Yoga: Can it be integrated with treatment of neuropathic pain?

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ABSTRACT

Background: Neuropathic pain (NP) is a debilitating condition that may result from spinal cord injury (SCI). Nearly 75% of all SCI results in NP affecting 17,000 new individuals in the United States every year, and an estimated 7–10% of people worldwide. It is caused by damaged or dysfunctional nerve fibers sending aberrant signals to pain centers in the central nervous system causing severe pain that affects daily life and routine. The mechanisms underlying NP are not fully understood, making treatment difficult. Identification of specific molecular pathways that are involved in pain syndromes and finding effective treatments has become a major priority in current SCI research. Yoga has therapeutic applications may prove beneficial in treating subjects suffering chronically with SCI induced NP, chronic back and associated pains if necessary experimental data is generated

Summary: This review aims to discuss the implications of various mechanistic approaches of yoga which can be tested by new study designs around various nociceptive molecules including matrix metalloproteinases (MMPs), cation-dependent chloride transporter (NKCC1) *etc* in SCI induced NP patients.

Key messages: Thus, yogic practices could be used in managing SCI induced NP pain by regulating the action of various mechanisms and its associated molecules. Modern prescriptive treatment strategies combined with alternative approaches like yoga should be used in rehabilitation centers and clinics in order to ameliorate chronic NP. We recommend practical considerations of careful yoga practice as part of an integrative medicine approach for NP associated with SCI.

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Introduction

Following an injury to the spinal cord, functional impairment and pain syndromes are prominent and present a significant complication towards recovery. SCI is persistent worldwide with an annual incidence up to 40 cases per million, with more than 17,000 cases each year in the United States alone[1]. NP is a common outcome following SCI occurring in up to 70% of SCI patients[2,3]. Currently, no globally acceptable treatment exists for SCI-induced neuropathic pain. The mechanisms behind the pain syndrome are not well understood due to its complexity and its likeliness to be induced by multiple causes. In addition to pain, the patient also experiences tremendous loss of function below the level of the lesion and quality of life. Yoga as an alternative medicine in rehabilitation has shown may increase pain tolerance in SCI and other patients with pain [4,5]. The impact of yoga on SCI has not been officially documented as there are no known published studies of this work. Most of the yoga studies are confronted with methodological limitations especially with regard to choice of control group and lack of blindness. These limitations also apply to majority of studies examining the effect of diet and exercise on disease management and wellness because human compliance to change in diet, exercise or yoga is not easy to address.

"Yoga" (/joʊgə/) is an ancient Indian combination of a physical, mental and spiritual practice. It is defined as a system of exercises for mental and physical health. In Hindu philosophy, the inner peace is achieved by controlling the body and mind functions. Further, in order to attain liberation and to achieve the supreme, yoga may help in achieving the mental control and well-being [6–10]. These studies show yoga is being practiced by several religious faiths like Hinduism, Jainism, and Buddhism, particularly Vajrayana Buddhism. Implication of yoga practice for insulin resistance syndrome, cardiovascular disease, and possible protection[11] as a complementary intervention for cancer[12], schizophrenia[13] and as an

alternative and complimentary treatment for asthma[14] has been documented. In general, these studies suggest that yoga acts as a preventive measure and helps in patient's psychological healing process.

The term "yoga" has changed much since its arrival into our world. It is derived from the sanskrit word *yuj* which means to unite and it is an ancient Indian way of life. The main aim of yoga is to achieve holistic health by following the 8-fold path of yoga. The eight paths include *yama (*universal ethics for the moral and spiritual development), *niyama* (individual ethics), *asana* (physical postures for physical development), *pranayama* (breath control for the improvement of physiological functions), *pratyahara (*control of the senses), *dharana (*concentration for making our mind alert and pointy), *dyana,* (meditation), and *Samadhi (*a bliss which helps in attaining inner peace)[15]. Different branches of yoga also exist which includes *Karma* (path of service), *Raja* (path of meditation), *Jnana* (path of sage or scholar), *bhakti* (path of devotion), and *Tantra* (path of rituals). Also there are various styles followed by different yoga practitioners like *Hatha* Yoga, *Kundalini* Yoga, Iyengar Yoga, *Ashtanga* Yoga etc.

David Gordon White in 2014 described the *pranayama* technique of controlling the body with regulated breathing [7]. However, there are always variations in practice but the main steps of this technique are consistent: 1) inhalation or inspiration, which in Sanskrit terminology is known as *puraka* which means filling up of lungs, (2) exhalation or expiration, which in Sanskrit is called *rechaka* meaning emptying the lungs, and (3) retention or holding the breath which is termed *kumbhaka*, a state where there is no inhalation or exhalation[16]. Regulation of breath affects the control of the autonomic nervous system, which further has beneficial effects on the different organs of the body. The autonomic nervous system is the involuntary response the body has to certain stimuli and is made up by the sympathetic and parasympathetic systems [17]. When Pranayama breathing is performed with long breath retention, the parasympathetic nervous system is amplified, resulting in lower metabolic rate and oxygen consumption. On the other hand, with brief breath retention there is an adverse result of augmented oxygen consumption and metabolic rate [18]. It is also observed that while performing '*kapalabhati'* yogic breathing (high frequency breathing) there is exaggerated sympathetic activity and during '*nadisudhi'* yogic breathing (Anulom Vilom or slow alternate nostril breathing) decreased sympathetic activity is observed. Since autonomic nervous system is the primary control center of the cardiovascular system, a strong sympathovagal balance ensures its stability.

