within OUD patients who do not vape suggest rates of 14-15 cigarettes per day (POST). • The number of cigarettes smoked per day by vapers does not differ greatly from those who do not vape, contrasting with participant beliefs and suggesting that vaping is supporting minimal reduction.
Vaping and Smoking Reduction	**Number of cigarettes per day among those reporting using e-cigarettes to reduce cigarette use vs. those who did not report this motivation for use.** Mean 10.4 cigarettes per day vs. 11 cigarettes/day		Control smoking cravings • Comments describing the motivation to vape to help avoid combustible cigarette cravings. Reduce smoking • Comments specifically describing the motivation to vape in order to reduce the number of combustible cigarettes consumed.	*Discordance* • Participants perceived vaping to support them in reducing the number of cigarettes smoked per day. • This diverges from quantitative data shows near equal daily cigarette consumption between those who reported using vaping to reduce cigarette use these perspectives and those who did not. • This difference signals that despite perceptions that cigarette consumption is being reduced, vaping is not, on average, resulting in reduction.
Vaping and smoking cessation	**Number of participants who do not use cigarettes vs. use cigarettes (within the group of individuals reporting vaping as a smoking cessation tool)** 11 reporting no current	n=34 20 female, 13 male, 1 non-binary **Substances vaped:** Cannabis only, n=5 Nicotine only, n=20 Nicotine & Cannabis, n=8	Smoking cessation • Comments specifically discussing the need or want to stop smoking using vapes/e-cigarettes.	*Discordance* • Participants perceived vaping to be helpful in quitting cigarette smoking, which contrasts with data showing that among those which reported this perspective (n=34), 68% continue with daily cigarette smoking. • This divergence suggests that vaping is ineffective in smoking cessation, and is contributing instead to dual use of nicotine.

	smoking, 23 current smokers	Water-flavour only, n=1		
Vaping and smoking cessation	**Mean number of years vaping** Mean 4.58 years vaping		Smoking cessation • Comments specifically discussing the need or want to stop smoking using vapes/e-cigarettes. Vaping is a superior smoking cessation tool • Comments describing vaping as a way to reduce or stop smoking, and the belief that vaping is more successful than alternative smoking cessation tools on the market.	*Discordance* • Participants reported vaping to be a smoking cessation tool, suggesting it to be superior to alternative cessation tools. • Beliefs of superior cessation are unsupported by evidence which shows that on average, participants have been vaping for 4.5 years, and many remain smoking. • This disagreement provides poor evidence for vaping as a smoking cessation tool.
Vaping and substance use	**"Why do you vape?" (Multiple response option)** Response: • 20 reported using vaping as a means of coping with substance cravings of various substances • 12 for tobacco cravings • 2 cannabis cravings • 3 crack/powder cocaine • 5 opioids (heroin,	n=21 11 female, 8 male, 1 non-binary Cannabis only, n=2 Nicotine only, n=12 Nicotine & Cannabis, n=5 Water-flavour only, n=1	Minimizes cravings/engagement with substances of abuse drug cravings • Vaping assists with or is used for the reduction in the use or in the cravings and habits associated with drugs other than methadone (i.e. crack, cocaine etc.). Vaping acts as a coping mechanism to support abstinence.	*Congruence* • Vaping was perceived to be helpful in managing cravings for illicit drugs. • Participants perceptions corresponded with 20 of 41 participants reporting "managing cravings for substances" as a reason for why they vape, mentioning not only cravings for tobacco, but also substances like cannabis, crack or powder cocaine, and opioids like fentanyl and heroin.

	fentanyl) • 2 methadone			
Vaping and substance use	**"Why do you vape?" (Multiple response option)** Response: 20 reported using vaping to avoid/substitute for other substances.		Minimizes cravings/engagement with substances of abuse drug cravings • Vaping assists with or is used for the reduction in the use or in the cravings and habits associated with drugs other than methadone (i.e. crack, cocaine etc.). Vaping acts as a coping mechanism to support abstinence. Habit replacement • Comments describing how vaping helps with oral fixation and sating hand-to-mouth impulses typical to cessation.	*Convergence* • Participants found vaping to be helpful for managing cravings for illicit substances, which parallels quantitative reports of using vaping to avoid/substitute for other substances. • This suggests that vaping is perceived by participants to impact their other substance cravings
Vaping and substance use	**Urinary toxicology screens (percent positivity)** Results: • 18.75% positivity for opioids • 6.25% positivity for benzodiazepines • 37.50% positivity for amphetamine • 28.57% positivity for cocaine		Minimizes cravings/engagement with substances of abuse drug cravings • Vaping assists with or is used for the reduction in the use or in the cravings and habits associated with drugs other than methadone (i.e. crack, cocaine etc.). Vaping acts as a coping mechanism to support	*Discordance* • Participants mentioned vaping helped with habit replacement and physical cravings related to illicit drugs. • Participant views contrasted with objective urine screen data which showed positive screens for not only the specifically mentioned substances, but also for other illicit substances. • This disagreement generates concerns that vaping is not an effective method for curbing cravings or coping, and may instead be resulting in another addiction.

	• 33.33% positivity for methamphetamine		abstinence. Habit replacement • Comments describing how vaping helps with oral fixation and sating hand-to-mouth impulses typical to cessation.	
Vaping is socially motivated	**In which of the following situations do you most typically vape?** 6 (14.6%) participants reported vaping most typically around others (two or more others)	n=15 10 female, 4 male, 1 non-binary **Substances vaped:** Cannabis only, n=1 Nicotine only, n=9 Nicotine & Cannabis, n=5	Social value • Comments related to improved social interactions or improved perceptions of self from members of one's social group after commencing vaping. Comments surrounding initiating or continuing vaping due to vaping occurring within their social group.	*Congruence* • Participants reported social situations motivating them to start and continue vaping, corresponding with 14.6% of participants reporting that they most typically vape around others. • Almost 1 in 7 participants vape most typically around others, meaning that others may vape around others, but this is less typical. This supports a strong social component for vaping, impacting vaping behaviour.
Vaping is socially motivated	**Why do you vape?** 8 (19.5%) reported vaping because others around me are also vaping.		Social value • Comments related to improved social interactions or improved perceptions of self from members of one's social group after commencing vaping. Comments surrounding initiating or continuing vaping due to vaping occurring within their social group.	*Congruence* • Participant views on deriving social benefit from vaping, consistent with participants also reporting they vape because others around them are vaping. • Both qualitative and quantitative data suggest that vaping can have a social component, and that social settings or interactions can motivate vaping.

