Diploma thesis

The Role of Non-Invasive Vagus Nerve Stimulation (nVNS) for the Treatment of Stress-Related Psychiatric Disorders

submitted by

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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, April 03, 2024 *Karolin Preis m.p.*

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Zusammenfassung

Einleitung: Chronischer oder unkontrollierbarer Stress kann stressbedingte psychiatrische Störungen (SRPD), wie eine posttraumatischen Belastungsstörung oder eine schwere Depression verursachen. Patient*innen mit SRPD zeigen eine Störung der Homöostase des autonomen Nervensystems und eine Dysregulation der Hypothalamus-Hypophysen-Nebennieren-Achse (HPA-Achse), was zu einer erhöhten Aktivität des sympathischen Nervensystems (SNS), einer verringerten Aktivität des parasympathischen Nervensystems (PNS) und veränderten Konzentrationen von peripherem Cortisol führt. Die nicht-invasive Vagusnerv-stimulation (nVNS) erhöht die Aktivität des PNS, welches die HPA-Achse reguliert und als Gegengewicht zum SNS fungiert. In der Literatur werden verschiedene Möglichkeiten der nVNS beschrieben, wie die transkutane elektrische nVNS oder Mind-Body-Interventionen (MBI). In dieser Literaturarbeit wird der therapeutische Nutzen der nVNS als wirksame Behandlungsoption für SRPD untersucht.

Methoden: Für dieses Review wurde eine Literaturrecherche in den Datenbanken PubMed und Web of Science durchgeführt. Für die Outcome-Beurteilung wurden mehrheitlich psychometrische Tests und vereinzelt Messungen der Herzratenvariabilität (HRV) oder des Speichel-Cortisols verwendet.

Ergebnisse: Nach Sichtung der Ergebnisse unter Einbeziehung der definierten Ein- und Ausschlusskriterien konnten insgesamt 15 Arbeiten in die Auswertung einbezogen werden. Bei den psychometrischen Tests oder Messungen der HRV oder des Cortisols zeigte die Interventionsgruppe, die MBI oder transkutane nVNS anwandte, in 13 der 15 Studien zumindest teilsignifikante Ergebnisse im Vergleich zur Kontrollgruppe, die entweder eine Standardtherapie erhielt oder eine Warteliste/Erhebungskontrolle war. Allerdings waren viele Studien von geringer methodischer Qualität.

Diskussion: Insgesamt erwiesen sich die nVNS-Methoden als vielversprechende und kosteneffiziente Therapieoptionen bei SRPD. Es sind jedoch weitere kontrollierte Studien erforderlich, um weitergehende Fragen zu beantworten, wie: Welche spezifische nVNS-Methode ist bei wem am geeignetsten? Darüber hinaus ist eine Nachuntersuchung erforderlich, um mehr über die langfristigen Auswirkungen von nVNS-Interventionen zu erfahren.

Abstract

Introduction: Chronic or uncontrollable stress can cause psychiatric reactions, which in turn can manifest in Stress-related Psychiatric Disorders (SRPD) such as Post-Traumatic Stress Disorder or Major Depressive Disorder. Patients with SRPD show a disruption of the homoeostasis of the autonomic nervous system and a dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, resulting in an increased Sympathetic Nervous System (SNS), a decreased Parasympathetic Nervous System (PNS) and altered concentrations of peripheral cortisol. Non-invasive Vagus Nerve Stimulation (nVNS) enhances the activity of the PNS, which regulates the HPA-Axis and acts as a counterbalance to the SNS. The literature describes various possibilities of nVNS such as the transcutaneous VNS or Mind-Body interventions (MBI). This manuscript reviews the therapeutic usefulness of nVNS as an effective treatment option for SRPD.

Method: For this review, a literature search was performed in the PubMed and Web of Science databases. The majority of the selected studies used psychometric tests for outcome assessment. In addition, measurements of heart rate variability (HRV) or salivary cortisol were carried out in individual studies in order to assess the intervention.

Results: After screening the results using the defined inclusion and exclusion criteria, a total of 15 papers were included in the analysis. In the psychometric tests or measurements of HRV or cortisol the intervention group performing MBI or transcutaneous nVNS showed at least partially significant results in 13 of the 15 studies compared to the control group, who either received standard therapy or were on a waiting list/assessment control. However, many studies were of low methodological quality.

Discussion: Overall, nVNS methods have been found to be promising cost-efficient therapy-options in SRPD. However, further controlled studies in clinical surroundings are needed to answer more far-reaching questions such as: Which specific nVNS method works the best for whom? Furthermore, follow-up assessment is warranted in order to learn more about the long-term effects of nVNS interventions.

Table of Contents

Abbreviations

ACh	Acetylcholine
ACTH	Adrenocorticotropic hormone
AE	Adverse events
AL	Allostatic load
ANS	Autonomic nervous system
AUC_i	Area under the curve increase
BA	Behavioral activation
BDI-II	Becks Depression Inventory – reversed version
BMP/T	Brief mindfulness program/training
BP	Blood pressure
CAM	Complementary and alternative medicine
CAPS-5	Clinician-administered PTSD Scale for DSM-V
CAR	Cortisol awakening response
CBT	Cognitive behavioral therapy
CGI-S	Clinical global impression – severity scale
CNS	Central nervous system
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
D	Day(s)
DHEA	Dehydroepiandrosterone
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiography
EMDR	eye movement desensitization and reprocessing
GABA	γ-aminobutyric acid
GAS	General adaption syndrome
GIT	Gastro-intestinal-tract
H	Hour(s)
HAM-D	Hamilton depression rating scale
HE	Health education

HPA	Hypothalamic–pituitary–adrenal
HR	Heart rate
HRV	Heart rate variability
ICD	International classification of diseases, eleventh revision
IES-R	Impact of Event Scale – Revised
IL-1	Interleukin-1
IL-6	Interleukin-6
ITT	Intention to treat
iVNS	Invasive vagus nerve stimulation
M	Month(s)
MADRS	Montgomery åsberg depression rating scale
MBI	Mind-body interventions
MBSR	Mindfulness-based stress reduction
MCID	Minimal clinically important difference
MDD	Major depressive disorder
Min	Minute(s)
MRP	Mantram repetition program
N	Study size
nVNS	Non-invasive vagus nerve stimulation
PCbMP	Primary care brief mindfulness program
PCL-5	PTSD Checklist for DSM-V
PCT	Present-centered therapy
PE	Prolonged exposure
PHQ	Patient health questionnaire
PNS	parasympathetic nervous system
PSS-I	PTSD Symptom Scale Interview
PTSD	Posttraumatic stress disorder
RCT	Randomized controlled trial
SCID	Structured clinical interview
SIP	Structured interview for PTSD
SKY	Sudarshan kriya yoga

SNRI	Selective serotonin noradrenaline reuptake inhibitors
SNS	Sympathetic nervous system
SRPD	Stress-related psychiatric disorders
SSRI	Selective serotonin reuptake inhibitors
STAI	State-Trait-Anxiety Inventory
TAU	Treatment as usual
TM	Transcendental meditation
TNF-α	Tumor necrosis factor-alpha
tVNS	Transcutaneous vagus nerve stimulation
VNS	Vagus nerve stimulation
Wk	Week(s)
Y	Year(s)

Figures

Tables

1 Introduction

In this literature review, first the relevance of the topic is presented and the current state of research on the background is highlighted. Furthermore, the procedure for selecting the studies included in the review is explained. Finally, the results of the studies are presented, and the strengths, weaknesses, and applicability of the results are discussed. The review does not claim to be a systematic review but is oriented towards its criteria. The novelty value lies in the consideration of the term "non-invasive vagus nerve stimulation" as a broadly defined parasympathetic stimulation and the relationship of posttraumatic stress disorder and depression to their (not exclusive) stress genesis.

1.01 Stress-related Psychiatric Disorders

Stress-related psychiatric disorders (SRPD) such as major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) are associated with significant lifetime prevalence. MDD is one of the most widespread psychiatric disorders, affecting 25% of women and 12% of men over the course of their lifespan, and enhances the psychological burden for the persons affected (1, 127, 128).

PTSD has a lifetime prevalence of maximum 6.1% globally, making it a serious health problem (2, 129).

1.02 Major Depressive Disorder

For a diagnosis of MDD according to the updated “International Classification of Diseases - eleventh revision” (ICD-11) criteria (90), the general criteria, all the major symptoms, and at least five of the additional symptoms must be present almost every day for most of the days over two weeks.

- General criteria: no history of (hypo-) manic symptoms or mixed episodes severe enough to meet the criteria for a manic or hypomanic episode, which would indicate a bipolar disorder.
  Exclusion: the episode is not due to abuse of psychotropic substances or an organic mental disorder.
- Major symptoms: depressive mood and loss of interest must persist almost every day for most of the day over two weeks.

- Additional symptoms: hopelessness, feelings of worthlessness or excessive or inappropriate guilt, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or slowness, and decreased energy or fatigue. In the case of a major depressive episode, psychotic symptoms can also occur: depressive stupor, hallucinations, or delusions.

1.03 Posttraumatic Stress Disorder

For the diagnosis of PTSD according to the updated ICD-11 criteria (91) required features for a diagnosis are:

- the individual was exposed (short-term or prolonged) to an event/situation of extraordinary threat or catastrophic magnitude.
- as a result, the following characteristic symptoms have developed, which last for multiple weeks:
  1) re-experiencing: vibrant memories or images; flashbacks (mild to severe), repetitive dreams or nightmares thematically related to the traumatic event(s).
  2) purposed avoidance memories that can trigger a re-experience of the traumatic event(s).
  3) continued perception of the present threat.
- The disorder leads to considerable restrictions in everyday life. If functioning can be maintained, then only through strong efforts.

1.04 Genesis of Stress-related Psychiatric Disorders

MDD and PTSD are multifactorial diseases that are determined by genetic predisposition and environmental variables. Environmental factors, that are associated with an increased risk of mood and anxiety disorders are adverse life events, especially early in childhood (early life stressors). Those can be severe forms such as abuse or neglect in childhood or other stressful forms of experiences, such as loss of parents, harassment, or low socioeconomic status. Furthermore, increasing studies suggest that prenatal stress or mood and anxiety disorders in the mother are also a risk factor for psychiatric disorders (4, 130).

In addition, a growing number of studies point to the importance of significantly elevated inflammatory markers (proinflammatory cytokines like Interleukin-1 = IL-1,

Interleukin-6 = IL-6, tumor necrosis factor-alpha = TNF-α, and C-reactive protein = CRP) in people suffering from depression, for the development of depression (7, 3). At the same time, studies show that patients with inflammatory processes, e.g., in the context of autoimmune diseases, are more likely to have depressive symptoms that can be reduced with anti-inflammatory drugs (5, 6).

On the other hand the inflammation hypothesis cannot be applied to all patients suffering from depression as not all patients show elevated inflammation markers (7).

A relatively safe predictor of elevated inflammation markers is early life adversary (ELA), here defined as “parental maltreatment and the low socioeconomic status during childhood” (8). ELA means lasting and severe stress to the children (7).

1.05 Vulnerability-Stress-Model

One model to explain the development of mental illnesses like MDD and PTSD is the Vulnerability-stress model or Diathesis-stress model. According to the vulnerability-stress model, mental disorders arise from current and chronic stresses of various kinds (social, psychological, biological) against the background of a person's increased "susceptibility" (diathesis, predisposition, vulnerability). Biological, genetic, cognitive as well as early environmental factors can lead to increased vulnerability. The model was expanded over time to include protective factors (coping strategies) (vulnerability-stress-coping model). If these factors are not sufficient as coping options in stressful situations, the disease is developed if there is a corresponding disposition (9).

1.06 Psychobiological Models of Stress

Stress is the response of an individual to a stressful factor, also called a stressor. It occurs when there is an imbalance between external demands and personal coping capabilities. In a stress reaction, homeostasis, the balance between the individual and the environment, is disrupted. The most popular stress model was described by Hans Selye. The model presents stress as a non-specific response of the organism to a disturbance of homeostasis, which happens in three phases. This response is also described as the general adaptation syndrome (GAS). The GAS describes the physiological response to stressors. It assumes that the reaction is always the same

regardless of the type of stressor. The general adaptation syndrome proceeds in three phases (10).

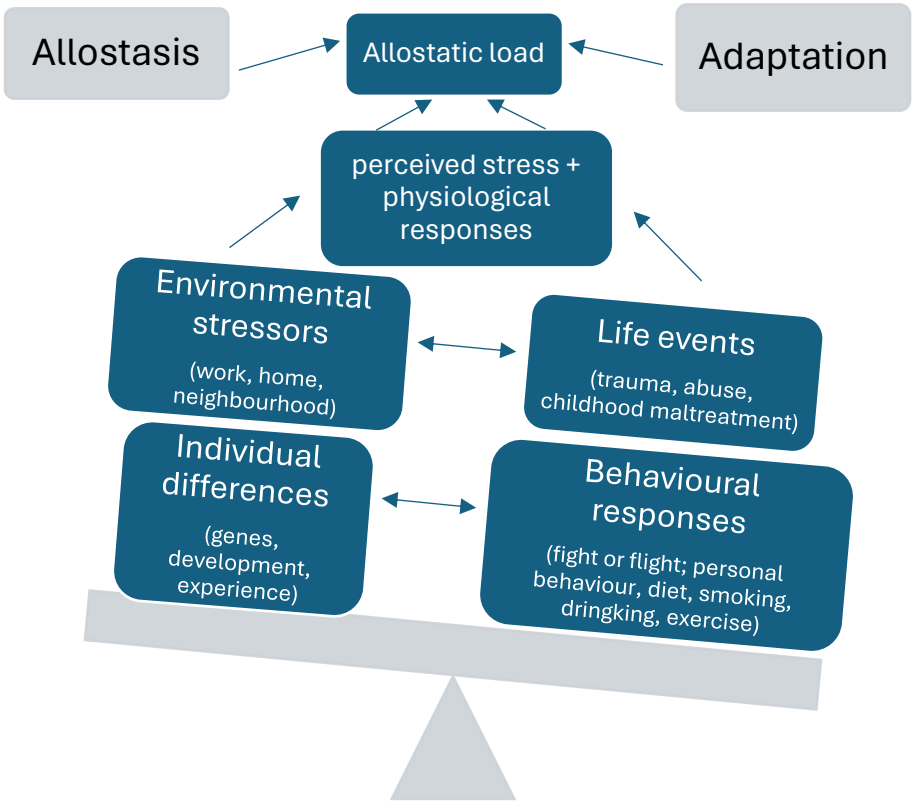
1) Alarm Reaction State: this state appears immediately after a stress stimulus hits the system. The reaction contains the stimulation of the sympathetic nervous system (SNS) with a catecholamine release and a mobilization of adreno-corticotropic hormone (ACTH) in the pituitary gland.

2) Resistance State: this state appears after the habituation to stress and includes an increased cortisol release because of ACTH release. It leads to an increased resistance to stress.

3) Exhaustion State: the last state appears in the case of chronic stress. It leads to a depletion of energy reserves and a weakening of the immune system.

For the illustration of the different influencing factors of the stress response and the build-up of allostatic load, see Figure 1.

Figure 1. The Stress Response and Development of Allostatic Load.



Note: The allostatic load is described in chapter 1.9. Illustration adapted from (11).

The psychoendocrine stress model according to Henry, on the other hand, describes specific reactions depending on the stress situation (stimulus-specific response). According to this model, stress can induce different emotions that lead to different behaviors with specific endocrine response patterns (10).

For the illustration of the response patterns according to Henry, see Table 1.

Table 1. The response patterns of the psycho-endocrine stress model

EMOTION	***BEHAVIOR***	***ENDOCRINE RESPONSE PATTERN***
ANGER / RAGE	*Fight*	↑ *Noradrenaline* ↑ *Testosterone*
FEAR	*Flight*	↑ *Adrenaline*
DEPRESSION	*Freeze,* *Subordination* *Loss of control,*	↑ *Cortisol* ↓ *Testosterone*

In addition to this, about 30% of people tend to respond to different stressors always in the same way (individual-specific response) (10).

1.07 Physiology: Autonomic Nervous System, Sympathetic and Parasympathetic Nervous System, and Vagal Nerve

To maintain a constant internal environment during changing conditions, the organism is dependent on adaptation processes. These are controlled by the central nervous system (CNS) via endocrine systems (slow) or through neuronal control processes (fast). The fast adaptation processes are functions of the autonomic nervous system (ANS) and are a part of the peripheral nervous system. These vegetative regulatory processes and reflexes are only subject to conscious control to a small extent, just as with the vegetative reflexes the afferents often do not penetrate consciousness (12, 119).

Anatomically, functionally, and biochemically, a distinction is made between the sympathetic and parasympathetic parts of the ANS, both of which reach their target organs via a chain of two interconnected neurons (13, 119).

The SNS provides all activating resources for the "fight-flight-or-freeze" (ergotropic) reaction. Whereas the parasympathetic nervous system (PNS) forms the counterpart, the activation-inhibiting system, that stimulates the "rest-and-digest"

(trophotropic) processes. However, these two partially and functionally antagonistic systems also have synergistic functions (12, 119).

Most of the time, the autonomic control of bodily functions oscillates back and forth between the SNS and the PNS to precisely coordinate various processes. Only in isolated cases, such as the fight-or-flight response, does the pendulum swing far to one side (14).

Both neuronal systems modulate the enteric (intestinal) nervous system, a plexus of afferent, efferent, and interneurons, which control the function of the gastrointestinal tract (GIT) via cholinergic and peptidergic synapses. The enteric nervous system communicates with the CNS predominantly using the afferent and efferent fibers of the vagus nerve (see below) (13).

1.07.1 Sympathetic Nervous System

The central sympathetic pathway originates in the hypothalamus and travels via the brainstem and spinal cord to the preganglionic cholinergic neurons in the thoracic and upper lumbar spinal cord. The circuitry takes place in the border ganglia arranged along the spinal column or in the unpaired abdominal ganglia. The fibers of the postganglionic neurons travel together with the blood vessels to the target ganglia. Norepinephrine usually serves as the transmitter of the postganglionic neurons (13, 119).

The effects of the SNS on the organism are mediated by adrenaline and noradrenaline (catecholamines), which are formed in the adrenal medulla (10, 119).