Yoga, a healing discipline which includes breath control, meditation and adaptation of various specific body poses or *asanas* assists in relaxation and pain relief. Meta-analysis of yoga practice has been suggested as a possible alternative medicine intervention for patients with physical and psychosocial symptoms, however, breast cancer patients showed small effect size on functional wellness[19]. Various studies have noted improvement in sleep, mood, and quality of life (i.e. depression, emotional function, anxiety) among cancer patients [20–22]. These studies indicate how yoga may be helpful in relief of some symptoms associated with cancer; however, there is no known study on pain improvement in cancer patients. Yoga is believed to provide relief to cancer patients (American Society of Cancer and NIH), however, there are no documented studies on the impact of yoga in alleviating the pain associated with malignancies and the effect it has on the overall well-being of cancer patients. Like cancer and other disorders, yoga may promote healing for SCI induced NP, by alleviating pain as it has shown promising results in the other pain disorders. One of the studies by Galantino *et al* has shown the impact of the modified Hath yoga practice in chronic low back pain. Results indicated the improvement in the balance and flexibility of the patients having low back pain [23] but a large trial is required. In another study on low back pain, Sherman and colleagues found Viniyoga, which is a therapeutically oriented yoga school, more significant as compared to control group in diminishing the low back pain and pain-related disability [24]. This defines potential role yoga may play in the healing processes of NP.

Chronic pain in relation to environmental factors

A large number of evidence from the patients suffering with pain as well as associated animal models has revealed that chronic pain is not uni-factorial but has many co-morbidities and consequently may lead to anxiety, depression and cognitive decline [25–30].

Pathophysiology

It is also observed that there is development of anxiety and depression among patients undergoing long-term pain, which results in the impairment of their cognitive functions, particularly working memory. Many studies suggest that non-pharmacological interventions can reduce the burden of chronic pain. Social and environmental manipulations have been shown to influence NP. Environmental enrichment weakens both nerve-injury induced mechanical and cold hypersensitivity. It is also believed to lower the calcitonin gene-related peptide (CGRP) and concentration of substance P (SP). On the other hand, an impoverished environment intensifies mechanical hypersensitivity[31]. Emerging targets like chemokines, *Wnt* pathway and proteases have been shown to increase spinal cord neuro inflammation and chronic pain [32] Pro-resolution lipid mediators and anti-inflammatory mediators have also been implicated to work on glial cells, immune cells, and neurons and result in resolution of synaptic plasticity, neuro inflammation, and pain. Targeting the increased neuroinflammation could provide newer therapeutic opportunities for treatment of chronic pain and related neurological disorders. The pain can be classified on the basis of its mechanism into five main types that are peripheral neuropathic, central sensitization, sympathetically maintained pain, nociceptive, and cognitive-affective[33]. The management and treatment of

NP depends on the incidence and underlying pathologies. The conventional Post herpetic neuralgia includes use of Topical lignocaine and anticonvulsants such as Gabapentin and Carbamezepine. Sodium channel blockers such as Lidocaine, SSRI (Selective serotonin reuptake inhibitors) such as Venlaflaxine, Duroxetine, Opioids such as Morphine and Fentanyl and transdermal patches remains an expensive intervention with various side-effects such as orthostatic hypotension, cardiac conduction defects, memory impairment, urinary retention and sedation. Even the latest modalities such as transcutaneous electrical nerve stimulation (TENS), conduction blocks, decompression surgeries and spinal cord stimulation have failed to provide the relief. Moreover, their increased cost and long term side effects call for an integrative approach which includes yoga [34,35].

Understanding molecular mechanisms of NP

NP following SCI is complex and the mechanisms underlying such pain syndromes are not well understood. Traumatic SCI leads to changes in the expression of several genes with significant functional consequences. Different therapies for pain and functional impairment in both acute and chronic state following SCI are being explored. To develop a workable therapy, it is a necessity to identify the specific molecular pathways that are altered as a function of time, following SCI. Several mechanisms based on animal models have been implicated in SCI-induced NP; however, no practical relationship of these novel findings has been established with yoga practice. Various studies have described the role of several nociceptive molecules including matrix metalloproteinases (MMPs), cation-dependent chloride transporter (NKCC1), CB1/CB2, Bradykinin1 (B1), and Vanilloid receptor TRPV1. Authors have speculated, through various grant proposals that by inhibiting up-regulation of such pain molecules in the early phase and/or late phase of injury, spinal cord damage and induced NP could be ameliorated. Our research findings from previous studies have helped in understanding novel mechanisms and treatments for SCI and NP employing a rat model [36–42]. This review aims to prompt new studies that examine the possible relationship of nociceptive proteins and its implications in translational approach of yogic processes in neuropathic pain.

Role of Cation-dependent chloride transporter

In our research group, we describe Cl-regulatory protein Na^+-K^+-Cl^- 1 (NKCC1) as a cation-dependent chloride transporter involved in NP following contusion SCI (cSCI)[43]. NKCC1 is inhibited by bumetanide (BU) in a rat model and resulted in the implication of NKCC1 in post-injury response that suggests contribution to NP following cSCI. After administration of Bumetanide to the subjects, thermal hyperalgesia (TH) and hind-paw withdrawal latency times are increased. A kinase known as the with-no-lysine (K)-1 (WNK1) is a regulator of NKCC1 activation by phosphorylation. In many systems, including nociception, mutations in this kinase with neuronal-specific exon of WNK1 in patients with hereditary sensory neuropathy type II (HSANII) show that patients with a mutation in nociception have a lessened awareness to pain, touch, and heat. The overall implication of NKCC1 and its activating kinase WNK1 shows their contribution in sensing and developing NP [37]. It will be interesting to investigate the relationship between NKCC1 and WNK1 upregulation as it relates to yoga practice.

