The efficacy of cognitive behavioral therapy for insomnia in a structured program of benzodiazepine withdrawal on cognitive function and sleep in the elderly: a pilot study.

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This is to certify that the thesis prepared

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Abstract

Background: Benzodiazepines are prescribed for anxiety and insomnia. In majority of cases, consumption of benzodiazepines becomes chronic and accompanies risks and comorbidities affecting a wide range of cognitive abilities. Cognitive behavioral therapy for insomnia (CBT-i) is the first line therapy for treating insomnia. Implementation of this therapy with benzodiazepine withdrawal programs can improve sleep quality and weaning success rate.

Objective: To evaluate the effect of CBT-i on cognition upon withdrawal from a prolonged benzodiazepine consumption for chronic insomnia.

Methods: 24 insomniacs aged 60 years or older, after undergoing a comprehensive sleep and cognitive evaluation, were randomly assigned into two groups of CBT-i (n=12) and waitlist (n=12). While both groups followed a structured and progressive benzodiazepine withdrawal program over 16 weeks, the CBT-i group additionally received 8 sessions of CBT-i therapy. At the end of the weaning program, both groups underwent the same sleep and cognitive evaluations.

Results: All of sleep diary measures improved in the CBT-i group. Both groups showed improvements in insomnia severity index (p=0.000) and Pittsburgh Sleep Quality Index (p=0.002), while the latter improved more notably in the CBT-i group (p=0.014). Actigraphy, highlighted improved sleep efficiency (p=0.000) and decreased wake after sleep onset (p=0.008) in CBT-i group. The cognitive tests showed improvements in the reading speeds (time, p=0.000; score, p=0.006) and recall copying ability (p=0.040) of the CBT-i group.

Conclusion: This study, highlight the benefits of supplementing benzodiazepine withdrawal with CBT-i related to improvements in sleep quality, while also sheds some lights on its possible effects on cognition.

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List of abbreviations:

ANOVA: Analysis of variance

CBT-i: Cognitive Behavioral Therapy for Insomnia

D-KEFS: Delis–Kaplan Executive Function System

DSST: Digit Symbol Substitution Test

EEG: Electroencephalography

EOG: Electrooculography

ESS: Epworth Sleepiness Scale

FCSRT: Free and Cued Selective Reminding Test

GABA: Gamma-Aminobutyric Acid

GAI: Geriatric Anxiety Inventory

GDS: Geriatric Depression Scale

ISI: Insomnia Severity Index

IUGM: Institut Universitaire de Gériatrie de Montréal

MMSE: Mini-Mental State Examination

MTCF: Modified Taylor Complex Figure

NREM: Non-Rapid Eye Movement

PSG: Polysomnography

PSQI: Pittsburgh Sleep Quality Index

TMT: Trail Making Test

Introduction:

Definition, prevalence and risk factors of insomnia

Primary insomnia is a prevalent sleep disorder that is not caused by medical conditions, psychiatric diseases, or environmental factors and is subjectively characterized by difficulties falling asleep (a latency of more than 30 minutes), staying asleep (more than 3 awakenings per night for more than 30 minutes), or having a non-restorative sleep affecting daytime functioning, which persists over three months (American Psychiatric Association, 2013). 15% of adults suffer from chronic insomnia (Reite, Weissberg, & Ruddy, 2008) while up to 60% report experiencing one or more of insomnia symptoms (Ancoli-Israel & Roth, 1999; Barbar et al., 2000; Foley, Monjan, Simonsick, Wallace, & Blazer, 1999; Foley et al., 1995; Schubert et al., 2002; Woodward, 1999). According to the 3-P model proposed for insomnia (Figure 1), there are many risk factors contributing to development or exacerbation of insomnia which can be classified into three main categories: predisposing factors; precipitating factors; and perpetuating factors (Spielman, Caruso, & Glovinsky, 1987). The predisposing factors are individual traits and mainly include biological traits such as aging, female gender (particularly after menopausal onset) (Johnson, Roth, Schultz, & Breslau, 2006), family history of insomnia, psychological and personality traits including anxiety and depression, as well as lifestyle factors like smoking habits (Ohayon, 2002). Precipitating factors, on the other hand, are external factors that contribute to insomnia complaints and include experiencing stressful life events (e.g., death of a close relative, divorce, unemployment), as well as medical or psychological complications (C.M. Morin, 1993; C. M. Morin, Rodrigue, & Ivers, 2003). Finally, perpetuating factors chiefly

contribute to exacerbation or preservation of insomnia and include poor sleep hygiene and habits such as wrong beliefs about insomnia, maladaptive coping strategies for insomnia, or using chronic sleep medications (C.M. Morin, 1993). Although the exact cause of insomnia is not yet defined, it is suggested that in elderly, presence of medical and psychological comorbidities contribute significantly to insomnia complaints (Ford & Kamerow, 1989; Katz & McHorney, 1998).

Pathophysiology of insomnia

Various models have been proposed to explain development of insomnia:

Psychiatric disorders: Forty percent of insomniacs have comorbid psychiatric disorders (Ford & Kamerow, 1989) among which mood and bipolar disorders, as well as depressive and anxiety disorders are the ones that associate most commonly with insomnia (Breslau, Roth, Rosenthal, & Andreski, 1996; Buysse et al., 1994; Simon & VonKorff, 1997).

Medical disorders: Chronic medical conditions are commonly associated with poor sleep quality. Insomniacs with respiratory disorders, whether obstructive or restrictive lung disease, commonly experience sleep disturbances due to apnea, hypopnea, blood oxygen desaturation, or coughing (Weitzenblum & Chaouat, 2004). Cardiovascular comorbidities can contribute to disrupted sleep related to hypoxia due to poorer blood perfusion, orthopnea, and paroxysmal nocturnal dyspnea (Hayes, Anstead, Ho, & Phillips, 2009). Among other medical conditions, gastrointestinal diseases can cause heartburn, dyspepsia, acid brash, coughing, or choking which can lead to awakenings after sleep onset and hence a disrupted sleep (Chen, Robert, & Orr,

2008; Shaker, Castell, Schoenfeld, & Spechler, 2003). Also, females, at the onset of menopause, report experiencing disturbances in sleep related to night sweats which can be explained by hormonal changes and the vasomotor instability (Ohayon, 2006).

Normal aging: Epidemiological data suggest worsening in various sleep measures associated with aging. Older adults, compared with younger ones, experience a longer sleep latency, more fragmented sleep, longer awakenings after sleep onset, lower sleep efficiency and a shorter sleep duration (Dement, Miles, & Carskadon, 1982; Rajput & Bromley, 1999; Reynolds et al., 1985). In addition, slow wave sleep, which has a key role in sleep homeostasis, is decreased with age (Dement et al., 1982). The changes in sleep architecture of older adults could be related to various factors. Changes in the psychosocial aspects of elderlies' life including retirement, loneliness, and isolation can directly or indirectly affect their sleep. Older adults are more likely to have reduced daily physical activity, which in turn by promoting daytime napping can decrease the drive to sleep and hence disturb the night time sleep (Ancoli-Israel & Ayalon, 2006). Throughout normal aging, certain biological processes change which can make sleeping more difficult. Elderlies experience shifts in their normal circadian rhythm such that they go to bed earlier and wake up too early in the morning (Wolkove, Elkholy, Baltzan, & Palayew, 2007). As previously discussed, presence of medical and psychiatric comorbidities related to aging can also lead to sleep complaints (Breslau et al., 1996; Buysse et al., 1994; Chen et al., 2008; Hayes et al., 2009; Shaker et al., 2003; Simon & VonKorff, 1997; Weitzenblum & Chaouat, 2004). Due to the complications and comorbidities related to aging, there is a combination of factors that contribute to the development insomnia in elderly.

Hyperarousal Model: Insomniacs, when compared to good sleepers, are thought to be in a state of hyperarousal, whether a physiological or a cognitive-emotional one (Bonnet & Arand, 2010). Physiological hyperarousal in insomniacs can be characterized by factors such as heart rate variability, neuroendocrine measures, sympathetic and parasympathetic responses, as well as functional neuroimaging. As such, insomniacs with physiological hyperarousal show peripheral vasoconstriction, increases in core body temperature, body movements, and heart rate, as well as a decrease in heart rate variability prior to and during sleep (Bonnet & Arand, 1998, 2003; Freedman & Sattler, 1982; Monroe, 1967). In addition, elevated free cortisol level measured in the insomniacs' urine evidences chronic stress response in this population (Vgontzas et al., 2001; Vgontzas et al., 1998) which correlates positively with the amount of time spent awake after sleep onset (Vgontzas et al., 1997). A positron emission tomography study reported higher cerebral glucose metabolism in insomniacs during the transition from wake to non-rapid-eye-movement (NREM) sleep, compared to good sleepers, further demonstrating a hyper aroused brain in this population (Nofzinger et al., 2004). Cognitive-emotional hyperarousal, is characterized by increased obsessive thinking on life stressors combined with poor stress coping skills which can in turn impede the ability to go to sleep and subsequently disturb sleep quality and continuity. Development of insomnia in these people can lead to a shift in focus from negative thoughts about life stressors to worrisome thoughts about the consequences of their insomnia which can further deteriorate their sleep quality (Harvey, 2002). The findings of quantitative electroencephalography (EEG) studies are also in line with the hyperarousal model proposed for insomnia. Unlike normal sleep where transition from wakefulness to sleep

is followed by a decrease in high frequency brain activity (beta and gamma power) and an increase in slow activity (delta power) (De Gennaro, Ferrara, & Bertini, 2001), insomniacs show increased beta and gamma activity prior to and during the sleep as well as decreased delta activity throughout the NREM sleep (Lamarche & Ogilvie, 1997; Staner et al., 2003).

Consequences of insomnia

Whether insomnia is developed due to physiological hyperarousal or cognitive-emotional one, insomniacs mainly experience various comorbidities and impaired daytime functioning affecting a wide range of domains including cognition (attention, memory, concentration, decision making ability, etc.), mood (irritability, motivation, and energy), daytime sleepiness, accidents, personal and social relationships, occupational and academic performance. In other word, the quality of life in this population is notably reduced (American Academy of Sleep Medicine, 2014; Fortier-Brochu, Beaulieu-Bonneau, Ivers, & Morin, 2012; Leger, Scheuermaier, Philip, Paillard, & Guilleminault, 2001). Insomniacs, compared to good sleepers, have slower reaction times, poorer vigilance and attention, higher degrees of daytime sleepiness, and are 2.5 to 4.5 times more prone to be involved in accidents (Balter & Uhlenhuth, 1992). In regards to the cognitive abilities, a large longitudinal study on men above the age of 50, reported an association between sleep disturbances and an increased risk for dementia and Alzheimer's disease (Benedict et al., 2015). Studies in younger adults have demonstrated that presence of insomnia symptoms among students significantly reduces their academic performance, as reflected in their grades (Trockel, Barnes, &

Egget, 2000). At work, insomniacs have poorer ability in performing more demanding tasks such as the ones requiring switching of attention (Shekleton et al., 2014) and also tend to be more frequently on sick leaves due to their insomnia (Simon & VonKorff, 1997). In addition to the daytime functioning impairments, insomniacs experience medical and psychological comorbidities related to their insomnia. It is reported that 40% of all insomniacs experience some types of psychiatric disorders – depression and anxiety being the most common ones, present in about 14% and 24% of the cases respectively (Becker, 2006). Although in the majority of cases the symptoms of psychiatric disorders coexist with insomnia, it is still not clear whether these are consequence of insomnia or a risk factor for it. This can possibly explain that a common physiological mechanism might exist that makes the individuals vulnerable to both conditions. Previous studies have consistently reported increased prevalence of medical conditions associated with insomnia symptoms. They highlighted that short sleep duration is associated with increased glucose intolerance and is shown to be a risk factor for development of type 2 diabetes (Gottlieb et al., 2005). Insomniacs generally have higher blood pressures compared to good sleepers when controlled for other major confounding variables. Studies have shown an association between short sleep duration and high risk for hypertensive diseases (Suka, Yoshida, & Sugimori, 2003; Vgontzas, Liao, Bixler, Chrousos, & Vela-Bueno, 2009).

Treatment options for insomnia

Various treatment possibilities are proposed for insomnia which can be broadly categorized into pharmacological and non-pharmacological treatments options.

1) Pharmacological options: Sedating antidepressants are the most prescribed medications for insomnia (National Institutes of Health, 2005). These hypnotics belong to either benzodiazepine or non-benzodiazepine family. The selection of the right option is influenced by several factors including symptoms and duration of insomnia, previous treatment experience, treatment goals, patient's preference, cost, and the medication side effects.

Benzodiazepine hypnotics are suppressants of the central nervous system acting through binding to both subtypes of gamma-aminobutyric acid (GABA) type A receptors (GABA-Benzodiazepine-1 and GABA-Benzodiazepine-2) which are ligand-gated chloride-selective ion channel in the central nervous system (Lieberman, 2007). Binding of the specific ligands and activation of GABA receptors leads to opening of the chloride channels, influx of chloride ions into the neuron, and hyperpolarization of the neuron. Because of the wide distribution of GABA receptors in the nervous system, GABA plays a role in various functions including regulating anxiety, pain, release of sex hormones, blood pressure, blood sugar, and etc. It is suggested that GABA also contributes to regulating memory and sleep. For instance, GABA-Benzodiazepine-1 is shown to regulate wake-sleep cycle and promote drowsiness while GABA-Benzodiazepine-2 is involved in regulating memory, cognitive performance, and psychomotor functioning (Wamsley & Hunt, 1991). A theory supporting the involvement of benzodiazepines in promoting sleep suggests that these ligands bind non-specifically to the two subtypes of GABA-A receptors and promote relaxation and drowsiness (Nutt, 2006), which can in turn treat problems related to the onset and maintenance of the sleep. Although benzodiazepines decrease the sleep onset latency, the total number of awakenings,

and also increase the total sleep time, they alter the sleep architecture. At the macro level, these hypnotics increase the proportion of sleep spent in stages N1 and N2 of NREM sleep, while suppressing the deep sleep (stage N3 of NREM sleep) and REM sleep (Greenblatt, 1991). At the micro level, chronic consumers of benzodiazepines show increased sleep spindles, higher brain activity in theta, sigma, and beta frequencies, and decreased slow wave activity. Benzodiazepines, like any other medication, are not free of side effects and their chronic use can lead to complications including impairments in psychomotor and cognitive performance, and anterograde amnesia (Ashton, 1994; Vgontzas, Kales, & Bixler, 1995). In long term, these medications can lead to development of tolerance, which in turn demands an increase in the medication dose to remain effective. This vicious cycle is usually followed by physiological and psychological dependence (Colbert, 2008; Vgontzas et al., 1995).

Non-benzodiazepines act similarly to benzodiazepines, except that unlike benzodiazepines, they selectively bind to GABA-Benzodiazepine-1 receptors, and promote drowsiness and sleep. Non-benzodiazepines, compared to sedatives in benzodiazepine family, are accompanied by less severe side effects (in cognitive and psychomotor performance), tolerance, and dependence, which could be explained by their low affinity towards binding to GABA-Benzodiazepine-2 receptors (Berlin et al., 1993; Mintzer, Frey, Yingling, & Griffiths, 1997; Wesensten, Balkin, & Belenky, 1996) and their shorter half-life.

Melatonin agonists: Melatonin is a hormone secreted by the pineal gland during the night, which binds to the melatonin receptors located in the suprachiasmatic nucleus and controls the circadian timing system (Arendt, 1988). Short term use of Melatonin

agonists such as Ramelteon has been associated with a decrease in subjective sleep latency and an increase in total sleep time (Kuriyama, Honda, & Hayashino, 2014; Roth et al., 2006). Since this medication decreases the sleep latency, it is more effective in treating sleep onset insomnia, rather than problems related to the sleep maintenance. Melatonin agonists, unlike benzodiazepines, accompany milder side effects (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008) and have smaller potentials to cause dependence. Although Melatonin agonists show promising improvements in sleep measures and are shown to be safer, the effect sizes for the data are relatively small.

Orexin receptor antagonists: Orexin – also known as hypocretin – is a hypothalamic neuropeptide that regulates sleep-wakefulness cycles. Two subtypes of hypocretins, Orexin A and B, play a key role in promoting wakefulness and regulating the sleep-wake cycle (Mieda & Sakurai, 2012). Limited number of studies have suggested potential effect of orexin receptor antagonist on improvements of insomnia. It has been proposed that Orexin receptor antagonists, by binding to orexin receptors, can inhibit the wakefulness promoting effect of orexins and hence help with natural transition from wakefulness into sleep (Colbert, 2008). Clinical trial studies have reported these medications as safe drugs with low level of physical dependence and withdrawal symptoms.

2) Non-pharmacological options: In addition to the pharmacological therapy option, there are psychological and behavioral techniques that can help treat insomnia, among which cognitive behavioral therapy for insomnia (CBT-i) is the most effective one (Suh, 2015). CBT-i, unlike pharmacotherapeutic options, is effective in longer term and

has minimal adverse effects (C. M. Morin et al., 2006). For this reason, many governmental bodies, including the National Institute of Health Consensus Statement (National Institutes of Health, 2005), American College of Physicians (Qaseem et al., 2016), and British Association of Psychopharmacology (Wilson et al., 2010) recommend CBT-i as the first line of treatment for insomnia. CBT-i is a structured therapy program, offered individually or in groups, that combines various psychological and behavioral components that aim to improve sleep habits and behaviors. These components include cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation which are further detailed bellow:

Cognitive therapy aims to identify and correct dysfunctional beliefs and misconceptions about sleep and insomnia, including wrong impressions about minimum daily sleep requirements, fears about losing sleep, or over-estimating the consequences of insomnia. Negative thoughts about insomnia prior to sleep could trigger the autonomic arousal system and hence negatively affect sleep quality and integrity (Harvey, 2002; Harvey, Sharpley, Ree, Stinson, & Clark, 2007; C. M. Morin et al., 2006).

Stimulus control aims to educate the patients to associate the bed only with sleeping and not with any other activity whether stimulating or not (C. M. Morin et al., 2006). These instructions include but not limited to, going to bed only when sleepy, not spending more than 20 minutes in bed awake, leave the bed if cannot fall asleep within this 20-minute time frame, and only return when sleepy again.

Sleep restriction component, as the name suggests, instructs the patients to limit their sleep and the time in bed (C. M. Morin et al., 2006; Spielman, Saskin, & Thorpy, 1987). Although this might sound counterintuitive to its role in improving the insomnia

complaints, sleep restriction increases the sleep pressure and the homeostatic drive to sleep and hence improves the sleep efficiency.

Sleep hygiene educates the patients about the environmental, physiological, behavioral, and habitual factors that promote a well-integrated sleep (C. M. Morin et al., 2006). The list includes but is not limited to avoiding daytime naps, restricting alcohol, caffeine, and nicotine intake, dietary advices, and instructions on how to keep the bedroom environment optimal for sleeping.