Vaping and health	**QVC question: "I am missing vaping right now"** 3.7 mean response	n=33 17 female, 15 male, 1 non-binary **Substances vaped:** Cannabis only, n=7 Nicotine only, n=16 Nicotine & Cannabis, n=9 Water flavour only, n=1	Vaping is addictive • Comments discussing vaping as addictive or potentially addictive, and/or descriptions of the addictive attributes of vaping when explaining their experiences. Vaping is not addictive, and I use it to stop smoking. • Comments describing using vaping as a means to stop smoking, while not considering vaping itself to be addictive.	*Congruence* • Some participants described vaping as potentially addictive and harmful, while others shared perspectives that vaping was nonaddictive, and something they could discontinue easily. • Participants' divided views align with participants level of agreement on "missing vaping" to disagree with neutral feelings toward the idea of "missing vaping."
Vaping and health	**QVC Score** Mean (SD)= 36.82 (16.13)		Vaping is addictive • Comments discussing vaping as addictive or potentially addictive, and/or descriptions of the addictive attributes of vaping when explaining their experiences.	*Congruence* • Participants described vaping as potentially addictive and thereby harmful toward health, which appears to agree with moderate levels of cravings within this population (max score: 70, min score: 10) • Moderate cravings scores are congruent with views that vaping may be addictive.
Vaping and health	**Comorbid Conditions** 51.2% report at least one mental health (anxiety, mood disorders, stress disorders)		Vaping has positive effects on health • Comments describing that the impacts of vaping on health, mental health in particular (i.e. anxiety, stress etc.)	*Discordance* • Well over half of the participants in this sample reported some form of positive health effect of vaping, particularly valuing the effect of vaping on mental health through easing stress and anxiety. • Participant perspectives appear to contrast with data on co-morbidities, which show that over half endorse some type of mental health

				diagnosis, though this data is does not reflect possible improvements in symptoms.
Vaping and health	**"How often do you vape?"** • Everyday vaping (n=35, 85.4%) • Every other day (n=2, 4.9%) • 2-3 times per week (n=3, 7.3%) 1-2 per month (n=1, 2.4%)	n=23 15 female, 8 male **Substances vaped:** Cannabis only, n=6 Nicotine only, n=12 Nicotine & Cannabis, n=5	Vaping is addictive • Comments discussing vaping as addictive or potentially addictive, and/or descriptions of the addictive attributes of vaping when explaining their experiences. Vaping is not addictive, and I use it to stop smoking. • Comments describing using vaping as a means to stop smoking, while not considering vaping itself to be addictive.	*Congruence* • Some participants described vaping as potentially addictive and harmful, while others shared perspectives that vaping was nonaddictive, and something they could discontinue easily. • Data on frequency of vaping shows that approximately 85.4% of participants vape every day, and most of the remaining vape at least multiple times per week. • Frequency data is congruent with perspectives that vaping is addictive and does not provide support for perspectives that vaping is not addictive.
Vaping and MOUD	**Urine toxicology screens, percent positivity for opioids at time of interview** 16.22% positivity for opioids	n=10 5 female, 4 male, 1 non-binary **Substances vaped:** Cannabis only, n=4 Nicotine only, n=2 Nicotine & cannabis, n=4	Vaping does not impact MOUD • Comments describing neutral/no effect of vaping on MOUD treatment. Vaping has some effects on MOUD • Comments describing positive effects on MOUD, and indirect benefits of vaping on	*Congruence* • Participants either no effect of vaping on MOUD or mild effects, mentioning it may help with tapering dose or coping with withdrawal symptoms, and thereby supporting treatment success. • The modest perceived effects are congruent with urine screens which are positive for opioids, suggesting that any perceived effects may be inconsistent and unreliable.

			MOUD treatment success.	
Vaping and Youth	**Mean age of the sample** Mean (SD) = 40.26 (12.23)	n=7 3 female, 4 male **Substances vaped:** Nicotine only, n=5 Nicotine & cannabis, n=1 Water flavour only, n=1	Vaping is popular among young people • Discussion of vape as something that is most common within a younger age group.	*Discordance* • Participants often discussed perceptions of vaping being common among youth, specifically students and young adults, which is incongruent with the mean age of the sample. • This inconsistency may be explained by perceptions of vaping in young people in the general population, and may not be reflective age-related trends within the OUD population.
Vaping and Youth	**Mean age when first tried vaping** Mean (SD) = 33.95 (12.70)		Vaping is popular among young people • Discussion of vape as something that is most common within a younger age group.	*Discordance* • Perceptions of vaping being popular among youth disagrees with the mean age of first trying vaping within this sample, which suggests that, on average, first attempts at vaping occur during the early to mid-thirties. • This inconsistency may be explained by perceptions of vaping in young people in the general population, and may not be reflective age of first trying vaping within the OUD population.
Vaping and Youth	**Mean age when first started vaping regularly** Mean (SD)= 34.85 (12.38)		Vaping is popular among young people • Discussion of vape as something that is most common within a younger age group.	*Discordance* • Perceptions of vaping being popular among youth conflicts with the mean age of first initiating regular vaping, which suggests regular vaping begins around age 35. • This inconsistency may be explained by perceptions of vaping in young people in the general population, and may not be reflective age of regular vaping within the OUD population.

