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EFFICACY OF A MINDFULNESS-BASED INTERVENTION FOR TREATING ADULTS WITH GENERALIZED ANXIETY DISORDER

EFICÁCIA DE UMA INTERVENÇÃO BASEADA EM MINDFULNESS PARA TRATAR ADULTOS COM TRANSTORNO DE ANSIEDADE GENERALIZADA

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ABSTRACT

Generalized anxiety disorder (GAD) is a chronic disorder with high individual and social burden. Many individuals diagnosed with GAD do not respond to treatment or they remain with residual symptoms. In order to contribute with the development of better treatments and better understanding of the disorder itself, this thesis investigated the efficacy of a Mindfulness-Based Interventions (MBI) to treat GAD as well as the mechanisms associated with improvement. First, a systematic review and multilevel meta-analysis with meta-regression of multiple outcomes was conducted considering MBIS efficacy to treat internalized symptoms in anxiety and stress-related disorders. After, we conducted a parallel three-arm randomized clinical trial (RCT) to assess the efficacy of a MBI (Body in Mind Training, BMT) in treating GAD as compared to pharmacologic treatment (Fluoxetine group, FLX) and to an active comparison group (Quality of Life and Psychoeducation group, QoL). Clinical efficacy results are presented, and we investigated psychological (emotional process) and biological (functional neuroimage and heart rate variability) mechanisms of improvement. MBIs seems promising to treat distress but not fear symptoms in anxiety and stress-related disorder. Our RCT suggested that all treatment modalities (BMT, FLX and QoL) were associated with symptoms improvement at the endpoint, however BMT was not non-inferior to FLX and not superior to QoL. Mediation analysis revealed that improvement in emotional regulation mediated the association between improvement in mindfulness measure and reduction in worry in BMT group, but not in FLX and QoL. Furthermore, better attachment style moderated the relationship between improvement in mindfulness and improvement in emotional regulation. Moreover, we reported different neuronal mechanisms. Improvement with BMT was associated with higher connection between amygdala with default mode and salience networks when compared to FLX group. Clinical as well as research implications of these results are discussed.

RESUMO

O transtorno de ansiedade generalizada (TAG) é um transtorno crônico com alto ônus individual e social. Muitos indivíduos diagnosticados com TAG não respondem ao tratamento ou permanecem com sintomas residuais. A fim de contribuir com o desenvolvimento de melhores tratamentos e uma melhor compreensão do distúrbio em si, esta tese investigou a eficácia de intervenções baseadas em *mindfulness* (MBIs) no tratamento da TAG, bem como nos mecanismos associados à melhora. Primeiro, uma revisão sistemática e uma meta-análise multinível com meta-regressão de múltiplos desfechos foi realizada investigando a eficácia de MBIs no tratamento de sintomas internalizantes em transtornos de ansiedade e relacionados ao estresse. Após, realizamos um ensaio clínico randomizado (ECR) paralelo de três braços para avaliar a eficácia de uma MBI (*Body in Mind Training*, BMT) no tratamento da TAG em comparação ao tratamento farmacológico (Grupo Fluoxetina, FLX) e a um grupo de comparação ativo (Grupo Qualidade de Vida e Psicoeducação, QoL). Os resultados da eficácia clínica são apresentados e investigamos os mecanismos psicológicos (processos emocionais) e biológicos (neuroimagem funcional e variabilidade da frequência cardíaca). Os MBIs parecem promissores no tratamento da dimensão *distress*, mas não da dimensão medo de sintomas de ansiedade e de transtornos relacionados ao estresse. Nosso ECR sugeriu que todas as modalidades de tratamento (BMT, FLX e QoL) estavam associadas à melhora de sintomas ao final do estudo; no entanto, o BMT não foi não inferior à FLX e não foi superior ao QoL. A análise de mediação revelou que a melhora na regulação emocional mediou a associação entre incremento nos níveis de *mindfulness* e redução da preocupação no grupo BMT, mas não no FLX e no QoL. Além disso, um estilo de apego mais funcional moderou a relação entre a melhora do *mindfulness* e melhora da regulação emocional. Além dos efeitos em processos emocionais, relatamos diferentes mecanismos neuronais. A melhoria com o BMT foi associada à maior conexão entre a amígdala com as redes de modo padrão e saliência quando comparada ao grupo FLX. As implicações clínicas e para a pesquisa desses resultados são discutidas**.**

LIST OF ABBREVIATIONS AND ACRONYMS

BMT: Body-in Mind Training

CBT: Cognitive Behavior Therapy

FLX: Fluoxetine Group

fMRI: Functional Magnetic Resonance Imaging

GAD: Generalized Anxiety Disorder

MBCT: Mindfulness-Based Cognitive Therapy

MBI: Mindfulness-Based Intervention

MBSR: Mindfulness-Based Stress Reduction

QoL: Quality of Life and Psychoeducation Group

SSRI: Selective Serotonin-Reuptake Inhibitor

SUMMARY

THEORETICAL FRAMEWORK

Why studying Generalized Anxiety Disorder?

Anxiety disorders – a group of disorders that share excessive fear and anxiety - are the most prevalent psychiatric disorders worldwide (1,2). Generalized anxiety disorder (GAD) – characterized by a chronic apprehension about many daily life circumstances - is the most prevalent anxiety disorder after specific phobia and social anxiety disorder affecting almost 6% of the population along the lifetime (3,4). Besides its high prevalence, GAD is associated with psychiatric and medical comorbidities as well as functional impairment. Moreover it is associated with high burden for the individual and society (5–9). Also, this disorder is frequently under-recognized and many patients seek medical care for somatic complaints, and less than one-third of patients are adequately treated (10,11).