Relaxation consists of a collection of techniques that can be used based on the patient's personal choice, including meditation, mindfulness, progressive muscle relaxation, guided imagery, and breathing techniques (C. M. Morin et al., 2006). The purpose of this component is to reduce the cognitive arousal and muscle tensions, and promote sleep.

While medications need to be continuously consumed in order to remain effective, CBT-i helps insomniacs to develop skills, which can be applied even after the termination of the intervention. In fact, this might explain why CBT-i shows a better efficacy in treating insomnia in the long term, compared to pharmacotherapeutic options. One study, evaluating the effect of non-pharmacological sleep therapy on brain functional activity in a small sample of chronic insomniacs (n=21), reported hypoactivation of prefrontal cortex in chronic insomniacs (compared to controls) which recovered upon receiving a six week non-pharmacological sleep therapy consisting of CBT-i, body temperature and bright light interventions, and physical activity counseling (Altena et al., 2008). Given the role of prefrontal cortex in attention and executive

function, CBT-I therapy complementing the benzodiazepine withdrawal could potentially help improve this domain.

Chronic use of benzodiazepines in Elderly

Benzodiazepines are prescribed extensively to elderly mainly for anxiety and insomnia complaints. In Canada, about 25% of adults over the age of 65 consume benzodiazepines (Hogan et al., 2003). Although the recommended treatment duration is usually between two to four weeks, in majority of cases this consumption becomes chronic either due to the dependency developed during the four weeks of consumption, or over-prescriptions by doctors. Accordingly, in Quebec, 20% of the elderly population take benzodiazepines in the long course (Egan, Moride, Wolfson, & Monette, 2000). This prolonged use is not free of risks. Many studies have demonstrated associations between chronic consumption of benzodiazepines and the occurrence of comorbidities in elderly. In particular, the chronic use of benzodiazepines is shown to be a risk factor for the cognitive decline, which can affect a wide range of cognitive functions such as memory, attention, concentration, and psychomotor performance (Barker, Greenwood, Jackson, & Crowe, 2004a; Golombok, Moodley, & Lader, 1988). A 15-year longitudinal study on 253 dementia patients revealed that the use of benzodiazepines increases the risk of development of dementia by 50% (Billioti de Gage et al., 2012). Chronic use of benzodiazepines does not only affect the mental and cognitive performance, but also the physical abilities. Older adults with chronic benzodiazepine consumption are at greater risks of mobility incidences and disabilities related to activities of daily living (i.e., bathing, eating, dressing, walking, doing the daily chores) (Gray et al., 2006). These

people are also at higher risks for falls and experiencing hip fractures (Cumming & Le Couteur, 2003; Ray, Griffin, Schaffner, Baugh, & Melton, 1987; Tom, Wickwire, Park, & Albrecht, 2016). The excessive use of benzodiazepines has a direct negative impact on the cognitive and physical well-being of the elderly population.

Benzodiazepines withdrawal in elderly

Given the detrimental effects of chronic benzodiazepine consumption on cognition and physical abilities, several studies have investigated whether these deficits would remain after weaning from these hypnotics. The result of these studies show that cessation of treatment with benzodiazepines improves all cognitive domains affected, notably improving attention, concentration, psychomotor speed, problem solving abilities, and visuospatial skills with a medium effect size or larger ($d>0.5$) (Barker, Greenwood, Jackson, & Crowe, 2004b). However, this recovery is not complete and the weaned patient would retain some residual deficits in most cognitive functions as compared to individuals who have never used these drugs (Barker et al., 2004b; Barker, Greenwood, Jackson, & Crowe, 2005). The persistence of these deficits could be explained by the maintenance or worsening of sleep disturbances secondary to weaning.

Although studies support the notion that withdrawal from benzodiazepines can help improve, even though partially, the affected cognitive and physical domains, there are limitations to this strategy. Primarily, the weaning success rate in chronic benzodiazepine users is not optimal. A randomized control trial evaluating the weaning success rate in an elderly population with chronic benzodiazepine use, reported that

only 48% of patients completely succeeded in becoming medication free (C. M. Morin et al., 2004). Withdrawal from benzodiazepines does not target correcting for the underlying problem that caused taking these medications in the first place. This is indeed important since an individual who had been taking benzodiazepines for sleep problems, would most likely experience the same troubles after weaning, if their insomnia is not treated during the weaning period.

Combination of CBT-i and benzodiazepine withdrawal

Given the limitations that weaning from benzodiazepines accompany (low weaning success rate, persistence of residual deficits, and rebound of the underlying condition), and the high efficacy of CBT-i in treating chronic insomnia, recent studies have investigated the efficacy of a combination therapy consisting of CBT-i and a structured weaning intervention. The results show that implementation of CBT-i can achieve a complete cessation of benzodiazepine use in 85% of elderly patients as opposed to 48% in case of withdrawal without CBT-I (C. M. Morin et al., 2004). Also, improvements in sleep quality related to benzodiazepines are not maintained in long term and sleep indices gradually return to the baseline values within a year (C. M. Morin, Colecchi, Stone, Sood, & Brink, 1999). However, combination of CBT-i and weaning intervention lead to improvements in sleep parameters which are maintained even one year after the intervention. Thus, not only these data represent CBT-i as the treatment of the choice for insomnia, they further highlight the key role of this psychotherapy in helping weaning from benzodiazepines.

The research rationale:

Even though the existing studies have shown that CBT-i improves the weaning success rate as well as the sleep quality in older adults (C. M. Morin et al., 2004; C. M. Morin et al., 1999), the effect of CBT-i on improving cognitive performance in elderly population is understudied.

Since CBT-i allows weaning with higher success rates among a greater proportion of patients (C. M. Morin et al., 2004) and this withdrawal is accompanied by a cognitive improvement (Barker et al., 2004b), even though partial, we expect that this psychological intervention leads to an improved cognitive recovery.

The research objectives:

Over the course of my Master's degree, we intended to evaluate the effect of CBT-i on sleep and cognition in elderly population upon withdrawal from a prolonged benzodiazepines consumption prescribed for chronic primary insomnia. We proposed to conduct a prospective randomized controlled study evaluating the sleep measures and neuropsychological performance before and after the withdrawal response, among a group of elderly who were randomly assigned into two groups, one initially receiving a cessation intervention only (waitlist group), and the other, a combined CBT-i and cessation intervention (CBT-i group). The objectives of the study were to evaluate the potential benefits of CBT-i on improving sleep and cognitive performance secondary to benzodiazepine withdrawal among an elderly population.

The research hypotheses:

Given the potential benefits of CBT-i on improving the sleep quality and weaning success rate in older adults with chronic insomnia, we propose a two-tiered hypothesis:

1) Upon weaning, the sleep quality, more particularly the subjective sleep measures, will improve in CBT-i group compared to the controls (waitlist group)
2) While both groups will show improved cognitive performance as a result of benzodiazepine withdrawal, this improvement is more pronounced in the CBT-i group, more particularly in attention and executive function.

Material and methods

A schematic of the study design is presented in Figure 2.

Participants

Participants were recruited via various methods, but mainly through outpatient clinics of Institut Universitaire de Gériatrie de Montréal (IUGM) where Dr. Dang-Vu is a consultant neurologist specialized in sleep disorders and researcher. Information sheets regarding the inclusion and exclusion criteria of the study were distributed to the doctors and staff and the information of the potential patients were entered in the IUGM participants' database. Patients were also recruited through local posters that were displayed at the research center of IUGM as well as a series of external pharmacies that previously participated in similar studies of benzodiazepine withdrawal. In addition, a few participants were recruited through a series of interviews with different newspapers/journals (e.g., Metro, Le Bel Age) as well as radio-television channels (e.g., Radio Canada).

Inclusion criteria: patients with the following criteria were deemed eligible:

1) 60 years of age or more
2) Having used benzodiazepines for chronic insomnia at more than 50% of the nights for the past 3 months.

Exclusion criteria: the patients should have not had any of the following:

1) Pronounced cognitive deficits (MMSE score less than or equal to 23/30);
2) Dementia;
3) Parkinson's disease;

4) Severe sensory or motor impairments;
5) History of epilepsy;
6) Current uncontrolled major depression defined by a clinical diagnosis for which no medication is being taken;
7) Psychotic disorders or current consumption of antipsychotic medications;
8) History of alcoholism or drug abuse;
9) Moderate to severe sleep apnea (more than 15 apnea and/or hypopnea events per hour);
10) Palliative care;
11) Insufficient knowledge of French language (since the CBT-i sessions are offered in French, and neurocognitive tests should be made in the same language across participants, to allow comparisons between subjects).

After an initial phone screening according to the above-mentioned inclusion/exclusion criteria, potentially eligible participants were personally interviewed, using semi-structured questionnaires, by a psychologist for further evaluating their general eligibility as well as a psychiatrist for assessing the psychiatric exclusion criteria. The ones who passed these screenings, after agreeing to continue participating in the study and signing the informed consent form, underwent a polysomnography (PSG) sleep recording using the SOMNO-screen device (SOMNOmedics, Randersacker, Germany) in the sleep lab located at the research center of IUGM. The PSG montage consisted of EEG and electrooculography (EOG) referenced to linked mastoids, as well as recordings of nasal/oral airflow, submental bipolar and bilateral tibialis electromyography, electrocardiography, transcutaneous finger pulse oximeter, as

well as thoracic and abdominal effort. This first in-lab PSG night was used to evaluate and rule out the presence of any possible sleep disorders besides insomnia, such as moderate to severe sleep apnea (index>15 events/hour) as they served as exclusion criteria. Additionally, this PSG recording acted as a habituation night, to minimize the effects of the new environment and the discomforts due to the PSG equipment on the quality of the sleep.

Sleep evaluations at the baseline

The participants who were still eligible after the PSG screening then underwent a comprehensive objective and subjective sleep evaluation. The objective sleep evaluations included a second night of in-lab PSG recording, as well as actigraphy recording using a wrist worn accelerometer (Actiwatch, Respironics, Pittsburgh, PA) that monitors sleep pattern by recording a combination of intensity, amount and duration of the wrist movement and light intensity.

The PSG recording was done at the research center of IUGM using a 33 channel SOMNO-screen device. The participants were given information about the PSG well in advance, and were asked to refrain drinking alcoholic and caffeinated drinks and also avoid intense physical activity for at least 8 hours prior to the PSG recording. On the day of the recording, subjects arrived to the sleep lab about two hours prior to their normal sleeping time to allow ample time for installation of the electrodes. The montage consisted of EEG and EOG referenced to linked mastoids as well as recordings of submental bipolar electromyography and electrocardiography. Participants went to bed at their usual bedtime and slept until spontaneous wake. The PSG recordings were

scored in 30-second epochs according to the American Academy of Sleep Medicine (AASM) scoring criteria (Iber, 2007). The PSG analyses allows characterization of the sleep microarchitecture and calculation of certain sleep parameters such as the latency to the sleep onset, total sleep time, duration of wakefulness after the sleep onset, as well as sleep efficiency and sustained sleep efficiency. Latency to the sleep onset, also known as sleep latency, is defined as the time it takes from the point that the individual tries to go to sleep until the sleep onset. Total sleep time is the duration from the sleep onset until the time the individual wakes up in the morning minus the total duration of the awakenings throughout the night. Sleep efficiency, reported in percentage, is calculated based on the ratio of the total sleep time to the time spent in bed while sustained sleep efficiency is total sleep time over time spend in bed after the sleep onset.

Since there is a large night to night variability in the sleep pattern and architecture of the insomniacs, and due to our limitation in having participants undergoing in-lab PSG recordings for multiple times, we also used actigraphy in order to evaluate the sleep pattern of the insomniacs over a 14-day period. Actigraphy is a method of monitoring the sleep pattern that uses a wrist-worn accelerometer which objectively evaluates the sleep patterns including sleep latency, duration, efficiency and wake after sleep onset based on the level of the lighting and participants' wrist activity through a validated automatic algorithm which was further validated based on participants self-reported daily bed and wake times.

In addition to the objective sleep measures, we evaluated the sleep quality using subjective questionnaires (Insomnia Severity Index, Pittsburgh Sleep Quality Index, and

Epworth Sleepiness Scale), as well as self-reported sleep diaries completed over the period of 14 days.

Insomnia severity index (ISI) (Bastien, Vallieres, & Morin, 2001) is a self-reported 7-item questionnaire, with a 5-point Likert scale (range: 0-4) for each item. ISI measures the nature, severity, and impact of insomnia over the past month by evaluating the problems related to sleep onset, sleep maintenance, and early morning awakenings, sleep dissatisfaction, association between sleep problems and daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. The total score for this questionnaire ranges from zero to 28, with the scores of 0-7 characterizing absence of insomnia; 8-14 sub-threshold; 15-21 moderate; and 22-28 severe insomnia.

Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), unlike ISI, does not specifically target insomniacs and can be applied to study the pattern and disturbances of sleep in the general population. This questionnaire consists of 7 components, each with a 4-point Likert scale (range: 0-3), yielding in a total score between 0-21. A total PSQI score of 5 or greater suggests poor sleep quality.

Epworth sleepiness scale (ESS) (Johns, 1991) is an 8-item self-administered questionnaire that assesses the daytime somnolence by evaluating the probability of dosing-off in eight different common life situations. ESS uses a 4-point Likert format ranging from 0-3, and yields in a total score between 0-24.

The participants were also given sleep diaries (Carney et al., 2012), in order to evaluate their day to day self-reported sleep measures, based on which we calculated

their sleep latency, duration, efficiency, as well as the wake after sleep onset averaged over a 14 day period.

Given the strong association between mood disorders with insomnia, we additionally assessed the anxiety and depression states of the participants using Geriatric Anxiety Inventory (GAI) (Pachana et al., 2007), a 20 item self-reported questionnaire that evaluates the anxiety levels over the past seven days as well as Geriatric Depression Scale (GDS) (Yesavage et al., 1982), a 30 item questionnaire identifying the depression symptoms over the past week.

Neuropsychological evaluations at the baseline

The morning after the second PSG night, participants met with a neuropsychologist and underwent a comprehensive neuropsychological examination in order to evaluate their cognitive performance before weaning from benzodiazepines. The rationale for performing these tests after the second PSG night, as opposed to the first night, was to ensure that all those tested were eligible according to our inclusion criteria and were not excluded due to sleep disorders detected by PSG. In addition, the second PSG night was closer to the start of the CBT-i therapy; as such, we thought that the scores obtained the morning after would be a better representative for the baseline values. Various neuropsychological tests were administered to assess performance in specific cognitive domains which have shown to improve more prominently upon benzodiazepine withdrawal including verbal memory, executive function, attention and concentration, visuospatial skills, as well as motor skills (Barker et al., 2004b). A

summary of these tests mapped to their corresponding cognitive domain are presented in Table 1.

Global Cognitive function: We used Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), an 11-item validated screening tool, to evaluate the global cognitive function of the participants, including the orientation to place and time, short-term memory, language, comprehension, attention, and language ability of the individual. MMSE has a maximum score of 30, and a score equal to or below 23 served as an exclusion criterion since it is indicative of cognitive impairments. In addition to the global cognitive function,

Verbal Memory: To assess this cognitive domain, the Free and Cued Selective Reminding Test (FCSRT) (Buschke, 1984; Ellen Grober & Buschke, 1987; E. Grober et al., 2008) was used. FCSRT is a 16-item assessment with six components. The first three components are immediate and measure free recall, total recall (sum of free and cued recalls), and cue efficiency, measured by the ratio of the recalls as a result of a cue over the number of items that were not initially recalled (% of cued recalls). The test is administered three times, and the score for free recall and total recall components is derived according to the sum of the three trials (range: 0-48). After 30 minutes of non-verbal activities, the participants are required to perform the same test – only once – and the free delayed recalls, total delayed recalls and percentage of cued delayed recalls (delayed recall cue efficiency) were measured.

Executive Function: This domain was assessed using the Color Word Interference Test – a subtest of Delis–Kaplan Executive Function Scale (D-KEFS) (Delis, Kaplan, & Kramer, 2001) test as well as the Trail making test (TMT) (Army

Individual Test Battery, 1944). The Color Word Interference Test evaluates the individual's ability to shift cognitive focus and deal with conflicting stimuli and consists of four different components including color naming, word reading, inhibition, and flexibility. Color naming consists of calling the color of a series of colored boxes printed on a paper as quick as possible without making mistakes and evaluates the speech motor function. In word reading section, which also evaluates speech motor function, participants are asked to read a series of color words which are printed in black and white. In verbal inhibition component participants are presented with a series of color words printed in conflicting colors and are asked to say the color of the ink – a task that requires performance of a less automatic task (calling the color) and inhibition of a more automatic task (reading the word). Finally, in cognitive flexibility, participants are presented with a set of color words printed in conflicting colors, half of which are enclosed in a box and are asked to call the color of the words for the ones that appear without a box enclosing them and to read the words out loud for the ones that a box encloses them. Each component yields in a completion time as well as a scaled score which is based on the normative data with a mean of 10 and standard deviation of 3, accounting for age. In addition, the total number of errors made during the four components was calculated. The trail making test consist of two parts and measures the cognitive flexibility and task switching ability. In part A of TMT, individuals are presented with numbers ranging 1-25 which are distributed randomly on a paper and are asked to connected them in an ascending order as fast as possible without lifting the pen. In Part B, instead of the numbers only, they are presented with a mix of numbers (1-13) and letters (A-L), and are asked to connected them in an ascending order and by alternating

between digits and letters (e.g. 1-A-2-B-3-C-4-D, etc.). Each component is scored individually based on the number of seconds taken to complete the task, and the z-score for each is calculated accounting for age and education levels.

Attention and Concentration: In order to evaluate the attention and concentration, participants completed the Digit Symbol Substitution Test (DSST) (Wechsler, 1981). In this assessment, subjects are presented with an array of 9 numbers each paired with a specific symbol, and are asked to note down the corresponding symbol for a long list of numbers randomly assorted for (a total of 140 numbers). The performance is scored based on the number of correct associations completed within 90 seconds.

Visuospatial Abilities: this was assessed using the Modified Taylor Complex Figure (MTCF) (Taylor, 1969), an assessment that requires the subjects to reconstruct a complex drawing presented to them. MTCF has two components, recognition and immediate recall. During the recognition part, participants are asked to copy a drawing by looking at it, while in immediate recall they reconstruct the same drawing from memory. The scores for this test include time taken to complete the recognition phase (copy time), as well as the accuracy of the recognition phase drawing (copy score) and immediate recall drawing (immediate recall score) calculated based on its location, accuracy, and organization. We obtained z-scores for copy and immediate recall scores accounting for age, sex, and education levels (SES z-score), given their documented effect on these two MTCF components (Tremblay et al., 2015). In addition, it has been shown that the copy time correlates with both copy and immediate recall scores, while copy score correlates with immediate recall scores (Tremblay et al., 2015). For this

reason, we also calculated z-scores (all variable z-score) for copy scores accounting for age, sex, education levels, and copy time; For immediate recall scores, we accounted for the same covariates plus copy score.