For the fight or flight reaction, the heart rate, respiratory rate, and blood pressure increase, muscle blood flow to the muscles is promoted, and glucose is provided as an energy source through gluconeogenesis and lipolysis (12).

1.07.2 Parasympathetic Nervous System

The parasympathetic cholinergic centers are located in the midbrain, in the medulla oblongata, and in the sacral medulla. The preganglionic neurons move to the parasympathetic ganglia near the organs they supply in the form of several cranial nerves. The cranial nerves III, VII, and IX connect to the inner eye muscles and glands of the head, and the cranial nerve X (vagal nerve) connect to the viscera of

the thorax and abdomen. Approximately about 75 % of all parasympathetic fibers run in the vagal nerve, which makes it the most important parasympathetic conduction pathway (12, 14, 119).

After the switchover from preganglionic to postganglionic neurons, the postganglionic neurons move to the target organs, with acetylcholine (Ach) serving as the transmitter (13, 119).

The pathways conduct sensory information from the visceral organs via the nucleus tractus solitaries (medulla oblongata) and the locus coeruleus (pons) into the CNS. Here, the information is processed in regions that influence emotion regulation and reaction to stress (amygdala, insula, hippocampus, anterior cingulate/prefrontal cortex) (15, 131) as well as parasympathetic output from the brain to the organs.

Further parasympathetic pathways originate at the lower end of the spine in the sacral region, which supplies the pelvic viscera via the nervi splanchnici (12).

The PNS can even amplify the effects of the SNS with its retraction (16).

The activation of the PNS determines the provision of all resources for the "rest-and-digest" processes, which means that blood is shifted to the intestines and sexual organs for supporting digestion, defecation, urination, and reproduction (12, 119).

For an illustration of the effects of the SNS and the PNS, see Table 1.

Table 2. Comparison of effects of the sympathetic and parasympathetic nervous system

Organ	*Sympathetic Activation*	*Parasympathetic Activation*
Heart Muscle	Frequency ↑ Contraction force ↑	Frequency ↓ Contraction force↓
Blood Vessels:		
Arteries	Vascular constriction (skin, mucosa, skeletal muscle, intestinal tract) Vasodilatation (skeletal muscle, coronary arteries)	Vasodilatation (Genital organs, cerebral arteries)
Veins	Vascular constriction	
GIT:		
Longitudinal Musculature	Motility ↓	Motility ↑
Circular Musculature	Contraction	Relaxation

Kidney	Renin secretion ↑	
Bladder:		
M. Detrusor Vesicae	Relaxation	Contraction
M. Sphincter internus	Contraction	Relocation
Genital Organs		
Uterus	Relaxation (depending on the hormonal status)	
Ductus Deferens, Vesica Seminalis, Prostata	Contraction	
Skin:		
Musculi Arrectores Pilorum	Contraction	
Perspiration Glands	Secretion	
Eyes	Mydriasis, Eyelid retraction, Bulbous protrusion	Miosis, Near accommodation
Bronchial Muscles	Relaxation	Contraction
Exocrine Glands of Digestive Tract	serous secretion mucous secretion	serous secretion secretion of HCL
Liver	Glycogenolysis, gluconeogenesis	
Fat Cells	Lipolysis	

Note: HCL = hydrochloric acid. Table adapted from (12).

The activity of the vagus nerve and thus that of the PNS can be measured via heart rate variability (HRV). Postganglionic nerve endings of the SNS and the vagus nerve have direct synaptic contact with the same effector cell in the sinuauricular node, the pacemaker center of the heart. Noradrenaline increases and ACh decreases heart rate at cardiac pacemaker cells (17). The constant interaction and variability of the activity of the SNS and PNS can be measured. HRV measures the spacing of the R-waves (depolarisation of the ventricles), and the interbeat intervals, in the electrocardiogram (ECG). These intervals fluctuate according to differences in the activity of the PNS and SNS (18).

HRV is influenced by sensory information sent from the heart to the CNS and efferent impulses from the CNS, which in turn processes central and peripheral information regarding danger and safety (19). HRV demonstrates the bidirectional connection between the heart and brain (20) and can thus be used as a potential indicator of how variably the ANS can respond to potential danger (SNS activity) and potential safety (PNS activity).

The heart rate is also subject to fluctuations during respiration. These fluctuations are called respiratory sinus arrhythmia. This state is also described as a state of "cardiac coherence". ANS disbalance with a decreased HRV seems to indicate decreased cardiac vagus tone and increased SNS activity. Recent studies show that patients with depression and anxiety disorders have particularly low HRV (19). A decreased HRV is furthermore associated with aspects of a hypo-activated prefrontal cortex such as emotional dysregulation, social involvement, and diminished psychological flexibility (21).

1.08 Stress Response

The stress response is the system's ability to respond to stressors and evolve to create the physiological conditions for fight or flight. This occurs via two pathways (10):

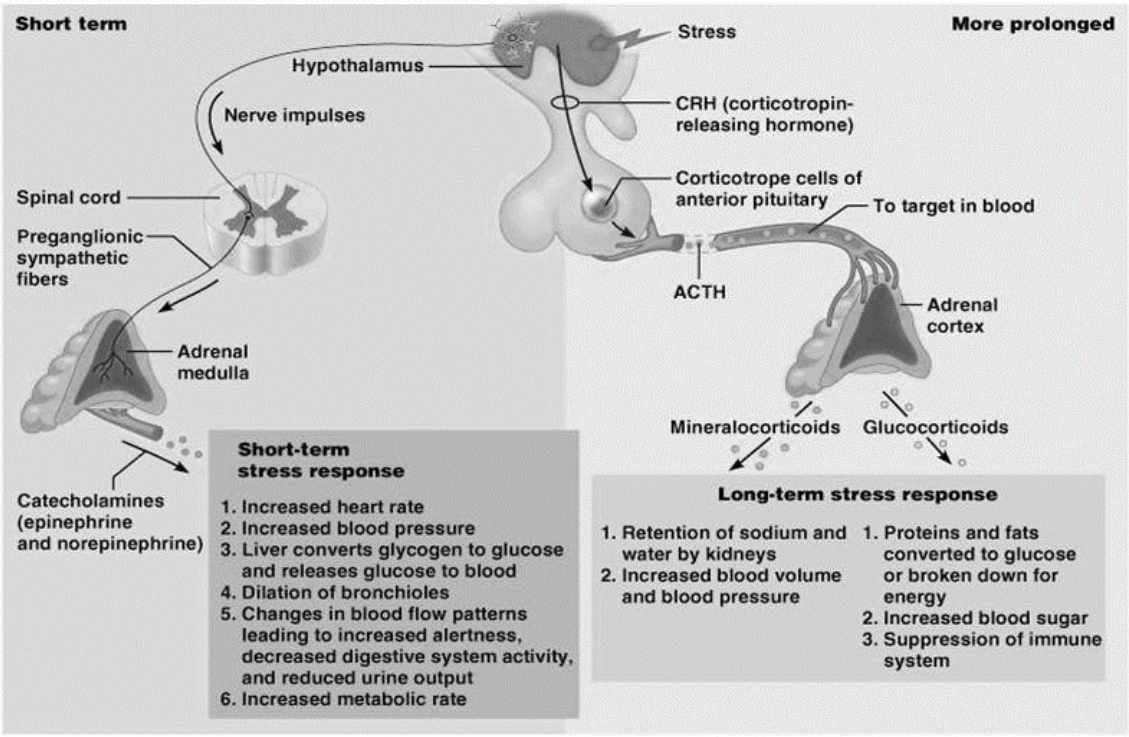
- **The hypothalamus-sympathetic-adrenal medullary system**:
  This pathway is regulated by the ANS and influences the end organs through the secretion of catecholamines (adrenaline and noradrenaline). It works fast (within seconds) as well as short-termed and leads to an immediate reaction as it is a neuronal pathway.
- **The hypothalamus-pituitary-adrenal cortical axis (HPA axis)**:
  This pathway is regulated by the HPA axis through the secretion of glucocorticoids (mainly cortisol). This system is slower to take effect and longer acting because it works through the endocrine system. The endocrine stress response is detailed as follows: In an acute phase of stress, the paraventricular nucleus of the hypothalamus secretes corticotropin-releasing hormone (CRH) into the pituitary gland. CRH in turn triggers the secretion of ACTH from the anterior pituitary gland into the bloodstream. Once in the adrenal cortex, it is stimulated to synthesize glucocorticoids. Cortisol is released and mobilizes stored glucose through gluconeogenesis, lipolysis, and proteolysis, increasing blood glucose concentration (22, 23, 118).
  In addition, cortisol has an immunosuppressive effect by inhibiting cytokine formation and release (e.g., of TNF- α, IL) and the T- and B-cell response (inhibition of activation and proliferation of B- and T-lymphocytes, promotion of apoptosis of B- and T-lymphocytes). Cortisol also affects the hematological

system, sexual hormones, electrolytes, bone metabolism, locomotor system, connective tissue, the CNS, and the mind, and inhibits growth in children (12, 118).

The activity of the HPA axis is subject to a negative feedback loop. When cortisol circulates in the bloodstream, the release of CRH from the hypothalamus and ACTH from the pituitary gland is inhibited. As a result, less cortisol is released, and the stress response can be stopped (24, 118).

For an illustration of the different pathways of the stress response, see Figure 2.

Figure 2. The two pathways of the stress response: hypothalamus-sympathetic-adrenal medullary system + hypothalamus-pituitary-adrenal cortical axis (HPA axis)



Note: ACTH = Adrenocorticotropin-releasing hormone. Illustration adapted from (24).

1.09 Chronic Stress

Usually, because of the feedback mechanism of the hypothalamus, prefrontal cortex, and hippocampus, increased cortisol levels drop to baseline levels when stress has ended (24).

The frequent and enduring stimulation of the HPA axis in chronic stress causes ongoing high cortisol levels in the system of the individual, which creates damage to cortical and hippocampal neurons (25). This damage affects the regions where the feedback inhibition takes place. Accordingly, the activity of the HPA axis is less inhibited, which causes even more secretion of cortisol (24, 132, 133).

Constant high cortisol levels are also leading to glucocorticoid resistance, which in turn provokes even more CRH secretion, that consequently enhances the overactivity of the HPA axis. In the long run, the homeostasis of the HPA axis and the ANS becomes disrupted and dysregulated (7, 26).

On the effect of chronic stress on cortisol secretion there are contradictory research results. Chronic stress is generally associated with low cortisol concentrations in the morning, but higher concentrations in the afternoon and evening so that the daily rhythm is flattened. Overall, cortisol secretion is increased. The time course also plays a role: immediately after the onset of the stressor it is the highest: The more time that passes, the more they drop again, to below-normal levels (10).

After the described initial increases in stress hormones (Growth hormone, ACTH + cortisol), an insufficiency prevails in the long term, which occurs both at the hypothalamic/pituitary level and in the area of the target glands such as the thyroid gland and the adrenal cortex (13).

In addition, chronic stress shows sympathetic hyperactivation with reduced parasympathetic activation and a decreased HRV. It is proposed that the measurement of the HRV could be an index of stress and vulnerability to stress (27).

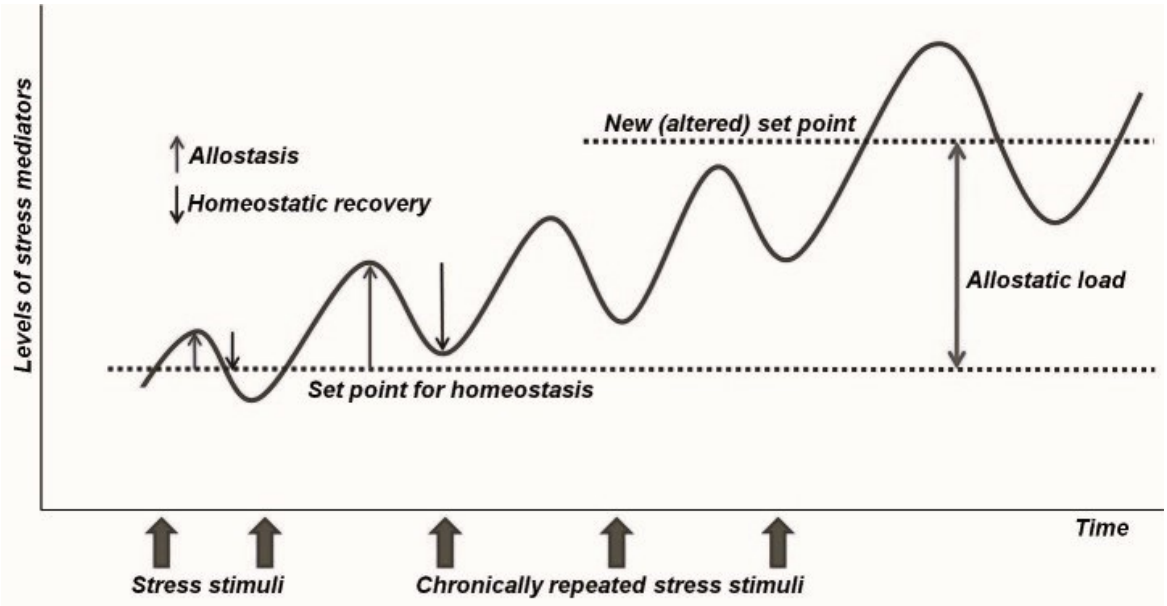
1.10 Allostatic Load

The homeostasis-allostasis model, which describes the stress resistance of our system, is a model that allows an adaptive response or a setpoint shift (allostasis) in the system so that the balance between the individual and the environment (so-called homeostasis) is maintained (28, 135). The physiological changes (e.g., increased cortisol level) as a reaction to stress are necessary and helpful in the short term to be able to react adequately to stimuli. In the case of prolonged stress, however, the altered physiological processes can hurt health as an allostatic load (AL). The AL accumulates in the individual that is confronted with repeated or

chronic stress and can result in somatic damage (29, 136). Whether a situation becomes a stressor depends largely on the subjective evaluation and the individual's ability to cope with the situation. The assessment of imminent danger and the subsequent mobilization of the conditions for fight or flight is dependent on individual differences in disposition (genes, evolution, experience), behavior (lifestyle factors and coping strategies), and personal history (traumatic experiences, ELA, abuse, formative events, stressful environmental factors, etc.), that constitute the individuals stress resilience (28). Moreover, whether stress ultimately leads to illness also depends on the disposition of the individual (cf. vulnerability-stress-coping model) (10).

For an illustration of the development of the allostatic load, see Figure 3.

Figure 3. The development of an allostatic load due to repetitive and/or sustained stressors.



Note: The arrows at the bottom symbolize repeated stress stimuli. Illustration adapted from (24).

Due to increasing trends in stress-related (psychiatric) disorders, it would be of great interest to be able to measure chronic stress, respectively the allostatic load, as a predictor of disease genesis (24).

In the literature some researchers define three stages of measurable outcomes that could be used as AL biomarkers. The first parameters that can be measured are

described as “primary mediators“. Those are adrenaline, noradrenaline, cortisol and its antagonist dehydroepiandrosterone (DHEA), and pro- and anti-inflammatory cytokines e.g., TNF-α, IL-6 (137). Chronically elevated primary mediators that cannot be compensated anymore can result in “secondary outcomes”. In this stage, parameters for the metabolic and cardiovascular state of the system and the immune system are increased, however in a range that has not yet been clinically relevant. Used metabolic markers were insulin resistance, cholesterol, triglycerides, and visceral fat. Systolic and diastolic blood pressure (BP) were defined as cardiovascular markers and CRP and fibrinogen were the immune markers. If the allostatic load continues to accumulate, the system will reach “allostatic overload” with “tertiary outcomes” that are manifested in diseases such as hypertension, diabetes, coronary heart disease, and neurodegenerative disorders (11, 28, 138).

1.11 Anti-Inflammatory Reflex

Recent studies show that vagal afferents can relay information about peripheral inflammation to the brain and stimulate an anti-inflammatory effect via vagal efferents. This so-called cholinergic anti-inflammatory reflex, in addition to anti-inflammatory cytokines and hypothalamic-pituitary adrenal, gonadal, or thyroid-hormone axis mediators such as corticosteroids, and thyroid and sex hormones, would be another way to reduce excessive activity of the immune system (30).

Vagus stimulation confirmed the anti-inflammatory effect of vagus efferents, significantly inhibiting cytokine production. These findings show the nervous system's influence in modulating the immune system (31).

Further studies have shown that the reduction in cytokine secretion (e.g., TNF, IL-10) takes place at specific cholinergic receptors (α7 subunit of the nicotinic ACh-receptor), with which the released ACh interacts (32, 33).

If we assume that the majority of patients with stress-associated psychiatric disorders have elevated inflammatory markers (34) and inflammatory markers are a predictive marker for the development of psychiatric disorders such as major depression (7), the therapeutical activation of the cholinergic anti-inflammatory reflex would be of great clinical interest.

1.12 Stress and Major Depression

Studies have shown that people with MDD have certain types of HPA axis dysregulation with an increased secretion of cortisol and in the function of glucocorticoid receptors. The dysregulation can be identified with the dexamethasone-suppression test, the dexamethasone corticotropin-releasing hormone test, or the investigation of the dexamethasone-induced gene expression (9, 26, 35).

Cortisol has many profound effects on the organism, which can make the latter more vulnerable to depression or exacerbate the MDD. When administered in high doses therapeutically, it can cause depression because of the affection of emotion. It suppresses the immune system, whereby in depression inflammatory (proinflammatory) cytokines (IL) are formed, which play a role in the development of MDD. Furthermore, the natural killer cells are reduced in people suffering from MDD. The CRP, which indicates inflammation, is also increased in MDD. However, the connection between depression and inflammatory indicators appears to be largely genetically mediated. The process leading to that is most likely the downregulation of cellular cortisol receptors through long-term excessive secretion of cortisol. This limits the cell's ability to respond to pro-inflammatory cytokines (e.g. IL-6). In addition, the HRV is decreased with an increased sympathetic and reduced parasympathetic tone (10).

1.13 Stress and PTSD

In PTSD, stress management is not successful. Long after a traumatic experience, intense images of the traumatic situation (flashbacks), even though (or maybe because) the patients try to avoid all thoughts or situations that remind them of the situation they experienced. On the one hand, those affected feel emotionally dulled. On the other hand, they suffer from physiological stress symptoms (10).