Vaping and Youth	**Flavour** Of the 8 participants younger than 30 years, 25% reported using flavours. Of the 33 participants, 36% of participants reported vaping flavoured products.		Vaping flavours are attracting youth • Discussion of how vaping flavour options are attractive to young people, including flavour options without nicotine or cannabis components.	*Discordance* • Participant perceptions suggest that flavours involved with vaping are attracting youth. • Data shows a higher proportion of those older than 30 are using vape flavours than though below 30. • If participant perceptions were accurate, proportions of those vaping flavors would be higher in the younger sub-group. This divergence suggests that perhaps these beliefs and observations may apply to the general population, and are less explanatory of flavour trends within the OUD population.
Vaping to get high	**Cannabis vaping in the sample** 33% vaping cannabis products in the full sample	n=7 3 female, 3 male, 1 non-binary **Substances vaped:** Cannabis only, n=3 Nicotine & cannabis, n=4	Vaping as a way to get "high" • Comments related to vaping in order to achieve a "high" or feeling of euphoria, typically discussed in the context of cannabis vaping.	*Congruence* • Motivations for vaping to get high are congruent with data showing that nearly 33% of the sample vapes cannabis products. • This suggests that participants are motivated to vape in order to get high, and are consuming cannabis.
Vaping to get high	**"Why do you vape?" (Multiple response options)** 13 participants reported "to get a high" as a reason for vaping		Vaping as a way to get "high" • Comments related to vaping in order to achieve a "high" or feeling of euphoria, typically discussed in the context of cannabis vaping.	*Congruence* • Motivations for vaping to get high are in agreement with participants including "to get high" as a reason for vaping in 32% of participants.
Vaping to get high	**Urinary toxicology screens (percent positivity)**		Vaping to get "high" • Comments related to vaping in order to	*Congruence* • Motivations for vaping to get high are congruent with data showing 33% positivity

	33% positivity for cannabis		achieve a "high" or feeling of euphoria, typically discussed in the context of cannabis vaping. •	for cannabis within the sample.

8.11, CHAPTER 5: Qualitative Codebook

Themes	Node	Description	Examples
1. Perceived convenience	Convenience/ease of use	Comments related to the ease of use of vapes/e-cigarettes in comparison to cigarettes and other forms of nicotine intake.	• "I don't mind using the vape inside, so that's nice." (Case 13, M/36) • "Um.. cause… cause like I buy a cart- like I'll buy a cartridge and then I'll buy a pack of cigarettes, and if I don't have the money, then I just use the vape." (Case 1, F/36) • "Um, the convenience of it, and that it doesn't smell like cigarettes and stink up the house?" (Case 3, F/33) • "And sometimes it's just having a couple of inhales of the vape- the vapourizer is quicker than trying to smoke a half cigarette." (Case 5, M/25) • "Yeah, I'm not having to go outside every time to, to have a cigarette. I don't mind using the vape indoors." (Case 13, M/36) • ""Um, I don't smoke in the house, where I live, so I don't always wanna go outside for a cigarette, and I keep a e-cigarette around just so, you know, just to be handy. Um, to, to vape when I can't get to a cigarette outside." (Case 3, F/33) • "That's $15.75 a day, plus I was smoking a pack and a half, so. It, it was getting too much. I couldn't afford it." (Case 6, F/29) • "I like it because it's um you don't have to do anything you know what I mean? Like all I have to do is open the the pen up and start puffing on it. I don't have get it all the.. you know to get papers ready and get crap all over my clothes and you know what I mean? Like it.. no.. there's no mess it's just you just open the package up and you start puffing." (Case 31, F/52)
	Cost	Comments discussing or initiating because it is cheaper or because others have recommended it as a method for cost savings.	• "Um, yeah so like smoking cigarettes was getting so expensive, uh, when I started smoking I remember like, a pack of smokes was like, well you getting a thing called presto packs, they were like $3 and you have to put the filters on yourself. Um, and so the last time I bought a pack of smokes it was like $20, so it was just like, I mean, some people go to the reservation, and you can get them for a lot cheaper there, but uh-uh I just couldn't afford it." (Case 27, F/39) • "Uh, just, she was like, trying to quit smoking, and she was like, hey, "you should try this". It- it made her feel healthier, it was cheaper, and so, she kind of, she actually gave me my first vape. Uh, my first rig, and was just kinda like, "oh, here, try this and hopefully you know, it'll help you quit smoking, save you some money" (Case 27; F/39).

			• "Yeah, I think it uh it has positive for sure like uh, my lungs are starting to clear up. I'm not coughing every morning and coughing up a lot of phlegm. Um, it's uh, it's slowing down the smoking, less money – doesn't cost as much. Lasts twice, three times, four times as longer than cigarettes do. I don't have to travel all the time to get them. I just gotta buy a bottle of juice and it lasts quite a long time. (Case 19; M/64) • "Because, cigarettes were though, the price on cigarettes – weren't getting them from the reserve, the price was getting out of control." (Case 19; M/64)
2. Perceived pleasure	Comfort	Comments detailing pleasant experiences with vaping related to social benefits (i.e., smell) and self-care habits such as relaxation, particularly when compared to cigarette smoking.	• "Just, I kinda got used to it, a little bit? Um, with the little setting when I was with my ex-boyfriend, so, I just kinda picked up the habit with him and I just continued to, you know, buy one once in a while. To have with me" (Case 3, F/33) • "Yeah. Like, my hands didn't smell afterwards. And stuff…" (Case 1, F/36) • "Um, it looked like a cleaner alternative to cigarettes. Made you smell good." (Case 11, M/43) • "Um, yeah, I have like, uh, uh, I only vape like maybe once a day if it's like nighttime and I'm watching a movie … Um, to, to vape when I can't get to a cigarette outside. Or when I don't feel like getting up." (Case 3, F/33) • "Sometimes it helps with relaxation when I'm at home and I don't wanna move, and I can just relax and I have my e-cigarette with me and uh, veg on the couch." (Case 3, F/33) • "So it was like, I hadn't completely shifted my mindset yet to replace like one thing with another, and then by the time – what happened was I went somewhere for the weekend and there was no cigarettes, and all I had was the vape, and by the time I got back to where my cigarettes were, and I lit one up, and it tasted horrible." (Case 27, F/39) • "So, now I just sit on my couch and kinda hang out. Which, is almost worse, cause I do like have this thing in my hand all the time." (Case 28, M/30) • "Uh the smell, uh I say that I work in restaurants right, so it's not like you go outside smoke come back in and not stink so, for certain reasons yes." (Case 17, M/41)
	Enjoyment	Comments pertaining to enjoying vaping due to qualities such as flavour, and responses stating how	• "Yup, um, so I had smoked for probably like, 25 years, when I started, or when I first got it, and had no intentions on quitting. But um, but I ended up quitting. I just, I really liked -- the flavour is much better, I enjoyed the "pull" over a cigarette "pull". Um, the house wasn't as disgusting, as it was with two of us smoking in there." (Case 18, F/41)

