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Abstract

Background: Cognitive behavioural therapy (CBT) is an evidence-based treatment for anxiety disorders. Patients engaging in CBT often have an ongoing pharmacological treatment, generally antidepressants. Benzodiazepines are also commonly used, although they are recommended as short-term adjunctive treatment due to side effects.

Aims: Exploring the influence of benzodiazepine use prior to group transdiagnostic CBT (tCBT) and the participants' experience of their use before, during and after therapy.

Method: Mixed methods study embedded in a randomized controlled trial of group tCBT. The experimental arm received tCBT and treatment-as-usual (TAU) (n = 117) for 12 weeks while the control arm received TAU (n = 114). Anxiety symptoms were assessed with the Beck Anxiety Inventory (BAI). Multiple linear regression analysis examined BAI pre-postdifferences with benzodiazepine use in the past 12 months, tCBT and their interaction. Semi-structured interviews were conducted with 13 participants reporting the use of benzodiazepines at baseline and analyzed using an interpretive descriptive method.

Results: tCBT had a significant effect on anxiety symptoms change, but this effect was non-differential according to benzodiazepine use in the past 12 months. Qualitative results provided nuances about the perceived helpfulness of benzodiazepines. Participants reported that benzodiazepines facilitated the experience of sharing in group therapy and conducting exposure exercises. Despite some benefits, participants perceived that benzodiazepines may have interfered with the effectiveness of exposure exercises and the acquisition of concepts due to a sedative effect.

Conclusions: Results highlight the importance of sensitizing therapists and patients to the potential effects of benzodiazepines on the experience of tCBT.

Keywords: benzodiazepines, anxiety disorders, CBT, group psychotherapy, transdiagnostic.

Public significance statement:

Participants expressed a need for guidance regarding their use of benzodiazepines, especially when they perceived that this medication could potentially interfere with some psychotherapeutic interventions. Therapists should be aware of the potential effects of the utilization of benzodiazepines on psychotherapy processes, and address this issue in their intervention plan, considering that many people choose to engage in CBT while undergoing pharmacological treatment.

Introduction

With a worldwide prevalence estimated at 11.6% (Baxter et al., 2013), anxiety disorders are among the most common class of mental disorders (Kessler et al., 2007; Kessler et al., 2010). Anxiety disorders present in adulthood are many, but all share common characteristics, such as excessive fear, anticipation, and avoidance behaviour (American Psychiatric Association, 2013). Anxiety disorders have a significant impact on psychosocial functioning (Saris et al., 2017) and quality of life (Comer et al., 2011; Olatunji et al., 2007) and increase the risk of comorbidities with other psychological and physical problems (American Psychiatric Association, 2013).

Canadian clinical practice guidelines indicate two broad categories of research-supported treatment for anxiety disorders: psychotherapy and/or pharmacotherapy (Katzman et al., 2014), but the most common intervention in clinical practice is pharmacotherapy (O'Donnell et al., 2017; Weisberg et al., 2014). Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) antidepressants are the first-line treatments due to their effectiveness and low rate of side effects (Bandelow et al., 2007). Benzodiazepines are also commonly used among patients with anxiety disorders, although they are recommended as a second-line therapy and should be used only in the short term and as an adjuvant to evidence-based treatment (Katzman et al., 2014). Guidelines generally recommend short-term use at the beginning of antidepressant treatment to address the delayed onset of action, to manage some SSRIs and SNRIs side effects, and to relieve acute anxiety such as agitation and panic attacks (Bandelow et al., 2012; Katzman et al., 2014). Caution is advised considering the risk of use above the guidelines, dependence, withdrawal symptoms and side effects such as sedation, memory impairment and decreased alertness (Katzman et al., 2014). In a survey conducted in primary care settings, 22.6% of adults with an anxiety disorder reported using benzodiazepines

and of this number, 88.4% were considered long-term users (Tanguay Bernard et al., 2018). As long-term benzodiazepine use is common in Canada (Esposito et al., 2009), many patients are using this medication when starting psychotherapy. This reality raises whether concomitant benzodiazepine use could influence the process and outcome of cognitive behavioural therapy (CBT), the most empirically supported psychotherapeutic approach for the treatment of anxiety disorders (Butler et al., 2006).

Participating in CBT requires acquiring new skills where memory and learning abilities are key elements for treatment outcomes (Harvey et al., 2014). Patients need to be involved in exercises and homework assignments founded on four treatment components. These include psychoeducation, which aims to help understand the causes and nature of anxiety. Then, cognitive restructuring guides patients in recognizing and re-evaluating automatic thoughts associated with fears. Exposure, one of the most important components of therapy, is intended to expose patients systematically and repeatedly to their fears. The final component of this therapy aims to establish a post-treatment intervention plan and strategies to adopt in the case of relapse (Arch & Craske, 2009).