Psychomotor Performance and Manual Dexterity: Using Purdue Pegboard test (Tiffin, 1968) we assessed the psychomotor performance and manual coordination. Participants are presented with a pegboard consisting of two rows of 25 holes, and are asked to place as many metal pegs as possible into the holes within a 30-second period using the dominant hand only, non-dominant only, and both hands. The score for each condition was calculated based on the number of rods (pairs of rods in case of bimanual component) placed in 30 seconds, and the z-scores accounted for age and sex.

Group assignment

After the baseline evaluations, participants were stratified into two groups of CBT-i and waitlist (delayed CBT-i), according to age, sex, medication type and duration, as well as education level. Given the nature of the CBT-i group therapy, and the need for the participants to interact with each other, each group consisted of 4 – 6 participants. The first cohort of the study was not matched for the education level.

Weaning protocol

All of the participants, regardless of their group assignment, went through a 16-week weaning protocol adapted from the randomized trial developed by Tannenbaum *et al*. in 2014 (Tannenbaum, Martin, Tamblyn, Benedetti, & Ahmed, 2014). The subjects were offered an information package containing self-assessment knowledge tests about

the risks of benzodiazepines, details on the possible side effects related to consumption of benzodiazepines, information about the possible drug interactions, alternative options for more efficient therapeutic substitutes, info on sleep hygiene, withdrawal success stories to increase the motivation, compliance and self-efficacy, as well as a step-by-step weaning plan. The de-prescription plan was visually presented in the information package, directing the participants to gradually decrease the dose of the medication from full pill to half and then to a quarter pill dose and eventually stop taking the medication completely. This intervention was personalized based on the type and the dose of the benzodiazepines that the patients were consuming. In order to facilitate the accessibility, all of the information included in the package were written in the language set at a 6th grade reading level and the participants were asked to discuss these recommendations with their physician or pharmacist. During the weaning intervention, we conducted biweekly telephone follow-ups in order to encourage the patients to continue following the guidelines, record their compliance to the protocols, and document any possible withdrawal symptoms.

CBT-i protocol

Concurrently with the weaning, only the participants in the CBT-i group received CBT-i therapy offered in small groups of 4-6 people, as recommended by the literature (Bastien, Morin, Ouellet, Blais, & Bouchard, 2004; C. M. Morin et al., 1999). The intervention consisted of eight 90-minute therapy sessions. The first four sessions were offered every week, and the remaining four were separated 2 weeks apart, resulting in a 16-week therapy period. The CBT-i, as explained above, focused on correcting the

behavioral, cognitive, and educational dimensions. The behavioral component was focused on educating the individuals to associate the bed only with sleeping and limit the time spent in the bedroom doing other activities. The cognitive component aimed to correct dysfunctional beliefs about insomnia and to limit the pre-sleeping negative thoughts that exacerbate insomnia. Finally, the educational component increased the individuals' awareness about sleep hygiene and the normal physiological changes in sleep related to aging.

Given the waitlist design of the study, participants in the waitlist group initially went through the weaning without the CBT-i therapy. However, at the end of the weaning and after completing the post intervention evaluations (described below) they were offered the opportunity to receive the CBT-i therapy. Interested participants, after going through the 16 weeks of the CBT-i therapy, completed another set of sleep and neuropsychological evaluations similar to the ones done at the end of the weaning period.

Post intervention evaluations

At the end of the 16-week weaning intervention (weaning and CBT-i therapy in the case of the CBT-i group), participants went through a similar set of comprehensive sleep and neuropsychological evaluations done at the baseline.

The sleep evaluations consisted of one in-lab PSG recording, actigraphy (14 days), series of subjective sleep questionnaires (ISI, PSQI, ESS), sleep diaries (14 days), and the anxiety and depression questionnaires (GAI, GDS). The neuropsychological tests were identical to the ones at baseline (FCSRT, D-KEFS Color

Word Interference Test, DSST, Purdue Pegboard) except MTCF which was replaced by Rey-Osterrieth complex figure (ROCF), a test similar to MTCF in nature which only differs in the drawing template. The choice to replace MTCF with ROCF at post intervention evaluations was made to prevent the learning effect as a result of repeated administration. It is well documented in the literature that both tests result in comparable accuracy scores and hence could be used interchangeably (Hubley & Jassal, 2006; Hubley & Tremblay, 2002; Yamashita, 2006). In order to minimize the effect of time of the day on the cognitive performance, these tests were performed in the morning at a time similar to the one performed at the baseline. To avoid a bias in cognitive evaluations, the neuropsychologist performing the tests was blinded to the grouping of the individuals.

Statistical analyses

Dependent variables: The primary outcomes for our study were the subjective sleep quality measures including sleep diary (total sleep time, sleep onset latency, sleep efficiency and wake duration after sleep onset), ISI and PSQI scores. Due to the night to night variability of PSG data, and the small sample size for the actigraphy data, we treated these measures as secondary variables. Also, because of the limited sample size and the fact that the cognitive measures require some time after the therapy to improve, we treated neuropsychological measures as secondary variables.

Independent variables: The independent variables of interest were CBT-i intervention (CBT-i group vs. waitlist), as well as weaning (pre-weaning vs post-weaning).

Statistical tests: The normality and variances of the data were analyzed and compared using Shapiro-Wilk and Analysis of variance (ANOVA). Demographics, sleep variables and cognitive performance of completers versus drop outs as well as CBT-i group versus waitlist were compared. We used independent t-test for demographics data, however, because of our small sample size and the fact that most of the sleep and cognitive variables of interest did not meet the normality assumptions, we used the Mann-Whitney U-test in order to compare the sleep and cognitive continuous variables at baseline. For discrete variables, we applied Pearson chi-square test, which is free of normality assumption.

In order to evaluate the effect of weaning as well as the CBT-i intervention on the improvements in our primary and secondary dependent variables and given the lack of normality in our data, we chose to perform the Generalized estimating equations – a test that does not assume normality of data (Wang, 2014) – using time (weaning) and group as in between-subject factor, and age, sex, and education level as covariates. We modeled the main effect of weaning and group interaction and the statistical differences were compared using Wald chi-square test. The withdrawal success rate (dichotomous measure evaluating whether participants achieved a complete cessation or not) across the two groups was compared using Pearson chi square test and the change in benzodiazepine consumption dose, measured in lorazepam dose equivalence, using Generalized estimating equations with the model and the covariates mentioned earlier.

Finally, in order to evaluate the effect of CBT-i on improvements in cognitive performance upon benzodiazepine withdrawal, with a larger power, we increased our sample size by pooling together the participants in the CBT-i group and the ones in the

waitlist who completed CBT-i after weaning, and evaluated the changes in cognitive performance from baseline to post-CBT-i using the Generalized Estimating Equations with a similar model to what described above. The significance in all of the analyses was set at $p<0.05$.

Results

Sixty one participants showed interest and were screened, among which 31 were either not eligible according to our study criteria or withdrew their consent before starting the study and being assigned to either group: 8 participants had high levels of anxiety and depression; 7 either had stopped taking benzodiazepines at the time of screening or were not taking it chronically; 4 had sleep apnea; 3 had chronic physical pain; 3 lacked the time required to commit to study; 3 found the IUGM laboratory far to commute; one consumed high amount of alcohol regularly; one lost interest to participate; and one did not like to spend the night at the laboratory bedroom.

Thirty participants met the inclusion criteria and were enrolled in the study, among which 6 dropped out after completing the baseline evaluations and being assigned to one of the two groups, due to the following reasons: one dropped out due to loss of interest; one moved permanently to United States; one fell sick and was not able to continue the study; one suddenly stopped benzodiazepine intake on their own at the baseline; and two were excluded due to apnea which was detected after completing the baseline evaluations. Only 24 participants completed the study and were included in the final analyses, half of which were part of the CBT-i group and the other half part of the waitlist.

A comparison between the demographics, sleep measures and cognitive performance of the dropouts and the ones who completed the study is presented in Table 2. There were no significant differences between the demographic features of the two groups including age, sex ratio, education level, benzodiazepine intake duration and dose. Objective sleep measures derived from polysomnography revealed a trend for

lower stage N2 NREM sleep duration (U=36.0, Z=-1.78, p=0.076) and percentage of total sleep time spent in stage N2 NREM sleep (U=38.0, Z=-1.67, p=0.095) among the dropout group while actigraphy did not reveal any differences. Subjective sleep questionnaires showed a higher sleep efficiency (U=31.0, Z=-2.13, p=0.034) and daytime somnolence (U=18.5, Z=-2.79, p=0.005) among the dropouts, as evidenced by sleep diary and ESS respectively. Moreover, there was a tendency for higher depression levels among the dropouts. In terms of the neuropsychological evaluations, none of the measures in any of the cognitive domains was found to be different across the two groups.

Differences between the CBT-i and the Waitlist group at the baseline

In order to ensure that the CBT-i and waitlist groups did not differ at the baseline, we compared their demographics data (Table 3), subjective and objective sleep measures, and anxiety and depression levels (Table 4), as well as their cognitive performance (Table 5) measured at the baseline. We found no significant differences between the demographic characteristics of the two groups including age, body mass index, the duration of benzodiazepines consumption, the weekly benzodiazepine dose consumed in equivalent lorazepam dose. However, we observed a trend for higher education levels in the CBT-i group (p=0.093), explainable by the fact that we did not match the participants for this measure in the first cohort of the study which consisted of five participants in the CBT-i group and four in the waitlist. The chi square test revealed no significant difference in terms of the sex distribution across the two groups, though the Female to Male ratio in the whole sample was 2:1 (16F, 8M), which is in line with the

higher prevalence of insomnia in females in the general population (Krishnan & Collop, 2006).

The objective sleep measures consisted of polysomnography recordings as well as actigraphy data. The polysomnography data was obtained from all of the participants and included the following variables: Sleep latency defined by the latency to stage N1 NREM sleep, wake duration after sleep onset, total sleep time, durations and proportion of each sleep stage in reference to the total sleep time, sleep efficiency calculated by the ratio of total sleep time to the time in bed, as well as sustained sleep efficiency measured by the ratio of total sleep time over time in bed after sleep onset. After evaluating our data for presence of outliers using box plots, we excluded one participant in the waitlist group from the PSG analyses for being an extreme outlier (total sleep time of 51 minutes and a sleep efficiency of 12%). None of the polysomnography measures at the baseline showed to be different across the two groups (Table 4). In terms of the actigraphy measures, we failed to obtain the data for all of the participants due to some technical difficulties related to the Respironics software which resulted in loss of some data. The actigraphy data which consisted of sleep latency, wake duration after sleep onset, sleep efficiency, and total sleep time was calculated for 9 participants in the CBT-i and 10 in the Wait-list group and did not reveal significant differences across the two groups (Table 4). None of the subjective sleep measures including any of the sleep diary variables (including sleep latency, duration, efficiency or wake after sleep onset), PSQI or ESS showed any differences, except the ISI which was higher among the waitlist group at baseline ($U=33.0$, $Z=-2.26$, $p=0.024$) (Table 4).

The performance in neuropsychological evaluations was measured for all of the participants at the baseline and was compared across the two groups (Table 5). The global cognitive function measured by the MMSE was not different across the two groups. Sub-components of the FCSRT, did not show differences in verbal memory. In terms of the executive function, waitlist group showed a trend for a better performance in the color section of the D-KEFS Color Word Interference Test as measured by their naming speed (U=42.5, Z=-1.71, p=0.088) and score (U=43.0, Z=-1.69, p=0.090). In addition, in the reading component of this test, the waitlist group performed better as evidenced by a significant difference in the reading speed (U=35.5, Z=-2.11, p=0.035) and a marginal difference in the score (U=39.5, Z=-1.90, p=0.058). Other D-KEFS Color Word Interference Test sub-components as well as TMT A and B were similar across the two groups. Digit Symbol Substitution Test demonstrated no difference in the attention and concentration domains across the two groups. Visuospatial abilities were contrasted according to the MTCF subcomponents, which consisted of the copy time, copy score, recall score and their respective z-scores. No differences in the visuospatial abilities were observed. Finally, evaluating the Purdue Pegboard scores showed a trend for better manual dexterity in dominant hand of the waitlist group (U=41.0; Z=-1.82; p=0.069) while it's z-score – accounting for age and sex – did not demonstrate such trend.

Changes in Sleep measures following the intervention

The result of our Generalized Estimating Equation analyses, evaluating the effect of weaning and CBT-i on improvements in different sleep measures, are presented in

Table 6. All of the participants in the CBT-i group were included in the analyses for the PSG measures, while one participant in the waitlist was excluded for being an extreme outlier, yielding a sample size of 12 in CBT-i versus 11 in waitlist. Also, two participants in the waitlist group lost their sleep diaries at the end of the intervention and for this reason, waitlist consisted of 10 participants for the sleep diary measures. The technical difficulty with the Respironics software and the loss of actigraphy data resulted in sample size of seven in the CBT-i group and five in the waitlist for this measure.

The effects of weaning and CBT-i on improvements in sleep measures are presented in Table 6. All of our primary sleep outcomes showed a significant interaction between weaning and CBT-i, except ISI. Subjective sleep quality measured by self-reported sleep diaries showed a significant effect of CBT-i on improvements in sleep quality. Sleep latency (figure 3) and wake after sleep onset (figure 4) decreased in the CBT-i group while waitlist showed an increase in both measures, with a significant interaction for each, (Wald $\chi2=7.19$; $p=0.007$) and (Wald $\chi2=8.32$; $p=0.004$) respectively. Sleep efficiency (figure 5) in CBT-i group improved while it deteriorated in the waitlist group, with a significant interaction effect (Wald $\chi2=16.78$; $p=0.000$). Total sleep time (figure 6) also highlighted a significant interaction (Wald $\chi2=6.94$; $p=0.008$) as this measure increased for the CBT-i group while it decreased for the waitlist. Sleep quality, measured by PSQI (figure 7), improved in both groups (Wald $\chi2=9.47$; $p=0.002$), but was more prominent in CBT-i group with significant interaction effect (Wald $\chi2=5.98$; $p=0.014$). ISI decreased in both groups (figure 8) (significant effect of weaning; Wald $\chi2=18.08$; $p=0.000$) with a tendency for a more prominent improvement

in the CBT-i group, as evidenced by a trend for the interaction effect (Wald $\chi2=2.72$; $p=0.099$).

In terms of the secondary sleep outcomes, polysomnography data showed a significant effect of weaning on increasing the wake after sleep onset (figure 9) (Wald $\chi2=4.39$; $p=0.036$) and a trend for decreased sustained sleep efficiency (Wald $\chi2=2.96$; $p=0.086$) in both groups. Additionally, both groups showed a trend for a decrease in duration of stage N2 NREM sleep (Wald $\chi2=3.13$; $p=0.077$) and an increase in stage N3 NREM sleep duration (Wald $\chi2=3.45$; $p=0.063$) which turned significant when evaluated in terms of its proportion to total sleep time (Wald $\chi2=4.12$; $p=0.042$) (figure 10). No group interaction was found in terms of the PSG data. On the other hand, the actigraphy data, as another objective sleep measure, highlighted a significant effect of CBT-i on sleep improvements. Wake after sleep onset (figure 11) decreased in the CBT-i group while it increased in the waitlist, with a significant interaction between CBT-i and weaning (Wald $\chi2=7.03$; $p=0.008$). Sleep efficiency derived from actigraphy also evidenced a significant interaction effect (Wald $\chi2=13.72$; $p=0.000$), as the CBT-i group improved in this measure and waitlist deteriorated (figure 12).

While no significant change was observed for anxiety levels across the two groups, we found a trend for an interaction effect in terms of the Geriatric Depression Scale (Wald $\chi2=3.10$; $p=0.078$), due to decreased depression levels among the waitlist group.

Changes in cognitive performance in different domains following the intervention

We evaluated the effect of weaning and CBT-i on improvements in cognitive performance in the two groups using the same model as the one mentioned before and the results are presented in the table 7. All of the participants in the CBT-i group (n=12) and the waitlist (n=12) were included in the analyses.

We did not find any differences in terms of the global cognitive function as measured by the MMSE. In terms of the executive function, reading speed (measured by the D-KEFS Color Word Interference Test) increased in the CBT-i group while it worsened in the waitlist, highlighting interaction effects for both test duration (Wald $\chi2=12.38$; $p=0.000$) (figure 13) and score (Wald $\chi2=7.53$; $p=0.006$) (figure 14). Both groups showed a decline in delayed verbal fluency as evidenced by a trend in effect of weaning on the FCSRT delayed total recall score (Wald $\chi2=2.72$; $p=0.099$) and a significant effect on the FCSRT delayed recall cue efficiency (Wald $\chi2=4.63$; $p=0.032$) (figure 15). Visuospatial abilities were measured by MTCF and ROCF. Both groups showed improvements in their copying accuracy as measured by Copy score (Wald $\chi2=5.99$; $p=0.014$) (figure 16), SES z-score (Wald $\chi2=6.17$; $p=0.013$) (figure 17), and all variable z-score (Wald $\chi2=6.59$; $p=0.010$) (figure 18), however, the improvements observed were more pronounced in the waitlist group (Copy score (Wald $\chi2=4.18$; $p=0.041$), SES z-score (Wald $\chi2=4.33$; $p=0.037$), and all variables z-score (Wald $\chi2=4.35$; $p=0.037$)). On the other hand, the immediate recall component of the MTCF/ROCF test, corrected for all variables, evidenced a significant interaction effect on the visuospatial domain as the CBT-i improved significantly in this measure while the waitlist deteriorated (Wald $\chi2=4.21$; $p=0.040$) (figure 19). In terms of the psychomotor

performance, although both groups improved in their non-dominant hand dexterity, measured by the Purdue Pegboard z-score (Wald $\chi 2=5.15$; $p=0.023$) (figure 20), bimanual dexterity showed a tendency for improvement in the waitlist and deterioration in the CBT-i group (Wald $\chi 2=3.19$; $p=0.074$).

Withdrawal success rates and changes in medication dosage

The benzodiazepine medication dose consumed prior to and after the intervention was calculated in weekly doses for each participant and for the sake of comparisons, were converted to equivalent lorazepam dose. Overall, 15 out of the 24 participants (62.50%) succeeded to fully stop their medication immediately after the intervention. No significant difference was observed in the withdrawal success rate between the CBT-i (66.66%) and the waitlist (58.33%) group, as measured by the Pearson chi-square test ($\chi 2$ value=0.178; df=1; $p=0.673$).