Despite its high prevalence, as well as, its individual and social impact, GAD is the least successfully treated anxiety disorder (12). About 50% of patients do not respond to first-line treatment with selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), pregabalin or cognitive behavior therapy (CBT) (13–15). Moreover, the remission rates along time decreased - one study reported that only 38% of patients remitted after five years (16) for example - and many remitted patients experience residual symptoms along time (17). Besides its limited response, first-line medications to treat GAD typically present adverse effects that sometimes are difficult to tolerate or treat as sexual dysfunction, gastrointestinal and sleep disturbances, weight gain, sedation, and dizziness (15).

Adjunctive next step strategies in patients who are considered treatment-resistant have limited and inconsistent evidence (Katzman et al., 2014), and they usually consist of using atypical antipsychotics, antihistamines, and benzodiazepines that, in long term, have well known severe metabolic, sedative, misuse and dependence side effects (15,18). Moreover, GAD is usually a chronic disorder and its diagnostic criteria definition required the presence of symptoms for at least 6 months (1). Also, GAD tend to have a waxing and waning course, requiring a long-term treatment (1,13).

Why investigating Mindfulness-Based Intervention to treat GAD?

Since GAD symptoms tend to be chronic with wax and wane course, it is interesting to investigate new psychological interventions that can be interesting tools to be used at long time. It is known that psychological intervention efficacy tends to be maintained during long-term and it is better tolerable than pharmacological interventions. On the other hand, there is a growing interest in integrating meditation practices, as mindfulness, into clinical and psychological interventions since the 70s in the West (19,20) as a way to foster self-regulation (20,21).

Despite many dialogues about how to define mindfulness (22), the classic definition was given by Kabat-Zinn who states that mindfulness *is* ***"the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment"*** (23). However, it is not simply an attentional training, a mind-emptying or a relaxing practice as it seems at first glance. Its concept incorporates particular qualities to attention to be cultivated - ***"an affectionate, compassionate quality within the attending, a sense of openhearted, friendly presence and interest"*** (23). It involves being conscious compassionately with whatever arises in awareness, moment-to-moment (19,23).

Historically, mindfulness has its roots in more than 2500 years of Buddhist practices and philosophy, and it aims to develop different aspects of the mind. It is integrated into a broader ethical basis that has as a purpose of suffering relieve and cultivate compassion (20,23). Practice means ***"actual engagement in the discipline, the inward gesture that invites and embodies it"***, i.e., ***"a way of being"*** (23). Considering this idea, it is not an intervention to be used "as needed". Moreover, it is discussed that the way mindfulness is delivered by the therapists is even more important than in any other psychological interventions since therapists need to be "embodied" in the practice more than just being a model (24). However, it is known that mindfulness is not exclusive of Buddhist framework. It is also present in different traditions and teachings (long before psychology), and it is also understood as an intrinsic human capacity or a trace (20). Besides being used to describe a stable characteristic, mindfulness is also used to describe the practice itself or a state (25,26). Nevertheless, it is important to highlight its spiritual origin since mindfulness practices should be incorporated into secular medical and psychological interventions with sensibility and respect (23), and one needs to understand that it was developed under a spiritual view of suffering (24).

It is hard to put into words how one formal practice occurs. The individual is oriented to keep an upright posture and to sustain the attention (to anchor) to some object of his/her sense perception, mental or emotional experience (since it is occurring here and now), i.e., attention to the present moment (27). Also, the individual is encouraged to bring some qualities to this attention that are crucial – acceptance and openness toward what it arises (22). Inevitably the mind will wander (as wander is what minds do). Cognitive, emotional and somatic experiences arise, and these conditions are observed as they are with an attitude of non-judge, interpret, strive or trying to change whatever is observed (27). When mind wandering occurs, individual is instructed to note and gently let this content goes while turning the attention back to the object (27). This is a single cycle that occurs many times along a practice event if it takes around 2 minutes (27). Also, this process refers to focused awareness. There are open awareness and positive emotions generation (love and kindness and compassion) practices too.

Fig 1: Mindfulness Process (28).

With practicing, it is expected that the individual develops the capacity to observe its own mental processes; to develop a perspective about inner experiences as mental events that do not accurately reflects the self or the reality. In this way, it is expected a shift in perspective (27). Worries and thoughts are potential future evidence, but not the reality itself; emotions and sensations are not

pleasant or unpleasant, but only mental events (27). This kind of awareness is much different from our daily experiences of mind wandering, worrying, ruminating, running on automatic pilot or trying to suppress unwanted experiences (22). And as a human intrinsic ability, this special kind of awareness can be trained.

Programs are composed of different practices that focus on developing different facets of mindfulness and may differ somewhat in procedure but share the main objective (27). They generally initiate with formal practices that evolve gradually to informal practices and practices whose intention is to develop the capacity to expand consciousness about the individual's mental function (23). The presence practices are characterized by core exercises as breathing and body scan and are able to enhance attention and awareness to the present moment facets of mindfulness; the perspective practices are exercises associated with observing thoughts and perspective taken dyad that are able to foster observing, describing and acceptance facets; and last, positive emotion generating practices, characterized by exercises that are loving-kindness and affect dyad, that are able to develop compassion, self-compassion, acceptance and nonjudgment facets (29). See below a figure from Hildebrandt et al. 2017 to clarify the types of mindfulness practices with which typically an MBI is consisted of:

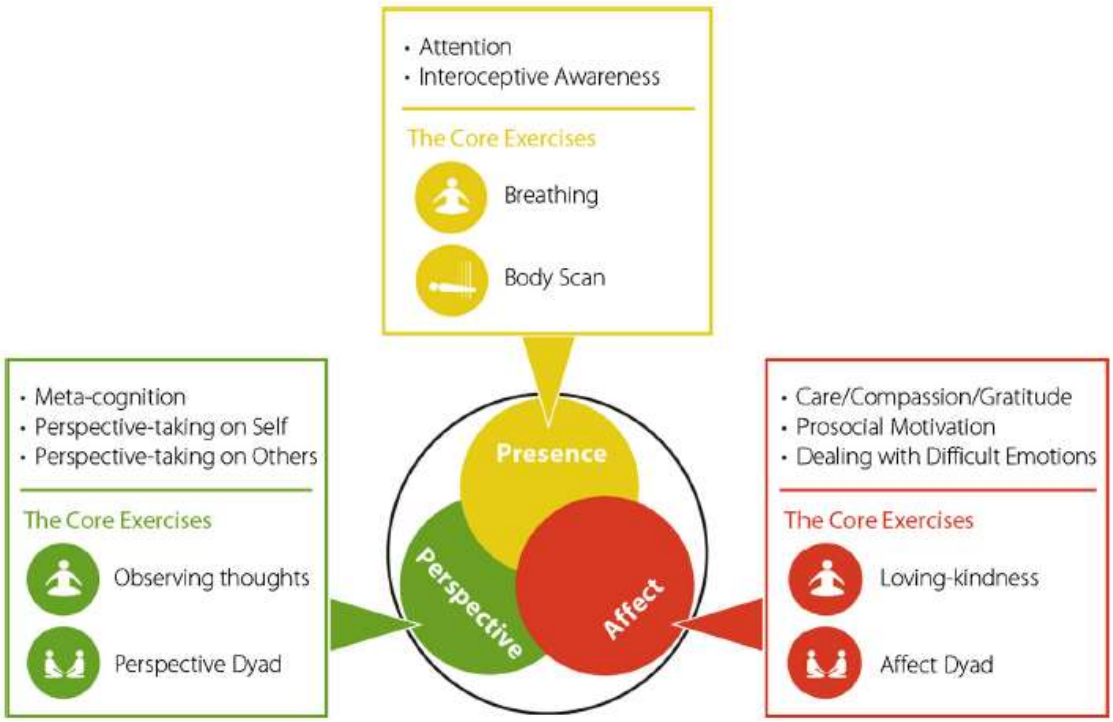


Fig 2: types of mindfulness practices (29).

It is possible that one individual may develop more than one facet of mindfulness at the same time through an exercise that at first glance seems simple as body scan or eating one raisin mindfully. ***"To let go of their expectations, goals, and aspirations for coming, even though they are very real and valid, to let go— momentarily, at least—even of their goal to feel better or to be relaxed in the body scan, or of their ideas about what raisins taste like, and to simply "drop in" on the actuality of their lived experience and then to sustain it as best they can moment by moment, with intentional openhearted presence and suspension of judgment and distraction, to whatever degree possible"*** (23) is a practice rich in challenges and learning.

The mechanisms of action through mindfulness exercises can improve mental suffering and well-being is a subject of many studies and several authors have proposed psychological and neurocognitive models to explain MBI's therapeutic mechanisms (26). Shapiro et al. (2006) proposed a model composed of three fundamental components: intention, attention, and attitude (21). Intention comprises revisiting purpose of why the individual is practicing, and it is a dynamic component since it can change with the evolution of the practicing along time. Shapiro et al. (2006) highlight an important issue about intention. When mindfulness was extracted from its original roots, the original intention - as a heart practice from Buddhism to enlightenment and compassion - changed. Disconnected from its original context, the authors assert that intention use to evolve from self-regulation, to self-exploration, to self-liberation and compassion (21). Attention refers to the observation of internal and external experiences without interpreting it (secondary processing), focusing on the experience itself (21). Attitude is about how we practice, i.e., it is the quality brought by the attention as acceptance, kindness, openness, curiosity, and non-striving (mindfulness qualities) (21), and it is crucial since paying attention to whatever comes without "heart qualities" may lead to self-criticism or self-judgment, bringing opposite intended consequences. Finally, these processes do not occur separated, but they are spliced aspects ***"of a single cyclic process and occur simultaneously"*** as mentioned above (21).

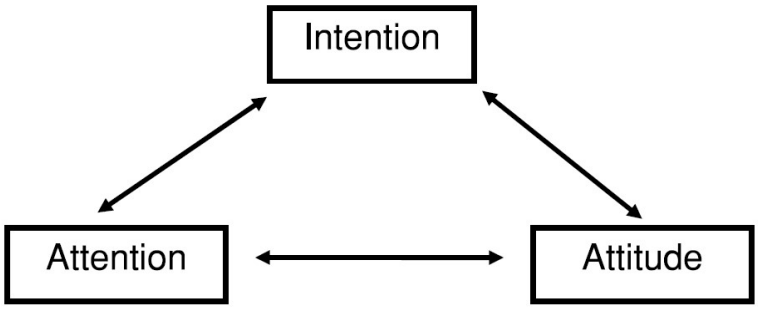


Fig 3: Shapiro's Model a single cyclic of mindfulness (21).

A meta-mechanism of action, "reperceiving", arises throughout the development of these three components. Then, four potential mechanisms responsible for the psychological outcomes come from reperceiving: (1) self-regulation; (2) values clarification; (3) cognitive, emotional, and behavioral flexibility; and (4) exposure (21) that will be better described below. Reperceiving (similar to decentering, detachment and cognitive defusion) means disidentify oneself from the contents of the mind as a view of the reality, leading to a shift in perspective and to the development of *"the observing self"* (21). So, rather than changing the mental content, mindfulness practices lead to changing one's relationship with mental experiences.

Understanding how mindfulness works, we have to know the evidence about if it really works. The first program was developed by Kabat-Zinn and colleagues in 1979 (23,30). The Mindfulness-Based Stress Reduction (MBSR) was offered at an outpatient clinic at the University of Massachusetts Medical Center to help patients to deal with emotional distress and pain that arises from chronic illness (19,23). More than three decades of studies have shown the positive effects of mindfulness-based interventions (MBIs) in both, mental and physical health. in healthy individuals or clinical samples (31). Many important and effective protocols derived from mindfulness as Mindfulness-based cognitive therapy (32), Dialectical Behavior Therapy (33) and Acceptance and Commitment Therapy (34). The MBCT to prevent relapse or recurrence for patients with three or more previous major depressive episodes is already recommended by the National Health Service in the United Kingdom since 2004 (20) and had been included in CANMAT as one of the first-line treatments to relapse prevention and second line for treating major depression with level 1 and level 2 of efficacy, respectively (35).