Taking benzodiazepines during CBT raises clinical concerns, as they may interfere with the intervention components. First, studies have shown that benzodiazepines interfere with episodic memory, producing anterograde amnesia that is more pronounced at higher doses, especially with acute administration (Scharf et al., 1988; Segura et al., 2021; Stewart, 2005). The use of benzodiazepines may therefore interfere with the acquisition of information related to the psychoeducation component throughout the CBT intervention because this medication impacts both learning and memory (Westra et al., 2004). More importantly, the inhibitory learning model supports that new safety information needs to be learned towards the feared stimulus to inhibit

the fear reaction and to maximize exposure exercises' effectiveness. Indeed, to improve fear extinction, a person needs to learn that the fear stimulus and the emotional experience during exposure are safe (Craske et al., 2014; Weisman & Rodebaugh, 2018). This new non-threatening association needs to be consolidated in memory (Craske et al., 2014; Tolin, 2019; Weisman & Rodebaugh, 2018), which may be impaired by benzodiazepine use. However, chronic use might have less of an impact on learning and memory than acute dosage (Hart et al., 1991). Through their anxiolytic actions (Starcevic, 2012), benzodiazepines may directly interfere with fear activation during exposure therapy, thereby impeding the retrieval of fearful expectations and the development of predictor error extinction learning (Craske et al., 2014; Craske et al., 2022). Further, as discussed by Craske et al. (2022), benzodiazepines may function as "conditional inhibitors (that directly predict non-occurrence of the unconditional stimulus) and negative occasion setters (modulatory stimuli that reduce the likelihood that the conditional stimulus will lead to the unconditional stimulus" (p. 4) during exposure therapy.

The interaction between benzodiazepine use and CBT is not fully understood in the scientific literature. A systematic review was conducted by Melani et al. (2020) to assess the impact of benzodiazepines on the effectiveness of exposure therapy for anxiety disorders and posttraumatic stress disorder. This review included 12 RCTs, and among them, 9 showed that benzodiazepine use had no impact on the effectiveness of the therapy. On the other hand, all RCTs reviewed had a high risk of bias and small sample sizes, so it is questionable to affirm that benzodiazepines do not compromise the efficacy of exposure therapy (Melani et al., 2020). A previous systematic review of 2 RCTs that aimed to explore the effectiveness of behavioural therapy for panic disorder combined with benzodiazepines compared to either treatment alone was also inconclusive regarding the combination between psychotherapy and benzodiazepines,

due to the lack of high-quality evidence (Watanabe et al., 2009). Most RCTs on the subject date back several years, but the problem does not seem to have been completely resolved.

We sought to explore the association of benzodiazepine use with CBT in the context of a pragmatic RCT on group transdiagnostic CBT (tCBT) for anxiety disorders in community-based settings. In addition to the examination of the overall association with CBT therapeutic components and treatment effects, CBT in this trial was delivered in a transdiagnostic approach and a group modality, which makes it of particular interest to examine benzodiazepine use due to the heterogeneous sample of participants as well as the group treatment modality that may present additional challenges. CBT offered in a group format may cause some apprehension and discomfort for the patients. Some may have difficulty sharing and opening up in front of a group of strangers, or experience fear of being confronted by other group members (Morrison, 2001). Other sources of anxiety may include concerns about judgment by other group members or worry about experiencing a panic attack. Knowing that people who use benzodiazepines may use this medication to feel more confident coping with anxious situations (Parr et al., 2006), what could be the pattern of benzodiazepine use during tCBT and what could be its impact? This study has two objectives: (a) to explore the influence of pretreatment benzodiazepine use on the association between tCBT and the reduction of anxiety symptoms; (b) to explore the participants' perception of their use of benzodiazepines before, during and after tCBT.

Method

We conducted a mixed methods study with a convergent design, where both quantitative and qualitative data were analyzed in parallel and compared when interpreting the results (Creswell & Plano Clark, 2011). To achieve the objectives of this study, we first conducted secondary analyses of data collected in a pragmatic RCT aiming to assess the effectiveness of

group tCBT for anxiety disorders as a complement to TAU (Roberge et al., 2018, 2020). Second, we conducted an original qualitative data collection embedded in the RCT for a subgroup of participants who received tCBT and reported the use of benzodiazepines in the past 12 months.

Pragmatic Randomized Controlled Trial

The design and the results of the pragmatic RCT are detailed elsewhere (Roberge et al., 2018, 2020). In summary, participants were recruited from the general population and were volunteers. To be included in the RCT, participants had to: (a) be between 18 and 65 years old; (b) be fluent in written and spoken French and (c) present at least one principal diagnosis, according to the Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5) (Brown & Barlow, 2014), of the four anxiety disorders targeted by the intervention: panic disorder, agoraphobia, social anxiety disorder, and generalized anxiety disorder. Interrater reliability was assessed for 25% of ADIS-5, by randomly selected clinical evaluators who listened to the interviews' audiotapes. The agreement for ADIS-5 principal diagnosis was 83.3% (clinician's severity rating ± 1 criterion). Participants meeting these criteria were excluded: (a) bipolar disorder, active suicidal ideation, psychosis or active substance abuse in the past 12 months; (b) cognitive impairment; and (c) consultation with a psychiatrist within the last 12 months. Following a screening process, selected participants were randomly assigned to the tCBT+TAU (n=117) or TAU arm (n=114).