In order to evaluate the effect of weaning and CBT-i on the changes in the medication dosage, we performed the Generalized Estimating Equations as explained above, which evidenced a significant reduction in medication consumption dose in both groups (Wald $\chi 2=18.07$; $p=0.000$), as the benzodiazepine dose, calculated in weekly equivalent lorazepam dose, decreased in both CBT-i group (from 67.60±69.48mg to 30.78±75.09mg) and the waitlist (from 95.89±140.11mg to 17.61±30.08mg). However, we found no significant interaction effect in dose reduction (Wald $\chi 2=3.36$; $p=0.186$).

Changes in cognitive performance in different domains in pooled CBT-i group

Our secondary analyses, evaluating the combined effect of CBT-i and weaning on changes in cognitive measures, within our pooled sample, are presented in table 7. Combined CBT-i and weaning in this sample showed to have a positive effect in improving immediate verbal memory, measured by the FCSRT – Free recall (Wald $\chi2=4.92$; $p=0.027$). On the other hand, the cue efficiency was found to decrease in the delayed component of the FCSRT (Wald $\chi2=4.25$; $p=0.039$). In terms of the executive function, we found a tendency for a decrease in total number of errors made in the four components of the D-KEFS Color Word Interference Test (Wald $\chi2=3.24$; $p=0.072$). Digit Symbol Substitution Test, measuring attention and concentration domains was found to improve with a marginal significance (Wald $\chi2=3.52$; $p=0.061$) upon completion of the weaning and CBT-i. We found a tendency for improvements in visuospatial abilities as shown in both immediate recall component of MTCF/ROCF score (Wald $\chi2=2.93$; $p=0.087$) and SES z-score (Wald $\chi2=3.26$; $p=0.071$). Finally, manual dexterity improved in the non-dominant hand, evidenced by a trend in the Purdue Pegboard score (Wald $\chi2=3.07$; $p=0.080$) and z-score (Wald $\chi2=6.17$; $p=0.013$).

Discussion

All of the 24 participants completed the study, however, two in the waitlist group lost their post intervention sleep diary, one was excluded from the PSG analyses for being an extreme outlier, and actigraphy recordings for 12 participants were lost due to a software problem. Our comparison between the completers and drop-outs revealed that in terms of sleep measures drop-outs had higher sleep efficiency and higher daytime somnolence and slightly higher depression levels while they did not differ in cognitive measures compared to the completers. Although it could be speculated that higher sleep efficiency could translate to lower desire to seek treatment and hence explain the reason for dropping out, but in our sample the reasons for dropping out were diverse and mostly irrelevant to the sleep characteristics of these participants (e.g., falling sick, moving away, being excluded due to sleep apnea). For most parts, the data pertaining to the variables of interest were not normally distributed which forced us to perform a statistical test independent from normality of the data (Generalized Estimating Equations).

Our data suggest that CBT-i can help improve sleep quality in a population of elderly insomniacs who are weaning from benzodiazepines, further to the effect of variations in age, sex, and education levels. The effect of CBT-i was evident in improving our primary variables of interest. All of the sleep diary measures including sleep latency, wake after sleep onset, sleep efficiency, and total sleep time improved in the CBT-i group at the end of the intervention while they all deteriorated in the waitlist group. PSQI improved in both groups, however, this improvement was more prominent in the CBT-i group. Improved PSQI upon benzodiazepine withdrawal has in fact been

reported in other studies as well (Petrovic, Pevernagie, Mariman, Van Maele, & Afschrift, 2002). Insomnia severity index improved upon weaning in both groups – in line with the previous findings (Petrovic et al., 2002) – and the CBT-i group showed a trend for more improvements in this measure compared to the waitlist. Given that previous studies reported significant interaction between weaning and CBT-i (C. M. Morin et al., 2004), we hypothesize that the absence of such effect could be due to the differences in ISI values of the two groups at the baseline; the changes in ISI should be interpreted cautiously as the CBT-i group had lighter insomnia symptoms (lower ISI scores) at baseline.

Our secondary variables of interest evaluating objective sleep quality also supported the efficacy of CBT-i in improving sleep quality, although not as extensive as the subjective sleep quality. Actigraphy measures of sleep efficacy and wake after sleep onset improved in the CBT-i group and deteriorated in the waitlist, in line with our sleep diary findings. None of the polysomnography measures highlighted an effect for CBT-i, which could be explained by the day-to-day variability of PSG data. On the other hand, polysomnography recordings highlighted the effect of weaning alone, on sleep measures. Wake after sleep onset increased and there was a trend for decreased sustained sleep efficiency in both groups. This could be explained due to reduction in the dose of sedatives consumed in both group and a subsequent increase in vulnerability to external stimuli and disturbing factors, especially when spending the night sleeping in a laboratory with a series of electrodes mounted on the head and face. Weaning alone also affected the sleep macro-architecture as stage N3 NREM sleep increased in both groups while the stage N2 NREM sleep showed a trend for decrease.

Withdrawal from benzodiazepines, which has been shown to suppress deep sleep (C. M. Morin et al., 2004), can explain the increase in proportion of sleep spent in stage N3 NREM sleep. The trend for decreased stage N2 NREM sleep could be a compensatory change as a result of increased deep sleep.

We chose to evaluate the improvements in cognitive performance of the subjects, from baseline to post-intervention, in the domains are affected in insomniacs or chronic benzodiazepine users. Insomnia has been consistently associated with declines in various cognitive domains including attention and concentration (Fortier-Brochu & Morin, 2014; Owsley, Burton-Danner, & Jackson, 2000; Persad, Abeles, Zacks, & Denburg, 2002), executive functioning (Fortier-Brochu et al., 2012; Haimov, Hanuka, & Horowitz, 2008; Mattay et al., 2006), episodic memory (Fortier-Brochu & Morin, 2014), working memory (Fortier-Brochu et al., 2012), and problem solving abilities (Fortier-Brochu et al., 2012). A recent study investigating the correlation between subcortical changes in chronic insomniacs and their cognitive functioning evidenced hippocampal atrophy and PSQI scores highlighted atrophic regions in amygdala, basal ganglia and thalamus that were associated with worse verbal and visuospatial memory (Koo, Shin, Lim, Seong, & Joo, 2017). Similarly, chronic use of benzodiazepines is shown to be detrimental for cognition in various domains including attention and concentration (Golombok et al., 1988; Petursson, Gudjonsson, & Lader, 1983), Verbal memory (Tata, Rollings, Collins, Pickering, & Jacobson, 1994), psychomotor (Gorenstein, Bernik, & Pompeia, 1994; Lucki, Rickels, & Geller, 1986; Petursson et al., 1983; Tata et al., 1994), visuospatial abilities (Bergman, Borg, & Holm,

1980; Golombok et al., 1988; Sakol & Power, 1988; Tata et al., 1994). CBT-i, on the other hand, is shown to improve cognition in attention, concentration, and executive functioning (Miro et al., 2011).

Our study was unique in a sense that to the best of our knowledge no other study investigated the effect of CBT-i on cognition upon weaning from benzodiazepines, in an elderly population. We observed an effect for CBT-i on improving the executive function, measured by the reading component of the D-KEFS Color Word Interference Test, as the CBT-i group improved. Although it is plausible to think that CBT-i had an effect on improvements in this domain, it could also be possible that lower executive performance at the baseline among the CBT-i group allowed more room for improvements in this measure. Weaning from benzodiazepines caused deteriorations in delayed verbal memory as both groups showed poorer performance in delayed recall cue efficiency of the FCSRT test, which was not in line with our initial hypotheses. Copying abilities – a subcomponent of visuospatial skills – improved in both groups, but contrary to our expectation, it improved more prominently among the controls. However, the recall component of the MTCF/ROCF, which is more challenging and requires patients to draw from memory, showed significant improvements among the CBT-i group while it deteriorated in the controls. Manual dexterity in non-dominant hand improved in both groups, while the controls marginally improved in terms of the bimanual dexterity. It is worthwhile to note that these results should be interpreted very cautiously as the small sample size limited the power of statistical tests, particularly with inclusion of covariates. Furthermore, one might argue that the improvements found in these measures could potentially be modulated or influenced by anxiety and depression levels. Our data show

that these two measures were not different across the two groups at the baseline and did not change significantly from pre- to post intervention. Future studies with sample sizes large enough that allows including more covariates, should still evaluate whether the changes in anxiety and depression levels have any effects on the cognitive changes.

Our findings related to cognitive changes were complex. We postulate that the lack of uni-directionality of the cognitive results could be due to the limited sample size, the baseline differences across the two groups, and the lack of time for cognitive measures to improve. In order to increase our statistical power and obtain a better impression of cognitive changes following benzodiazepine withdrawal complemented with CBT-i, we pooled the pre- and post-CBT-i data of both groups together and evaluated the changes in cognitive performance. With a larger sample size of 18, observed a different set of results. The number of errors made during the D-KEFS test (measuring the executive function) marginally decreased, and the attention and concentration showed a trend for increase. Verbal memory improved both in immediate and delayed components, manual dexterity improved in non-dominant hand, and the copying component of the MTCF/ROCF test showed a trend for improvement. Previous studies looking at the effect of benzodiazepine withdrawal demonstrated that cognitive improvements require a minimum of six months to reinstate (Barker et al., 2004b). Given this evidence, it is plausible to expect more concrete and coherent functional improvements in cognitive domains in longer terms follow-ups.

Overall, 62.5% of the participants managed to completely wean from benzodiazepine consumption and we found no significant differences between the

cessation success rates across the two groups. The high cessation success rate in the control group and similarity of this measure to the CBT-i group highlights the effectiveness of our structured weaning protocol. Achieving such high cessation success rate is particularly remarkable despite the worsened sleep measures evidenced in this group. A follow up study will be interesting to evaluate whether these patients remain benzodiazepine free in presence of worsened sleep quality or return to consuming these hypnotics to mask their insomnia symptoms.

Our study was limited in many ways: the sample size of 12 versus 12 was small and the statistical tests could have potentially been underpowered, particularly with the inclusion of the covariates. The skewness of the variables of interest and lack of normality of data could also be explained in parts by the limited sample size. Although the group assignment was not stratified based on ISI, the CBT-i group ended up having lighter insomnia symptoms at baseline, which could explain the improvements in sleep measures in this group. We expect that addition of more participants shall mask the differences in ISI at baseline. Previous studies have suggested allowing at least 6 months for the cognitive measures to improve upon withdrawing from benzodiazepines. Follow-up neuropsychiatric evaluations at 6 months and 1 year with larger sample size would have allowed us to draw more concrete conclusions about the changes in cognitive performance. Also, the low number of errors made in the D-KEFS executive function could suggest that some of the cognitive tests might have not been difficult enough to differentiate subtle improvements in certain cognitive domains.

Here we demonstrate that a structured benzodiazepine withdrawal program can be effective in weaning elderly insomniacs from these hypnotics, and highlights that

complementing this withdrawal with CBT-i can be very beneficial in terms of improving the sleep quality in this population. However, the role of CBT-i on cognitive performance, when complementing the withdrawal, is not very clear. Future studies with larger sample size, should evaluate the benefits of CBT-i in a structured benzodiazepine withdrawal program on cognitive performance, after allowing ample time for changes in cognitive domains to occur.

Tables

Table 1. Neuropsychological tests performed mapped to their corresponding cognitive domain

Cognitive Domain	**Neuropsychological Test**
Global Cognitive Function	Mini-Mental State Exam (score)
Executive Function	D-KEFS Color Word Interference Test – Color (sec)
	D-KEFS Color Word Interference Test – Color (score)
	D-KEFS Color Word Interference Test – Reading (sec)
	D-KEFS Color Word Interference Test – Reading (score)
	D-KEFS Color Word Interference Test – Inhibition (sec)
	D-KEFS Color Word Interference Test – Inhibition (score)
	D-KEFS Color Word Interference Test – Flexibility (sec)
	D-KEFS Color Word Interference Test – Flexibility (score)
	D-KEFS Color Word Interference Test – Total Number of Errors
	Trail Making Test – Part A (sec)
	Trail Making Test – Part A (z-score)
	Trail Making Test – Part B (seconds)
	Trail Making Test – Part B (z-score)
Attention and Concentration	Digit Symbol Substitution Test (score)
Verbal Memory	FCSRT – Free Recall (score)
	FCSRT – Total Recall (score)
	FCSRT – Cue Efficiency (%)
	FCSRT – Delayed Free Recall (score)
	FCSRT – Delayed Total Recall (score)
	FCSRT – Delayed Recall Cue Efficiency (%)
Visuospatial Skills	MTCF/ROCF – Copy (sec)
	MTCF/ROCF – Copy (score)
	MTCF/ROCF – Copy (z-score corrected for SES)
	MTCF/ROCF – Copy (z-score corrected for All variables)
	MTCF/ROCF – Immediate Recall (score)
	MTCF/ROCF – Immediate Recall (z-score corrected for SES)
	MTCF/ROCF – Immediate Recall (z-score corrected for All variables)
Motor Skills	Purdue Pegboard Dominant Hand (Score)
	Purdue Pegboard Dominant Hand (z-score)
	Purdue Pegboard – Non-Dominant Hand (Score)
	Purdue Pegboard – Non-Dominant Hand (z-score)
	Purdue Pegboard – Both Hands (score)
	Purdue Pegboard – Both Hands (z-score)

Table 2. Comparison between demographics, sleep and cognitive measures of the completers and dropouts.

Parameters	*Completers (n=24)*	*Drop-Outs (n=6)*	*Mean difference*	*t value*	*p value*
Demographics					
Age (years)	69.29±7.18	66.33±2.73	2.96	0.98	0.335
Sex (M:F)	8:16	1:5			0.426
Education Level (years)	15.38±3.03	15.17±3.13	0.21	0.15	0.882
Body Mass Index (kg/m^2)	25.12±4.56	27.08±1.33	-1.96	-1.03	0.311
Medication Duration (years)	13.67±11.86	5.25±6.06	8.42	1.67	0.106
Weekly Benzodiazepine dose (lorazepam dose equivalence)	81.74±109.12	20.42±18.42	61.33	1.35	0.186
Parameters	*Completers (n= 24; PSG n=23; Acti n=19)*	*Drop-Outs (n=6; Acti n=5)*	*Test U*	*Z value*	*p value*
Sleep Measures					
Sleep Diary Measures					
Sleep Latency (min)	41.67±34.67	30.28±32.94	55.5	-0.86	0.392
Wake After Sleep Onset (min)	48.44±42.72	20.03±17.34	37.0	-1.81	0.070
Sleep Efficiency (%)	79.77±10.85	89.86±7.47	31.0	-2.13	**0.034***
Total Sleep Time (min)	402.48±81.05	422.89±37.89	60.0	-0.62	0.534
Pittsburgh Sleep Quality Index	11.33±3.77	9.83±4.02	57.5	-0.76	0.448
Insomnia Severity Index	14.54±5.45	13.33±4.37	63.0	-0.47	0.640
Epworth Sleepiness Scale	4.83±2.63	10.83±5.67	18.5	-2.79	**0.005***
Geriatric Anxiety Inventory	6.17±5.39	9.83±6.97	47.5	-1.28	0.201
Geriatric Depression Scale	12.17±3.48	14.50±2.59	36.5	-1.85	0.064
Polysomnography Measures					
Sleep Latency (min)	19.60±20.91	19.17±19.67	64.0	-0.27	0.788
Wake After Sleep Onset (min)	100.99±72.30	70.55±41.09	50.0	-1.02	0.306
Sleep Efficiency (%)	74.18±16.36	81.07±10.21	52.0	-0.92	0.360
Sustained Sleep Efficiency (%)	77.15±16.64	83.85±10.46	47.0	-1.18	0.236
Total Sleep Time (min)	354.67±101.34	377.61±81.48	68.0	-0.05	0.957
N1 Duration (min)	42.21±23.15	34.06±20.37	58.0	-0.59	0.554
N1 % of TST (%)	13.75±12.06	10.30±7.36	58.0	-0.59	0.554
N2 Duration (min)	212.88±62.54	174.92±67.79	36.0	-1.78	0.076

N2 % of TST (%)	58.47±9.78	52.97±8.16	38.0	-1.67	0.095
N3 Duration (min)	43.35±33.27	62.30±62.33	65.0	-0.22	0.829
N3 % of TST (%)	11.47±8.51	16.23±13.15	58.0	-0.59	0.554
REM Duration (min)	55.94±31.24	69.55±43.45	59.0	-0.54	0.590
REM % of TST (%)	14.39±7.07	20.50±7.30	42.5	-1.43	0.153
Actigraphy Measures					
Sleep Latency (min)	43.41±32.79	35.08±26.17	40.0	-0.53	0.594
Wake After Sleep Onset (min)	40.90±20.01	29.87±10.08	29.0	-1.32	0.189
Sleep Efficiency (min)	80.86±7.07	82.37±4.71	46.0	-0.11	0.915
Total Sleep Time (min)	413.47±60.79	391.80±38.31	32.0	-1.10	0.270
Cognitive Measures					
Mini-Mental State Exam (score)	28.29±2.22	28.17±1.83	67.0	-0.27	0.787
D-KEFS Color Word Interference Test – Color (sec)	31.17±7.09	26.67±4.08	42.0	-1.56	0.119
D-KEFS Color Word Interference Test – Color (score)	10.83±2.71	12.00±2.00	56.5	-0.81	0.416
D-KEFS Color Word Interference Test – Reading (sec)	22.50±4.39	22.00±3.85	68.5	-0.18	0.855
D-KEFS Color Word Interference Test – Reading (score)	11.25±2.25	11.33±1.97	72.0	0.00	1.000
D-KEFS Color Word Interference Test – Inhibition (sec)	66.46±18.46	59.00±5.18	59.5	-0.65	0.516
D-KEFS Color Word Interference Test – Inhibition (score)	11.21±2.54	11.83±0.75	66.0	-0.32	0.753
D-KEFS Color Word Interference Test – Flexibility (sec)	67.88±17.07	70.50±32.02	63.0	-0.47	0.641
D-KEFS Color Word Interference Test – Flexibility (score)	11.67±2.01	11.17±4.54	63.0	-0.47	0.637
D-KEFS Color Word Interference Test – Total Number of Errors	2.67±2.68	2.67±4.27	57.5	-0.76	0.445
Trail Making Test – Part A (sec)	41.83±11.68	42.67±17.39	67.0	-0.26	0.795
Trail Making Test – Part A (z-score)	0.64±1.32	1.21±2.64	66.5	-0.29	0.775
Trail Making Test – Part B (seconds)	107.79±77.31	101.83±78.79	51.5	-1.06	0.288
Trail Making Test – Part B (z-score)	1.02±2.42	3.19±8.67	56.0	-0.83	0.407
Digit Symbol Substitution Test (score)	44.21±9.91	48.50±10.78	58.0	-0.73	0.466
FCSRT – Free Recall (score)	30.75±5.37	28.50±8.22	63.5	-0.44	0.659
FCSRT – Total Recall (score)	45.75±2.66	44.83±4.96	69.5	-0.13	0.894
FCSRT – Cue Efficiency (%)	89.90±12.45	88.28±15.01	65.0	-0.37	0.710
FCSRT – Delayed Free Recall (score)	12.21±2.40	10.33±3.67	49.0	-1.20	0.229
FCSRT – Delayed Total Recall (score)	15.79±0.41	15.17±1.60	60.5	-0.81	0.418