HPA axis dysregulation has also been found in PTSD subjects, who had shown elevated CRH concentration in their cerebrospinal fluid (140). Furthermore, Patients who have PTSD often display a shifted ANS activity towards an elevation of SNS activity and a reduction in PNS tone, which could be measured with the HRV and a decreased activity in the GABA (γ-aminobutyric acid) system (141-143). It was found that a low plasma concentration of GABA in a posttraumatic situation could be used

as a positive predictor for the occurrence of PTSD (36, 139). GABA concentration can be measured in urine and serum. Still, GABA can cross the blood-brain barrier only to a small extent, so cortical GABA concentration cannot be determined directly from peripheral values. Cortical GABA concentration can be measured with the means of proton magnetic resonance spectroscopy, which is a time-consuming and expensive procedure and therefore does not play a role in everyday clinical practice despite evidence that cortical GABA is decreased in subjects with MDD compared to healthy subjects (37).

Some studies suggest that hippocampus atrophy is a mere risk factor for the development of PTSD and/or a consequence of the chronic stress experienced. A reduction in hippocampus size was found in depressive patients and Vietnam veterans and their identical twin brothers who didn't go to war. Long-term cortisol overproduction leads to atrophy of the hippocampus, a brain structure important for the limbic system (10).

1.14 Treatment of SRPD

The conventional treatment (Treatment as usual = TAU) of SRPD includes psychotherapy and/or medication (39, 144).

For PTSD all international guidelines recommend trauma-focused psychotherapy as first-line treatment. Usually, first-line psychological therapy is cognitive-behavioral therapy (CBT) followed by cognitive processing therapy, cognitive therapy, and prolonged exposure therapy (PE). In addition, brief eclectic psychotherapy, specific cognitive behavioral therapies for PTSD, eye movement desensitization and reprocessing (EMDR), and narrative exposure therapy are recommended. First-line psychopharmacological treatment is Selective Serotonin Reuptake Inhibitors (SSRI) (50 - 52).

For MDD first-line recommendations for pharmacotherapy are SSRIs, selective serotonin noradrenaline reuptake inhibitors (SNRIs), bupropion, mirtazapine, vortioxetine, and agomelatine (56).

The Anglo-American guideline recommendations for psychotherapy are CBT, behavioral activation (BA), and interpersonal psychotherapy, followed by psycho-dynamic therapy, problem-solving therapy, and emotion-focused therapy (54). The

German guideline recommendations are systemic therapy, psychoanalysis, and talking therapy (53). Supreme treatment is the combination of psychotherapy with psycho-pharmacological treatment (56).

However, a body of research indicated that those therapies have drop-out rates of up to 50% in PTSD (145, 146). The first-line medication for SRPD is SSRI (39). Although SSRIs often show insufficient efficacy in the treatment of PTSD and MDD. Furthermore, the efficacy of SSRIs in PTSD is not backed up with enough evidence (38). Ballenger et al. 2004 discovered that only about one-third of patients with PTSD achieve a satisfactory therapeutic outcome (39). Likewise in patients with MDD about one-third have experienced significant symptom relief through first-line medication (antidepressants), and about two-thirds would eventually reach remission criteria only after several therapeutic cycles of psychotherapy and trying several different groups of antidepressants (40).

These results emphasize the necessity of finding treatment options that meet the individual patient's needs, improve self-efficacy, are cost-effective, and produce fewer side effects (41, 42).

1.15 VNS-Stimulation

Stress unbalances the ANS (decreased HRV with increased SNS and decreased PNS), promotes underactivity in the gamma amino-butyric acid (GABA) system, the predominant neurotransmitter system for inhibition, and leads to an accumulation of allostatic load (36).

Provided that stress plays a significant factor in the development and treatment of SRPD, stress reduction would be a promising therapeutic approach.

An increasing number of studies have investigated and confirmed the effects of stress-reducing approaches such as vagus nerve stimulation (VNS), the stimulation of the major peripheral conduction path of the PNS, in the therapy of SRPD. The desired effects of the VNS are (36):

1) balancing the ANS, with an increase in PNS activity respectively vagal tone, and a reduction of SNS activity, which can be measured in an increased HRV.

2) a reduction of the allostatic load, measured in markers such as adrenaline, noradrenaline, cortisol and its antagonist DHEA, and pro- and anti-inflammatory cytokines, e.g., TNF-α, IL-6.

3) stimulation of the GABA system.

4) stimulation of the anti-inflammatory reflex (inhibition of cytokine production).

5) modulation of emotion in central brain areas (nucleus tractus solitarius, which is projecting on various areas of the limbic system and the frontal lobe) (4, 31, 134, 147).

There are two ways to carry out the electrical stimulation of the vagal nerve: invasive VNS (iVNS) and transcutaneous non-invasive stimulation (tVNS) (43).

To implement the direct iVNS, a small pulse generator with electrodes is implanted surgically in the left thorax nearby the left cervical vagus. The electrodes are connected to the vagal nerve through a pipe, both lying in the subcutaneous layer. The pulse generator provides periodical electrical impulses to the vagal nerve (44).

In indirect tVNS, a stimulator is attached noninvasively to the auricular concha, where it emits electrical impulses to the afferent auricular branch of the vagus nerve (95).

A growing body of research suggests that mind-body practices can increase HRV (148). Therefore, such interventions are non-invasive ways to stimulate the vagus nerve. The term “mind-body interventions” (MBI) summarizes various techniques such as biofeedback, deep breathing, meditation, mindfulness programs such as Mindfulness-based stress reduction (MBSR), Qi Gong, Tai Chi and Yoga. These techniques intend to improve the body's physical functioning with mental and physical exercises (45, 149).

These questions might be particularly relevant for women, as women are affected by SRPD up to twice as often as men SRPD (124). At the same time, men suffer more often from substance-related disorders such as alcohol and tobacco abuse (47).

1.16 Working Hypothesis

Patients with SRPD show a disruption of the homeostasis of the ANS and a dysregulation of the HPA axis, resulting in an increased SNS, a decreased PNS with a decreased HRV, and altered concentrations of peripheral cortisol and other allostatic load markers. Non-invasive vagus nerve stimulation (nVNS) enhances the activity of the PNS, which regulates the HPA axis and acts as a counterbalance to the SNS.

The literature describes various possibilities of nVNS such as the transcutaneous VNS with an electronic stimulator applied to branches of the vagus nerve. Furthermore, multiple methods of nVNS stimulations through MBIs intend to address mental and physical fitness. Hereby, various techniques such as Yoga and MBSR, where controlled breathing, focused meditation/attention, movement, or posture play an important role.

This thesis aims to summarize the mechanisms of action of nVNS therapy in MDD and PTSD. Further on, interventional studies of the last 10 years (2010-2020) before the COVID-19 pandemic of nVNS as a treatment of MDD and PTSD shall be summarized and compared in terms of efficacy, clinical usefulness, and data quality regarding the following questions:

Question 1: which nVNS procedures have a symptom-reducing effect on SRPD, quantified using validated questionnaires?

Hypothesis 1: it is hypothesized that nVNS procedures reduce specific symptoms of MDD and PTSD such as subjective stress and depression scores.

Question 2: which nVNS procedures have a positive effect on the balance of the ANS, in the sense of stimulating parasympathetic activity and reducing sympathetic activity, measurable by an increase in HRV?

Hypothesis 2: it is hypothesized that nVNS balance the ANS with an increase in the HRV.

Question 3: which nVNS procedures have a lowering effect on the chronic stress experience of the patient, measurable by the allostatic load markers such as cortisol?

Hypothesis 3: it is hypothesized that nVNS procedures reduce allostatic load markers by reducing chronic stress.

2 Material and Methods

2.1 Method

The method chosen for the preparation of this diploma thesis is a literature review. The review was prepared inspired by the guidelines published in the PRISMA-statement (“Preferred Reporting Items for Systematic Reviews and Meta-Analyses“) (48). The selection of studies was based on boolean operators and defined inclusion and exclusion criteria (see below).

The search for the studies was performed in the scientific databases *PubMed* and *Web of Science*. The search terms used were the boolean operators: ((MDD OR major depression OR major depressive disorder OR PTSD OR posttraumatic stress disorder OR post-traumatic stress disorder) AND (vagal nerve OR noninvasive vagal nerve stimulation OR nVNS OR yoga OR meditation OR mind-body intervention OR mindfulness-based stress reduction OR MBSR OR breathing exercises))) with the following filters applied in Pubmed: Clinical Trial, Controlled Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review, Humans, English, German, Adult: 19+ years and 2010-2020.

The search yielded 202 papers in *Pubmed* (17.1.23 11:55h.) and 987 papers in *Web of Science Core Collection* (18.01.23 9:00h.) and after the exclusion of duplicates by Mendeley the search returned 1063 articles. This was followed by the sorting out of items that were outside the period (n=22) and that were retracted (n=2). Now the titles of the articles were examined for suitability. Articles were excluded that were not captured by the duplicate filter and the articles that did not meet the inclusion criteria. The articles that were left (398) were examined in abstract and full text for appropriateness and those that did not meet the following inclusion criteria were screened out.

Inclusion Criteria:

a) Type of study: randomized controlled trials (RCTs) with cross-over study design and randomized parallel group design studies. Clinical studies with human clinical population. Intervention studies that used validated questionnaires on stress (58, 79) and depression (59), intervention studies

that have performed measurements of HRV and cortisol levels in saliva in the study collective.

Eligible PTSD-questionnaires: “Clinician-Administered PTSD Scale for DSM-5” (CAPS-5), “PTSD Symptom Scale Interview” (PSS-I, PSS-I-5), “Structured Clinical Interview; PTSD Module” (SCID PTSD Module), “Structured Interview for PTSD” (SIP or SI-PTSD), “PTSD Checklist for DSM-5” (PCL-5) “Impact of Event Scale – Revised” (IES-R).

Eligible MDD-questionnaires: “Beck Depression Inventory” (BDI), “Hamilton Depression Rating Scale” (HDRS/HRSD/HAM-D), “Montgomery Åsberg Depression Rating Scale” (MADRS), “Patient Health Questionnaire” (PHQ), “Clinical Global Impression – severity scale” (CGI-S).

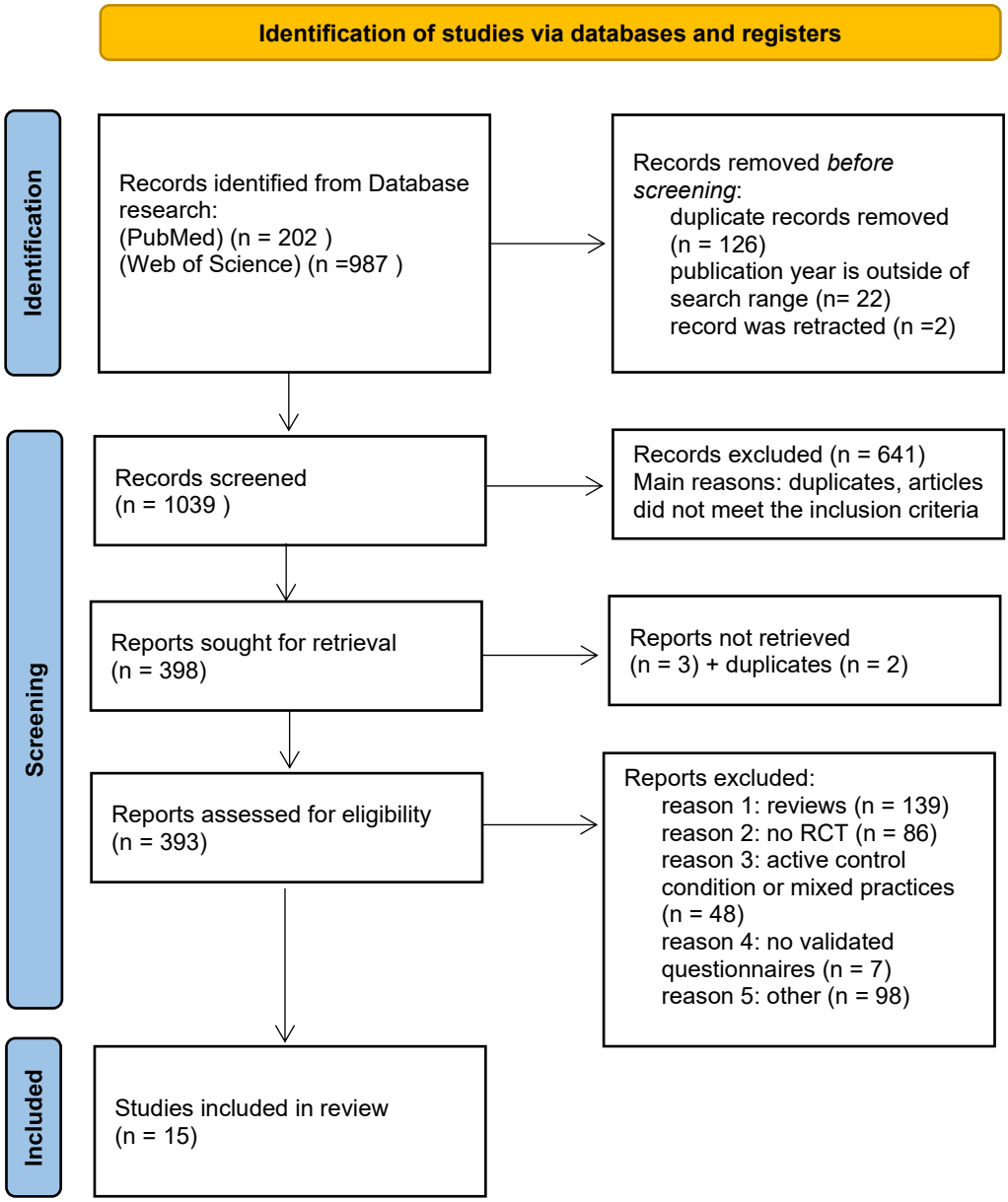
b) Study population: humans, adults, gender (female/male/diverse), clinical population with diagnosed disease of MDD or PTSD according to ICD-10, ICD-11, “Diagnostic and Statistical Manual of Mental Disorders” (DSM) IV, or DSM V. Eligible questionnaires for the diagnosis of PTSD: PCL, CAPS.
c) Time period: only studies that were published from 2010-2020 were eligible. A period before the start of the Covid-19 pandemic was chosen because the pandemic was a major life event globally. Many studies had to be interrupted and recurring lockdowns affected the study routine. In addition, the lockdowns and behavioral changes as well as the risk of Covid-19 disease had far-reaching psychological consequences (82, 83, 109, 112). In this review, a comparison of different interventions in a pre-pandemic period was chosen.
d) Interventions: studies were included when they compared tVNS, Yoga, meditation, MBSR, Yoga Nidra, non-specific mind-body programs, or biofeedback to a control group with TAU, sham-stimulation, waitlist control, or assessment control. Co-interventions were eligible if the participants in all the study arms participated in the same interventions. TAU is defined as non-specific psychopharmacological and/or psychotherapeutic guideline therapy.
e) Journal: only articles published in peer-reviewed journals were eligible.
f) Number of study participants (N): only studies, with n≥20 were eligible.

Exclusion Criteria:

a) Studies were excluded if the study collective had defined co-occurring diseases when the program was exclusively online.
b) Studies were excluded if the following interventions were applied: laughter Yoga, exercise program/physical activity, acupuncture, and other complementary and alternative medicine (CAM) approaches.
c) Specialised programs where mindfulness is integrated into acknowledged psychotherapy: Mindfulness-based exposure therapy and mindfulness-based cognitive therapy.
d) Specialised programs with mixed methods other than MBSR, its abridged version brief mindfulness program/training (BMP/T), and the Mantram Repetition Program (MRP).
e) Combined interventions in one control arm.

After a thorough search, 15 articles were selected that sufficiently met the inclusion criteria. The flow chart of the sorting process of the literature search is displayed in Figure 4.

Figure 4. Flow Diagram of Database search, Article identification, screening, and inclusion. Illustration adapted from (49)



2.2 Material

2.2.1 PTSD Questionnaires

Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

CAPS is the gold standard in the assessment of PTSD designed by the “U.S. Department of Veterans Affairs National Center for PTSD” and is performed by a clinician/clinical researcher. The CAPS-5 is specific for PTSD diagnostics according to DSM-V and symptom severity in the form of a structured interview with 30 items. The former CAPS-4 was designed for diagnostics according to DSM-IV. The CAPS can be used to assess PTSD symptoms within the last week, current (past month), or lifetime (worst month). B (Items 1-5), C (Items 6-7), D (Items 8-14), and E (15-20) symptoms are captured in quality (intensity) and quantity (frequency), except for Items 8 and 12 where the extent and intensity are evaluated, criterion F + G are queried. For assessing the severity scores, individual items in each cluster must be summarized. A PTSD can be diagnosed when the following applies: minimum one Criterion B + C symptom, minimum two Criterion D + E symptoms, Criterion F is fulfilled (the disruption persisted for one month) and Criterion G is fulfilled (the disorder causes either clinically significant distress or functional impairment) (63, 64, 65).

Symptom severity rating scale:

0 = absent, 1= mild/subthreshold, 2 = moderate/threshold, 3 = severe/markedly elevated, 4 = extreme/incapacitating

PTSD Symptom Scale Interview (PSS-I, PSS-I-5)

The PSS-I is a semi-structured interview comprising 17 (PSS-I) respectively 24 (PSS-I-5) items that evaluate the occurrence and severity of PTSD symptoms during the past month. The questionnaire captures the 20 DSM-V PTSD symptoms in their presence and severity and four supplementary questions concerning the impact in daily life, symptom incipience, and duration.

For a diagnosis according to DSM-V, the following must be clinically significant and applicable (score ≥2 on relevant items): one intrusion symptom, one avoidance

symptom, two changes in cognition and mood symptoms, and two hyperarousal symptoms (66, 67, 68, 69).

Structured Clinical Interview; PTSD Module (SCID PTSD Module)

The SCID-5 was designed for diagnosis according to DSM-V in the form of a semi-structured interview, performed by a trained qualified professional or clinician. It is the successor version of the SCID-I, which was used for the DSM-IV diagnosis. The symptoms are not scored quantitatively but in the severity categories: present, subthreshold, and absent (70, 73).