The RCT was conducted in three administrative regions of the province of Quebec in Canada from October 2016 to May 2018. The experimental intervention was based on 12 weekly group sessions of manualized tCBT protocol (Norton, 2012) comprising psychoeducation (1.5 sessions), cognitive restructuring (1.5 sessions), exposure (6 sessions), schema-based cognitive restructuring (2 sessions) and relapse prevention (1 session). The intervention protocol and

patient manual focused only on psychotherapeutic components; no instructions regarding medication use were provided. Groups of 8–10 participants were led by two therapists and sessions lasted 2 hours per week. Deferred tCBT was offered to participants of the TAU arm. For participants in the TAU arm, no restrictions were imposed on the use of health services (e.g., general practitioner, psychologist, alternative medicine) and medication, to compare the added value of tCBT in real-world conditions.

The primary outcome measures were the Beck Anxiety Inventory (BAI) (Beck et al., 1988) and the ADIS-5 (Brown & Barlow, 2014). Also, the secondary outcome measures of the RCT included self-reported specific anxiety and depression symptoms, functioning, quality of life, service utilization and medication use. For the present study, we only used measures related to anxiety symptoms and medication use.

Quantitative Secondary Analysis Component

Participants

In addition to the main study's inclusion and exclusion criteria, completion of the BAI at baseline and post-test was required for analytical purposes. This resulted in available data for 198 participants for this secondary analysis. Of the 95 participants in the tCBT+TAU arm and 103 participants in the TAU arm, 36 and 31 participants reported pretreatment benzodiazepine use, respectively. With a standard deviation of 12 points on the BAI pre-post difference, this gives a power between 65% and 91% to detect a clinically significant difference of 7 points in the reduction of anxiety symptoms (Oei & McAlinden, 2014) between participants that reported using benzodiazepines X arm subgroups with a bilateral significance level set at 5%.

Measures

We used the Beck Anxiety Inventory (BAI), a 21-item self-reported general measure of anxiety symptoms. The BAI reports the frequency of anxiety symptoms during the last 7 days and provides a continuous score ranging from 0 to 63 (Beck et al., 1988). The severity of symptoms of the principal anxiety disorder diagnosis at pretreatment was assessed with the ADIS-5, a semi-structured interview administered by a clinician to assess DSM-5 diagnostic criteria for anxiety and related disorders. It indicates the clinical severity of symptoms on a scale of 0 (no symptoms) to 8 (extremely severe symptoms) (Brown & Barlow, 2014). A questionnaire on medication use (molecule, dosage, length of time) was used to provide information on benzodiazepine use 12 months preceding the baseline. For analyses purposes, a person was classified as a pretreatment participant that used benzodiazepines if he/she reported taking some at least once during the previous 12 months. Participants that use benzodiazepines included occasional users (use as needed) and regular users (daily use). Socio-demographic data were also used.

Analysis

Means, standard deviations, frequencies, and proportions were first calculated to describe the characteristics of the analyzed sample. Subsequently, bivariate analyses relating participants' characteristics to BAI post-pre difference were undertaken. Variables were selected based on a literature search and included sex, age, education level, presence of psychiatric comorbidity, the severity of symptoms of the main anxiety disorder and the use of antidepressants. Variables significantly related to BAI change (at the $\alpha = .10$ level) were included as confounders in a multiple linear regression model along with tCBT, prior benzodiazepine use, and their interaction (tCBT* BZD). Residual analysis was performed to assure that no outliers were too influential

and that the assumptions underlying multiple linear regression were met. Statistical analysis was performed using SPSS 25 software. The significance level was set at $\alpha = .05$, except where mentioned otherwise.

Qualitative Component

To meet the qualitative objective of this study, an interpretative descriptive design (Thorne, 2016) was used, in concordance with the interpretative paradigm.

Participants

To be eligible for the qualitative interviews, participants had to report using benzodiazepines 12 months preceding baseline and attended at least 9 tCBT sessions, to ensure good adherence to treatment. Potential participants were recruited from the last experimental groups and the delayed intervention groups. We used a purposive sampling strategy based on sex and specific anxiety disorders. Eligible participants were contacted by telephone and offered the opportunity to participate in an interview conducted either by telephone or videoconferencing (Zoom). Participants received $40 financial compensation, for their time and contribution during the interview. Recruitment was done to the point of data saturation, meaning that the interview process stopped when there was redundancy in participants' responses (Saunders et al., 2018).

Data Collection

Data were collected through semi-structured interviews in French between February and May 2020. The research team developed an interview guide to cover three different themes: (a) benzodiazepine use behaviour surrounding tCBT (12 months before, during, after intervention until interview); (b) use of benzodiazepines during each intervention component of tCBT; and (c) perceived impacts of benzodiazepines on the effectiveness of intervention components

(Supplemental Material A). The average length of the interviews was 35 minutes, and the interview guide was enhanced as the interviews progressed.

Analysis

Data Analytic Strategies

Data analysis was conducted using a general inductive approach (Thomas, 2006). Following transcription, each interview was read and coded in NVivo software. Guided by the interview outline, all text segments were labelled to create categories. All the text segments specific to different themes were labelled following the encoding process to create categories. After proofreading, similar categories were reduced. A template including the reduction of these most significant categories was created. This final set of reduced categories represents the end of the analysis.