In relation to non-pathological anxiety, MBIs seem to be effective to reduce anxiety symptoms in healthy individuals (36). However, studies assessing the efficacy of MBIs in pathologic anxiety are

conflicting (37). Six previous studies investigated the role of MBIs in treating patients with GAD (38–43); however, two had open-label design (39,41), two included participants with anxiety disorders other than GAD (J. Kabat-Zinn et al., 1992; Kim et al., 2009), and one assessed MBIs adjunctive to pharmacological treatment (42). Three randomized clinical trials (RCT) have already evaluated MBIs in treating GAD (38,40,43). However, they also reported conflicting results. Hoge et al (2013) showed that Mindfulness-Based Stress Reduction (MBSR) was superior to active control when symptoms were evaluated by the Beck Anxiety Inventory but not assessed with Hamilton Anxiety Rating Scale (the primary outcome of the study); whereas Wong et al (2016) reported that MBCT was superior to usual care but not superior to psychoeducation. Asmaee Majid et al. (2012) reported a greater improvement in HAMA and PSWQ in MBSR when compared to control group, but there was no information about the content of control group. Considering data described above, the role of MBIs in treating GAD is already inconclusive. Below is a summary of the studies evaluating MBIs to treating GAD:

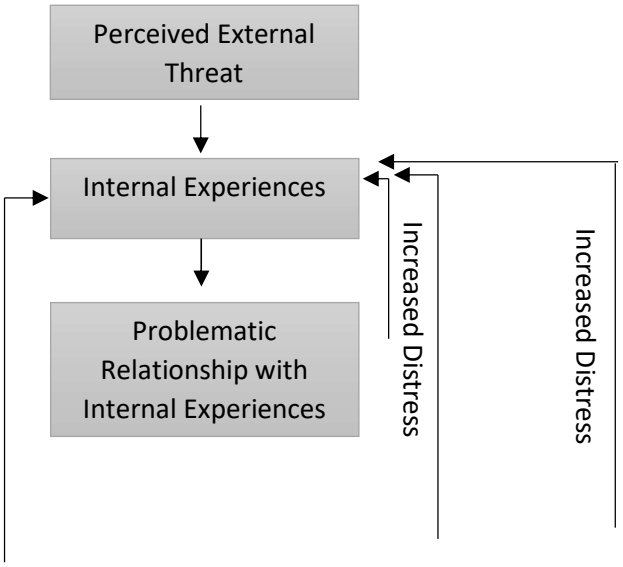
Table 1: Studies assessing MBIs to treating GAD

Study	Design	Interventions	Sample Size	Results
J. Kabat-Zinn et al., 1992	Open trial	MBSR	Mixed sample (8 GAD/22)	Reduction in HAMA and BAI.
Evans et al., 2008	Open trial	MBCT	11	Reduction in BAI and PSWQ.
Kim et al., 2009	RCT	MBCT+ medication *versus* Education Program	Mixed sample (11 GAD/46)	Greater improvement in HAMA and BAI in MBCT.
Asmaee Majid et al., 2012	RCT	MBSR *versus* Control	31 (16 MBSR, 15 control)	Greater improvement in HAMA and PSWQ in MBSR.
Hoge et al., 2013	RCT	MBSR *versus* Stress Management Education	89 (48 and 41 respectively)	Better improvement in BAI in MBSR, but not in HAMA.
Wong et al., 2016	RCT	MBCT *versus* Psychoeducation *versus* Usual Care	182 (61, 61 and 60 respectively)	Greater reduction in BAI in MBCT and Psychoeducation group when compared to Usual Care. No difference between MBCT and Psychoeducation group. MBCT was not superior to

	Usual care in reducing PSWQ.

Notes: BAI, Beck Anxiety Inventory; HAMA, Hamilton Anxiety Rating Scale; PSWQ, Penn State Worry Questionnaire.

Certain cognitive and biological findings in GAD seem to be rightly counterbalanced by certain proposed mindfulness mechanisms. First, one of the cognitive models proposed to developing GAD is the Acceptance-Based Model (ABM) (45). This model was developed by Roemer and Orsillo upon Hayes and colleagues' Model of Experiential Avoidance and Borkovec's one (45). They proposed that GAD individuals have a problematic relationship with internal experiences (thought, feelings and bodily sensations) manifested in two forms (1) negatively reacting to internal experiences (judgment of emotional responses as extreme or undesirable, or fear of fear), and (2) fusion with internal experiences (i.e., belief that transient negative reactions to internal experiences are permanent and thus a defining characteristic of the individual). So, individuals experience difficulties in monitoring, accepting, and interpreting emotions (i.e., deficit in emotional regulation) (46), and worry is understood as an experiential avoidance, in which individual believes that the worry decreases the probability of future negative events or is a strategic or automatic avoidance of internal experiences (47–49). Finally, this model understands that GAD individuals have less involvement in valued actions (behavioral restriction; e.g., spending time with family) since they have chronic apprehension of potential future threat (50), contributing to reduced awareness of the present moment (49).