FCSRT – Delayed Recall Cue Efficiency (%)	97.00±5.88	91.12±14.39	56.0	-0.93	0.351
MTCF – Copy (sec)	160.58±43.31	140.83±41.28	49.5	-1.17	0.243
MTCF – Copy (score)	31.58±2.41	31.17±1.17	59.0	-0.68	0.495
MTCF – Copy (z-score corrected for SES)	0.07±0.69	-0.12±0.40	56.0	-0.83	0.407
MTCF – Copy (z-score corrected for All variables)	-0.03±0.71	-0.24±0.42	54.0	-0.93	0.351
MTCF – Immediate Recall (score)	16.38±5.07	14.75±3.56	56.0	-0.83	0.406
MTCF – Immediate Recall (z-score corrected for SES)	0.12±0.93	-0.19±0.58	55.0	-0.88	0.378
MTCF – Immediate Recall (z-score corrected for All variables)	-0.24±1.01	-0.65±0.49	53.0	-0.99	0.325
Purdue Pegboard Dominant Hand (Score)	12.67±1.74	13.00±3.22	68.0	-0.21	0.833
Purdue Pegboard Dominant Hand (z-score)	-0.16±1.07	-0.68±2.15	57.5	-0.75	0.452
Purdue Pegboard – Non-Dominant Hand (Score)	12.25±1.36	13.50±2.74	44.0	-1.48	0.138
Purdue Pegboard – Non-Dominant Hand (z-score)	-0.14±0.70	-0.03±1.94	56.0	-0.83	0.406
Purdue Pegboard – Both Hands (score)	10.00±1.47	10.00±1.55	68.0	-0.21	0.831
Purdue Pegboard – Both Hands (z-score)	0.25±1.44	0.09±2.06	58.5	-0.70	0.483

Means ± standard deviations are presented and statistically compared using independent t-test (demographics data except Sex) or Generalized Estimating Equations (sleep and cognitive measures). For differences in sex distribution, which used Pearson's $\chi 2$ test.
**denotes statistical significance at $p<0.05$.*
Abbreviations: D-KEFS, Delis-Kaplan Executive Function System; FCSRT, Free and Cued Selective Reminding Test; MTCF, Modified Taylor Complex Figure; REM, Rapid Eye Movement; SES. Socioeconomic status; TST, Total Sleep Time

Table 3. Demographics, anxiety and depression levels of CBT-i and Waitlist group at baseline.

Parameters	*CBT-i (n=12)*	*Waitlist (n=12)*	*Mean difference*	*t value*	*p value*
Age (years)	71.58±7.46	67.00±6.37	4.58	1.62	0.120
Sex (M:F)	5:7	3:9			0.386
Education Level (years)	16.42±13.32	14.33±2.42	2.08	1.76	0.093
Body Mass Index (kg/m^2)	25.87±4.86	24.38±4.31	1.49	0.80	0.435
Medication Duration (years)	15.00±13.02	12.335±10.99	2.67	0.54	0.593
Weekly Benzodiazepine dose (lorazepam dose equivalence)	67.60±69.48	95.88±140.11	-28.28	-0.63	0.537

*Means ± standard deviations are presented and statistically compared using independent t-test, except sex, which used Pearson's χ2 test. * denotes statistical significance at p<0.05.*

Table 4. Sleep measures of CBT-i and Waitlist group at baseline.

Parameters	*CBT-i (n=12; Acti n=9)*	*Waitlist (n=12; PSG n=11, Acti n=10)*	*Test U*	*Z value*	*p value*
Sleep Diary					
Sleep Latency (min)	42.51±34.67	40.83±36.20	68.0	-0.23	0.817
Wake After Sleep Onset (min)	44.48±43.97	52.40±43.00	58.5	-0.78	0.436
Sleep Efficiency (%)	72.39±25.01	80.12±11.15	68.0	-0.23	0.817
Total Sleep Time (min)	403.75±75.94	401.20±89.24	71.0	-0.06	0.954
Pittsburgh Sleep Quality Index	11.33±4.31	11.33±3.34	69.0	-0.18	0.861
Insomnia Severity Index	12.25±5.46	16.83±4.55	33.0	-2.26	**0.024***
Epworth Sleepiness Scale	4.75±2.70	4.92±2.68	72.0	0.00	1.000
Geriatric Anxiety Inventory	5.33±5.23	7.00±5.64	58.0	-0.81	0.415
Geriatric Depression Scale	11.25±2.26	13.08±4.29	53.5	-1.08	0.281
Polysomnography Measures					
Sleep Latency (min)	21.32±25.73	18.33±16.37	63.0	-0.18	0.854
Wake After Sleep Onset (min)	89.50±52.43	87.78±24.92	58.0	-0.49	0.622
Sleep Efficiency (%)	76.82±10.58	76.93±9.64	63.5	-0.15	0.878
Sustained Sleep Efficiency (%)	80.03±10.64	79.95±8.10	61.0	-0.31	0.758
Total Sleep Time (min)	359.11±74.00	377.40±88.32	54.5	-0.71	0.479
N1 Duration (min)	39.13±27.87	46.49±18.35	50.0	-0.99	0.325
N1 % of TST (%)	11.16±7.84	12.18±4.73	53.0	-0.80	0.424
N2 Duration (min)	215.14±49.58	228.01±47.83	59.0	-0.43	0.667
N2 % of TST (%)	59.91±6.02	58.76±11.62	65.0	-0.06	0.951
N3 Duration (min)	47.08±32.25	43.23±34.59	58.0	-0.49	0.622
N3 % of TST (%)	13.38±9.01	10.44±7.66	52.0	-0.86	0.389
REM Duration (min)	57.45±23.73	59.38±36.00	55.0	-0.68	0.498
REM % of TST (%)	15.55±4.55	14.43±8.36	63.0	-0.18	0.853
Actigraphy Measures					
Sleep Latency (min)	40.09±34.54	46.40±32.70	38.0	-0.57	0.568
Wake After Sleep Onset (min)	39.75±18.65	41.94±22.12	42.0	-0.24	0.806
Sleep Efficiency (min)	82.10±7.93	79.75±6.41	30.0	-1.22	0.221
Total Sleep Time (min)	434.56±45.61	394.50±68.53	27.5	-1.43	0.153

*Means ± standard deviations are presented and statistically compared using Generalized Estimating Equations. * denotes statistical significance at p<0.05. Primary outcome parameters are bolded.*
Abbreviations: REM, Rapid Eye Movement; TST, Total Sleep Time

Table 5. Cognitive performance of CBT-i and Waitlist group at baseline.

Parameters	*CBT-i (n=12)*	*Waitlist (n=12)*	*Test U*	*Z value*	*p value*
Mini-Mental State Exam (score)	28.33±1.78	28.25±2.67	65.0	-0.43	0.670
D-KEFS Color Word Interference Test – Color (sec)	32.83±6.48	29.50±7.56	42.5	-1.71	0.088
D-KEFS Color Word Interference Test – Color (score)	10.25±2.30	11.42±3.06	43.0	-1.69	0.090
D-KEFS Color Word Interference Test – Reading (sec)	24.25±3.84	20.75±4.35	35.5	-2.11	**0.035***
D-KEFS Color Word Interference Test – Reading (score)	10.42±2.02	12.08±2.23	39.5	-1.90	0.058
D-KEFS Color Word Interference Test – Inhibition (sec)	69.55±18.32	63.17±18.81	51.5	-1.18	0.236
D-KEFS Color Word Interference Test – Inhibition (score)	11.00±2.66	11.42±2.50	67.0	-0.29	0.771
D-KEFS Color Word Interference Test – Flexibility (sec)	71.50±17.67	64.25±16.38	52.5	-1.13	0.260
D-KEFS Color Word Interference Test – Flexibility (score)	11.08±2.27	12.25±1.60	52.0	-1.18	0.239
D-KEFS Color Word Interference Test – Total Number of Errors	2.75±2.34	2.58±3.09	63.0	-0.53	0.598
Trail Making Test – Part A (sec)	42.33±12.71	41.33±11.11	71.5	-0.03	0.977
Trail Making Test – Part A (z-score)	0.43±0.90	0.86±1.66	65.0	-0.40	0.686
Trail Making Test – Part B (seconds)	110.92±72.45	104.67±85.01	55.0	-0.98	0.326
Trail Making Test – Part B (z-score)	1.20±3.12	0.83±1.56	59.0	-0.75	0.453
Digit Symbol Substitution Test (score)	42.50±9.12	45.92±10.77	61.0	-0.64	0.524
FCSRT – Free Recall (score)	30.33±6.30	31.17±4.49	63.5	-0.49	0.623
FCSRT – Total Recall (score)	45.75±2.60	45.75±2.83	66.0	-0.36	0.721
FCSRT – Cue Efficiency (%)	88.89±12.27	90.92±13.10	60.5	-0.68	0.495
FCSRT – Delayed Free Recall (score)	11.92±2.15	12.50±2.68	58.5	-0.79	0.431
FCSRT – Delayed Total Recall (score)	15.75±0.45	15.83±0.39	66.0	-0.49	0.623
FCSRT – Delayed Recall Cue Efficiency (%)	96.38±6.62	97.69±5.19	60.0	-0.51	0.609
MTCF – Copy (sec)	165.00±50.88	156.17±35.94	59.5	-0.72	0.470
MTCF – Copy (score)	32.00±1.91	31.17±2.86	62.0	-0.58	0.560
MTCF – Copy (z-score corrected for SES)	0.15±0.57	-0.01±0.81	65.0	-0.40	0.686
MTCF – Copy (z-score corrected for All variables)	0.06±0.57	-0.12±0.84	65.0	-0.40	0.686
MTCF – Immediate Recall (score)	15.21±4.83	17.54±5.24	52.0	-1.16	0.247
MTCF – Immediate Recall (z-score corrected for SES)	-0.10±0.90	0.35±0.95	55.5	-0.95	0.341
MTCF – Immediate Recall (z-score corrected for All variables)	-0.55±0.90	0.07±1.06	46.0	-1.50	0.133
Purdue Pegboard Dominant Hand (Score)	12.00±1.81	13.33±1.44	41.0	-1.82	0.069
Purdue Pegboard Dominant Hand (z-score)	-0.35±1.21	0.04±0.93	52.5	-1.13	0.260
Purdue Pegboard – Non-Dominant Hand (Score)	12.00±1.41	12.50±1.31	66.0	-0.36	0.720
Purdue Pegboard – Non-Dominant Hand (z-score)	-0.16±0.88	-0.13±0.51	71.0	-0.06	0.954
Purdue Pegboard – Both Hands (score)	9.92±1.68	10.08±1.31	68.5	-0.21	0.836
Purdue Pegboard – Both Hands (z-score)	0.19±1.46	0.30±1.48	70.0	-0.12	0.908

*Means ± standard deviations are presented and statistically compared using Generalized Estimating Equations. * denotes statistical significance at p<0.05.*
Abbreviations: D-KEFS, Delis-Kaplan Executive Function System; FCSRT, Free and Cued Selective Reminding Test; MTCF, Modified Taylor Complex Figure; SES. Socioeconomic status.

Table 6. Sleep measures of CBT-i and Waitlist group at baseline and immediately after weaning, accounting for differences in age, sex and education levels.

Parameters	***CBT-i (PSG n=12; SD n=12 ; Acti n=7)***		***Waitlist (PSG n=11; SD n=10; Acti n=5)***		***Effect of weaning***		***Effect of Group X weaning***	
	Pre	*Post*	Pre	*Post*	*Waldχ 2*	*p value*	*Waldχ 2*	*p value*
Sleep Diary								
Sleep Latency (min)	42.51±34.67	32.41±31.77	45.69±37.51	65.31±48.36	0.52	0.472	7.19	**0.007***
Wake After Sleep Onset (min)	44.48±43.97	21.39±15.76	58.06±43.90	73.34±41.71	1.14	0.285	8.32	**0.004***
Sleep Efficiency (%)	72.39±25.01	81.17±26.26	79.20±11.59	71.11±13.78	0.04	0.839	16.78	**0.000***
Total Sleep Time (min)	403.75±75.94	430.40±68.56	397.62±78.08	348.41±65.58	0.98	0.322	6.94	**0.008***
Pittsburgh Sleep Quality Index	11.33±4.31	8.17±4.26	11.33±3.34	10.92±2.87	9.47	**0.002***	5.98	**0.014***
Insomnia Severity Index	12.25±5.46	6.92±6.01	16.83±4.55	13.08±6.39	18.08	**0.000***	2.72	0.099
Epworth Sleepiness Scale	4.75±2.70	5.00±4.09	4.92±2.68	4.42±3.09	0.06	0.809	0.48	0.489
Geriatric Anxiety Inventory	5.33±5.23	4.75±4.81	7.00±5.64	6.25±6.51	0.89	0.345	0.00	0.991
Geriatric Depression Scale	11.25±2.26	11.42±3.15	13.08±4.29	12.00±3.28	1.56	0.212	3.10	0.078
Polysomnography Measures								
Sleep Latency (min)	21.32±25.73	17.12±20.04	18.33±16.37	29.61±38.58	0.20	0.653	1.59	0.207
Wake After Sleep Onset (min)	89.50±52.43	103.10±65.60	87.78±24.92	124.20±59.86	4.39	**0.036***	0.35	0.552
Sleep Efficiency (%)	76.82±10.58	75.40±14.25	76.93±9.64	70.05±11.78	2.54	0.111	1.15	0.283
Sustained Sleep Efficiency (%)	80.03±10.64	77.73±13.59	79.95±8.10	73.74±11.84	2.96	0.086	0.67	0.413
Total Sleep Time (min)	359.11±74.00	361.87±67.33	377.40±88.32	346.71±51.15	0.52	0.470	0.74	0.388
N1 Duration (min)	39.13±27.87	31.08±17.21	46.49±18.35	42.17±22.01	1.48	0.223	0.12	0.729
N1 % of TST (%)	11.16±7.84	8.94±4.60	12.18±4.73	12.59±6.43	1.38	0.240	0.11	0.735
N2 Duration (min)	215.14±49.58	204.50±51.93	228.01±47.83	199.07±38.94	3.13	0.077	0.70	0.402
N2 % of TST (%)	59.91±6.02	56.53±11.43	58.76±11.62	57.58±8.63	1.79	0.181	0.00	0.952
N3 Duration (min)	47.08±32.25	71.58±40.14	43.23±34.59	50.16±39.44	3.45	0.063	1.19	0.275
N3 % of TST (%)	13.38±9.01	19.77±10.53	10.44±7.66	13.12±9.70	4.12	**0.042***	0.28	0.596
REM Duration (min)	57.45±23.73	54.31±24.82	59.38±36.00	58.65±20.31	3.55	0.160	1.51	0.220
REM % of TST (%)	15.55±4.55	14.77±4.86	14.43±8.36	16.69±4.71	0.14	0.706	0.82	0.364
Actigraphy Measures								

Sleep Latency (min)	32.11±17.08	25.62±20.52	52.15±39.97	49.72±18.58	0.72	0.396	1.34	0.247
Wake After Sleep Onset (min)	39.03±14.47	30.54±12.51	50.31±24.85	74.92±52.92	0.99	0.320	7.03	**0.008***
Sleep Efficiency (min)	83.21±3.67	87.83±5.63	79.98±8.61	74.65±4.51	0.00	0.970	13.72	**0.000***
Total Sleep Time (min)	447.57±40.05	445.86±83.03	414.80±53.78	386.60±29.02	0.01	0.939	0.41	0.520

*Means ± standard deviations are presented and statistically compared using Generalized Estimating Equations. * denotes statistical significance at p<0.05. Primary outcome parameters are bolded.*
Abbreviations: REM, Rapid Eye Movement; TST, Total Sleep Time.

Table 7. Cognitive measures of CBT-i and Waitlist group at baseline and immediately after weaning, accounting for differences in age, sex, and education levels.