Methodological Integrity

To ensure the integrity of the qualitative component, various criteria of rigour were applied (Cypress, 2017). For credibility, feedback was given following interviews, either by listening to the audiotapes or by reading the transcripts, by one of the principal investigators of the RCT. Although there is no consensus regarding the proportion of data that should be used to assess intercoder reliability (O'Connor & Joffe, 2020), co-coding was done for an entire interview with one of the team's research professionals. The few disagreements were addressed by consensus, where they were discussed and clarified to ensure the rigour of the coding process (Campbell et al., 2013). One of the co-authors also revised a quarter of the text segments related to the different categories. To ensure the reliability of the study, a logbook was kept when the interviews were conducted, and during the analysis. As the interviews were conducted in French,

the verbatim presented in this article were translated, and a bilingual research professional verified the integrity of the translations.

Ethical Statement

The RCT research protocol was approved by the ethics committees of the Integrated Health and Social Services Centers in Estrie (#MP-22-2016-570), Québec City (#2017-166) and Laval (#2016-2017-C54). An amendment request for this research project was approved by the Research Ethics Committee of the CIUSSS of Estrie - CHUS on December 16, 2019.

Results

Quantitative Findings

As seen in Table 1, the sample was primarily composed of women, with an average age of 37 years old. Most participants were living with a spouse, and reported a post-secondary/vocational or university education level and a very good to excellent economic situation. More than half of the sample had a generalized anxiety disorder as their principal diagnosis. About three quarters of the participants had a comorbidity with another anxiety disorder. For the presence of comorbidity with a depressive disorder, about a quarter of the sample had a major depressive disorder or a persistent depressive disorder. In terms of medication use, more than half of the participants were using SSRIs and SNRIs as antidepressants. Sixty-seven participants reported using benzodiazepines at least once in the past 12 months. Among these participants, the majority were occasional users and more than half had used benzodiazepines for more than a year. Clonazepam (Rivotril) and lorazepam (Ativan) were the most commonly used molecules.

Insert Table 1

Bivariate analyses indicated that, among all the potentially confounding variables analyzed (sex, age, education level, presence of psychiatric comorbidity and severity of symptoms), the severity of symptoms of the main anxiety disorder was the only participant characteristic related to BAI pre-post change. Therefore, it was included as a confounder in the multiple linear regression model presented in Table 2. A multiple linear regression analysis was also conducted without this variable as an exploratory analysis (Supplemental Material B). The tCBT X benzodiazepine interaction was not significant, indicating that although tCBT had a significant effect on anxiety symptoms change (larger negative post-pre difference in the experimental arm), this effect was non-differential according to pretreatment benzodiazepine use in the past 12 months. This is illustrated in Figure 1. Subdividing users according to their self-reported frequency of use in additional exploratory analysis, we found no difference between occasional and regular users on anxiety symptom reduction (Supplemental Material B)

Insert Table 2 and Figure 1

Qualitative Findings

Qualitative results were based on the perceptions of 13 participants that use benzodiazepines in the 12-month prior to the beginning of group tCBT in the experimental group (n = 4) or the delayed treatment for the TAU group (n = 9). For participants in the experimental arm, an average of 24 months elapsed between the end of the tCBT and the interview, while for the delayed intervention group 11 months elapsed. Participants included a majority of women and persons who occasionally used benzodiazepines. Generalized anxiety disorder was again the most prevalent principal diagnosis. A description of the 13 cases is presented in Table 3.

Insert Table 3

Theme 1: Evolution of the Use of Benzodiazepines Before, During and After tCBT

Before tCBT

In the 12-month before the beginning of group tCBT, what emerged from the participants was that they were experiencing some distress and needed help. They were using benzodiazepines to relieve discomfort and a general state of anxiety. The consumption of benzodiazepines was intended to relieve symptoms such as intrusive thoughts, panic attacks, nausea, and heart palpitations.

> "I didn't want to go out for groceries. I didn't want to… I bought a gym membership; I couldn't get out to go to the gym. I was really, really not feeling well. So, it was a really bad moment. I had approached my employer for therapy. Then that didn't work either. Twelve months ago, it was horrible." (Case #13)

During tCBT

Therapist Instructions

When asked about their use of benzodiazepines during tCBT, some participants spontaneously reported that they had received instructions from therapists about using benzodiazepines during psychotherapy. Some participants were told to continue taking their benzodiazepines, while others were advised to discontinue their use. Also, there were participants for whom therapists did not discuss the use or non-use of benzodiazepines during tCBT. These differences in benzodiazepine use instructions have influenced some participants in their utilization.

> **"**But as they used to say, "Don't bother. Don't worry, you're going to do the exercises the same way. If you need it, take it. "That's it, I started, I just took it

> as I did it occasionally. Of course, when we were working deep in my problem, I needed it. I could see that everyone wasn't shy. I thought?: I'll take some too. I asked them if it could stop me from understanding or assimilating all this. They said, "Well, no, it's just going to make you feel better." You know, when you're stressed, when you can't deal with it anymore…" (Case #1)

> "No. The therapists had asked us not to do it, I did respect the . . . rule. I didn't know we couldn't. . . Never before the group. They had asked not to take any." (Case #3)