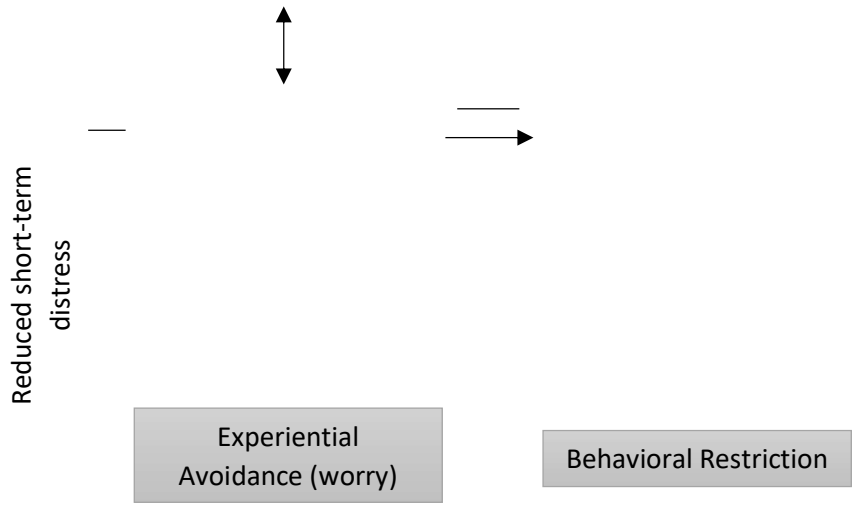


Fig 3: The Acceptance-Based Model for GAD adapted from (45).

In order to better explain how mindfulness can help individuals with GAD according to Shapiro et al. (2006) mindfulness's mechanisms of action and ABM model of GAD, an example of a classically reported situation by GAD patients will be given:

> *Anna is a mother of two children of eight and fourteen years old. All the time they go to school, she is scared about something bad that could happen to them: kidnapping in the way to and back school or be bullied by colleagues for example. Worrying about this daily fact, she feels anxious, tense, with mental inquietude, and behaves in order to, illusory; try to control this situation sending text messages in each hour to their children. Also, Anna knows that worries a lot. She blames herself for the way her mind works and feels it bother her children but cannot control it.*

Anna started to practice mindfulness and, as she practices, worried thoughts, somatic tense sensations as headache, chest tightness, anxiety and angst come and go through her experience. Now Anna is aware that these mental phenomena are transient and do not represent the objective reality. Anna learned to step back and disidentify herself from her experience, developing the meta-mechanism **"reperceiving" or *"the observing self"***. It brings to Anna a higher level of tolerance for

unpleasant internal states that allows Anna better **self-regulate** herself. Moreover, rather than self-criticize of self-blame, she is instructed to bring an attitude of kindness, non-judgmental, curiosity and a sense of suffering as humanity's common experience with what she perceives in her experience.

Through the development of the capacity to observe how her mind function moment by moment, Anna was able to neither overidentify her with anxiety when it arises nor to engage in a cascade of catastrophic thoughts that arouse more tense sensations and anxiety. Also, Anna did not try to regulate herself sending text messages to her children anymore. Anna is no longer controlled by anxiety state but is instead able to use her mental experiences to improve insight about herself. She can now choose to respond accordingly to her values, instead of reacting automatically to the situations. She is more **cognitively, emotionally and behaviorally flexible**. She understands that trying to control what she fears through worry is illusory, and she chooses to focus on processes that are occurring in the present rather than focuses on desired outcomes or fears that are in the future and, do not really exist.

Since worry is understood as an avoidant behavior as it is a linguistic process that avoids individual to make contact with faired images whose emotion arousal is more intense, one can hypothesized that mindfulness practices can help Anna to **exposure** herself to her feared image, promoting habituation (21,51) to contents that no longer triggers strong emotions, thoughts, and sensations. Finally, it is known that GAD individuals have less involvement in valued actions and reduced awareness of the present moment (49). Then, through practices, Anna becomes more aware of her **true values** and may choose to behave in life more congruent with it.

Some of the proposed therapeutic mechanisms of MBIs have already been the focus of recent studies. First, an important question is whether mindfulness itself is one of the underlying therapeutic mechanisms of MBIs. Despite some studies failed to report post-intervention improvement in mindfulness or report no greater improvement as compared to comparison groups (22), a systematic review and meta-analysis of mediation studies published in 2015 reported, with moderate consistency, that improvement in mindfulness measure is a mediator of improvement in psychological outcomes (52). Specifically investigating MBCT mechanisms, a review by van der Velden et al. (2015) found the same data about mindfulness as a mediator of improvement in the treatment of recurrent major depressive disorder (53) and a recent review reported an improvement in meta-awareness, self-compassion, emotional reactivity, attention and cognitive flexibility following MBCT (30). Furthermore,

investigating mechanisms in a mixed sample of physical or psychological conditions, a review reported that mindfulness was the most consistent mediator of improvement (54).

Other components as cognitive and emotional reactivity (52,54), compassion and acceptance (Gu et al., 2015; van der Velden et al., 2015; Alsubaie et al., 2017), attention (53,54), and meta-awareness (53,55) have already been associated with improvement in emotional outcomes. Gu et al. (2015) reported preliminary evidence for psychological flexibility and self-compassion (52). Finally, following MBCT for depressive patients, and improvements in mindfulness skills – and specifically in acting with awareness - predicted improvement in neuroticism (56).

Regarding transversal studies considering mindfulness as a trace and investigating its association with anxiety outcomes, Van Dam et al. (2011) reported that self-compassion - specially isolation (in opposition to sense of common humanity), self-judgment and over-identification - predicted anxiety and worry severity more than mindfulness measure (assessed by Mindful Attention Awareness Scale) in a community sample (57). Another cross-sectional data considering patients with GAD or depression showed that non-judgement and non-reaction were inversely correlated with worry while cognitive and psychological inflexibility was positively correlated with worry (58). Also, neuroticism – an important trace to GAD – was negatively associated with nonreactivity and nonjudging (59).