		the flavours of vaping were the only thing preventing them from using cigarettes again.	• "Any fruit flavours I tried. You know, grape, lemon, umm a lot of the citrus flavours I enjoyed, like apple, um you know, you name it, plum, you know, plums, anything, anything that was fruit flavoured. It was all I bought, exclusively, 100%." (Case 19, M/64) • "Like, um, so, one of my buddies, was like oh you know, there's like, there's good flavours. And like, kind of slowly convinced me. Um, and yeah, like. The second that I picked this thing up, I-I stopped smoking cigarettes, that way." (Case 28; M/30)
3. Perceived Agency	Control	Comments related greater control over their consumption	• "Yeah. So, like, I mean, I just like the ability to, um, begin, and and stop whenever I choose." (Case 4, F/41) • "Um, and, if like, yeah I fi-, cause now I'm not doing it all, you know what I mean? When you light a cigarette, you smoke a full cigarette." (Case 4, F/41)
	Autonomy	Comments related to regaining independence over the time spent in acquiring nicotine and managing cravings.	• "Um, I really, don't do much research into that kinda stuff, like I just kinda go with my day and go with the flow, and um, for me, not to have to smoke a full cigarette or not to – like I just find that it, it fixes my craving, um, within one puff. Which, as I say, one puff is like 5 times a day, that's like smoking [emphasis] a cigarette in a day." (Case 4, F/41) • "Oh yeah, I have [tried to quit]. It was very easy, I just put it down and I don't touch it." (Case 4, F/41) • "And sometimes it's just having a couple of inhales of the vape- the vapourizer is quicker than trying to smoke a half cigarette." (Case 5, M/25)
4. Perceived smoking reduction	Control smoking cravings	Comments describing the motivation to vape to help avoid combustible cigarette cravings.	• "Yeah, I ran out of cigarettes and he was like "here try this", so I tried it and it, um, helped with um, the cravings, and then – I still smoked, but you know I would try once in a while. Or do it with him." (Case 3, F/33) • "Like I don't see, it's – but then again I'd have to smoke cigarettes so." (Case 9, M/31)

	Reduce smoking	Comments specifically describing the motivation to vape in order to reduce the number of combustible cigarettes consumed.	• "I'm more addicted to cigarettes, like I've smoked cigarettes since I was 14 years old. And with vaping, I usually just uh, I usually just do it to try and see if I can go a day or – a couple days without smoking cigarettes." (Case 5, M/25) • "Uhhh, well it all depends right, it's been off and on for the last 10 years or so. Since I started vaping. So, there's been times where I'll smoke more than I vape, right?" (Case 7, M/33) • "Somewhat, I cut down, but not. Like." (Case 10, F/33) • "Yeah, like, not completely I guess, like I still smoke cigarettes and I still vape. But…" (Case 5, M/25) • "It was usually a matter of going back to cigarettes, or going down on the cigarettes and choosing the vape more." (Case 11, M/43)
5. Vaping is perceived to be a smoking cessation tool	Smoking cessation	Comments specifically discussing the need or want to stop smoking using vapes/e-cigarettes.	• "So, um, like I'd say the first month I was still smoking, like cigarettes, strongly. But after that, and I, um, I almost went three months straight without, no cigarettes." (Case 7, M/33) • "And, um, I wanted something to, you know what I mean? You, you always have those things where you put a cigarette in your mittens, your fingers, and not light it. Or people have their different ways." (Case 4, F/41) • "It, it, it… it just, it helped me a lot with quitting smoking, and if it helped me, it could help other people. You know, I had a really hard time with quitting drugs, um, and so I thought, quitting smoking would never [emphasis] be an option." (Case 6, F/29) • "Sure. Uh, uh I vape, um, I vape as a tool to- to- to- quit cigarettes, to quit cigarettes. So, basically I vape to- to- to- um, yeah, to help the void from cigarettes." (Case 9, M/31) • "I just, I don't know, I use it as a replacement for cigarettes, and um I guess I'm addicted to it now." (Case 16, M/45) • "It was a substitute for cigarettes." (Case 17, M/41)
	Vaping is a superior cessation tool	Comments describing vaping as a way to reduce or stop smoking, and the belief that vaping is more successful than alternative smoking	• "Yeah. All the nicotine patches, the little puffer things, yeah, […] nothing worked [as a cessation tool]." (Case 12, F/46) • "Um, yeah because I had heard of it as an alternative to cigarettes. It was all because I wanted to quit cigarettes so I was looking for options, and there hasn't ever been many options other than like, you know, nicotine gum and stuff, and that stuff just doesn't work." (Case 9, M/31) • "Um. Tell you a little bit about my experience. So, um I guess my two cents on that is um, uh, I I I pri-, I don't know I have a strong belief that it's a great

		cessation tools on the market.	tool for quitting cigarettes, so my experience is is is overall decent. Like, um […] Um, it's good, it's really good. Uh, I don't think, in comparison to the amount of cigarettes I smoke, the amount I vape is nil in comparison to what I smoke for cigarettes." (Case 9, M/31)
	Vaping is not an addiction	Comments describing that vaping is not seen as something that is addictive or something they wish to stop.	• "But uh, again there's that whole hand to mouth thing also, so that's why I'm hesitant to say I'll withdraw it [vaping] altogether." (Case 13, M/36) • "No, I would never, I wouldn't even see vaping as something that I'd need to quit. Like wouldn't be a problem." (Case 11, M/43) • "Because… no, no. I haven't tried to quit vaping. Uh, its an interesting question because um, I never thought of it that way. I feel like vaping is almost one of those things where I, if I didn't wanna vape I just wouldn't." (Case 9, M/31) • "Um, because I've never really been a regular, regular vaper I guess? So I never saw it as something I should try and quit. (Case 3, F/33)
	Vaping is different than cigarettes	Comments stating that vaping is different, better and healthier than cigarettes, offering a multitude of benefits compared to combustible cigarette smoking./smoking cannabis	• "Um, it looked like a cleaner alternative to cigarettes. Made you smell good." (Case 11, M/43) • "Uh, just, for the health, and the not having to inhale the smoke, and uh, for the smell." (Case 13, M/36) • "There's a little bit of a different effect. Like not a different effect, but there's a little – it just, I can't really explain it, it just. It um, it tastes a little bit different?" (Case 4, F/41) • "That, and it's, it's a good, it's a good delivery system for the products I want to consume." (Case 8, M/36) • "Um, I wouldn't even say a lowered intake, just a different method of intake, uh, but no that's definitely the number one reason." (Case 13, M/36) • "You know? Like I mean, I just find, for myself, um, its, to me its healthier, to me it doesn't smell, you know what I mean? There's a lot of pros to vaping for me, um, especially when I have children." (Case 4, F/41)
	Nicotine Satiation	Comments expressing desire to vape to satisfy cravings for nicotine.	• "Um I didn't think about that [health effects of vaping], anything about my health at all, it just helped me stop smoking…" (Case 12, F/46) • "But you're still getting your fix of the nicotine too, so it actually just kinda kills two birds with one stone" (Case 4, F/41) • "Yeah, I ran out of cigarettes and he was like "here try this", so I tried it and it, um, helped with um, the cravings, and then – I still smoked, but you know I would try once in a while. Or do it with him." (Case 3, F/33) • "Why I do it. To keep my addiction at bay. Cause I'm – I can get pretty