Structured Interview for PTSD (SIP or SI-PTSD)

The SI-PTSD is a clinical interview that assesses the 17 PTSD symptoms according to DSM-IV Criteria in the form of a severity survey, rating frequency, and intensity as well as survival and behavioral guilt. It can be used to assess the symptoms of the last four weeks as well as of the worst period in life. The symptom severity is scored 0-4, where a score ≥ 2 (moderate) is rated as positive. For the diagnosis, it is determined whether the symptoms correspond to the DSM-V criteria B, C, and D for PTSD (74).

PTSD Checklist for DSM-5 (PCL-5)

The PCL-5 is a 20-item self-report questionnaire designed at the “VA National Center for PTSD” referring to the DSM-V symptoms of PTSD. It can be applied to screen for PTSD and make a provisional diagnosis or to record symptom changes during and after treatment. The PCL was the former version corresponding to DSM-IV with 17 Items. That questionnaire was available in three forms: PCL-M (military), PCL-C (civilian), and PCL-S (specific). The PCL-5 does not have corresponding versions and PCL-5 scores are not compatible with scores from PCL (75, 76).

Cut-off scores: PCL- M: ≥ 36 (62), PCL-C: ≥ 30 (61), PCL-5: ≥ 34, resp. 31-33 (60, 76).

Impact of Event Scale – Revised (IES-R)

The IES-R is a 22-item self-report questionnaire corresponding to the DSM-IV symptoms of PTSD. The IES was designed for DSM-III. There is no updated version according to the DSM-V criteria for PTSD.

The questionnaire asks to select an individual stressful life event and rate the subjective distress in the course of the past seven days on a scale from zero (not at all) to four (extremely). For the scoring all individual items are summarized, which results in a total score of zero to 88. It is not applied for diagnosis but for the assessment of distress and potential screening of individuals with potential PTSD (77, 78).

Cut-off score: ≥ 46 (60)

State-Trait-Anxiety Inventory (STAI, -S = State, -T = Trait)

The STAI is a 40-item self-report instrument that measures state anxiety (nervousness, fear, etc. caused by situations) and trait anxiety (experience of stress, discomfort, etc. daily) on a 4-point scale. Higher values usually indicate a higher anxiety level (92).

2.2.2 MDD Questionnaires

Becks Depression Inventory-II (BDI-II)

The BDI is a validated psychological test, that measures depressive symptoms. In the form of a 21-item questionnaire, the patient self-reports about the frequency and severity of depressive symptoms. Each item is rated with zero to three resulting in an overall score of 0-63, where a higher score indicates a more severe depressive mood (80, 81).

Hamilton Depression Rating Scale (HDRS/HRSD/HAM-D)

The HAM-D measures the severity of depression in individuals related to the last days or weeks before the interview. It is a 21-item external rating scale assessed by a healthcare professional. It can be used to monitor depression before, during, and after an intervention. The scoring is based on the first 17 items and measured on 3- to 5-point scales, all added together to result in the total score. The higher the total score, the more severe the depression (84, 85).

Montgomery Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item external rating scale that evaluates the severity of depression. The assessment period is related to the past week. It is an adaptation of the HAM-D, designed to improve its weaknesses. Each item is rated on a 7-point

scale. For the total score (0-60) all individual items are summed up (86). The literature describes the MADRS as being sensitive to change and treatment effects in individuals (87).

Patient Health Questionnaire (PHQ)

The PHQ-9 is a 9-item self-report instrument applied to screen individuals for depressive symptoms. Each of the nine questions addresses one of the nine DSM-IV criteria for depression. Every item is rated on a 4-point scale. For the total score (0-27) all items must be added (88, 89).

Clinical Global Impression (CGI)

The CGI is a 3-item external rating scale, where the health care professional makes an impression on the severity of illness of the patient. It can be applied to measuring the treatment response and the efficacy of interventions in studies. The 3 items assess the severity of illness (CGI-S), global improvement (CGI-I), and efficacy index (CGI-I) (71).

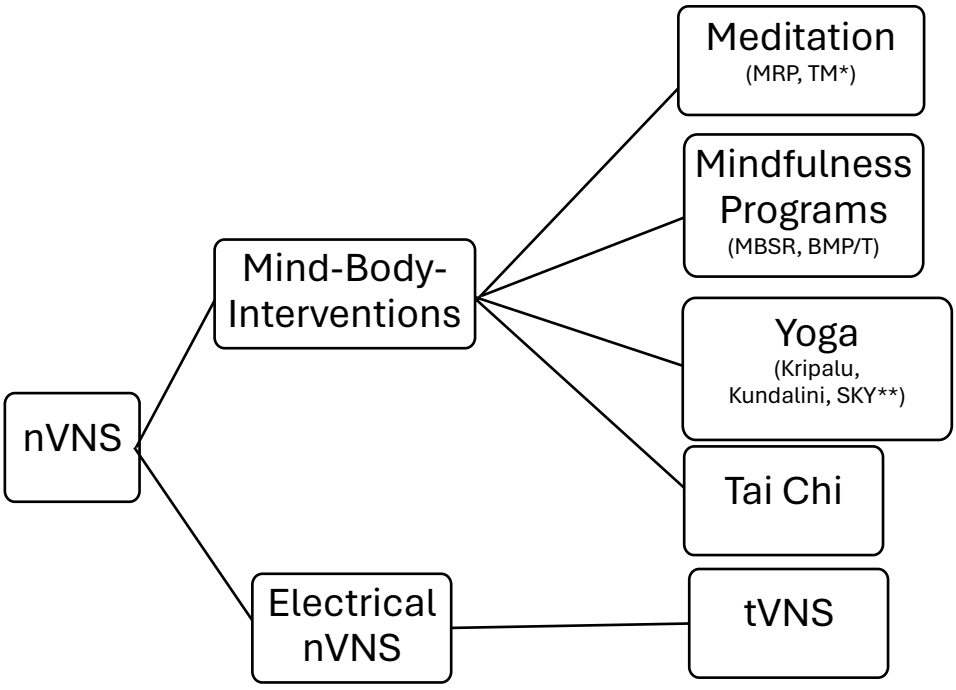
3 Results

The following 15 articles with total 1130 (985 completed) study participants were selected for the review: Kumar S. et al. 2019 (93), Yeung A. et al. 2012 (94), Hein E. et al. 2013 (95), Sharma A. et al. 2017 (96), Bormann J. et al. 2018 (97), Bormann J. et al. 2013 (98), Polusny M. et al. 2015 (99), Rees B. et al. 2013 (100), Nidich S. et al. 2018 (101), Mitchell K. S. et al. 2014 (102), Gurel N. Z. et al. 2020 (103), Kearney D. J. et al. 2013 (104), Jindani F. et al. 2015 (105), Bergen-Cico D. et al. 2014 (106) Possemato K. et al. 2016 (107).

3.1 Interventions

The interventions represented in the articles selected for the review are pictured in Figure 5.

Figure 5. nVNS Interventions represented in articles.



**TM = Transcendental Meditation; **SKY = Sudarshan Kriya Yoga*

Meditation

Many forms of meditation have been practiced in different traditions for thousands of years. The main content of meditation involves introspection, conscious control of attention, and focus on the present moment. Meditation teaches practitioners to

observe inner and bodily sensations, thoughts, and emotions in a nonjudgmental, accepting, and open attitude to help them with self-regulation (72, 108).

In the studies selected for this review, mantra meditation is practiced in the form of two different programs: the Mantram Repetition Program (MRP) and Transcendental Meditation® (TM).

The MRP is based on mantra meditation, which involves the mental repetition of a self-chosen word or phrase that has a spiritual meaning to the practitioner. Mantra repetition can be practiced throughout the day parallel to other activities, in movement, or a resting position (97).

TM is a sitting meditation practiced twice daily à 20 minutes with closed eyes. It also uses mantra repetition, with certain mantras chosen by the TM organization. The TM aims to overcome mental activity and is taught as a transcendence toward pure consciousness (101).

Mindfulness Programs

MBSR is an eight-week standardized mindfulness program for stress management through mindfulness, which originates in Buddhism and was designed by Prof. Jon Kabat-Zinn and his colleagues at the University Hospital of Massachusetts (USA). It consists of weekly classes à 2,5h, daily home practice, and a one day-long retreat. Practices of the course are body-scan, Yoga postures, walking meditation, breathing exercises, and mindfulness in activities of daily life. MBSR draws on elements of Yoga and the Buddhist schools of Zen and Vipassana (110, 111).

Due to problems with the feasibility and acceptance of the time-consuming MBSR program, a shortened version, the brief mindfulness program/training, was created (BMP/T). Beyond the practices described above, it includes group reflection (107).

Yoga

Yoga has been embedded in the Indian philosophy for about 5000 years. Traditional Yoga (Hatha Yoga) is a multidimensional spiritual practice and consists of guidance on an ethical way of living (Yama + Niyama), physical activity respectively Yoga postures (Asanas), breathing exercises (Pranayama) and meditation (Dhyana) (1).

Aspects of the practices, especially Asanas, reached wide popularity in the West. Nowadays there is a broad variety of Yoga schools with different focuses available.

In the studies selected for this review, the following Yoga schools were applied: Kripalu Yoga, Kundalini Yoga, and Sudarshan Kriya Yoga (SKY).

Kripalu Yoga is a form of Hatha Yoga, which consists of breathing exercises, postures, relaxation, and meditation. It was founded by Swami Kripalu. “Kripalu” means compassion and therefore the practice teaches compassionate introspection and being present in the moment (102).

Kundalini Yoga in the West is taught by Yoga Bhajan and consists of a meditative physical movement practice. The meditation usually involves a mantra and the movement sequences are performed dynamically (105).

SKY is a Yoga school based on meditative breathing exercises, which are rooted in the tradition of cleansing exercises (Kriyas = cleansing techniques) (96).

Tai Chi

Tai Chi is an MBI rooted in China and it was originally founded as a martial art. The practice consists of basic strengthening and relaxing exercises such as individual intentional movements, standing and breathing exercises, and standing meditations. It aims to prepare the mind-body for the obstacle-free flow of “life energy” (Qi) (94).

3.2 Study Outcome Overview

Table 3 provides an overview of the articles regarding the population including study sample, psychometric instruments and/or measurements, type of intervention, and outcome.

Table 3. Overview of study characteristics of articles selected for the review

Author and Year of Publication	Population/study sample	Psychometric instruments and/or measurements	Intervention	Outcome
Kumar S. et al. 2019 (93)	**Diagnosis:** MDD (DSM-IV) **Study size:** N = 87, 80 completed (92%). **Demography:** Sex: female: 40, male: 40. Age: M=38.19y, SD=11.73y. Yoga group vs. control Socioeconomic status: lower 47.5% vs. 50%, middle 47.5% vs. 42.5%, upper 5% vs. 7.5%. Marital status: single 12.5% vs. 22.5%, married 87.5% vs. 77.5%. Total duration of illness (months): M=31.48, SD=46.84 vs. M=34.06, SD=54.25. Current duration of illness (months): M=1.83, SD=1.62 vs. M=1.86, SD=1.17. Episode number: M=2.30, SD=2.12 vs. M=2.55, SD=3.41.	**Questionnaires:** MADRS, CGI **Assessment points**: -MADRS + HADS at baseline, day 10 + 30. -CGI at baseline + day 30. Further collected data: HADS.	Yoga therapy + TAU (N= 44, 40 completed) vs. TAU (N = 43, 40 completed). **Duration:** 30d (minimum 20 supervised Yoga sessions, 5/wk à 45min). **Follow-up:** no (post-treatment -> day 30). **Randomization:** computer-generated random numbers. **Blinding:** no blinding. **Note:** TAU: antidepressants + psychological intervention.	**Adverse events (AE):** not mentioned. **Drop-out:** 9% Yoga vs. 7% TAU. **Depression** -MADRS -> mean fall from baseline to day 30: M=-24.43 Yoga vs. M=-21.70 TAU; *p*=.042 -> significant fall in depression score. -CGI -> significantly greater improvement in CGI scores at day 30 in the Yoga group. => Yoga group showed a significant improvement in depression scores and clinical global impression from baseline to the 30th day compared to the control group. **Note**: statistical significance was set at p<.05.
Yeung A. et al. 2012 (94)	**Diagnosis:** MDD (DSM-IV + ≥12 on HAM-D17). **Study size:** N = 39 (30 completed = 77%). **Demography:** Sex: female: 30, male: 9. Age: M=55y, SD=10y. Chinese Americans, fluent Chinese speakers. Tai Chi vs. control -Married: 68% vs. 39%. -Education: M=12.8y vs. M=11.4y. -Employed: 46% vs. 69%. -Antidepressants: 24% vs. 46%. **Note:**	**Questionnaires:** HAM-D17, CGI-I, CGI-S. **Assessment points**: baseline, week 6 + week 12. At each class -> attendance sheet, AE log, adherence to practice in last week's log.	Tai Chi intervention (N = 26 -> 19 completed) in Chinese vs. waitlist control (N = 13, 11 completed) in a 2:1 ratio. **Duration:** 12wk (2/wk à 1h + home practice advised ≥ 3/wk). **Randomization:** computer-generated numbers (no restriction). **Blinding**: single-blind (only outcome assessors). **Follow-up:** no (posttreatment -> week 12). **Note:**	**Adverse events:** no AE reported. **Drop-out:** 27% Tai Chi, 15% control. **Depression** -HAM-D_{17} -> mean changes from baseline to week 12 -> no significant differences between the intervention group (completers/non-completers) and the control group. -CGI-I/S -> no significant differences in the change between the intervention group and the control group. **Response rates**: Tai Chi: 24%, completers = 26%, non-completers = 14%, control = 0% (*p*=.15) -> positive, but no statistical significance. **Remission rates**: Tai Chi: 19%, completers = 21%, non-completers = 14%, control = 0% (*p*=.30). -> positive but no statistical significance.

	between-group differences -> no statistical significance.		study completion: attending at ≥15 sessions.	=> results show trends towards symptom reduction in the Tai Chi group compared to the control, but statistical significance was not given.
		Further collected data: Q-LES, MSPSS.		**Notes:** -positive treatment response was defined by a decline of HAM-D17 score of ≥50%. -remission was defined as a score of ≤7 on HAM-D.
Hein E. et al. 2013 (95)	**Diagnosis:** MDD (ICD-10 + DSM-IV). **Study size:** N = 37. **Demography:** Sex: female: 22, male: 15. Age: M=46,96y. Profession: employee: 14, unemployed: 11, retired: 6, non-skilled worker: 2, self-employed 2, manager: 1, not available: 1. Episode: single: 12, recurrent: 25. **Note:** no significant differences in groups at baseline (sex, type of depression, age, current episode, total years from onset).	**Questionnaires:** HAM-D, BDI. **Assessment points**: day 0 + 14.	tVNS vs. sham tVNS. **Duration:** 2wk (5d/wk) -study 1: N = 22; stimulation once per day (N=11 each group). -study 2: stimulation once (N=6) or twice (N=9) per day (tVNS N=7, sham N=8). **Randomization:** alternated randomization. **Blinding:** single-blind (patients). **Follow-up:** no (posttreatment -> day 14). **Note:** two studies.	**Adverse events:** no AE reported. **Drop-out:** no. **Depression** -HAM-D -> significant decline in both groups, no significant changes between groups (U=161, n.s.). -BDI -> mean decrease M=-12.6, SD=6.0 points tVNS group vs. M=-4.4, SD=9.9 sham group. -pooled data (N=37) -> significant fall of mean BDI scores: M=-12.6 in the tVNS group (t=8.7, *p*<.0001), whereas the sham group reached no statistical significance (mean fall M=-4.4, n.s.). -change differences in BDI scores between groups were significant (U=265.0, *p*=.004). => significant antidepressant effect in patients with MDD.
Sharma A. et al. 2017 (96)	**Diagnosis:** MDD (DSM-IV) with inadequate response to antidepressant treatment. **Study size:** N = 25 (23 completed = 92%). **Demography:** Sex: female: 18, male: 7. Age: SKY: M=39.4y, control: M=34.8y. Caucasian: N=23, African Asian: N=2. Education: high school: N=4, college: N=14, graduate: N=7. Duration of current episode: 0-6m: 9, 6-12m: 9, >12m: 7. Number of lifetime episodes: SKY M=5.6, SD=3.1; control M=5.3, SD=2.5.	**Questionnaires:** HAM-D_{17}, BDI. **Assessment points:** baseline, 1m + 2m + log sheet -> adherence. Further collected data: BAI.	SKY (N = 13, 1 completed) vs. waitlist control (N = 12, all completed). **Duration:** 8wk -phase 1 = week 1-> 6 sessions SKY (Yoga postures, meditation + stress education) à 3,5h/d -phase 2 = week 2-8 -> weekly SKY follow-up sessions à 20-25min + home practice. **Randomization:** software with randomized blocks (age + sex = blocking factors). **Blinding:** single-blind (rater). **Follow-up:** no (posttreatment -> 2m).	**Adverse events:** no AE reported. **Drop-out:** 23% SKY, 0% control. **Depression** -HAM-D_{17} -> mean fall from baseline to 2 months: M=-9.77 (completer: M=-11.55) in the SKY group vs. M=0.50 control (*p*=.0032, completer: *p*=.0014). -> greater reduction in the SKY group. -BDI -> mean fall from baseline to 2 m: M=-17.23 (completer: M=-20.36) in the SKY group vs. M=-1.75 control (*p*=.0101, completer: *p*=.0043). -> greater reduction in the intervention group. **Response rates**: SKY 46.15% (completers 54.54%) vs. control 8.33%. **Remission rates**: SKY 30.77% (completers 36.36%) vs. control 8.33%.