Matrix metalloproteinases (MMPs)

Following NP, matrix metalloproteinases (MMPs) are triggered to be released, both as early (MMP9) and late (MMP2) reactions. The release of these MMPs trigger inflammatory cytokines, which in turn results in NP after injury via interleukin-1β (IL-1β)-mediated activation in a spinal nerve ligation model of rat and mice. By using tissue inhibitors of MMPs (TIMPs) and intrathecal injections of siRNAs, MMP levels are reduced, and resulting in a decreased amount of inflammatory markers in comparison with wild type mice[44]. Following induced cSCI in male adult Sprague-Dawley rats, we studied MMP2 in SCI-induced NP, the role of β-catenin in the WNT signaling pathway, and extracellular signaling kinase within the MAPK cascade [40].

ATP receptors

These receptors exist in the peripheral as well as the central nervous system and could be implicated in pain signaling. ATP is discharged from cells following damage and activates sensors, which in turn activates sensory neurons. Therefore, these sensory neurons could be involved in sensing NP, such as the P2X4 receptors [44,45]. A common response following nerve injury induced P2X4 in the ipsilateral spinal cord and induced hyperactive microglia. After administration of P2X4 antisense oligodeoxynucleotide, tactile allodynia was subdued from the depreciated activation of P2X4 receptors. To confirm this, the induction of P2X4 receptors increased tactile allodynia in a normal rat model[46]. Microglia are suggested intermediates in the pathway of induction of hypersensitivity following NP. The p38 mitogen-activated protein kinases and P2X4 receptors are necessary molecules that are activated after peripheral nerve injury in the spinal cord[47]. ATP is believed to be involved in acute pain as it is released from all the injured cells and excites the initial sensory neurons by stimulating their receptors [45]. However, in sensory neurons or in the spinal cord, suppressing the expression of P2X/Y receptors by molecular targeting and blocking P2X/Y receptors pharmacologically didn't show any improvement in acute physiological pain. Understanding the importance of ATP receptors including P2X4 receptors may prove to be a cornerstone for newer strategies in the NP management.

Cannabinoid receptors

Hama and Sagen report that by injecting the nonselective CB receptor agonist WIN 55,212–2 (WIN) SCI-induced

mechanical allodynia following a thoracic-level compression SCI was reduced [48]. The emerging role of AEA-specific-fatty acid amide hydrolase and 2AG-specific monoacylglycerol lipase as regulators of catabolism and biosynthesis of the CBs is reported [49]. In our research group, pretreatment with CB-1 antagonist AM 251 had not affected the anti-hyperalgesic effect of WIN while pretreating with the CB-2 receptor antagonist AM 630 reduced the effect of WIN significantly, suggesting a modulating role of the CB receptor in SCI-induced TH [42]. Selectively activating the CB receptors and its possible therapeutic value for treating SCI patients has been discussed as potential for analgesic effects on NP.

Bradykinin-1 and TRPV-1 receptors

Following a rat cSCI model of NP in our lab, we have demonstrated B1 and vanilloid (TRPV-1) receptor genes are highly expressed following injury of animals displaying thermal hyperalgesia in comparison to similarly injured animals without hyperalgesia [50]. In animals exhibiting hyperalgesia, more than two-fold increase in the expression of these two genes were detected in the epicenter region of the spinal cord when compared with animals with SCI that did not display hyperalgesia. This finding is consistent with others findings revealing contribution of B1 and vanilloid (TRPV1) receptors in nociception.

Brain-derived neurotrophic factor (BDNF) and serotonin

In certain animal models of chronic pain, BDNF signaling contributed to central sensitization. By deleting trkB.T1, which is spliced truncated isoform of the BDNF receptor tropomyosin-related kinase B.T1 in a mice model, there is a notable decrease in post-SCI locomotor dysfunction, mechanical hyperesthesia, and white matter loss. This suggests that the mechanism of SCI-induced chronic pain includes trkB.T1 in its cycle pathway [51].

Astrocyte Contribution to Pain Signaling

Glial cells in the spinal cord are important regulators of chronic pain. Specifically, astrocytes play a prominent role in up regulating signaling pathways that contribute to chronic pain. This is distinct from microglial mechanisms in that astrocyte activation is longer lasting and more persistent. Multiple chemokines, CCL2 and CXCL1, released by spinal cord astrocytes have been found to contribute to NP [52–54]. It is unclear how astrocytes regulate NP sensitization via the release of astrocytic mediators. CCI provoked the increase of astrocytic connexin-43 in spinal astrocytes. Three weeks post-injury, mechanical allodynia can be reduced by intrathecal injection of carbensoxolone, a non-selective hemi channel blocker and selective connexin-43 blocker. TNF-α leads to the release of chemokine CXCL1 which is further blocked by carbenoxolone, connexin-43 small interfering RNA, and Gap26/Gap27. TNF-α-activated astrocytes induced persistent mechanical allodynia which is restrained by CXCL1 neutralization, antagonist CXCL1 receptor (CXCR2), and pretreated astrocytes with RNA of connexin-43. In nerve injury, there is increase of excitatory synaptic transmission which was suppressed by carbenoxolone and Gap27 [54].

The hemi channel protein Cx43 provides a release portal for astrocyte mediators such as chemokines. Post nerve injury, astrocyte junction signaling may switch from fast gap-junctions to a slow paracrine route through Cx43 hemi channels. Cx34 contributes to pain hypersensitivity in mouse with SCI. Additionally, Cx34 was shown to play a role in chronic pain maintenance after CCI. The intrathecal injection of carbenoxolone (CBX), a Cx43 blocker, was shown to weaken mechanical hypersensitivity post-CCI. Electrophysiological experiments showed that spontaneous excitatory postsynaptic currents (EPSCs) were higher in CCI models compared to controls, a result lowered by CBX or mimetic peptides [55].