			grouchy if I'm – as anybody – without – I go into my nic-fit." (Case 28, M/30) • "Yes. It's just it's just only if I'm out of cigarettes I'll pick it up." (Case 30, F/40) • "Well, I didn't try to quit, it just happened that I quit and smoked more cigarettes than vaping." (Case 15, F/59)
	Vaping is a maintenance treatment	Comments likening vaping to maintenance treatment for discontinuation of cigarettes, specifically methadone treatment.	• "But I mean I vape nicotine for pretty much to continue like it's like how methadone like keeps you from relapsing on opiates. It's the same thing, like vaping keeps me from relapsing on cigarettes. Cause if I have no nicotine, I'm more likely to be anxious…" (Case 6, F/29) • "Yeah, it's the same concept, basically, its like, my uh – the vaping is like the methadone for my smoking, um – that's what it reminds – although I'm having a lot harder time tapering off methadone, than I am off the nicotine. So." (Case 27, F/39) • "Um, not really. Just that it it has it it's replaced smoking in a lot of situations. Um, so I I I see it as a positive thing. Um as a tool. As a tool to get off of the the smoking kind of like what methadone would be for opiates. I, um, I'm using it in the same manner. So I've enjoyed my experience vaping, um, and uh, it is it is definitely in my mind something temporary." (Case 41, F/39) • "But I mean I vape nicotine for pretty much to continue like it's like how methadone like keeps you from relapsing on opiates. It's the same thing, like vaping keeps me from relapsing on cigarettes. Cause if I have no nicotine, I'm more likely to be anxious…" (Case 36, 24/N)
	Vaping is addictive and I use it to stop smoking.	Comments describing using vaping as a means to stop smoking, while acknowledging vaping to be addictive.	• "I just, I don't know, I use it as a replacement for cigarettes, and um I guess I'm addicted to it now." (Case 16, M/45) • "Um, overall, I've had uh – I've had a good experience with it. I've like um, I just was saying this earlier, it uh, I find its made me feel a lot better, in my health, and just, um, yeah, its its, it's been really handy to come off of smoking. Uh, to have it as a backup. I, I do think though it, its something that I would like to quit doing. Like I don't wanna do this the rest of my life. So." (Case 27, F/39) • "Um, but I guess, I would just say like, I think that there is a positive side to it. Um, because I think it is less - I think if you're doing it in a way to help you quit smoking, and you're not just like, trying to get big clouds, or not really nicotine levels, and you're – I think it has been really helpful for a lot

			of people" (Case 27, F/39) • Like, I'm already addicted to nicotine, but it's not like I'm, you know, not smoking nicotine? […] When I'm vaping. I'm still doing that, so. I'm aware of that. (Case 24; F/33)
	Vaping is not addictive, and I use it to stop smoking	Comments describing using vaping as a means to stop smoking, while not considering vaping itself to be addictive.	• "Um, I don't find it, I don't need it – I, I only use it when I, when I feel like using it. I don't have like, uh, uh uh, a strong – it doesn't have a strong hold on me, like I don't need it every day." (Case 29, F/53) • [Interviewer: "Is vaping something that, um, you view as problematic or something that you would ever want to try to quit?"] Participant: "Neh." (Case 1, F/36)
6. Perceived changes in substance use	Minimizes cravings/engagement with substances of abuse drug cravings	Vaping assists with or is used for the reduction in the use or in the cravings and habits associated with drugs other than methadone (i.e. crack, cocaine etc.). Vaping acts as a coping mechanism to support abstinence.	• "Well, to be honest with you, I was in active addiction, um, and um, uh, I went in and quit. I got clean. And when I went and got clean, I decided to quit smoking. Smoking weed, and quit- quit doing dope…And, um, I wanted something to, you know what I mean? You, you always have those things where you put a cigarette in your mittens, your fingers, and not light it. Or people have their different ways." (Case 4, F/41) • "For sure. Absolutely. I have a lot of dreams about [crack cocaine] – and it's weird because that was not my drug of choice, and, it's weird that I get cravings where I'm wanting to smoke it, but when I do, I will smoke my vape, and honestly, right away, it's just gone. And because, in my head I don't want to ever go back to that lifestyle." (Case 6, F/29) • "Um, yeah it like just keeps me from, like, being bored, stuff like… Takes my mind off of things." (Case 1, F/36) • "Uh, the one reason is because I had been trying to get off of the fentanyl. And, if I couldn't get it, it would take away the physical ummm, withdrawal symptoms that I was - uh – going through. Like the stomach aches, the bone aches. The, the, the overall creepy feeling that you get. The vaping would take that away." (Case 29, F/53) • "Not at all, it's not a social thing at all right now, it's more so, yeah like boredom stress release, especially since I quit smoking other things which were kinda my coping mechanism." (Case 14, F/18)
	Habit replacement	Comments describing how vaping helps with oral fixation and sating hand-to-mouth	• "I think the big thing is that hand umm.. or the hand motion. That's like the biggest thing for anyone who's a smoker so whether that be like [inaudible] or tic tacs or anything." (Case 35, F/20) • "Like for relaxation. And like I find that like having something in my hand is really helpful. Um. I mean there's fidget toys for autistic people like