Bormann J. et al. 2018 (97)	**Diagnosis:** PTSD (CAPS). **Study size:** N = 173 (141 completed = 81.5%). **Demography:** Veterans (military trauma). Sex: male: 147, female: 26 Age: M=48.9y, SD=14.54y. MRP vs. PCT Hispanic: 15% vs. 20%. Race (self-reported): White: 67% vs. 61%, African American: 16% vs. 13%, American Indian/Alaska Native: 2% vs. 5%, Native Hawaiian/Pacific Islander 1% vs. 7%, Asian 4% vs. 2%, more than one race 10% vs. 12%. Married/partnered: 34% vs. 33%. Education: high school or less: 26% vs. 24%, some college: 46% vs. 61%, bachelor's degree or higher 28% vs. 15%. Employment: full-time: 16% vs. 15%, part-time: 4% vs. 11%, unemployed: 80% vs. 74%. Income: ≤$20K 30% vs. 41%, $20-40K 40% vs. 26%, >$40K 30% vs. 33%. Receiving medications (PTSD): 66% vs. 64%. **Note:** no significant differences between groups at baseline. Completers + non-completers: significant baseline differences in age. In MRP arm: age + baseline CAPS -> significant difference (younger age -> rather dropout).	**Questionnaires:** CAPS, PCL-M, PHQ-9, STAI. **Assessment points**: baseline, posttreatment (week 9) + follow-up (week 17). -self-reported Mantram sessions. Further collected data: Insomnia Severity Index, short form, FACIT-Sp, FFMQ, WHOQOL brief form. **Note:** clinically meaningful improvements: ≥10-point CAPS.	MRP (N =89, 69 completed, 65 completed follow-up) vs. Present-Centered Therapy (PCT, N = 84, 72 completed, 71 completed follow-up). **Duration:** 8wk (8 weekly sessions à 60min). **Follow-up:** 8wk posttreatment (16wk from baseline). **Randomization:** computer-generated numbers (prescribed medication for PTSD yes/no -> separate blocks). **Blinding:** single-blind (raters).	**Adverse events:** four AE, all were rated as not being associated with the study protocol. **Drop-out:** at posttreatment 22.5% MRP, 14.3% PCT (*p*=.16), at follow-up MRP 26% vs. PCT 15% -> no significant difference between groups. **Attendance:** 7.80/8 sessions on average in MRP completers vs. 7.75/8 sessions in PCT completers. Home practice: 6d/wk with 10 sessions/d on average during the last week of treatment. No significant correlation between practice frequency and PTSD symptoms (beta=-1.84, *p*=.39). **Subjective stress (PTSD)** -CAPS -> mean decrease from baseline: to posttreatment M=-25.07, to follow-up M=-26.85 MRP (d=.49) vs. M=-13.54, M=-16.61 (d=.46) PCT -> MRP group showed significantly larger improvements with moderate effect size. -clinically meaningful changes: 75% MRP vs. 61% PCT -> no significant difference. -PCL-M -> mean decrease from baseline to posttreatment M=-13.91 and to follow-up M=-14.49 (d=.43) MRP vs. M=-7.37, M=-9.15 (d=.33) -> difference between groups significant at posttreatment, not at follow-up. -STAI-S/State anger -> mean reduction from baseline: M=-2.22 at posttreatment, M=-2.21 at follow-up in the MRP group and M=-0.8, M=-1.73 in the PCT group (effect size d=.11 at posttreatment, d=.03 at follow-up). -STAI-T/Trait anger -> mean reduction from baseline: M=-1.44 at posttreatment, M=-2.81 at follow-up in the MRP group and M=-1.52, M=-3.27 in the PCT group (effect size d=.03 at posttreatment, d=.06 at follow-up). **Depression** -PHQ-9 -> mean reduction from baseline: M=-4.74 at posttreatment, M=-4.91 at follow-up in the MRP group and M=-2.34, M=-2.97 in the PCT group (effect size d=.31 at posttreatment, d=.2 at follow-up). **Remission rates:** 59% MRP vs. 40% PCT (*p*<.04) at follow-up -> significant difference between groups. => MRP might be effective in reducing PTSD symptoms.

Bormann J. et al. 2013 (98)	**Diagnosis:** PTSD (CAPS). **Study size (N):** N = 146 (137 completed =93%). **Demography:** Veterans (military trauma). Sex: female: 4, male: 142. Age: M=57y, SD=10.10y. Years of education (7-21): M=14, SD=2.13. Years in military[a] (1-30): M=8, SD=7.33. Months in combat[a] (0.5-84): M=13, SD=9.94. Years of PTSD (0.5-63): M=32, SD=11.95. Ethnicity: White 58%, African American 25%, Hispanic 10%, other: 7%. Marital status: not married/partnered 49%, married/partnered 51%. Employment: none 61%, some 39%, wounded (yes) 44%. Antianxiety: 10%; antidepressants: 83%. Religious[a] (yes): 80%, spiritual[a] (yes): 77%. Current MDD: 80%, dysthymic disorder: 62%, obsessive-compulsive disorder (34%), generalized anxiety disorder: 56%. [a]: missing data for this variable. **Note:** no significant differences in demographic or outcome variables between the completers and non-completers.	**Questionnaires:** CAPS, PCL. **Assessment points**: pretreatment + posttreatment + 6wk follow-up CAPS (videotaped). Mantram practice -> wrist worn counter (golf scorer) + daily tracking-log (-> number of sets). Monitoring of provider visits + changes in medication. Further collected data: BSI-18, SF-12, FACIT-Sp. **Note:** clinically meaningful improvement in PTSD symptom severity: ≥10-point reduction on the CAPS + a score ≤45.	MRP + TAU (N=71, 66 completed) vs. TAU (N=75, 70 completed). **Duration:** 6wk (6 weekly sessions à 90min). **Follow-up:** 6wk posttreatment (12wk from baseline). **Randomization:** computer-generated random numbers. **Blinding:** single-blind (raters).	**Adverse events:** no AE reported. **Drop-out**: 7% in both groups. Medication changes: 20 (MRP) vs. 16 (TAU), 21 (MRP) vs. 28 (TAU) case management visits. **Adherence**: mantram practice in last week-> M=7.60, SD=6.47, (Mdn=7.0) sessions/d (1-40), M=6.30 d/wk, SD=1.02, (Mdn=6.0, 3-7d/wk). 97% in MRP+TAU -> moderate or high treatment satisfaction. **Subjective stress (PTSD)** -CAPS -> mean reduction from baseline to posttreatment M=-16.92, and to follow-up M=-21.26 MRP vs. M=-10.24 TAU posttreatment -> significantly larger improvement in MRP group. -pretreatment: score in the “very severe” range (M=82.95, SD=17.86). -clinically meaningful improvement at posttreatment: 24% MRP vs. 12% TAU (p=.047). -PCL -> mean reduction from baseline to post-treatment M=-5.62, and to follow-up M=-6.46 vs. M=-2.47 TAU (p<.05) -> significantly larger improvements in MRP group. => MRP might be effective and beneficial for treating PTSD symptoms.
Polusny M. et al. 2015 (99)	**Diagnosis:** PTSD (full or subthreshold DSM-IV). **Study size:** N = 116 (99 completed = 85.3%). **Demography:** Veterans (military trauma). Sex: female: 18, male: 98 (women 10.3% (PCT) vs. 20.7% MBSR). Age: M=58.5y, SD=9.8y. PCT vs. MBSR Race: White 86% vs. 81%, African American 10.3% vs. 5.2%, American	**Questionnaires:** PCL, CAPS, PHQ-9. **Assessment points:** baseline, during treatment (week 3+ 6), posttreatment (week 9) + 2-month follow-up (week 17). **Note**: minimal clinically important	MBSR (N = 58, 45 completed) vs. PCT (N = 58, 54 completed). -completed = ≥ 7 sessions. **Duration:** 8wk (9 sessions 8 weekly 2.5h group sessions and 1 daylong retreat) PCT: 9 weekly 1.5h group sessions focused on current life problems -> (13h less contact time). **Follow-up:** 2m posttreatment (week 17).	**Adverse events:** one serious AE in the PCT group (suicide attempt). **Drop-out:** higher in the MBSR group (23% vs. 7%). **Subjective stress (PTSD)** -PCL -> mean change from baseline: M=-7.9 at posttreatment, M=-9.2 at follow-up in the MBSR group vs. M=-3, M=-2 in the PCT group (between-group difference 4.95, p=.002; mean difference improvement, 6.44, p<.001, d=.40). -> MBSR greater improvement. -clinically important symptom reduction: 48.9% MBSR vs. 28.1% PCT (p=.03).

	Indian 3.4% vs. 0%, mixed ethnicity 0% vs. 10.3%. **Notes:** no significant differences between groups except for ethnicity + sex. MBSR group: more frequent sexual trauma 37% (vs. 19% PCT) + greater severity of PTSD symptoms at baseline (PCL mean score 63.6 vs. 58.8 PCT; CAPS mean score 69.9 vs. 62.5 PCT).	difference (MCID): PCL reduction of ≥ 10 points.	**Randomization:** SAS PROC PLAN (blocks of 4). **Blinding:** single-blind (raters).	-CAPS -> mean change from baseline: M=-13.6 at posttreatment, M=-20.1 at follow-up in the MBSR group vs. M=-10.8, M=-11.9 in the PCT group (significant group x time interaction *p*=.03; mean difference in improvement, t=2.91; *p*=.004; d=.41). -> both groups show significant improvement, which was larger in the MBSR group, but both groups show a similar percentage in significant symptom reduction at follow-up. **Loss of Diagnosis:** insignificant (53.3% MBSR bs. 47.3% PCT; difference, 6.0%; *p*=.55). **Depression** -PHQ-9: mean change from baseline: M=-1.9 at posttreatment, M=-2.2 at follow-up in the MBSR group and M=-0.7, M=-0.8 in the PCT group (mean difference in improvement, 1.34, t=1.87, *p*=.06, d=.26) -> MBSR larger improvement, but no statistical significance. => study results show a modest effect for MBSR. MBSR might be beneficial as a treatment option for patients suffering from PTSD.
Rees B. et al. 2013 (100)	**Diagnosis:** PTSD (PCL-C≥40). **Study size:** N = 42 (100% completed PCL-C scores at baseline, 30d + 135d). **Demography:** Refugees from eastern Democratic Republic of Congo. Sex: female: 16, male: 26. Age: TM: M=32.8y, SD=7.3y, delayed start: M=31.2y, SD=7.8y. Temporarily based in Kampala in shelters, commonly unemployed, basic entry to mental health supply.	**Questionnaires:** PCL-C. **Assessment points**: baseline, 30d + 135d posttest. **Note**: clinically significant: PCL-C reduction of ≥ 10 points.	TM (N=21, 100% completed) vs. waitlist control (N = 21). **Duration:** 5 sessions (1h introductory lectures, 1,5h personal instruction + 3 2h follow-up meetings). **Follow-up:** 135d posttest. **Randomization**: 1) computer-generated numbers (stratified on PCL-C, age + sex). 2) 30 participants of the TM group have not appeared for the instruction. 21 TM participants were paired with 21/51 participants of waitlist group regarding age, sex + PCL-C scores. **Blinding:** single-blind (test administrators).	**Adverse events:** no AE reported. **Drop-out:** no dropout. **Adherence:** “good”. 50% of participants meditated 2/d, the other half ≥ 1/d. **Subjective stress (PTSD)** -PCL-C -> mean change from baseline: M=-36 at day 30 and M=-38.5 at day 135 in the TM group vs. M=+6.8 and M=+6 in the control. -> scores in the TM group showed a significant reduction (*p*=.003) whereas the score of the control group increased (*p*=.45). -significant group × PCL score interactions (*p*<.001). -effect size: d>1.0 = high.

Nidich S. et al. 2018 (101)	**Diagnosis:** PTSD (CAPS ≥ 45). **Study size:** N = 203 (166 completed = 82%). **Demography:** Veterans (military trauma). Sex: female: 34, male: 168. TM vs. PE vs. HE Age: M=46,4y, SD=14.3y vs. M=48,5y, SD=15.6y vs. M=46.2y, SD=16.4y. Married/partner: 53% vs. 52% vs. 55%. Race: Black: 30% vs. 21% vs. 27%, Hispanic: 12% vs. 31% vs. 24%. Asian: 7% vs. 4% vs. 9%, White: 56% vs. 63% vs. 49%, Native American: 0% vs. 3% vs. 5%, other: 7% vs. 9% vs. 11%. Combat duty: 49% vs. 52% vs. 53%. Years of active duty: M=8.8, SD=6.8 vs. M=10.5, SD=8.2 vs. M=9.1, SD=7.7. Combat exposure: 82% vs. 85% vs. 86%. Years since military release: M=17.9, SD=15.7 vs. M=18.3, SD=17.3 vs. M=17.9, SD=16.3. PTSD medication: 78% vs. 66% vs. 61%. For psychiatric comorbidities, Trauma events + detailed PTSD medications see (102).	**Questionnaires:** CAPS-IV, PCL-M, PHQ-9. **Assessment points**: CAPS at baseline + 3m posttest, PCL-M at baseline, week 4, 6, 8, 10 + at 3m posttest. Further collected data: POMS, Q-LES. **Note:** minimal standard for clinically significant improvement in PTSD symptoms: CAPS + PCL-M decrease of ≥10 points +PHQ-9 decrease of ≥5 points.	TM (N = 68, 53 completed post-testing) vs. PE (N = 68, 57 completed post-testing) vs. Health Education (HE; N = 67, 56 completed post-testing). **Duration:** 12wk -TM: 12 sessions à 90min (multiple sessions in the first week + subsequent distributed sessions in following weeks). -PE + HE: weekly treatments for 12wk. **Follow-up:** 3m posttest. **Randomization:** stratified block randomization (gender + years since military service dismissal). **Blinding:** single-blind (raters).	**Adverse events:** no treatment-related AE, but 3 serious AE in TM (1 non-suicidal death, 2 suicide attempts), 2 in PE (drug overdose + illness), 2 in HE (psychiatric hospitalization). **Drop-out:** 22% TM, 16% PE, 16% HE. **Adherence**: sessions attended + frequency of home-practice (self-report). **Subjective stress (PTSD)** -CAPS -> mean reduction from baseline to 3m posttest: M=-16.1 (p<.0001) TM group, M=-11.1 PE group (p=.0006), M=-2.5 HE group. -> significant improvement in TM + PE group -clinically significant improvement: 61% TM, 42% PE, 32% HE. -PCL-M: -> mean reduction from baseline to 3m posttest: M=-13.4 TM group (p<.0001), M=-10.7 PE group (p<.0001), M=-3.4 HE group (p=.058) -> significant improvement in all groups. **Depression** -PHQ-9: -> mean reduction from baseline to 3m posttest: M=-6.8 (p<.0001) TM group, M=-4.9 PE group (p<.0001), M=–1.9, (p=.028) HE group -> significant improvement in TM +PE. -effect sizes: TM 0.9-1.2, PE 0.63-0.89, HE 0.14-0.34. Larger when attended at ≥8 sessions.
Mitchell K. S. et al. 2014 (102)	**Diagnosis:** PTSD (positive on PC-PTSD screen -> diagnostic assessments SCID -> DSM-IV + PSS-I). PCL total mean -> 51.94. 29 (70.7%) met the full criteria for PTSD according to PSS-I, 9 (22%) subthreshold PTSD; + 34,2% met criteria for MDD. **Study size:** N = 38 (32 completed = 84%). **Demography:** Sex: female only Age: M=44.7y, SD=12.37y. 9 veterans (M=49.67y), 29 civilians (M=42.72y). Yoga vs. control	**Questionnaires:** PSS-I, SCID-I/P -> diagnosis, PCL-C, STAI. **Assessment points**: -TLEQ + demographic assessment at baseline. -PSS-I at baseline. -PCL, STAI: baseline, postintervention, 1-month follow-up. -PCL weekly:	Kripalu Yoga (N = 20, 14 completed) vs. assessment control (N = 18, 12 completed). **Duration:** 6wk/12wk (12 sessions à 75min sessions), either twice per week for 6wk (biweekly group; N = 11) or once per week for 12wk (weekly group; N = 9). **Follow-up:** 1-month postintervention. **Randomization:** random numbers function (Microsoft Excel). **Blinding:** no blinding.	**Adverse events:** no AE. **Drop-out:** 30% Yoga, 33.3% control. **Subjective stress (PTSD)** -PCL -> mean reduction from baseline: M=-12.87 at postintervention, M=-11.03 at follow-up in the Yoga group and M=-14.35, M=-11.26 In the control group -> significant improvement in both groups. Individual calculations: significant results in the Yoga group, marginally significant results in the control group. -STAI-S -> mean reduction from baseline: M=-5.75 at postintervention, M=-10.9 at follow-up in the Yoga group and M=-7.24, M=-6.11 in the control group -> significant improvement, but group-impact was nonsignificant (B=0.01, t=0.35, p=.727). Separate calculations: significant improvement in scores of the

	Race/ethnicity: White/Caucasian 60% vs. 44.4%, Black/African American: 30% vs. 44.4%, Asian American: 0% vs. 11.1%, mixed/ others: 10% vs. 0%. Years of education: high school diploma: 10% vs. 0%, some college: 20% vs. 61.11%, 4y-degree: 30% vs. 22.2%, postbaccalaureate degree: 40% vs. 16.7%. ≥1 previous Yoga class: 45% vs. 50%. Regular Yoga practice: less than 1 month: 76.9% vs. 63.6%; 1.5m: 7.7% vs. 0%, 3m: 7.7% vs. 18.2%, 6m: 0.0% vs. 9.1%, 24m: 0.0% vs. 9.1%, 29m: 7.7% vs. 0.0%. Prior mental health contact: 85% vs. 82.4%. PTSD psychotherapy: 46.7% vs. 25.7%. **Note:** no significant differences in ethnicity, education, previous Yoga practice, or baseline scores, but in age between groups.	sessions 1, 3, 5, 7, 9, 11. -control group: 12 weekly assessment sessions. Further collected data: PC-PTSD, TLEQ, CES-D.		control group, but not of the Yoga group. Between-group effect size: .12 = small. -<u>STAI-T:</u> -> mean reduction from baseline: M=-4.62 at postintervention, M=-8 at follow-up in the Yoga group, and M=-7.8, M=-6.44 in the control group -> significant decrease in both groups, but no group effect (B=0.01, t=0.38, *p*=.704). Separate calculations: significant improvement in scores of the control group, but not of the Yoga group. Between-group effect size: .10 = small. => differences between the Yoga group and the control group were not significant. Effect sizes between the groups were small to moderate (d=.08-.31). **Note**: *p*<.01 = considered significant.
Gurel N. Z. et al. 2020 (103)	**Diagnosis:** PTSD (SCID Interview DSM-IV, CAPS). **Study size:** N = 25. **Demography:** Sex: female: 19, female: 6 Age: M=35y, SD=13y.	**Questionnaire:** CAPS. **Measurements:** -HR + (HF + LF) HRV: calculated by using the R-peaks of the ECG -> SD1/SD1. -HR-PET. Further collected data: SCG, RSP, BP (SBP + DBP), PEP, amplitude of PPG, PAT, RR, RW, RP.	tVNS (N=13) vs. sham tVNS (N= 12). **Duration:** 3d -1st day: before the first scan: baseline physiological and blood data were collected. Scan 1 + 2: "neutral" pleasant scenery recordings delivered audibly. Scans 3 + 4: traumatic stress recordings were delivered immediately followed by stimulation -> 90min break -> 4 more scans (2 neutral + 2 traumatic recordings) -> stimulation. -2nd + 3rd day: the same -> no PET. More non-personalized mental stressors (public speech -> self-defending after being	**Adverse events:** not mentioned. **Drop-out:** not mentioned. **Physiological measurements:** -<u>without acute stress</u>**:** tVNS reduces SNS-tone in the absences of stress throughout multiple days when compared to sham -> increase in SD1/SD2 (poststimulation, β=14.1%, d=.43, *p*=.019), decrease in HR (following stimulation, β=2.7%, d=.21, *p*=.009) -> active group experienced a change trending towards parasympathetic dominance (increased HRV, reduced HR). -no significant changes in other measures regarding the type of HRV (LF, HF, LF/HF), RSP (RR; RW, RP), and BP (SBP, DBP, PP). <u>-during exposition to trauma scripts</u>: tcVNS paired with personalized traumatic scripts decreased HR (adjusted β=5.7%, d=.43, *p*=.003 during stimulation; β=3.9%, d=.29, *p*=.013 post-stimulation) + sympathetic function. -the reduction of SNS activity persisted throughout several days.