Parameters	***CBT-i (n=12)***		**Waitlist (n=12)**		***Effect of weaning***		***Effect of Group X weaning***	
	Pre	*Post*	Pre	*Post*	*Wald χ^2*	*p value*	*Wald χ^2*	*p value*
Mini-Mental State Exam (score)	28.33±1.78	28.50±2.20	28.25±2.67	28.00±2.17	0.01	0.925	0.21	0.645
D-KEFS Color Word Interference Test – Color (sec)	32.83±6.48	31.75±6.25	29.50±7.56	30.17±8.74	0.07	0.785	1.86	0.173
D-KEFS Color Word Interference Test – Color (score)	10.25±2.30	10.50±2.39	11.42±3.06	11.17±3.66	0.00	0.969	0.87	0.351
D-KEFS Color Word Interference Test – Reading (sec)	24.25±3.84	23.58±4.56	20.75±4.35	22.42±5.05	2.27	0.132	12.38	**0.000***
D-KEFS Color Word Interference Test – Reading (score)	10.42±2.02	10.75±2.42	12.08±2.23	11.33±2.42	0.87	0.350	7.53	**0.006***
D-KEFS Color Word Interference Test – Inhibition (sec)	69.55±18.32	69.67±25.50	63.17±18.81	58.83±15.86	1.24	0.266	1.16	0.282
D-KEFS Color Word Interference Test – Inhibition (score)	11.00±2.66	10.67±2.81	11.42±2.50	12.17±2.17	0.11	0.737	0.93	0.335
D-KEFS Color Word Interference Test – Flexibility (sec)	71.50±17.67	68.67±20.88	64.25±16.38	62.25±8.95	1.15	0.284	0.02	0.896
D-KEFS Color Word Interference Test – Flexibility (score)	11.08±2.27	11.50±2.65	12.25±1.60	12.33±1.23	0.80	0.372	0.38	0.538
D-KEFS Color Word Interference Test – Total Number of Errors	2.75±2.34	1.67±2.53	2.58±3.09	3.08±2.07	0.61	0.436	0.44	0.506
Trail Making Test – Part A (sec)	42.33±12.71	41.75±12.26	41.33±11.11	39.08±11.52	0.52	0.472	0.19	0.665
Trail Making Test – Part A (z-score)	0.43±0.90	0.36±0.87	0.86±1.66	0.44±1.11	0.93	0.336	0.48	0.488
Trail Making Test – Part B (seconds)	110.92±72.45	99.08±56.87	104.67±85.01	93.83±43.99	2.03	0.155	0.00	0.982
Trail Making Test – Part B (z-score)	1.20±3.12	0.50±1.07	0.83±1.56	1.01±1.76	0.28	0.597	0.77	0.381
Digit Symbol Substitution Test (score)	42.50±9.12	42.83±9.40	45.92±10.77	48.00±9.99	0.89	0.346	0.44	0.509
FCSRT – Free Recall (score)	30.33±6.30	31.08±6.43	31.17±4.49	32.00±5.74	0.92	0.337	0.00	0.970
FCSRT – Total Recall (score)	45.75±2.60	44.92±3.96	45.75±2.83	45.42±3.53	0.75	0.386	0.14	0.709
FCSRT – Cue Efficiency (%)	88.89±12.27	85.48±14.77	90.92±13.10	86.18±16.84	2.20	0.138	0.05	0.818
FCSRT – Delayed Free Recall (score)	11.92±2.15	12.08±2.64	12.50±2.68	13.08±1.93	0.63	0.427	0.18	0.672
FCSRT – Delayed Total Recall (score)	15.75±0.45	14.00±4.22	15.83±0.39	14.67±4.31	2.72	0.099	0.12	0.726
FCSRT – Delayed Recall Cue Efficiency (%)	96.38±6.62	84.46±18.67	97.69±5.19	94.32±15.17	4.63	**0.032***	1.83	0.177
MTCF/ROCF – Copy (sec)	165.00±50.88	173.83±63.20	156.17±35.94	151.58±45.17	0.03	0.852	0.47	0.494
MTCF/ROCF – Copy (score)	32.00±1.91	32.25±3.08	31.17±2.86	34.00±2.00	5.99	**0.014***	4.18	**0.041***

MTCF/ROCF – Copy (z-score corrected for SES)	0.15±0.57	0.22±0.78	-0.01±0.81	0.76±0.56	6.17	**0.013***	4.33	**0.037***
MTCF/ROCF – Copy (z-score corrected for All variables)	0.06±0.57	0.14±0.77	-0.12±0.84	0.66±0.58	6.59	**0.010***	4.35	**0.037***
MTCF/ROCF – Immediate Recall (score)	15.21±4.83	17.67±3.23	17.54±5.24	17.29±6.51	1.35	0.245	1.98	0.159
MTCF/ROCF – Immediate Recall (z-score corrected for SES)	-0.10±0.90	0.33±0.65	0.35±0.95	0.31±1.15	1.28	0.257	1.81	0.178
MTCF/ROCF – Immediate Recall (z-score corrected for All variables)	-0.55±0.90	-0.03±0.98	0.07±1.06	-0.54±1.31	0.03	0.868	4.21	**0.040***
Purdue Pegboard Dominant Hand (Score)	12.00±1.81	12.08±2.07	13.33±1.44	13.75±1.86	0.76	0.383	0.31	0.581
Purdue Pegboard Dominant Hand (z-score)	-0.35±1.21	-0.28±1.30	0.04±0.93	0.30±1.09	0.56	0.456	0.19	0.664
Purdue Pegboard – Non-Dominant Hand (Score)	12.00±1.41	12.33±1.30	12.50±1.31	12.17±2.82	0.00	0.996	0.59	0.442
Purdue Pegboard – Non-Dominant Hand (z-score)	-0.16±0.88	0.28±1.01	-0.13±0.51	0.24±0.84	5.15	**0.023***	0.04	0.841
Purdue Pegboard – Both Hands (score)	9.92±1.68	9.67±2.06	10.08±1.31	10.75±1.71	0.59	0.443	3.19	0.074
Purdue Pegboard – Both Hands (z-score)	0.19±1.46	0.15±1.62	0.30±1.48	0.66±1.45	0.26	0.608	0.43	0.514

*Means ± standard deviations are presented and statistically compared using Generalized Estimating Equations. * denotes statistical significance at p<0.05.*
Abbreviations: D-KEFS, Delis-Kaplan Executive Function System; FCSRT, Free and Cued Selective Reminding Test; MTCF, Modified Taylor Complex Figure; SES. Socioeconomic status.

Table 8. Cognitive measures of Pooled CBT-i group (CBT-i and Waitlist who completed CBT-i post weaning) at baseline and immediately after CBT-i, accounting for differences in age, sex, and education levels.

Parameters	***Pooled CBT-i (n=18)***		***Mean Difference***	***Effect of CBT-i***	
	Pre CBT-i	**Post CBT-i**		*Wald χ2*	*p value*
Mini-Mental State Exam (score)	28.44±1.71	28.56±1.80	0.11	0.05	0.816
D-KEFS Color Word Interference Test – Color (sec)	30.94±6.25	28.94±7.48	-2.00	2.65	0.103
D-KEFS Color Word Interference Test – Color (score)	10.94±2.30	11.22±2.44	0.28	1.17	0.279
D-KEFS Color Word Interference Test – Reading (sec)	22.61±4.18	21.33±5.35	-1.28	2.37	0.123
D-KEFS Color Word Interference Test – Reading (score)	11.17±2.14	11.33±2.33	0.17	0.44	0.505
D-KEFS Color Word Interference Test – Inhibition (sec)	67.39±16.18	64.17±23.22	-3.22	1.42	0.234
D-KEFS Color Word Interference Test – Inhibition (score)	11.17±2.46	11.56±2.79	0.39	0.28	0.597
D-KEFS Color Word Interference Test – Flexibility (sec)	67.39±16.18	64.17±23.22	-3.22	0.845	0.358
D-KEFS Color Word Interference Test – Flexibility (score)	11.61±2.11	11.72±2.64	0.11	0.09	0.766
D-KEFS Color Word Interference Test – Total Number of Errors	2.83±2.83	1.67±2.11	-1.17	3.24	0.072
Trail Making Test – Part A (sec)	42.28±11.79	38.61±11.64	-3.67	2.05	0.153
Trail Making Test – Part A (z-score)	0.72±1.29	0.25±1.03	-0.48	2.04	0.153
Trail Making Test – Part B (seconds)	99.00±59.25	94.06±48.00	-4.94	0.46	0.500
Trail Making Test – Part B (z-score)	0.96±2.48	0.56±1.19	-0.41	0.45	0.504
Digit Symbol Substitution Test (score)	42.89±8.61	45.78±10.76	2.89	3.52	0.061
FCSRT – Free Recall (score)	30.56±5.25	32.78±5.87	2.22	4.92	**0.027***
FCSRT – Total Recall (score)	45.56±2.73	45.61±3.30	0.06	0.00	0.947
FCSRT – Cue Efficiency (%)	87.81±12.96	87.62±12.53	-0.19	0.00	0.957
FCSRT – Delayed Free Recall (score)	12.17±2.14	12.44±2.24	0.28	0.29	0.593
FCSRT – Delayed Total Recall (score)	15.78±0.42	14.61±3.42	-1.17	1.89	0.169
FCSRT – Delayed Recall Cue Efficiency (%)	96.79±6.05	88.21±17.66	-8.58	4.25	**0.039***
MTCF/ROCF – Copy (sec)	165.22±43.01	161.67±55.75	-3.56	0.07	0.795
MTCF/ROCF – Copy (score)	31.94±1.99	32.06±2.72	0.11	0.03	0.862
MTCF/ROCF – Copy (z-score corrected for SES)	0.14±0.59	0.17±0.71	0.03	0.04	0.848
MTCF/ROCF – Copy (z-score corrected for All variables)	0.05±0.61	0.08±0.71	0.03	0.02	0.876
MTCF/ROCF – Immediate Recall (score)	16.08±5.43	17.78±4.40	1.69	2.93	0.087
MTCF/ROCF – Immediate Recall (z-score corrected for SES)	0.05±0.98	0.36±0.83	0.30	3.26	0.071
MTCF/ROCF – Immediate Recall (z-score corrected for All variables)	-0.35±1.00	-0.01±0.95	0.34	1.43	0.232
Purdue Pegboard Dominant Hand (Score)	12.33±1.67	12.72±1.91	0.39	1.90	0.169
Purdue Pegboard Dominant Hand (z-score)	-0.33±1.15	-0.21±1.07	0.13	0.25	0.620

Purdue Pegboard – Non-Dominant Hand (Score)	12.22±1.31	12.72±1.41	0.50	3.07	0.080
Purdue Pegboard – Non-Dominant Hand (z-score)	-0.20±0.73	0.22±0.88	0.42	6.17	**0.013***
Purdue Pegboard – Both Hands (score)	10.06±1.39	10.06±1.87	0.00	0.00	1.000
Purdue Pegboard – Both Hands (z-score)	0.15±1.27	0.20±1.47	0.05	0.02	0.879

*Means ± standard deviations are presented and statistically compared using Generalized Estimating Equations. * denotes statistical significance at p<0.05.*
Abbreviations: D-KEFS, Delis-Kaplan Executive Function System; FCSRT, Free and Cued Selective Reminding Test; MTCF, Modified Taylor Complex Figure; SES. Socioeconomic status.

Figures

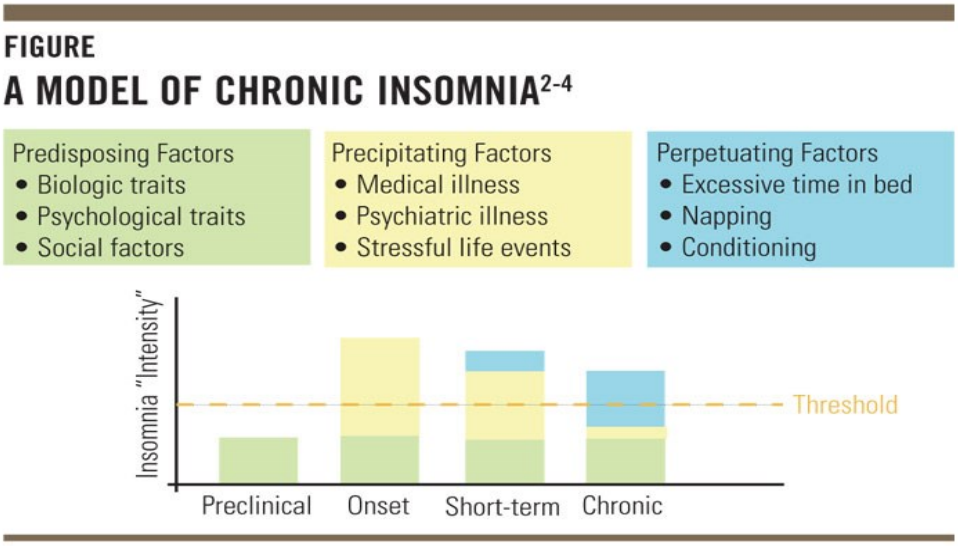

Figure 1. Spielman's 3P model of insomnia (Spielman, Caruso, et al., 1987).

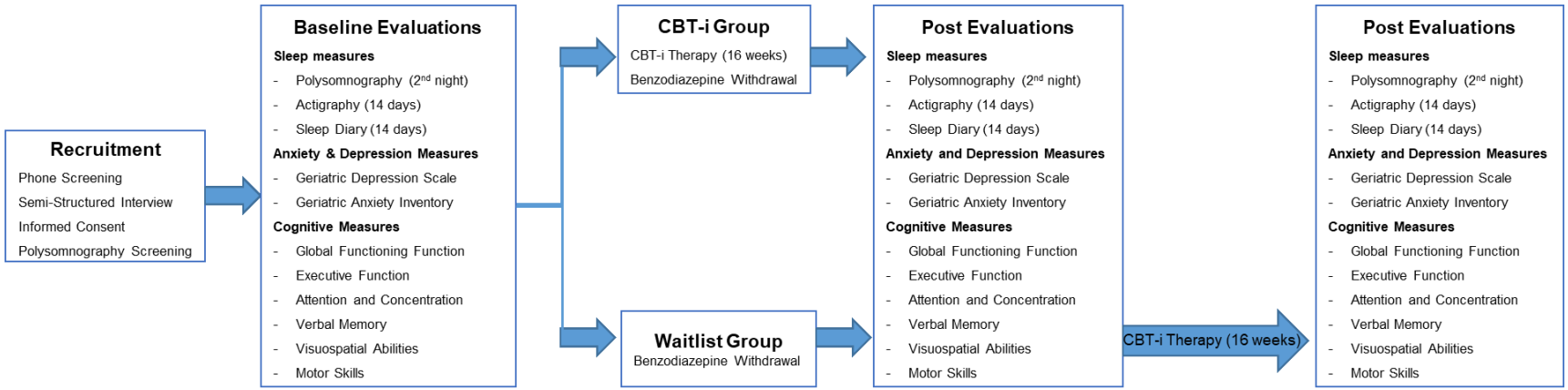

Figure 2. Schematic representation of the study procedure, demonstrating recruitment, baseline evaluations, group assignment and intervention received in each group and evaluations after interventions.

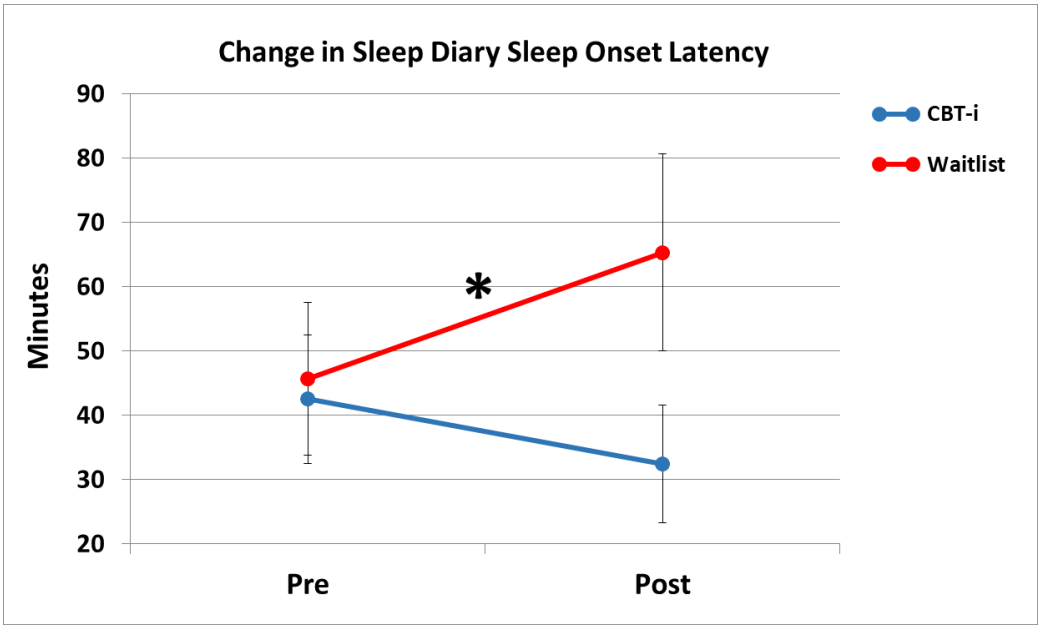

Figure 3. Changes in the sleep diary sleep latency from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was no effect of weaning alone (p=0.472), but there was a significant time-group interaction (p=0.007).

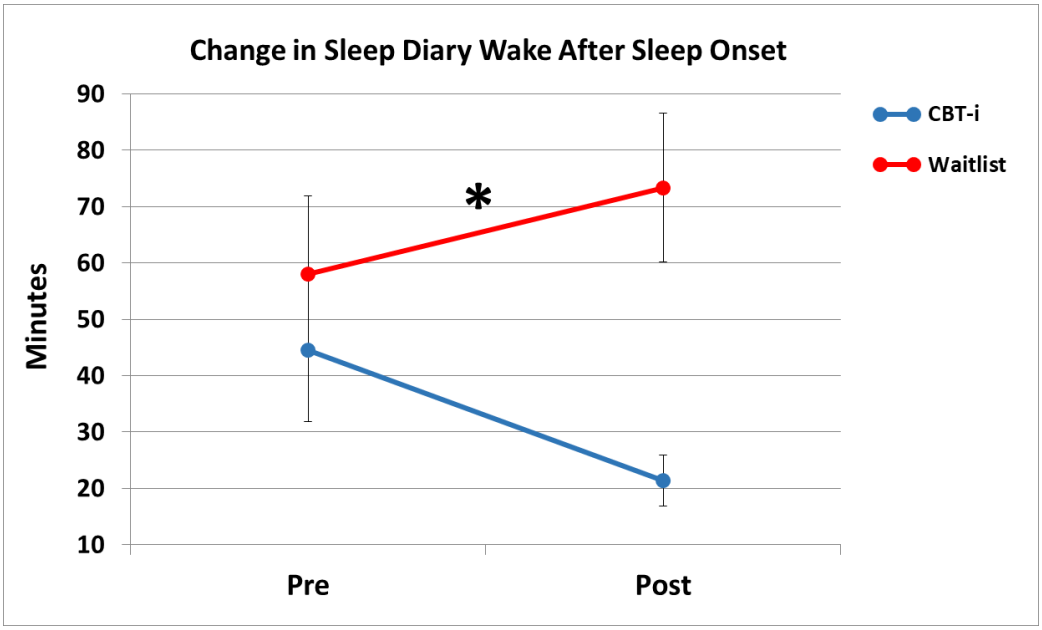

Figure 4. Changes in the sleep diary wake after sleep onset from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was no effect of weaning alone (p=0.285), but there was a significant time-group interaction (p=0.004).

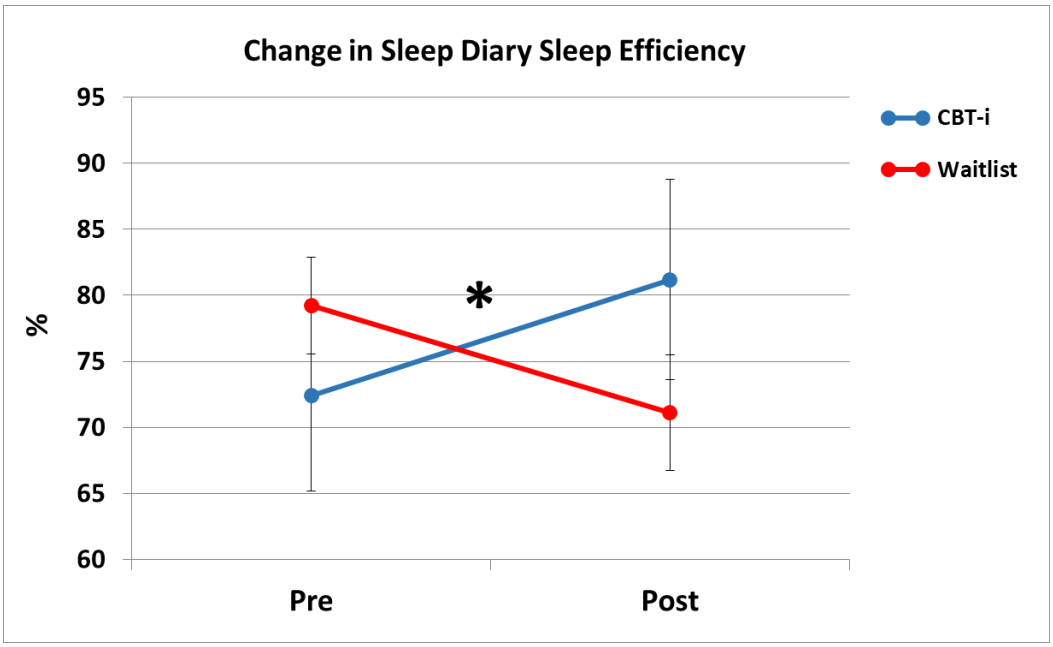

Figure 5. Changes in the sleep diary sleep efficiency from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was no effect of weaning alone (p=0.839), but there was a significant time-group interaction (p=0.000).