		impulses typical to cessation.	myself but there is you know when you're an adult like you really like "why are you playing with a toy"? You know what I mean." (Case 36, N/24) • "Um, I wouldn't even say a lowered intake, just a different method of intake, uh, but no that's definitely the number one reason, but uh, again there's that whole hand to mouth thing also, so that's why I'm hesitant to say I'll withdraw it altogether." (Case 13, M/36) • "Um because I have an oral fixation." (Case 15, F/59)
7. Perceived lack of information about vaping	Knowledge acquisition	Comments related to the dearth of information on vaping and its effects (largely physical health effects) and the desire to learn more about the effects of vaping from external sources (media, doctors etc.) .	• "Um, I am weary of vaping because there's not that much – I'm not sure about the statistics on it? I know cigarettes cause cancer and stuff like that, but, I feel like vaping has gotta be – there's gotta be some, some sort of medical downfall to vaping. Um, it's just another toxin that we're putting into our bodies. So, I figure there's gotta be something bad about it, we just haven't found out yet." (Case 3, F/33) • "Hmm, not really, um, just that it's not as good for you as people think it is" (Case 2, F/46) • [Interviewer: Do you think you would have started, um, vaping, even socially, uh, if you had known, earlier, about the effects on the lung?] Participant: "No " (Case 2, F/46) • [Interviewer: Okay. And who told you, um, just out of curiousity, who, uh, mentioned – or where did you hear that it was bad?] Participant: "On youtube". (Case 2, F/46) • "Um, I just, a question mark on negative health effects [unintelligible], but uh, I haven't done too much research into it myself so." (Case 13, M/36) • "It'd be interesting actually, what your research finds when it comes to that, like how many people it actually helped feel better, and how many people felt worse from it – " (Case 27, F/39) • "It's been around for, I think, 8 years or 10 years or something, but it's still new in-in-in, as far as like what we know what it does to us." (Case 27, F/39) • "…So that's why I don't do it as regularly like I initially wanted to to use it to quit smoking cigarettes but I didn't um continue really because there's not enough research about it." (Case 30, F/40)
8. Perceived social benefits motivate	Stigma	Comments attributing perspectives of external sources, specifically related to	• "…I was really proud of myself for like so, and a lot of people around me were proud cause I had smoked cigarettes for 15 years. And, and then this crazy stigma came in with like how bad vaping was and then I started hearing ridiculous people talking about like – "Oh vaping is terrible, it's even worse

vaping behaviours		the negative consequences of vaping, to stigma. Association of external information with stigma and misinformation, urging that the positive effects of vaping as a smoking cessation tool are yet to be discussed.	than cigarettes." And then that really bummed me out, because uh I found like, it was such a good tool to help people save their lives from cigarettes. And it was all because uh, this whole mix up with people dying from it. But there was a stigma around – the research – cause I was into it, I did a lot of research, and it, it turns out that it had a lot to do with uh, vaping um THC and some type of knock-off cartridges from – that's what was killing people. People, don't understand that." (Case 9, M/31) • "So, so, in combination with um, with the lockdown and everything, there was that, plus at that exact time uh, there was this huge stigma going on, there was, it was all over the news about like vaping being, like killing people. It was all over the news and media. And uh, a lot of stuff was happening and there was a lot of misinformation at the time." (Case 9, M/31) • "That I've talked to. Um, so I – I don't know how you can combine that into your research, as far – I just, would like people to be aware that it's not – it's not as, as bad as it's kind been stigmatized as." (Case 27, F/39)
	Social value	Comments related to improved social interactions or improved perceptions of self from members of one's social group after commencing vaping. Comments surrounding initiating or continuing vaping due to vaping occurring within their social group.	• "Yeah. Yeah, um, totally, and that was like, that was huge for me. Like even people that knew me were like holy like – um, they just even would remark like "oh," I think it was my neighbour that said, I would sit outside with like a cigarette and my coffee in the morning. And my neighbour was like: "Oh I don't hear you coughing anymore" and it just made me realize that even other people were aware of like – you know, me sitting out there in the morning, coughing, like – I didn't – I wasn't even aware of it. (Case 27, F/39) • "Um, he doesn't like me smoking so he suggested I started to vape." (Case 14, F/18) • "Well I vape to kind of slow down my tobacco use, um, and I-I like the way it doesn't make my clothes smell, it doesn't make my hair smell. Um, it looks a lot more friendlier around my kids." (Case 24; F/33) • "Oh okay, uh, um, it's – ju – really it's been – it's actually positive. Uh, one because, at this age, you're sick and tired of the, of the smoke, like you-your just trying to just s–s- like um, discreetly, use. You know, like you're not trying to tell the world, you know, banners all over the place – I'm not an activist, so I try to keep – I'm very low key." (Case 42; M/65) • "It's a little cleaner. Um, in, in society now, it seems to be more accepted." (Case 37; F/52) • "Um, yeah well it felt like cooler more like technology, like futuristic technology kind of. Like I could tell that it was the future of nicotine use.

			Um in a lot of ways. And I I felt like uh when I was assembling it I felt like uh it definitely was clunky kind-of designed and I felt like it could have been improved upon. But like um overall I I thought like it was pretty cool. I felt like cool when I was vaping which sounds so stupid to say cause I mean you look back on your high school years and think none of that was cool, heh. But, I mean." (Case 36, N/24)
9. Perceived positive health effects of vaping	Vaping is healthier for me than cigarettes	Comments describing the impact of vaping on physical health (i.e. decrease negative lung effects, taste and smells is coming back, more energy etc.) in comparison to effects of cigarette smoking. Comments describing vaping as better for their health than cigarettes, as evidenced by improvements in physical health, and vaping as more congruent with a healthier overall lifestyle.	• "It [coughing and breathing] got hugely better, cause like I'm not smoking a half and a pack a day." (Case 6, F/29). • "You know? So for me, I feel like I breathe better…I don't cough as much." (Case 4, F/41) • "Less phlegm, less phlegm in my throat, for coughing. Like, there's, smoking causes me to cough more." (Case 11, M/43) • "So, for me, it's been a positive, its helped my health because I am not smoking a lot of cigarettes." (Case 9, M/31) • "And then, and then I also, throughout like that whole period of time, started trying to like, be more healthy overall. So like, I started doing yoga, and stuff, and I totally noticed a – I noticed a huge difference in just like – um, cause breathing was such a big part of it. And I noticed my lung capacity changed, my um, just, yeah, so much about like my physical, I just – I know people are like oh it's still not healthy, and I understand that, like, vaping's still not considered healthy, but personally, its – its been like 80% more healthy for me." (Case 27, F/39) • "Oh, I was just gonna say, I used to get pneumonia a lot when I smoked […] But I haven't, since I started vaping." (Case 27, F/39) • "Um, well I just find it's, it's, um less like I breath better when I'm vaping, um I like it better than the cigarettes, like the cigarettes seem to be really harsh and really hard on my throat where this doesn't seem to be." (Case 16, M/45)
	Vaping has positive effects on health	Comments describing that the impacts of vaping on health, mental health in particular (i.e. anxiety, stress etc.)	• "So, it's one of those things where, if I'm stressed out, or, if I'm driving, or, any other time that I would, you know, normally light up a cigarette, I would just, I would just vape. And I'd like maybe take one or two puffs and then I'd put it away and then its, you know – and then its done for…" (Case 4, F/41) • "It's just something that calms the, you know what I mean? Calms the stress, calms the, yeah." (Case 4, F/41) • "Uh, yeah. Sometimes it helps with relaxation when I'm at home and I don't wanna move, and I can just relax and I have my e-cigarette with me and uh,