			accused of thievery + arithmetic questions, accompanied by negative feedback for mistakes). **Follow-up:** no. **Randomization:** simple randomization with group allocation by using an online tool. **Blinding**: double-blind during the intervention period, single-blind (un-blinding of raters) during the interpretation period.	-with acute stress -> mental stressors stimulation was applied after the tasks and showed increased SD1/SD2 after the public speech (during stimulation: β=23.1%, d=.71, *p*=.033) and after the math test (during stimulation, β=41.2%, d=.44, *p*=.001). -> tVNS combined with mental stress led to reduced SNS activity compared to the sham. -no significant results in further measures (*p*>.05). => tVNS might be beneficial for enhancing resilience regarding handling of repeated stress and physiological measures might serve for monitoring the therapy response.
Kearney D. J. et al. 2013 (104)	**Diagnosis:** PTSD (established diagnosis of chronic PTSD). **Study size:** N = 47 (43 completed, 91,5%). **Demography:** Veterans (military trauma). Sex: male: 37, female: 10 Age: M=52y, SD-MBSR=13.4y, SD-TAU=11.7y. MBSR vs. TAU Ethnicity/Race: Caucasian: 76% vs. 59.1%, African American: 20% vs. 9.1%, Hispanic/Latino: 0% vs. 13.6%, Asian/ Pacific: 0% vs. 13.6%, other: 4% vs. 4.5%. Religion: Christian: 52% vs. 59.1%, Buddhist: 4.0% vs. 0%, other: 8% vs. 22.7%, unknown: 44% vs. 22.7%. Number of lifetime trauma exposure: M=10, SD=5 (both groups). For detailed psychotropic medication, psychotherapy sessions, and mental health services (105). **Note:** no significant differences at baseline regarding PTSD (PCL) or depression (PHQ-9).	**Questionnaires:** PCL-C, PHQ-9 **Assessment points:** baseline, posttreatment (2m after baseline) + 4-month postintervention = follow-up. Further collected data: HRQOL, SF-8, FFMQ, BADS, LEC.	MBSR (N=25, 21 completed) vs. TAU (N=22). **Duration:** 8wk (2,5h weekly for 8wk + one 7h session on a Saturday + homework -> daily meditation or Yoga for 45min for 6d/wk). **Follow-up:** 4 months postintervention. **Randomization:** concealed allocation. **Blinding:** not mentioned.	**Adverse events:** not mentioned. One Patient in each group experienced worsening of symptoms (inpatient psychiatry) and was discharged. TAU: participants received more benzodiazepines. **Drop-out:** 16% MBSR, 4.5% TAU. **Adherence:** 84% attended at ≥4 classes = compliant, M=7, SD=2, Modal=9 (=all sessions). **Subjective stress (PTSD)** -PCL -> mean reduction from baseline: at posttreatment M=-7, at follow-up M=-5 for the MBSR group and M=-4, M=-3 for the TAU group. -clinically significant change in symptom severity at posttreatment: 36.4% MBSR vs. 25% TAU (*p*=.426) and at follow-up 39.1% MBSR vs. 26.3% TAU (*p*=.381) -> no significant difference between groups. -within-group effect sizes: the MBSR group reached medium-to-large effect sizes at posttreatment (d=−.63, *p*=.035) and contained zero at follow-up, whereas the TAU group effect sizes always contained zero. -between-group effect size: the 95% CIs contained zero at posttreatment + follow-up. **Depression** -PHQ-9 -> mean reduction from baseline: at posttreatment M=-3, at follow-up M=-3 for the MBSR group and M=-2, M=-1 for the TAU group. -within-group effect sizes: the MBSR group showed medium-to-large effect sizes (d=−0.65, *p*=.033) at posttreatment and contained zero at follow-up. The

				effect sizes of the TAU group always contained zero. -between-group effect sizes: medium-to-large effect size at posttreatment, but at follow-up the 95% CIs contained zero. => the analysis of the Intention-to-treat sample revealed no dependable effects of MBSR on MDD or PTSD, whereas the analysis of the completer sample detected medium to large effect sizes between groups for MDD.
Jindani F. et al. 2015 (105)	**Diagnosis:** PTSD (PCL-17 ≥57). **Study size:** N = 50 completed. **Demography:** Sex: female: 71, male: 9. Age: M=41y. Yoga vs. control PTSD diagnosis: 64% vs. 57%. Therapy: current: 39% vs. 57%, past: 17% vs. 19%, none: 44% vs. 24%. Yoga practice: past: 19% vs. 5%. Meditative practice: 15% vs. 0%. Prescribed medication: 49% vs. 43%. **Note:** PCL-scores higher in Yoga group (M=59.48, SD=9.33) vs. control (M=55.14, SD=11.86).	**Questionnaires:** PCL-17, PSS **Assessment points**: pretreatment, mid-treatment, end-of-treatment. Further collected data: DASS 21, RS, PANAS, FFMQ, ISI.	Kundalini Yoga (N = 29, 4 males (7%)) vs. waitlist control (N = 21, 5 males (24%)). **Duration:** 8wk (90min weekly sessions, encouraged to devote 15min/d at home). **Follow-up:** no (after treatment -> 8wk from baseline). **Randomization:** random number generator. **Blinding:** no (rater side not mentioned).	**Adverse events:** not mentioned. **Drop-out:** 31% Yoga. **Subjective stress (PTSD)** -PCL -> mean reduction from baseline: M=-11 at midtreatment, M=-17.7 end-of-treatment in the Yoga group and M=-2.6, M=+0.3 in the control group -> significantly lower scores in the Yoga group (p<.05). -PSS -> mean reduction from baseline: M=-9.5 at midtreatment, M=-12.5 end -of-treatment in the Yoga group and M=-3, M=-3.2 in the control group. -> significant improvement of scores in the Yoga group (p<.05) compared to the control group which showed a marginal reduction.
Bergen-Cico D. et al. 2014 (106)	**Diagnosis:** PTSD (CAPS). **Study size:** N = 40 (30 completed = 75%). **Demography:** Veterans (military trauma). Sex: female: 2, male: 38. Age: M=48y. Ethnicity: White: 80%. **Note:** no significant differences at the baseline.	**Measurements**: salivary diurnal cortisol (n = 5/d at specified times for 2 following days -> 10 samples). **Assessment points**: baseline + 4wk from the start of the intervention (= follow-up). **Questionnaire**: PCL, CAPS, PHQ-9.	Primary Care brief Mindfulness Program (PCbMP, N = 19, 9 completed) + TAU vs. TAU (N = 21). **Duration:** 4wk (4 weekly sessions in-person à 1,5h). **Follow-up:** 12wk from baseline (+4wk salivary diurnal cortisol). **Randomization:** method unclear. **Blinding:** unclear. **Note:**	**Adverse events:** not mentioned. **Drop-out:** 53.6 % PCbMP, 0% TAU. -3 groups in the final analysis: PCbMP completers, PCbMP non-completers (1-3 sessions), PC-TAU. -no correlation between compliance with cortisol collection procedures and baseline PTSD severity (r=.04, p=.8) or depression (r=-.07, p=.6). **Cortisol** -between-group discrepancies: group x time -> significant treatment effect on AUC_i[a] (p=.01) with a significant gain in AUC_i within the TAU group (M=-88, SD=135 to M=-154, SD=480), at the same time the MBSR AUC_i dropped from baseline (M=-78, SD=72) to follow-up (M=-61, SD=132). -AUC_g[b] + CAR[c] -> not significant.

		Assessment points: baseline, week 4 + 12 (=follow-up).	-PCBMT group -> more contact time. -study completion: attending all 4 sessions.	-<u>within-group discrepancies</u>: a significant reduction in CAR by a mean of 0.2µg/dL, $p \leq .05$ took place in participants, who completed 4 sessions. Additionally the cortisol AUC_i showed significant changes in comparison to TAU participants ($p \leq .05$). The CAR of the TAU group and non-completers had no significant changes. Additionally, all other cortisol measures were not significant in non-completers. => study shows that with a minimum of 4 weeks of practice, PCbMP might be beneficial (dosing effect?). -<u>scores</u>: the groups did not show a significant correlation between cortisol (CAR, AUC_i, AUC_g) and questionnaire outcome (PHQ-9, PCL), but individual analyses showed a significant negative correlation in changes in AUC_i and PHQ-9 (-0.39, p=.02). [a]: AUCi -> area under the curve increase. [b]: AUCg -> area under the curve ground. [c]: cortisol awakening response.
Possemato K. et al. 2016 (107)	**Diagnosis:** PTSD – full or subthreshold (CAPS). **Study size:** N = 62 (50 completed = 80.6%). **Demography:** Veterans (military trauma). Sex: female: 8, male: 54. Age: M=46.4y, SD=16.3y Race: White: 87.1%; Hispanic: 3.2%. Partnered: 70%. Employed: 36.8%. Education: M=14.2y, SD=2.0y (range: 10-18y). Annual income: M=$46K, SD=$29K (range $9K-$110K). Iraq/Afghanistan: 41.9%. Diagnostic PTSD: 48.8%.	**Questionnaires:** CAPS, PCL-S, PHQ-9. **Assessment points:** baseline, posttreatment + 8wk. postbaseline = follow-up. Further collected data: MAAS, FFMQ. **Note**: clinically significant decrease in PTSD severity: decrease of ≥15 points on the CAPS or ≥10 points on the PCL.	Brief Mindfulness Training (BMT, N = 36, 29 completed all assessments) vs. TAU (N = 26, 21 completed all assessments). **Duration:** 4wk (4 weekly in-person sessions à 1,5h). **Follow-up:** 8wk from baseline. **Randomization:** 1:1 randomization -> diagnostic-level or subthreshold PTSD. **Blinding:** single-blind (research staff, study coordinator was unblinded).	**Adverse events:** no AE related to the study. **Drop-out:** 19.5% BMT, 19.3% TAU. **Attendance:** ≥3/4 sessions -> clinically significant decrease in symptoms (PTSD + depression). **Subjective stress (PTSD)** -<u>CAPS</u> -> mean reduction from baseline: M=-8.4 (completers M=-13.7) at posttreatment in the BMT group and M=-6.3 (completers: -11.4) in the control group. Between-group effect size: p=.34, d=.24. -medium to large effect sizes for completion on PTSD. -> completers: significantly greater decreases. 75% of the completers showed a clinically significant decrease in symptoms from pre- to posttreatment and maintained gains at follow-up. -<u>PCL-S</u> -> mean reduction from baseline: M=-7.4 at posttreatment, M=-6 at follow-up in the BMT group and M=-7, M=-7.6 in the control group. Effect size (between BMT + TAU) p=.63, d=.26 -> similar reduction of PTSD severity in both groups. **Depression** -<u>PHQ-9</u> -> mean reduction from baseline: M=-3.4 at posttreatment, M=-2 at follow-up in the BMT group and M=+0.5, M=-0.1 in the control group. Effect size (between BMT + TAU) p=.04, d=.86 -> significant decline of symptoms (BMT) compared to

				TAU from pre- to posttreatment. Improvement was maintained at follow-up. Both groups were comparable at follow-up. PHQ-9 mean scores in the completer sample declined from the “moderate severity” level (pretreatment) to the “mild severity” level (posttreatment). -completers: medium to large effect sizes.

Note. Description of abbreviations of the following questionnaires used for assessment in studies: BAI (Beck Anxiety Inventory), BADS (Behavioral assessment of Dysexecutive Syndrome), BSI-18 (Brief Symptom Inventory – 18-items), CES-D (Center for Epidemiologic Studies – Depression scale), DASS-21 (Depression Anxiety Stress Scale (72)), FACIT-Sp (Functional Assessment of Chronic Illness Therapy – Spiritual Well-Being), FFMQ (Five Facet Mindfulness Questionnaire), HADS (Hospital Anxiety and Depression Scale), HRQOL (Health-Related Quality of Life), ISI (Insomnia Severity Index), MAAS (Mindful Attention Awareness Scale), MSPSS (Multidimensional Scale of Perceived Social Support), LEC (Life Events Checklist), PANAS (Positive and Negative Affect Schedule), PC-PTSD (Primary Care PTSD Screen), POMS Profile of Mood State), Q-LES (Quality of Life Enjoyment and Satisfaction), RS (Resilience Scale, 25-items), SF-8, SF-12, SF-12v2 (Short Form Health Survey, 12-item; 8-item; v2 = Version 2), TLEQ (Traumatic Life Events Questionnaire), WHOQOL (World Health Organization Quality of Life).

Description of abbreviations of physiological parameters (Gurel et al. 2020): BP (Blood Pressure), DBP (Diastolic Blood Pressure), ECG (Electrocardiography), HF (High-Frequency HRV), HR (Heart Rate), HR-PET (High-Resolution Positron Emission Tomography), LF HRV (Low-Frequency HRV), PAT (Amplitude Pulse Arrival Time), PEP (Pre-Ejection Period), PPG (Photoplethysmography), RP (Respiration Prominence), RSP (Respiration), RR (Respiratory Rate), RW (Respiration Width), SBP (Systolic Blood Pressure), SCG (Seismocardiography), SD1/SD2 (non-linear HRV).

Further abbreviations used in Table 3: CIs (Confidence Intervals), d (days), h (hour(s)), K (thousand), M (Mean), m (month), Mdn (Median), min (minutes), n.s. (non-significant), SD (Standard Deviation), wk (week(s)), y (year)

3.3 Study Types

All studies included in this review are RCTs. Four studies included participants with MDD and 11 studies included participants with PTSD, of which seven studies included only veterans. All the studies compared a nVNS method to a control group or a TAU group. Of the interventions that were analyzed, two were tVNS, one was Tai Chi, four were different forms of Yoga, four were different forms of Meditation, and four were different mindfulness programs. The most common study design was Intervention vs. TAU (six studies), followed by Intervention vs. waitlist control (four studies), Intervention + TAU vs. TAU (two studies), intervention vs. sham (two studies), and intervention vs. assessment control (one study). Of the 15 studies analyzed, 13 showed significant improvements in at least one psychometric or other measure compared to the control group. For an overview of the evaluated study outcomes, see Table 4.

Table 4. Overview of study outcome.

(↑) positive effect on symptoms, (-) no significant results, (n.s.) non-significant

Author/ Year of Publication	Psychometric instrument/ measure	Outcome Intervention group	Compared to the control group	Study design
Kumar S. et al. 2019 (93)	MADRS CGI	↑ ↑	-> significant differences between groups	Intervention + TAU vs. TAU
Yeung A. et al. 2012 (94)	HAM-D CGI-I/S	- -	-> n.s. differences between groups	Intervention vs. waitlist control
Hein E. et al. 2013 (95)	HAM-D BDI	↑ ↑	-> n.s. differences between groups -> significant differences between groups	Real vs. sham
Sharma A. et al. 2017 (96)	HAM-D BDI	↑ ↑	-> significant differences between groups	Intervention vs. waitlist control
Bormann J. et al. 2018 (97)	CAPS PCL-M	↑ ↑	-> significant differences between groups -> significant differences between groups at posttreatment, not at follow-up	Intervention vs. TAU
Bormann J. et al. 2013 (98)	CAPS PCL	↑ ↑	-> significant differences between groups	Intervention + TAU vs. TAU
Polusny M. et al. 2015 (99)	CAPS PCL PHQ-9	↑ ↑ ↑	-> significant differences between groups -> significant differences between groups -> n.s. differences between groups	Intervention vs. TAU
Rees B. et al. 2013 (100)	PCL-C	↑	->significant differences between groups	Intervention vs. waitlist control
Nidich S. et al. 2018 (101)	CAPS PCL-M PHQ-9	↑ ↑ ↑	-> significant differences between TM + HE groups -> n.s. differences between groups -> significant differences between TM + HE group	Intervention vs. TAU
Mitchell K. S. et al. 2014 (102)	PCL STAI-S STAI-T	↑ ↑ ↑	-> n.s. differences between groups	Intervention vs. assessment control
Gurel N. Z.	HR HRV	↑ ↑	-> significant differences between groups	Real vs. sham

et al. 2020 (103)				
Kearney D. J. et al. 2013 (104)	PCL-C PHQ-9	↑ ↑	-> n.s. differences between groups -> significant differences between groups at posttreatment, not at follow-up	Intervention vs. TAU
Jindani F. et al. 2015 (105)	PCL-17 PSS	↑ ↑	-> significant differences between groups	Intervention vs. waitlist control
Bergen-Cico D. et al. 2014 (106)	Cortisol	↑	-> significant differences between groups	Intervention vs. TAU
Possemato K. et al. 2016 (107)	CAPS PCL-S PHQ-9	↑ ↑ ↑	-> significant differences between completers and non-completers/control -> n.s. differences between groups -> significant differences between groups	Intervention vs. TAU

3.4 Results nVNS for MDD

All studies with MDD participants used only psychometric measures to evaluate the treatment effect, whereas the HAM-D (three studies) was the most common questionnaire applied followed by the BDI (two studies) and the CGI (two studies). One study applied the MADRS. Kumar S. et al. 2019 described significant decreases in MADRS and CGI scores in the Yoga group compared to the intervention group at day 30 with no significant differences in the drop-out rates between groups and no mentioned AE. Yeung A. et al. 2012 described no significant differences in the change of scores (HAM-D, CGI) between the intervention group (Tai Chi) and the control group, even though the Tai Chi group showed higher response and remission rates compared to the control group, but those were not statistically significant. No AE were reported and drop-out rates were higher in the Tai Chi group. Hein E. et al. 2013 described a significant reduction of HAM-D scores in both groups, but no significant difference between groups. The BDI score was significantly reduced in the tVNS group (intervention group) but not in the control group. No AE and no drop-outs were reported. Sharma A. et al. 2017 described significant falls in HAM-D and BDI scores in both groups with a greater reduction in the intervention group (SKY). Significantly higher response and remission rates are described in the intervention group. No AE were reported and drop-out rates were 23% in the intervention group compared to 0% in the control group.