Motives Behind Benzodiazepine Use

During tCBT, most participants continued using benzodiazepines, except three, who either did not feel the need to take them or were given that indication by their therapist. For those who used benzodiazepines during therapy, taking a benzodiazepine was described as their first impulse to relieve their anxiety, particularly at the beginning of tCBT. The group therapy format was considered a major stressor for many, having to work on themselves and opening up in front of a group of strangers rather than a single therapist. Specifically, participants mentioned using benzodiazepines before, during or after tCBT sessions. Some took a benzodiazepine the night before the sessions to calm anticipation of attending the group therapy and get a good night of sleep. Others took a benzodiazepine on their way to therapy to reduce their apprehension, social anxiety, to overcome avoidance behaviour and to be able to leave their home to receive treatment. Some participants reported using benzodiazepines during tCBT sessions, either when sharing with other patients or during certain exercises, when the anxiety they experienced exceeded their perceived tolerance threshold. Finally, others took a benzodiazepine when they returned home on their own from a session, following challenging emotions that had emerged from tCBT. However, throughout the sessions, as they became more able to manage their anxiety and following discussions with patients who did not report using benzodiazepines, the majority

found that there were other ways to manage their anxiety that were just as effective, if not more effective, than benzodiazepines.

> "I remember going out of class at one point. Going to the bathroom, then taking a moment because there… I needed to take my Ativan because… I couldn't really leave. Well… I could have, but, you know, I wanted to stay. But in order for me to be able to stay, I had to… be able to stay." (Case #9)

After tCBT

After the 12-week group tCBT, different user profiles emerged: benzodiazepine use remained the same for 5 participants, while it decreased for 2, stopped for 4, or increased to the point of dependence for the 2 others. One recurrent term that emerged for most participants was that taking benzodiazepines was a "crutch" in their anxiety management and that they could not get rid of it overnight. Some participants for whom reducing or stopping benzodiazepine use was challenging, but for others getting rid of the safety behaviours associated with benzodiazepines (i.e., getting out of the house without their medicine bottle) was equally challenging.

> "I had told myself: if I'm in psychotherapy, it's to get rid of the crutch. It doesn't give me anything to live with that crutch. So, I try – you know, at this time, I go out, but without this medication. It's not always easy, but at least I'm not addicted to the medication anymore." (Case #2)

Theme 2: Components of tCBT and Benzodiazepine Use

Psychoeducation

According to participants, the components of the therapy for which they felt most compelled to use benzodiazepines were psychoeducation, exposure, and homework. Some participants mentioned that psychoeducation, which was part of the first therapy sessions, led to anticipation. They were faced with the therapists' explanations of the steps to go through to understand the

causes and nature of their anxiety and concerning eventual exposure. Participants were therefore confronted with all the work they would have to do to get better and benzodiazepines were used to reduce this anticipation.

> "I created scenarios based on what the psychologist explained to us. So, you know, when she said that we were going to be confronted with some of our anxieties, for me it was really – I didn't understand how I was going to get through that stage. That makes me think that it was really in the first stage that I took the most, because I was anticipating the actions." (Case #8)

Exposure

The exposure sessions also motivated benzodiazepine use, when they addressed fears through imagination or situational exposure exercises. Benzodiazepines could be used when exercises were perceived as exceeding the limit of their anxiety tolerance or bringing participants too far out of their comfort zone.

> "It's the exposure because it was really going to be . . . the most difficult thing for me. It forced me to do things that I really didn't want to do. It was totally out of my comfort zone. It's really the exposure." (Case #10)

Homework

Participants also raised the point that homework assignments regarding exposure exercises could motivate the intake of benzodiazepines. Some participants mentioned that being alone, without the support of a therapist and the group, to expose themselves, brought anxiety and a high level of discomfort.

Theme 3: Perceived Impacts of Benzodiazepines on the Effectiveness of tCBT Components

Taking benzodiazepines during therapy was described as a strategy to calm anticipation and alleviate some fears related to group participation. Integration into the group and active participation in therapeutic activities were facilitated, as participants were relieved of some

forms of anxiety and felt a decrease in their shyness. Some participants mentioned how reducing their anxiety load made them more receptive to focus on the contents presented and more willing to expose themselves. On the other hand, participants also perceived some disadvantages. They recognized that since their anxiety levels were reduced, their anxiety experiences were also reduced. Since they could not fully experience their anxiety, they perceived that the effectiveness of certain exercises, such as exposure, was impaired. Specifically, by being under mild sedation, they could not push their anxiety and discomfort levels to the maximum to fully extract the benefits of the exposure. In addition, some participants perceived that although benzodiazepines could reduce their anxiety level and thus help them participate more actively, they could also affect their concentration and attention during the therapy sessions. Others also felt that their memory skills could be affected during the sessions, especially when they had to apply the content seen in the session to their homework.

> "It impairs your judgment; it impairs your perception of things. Of course, if you have to expose yourself to something and then it's not tolerable… If every time you do it, you have benzos in your body, well, I don't see the point. I mean, maybe yes, the first time you're going to take them, but you have to learn how to do it without them. I think that's what psychotherapy is all about. It's to move through life without always needing a little pill to give you the courage to do it. It's treacherous, a little bit, these drugs. " (Case #7)