			veg on the couch" (Case 3, F/33) • "Oh yeah, there's definitely positive effects, you have a lot more energy, I have a lot more energy. My taste and my smell is coming back, and everything so…" (Case 7, M/33) • "It was calming, it, uh, relaxed me, and uh, I just, I – it made me feel – it made me feel, happy." (Case 29, F/53) • "Yeah, it's had positive affects in like stressful situations or boredom, it helps me from doing other things when I'm bored and stuff like harder drugs, I guess." (Case 14, F/18)
	Vaping as a health risk mitigation strategy	Comments related to motivation to vape to help avoid the risks and harms associated with alternative methods of consumption.	• "So, when I realized that I could get my daily THCs for cheaper and easier and less - health – like- harm reduction wise." (Case 8, M/36) • "Uh, just, for the health, and the not having to inhale the smoke, and uh, for the smell." (Case 13, M/36) • "Umm, because it's the safest way I have to consume the both, the cannabis and nicotine right now, --- and I'm all about harm reduction." (Case 18, F/41). • "Umm, yeah it does for sure. Like it reduces my stress levels, um, so I don't always get to that point where I'm gonna be craving something […] Kinda prevents, preventative measures" (Case 18, F/41). • "Ummm, yeah, it it does for sure. Like it reduces my stress levels, um, so I don't always get to that point where I'm gonna be craving something. […] Kinda, prevents, preventative measures." (Case 18, F/41) • "And say you had asthma conditions and stuff, and you still wanted to, to, s-smoke, you were definitely better to be vaping, uh, then then, smoking, if you had any kinda asthma condition. And you couldn't get off that that urge to, you know that Oedipus urge to smoke. You know?" (Case 19, M/64)
10. Perceived negative health effects of vaping	Negative physical health symptoms when starting vaping	Harsh or strong physical health experiences with vaping when initiating use as participants tried to find nicotine levels that were ideal for them	• "It was, it was, um, I don't know, it was a bit too strong. Like I couldn't, I wasn't used to, it took me a while to find the right nicotine strength…. I kept trying til I found what worked for me." (Case 11, M/43) • I found at first, it uh, if I was smoking it too much, I felt nauseous, and I would get headaches. Um, so I slowed down on it. Um, and still if, if I take too many puffs of it, I'll get like a light-headed – I don't like that feeling. So, I'll try to keep it to a minimum and do like two or three puffs at a time. (Case 6, F/29) • "Um, I've had – okay experiences– I'm not huge on it because I find that it-it's very harsh. I know with the, the big rig setup that my ex-boyfriend had,

			um, you could change the settings to go lower and higher. Um, I find it was just really harsh on my lungs. Um, I felt like I was gonna cough or like – it was, just too much, I guess it's a different kind of - you know, its vapour instead of a cigarette, but I'm a smoker, so, it was just different for my lungs and I didn't – I never really got used to it." (Case 3, F/33) • "I coughed and uh didn't care for it very much." (Case 15, F/59) • "Yes, I do get short of breath when I vape." (Case 15, F/59)
	Negative health effects caused by vaping	Stated negative health effects caused by vaping and/or stated negative effects stopped after stopping vaping	• "So, I, it, it just took some getting used to. Um, I can smoke now, and it's fine, but like at the beginning I would cough or – um, it would just, um, feel really harsh on my lungs, like too strong." (Case 3, F/33) • "I found at first, it uh, if I was smoking it too much, I felt nauseous, and I would get headaches. Um, so I slowed down on it. Um, and still if, if I take too many puffs of it, I'll get like a light-headed – I don't like that feeling. So, I'll try to keep it to a minimum and do like two or three puffs at a time." (Case 6, F/29) • "Cause I heard it was really bad for your, lungs. (Case 2, F/46) • "It suppressed my appetite…" (Case 2, F/46) • "Um, well I started to feel kind of short of breath" (Case 2, F/46) • "I find that it burns my lungs" (Case 29, F/53) • "Yeah, the more you vape, the more it burns." (Case 29, F/53) • "Hmm, not really, um, just that it's not as good for you as people think it is." (Case 2, F/46) • "So there are times where like I notice uh, that like the night before, if I vape like twice as much, or whatever, than I usually do, and I wake up the next morning and it's like I feel it, it's like oh shit, I vaped too much last night. (Case 27, F/39) • "I guess? Like that first inhale, when you first wake up and it's like, and its like [inhales] uhhh – oouuu, like tenderness, almost? Almost like you pulled a muscle? Or something? Maybe not that extreme, but like you overused a muscle but instead it's your lungs. And there is almost like a hungover feeling as well, like, like uh, like gross taste in your mouth, or like, something, like a grogginess." (Case 27, F/39) • "Well definitely your lungs right, anything you put into your lungs is not going to be healthy for you, so." (Case 17, M/41)
	Vaping is addictive	Comments discussing vaping as addictive or	• "Well, for-first of all, it was a – a so-social thing and then I started to, to - like it." (Case 2, F/46)