3.5 Results nVNS for PTSD

The studies with PTSD participants in the first line applied psychometric instruments, but also cortisol measures (one study) and measures of the heart rate (HR) and HRV (one study). Of the used questionnaires the most common one was

the PCL (nine studies) followed by the CAPS (five studies), the PHQ-9 (four studies), the STAI (two studies), and one study applied the PSS.

3.5.1 Veteran Studies

The following studies which will be described included only veterans. Bormann J. et al. 2018 described a significantly greater reduction in CAPS scores in the intervention group (MRP) compared to a control group with moderate effect sizes, no significant differences in clinically meaningful changes between groups, a significant difference between groups in the PCL score at posttreatment but not at follow-up as well as significantly higher remission rates in the intervention group compared to the control group. The attendance at classes was overall the same in both groups and drop-out rates were higher in the intervention group, but not significantly. Four AE were described, all of which were rated as not being associated with the study. Bormann J. et al. 2013 described significantly larger improvements in CAPS scores of the intervention group (MRP) compared to the control group and a significantly higher rate of clinically meaningful improvement in the intervention group. Additionally, the PCL scores of the intervention group significantly improved compared to the control. No AE were reported, drop-out rates were similar in both groups, and participants of the intervention group indicated a high level of satisfaction. Polusny M. et al. 2015 described a significantly greater improvement in the PCL score in the intervention group (MBSR) compared to the control group and a significantly higher rate of clinically important symptom reduction in the intervention group. Both groups showed a significant improvement in the CAPS score, of which the MBSR group showed a larger improvement. The rate of loss of diagnosis was insignificant in both groups. The PHQ-9 scores of both groups showed a significant reduction, of which the MBSR group had a larger but insignificant improvement. One serious AE (suicide attempt) was reported in the control group and drop-out rates were higher in the MBSR group, even though the authors describe minor attrition rates compared to studies with veterans receiving PE only group therapy (99). Nidich S. et al. 2018 had three treatment arms. The study reported a significant improvement in the CAPS score of the TM and PE group as well as a clinically significant improvement in all groups, with the TM group having the highest rates. All groups showed a significant reduction in the PCL score. The PHQ-9 score was significantly reduced in the TM and the PE group. Drop-out rates

were similar in all groups, but highest in the TM group. There were three serious AE in the TM group, two in the PE group, and two in the HE group, all of which were judged not to be related to the treatment. Kearney D. J. et al. 2013 described medium to large effect sizes in the intervention group (MBSR) at posttreatment but contained zero at follow-up. In contrast the control group always contained zero, calculated with PCL and PHQ-9 scores. Both groups showed clinically significant changes in symptom severity, but there were no significant differences between the groups. Overall, in the intention-to-treat sample, no dependable effects of MBSR on MDD or PTSD were found. AE were not described, but one participant in each group was discharged due to worsening of symptoms and inpatient psychiatry treatment. Drop-out rates were higher in the MBSR group. Bergen-Cico D. et al. 2014 described significant changes in CAR and AUC_i in participants who completed the intervention compared to non-completers and the control group. Drop-out rates were high in the intervention group (PCbMP) compared to zero in the control group. No AE were mentioned. Possemato K. et al. 2016 described significantly larger improvements in CAPS scores of the completer sample of the intervention group (BMT) compared to the non-completers and the control group. Additionally, the majority of this sample showed a clinically significant symptom reduction. In PCL scores both groups showed a similar reduction of symptom severity. In the PHQ-9 score, the BMT group showed a significant decline of symptoms compared to the control group at posttreatment, but at follow-up both groups were comparable. Drop-out rates were similar in both groups and no AE were reported.

3.5.2 Civilian Studies

The following studies included civilians and partly veterans. Jindani F. et al. 2015 described a significantly larger reduction of PCL and PSS scores in the intervention group (Kundalini Yoga) than in the control group. No AE were mentioned. The Yoga group had a high drop-out rate compared to zero drop-out in the control group. Rees B et al. 2013 described a significant fall in PCL scores of the intervention group (TM), whereas the control group's scores increased. No AE or drop-outs were reported. Mitchell K. S. et al. 2014 described significant improvements in PCL scores in both groups with larger improvements in the intervention group (Kripalu Yoga) compared to the control group. The STAI-S and STAI-T scores showed no significant symptom reduction for the intervention group. Both groups had similar

drop-out rates and no AE were reported. Gurel N. Z. et al. 2020 reported a significant SNS-tone reduction in the tVNS group compared to the sham group in all scenarios: without acute stress, during the exposure to personalized trauma scripts and during the exposition to mental stressors. This article didn’t mention AE or drop-out rates.

4 Discussion

This thesis examined whether there are studies that show positive effects of nVNS methods on the symptoms of MDD, PTSD, and stress markers such as cortisol and HRV. The novelty value of this review is that vagus stimulation is considered more broadly than electrical stimulation. Various parasympathetic stimulation procedures were included in this review. The search with the selected operators yielded many results, only a few RCTs however, met the inclusion criteria. In total, 15 randomized controlled trials were examined.

4.1 Summary of the Results

4.1.1 MDD

Of the studies that included patients with MDD, three out of four studies showed significant improvements in scores of at least one psychometric test in the study population. In the between-groups comparison from baseline to postintervention two studies (93, 96) showed significant improvements in all applied scores (MADRS, CGI, HAM-D, BDI) in the intervention group, one study (95) showed significant improvements in one out of two scores (BDI significant: between-group difference p=.004, HAM-D n.s.) and one study (94) did not show any significant improvement (HAM-D, CGI n.s.). None of the studies had a follow-up assessment. In summary, it can be concluded that nVNS methods like Yoga, Tai Chi, or tVNS may be a promising, feasible, and safe additional treatment option for patients suffering from MDD, however, further studies are needed for the evaluation.

4.1.2 PTSD

Of the studies that included patients with PTSD, 10 out of 11 studies showed significant improvements of at least one psychometric test, in cortisol or HRV measures, at least at one assessment point in the study population. In the between-groups comparison five studies (98, 100, 103, 105, 106) showed significant improvements of all applied scores (CAPS, PCL, PSS) and measures (HR, HRV, Cortisol) in the intervention group at all assessment points. One study (97) showed significant improvement in all scores (CAPS, PCL), but only at posttreatment. Four studies (99, 101, 104, 107) showed significant improvements of at least one score out of two to three (CAPS, PCL-C/-M/-S/, PHQ-9), at least at one assessment point.

And one study (102) did not show any significant improvement (PCL, STAI n.s.). Nine out of 11 studies had a follow-up assessment.

Interestingly it appeared in the most common study design “Intervention vs. TAU” that self-report measures (PCL: 2/5 significant + PHQ-9: 3/4 significant) were less likely to show significant differences between groups than external ratings (CAPS), which were significant in all studies of this category and also had the most matches in the selected questionnaires.

In summary, many of the veteran studies reported significant results for symptom reduction through nVNS methods in veterans suffering from PTSD and offered overall safe additional treatment options, even though some drop-out rates were high and further optimization of feasibility is needed. The results of the studies with civilians show that nVNS might be a promising, feasible, and safe additional treatment option for civilians suffering from PTSD.

In conclusion, the studies selected for the review offer promising effects of nVNS methods on PTSD and depression, even though larger studies are needed for further evaluation.

The results of this review are in line with other systematic reviews, which mainly describe studies with low methodological quality and positive effects, that however often do not exceed significance (1, 2, 15, 108).

4.2 Limitations of the included Studies

Within the studies, there were several methodological strengths and weaknesses. An overview of the limitations of the studies is highlighted below.

4.2.1 Sample Size

The sample size of the studies was often small and had a large variety. The majority of the studies (seven) had a study population of n=30-50, four studies had a study population of n>100, two studies had n<30, and two studies had an n=51-100. The small sample sizes are lacking in statistical accuracy and the variety makes a comparison between the studies difficult.

4.2.2 Follow-up and Blinding

Only nine out of 15 studies included a follow-up with the longest period being four months, which makes conclusions about long-term effects difficult. The lack of a follow-up and the small sample sizes were also because five of the studies (94, 95, 96, 102, 104) were pilot studies.

Another methodological problem was blinding. Only the tVNS interventions may offer the possibility of a double-blind study, provided that the devices for sham stimulation and real stimulation look the same and are applied in the same way. Only one (103) of the two tVNS studies chose a double-blind setting during the intervention period, but the research staff was unblinded during the interpretation phase. In the other tVNS study (95) the patient's side was blinded. Most studies were conducted in a single-blind setting with the rater side being blinded (94, 96, 97, 98, 99, 100, 101, 107 = research staff was blinded, study coordinator was unblinded). Two studies did not carry out blinding (93, 102) and three studies did not mention how or whether blinding was performed (104, 105, 106).

4.2.3 Study Designs

Additionally, the different study designs complicate the comparison of the study results as the effect of the individual interventions or the effective components of the interventions are difficult to filter out. Uncertain factors such as an active control group (TAU), different contact times with the patients between the intervention and control group, and different elements within interventions (physical postures, meditative aspects, psychoeducation, etc.) complicate the findings.

Beyond that, most of the MBIs are not standardized. Six studies compared an intervention to TAU (97, 99, 101, 104, 106, 107), four studies compared an intervention to a waitlist control (94, 96, 100, 105), two studies compared an intervention and TAU condition to a TAU-only condition (93, 98), two studies compared an intervention to a sham-intervention (95, 103) and one study compared an intervention to an assessment control condition (102).

4.2.4 Drop Out and Study Locations

Drop-out rates were higher in eight studies in the intervention group compared to the control group (94, 96, 97, 99, 101, 104, 105, 106), which raises questions of acceptance and feasibility. In one study the drop-out rate was not mentioned (103).

The majority (seven out of 11) of the PTSD studies dealt with above all white and male veterans, also the majority of studies took place in North America (U.S.A: 94 Chinese Americans, 96, 97, 98, 99, 101, 102, 103, 104, 106, 107; Canada: 105), one in Kampala/Uganda with Congolese refugees (100), one in India (93), and one in Germany (95). The application of the results to the general population should therefore be treated with caution.

4.2.5 Diagnoses

Many studies have included patients with subthreshold to full PTSD in PTSD studies and patients with mild, moderate, and severe depression in MDD studies, excluding patients with acute suicidality. The distribution of the diagnosis criteria was as follows: within the MDD studies, three studies (93, 94, 95) included participants with MDD, which was not described in detail and one study included participants with MDD with an inadequate response to antidepressant treatment (96). In the PTSD-studies seven studies included participants with PTSD, which was not described in detail (97, 98, 100, 101, 103, 105, 106), one included participants with an established diagnosis of chronic PTSD (104), and three studies included participants with full or subthreshold PTSD (99, 102 -> 70.7% full, 22% subthreshold, 107). Due to the variability of diagnoses in the studies, it is unclear to which patients the results can be applied collectively.

4.2.6 Safety and Adverse Events

A further weakness of some studies was the inadequate report-of-safety regarding AE. Five studies (93, 103, 104, 105, 106) did not mention whether there were AE during the intervention. In seven studies no AE were reported (94, 95, 96, 98, 100, 103, 107). In three studies (97, 99, 101) there were AE in the intervention and/or the control group, all of which were judged not to be related to the treatment. As published studies indicate an increased incidence of AE in patients with psychiatric

disorders when practicing various mind-body methods such as Yoga and meditation, the safety aspect is particularly important (113, 114, 115, 116).

4.2.7 Weaknesses of Methodology

A large number of different psychometric instruments were used in the studies examined, although their application in the results was restricted by the defined inclusion criteria. However, there are also several different statistical procedures for the calculation as well as differently defined significance levels (p<.01, p<.05). This limits the comparability of the studies with one another.

4.2.8. Specific Limitations of Individual Studies

The limitations of the individual studies are discussed below.

4.2.8.1 MDD

The main limitations of the Study of Kumar S. et al. 2019 (93) were not-reporting about AE, no follow-up assessment, and no blinding. The intervention group had more contact time within the group and with therapeutic staff than the other group and the Yoga program was not standardized. The study of Yeung A. et al. 2012 (94) lacked a follow-up and had a small sample size, which could be the reason for the insignificant results. The study design was a comparison of an intervention with waitlist control, which raises the question of whether the improvement in the intervention group was due to social interaction and group time or whether it can be attributed to the effects of Tai Chi. Additionally, the study population consists of Chinese immigrants; it is therefore unclear whether the results can be applied to the general population or other minorities. The study of Hein E. et al. 2013 (95) also lacked a follow-up and had a small sample size. Even though the participants were blinded, the study described that it was unclear whether the patients noticed if there was real stimulation. It was reported that the tVNS group felt electrical sensations. The sham group may therefore have concluded that they were in the placebo group if they did not feel any sensations, so unblinding may have taken place. In addition, the randomization method of alternating allocation is also controversial (117, selection bias). Also, 14 days is a very short observation period for depressed patients at an inpatient psychiatry especially because tVNS was used in addition to TAU. It was also noticeable that the self-ratings showed an improvement after two

weeks of using tVNS, but the external ratings did not. Beyond that, the intervention group was quite inhomogeneous. The study of Sharma A. et al. 2017 (96) had a small sample size and no follow-up. The study design was a comparison with a waitlist control. The control did not have as much clinical contact and group support. Interestingly, the control did not show any improvement during the study period. The intervention group also contained lectures on stress education, which complicates the interpretation of the outcome results, because treatment effects could be attributed to nonspecific treatment benefits such as group time and/or psychoeducation.

4.2.8.2 PTSD

4.2.8.2.1 Veteran Studies

The study of Bormann J. et al. 2018 (97) also included lectures, which are not further specified. The active and the control group had about the same contact time. The inclusion process of participants could limit the representativeness of the results because study participants were self-selected, which results in only people registering who are open to mind-body methods and experience with trauma therapy before enrolment was not equal within the study groups (volunteer bias, selection bias). There was a significant age and baseline CAPS difference between the completer and the non-completer sample, where younger participants were more likely to drop out of the study, which can be considered for applicability and subsequent studies. The follow-up was six weeks post-treatment, which is too short to assess long-term improvement. Also, the data on the mantram practice was collected within the last week. As a result, the intensity of the practice was not recorded over the study period and no connection can be made between the quality and quantity of the practice and treatment outcomes. The study of Bormann J. et al. 2013 (98) also has the limitations of lectures and self-selection (volunteer bias, selection bias), as described above. Here, the TAU group did not meet weekly whereas the intervention group met weekly, therefore improvements might be related to nonspecific treatment benefits. As in some of the other studies, the study participants were exclusively veterans suffering from military trauma, which limits applicability to other types of trauma and other population groups. The study of Polusny M. et al. 2015 (99) compared a standard MBSR course design (2.5h

sessions) to a standard PCT group therapy design (1.5h sessions), which resulted in 13h difference in the contact time between the groups. In addition, the follow-up period was two months posttreatment, which is too short to assess long-term effects. Beyond that, the control group had at baseline lower severity in PTSD symptoms, which may have altered results, and the study sample was quite homogeneous, consisting of mainly white veterans from the same area who served during the Vietnam War era. Major limitations of the study of Nidich S. et al. 2018 (101) are that it predominantly included male veterans with a "severe" baseline level of PTSD. So no conclusions can be made about applicability to women and people with other forms of trauma, and the results may be different for seriously ill people. In addition, no further follow-up was conducted after a three-month post-test assessment. There was a significant dropout in all groups, albeit insignificant between groups, a difference in teaching experience between therapists in the different groups, and a difference in academic education level, with TM teachers having the lowest academic education level. The TM teachers had the most teaching experience, but all teachers were novices in teaching PTSD veterans. The major limitation of the study of Kearney D. J. et al. 2013 (104) was the design as a pilot study, naturally coming along with a small sample size. The intervention group had more contact time with therapists, so nonspecific effects may have caused the improvement. The completer definition was quite liberal, which states that four out of nine units must be attended. This equals less than half of the classes. However, it has been shown that participation in four units (equivalent to 10 hours) can already bring significant improvements. Further limitation were that the homework of the MBSR group was not monitored and at baseline and the PTSD diagnosis was not formally assessed. Additionally, the control group received more benzodiazepines throughout the study period, which might have influenced the results, and the questionnaires assessing PTSD symptoms (PCL) and depression (PHQ-9) are both self-report questionnaires. The study of Bergen-Cico D. et al. 2014 (106) has limitations, such as a very small sample size, especially of the completer sample (N=9), and no follow-up of the cortisol measurements beyond the study period. Beyond that randomization method was unclear. In addition, the predictive power of the CAR values can only be seen with limitations as many factors influence the CAR, in particular expectations of the challenges of the day ahead as well as events and experiences

of the previous day. The significant results after four weeks of participation in the study raise the question of whether there is a dose-response effect or threshold effect after four weeks of practice and whether this is due to unspecific factors or the implementation of mindfulness in daily life. The main limitations of the study of Possemato K. et al. 2016 (107) were a small sample size and the short follow-up period. Also, the randomization process, which is not comprehensible, is worth mentioning. The study authors point to the significantly lower number of study participants than desired. No correlation with the severity of symptoms or other baseline characteristics could be identified as influencing factors for enrolment or not. The authors suspect a lack of information about the benefits and content of the intervention among the study participants, which is why an informal information event was suggested. In the assessment of the feasibility of the study format, it is discussed that participants who did not attend a session made less use of mental health services overall. One factor that may have influenced the outcome was that the randomization ratio was changed during the study.