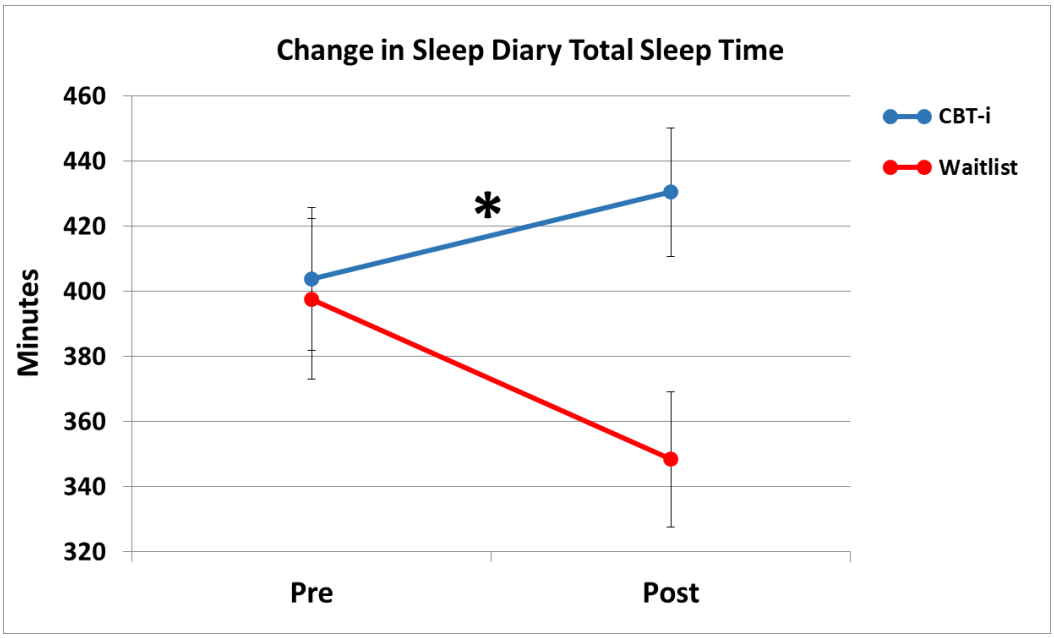

Figure 6. Changes in the sleep diary total sleep time from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was no effect of weaning alone (p=0.322), but there was a significant time-group interaction (p=0.008).

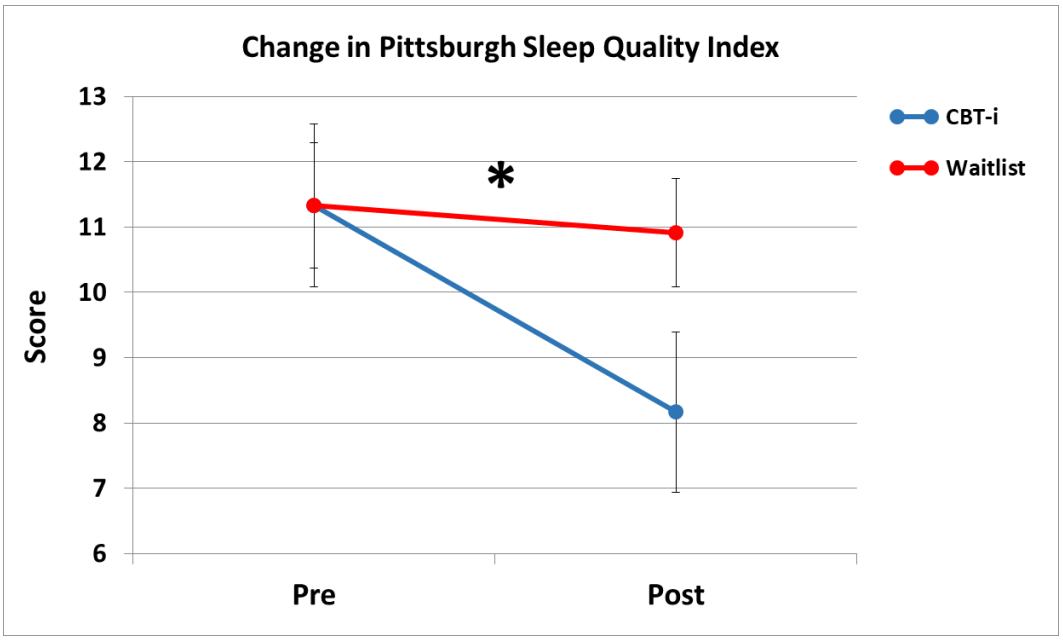

Figure 7. Changes in the Pittsburgh sleep quality index from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was a significant effect of weaning alone (p=0.002), and a significant time-group interaction (p=0.014).

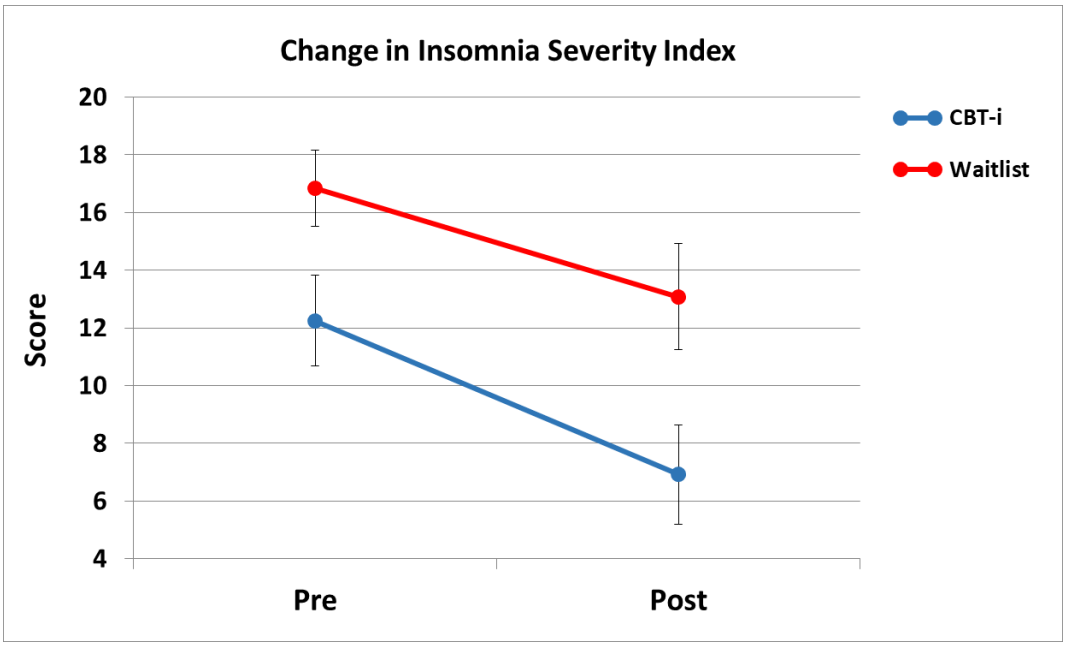

Figure 8. Changes in the insomnia severity index from pre- to post-intervention. The dots represent the mean value, and the bars show the standard error of the mean. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was a significant effect of weaning alone (p=0.000), and a trend for time-group interaction (p=0.099).

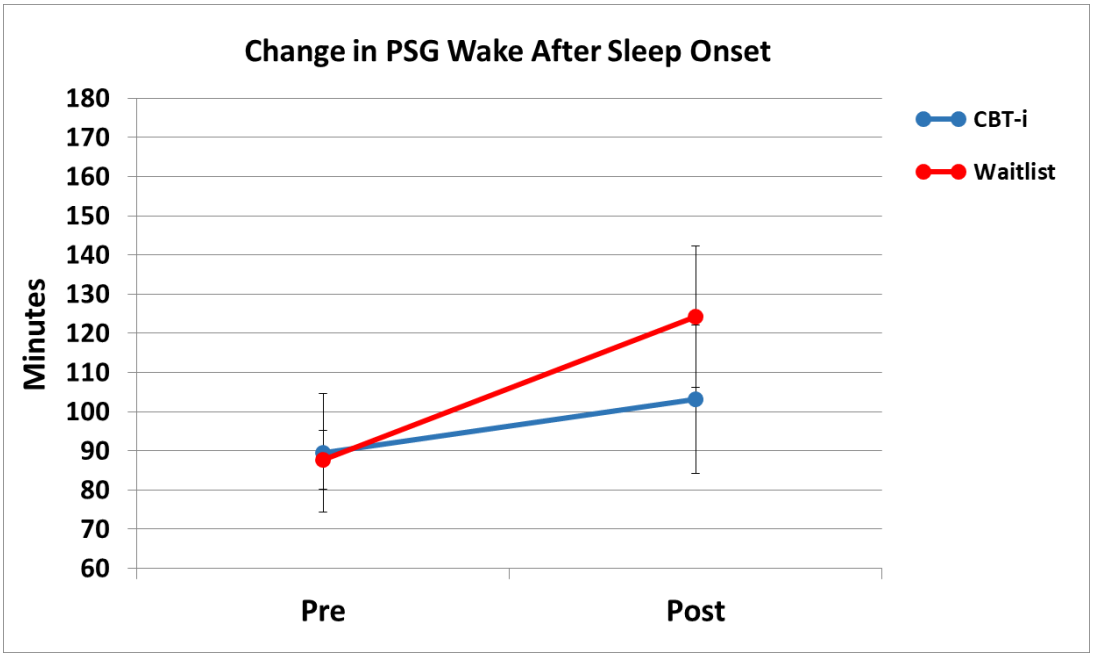

Figure 9. Changes in Polysomnography wake after sleep onset from pre- to post-intervention. The dots represent the mean value, and the bars show the standard error of the mean. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was a significant effect of weaning alone (p=0.036), but no time-group interaction (p=0.552).

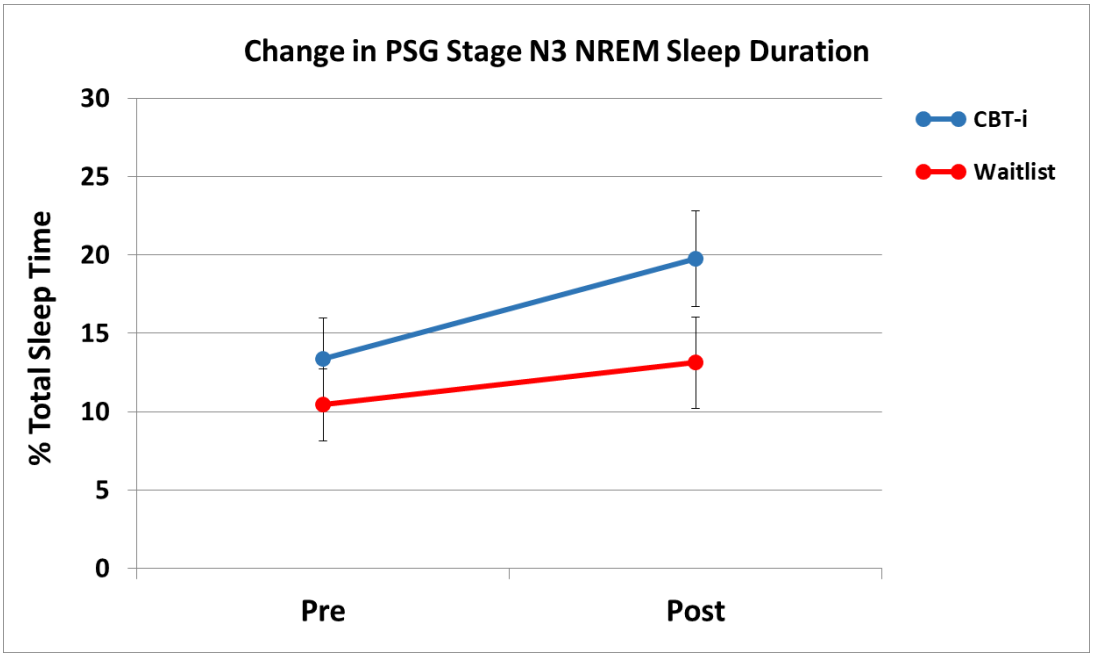

Figure 10. Changes in Polysomnography stage N3 NREM sleep duration from pre- to post-intervention. The dots represent the mean value, and the bars show the standard error of the mean. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was a significant effect of weaning alone (p=0.042), but no time-group interaction (p=0.596).

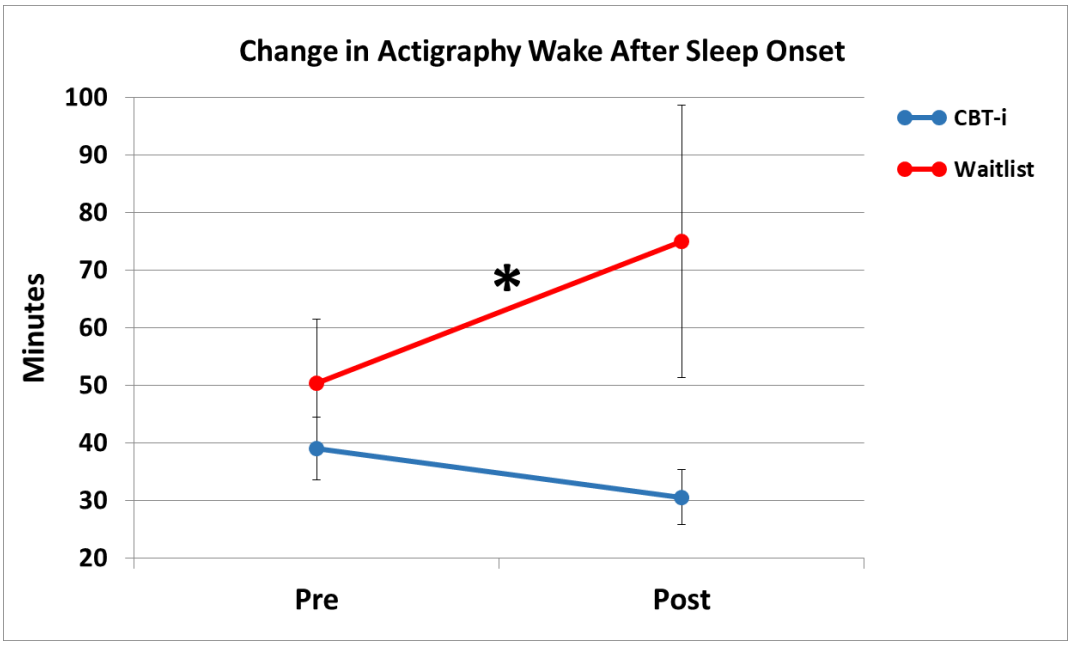

Figure 11. Changes in actigraphy wake after sleep onset from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was no effect of weaning alone (p=0.320), but there was a significant time-group interaction (p=0.008).

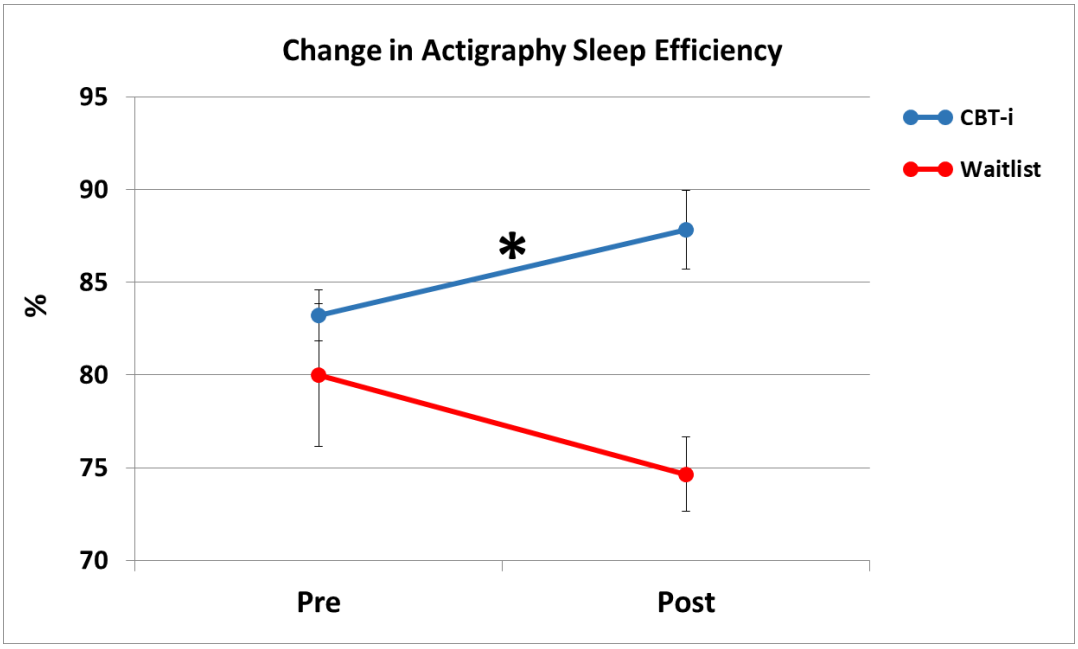

Figure 12. Changes in actigraphy sleep efficiency from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was no effect of weaning alone (p=0.970), but there was a significant time-group interaction (p=0.000).