Discussion

This mixed methods study investigated benzodiazepine use during group tCBT, a therapy shown to be effective in the treatment of anxiety disorders (Newby et al., 2015; Roberge et al., 2020). The secondary data analysis of the BAI measure from the clinical trial dataset indicated globally that the positive impact of psychotherapy on reducing anxiety symptoms was not significantly different whether or not benzodiazepines were taken 12 months prior to tCBT

initiation. These results are consistent with studies that also found that benzodiazepines had no impact on CBT outcomes (Arch & Craske, 2007; Melani et al., 2020; Schmidt & Smith, 2005; Watanabe et al., 2009; Westra et al., 2002). The qualitative interviews provided a complementary and in-depth perspective, through the nuanced contributions of the participants. Getting involved in a therapy process where you must do personal work, particularly in front of a group of people, can be frightening. The participants' perceptions of the group modality stressors were related to what was found in previous studies: opening up and sharing one's experience with strangers can be a very challenging experience (Morrison, 2001). Participants' interviews indicated that benzodiazepines can be perceived as helpful in coping with the group treatment modality and being more receptive to CBT's therapeutic content. Also, for some participants for whom leaving their home was a source of anxiety, benzodiazepine use was helping them to reduce their anxiety to be able to attend the therapy group. Participants also provided information about which components of therapy were most likely to lead to the use of benzodiazepines: psychoeducation, exposure, and homework. Benzodiazepine use may be motivated by a desire to feel confident in a stressful situation (Parr et al., 2006), and our study underlined how the unknown of the first sessions and the anticipation of what may happen next in tCBT can lead participants to use benzodiazepines. Taking benzodiazepines during exposure sessions had been noted in the literature as potentially making these exercises less effective (Otto et al., 2010), and those concerns were also raised by participants indicating that they could not reap the full benefits of exposure as benzodiazepines decreased their experience of anxiety. While benzodiazepines can help calm this anxiety, they can also complicate the learning and the memorization of some content, which is caused by the known effects of benzodiazepines regarding mild sedation and cognitive functioning (Buffett-Jerrott & Stewart, 2002). Although some participants mentioned

that taking benzodiazepines during periods of exposure could decrease their anxiety and help them with their exposure exercises, due to the lack of scientific evidence about the effects of benzodiazepines on exposure, the use of benzodiazepines during those sessions should be evaluated with caution (Melani et al., 2020). Beyond the benefits and drawbacks of taking benzodiazepines during tCBT, participants emphasized the risk of dependence associated with this medication, again illustrating that benzodiazepines should be used with caution, as outlined in clinical practice guidelines (Katzman et al., 2014).

Some of the experiences reported by participants about therapists' instructions regarding the use of benzodiazepines during tCBT underlined that this topic was also ambiguous for them. Even though tCBT provided a detailed psychological intervention manual for therapists and a workbook for participants, the topic of medication use was not addressed. Our results suggest that consistent instructions need to be given to therapists in CBT protocols regarding the use of benzodiazepines during therapy. This also raises the point that it could be helpful to add a specific psychoeducation intervention regarding medication use, such as safety behaviour (Thwaites & Freeston, 2005) and tapering off. As outlined in the intervention protocol, the psychoeducation component already addresses some safety behaviours, but not specifically benzodiazepine use. The topic of benzodiazepine use could be discussed at the beginning of therapy to make participants aware of the potential effects of benzodiazepines on tCBT and help them make an informed decision about their use.

As identified in this study, tCBT does not necessarily lead to benzodiazepine discontinuation. When dealing with problematic benzodiazepine use, it would be helpful to refer participants to benzodiazepine withdrawal interventions. There are CBT protocols that

specifically address this issue, designed to help people change their benzodiazepine use (Darker et al., 2015; Lader et al., 2009).

This mixed methods study contributes to advancing knowledge about benzodiazepine use on CBT, a question previously examined mainly from a quantitative perspective. However, since we achieved our objectives in an already existing RCT, the study was not primarily conducted to assess the efficacy of combining or not tCBT with benzodiazepines. Therefore, the RCT design and measurement of benzodiazepine use over time were not optimal for our study objectives. Future studies would benefit from monitoring participants' patterns of use more closely, for example, by asking them to complete a diary for each therapy session and context of use more accurately. Completing a medication diary would also document patterns of benzodiazepine use, such as whether or not participants use them as prescribed. A limitation concerning the generalizability of the results of this study can also be raised, considering that the sample was mainly composed of highly educated and financially stable women. In addition, since the qualitative interviews were conducted approximately one year after participants received tCBT, the potential memory bias must be emphasized.

This study illustrates that the debate about the potential effects of benzodiazepines during tCBT is not over. Participants' sharing also revealed the importance of this subject to them and their desire for more guidance on an issue that directly affects their participation in CBT and potential treatment outcomes. It is clear from this study that research about benzodiazepines and CBT must be continued, and that clinical concerns of participants engaging in CBT must also be addressed.