Spinal p38 mitogen-activated protein kinase (MAPK)

Spinal p38 MAPK plays a crucial role in pain induced by inflammation while activated spinal microglia plays a direct role in spinal nociceptive processing. As compared to post-treatment, pre-treatment with p38 MAPK blocks spinal sensitization which is manifested by up regulation of cyclooxygenase-2 (COX2) and appearance of Fos-positive neurons [56]. It has been suggested that the stimulation of the Src/p38MAPK signaling cascade gives rise to persistent mechanical hyperalgesia in late stages which is excited by formalin injection into the paw of the animal [57]. Furthermore, this unique finding is of significance for clinicians while developing therapeutic treatment during acute and persistent pain state.

Role of Glutamate Receptor-5 and Protein Kinase C-epsilon

The capsular ligament and cervical facet joint are the most common causes of neck pain in adults which is not explored in adolescents. In one study, a bilateral C6-C7 facet joint distraction induced mechanical hyperalgesia 7 days after injury and significantly augmented protein kinase C-epsilon (PKCε) expression in small as well as medium sized neurons. Post-injury MGluR5 expression was increased significantly in small sized neurons while activation of microglia was highest in naïve animals. Overall, the results show that young individuals have a lower induced pain tolerance in comparison to adults[58].

Management of pain through yoga

Insular cortex moderates increased pain tolerance in yoga practitioners.

Today, yoga is being considered more often to treat painful conditions. Studies are in progress to investigate the possible neuroanatomical changes after practicing yoga and use sensory testing and magnetic resonance imaging (MRI) techniques to test its benefits. One study has shown that North American yogis had more tolerance to pain as compared to individually

matched controls [59]. This study also examined the effect of long term and regular yoga practice of yoga on the experienced North American yogis as compared to the control and had analyzed the thermal detections, pain thresholds, and cold pain tolerance in both groups. Analysis on the structural changes in the brain gray matter and white matter have revealed that yogis had increased left intrainsular white matter integrity as compared to controls and, due to their parasympathetic activation and increased awareness, they are able to tolerate more pain as compared to the control group.

A summary of inquiries and findings in pain management in yoga practitioners

Studies compiled in Table 2 [60–63] describe the non pharmacological management of pain. Despite the heterogeneity in the yoga intervention, all the studies have shown the improvement in the yoga practitioners group as compared to the other control group. This may clearly indicate that the Mind body techniques are quite useful in treatment of back pain or other type of pain.

Meditation, yoga and cognitive behavioral therapy

Chronic pain is deemed to be an emerging problem of the modern world with many people suffering from back pain, headaches and arthritis [64]. Since pharmacological treatment is not giving much relief, people are looking for other modalities in the form of mind–body therapies (MBT), including meditation, yoga and cognitive behavioral therapy. Furthermore, mind–body therapies affect the neural mechanisms underlying the use of cognitive and emotional states for modulating the pain.

Yoga as a healing approach for spinal cord injury

Potential of yoga in rehabilitation of spinal cord injury patients

When disruption of spinal cord occurs, the communication is affected in parts that are innervated at or below the lesion. Almost half of the spinal cord injuries are an outcome of motor vehicle crashes and the other half are due to falls or sports injuries, etc. Apart from the trauma, other factors responsible for the spinal cord injury are bleeding, swelling, and oxygen deprivation which are further accompanied by the release of toxic substances and inflammatory cytokines. Several neuroprotective agents, which include methylprednisolone, are being used as the treatment for spinal injuries and may prevent cell death. SCI is followed by several complications for which there is need of rehabilitation [65]. Existing SCI centers are trying to incorporate and redevelop skills in SCI patients. Teams of nurses, physicians, psychologists, social workers, physical, and occupational therapists provide multidisciplinary services for rehabilitation of SCI patients but the area of yoga as a therapy is unexplored in this field. Yoga is a holistic approach, which is believed to stimulate neural pathways and neurotransmitters. With proper adaptation and through guided assistance, different yogic techniques may act as a valuable healing tool in the regeneration of nerve fibers in SCI patients for which many research studies are being undertaken [5,66].

Role of Iyengar Yoga as a treatment therapy for SCI patients

After SCI, prevalence of sedentary lifestyle leads to secondary impairment and deterioration of the functional activities. For performing movements and overcoming the side effects of pharmacological approaches, SCI patients need special exercise programs, mind body techniques and assisted guidance to overpower these problems. Existing evidence is available which shows Iyengar form of yoga is a boon for SCI patients. B. K.S Iyengar introduced Iyengar yoga which empowers the strength, flexibility, and physical balance through stretching of muscles. The *asanas* in this style of yoga are modifiable and the use of props makes it more innovative. Some studies have provided instructions regarding the integration of Iyengar yoga as rehabilitation for SCI patients [64]. According to these authors, the Iyengar form of yoga helps to empower the patient by building symmetric and asymmetric postures to gain flexibility and awareness of the body structure by integration of *Pranayama* into the postures and focuses on the weight and time management of muscle contraction and relaxation [67].