However, longitudinal studies depict results that represent mechanism of action or active therapeutic ingredients of MBIs. Reduction in trait anxiety after MBSR has already been mediated by preceding increases in mindfulness, while increasing in mindfulness precipitate increasing in self-compassion (60). Moreover, GAD individuals exposed to a mindful-breath had improvement in cognitive flexibility measured through Stroop test (61). One RCT assessing a sample of heterogeneous anxiety disorders reported that mindfulness skills were a mediator of the relationship between MBSR and improvements in anxiety and worry without, however, a temporal analysis despite longitudinal data (62). Two previous RCT studied specifically mindfulness mechanisms in treating GAD. One reported that improvement in decentering mediated the relationship between MBSR and anxiety while awareness and no reactivity mediated the relationship between MBST and worry improvement (55). Another study showed that greater modifications in experiential avoidance after Acceptance-based Behavior Therapy predicted improvement in worry (Eustis, Hayes-Skelton, Roemer, & Orsillo, 2016).

Besides cognitive factors through mindfulness that can help individuals with GAD, there are some interesting biological features that have been studied as potentially associated to MBIs changes in GAD. It is known that anxiety is the anticipation (mental process) of future threat, characterized biologically by fear (real) response. As GAD individuals perceived daily activities as threats, it is expected they have chronically autonomic arousal for fight and flight response and, consequently, chronic levels of stress markers. At the same time, the mindfulness literature has proposed improvement in the same biological findings reported as altered in GAD as heart rate variability (HRV) and some findings in functional magnetic resonance image (fMRI). HRV is a physiological measure associated to chronic stress as it reflects specially parasympathetic (vagal) modulation and autonomic flexibility (63). The recent literature demonstrates that chronic anxiety and GAD is associated with reductions in HRV (64,65). In contrast, mindfulness meditation practice is associated with increase in autonomic regulation by stimulating the parasympathetic system (66,67). Interestingly, Mankus et al reported that generalized anxiety interacted with mindfulness traits in the prediction of HRV, suggesting that mindfulness may enhance parasympathetic influences on the heart rate in severe symptomatic individuals (68). Also, neuroimaging studies suggest that GAD individuals have a reduced prefrontal cortex (PFC) and limbic connection, leading to fail to engage PFC to suppress threat (69,70). So, they have an insufficient top-down regulation of emotions. MBIs studies, however, have reported an improvement in fronto-limbic connectivity and consequently emotional regulation (71).

Finally, studies have shown that anxiety is inversely related to self-compassion (72) and, more specifically, GAD has already been associated with lower self-compassion. Self-compassion has already been negatively correlated with severity of anxiety, worry, and anxiety sensitivity (73). Compassion is conceptualized in Western psychology as a combination of motives, emotions, thoughts and behaviors that open us to the suffering of others (74). Self-compassion concept comprises three components: (a) self-kindness: thinking about oneself with warmth and understanding rather than in an attacking, critical, or judgmental way; (b) sense of common humanity: being aware that all human beings are fallible, that things will go wrong, be suboptimal, and that mistakes, suffering, and unfairness are part of the human condition; and (c) mindfulness of one's present moment experience, do neither ignores nor ruminates on disliked aspects of oneself or one's actions/life (74). Interventions focused on compassion have been studied to mental health problems primarily linked to high shame and self-criticism. These hypotheses lead to MBIs protocols to be composed by compassion or self-compassion practices. The processes by which compassion is associated with improvements in

health outcomes and psychopathology have been studied. Self-compassion appears to attenuate people's reactions to negative events (75). This mechanism, for example, seems to be important for individuals with GAD if we consider the Acceptance-Based Model mentioned above. Also, brief training in self-compassion moderated psychological responses to a social stressor task in women when compared to attention (placebo) and no-training control by diminishing sympathetic and subjective anxiety responses, and more adaptative parasympathetic functioning (76).

Taking advantage of RCT design for studying GAD mechanisms

Besides being the least successfully treated, GAD is also the least knowing and understanding anxiety disorder. RCTs can be useful in analyzing improvement mechanisms through which we can hypothesize and better understand the mechanisms of the disorder itself. Moreover, trying to understand GAD mechanisms, as well as improvement mechanisms, is imperative to develop better and more personalized treatment. Some GAD issues that are badly understood are attachment parenting style, cognitive model, and biological factors.

Little is known about GAD risk factors as attachment style, and it seems important since early childhood experiences of a protective figure can come to light in hard moments according to Bowlby's theory. Some studies report a worst attachment parenting style in childhood as GAD individuals experience less maternal love, greater maternal rejection/neglect, and more maternal role-reversal/enmeshment (77), as well as attachment-related anxiety and avoidance and lower mother's care (78). However, a study reported that GAD symptoms influence the perception of parental behaviors, so the attachment results can represent a bias in a way individual perceive their primary attachment (79). On the other hand, if GAD have altered attachment style in childhood, it can reflect on abnormalities in neural structures (80) that can impact treatment, since individuals with different styles of attachment can respond to therapies in a different way (81). Thus, better understanding attachment style can help the development of more efficacious and personalized GAD treatment.

Different from other anxiety disorders, GAD has at least five cognitive models that try to explain its pathology in psychological terms of view (45). Most of them agree that GAD individuals have a problematic relationship with internal experiences and emotions (i.e., deficit in emotional regulation).

Worry is an avoidant mechanism as the individual believes that the worry decreases the probability of future negative events or individual uses it as a strategic or automatic avoidance of internal experiences, and of intolerance to uncertainty plays a central role in this disorder (45). However, how these variables evolve with treatment and which psychological factors respond best to which intervention is unclear. And once again, better understanding of psychological processes can help the development of more efficacious and personalized treatment.