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Table 1

Sociodemographic Baseline Characteristics of the 198 Participants

	n	(%)
Age (years; mean ± SD)	37.7 ± 11.98	
Sex (woman)	168	(84.8)
Marital status		
Married/Living together	112	(56.9)
Single	72	(36.5)
Separated/Divorced	13	(6.6)
Canadian citizenship at birth	161	(81.8)
Education		
High school or less	21	(10.7)
Vocational	20	(10.1)
College	69	(34.8)
University	88	(44.4)
Occupation		
Full-time work	121	(61.1)
Full-time student	36	(18.2)
Part-time work	17	(8.6)
Retirement	7	(3.5)
Other	17	(8.6)
Economic situation		
Comfortable or sufficient income	159	(80.3)
Poor	32	(16.2)
Very poor	6	(3.0)
Number of persons living in the household		
One person	46	(23.2)
Two persons	71	(36.2)
Three persons or more	81	(40.9)
Principal anxiety disorder		
Generalized anxiety disorder	108	(54.5)
Social anxiety disorder	55	(27.8)
Panic disorder – agoraphobia	35	(17.6)
Comorbidity with other anxiety disorders	147	(74.2)
Comorbidity with a depressive disorder	55	(27.8)
Use of psychotropic medication	152	(76.8)
Use of SSRIs and SNRIs	110	(55.6)
Use of benzodiazepines	67	(33.8)
Frequency of use (occasional)	54	(81)
Duration of use (at least 12-month)	38	(56)

Molecule used		
Clonazepam	28	(42)
Lorazepam	28	(42)
Bromazepam	2	(3)
Alprazolam	4	(6)
Oxazepam	5	(7)

Table 2
Multiple linear regression analysis of the effect of baseline benzodiazepine use on the association between group tCBT and change in anxiety symptoms

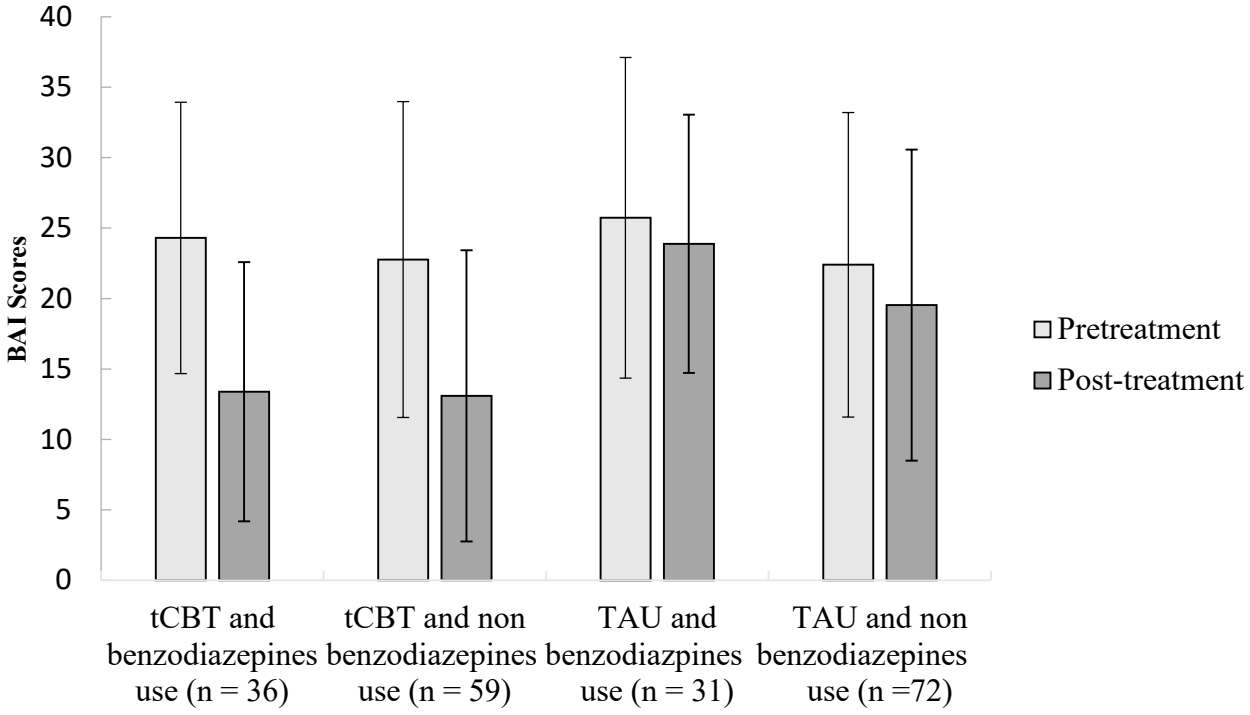
	Unstandardized coefficients		Standardized coefficients		
Model	ß	Standard error	Beta	T	*p*
Constant	10.84	4.21		2.58	0.011
tCBT	-6.46	1.89	-0.28	-3.43	0.001
Benzodiazepine use	1.02	2.30	0.04	0.45	0.665
tCBT*Benzodiazepine	-2.56	3.23	-0.85	-0.79	0.429
Severity of anxiety symptoms	-2.42	0.71	-0.23	-3.42	0.001

Note. Dependent variable: BAI score post-pre change ($R^2 = 0.16$).

Table 3
Cases presentation

Case	Sex	Age group	Type of user 12 months before baseline	Principal anxiety disorder	Number of tCBT sessions
1	F	35-45	Occasional	Generalized anxiety disorder	11
2	M	35-45	Occasional	Agoraphobia	11
3	F	55-65	Regular	Generalized anxiety disorder	8
4	F	45-55	Regular	Generalized anxiety disorder	10
5	F	35-45	Occasional	Generalized anxiety disorder	12
6	F	35-45	Occasional	Social anxiety disorder	10
7	F	25-35	Occasional	Generalized anxiety disorder	10
8	F	25-35	Regular	Panic disorder	11
9	M	25-35	Occasional	Panic disorder	11
10	F	35-45	Occasional	Social anxiety disorder	10
11	M	35-45	Regular	Social anxiety disorder	12
12	F	35-45	Regular	Generalized anxiety disorder	8
13	F	55-65	Occasional	Social anxiety disorder	10

Figure 1
BAI scores at pretreatment and post-treatment



Note. Error bars show standard deviations.