Asana, Pranayama and meditation in other dysfunctions of SCI

SCI patients suffer from many dysfunctions including bowel, bladder, sexual, pain, and depression, etc. To overcome and reduce loss, specific yogic forms and different limbs of yoga are believed to help. Evidence shows that yoga may help in the treatment of pain, depression, anxiety levels, brain metabolism, and neurotransmitters. One studied the reaction time after performing bellows type breathing and breathe awareness. Reaction time was analyzed in two groups containing 35 participants, yoga group, and control group with mean age of 29 years. The yoga group had a prior 6-month experience of yoga practice, while the control group was not involved in any kind of yoga practice. The yoga group was assessed in two sessions. The first was Bellows breathing and the second was breath awareness. Assessments were made using a multi-operational apparatus for reaction time. Results concluded a significant reduction in number of anticipatory responses following 18 minutes of *Bhastrika* as compared to that before practice. This indicated that *Bhastrika Pranayama* might modify the responses to stimuli[68].

The analyses of above arguments or pathologies are not meant to generate misleading recommendations of Yoga being responsible for regeneration of nerve fibers in SCI. This should be viewed with caution although extense review of the literature about spinal cord regeneration has been avoided in this review.

Yoga for post-traumatic stress disorder (PTSD)

Chronic pain patients show associated anxiety and depression; and various mind body practices can alter pain and

pain related ailments [69,70] . Post-traumatic stress disorder (PTSD) is a chronic mental health condition that starts by witnessing or experiencing a terrifying event. People who acquire PTSD have difficulty adjusting to their daily activities and experience symptoms such as nightmares and severe anxiety. There is prevalence of posttraumatic stress disorder after spinal cord injury [71]. Many people with PTSD do not fully recover and go through episodes of this condition through their lifetime. People who are most likely to be impacted are war veterans who have just witnessed the disturbing images surrounding war. Previous studies have shown the promising results in management of PTSD by using complementary and alternative treatments [72,73].The University of Wisconsin-Madison is testing a new treatment program for PTSD that does not involve drugs or traditional therapy. These scientists hypothesized that yoga and mindful breathing may help PTSD victims more effectively with treatment of the disease. The Center for Investigating Healthy Minds at the University of Wisconsin is actively researching to gain understanding of treatment through yoga.

Effect of yoga on neurotransmitters

Regular practice of yogic exercise has shown alteration of various neurotransmitters in the brain. One study showed that PET during Yoga *Nidra* meditation increased endogenous dopamine release in the ventral striatum [74]. In another study, a 60 minute yoga session increased the brain GABA levels as compared to controls performing 60 minutes reading [75] This study aimed to explore the practice of regular yoga as one of the strategies for the treating anxiety and depression related disorders. Furthermore, another study revealed that yogic practice daily for one hour for a period of three months helps in lowering ACTH and cortisol, while elevating serotonin, dopamine, and BDNF in healthy active men [76].

Sudarshan Kriya Yoga's (SKY) effect on depression and anxiety

One group studied the response of P300 amplitude and antidepressant to SKY [77]. They recruited 30 drug-free depressed patients and were assessed at three intervals: pretreatment, after one month, and after three months. The antidepressant effects of SKY were measured through P300 ERP amplitude. Twenty-two patients responded well to the treatment which showed the effectiveness of SKY in depression. Another study involved 103 Swedish individuals, 55 in a *Sudarshan Kriya* & *Pranayama* group and 48 individuals in the control (a simply relaxed) group [78]. At the end of six weeks participants in SK&P were found to have lower degree of anxiety, depression, and stress as compared to the control group. Another study demonstrated that serum BDNF levels change after practicing a yoga module consisting of loosening exercise, *asana*, *Pranayama,* and meditation [79]. This study had a total of 137 patients, aged 18–55, and were recruited and segregated into three groups. The first group (n = 23) received only Yoga therapy, the second group (n = 78) received only medication, and the third group (n = 36) received yoga therapy and medication for twelve weeks. The results showed significant decrease in Hamilton Depression Rating Scale (HDRS) scores of three groups but more reduction was observed in patients receiving yoga session without medication as compared to medication alone group. The patients suffering from depression reported antidepressant effects which were correlated with increased serum BDNF levels. HDRS scores reduction and rise in BDNF levels were reported in yoga group alone[79].

Yoga for Chronic Low Back Pain

In two studies that examined the effects of yoga on chronic lower back pain, randomized control designs (RCTs) followed a 12-week yoga trial test group verses a control group[80,81]. 312 participants were randomized into 2 groups and were followed up at 3, 6 and 12 months. Females with a mean age of 46 years compromised about 70% of the participants. In the other study done a three-arm trial was performed[81].A total of 229 Participants were randomized to three different groups, self-care book, yoga, and active stretching intervention. Each group was led for 12 weeks by physical therapists. The participants of the yoga group as compared to the self-care group showed significant improvement. However, yoga classes were not more effective as compared to stretching classes in treating chronic low back pain.

A review about pain medicine for primary care providers has highlights six topics including pain management by some intervention, neuropathic pain, opioid dose and risk of overdose death, yoga for chronic low back pain, behavioral therapy and cognition, and treating back pain with evidences for the benefits. Overall it discussed a systematic approach, the risks and the limitations of the different modalities for the treating chronic pain [82]. Additionally, many other studies have suggested the benefits of yoga in treating a variety of pain conditions[69,83]. In both trials, participants were adults having low back pain and were instructed in a 12-week yoga classes. A standardized protocol which includes physical postures, breathing, and relaxation exercises was considered. At the 3 month time point, pain was assessed by the RMDQ score. Results indicate that this 12-week protocol for adults had improved lower back pain. In another study done in England, 851 participants were randomized into 2 groups: intervention group (N = 568) and control group (N = 283). The initial intervention was based on the nine-item Keele STaRT Back Screening Tool, in which subjects were divided based on low, medium, or high risk for persistent pain and disability. Patients at low-risk were excluded while medium and high-risk patients were considered for standardized physical therapy to address symptoms and function. It was reported that a stratified approach has better implications for better management of back pain than non-stratified approach [84].