		potentially addictive, and/or descriptions of the addictive attributes of vaping when explaining their experiences.	• "Other than that, I feel, it feels pretty good because it helped me quit smoking and I didn't need the vape all day. And also, I – I – I did not get physically addicted to the vape, and I'm not saying no one, no one else can either, but I don't know." (Case 12, F/46) • "So, I had to start to, kinda like, be more mindful of it, and kinda be like okay I'm gonna leave it in another room, I'm gonna like, uh, not – allow myself to not vape in this room. Cause, in my house, for example, um, I would just – they're'd be like no boundary, I would just sit there and vape. So I had to, at one point, be more mindful of how much I was vaping, um, for some reason once I went from 6 to 3, that – I noticed, it got a lot easier for me, it was almost like that, um, I don't know if you've ever smoked or or not, but when you have like, a nicotine craving, you kinda like "nic" out, like it-it, you get like this anxiety or like this tightness, a lot of people get like, a temper, makes you just kind of snap." (Case 27, F/39) • "It definitely could be addictive, especially for people who, 1 haven't smoked anything before and they're just picking up vaping just because they want to um […] It definitely gets addictive in that scenario, um also for um people who are um cigarette smokers, it would be addictive in the sense that you are already kind of addicted to that in the nicotine so yeah" (Case 14, F/18)
	Vaping can be dangerous	Comments discussing vaping as dangerous due to the substances within vaping liquids or components.	• "Um, actually, one thing is, um, those cartridges, I don't know what it – I don't know if uh, there're different materials like they make out of, but like, the cartridges I buy, are glass, and the ones that I've gotten before were actually like a really hard, uh plastic material, and I was using it, and it actually started to bubble. And it almost looked like it was about to burst on me, so – that is kind of iffy of getting one that isn't glass and it getting high heated, and it bursting on you and maybe blinding you or hurting you somehow." (Case 26, M/33)) • "So, yeah, some of the vials, they're glass, right, and then some are plastic and uh, the plastic ones – if you're using it a lot, uh like I said, a bubble had formed, started like molding and almost like bursting, and yeah, that's uh, what happened to me." (Case 26, M/33)
11. No perceived impact of vaping on MOUD	Vaping does not impact MOUD	Comments describing neutral/no effect of vaping on MOUD treatment.	• "Uh, no. I, uh – if it does, I haven't noticed it…" (Case 5, M/25) • "Um, no, never, never did any, never effected it at all, I don't think." (Case 12, F/46) • "Uh, never really thought of it, I smoked before I ever started any kind of opiates and I continued smoking through, so…" (Case 13, M/36)

			• "N-n-no, no, no, no interaction. It's a totally – apples and oranges. For uh – […] Or fruits and vegetables, no-no-no, no bearing, one doesn't have any bearing on the other." (Case 19, M/64)
12. Vaping has some perceived effects on MOUD	Vaping has some perceived effects on MOUD	Comments describing positive effects on MOUD, and indirect benefits of vaping on MOUD treatment success.	• "I find that it makes the methadone seem to last longer." (Case 29, F/53) • "Right. Like you'll get the stomach cramps or whatever – The-the vaping will take that away." (Case 29, F/53) • "If I um, end up missing my drink or end up throwing it up or something, then the metha-or the weed can help subside some of that stuff. Cause I'll start to feel sick and my legs'll start to hurt –" (Case 23, M/28) • "So it doesn't stop it but it kinda helps and just kinda easing my mind to try not to think about it and" (Case 23, M/28) • "Um I think it's helped me decrease my methadone." (Case 32, F/51) • "…a lot of people find the same thing as me that it's really complimentary. And um, weed fills in the cracks where methadone is not perfect cause no medication can be perfect, right?" (Case 36, N/24)
13. Perception that vaping is for the youth	Vaping is popular among young people	Discussion of vape as something that is most common within a younger age group.	• "Like a little younger, youths, and even uh, students, and I find, uh, their, uh, like a lot of younger people are using it rather than older people, right?" (Case 5, M/25) • "Yeah, like, I can't name, I can't name anybody that I know that is underage that vapes, but, I uh, I could imagine, just because of all the different flavours and stuff… that, uh, yeah, I don't know." (Case 5, M/25) • "The only thing I've heard is that the young kids, the teenagers, they, they get into the, they vape around with no nicotine in it, or something, I don't know. My kids don't do that. But, um. So I don't know, I don't know if it. That's it. I don't know if it's a negative thing or, if there's any nicotine in it, I don't know if does anything for them or not. You know." (Case 12, F/46) • "Um, but again, I-I don't even know – cause I know they wanna change the flavours, because they're like "oh kids are smoking" – like a lot of kids are vaping now. And to that I'd like to say, like, I started smoking in high school, I started smoking cigarettes in high school, so – I mean I don't know if more kids are vaping than kids started smoking in high school – I think that would be an interesting thing to kind of research." (Case 27, F/39) • "That kind of high school group. Is doing that. Where, they're not even smoking cigarettes, they're just buying these things to smoke 'em, which – that I can kinda understand, where the government's coming from, with all the flavours and everything" (Case 28, M/30)

	Vaping flavours are attracting youth	Discussion of how vaping flavour options are attractive to young people, including flavour options without nicotine or cannabis components.	• Yeah, like, I can't name, I can't name anybody that I know that is underage that vapes, but, I uh, I could imagine, just because of all the different flavours and stuff… that, uh, yeah, I don't know (Case 5, M/25) • "Um, I think that kid's need to be more aware of it, I've seen 11-year-olds out there vaping like candy flavours and stuff…" (Case 17, M/41) • "So, it's – as a quitting tool, it's amazing. But, I do definitely, that's why I'm super hyped to help with any research. Cause, like, I wanna give - see what's going on and learn, especially with like I say, with people who have been picking it up because their friend's doing it. Or because it tastes good, or you know." (Case 28, M/30)
14. Vaping to get high	Vaping to get "high"	Comments related to vaping in order to achieve a "high" or feeling of euphoria, typically discussed in the context of cannabis vaping.	• "Well I felt that I could control my high more through vaping." (Case 34; F/69) • "Um, they just said that I um, tend to like weed, I should give shatter a try. Um, and they said I could use less of it and get more high. So I tried his pen and then I liked it so I went out and grabbed one of mine and I've been smoking it ever since." (Case 23, M/28) • "So, I'll just vape it, like just to get high. And it will be like a hit here and there." (Case 7, M/33)

Participant information is given as (Case No., Gender/Age)
M: Male; F: Female; N: Non-binary; MOUD: Medication for Opioid Use Disorder