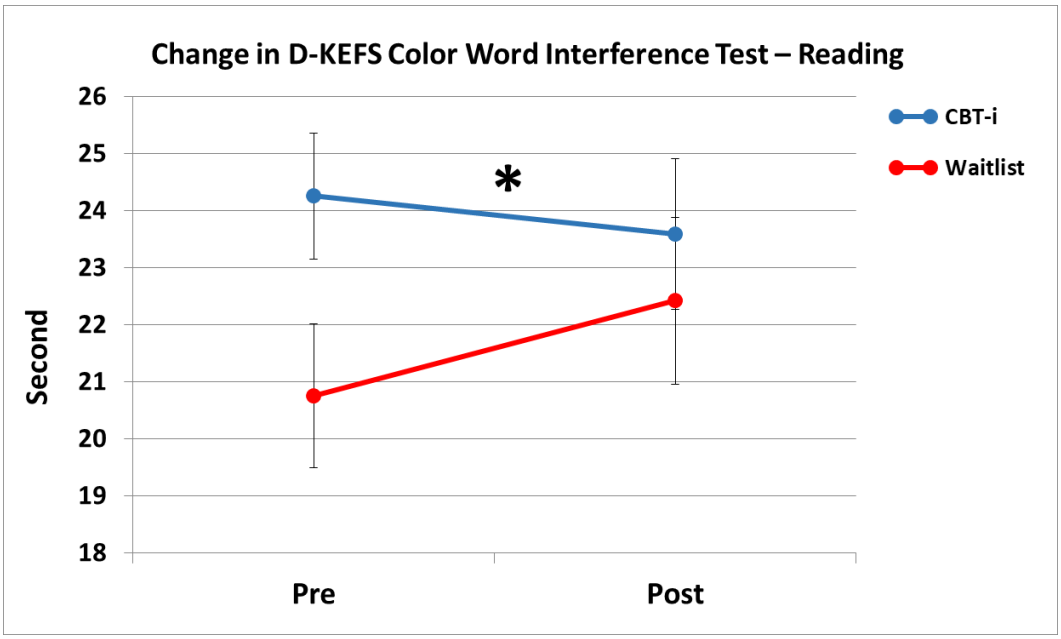

Figure 13. Changes in reading component of Delis–Kaplan executive function system (measured in seconds) from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was no effect of weaning alone (p=0.132), but there was a significant time-group interaction (p=0.000).

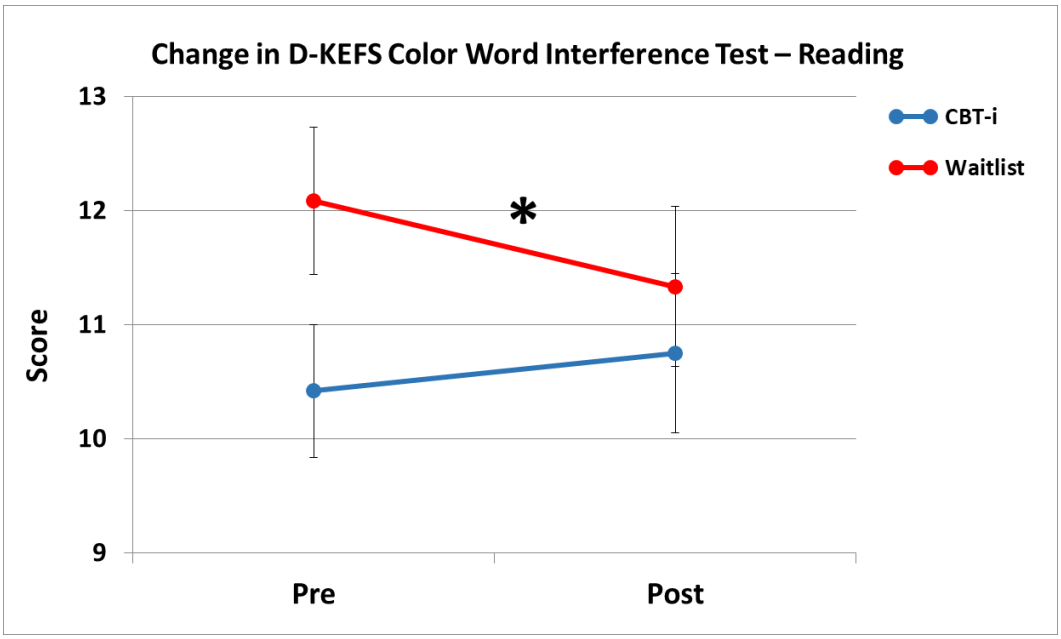

Figure 14. Changes in reading component of Delis–Kaplan executive function system (scaled score, accounting for age) from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was no effect of weaning alone (p=0.350), but there was a significant time-group interaction (p=0.006).

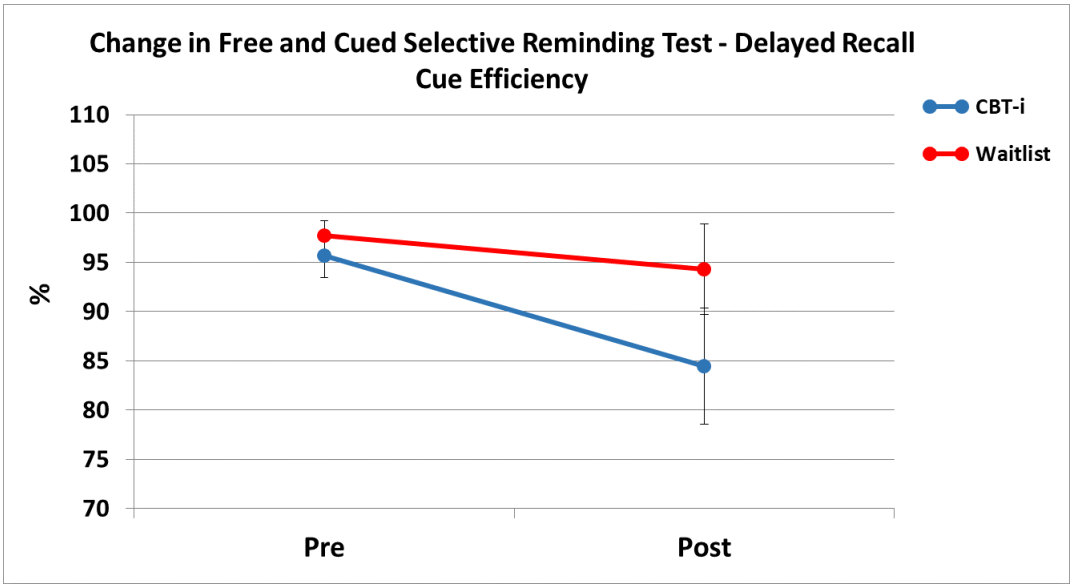

Figure 15. Changes in delayed recall cue efficiency component of the free and cued selective reminding test from pre- to post-intervention. The dots represent the mean value, and the bars show the standard error of the mean. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was a significant effect of weaning alone (p=0.032), but there was no significant time-group interaction (p=0.177).

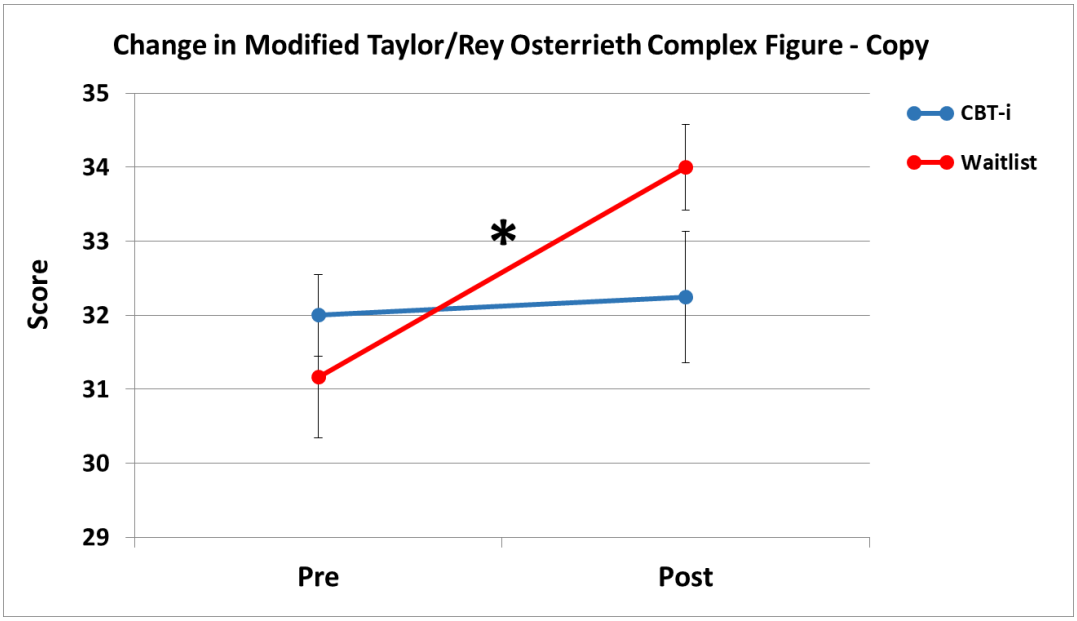

Figure 16. Changes in the copy component of the modified Taylor/Rey Osterrieth complex figure (score) from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was a significant effect of weaning alone (p=0.014), and a significant time-group interaction (p=0.041).

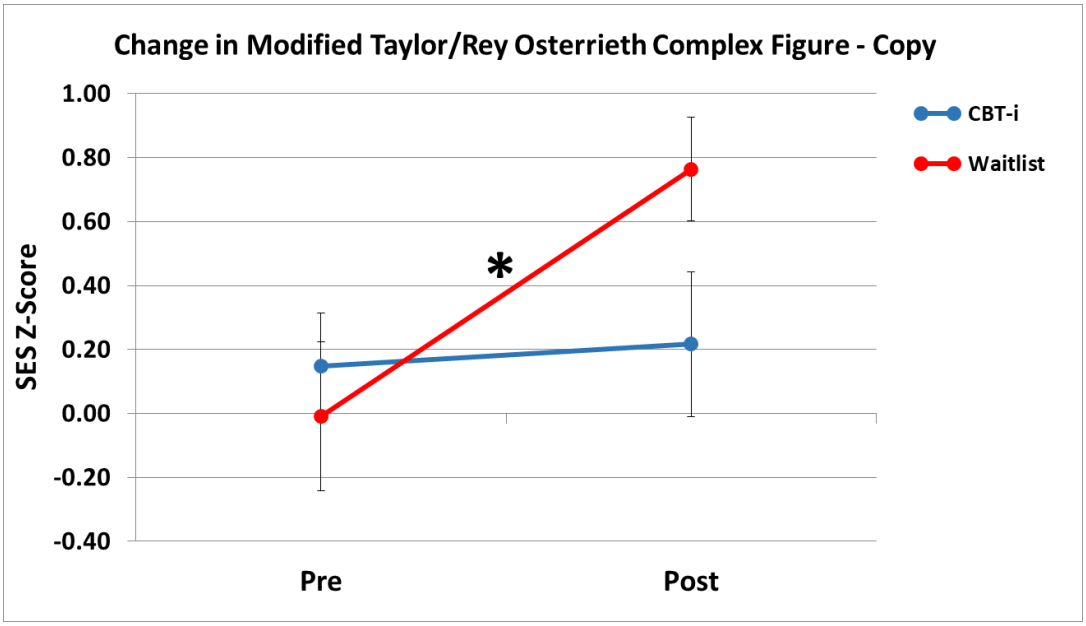

Figure 17. Changes in the copy component of the modified Taylor/Rey Osterrieth complex figure (SES Z-score) from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was a significant effect of weaning alone (p=0.013), and a significant time-group interaction (p=0.037).

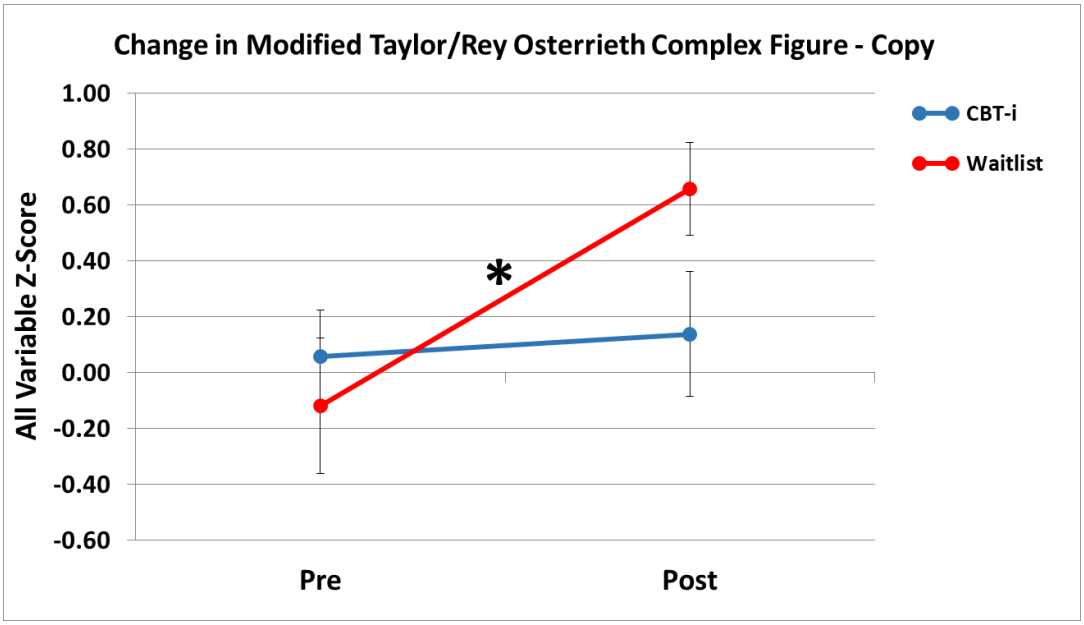

Figure 18. Changes in the copy component of the modified Taylor/Rey Osterrieth complex figure (all variable Z-score) from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was a significant effect of weaning alone (p=0.010), and a significant time-group interaction (p=0.037).

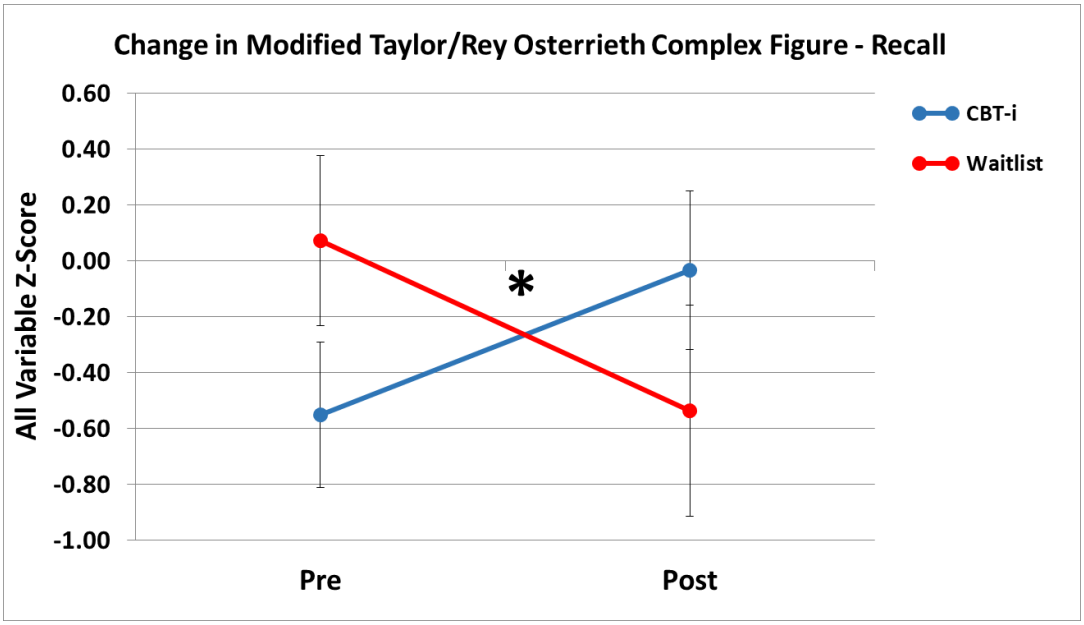

Figure 19. Changes in the recall component of the modified Taylor/Rey Osterrieth complex figure (all variable Z-score) from pre- to post-intervention. The dots represent the mean value, the bars show the standard error of the mean, and the asterisk denote significant group-time interaction. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was no effect of weaning alone (p=0.868), but there was a significant time-group interaction (p=0.040).

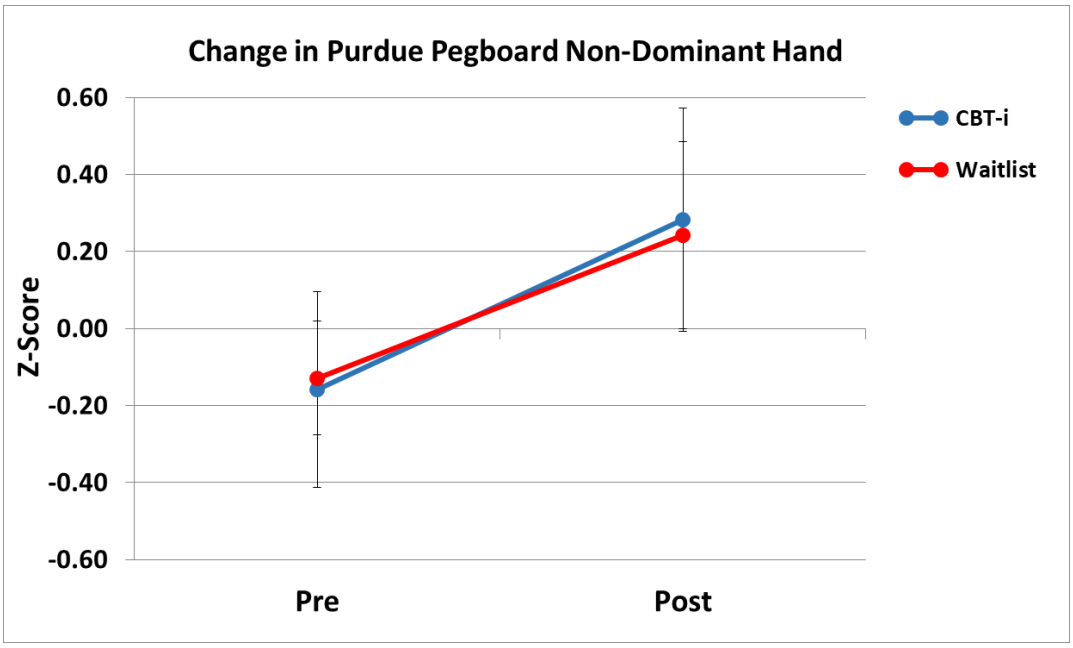

Figure 20. Changes in non-dominant hand component of Purdue pegboard test (z-score) from pre- to post-intervention. The dots represent the mean value, and the bars show the standard error of the mean. Generalized Estimating Equation was used, accounting for age, sex, education level with significance set at p<0.05. There was a significant effect of weaning alone (p=0.023), but there was no significant time-group interaction (p=0.841).

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