A randomized control study comparing the effect of yoga on pain and spinal flexibility in 80 subjects with chronic low-back pain (CLBP) group in to a physical exercise group found positive results [85]. The yoga program consisted of physical

postures, Pranayama, meditation, and philosophical lessons on yoga for a period of one week. A physical exercise group acted as control exercising under guidance of a trained physiatrist and was matched for time. Researchers administered the Oswestry Disability Index (ODI) to measure pain related outcomes and a goniometer was used to asses spinal flexibility pre- and post- intervention. The yoga group showed a significant decrease in the ODI scores as compared to the physical exercise group. Furthermore, both groups showed improvement in spinal flexibility, but the yoga group showed more. Short-term yoga programs can help mitigated pain-related disability and improve flexibility in the spine.

Yoga Case reports as drivers of Integrative Medicine

A case study of a 40 year old male, shows how yoga can be used following a spinal cord injury [86]. The patient experienced such an injury in the thoracic (T4–6) in 1978, resulting in paralysis, and since then has been teaching yoga to others who have experienced a similar SCI. He teaches the practice of yoga for paralysis patients. By having reduced sensory stimuli, patients suffering from paralysis have clarity of mind and "presence" by experiencing yoga. This "presence" has very real, tangible effects, including being more balanced and grounded, having improved bowel-and-bladder sensation, being more efficient and powerful in movements, increased sexual ability, and even the possibility of regaining some physiological function. Different *asanas*, which are extremely relevant to the practice of yoga, are chosen specifically to line up all systems within the body, including digestive, circulatory, immune, etc. This teaching is also known as Iyengar yoga and has greater emphasis on sustained alignment and precision.

A different case study of a gunshot wound victim helps us understand the integration of Iyengar yoga in rehabilitation therapy [87]. The patient experienced injury at the T4 level resulting in paraplegia. After some evaluations, Iyengar yoga was integrated into his rehabilitation therapy to improve his strength, flexibility, relaxation, awareness and self-reflection. A modified *virasana* position, supine *virasana* and *paschimotan asana* with the use of props like blankets and bolsters were utilized in the therapy. In a different study, mindfulness is negatively associated with pain catastrophizing in a fear-avoidance model of chronic pain and might be a useful addition to the fear-free model for clinical studies [88].

Management of Pain through Pranayama *and* SudarshanKriya *(SKY)*

One of the approaches of yoga is *Pranayama*, a type of voluntary breathing regulation generally performed with the physical exercise of yoga. There are many different ways to practice *pranayama*, but three steps to perform it are consistent. There is the inhalation "*puraka*", the retention of the breath "*kumbhaka*", and finally the exhalation "*rechaka*". Regulation of breath in a stepwise manner affects the control of autonomic nervous system, which has further beneficial effects on different organ systems in the body. When pranayamic breathing is performed with long breath retention, the parasympathetic nervous system is amplified, seen by the lowering of metabolic rate and oxygen consumption. On the other hand, with brief breath retention there is an adverse result of augmented oxygen consumption and metabolic rate. *Pranayama* is a vital component of yoga associated with breathing. In chronic pain, breathing is strained and becomes shallow and uses more thoracic muscles. If the breathing pattern can be corrected with the help of yogic breathing then, certainly it may help in the management of pain. Alterations in neurotransmitters, like serotonin, have a vital action in the NP and have demonstrated interactions with immunocytes [89]. Another study treated NP in patients with diabetic peripheral neuropathic pain (DPNP) using duloxetine, a selective serotonin and norepinephrine reuptake inhibitor [90] SKY has also been reported as a useful, low-risk, low-cost alternative for depression, anxiety, post-traumatic stress, stress-related medical illnesses, and criminal offenders for treatment in rehabilitation [91]. Studies also show that *Pranayama* can be a prescriptive treatment to modulate neurotransmitters. They have demonstrated beneficial effects of yogic practice which involved Pranayama, meditation, and asana on immune function and the release of stress hormones [92]. The study was randomized, double-blinded, and performed on healthy volunteers from the university. They analyzed the immune-related cytokines in serum or plasma, in addition to oxidative stress, antioxidant components, and stress hormones. They found that Yogic practice had markedly raised immune-related cytokines in serum which included interleukin-12 and interferon-γ, and low levels of adrenalin in plasma along with enhanced levels of serotonin in plasma when compared to the control group who were not involved in any kind of exercise. Thus, they concluded that regular practice of yoga will reduce oxidative stress and improve antioxidant levels in addition to the reducing the release of stress hormones and improving the immune system. *SudarshanKriya* (SKY) is a cyclic controlled breathing practice, which includes *Ujjayi*, *Bhastrika* and Om chanting. This breathing practice also has a role in alleviating pain involved in the pathology of certain diseases. One study demonstrated that SK and *Pranayama* act as an effective intervention in decreasing stress and pain among patients of advanced stage breast cancer[93]. This study was based on 147 women participants and randomized into two groups: a yoga group (n = 78) and a standard group (n = 69). The yoga group performed exercise for 18 hours over three days and they had to practice it daily for 20 min at home. Results showed a significant difference in the blood cortisol levels after three months of practice. Pain perception as measured on 0–10 verbal scale of pain, was reduced by 3 points in the yoga group as compared to standard group. This showed the effectiveness of Pranayama and SKY exercise in patients suffering from advanced stages of cancer. However, the direct role of SKY in NP needs to be evaluated.

Do breathing exercises enhance stem cell migration to treat NP?