Finally, some biological factors mentioned above – as HRV an fMRI finding – can help us to better understand GAD physiopathology. HRV is a physiological measure associated to chronic stress (63) and it is well established that GAD individuals have decreased HRV (65,82). However, the mechanisms that mediate the relationships between GAD and reduced HRV as well as if treatments could revert autonomic dysregulation in parasympathetic system is not clear. This is very important issue since reduced HRV is predictive of all causes of mortality (83). Neuroimaging studies are also more inconclusive. However, the more congruent finding is that the neural basis of GAD involves an abnormal amygdala function (exaggerated response) and disrupted functional connectivity in fronto-limbic pathway; i.e., a deficit in top-down emotional processing (84,85). So, biological studies suggested an autonomic and neurologic inflexibility that reflexes on cognitive rigidity and difficulty in emotional regulation. In this way, better understanding of how GAD symptoms interact with these biological findings can help a better understanding of the disorder mechanisms as well as better development of personalized treatment.

JUSTIFICATION

GAD is a chronic disorder with wax and wane course and high prevalence and disabilities rates. Furthermore, despite pharmacological and psychotherapy interventions have been recommended as first-line treatment for GAD, many patients present residual symptoms over time and this disorder is associated with a high relapse rate. Evidence has suggested the importance of psychological acceptance associated with the successful outcome of psychotherapy what is different from traditional CBT. Mindfulness has been integrated with CBT to treat psychiatric disorders, with preliminary evidence that MBIs have a potential role to treat GAD. However, these studies present important methodological limitations. More recently, the importance of mindfulness based intervention associated with body movement (BMT) has been studied and there are no studies evaluating this intervention in GAD patients. MBIs aims to foster self-compassion which seems important to be developed by patients with GAD since self-compassionate individuals deal with negative thoughts and feelings with a broader awareness, care, understanding, and with a sense of humanity's suffering. Rather than avoiding thoughts and feelings, compassionate individuals turn them towards less disturbed emotional states, allowing a deeper understanding of the mental function and adopting more effective behaviors. BMT is a protocol that involves mindfulness, somatic focus, and compassion training. Thus, we hypothesized that BMT may be effective for GAD patients since. Patients with GAD tend to have problematic relationships with internal experiences, through negative judgment and difficulty of accepting them. Therefore, they tend to avoid these relationships. Moreover, GAD patients also have reduced mindfulness traits lead them to participate less in meaningful activities.

OBJECTIVES

General objective:

- ✓ To assess the efficacy of a Mindfulness-Based Intervention (MBI) to treat individuals with Generalized Anxiety Disorder (GAD).

Specific objectives:

- ✓ (a) To assess the efficacy of MBI (Body in Mind Training, BMT) to treat individuals with GAD as compared to a comparison active group (Quality of Life and Psychoeducation Group, QOL) and to a first-line pharmacologic treatment group (Fluoxetine, FLX).
- ✓ (b) To study GAD psychological mechanisms as well as to understand improvement concerning psychological mechanisms among the three different treatments (emotional process and attachment style).
- ✓ (c) To study GAD biological mechanisms as well as to understand improvement throughout biological mechanisms among the three different treatments (neuroimaging).

HYPOTHESIS

- ✓ Hypothesis 1: BMT would be more efficacious than QoL, but not superior to FLX as measured by the primary outcomes (PSWQ and HAM-A).
- ✓ Hypothesis 2: BMT will improve worry according to a top-down psychological mechanism, while FLX will improve worry according to a bottom-up mechanism.
- ✓ Hypothesis 3: Attachment style will moderate the improvement in BMT group.
- ✓ Hypothesis 4: neurological mechanisms of improvement in BMT will disclose a more top-down mechanism when compared to FLX group.

ETHICAL CONSIDERATIONS

The ethical review board of Hospital de Clínicas de Porto Alegre approved the study (Ethics Committee of Hospital de Clínicas de Porto Alegre, number 20160301).

The trial was registered at ClinicalTrials.gov (NCT03072264).

All participants signed written informed consent prior to inclusion.

Data were de-identified so identification of participants was not possible.

FINAL CONSIDERATIONS

Generalized anxiety disorder (GAD) is a chronic disorder with high individual and social burden. Many individuals diagnosed with GAD do not respond to treatment or they remain with residual symptoms. GAD is considered the least successfully treated anxiety disorder. In order to contribute with the development of better treatments and also to the better understanding of the disorder mechanisms itself, this thesis investigated the efficacy of a Mindfulness-Based Interventions (MBI) to treat Generalized Anxiety Disorder as well as its mechanisms of improvement.

We first begin our investigation studying if MBIs are a valuable treatment modality to GAD patients throughout a systematic review and multilevel meta-analysis with meta-regression. We conducted this multilevel meta-analysis of multiple outcomes considering MBIS efficacy to treat internalized symptoms in anxiety and stress-related disorders. Our study suggested that MBIs were superior to control interventions for internalizing and distress, but not for fear symptoms whereas cognitive-behavior therapy (CBT) was not superior to MBIs for internalizing and distress but was superior to MBIs for treating fear symptoms. Moreover, quality analyses revealed that studies included had a high risk of bias, small sample size, and publication bias. Therefore, more research was needed to recommend MBIs for treating anxiety disorders (study 1). After, a parallel three-arm randomized clinical trial (RCT; ClinicalTrials.gov ID: NCT03072264) was conducted assessing the efficacy of a MBIs (Body in Mind Training, BMT) in treating GAD and compared it to pharmacologic treatment (Fluoxetine group, FLX) and to an active comparison group (Quality of Life and Psychoeducation group, QoL). BMT is a MBI protocol that uses body movement to enhance the anchoring of attention (86,87) in order to better help individuals who struggle to relax or experiencing intense distress (88). Two hundred forty nine (n=249) participants were included and 223 were analyzed (76 BMT, 79 FLX, 68 QoL). Despite all groups improved at the endpoint, our results showed that BMT was not superior to QoL and also failed to show non-inferiority to FLX for improving GAD symptoms (study 2).