Supplemental Material A: Interview guide

Introduction

- Thank the participant for participating in today's interview.
- Explain the purpose of the interview.
- Explain that there are no right or wrong answers to the questions.
- Share the reality of adults with anxiety disorders starting psychotherapy: *many people use medication before starting psychotherapy.*

Icebreaker Questions

Can you tell me a bit about your experience in this psychotherapy?

- *How did the intervention help you?*
- *What challenges have you encountered?*

What did you think of an intervention offered in a group format?

- Benefits?
- Limitations?

How would you qualify your participation in the program?

- Number of sessions
- Involvement in the sessions
- Participation in the exercises and homework

General questions about medication use

Can you share with me your experience using medication for your anxiety disorder?

- Classes of medication used?
- Regular? Occasionally?
- For how long?

Benzodiazepine use behaviours and tCBT

Spontaneously, what comes to your mind when I ask you about your use of benzodiazepines for your anxiety?
How are you feeling after taking benzodiazepines?

If we go back in time, <u>12 months before tCBT</u>, in which context did you use benzodiazepines?

- *Under what circumstances?*
    - Was it associated with any particular situations?
- *Was it associated with any particular anxiety symptoms?*

<u>During tCBT</u>, how was your use of the benzodiazepines?

- *Under what circumstances?*
    - Was it associated with any particular situations?
- *Was it associated with any particular anxiety symptoms?*
- *Throughout the sessions, did your use decrease? Increased? Remain stable?*
- *What were the therapists' instructions about benzodiazepine use during sessions?*

<u>Twelve months after tCBT</u>, what was your benzodiazepine use like?

- Under what circumstances?
    - Was it associated with any particular situations?
- Was it associated with any particular anxiety symptoms?

Components of tCBT and benzodiazepine use

The following questions are about your use of benzodiazepines in the context of your participation in tCBT.

- *I would like to understand the impact of a therapy offered in a group format on your benzodiazepine use. Can you tell me more about it?*
- *How might group therapy have influenced your use of benzodiazepines?*
- *Did you feel any impact on your participation and involvement in the group? If so, which impacts?*
- *If therapy had been offered in an individual format, how would your benzodiazepine use be?*

Secondly, I would like to know more about your use of benzodiazepines regarding the themes and exercises discussed in therapy.

*** Reminder of the themes (psychoeducation, cognitive restructuring, exposure, relapse prevention) and provide concrete examples.*

- *What components were most likely to motivate the use of benzodiazepines? Why?*
- *Is it associated with any particular exercises or themes? If so, which ones?*
- *Did you experience any impacts (+ or -) from your use of benzodiazepine on your participation in exercises? If so, which ones?*

Perception of the potential influence of benzodiazepines on tCBT

I would like to understand your perception of the potential impact of your use of benzodiazepines on tCBT.

- *Is using benzodiazepines during therapy... more helpful? Less helpful? Can you tell me more about it?*
- *Do you believe that your use of benzodiazepines had an impact (+ or -) on your therapy experience? If so, what was it?*
- *What would you recommend to someone using benzodiazepines interested in participating in this therapy?*

Safety behaviours

Explain what safety behaviours are and give some examples.

- *Other than using benzodiazepines, do you use other safety behaviours?*
- *Under what circumstances?*
- *When did you start using them?*
- *How do these behaviours help you?*

Conclusion of the interview

Questions, comments?

Thank the participant for his or her sharing and contribution.

Supplemental Material B: Exploratory analyses

Table 1.
Multiple linear regression analysis of the effect of baseline benzodiazepine use on the association between group tCBT and change in anxiety symptoms, without the severity of anxiety symptoms variable

	Unstandardized coefficients		Standardized coefficients		
Model	ß	Standard error	Beta	T	*p*
Constant	-2.86	1.30		-2.20	0.029
tCBT	-6.82	1.94	-0.29	-3.53	0.001
Benzodiazepine use	1.00	2.36	0.04	0.42	0.672
tCBT*Benzodiazepine	-2.25	3.32	-0.07	-0.68	0.499

Note. Dependent variable: BAI score post-pre change.

Table 2.
Multiple linear regression analysis of the effect of baseline benzodiazepine use on the association between group tCBT and change in anxiety symptoms, by comparing occasional and regular users

	Unstandardized coefficients		Standardized coefficients		
Model ¥	ß	Standard error	Beta	T	*p*
Constant	11.82	4.46		2.65	0.009
tCBT	-10.87	2.96	-0.47	-3.67	0.001
No benzodiazepine use	-1.01	2.36	-0.04	-0.43	0.670
Regular benzodiazepine use	0.37	7.86	0.01	0.05	0.963
tCBT*No benzodiazepine	4.40	3.51	0.17	1.26	0.211
tCBT*Regular benzodiazepine use	5.23	8.73	0.11	0.60	0.550
Severity	-2.41	0.71	0.23	-3.40	0.001

Note. Reference group: occasional users in the TAU group