NP shows scarce response to the conventional drug therapies, thus requiring novel approaches to combat the limitations of the previous therapy. Stem cells may be one approach to alleviate the limitations of current therapies. By production of brief intermittent hypoxia through *Pranayama*, migration of the stem cells from their niche has not been explored and therefore it cannot be ruled out whether it contributes to alleviation of NP, which needs comprehensive investigation [94,95]. Pathogenesis and maintenance of NP is due to the interactions between the neurons, pro- and anti-inflammatory cytokines, glial cells and inflammatory immune cells [43]. Different stem cells treatments from different origin have been studied for treating NP induced in experimental animal models.

Search Strategy

Databases and online search terms

The bibliography database that was searched to compile the review includes PubMed, Scopus, Science Direct and Google scholar databases. The keywords used in the search include: [yoga] AND [Neuropathic Pain], [yoga] AND chronic pain, Neuropathic pain [(mechanism OR pathway)]. [SKY] AND pain, [(Spinal cord injury OR Yoga)] etc.

Conclusion

Above mentioned studies have shown the role of NKCC1 Cl^- protein in SCI induced NP rat model by involving kinase WNK1 which indicate the implication of ionic channel/gate in pain perception. Similarly, the increased expression levels of MMPs in SCI an induced animal model is mediated through *wnt* signaling process. Moreover, P2X4, is one of the pain sensing protein which transmit the signaling process in pain perception mediated by p38MAPK by interacting with P2X4 receptor. ATP receptor induces the P2X4 protein to carry out the process. Various cannabinoid molecules and its receptors have also been shown to have significance in pain, examined through various animal models. Similarly, Bradykinin-1 and TRPV-1 receptors have also been found to have increased two-folds in case of thermal hyperalgesia model. Role of BDNF has been studied in animal models of pain. It is well established that yogic practice influences the sympathetic nervous (SNS) and hypothalamus pituitary axis (HPA) [96]. Further, yoga is believed to modulate the action of nitric oxide release/endothelial function, endogenous endocannabinoids and opiates [97]. Although the molecular aspect of yoga on various pathological conditions is not well established [98] we have attempted to pave way for future study designs that examine their relation to NP.

Modern prescriptive treatment strategies and reductionist therapeutic approaches, pertaining to a few or most of the systemic and psychological disorders, have various metabolic side effects. The use of yoga will help to cope these well-defined side effects and will boost the quality of health care. Overall, the simplicity and practicality of yoga practices makes it a viable therapy that should be utilized in rehabilitation centers or clinics in order to help ameliorate NP [6,7,17–19].

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Authorship contribution

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Conflict of interest

No conflict of interests exists.

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References

1. National Spinal Cord Injury Statistical Center: Spinal Cord Injury Facts and Figures at a Glance., 2016,
2. Barrett H, McClelland JM, Rutkowski SB, Siddall PJ: Pain characteristics in patients admitted to hospital with complications after spinal cord injury. Archives of physical medicine and rehabilitation 2003;84:789–795.
3. Finnerup NB, Otto M, Jensen TS, Sindrup SH: An evidence-based algorithm for the treatment of neuropathic pain. Medscape general medicine 2007;9:36.
4. Cardenas DD, Jensen MP: Treatments for chronic pain in persons with spinal cord injury: a survey study. Journal of Spinal Cord Medicine 2006;29:109.
5. Zwick D: Integrating Iyengar yoga into rehab for spinal cord injury. Nursing2015 2006;36:18–22.
6. White DG: Yoga, brief history of an idea. Yoga in practice 2012;5:1–23.
7. White DG: The" Yoga Sutra of Patanjali": A Biography. Princeton University Press, 2014.
8. Trungpa C: The Lion's Roar: An Introduction to Tantra. Shambhala Publications, 1992.
9. Yeshe T, Courtin R, Cameron A: The bliss of inner fire: Heart practice of the Six Yogas of Naropa. Simon and Schuster, 1998.
10. Sarbacker SR: Samadhi: the numinous and cessative in Indo-Tibetan yoga. SUNY Press, 2012.
11. Innes KE, Bourguignon C, Taylor AG: Risk indices associated with the insulin resistance syndrome, cardiovascular disease, and possible protection with yoga: a systematic review. The Journal of the American Board of Family Practice 2005;18:491–519.
12. Smith KB, Pukall CF: An evidence-based review of yoga as a complementary intervention for patients with cancer. Psycho-Oncology 2009;18:465–475.
13. Vancampfort D, Vansteelandt K, Scheewe T, Probst M, Knapen J, De Herdt A, De Hert M: Yoga in schizophrenia: a systematic review of randomised controlled trials. Acta Psychiatrica Scandinavica 2012;126:12–20.
14. Sharma M, Haider T, Bose PP: Yoga as an Alternative and Complementary Treatment for Asthma A Systematic Review. Journal of Evidence-Based Complementary & Alternative Medicine 2012;17:212–217.
15. Sengupta P: Health impacts of yoga and pranayama: A state-of-the-art review. International journal of preventive medicine 2012;3
16. Sharma R: Pranayama for better life. Lotus Press, 2006.
17. McCorry LK: Physiology of the autonomic nervous system. American journal of pharmaceutical education 2007;71
18. Jerath R, Edry JW, Barnes VA, Jerath V: Physiology of long pranayamic breathing: neural respiratory elements may provide a mechanism that explains how slow deep breathing shifts the autonomic nervous system. Medical hypotheses 2006;67:566–571.