4.2.8.2.2 Civilian Studies

The main limitation of the study of Rees B. et al. 2013 (100) is the self-report PCL-score being the only psychometric test, as this study relies exclusively on the self-assessment of the study participants and no external ratings were carried out by professionally trained personnel throughout the study. Another major limitation is that the raters were unblinded during the study period because they met some of the study participants after 30 days and almost all of them after 90 days (performance bias). To cover the unblinding, independent blinded Congolese consultants were hired to perform a 135-day post-test. Due to the study design, which gave the study participants food and soap in return for participation, the problem arose that after the baseline measurement 30 participants who were randomized to the intervention group dropped out after they had been given soap and food. As a result, participants in the intervention group and the control group had to be subsequently matched for sex, age, and PCL score, therefore the randomization was broken. The authors report that a social bias may have occurred. Further limitations were inadequate monitoring of TM practice quantity, a waitlist-control study design, the study design that offered people in need necessary food and soap in exchange for study participation, and the use of a non-standardized

translated version of the PCL questionnaire. The main limitation of the study of Mitchell K. S. et al. 2014 (102) was the small sample size, a short follow-up period (one month), and no blinding (performance bias). Beyond that the non-completers had marginally significantly higher baseline PCL scores (M=59.20) than the completers (M=49.83), $t_{(31)}$=2.08, *p*=.04, which raises the question of the feasibility of a Yoga intervention in patients who are more severely ill. The major limitations of the study of Gurel N. Z. et al. 2020 (103) were the small sample size, no follow-up assessment, and the short study period of three days only, representing an acute study with short stressor and stimulation periods and short-term recordings naturally resulting in non-significant findings in non-acute parameters. The intervention group was dominated by female participants, such that the applicability of the results on males and other sex should be treated with caution, whereby it should be noted that PTSD has double the prevalence in women than in men. The study of Jindani F. et al. 2015 (105) especially lacked a follow-up, a sample size with statistical power, and a blinding (performance bias). The study design was intervention vs. waitlist control, where the intervention included a discussion part. Therefore, the effects of these factors are unclear. Attrition was higher in the intervention, which may have affected the results, and the study sample was predominantly Caucasians (85%) with the majority being female.

4.3 Limitations of this Review

A critical aspect of the method I have chosen is the narrow inclusion and exclusion criteria. Consistently applying hard criteria to exclude studies means that some well-conceptualized studies with informative results cannot be included in the final selection. Unfortunately, some studies that examined physiological parameters (HRV, cortisol, inflammatory markers) and fMRI studies were also excluded, because, for instance, they were not RCTs, they had active control groups or combined practices in an intervention that did not fall under the inclusion criteria, they did not use the specified questionnaires, the subjects had comorbidities to be considered and the research question did not correspond to the defined research questions. As a result, only a few studies on the selected practices remain, which makes it difficult to compare the individual studies on the respective practices.

In addition, many studies with active controls (except TAU) were excluded. The reason for this was that it is difficult to compare two little-researched procedures with each other, as effective factors cannot be filtered out. However, the active procedures in the case of the review of the "TAU groups", were often not designed with a similar intensity, especially in terms of group time, time with therapists, and homework, making it difficult to predict nonspecific effects. Nonetheless, to test the effectiveness of an intervention, an active control is needed that is designed to be similarly intensive.

Another critical aspect of this review is that not all parasympathetic stimulating methods are represented here. Many other relaxation techniques are worth investigating in further studies such as sports, music, laughter Yoga, dancing/clubbing, sexuality, acupuncture, CAM, etc. and other special programs that were excluded. In addition, the interpretation of the parameters was limited when in some cases only the intra-group analysis showed significant results whereas the analysis between the groups showed no significant results, which could be due to the small sample size in many of the studies. In addition, the interpretation was complicated by the inconsistency of the published results/parameters and differences in the significance thresholds within the various studies.

Another point of criticism of the method is the short publication period of 2010-2020, which did not include the most recent studies, which would certainly have been interesting to compare due to the additional factor of the Covid-19 pandemic affecting individuals. However, the Covid-19 pandemic has created many uncertainties in the evaluation of studies, particularly for people with psychiatric illnesses. This is because the illness itself as well as the lockdowns and restrictions on daily life with curfews, social distancing with restrictions of touch or interpersonal closeness had a strong impact. In addition, the measures often meant that studies could not be carried out as planned.

4.4 Gender Aspects

»Depression, somehow, is much more in line with society’s notions of what women are all about: passive, sensitive, hopeless, helpless, stricken, dependent, confused, rather tire-some, and with limited aspirations.« (120)

The first thing I would like to criticize in this context is the basis of the epidemiology of MDD, in which women are generally diagnosed with MDD 1.5-fold (123) to double (124) as often as men. Generally, MDD tends to be underdiagnosed in both genders, however more among men than women. Women are more likely to recognize MDD in themselves and seek help earlier whereas men tend not to recognize the symptoms and seek help later (122). In the epidemiology hormonal and genetic influences, differences in disease behavior and assessment, and gender-differentiated detection rates and symptoms are discussed (124). Furthermore, the social gender role and societal influences on coping with emotions and concepts of femininity and masculinity are possible influencing factors (123, 125, 126).

Despite the criticisms of the diagnosis, many women do suffer from depression. There is even evidence that SSRIs work better during the menstrual cycle in the presence of estrogen (121) and less so in its absence, i.e. in the luteal phase, when premenstrual syndrome or premenstrual dysphoric disorder occurs. Research into gender-specific therapy, considering the menstrual cycle as well as pregnancy and menopause, is therefore essential. However, many of the studies in this review focus on white men (veteran studies). Therefore, the results do not apply to the general population.

In addition, in some studies included in the review, only the number of people of one gender was mentioned (97, 103, 104), usually the male study population, where far more study participants were included. It is therefore not possible to draw conclusions about the gender of other study participants who are not of the specified gender. As it must be taken into account that there are other gender categories in addition to the binary gender categories.

4.5 Clinical Implications

The studies included in the review show overall results that indicate relief of PTSD and MDD symptoms by practicing MBI or nVNS. However, many of the studies are of low methodological quality. Further studies are needed to use MBI methods and nVNS as another therapeutic option in the treatment of PTSD or MDD.

For clinical application, the results indicate that nVNS and MBI might be effective, cost-efficient, accepted therapy supplements with few side effects. Once the

techniques have been learned, they can also be administered independently and are therefore labor-saving.

MBI and tVNS practices could be trained in different settings. For example, methods could be learned during a clinical therapy stay or in a rehabilitative setting, as this would provide a longer period of practice where any uncertainties and questions could be clarified. After discharge patients can continue practicing at home. Standardized guidebooks that patients could take with them would be useful here to support further practice. However, such courses for learning MBI could also be conducted in outpatient settings by adequately trained staff. An example would be a format similar to the standardized MBSR course, with a weekly course, a one-day retreat and homework in which the techniques can be learned or practiced independently during the course and questions that arise can be discussed at the weekly meetings. However, the courses should be offered on a disease-specific basis so that the staff can guarantee the necessary qualifications. For tVNS, the electrical stimulators would be needed, which can be handed out in the clinic but also on an outpatient basis and their use can be explained and practiced. Continuing psychiatric care should be guaranteed during the application of all procedures. The MBIs that can be offered as an official treatment option should be taught according to standardized guidelines, which ideally should be based on evidence. The staff teaching these courses should have minimal clinical training, enabling them to provide disease-specific teaching and to recognize disease-specific adverse events, contraindications and complications.

4.6 Suggestions for Future Studies, Open Questions for Future Studies

Future study designs could benefit from a larger and more diverse study population, longer intervention periods, and longer follow-up periods (> six months). It would also be useful to compare an intervention with an active control group that has the same intensity of group time and therapy time. This might produce higher quality results and possibly improves significance of results in future research.

In future studies, adverse effects should also be closely monitored to obtain further data on the safety of the applications.

For the feasibility of the study, participation in the study should ideally not entail any additional effort compared to active control, as this often impairs adherence to the

conduct of the study (55). This effect was also observed in some of the studies described in this review, in which the intervention group sometimes had higher drop-out rates. In some studies, it also turned out that the participants' expectations were not met during the study, or they did not know exactly what they were embarking on beforehand, which explains some of the attrition rates (107). To reduce this effect, a low-threshold information event could be held before the start of the study, in which expectations and questions can be clarified. Then only those people who can realistically imagine participating to the full extent can take part in the study. Of course, this selection of test subjects would not be representative of the general population.

In addition, there are still many unanswered questions that can be addressed in future studies. For example: who benefits most from which practices, in which setting (acute, rehabilitation, maintenance therapy) can they be used most effectively, to what extent can these practices be learned and applied at home. Further questions which arise are: whether regular use at home and at what intervals has an impact on the course of the disease and on long-term remission rates, and up to what severity of the disease the therapeutic use of which practices makes sense.

4.6 Conclusion

The review on nVNS in SRPD showed that those practices are promising cost-efficient therapy options in MDD and PTSD. Further controlled studies are needed, especially those measuring the effect through physiological parameters, to answer questions such as: which method is most beneficial for whom? How are the effects in the long run? Which format is the most feasible and accepted for whom? Are those methods safe in the long run?

Appendix

Table 5. Psychometric outcomes in detail

	Score	Time period	Change in Scores	Note
Kumar S et al. 2019	MADRS	baseline – day 10	Yoga: M=12.98, SD=5.28, p=.765 Control: M=12.60, SD=5.87	Fall in scores
		day 10 – day 30	Yoga: M=11.45, SD=6.08, p=.047 Control: M=9.10, SD=4.08	
		baseline – day 30	Yoga: M=24.43, SD=7.78, p=.043 Control: M=21.70, SD=7.35	
Yeung A et al. 2012	HAM-D_{17}	baseline – week 12	Tai Chi: M=5.2, SD=5.1, p=.82 Control: M=4.5, SD=2.4	
	CGI-S		Tai Chi: M=1.0, SD=1.0, p=.5 Control : M=0.67, SD=1.2	
	CGI-I		Tai Chi: M=3.0, SD=1.2, p=.21 Control: M=3.5, SD=1.0	
Hein et al.2013	HAM-D	Day 0 - day 14	tVNS: from 16.6 to 11.2, t=3.9, p=.001 sham: from 18.1 to11.5, t=3.9,p=.001	
	BDI	Study 1	tVNS: from 27.0 to 14.0, t=6.2, p<.000 sham: from 31.0 to 25.8, t=1.4, n.s.	
		Study 2	tVNS: from 29.4 to 17.4, t=6.3, p<.05 sham: from 28.6 to 25.4, t=1.3 n.s	
Sharma A et al. 2017	HAM-D_{17}	Baseline – 2m	SKY: M=-9.77 (completers: M=-11.55) vs. Control: M=0.50, p=.0032; M=-10.27; 95% CI -5.04 to 15.50, p=.0014 (completers: M=-12.05; 95% CI -6.71 to -17.38; p=.0014)	Mean reduction in total score Mean difference Mean reduction in total score
	BDI		SKY: M=-17.23 (completers: M=-20.36) vs. Control: M=-1.75 M=-15.48, 95% CI -8.34 to -22.62; p=.0101 (completers: M=-18.61, 95% CI -11.81 to -25.42; p=.0043)	ITT* mean difference
Bormann J et al. 2018	CAPS	baseline – posttreatment – follow up	MRP: from M=77.46, to M=52.39, to M=50.61 PCT: from M=75.61, to M=62.07, to M=59.00	d=.49 (posttreatment) d=.46 (follow-up)
	PCL-M		MRP: from M=59.23, to M=45.32, to M=44.74 PCT: from M=57.57, to M=50.20, to M=48.42	d=.43 (posttreatment) d=.33 (follow-up)
	PHQ-9 depression		MRP: from M=15.42, to M=10.68, to 10.51 PCT=: from M=15.15, to M=12.81, to M=12.18	d=.31 (posttreatment) d=.21 (follow-up)
	STAI-S/ State anger		MRP: from M=23.43, to M=21.21, to 21.22 PCT=: from M=23.00, to M=22.20, to M=21.27	d=.11 (posttreatment) d=.03 (follow-up)
	STAI-T/ Trait anger		MRP: from M=22.34, to M=20.90, to 19.53 PCT=: from M=21.89, to M=20.37, to M=18.62	d=.03 (posttreatment) d=.06 (follow-up)
Bormann J et al. 2013	CAPS	pretreatment – posttreatment – follow up	MRP: from M=83.08, SD=16.17, to M=66.16, SD=23.58, p=.05; follow-up: M=61.82, SD=23.53 Control: from M=82.83, SD=19.44 to M=72.59, SD=24.97 p=.05	
	PCL		MRP: from M=61.39, SD=11.62 to M=55.77, SD=14.30; follow-up: M=54.93, SD=13.78 Control: from M=62.70, SD=10.40 to M=60.23, SD=12.17	

Polusny M et al. 2015	CAPS	baseline – posttreatment – follow-up	MBSR: from M=69.9 to M=56.3, to M=49.8 PCT: from M=62.5, to M=51.7, to M=50.6	
	PCL		MBSR: from M=63.6, to M=55.7, to M=54.4 PCT: from M=58.8, to M=55.8, to M=56.0	
	PHQ-9		MBSR: from M=15.5, to M=13.6, to M=13.3 PCT: from M=14.6, to M=13.9, to M=13.8	
Rees B et al. 2013	PCL-C	Baseline – 30d – 135d	TM: from M=65.2, SD=7.3 to M=29.2, SD=6.1 to M=26.5, SD=5.4 Control: from M=67.8, SD=6.5 to M=74.6, SD=7.1 to M=73.98, SD=5.2	
Nidich S et al. 2018	CAPS-IV	Baseline – 3-m post-test	TM: from M=80.5, SD=17.7, to M=64.4, SD=33.0 PE: from M=80.6, SD=16.9, to M=69.5, SD=31.5 HE: from M=77.6, SD=18.7, to M=75.1, SD=26.5	Effect size: .90 Effect size: .63 Effect size: .14
	PCL-M		TM: from M=60.5, SD=12.7 to M=46.9, SD=18.2 PE: from M=61.3, SD=11.6, to M=50.6, SD=18.5 HE: from M=58.8, SD=12.5 to M=55.2, SD=15.3	Effect size: 1.10 Effect size: .87 Effect size: .28
	PHQ-9		TM: from M=17.0, SD=6.1 to M=10.2, SD=7.3 PE: from M=17.0, SD=5.0, to M=12.0, SD=6.6 HE: from M=15.9, SD=5.6 to M=14.0, SD=6.6	Effect size: 1.22 Effect size: .89 Effect size: .34
Mitchell K S et al. 2014	PCL-C	baseline – postintervention – follow-up	Yoga: from M=51.94, SD=14.36 to M=39.07, SD=16.01 to M=40.91, SD=18.89 Control: from M=53.44, SD=10.56 to M=39.09, SD=12.65 to M=42.18, SD=14.20	
	STAI-S		Yoga: from M=47.75, SD=14.73 to M=42.00, SD=16.84 to M=36.85, SD=17.62 Control: from M=47.94, SD=11.68 to M=40.70, SD=13.61 to M=41.83, SD=15.09	
	STAI-T		Yoga: from M=52.33, SD=16.34 to M=47.71, SD=15.68 to M=44.33, SD=16.91 Control: from M=54.44, SD=10.30 to M=46.64, SD=10.43 to M=48.00, SD=7.95	
Gurel N Z et al. 2020	CAPS		Physiological Parameters	
Kearney D J et al. 2013	PCL-C	baseline – posttreatment – follow-up	MBSR completers: from M=59, SD=11.5; to M=52, SD=13.1; to M=54, SD=14.8 TAU completers: from M=63, SD=10.8; to M=59, SD=11; to M=60, SD=12.5	between group effect size: d=-.56 (posttreatment), d=-.47 (follow-up) between group effect size: d=-.70 (posttreatment), d=-.73 (follow-up)
	PHQ-9		MBSR completers: from M=15, SD=6.21; to M=12, SD=5.69; to M=12, SD=5.84 TAU completers: from M=17, SD=5.49; to M=15, SD=5.06; to M=16, SD=5.03	
Jindani F et al. 2015	PCL-17	baseline – midtreatment – after treatment	Yoga: from M=59.5, SD=9.3; to M=48.5, SD=14.3; to M=41.8, SD=12.0 Control: from M=55.1, SD=11.9; to M=52.5, SD=11.6; to M=55.4, SD=13.5	
	PSS		Yoga: from M=24.9, SD=7.6; to M=15.4, SD=12.0; to M=12.4, SD=11.4 Control: from M=24.8, SD=7.2; to M=21.8, SD=6.6; to M=21.6, SD:4.8	

Bergen-Cico D et al. 2014	CAPS PCL PHQ-9		Only Cortisol-results in paper	
Possemato K et al. 2016	CAPS	baseline – posttreatment – follow-up	PCBMT: from M=46.4, SD=14.3; to M=38.0, SD=17.1; Group x time $F_{(1,60)}$=0.9 PCTAU: from M=45.3, SD=15.6; to M=39.0, SD=23.4; Group x time $F_{(1,40)}$=5.21	Effect size (between PCBMT + PCTAU) p=.34, d=.24 Effect size (between PCBMT + PCTAU) p=.63, d=.26
	PCL-S		PCBMT: from M=50.5, SD=13.2; to M=43.1, SD=14.8; Follow-up: M=44.5, SD=13.8; Group x time $F_{(2,59)}$=0.5 PCTAU: from M=49.3, SD=12.6; to M=42.3, SD=13.9; Follow-up: M=41.7, SD=13.3; Group x time $F_{(2,39)}$=2.1	Effect size (between PCBMT + PCTAU) p=.04, d=.86
	PHQ-9		PCBMT: from M=11.2, SD=7.2; to M=7.8, SD=6.5 ; Follow-up: M=9.2, SD=7.1 PCTAU: M=9.0, SD=5.5; to M=9.5, SD=5.6; Follow-up: M=8.9, SD=5.7; Group x time $F_{(2,59)}$=3.4	

*ITT = Intention to treat

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