In order to help future development of more efficacious as well as personalized treatment, we take advantage of gold standard experimental design to investigate psychological and biological mechanisms of improvement. A mediation analysis was performed using data from the RCT investigating the different mechanisms of worry in BMT, FLX and QoL groups. Our data showed that, in BMT group, change in mindfulness trait was associated with change in worry mediated by change in

emotional dysregulation. Thus, emotional regulation was a key mechanism to anxiety improvement. Also, feelings of perceived threat and submissiveness in childhood moderated the association between improvements of mindfulness trait and change in emotional dysregulation. These mechanisms were BMT specific and were not reported in patients submitted to FLX or QoL groups (study 3). To investigate neural correlates of GAD symptomatology improvement, thirty-five subjects from the RCT were submitted to functional magnetic resonance imaging. Considering all sample, symptoms improvement was associated with greater connectivity between left amygdala and right frontal orbital cortex. Furthermore, a difference in the coupling mechanisms between amygdala connection with default mode and salience networks was higher in BMT group when compared to FLX group (study 5).

The main strength of this thesis was the improvement of previous study design assessing MBIs efficacy as many well-known authors have already suggested (23,89,90). Previous studies had many important methodological problems (23) as lack of active control groups (89) and small sample sizes. Therefore, we carefully developed a control group that match common factors of group improvement (especially therapeutic alliance, social support, attention from therapists, and learning new habits) as well as structure and duration (90). Also, we compared BMT to a first-line pharmacologic treatment using a non-inferiority analysis. Thus, we enriched the literature conducting a more methodologically restrict RCT in order to investigate both the clinical efficacy and the possible improvement mechanisms since we compared BMT to two different treatment modalities with an adequate sample size.

However, results may be interpreted carefully. First, it is possible that the lack of superiority of BMT in relation to comparison group was due to not adapting the BMT protocol to specifically treating GAD. Despite some authors argue that MBIs can be used as a single intervention to treat different mental disorders since trained skills focus on processes that potentially underlie many disorders (30) – as emotional dysregulation - , others authors are against this idea and suggested that mindfulness should be applied different to each disorder (24). Teasdale et al. (2003), for example, agree that mindfulness may benefit different disorders since it assesses common process, but defend that one should formulate and match the intervention to the disorder since some mindfulness skills (for example, reduction of experiential avoidance) may be more important for some disorders (for example, anxiety disorders). Another important limitation of this thesis is that we could not assess how patients embodied the practices in their lives - even the homework frequency. And, as an experiential technique, perhaps the most important therapeutic factor is the engagement and the intention in which subjects get involved (23,90) what is very hard to be measured. Moreover, we did not use any

fidelity instrument to measure how BMT was delivered as well as there is no instrument to assess how much embodied the therapist was during treatment (23). Howbeit, the therapist that delivered mindfulness was a psychologist with eight years of experience and received BMT training directly from the protocol developer, as well as advisor to each session.

Second, different from FLX, BMT group needs more commitment and perseverance. Instead of just swallowing a pill in the morning, mindfulness need more involvement since it is *"more akin to an art form that one develops over time, and it is greatly enhanced through regular disciplined practice, both formally and informally, on a daily basis*" (23). Mindfulness needs more effort from its participants. Furthermore, different from the pharmacologic intervention, it is difficult to titrate the dose the subject is receiving (90). The lack of superiority of BMT as compared with QoL did not mean that BMT do not promote symptom improvement since it was compared to an active control group. However, it is difficult to differentiate both groups since different interventions can lead to same outcomes through different mechanisms (90). Therefore, results from the comparison of BMT with FLX and QoL should be interpreted carefully.

Despite some limitation of this thesis, there is a range of limitations when interpreting results that arises from studying mindfulness itself. First, there are different intentions between scientists and meditators (23). Efficacy studies mainly focus in hard outcomes (such as remission of a disorder for example) while meditators may have different goals ranging from enlightenment and compassion (in Buddhist framework) to self-regulation, self-exploration or self-liberation (as stated in the introduction section of this thesis). Kabat-Zinn alert that "*mindfulness is not simply seized upon as the next promising cognitive behavioral technique or exercise, decontextualized, and "plugged" into a behaviorist paradigm with the aim of driving desirable change, or of fixing what is broken"* (23). Also, this thesis investigated individuals with GAD known to have experiential avoidance. If mindfulness is about to look at the full spectrum of our experience without suppressing it (with a different perspective), we can expect that individual became more aware of mental process (88). Thus, individuals can rate higher in a self-rated symptoms scale and appear "worse" while the main purpose is to change the relationship of de individual with the symptoms in order to turn symptoms less disturbed. But how can we measure these changes if they really happen? As Teasdale et al. stated, *"there may be many dimensions of effectiveness underlying the apparent simplicity of mindfulness*" (24). On the other hand, how can we compare the changes in perspective leading to release of distress

to the results of the initial studies that showed that MBIs might increase the awareness of difficult emotional content and worsen mental problems? (89).

Concluding, BMT was not non-inferior to FLX and not superior to QoL, but improved symptoms thorough different mechanisms as compared to the other two different group modalities. Those individuals who better regulated their emotions through improvement in mindfulness measurement had a reduction in worry, the core symptom of GAD. Moderation analysis suggested that better attachment style moderated the relationship between improvement in mindfulness and improvement in emotional regulation. Trying to understand what intervention is better for whom, we can hypothesize that individuals with better attachment styles better respond to BMT for reducing anxiety symptoms. Moreover, those with worst attachment style need more intense mindfulness intervention. In relation to neural basis, we found that improvement in anxiety symptoms was associated with an increasement in connectivity between frontolimbic pathway, specially left amygdala and right Frontal Orbital Cortex, areas that have been already associated to emotional regulation. Also, different neuronal mechanisms of improvement between BMT and FLX were reported. Significant difference in the coupling between amygdala connection with DMN and SN adjusted to symptoms improvement was found when compared BMT to FLX group, networks associated with self-reference and stimulus selection. Therefore, it seems that BMT has its place to treat anxiety, but not as a single intervention. Further studies may assess if BMT practices may enhance the efficacy of existing CBT protocols for GAD.

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