19. Buffart LM, Van Uffelen JG, Riphagen II, Brug J, van Mechelen W, Brown WJ, Chinapaw MJ: Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials. BMC cancer 2012;12:1.
20. Blank S, Kittel J, Haberman M: Active practice of Iyengar yoga as an intervention for breast cancer survivors. International Journal of Yoga Therapy 2005;15:51–59.
21. Carson JW, Carson KM, Porter LS, Keefe FJ, Seewaldt VL: Yoga of Awareness program for menopausal symptoms in breast cancer survivors: results from a randomized trial. Supportive care in cancer 2009;17:1301–1309.
22. Galantino ML, Cannon N, Hoelker T, Iannaco J, Quinn L: Potential benefits of walking and yoga on perceived levels of cognitive decline and persistent fatigue in women with breast cancer. Rehabilitation Oncology 2007;25:3.
23. Galantino ML, Bzdewka TM, Eissler-Russo JL, Holbrook ML: The impact of modified Hatha yoga on chronic low back pain: a pilot study. Alternative therapies in health and medicine 2004;10:56.
24. Sherman KJ, Cherkin DC, Erro J, Miglioretti DL, Deyo RA: Comparing yoga, exercise, and a self-care book for chronic low back pain: a randomized, controlled trial. Annals of Internal Medicine 2005;143: 849–856.
25. Bushnell M, Case L, Ceko M, Cotton V, Gracely J, Low L, Pitcher M, Villemure C: Effect of environment on the long-term consequences of chronic pain. Pain 2015;156:S42.
26. Matsuzawa-Yanagida K, Narita M, Nakajima M, Kuzumaki N, Niikura K, Nozaki H, Takagi T, Tamai E, Hareyama N, Terada M: Usefulness of antidepressants for improving the neuropathic pain-like state and pain-induced anxiety through actions at different brain sites. Neuropsychopharmacology 2008;33:1952–1965.
27. Miller LR, Cano A: Comorbid chronic pain and depression: who is at risk? The Journal of Pain 2009;10:619–627.
28. Wallace VC, Segerdahl AR, Blackbeard J, Pheby T, Rice AS: Anxiety-like behaviour is attenuated by gabapentin, morphine and diazepam in a rodent model of HIV anti-retroviral-associated neuropathic pain. Neuroscience letters 2008;448:153–156.
29. Seminowicz DA, Laferriere AL, Millecamps M, Jon S, Coderre TJ, Bushnell MC: MRI structural brain changes associated with sensory and emotional function in a rat model of long-term neuropathic pain. Neuroimage 2009;47:1007–1014.
30. Summers JD, Rapoff MA, Varghese G, Porter K, Palmer RE: Psychosocial factors in chronic spinal cord injury pain. Pain 1991;47:183–189.
31. Vachon P, Millecamps M, Low L, Thompsosn SJ, Pailleux F, Beaudry F, Bushnell CM, Stone LS: Alleviation of chronic neuropathic pain by environmental enrichment in mice well after the establishment of chronic pain. Behavioral and brain functions 2013;9:1.
32. Ji R-R, Xu Z-Z, Gao Y-J: Emerging targets in neuroinflammation-driven chronic pain. Nature reviews Drug discovery 2014;13:533–548.
33. Kumar SP, Saha S: Mechanism-based classification of pain for physical therapy management in palliative care: A clinical commentary. Indian journal of palliative care 2011;17:80.
34. Fields HL: Should we be reluctant to prescribe opioids for chronic non-malignant pain? Pain 2007;129:233–234.
35. Chou R, Huffman LH: Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Annals of internal medicine 2007;147:492–504.
36. Schomberg D, Miranpuri G, Duellman T, Crowell A, Vemuganti R, Resnick D: Spinal cord injury induced neuropathic pain: Molecular targets and therapeutic approaches. Metabolic brain disease 2015;30: 645–658.
37. Ahmed MM, Lee H, Clark Z, Miranpuri GS, Nacht C, Patel K, Liu L, Joslin J, Kintner D, Resnick DK: Pathogenesis of spinal cord injury induced edema and neuropathic pain: expression of multiple isoforms of wnk1. Annals of neurosciences 2014;21:97.
38. Kim HT, Kim T, Novotny B, Khan N, Aksamit J, Siegel S, Miranpuri GS, Resnick DK: Thermal hyperalgesia assessment for rats after spinal cord injury: developing a valid and useful pain index. The Spine Journal 2014;14:984–989.
39. Lee HK, Ahmed MM, King KC, Miranpuri GS, Kahle KT, Resnick DK, Sun D: Persistent phosphorylation of NKCC1 and WNK1 in the epicenter of the spinal cord following contusion injury. The Spine Journal 2014;14:777–781.
40. Miranpuri GS, Schomberg DT, Alrfaei B, King KC, Rynearson B, Wesley VS, Khan N, Obiakor K, Wesley UV, Resnick DK: Role of Matrix Metalloproteinases 2 in Spinal Cord Injury-Induced Neuropathic Pain. Annals of Neurosciences 2016;23:25–32.
41. Krueger EM, Miranpuri GS, Resnick DK: Emerging role of WNK1 in pathologic central nervous system signaling. Annals of neurosciences 2011;18
42. Hasbargen T, Ahmed MM, Miranpuri G, Li L, Kahle KT, Resnick D, Sun D: Role of NKCC1 and KCC2 in the development of chronic neuropathic pain following spinal cord injury. Annals of the New York Academy of Sciences 2010;1198:168–172.
43. Cramer SW, Baggott C, Cain J, Tilghman J, Allcock B, Miranpuri G, Rajpal S, Sun D, Resnick D: The role of cation-dependent chloride transporters in neuropathic pain following spinal cord injury. Molecular pain 2008;4:1.
44. Kawasaki Y, Xu Z-Z, Wang X, Park JY, Zhuang Z-Y, Tan P-H, Gao Y-J, Roy K, Corfas G, Lo EH: Distinct roles of matrix metalloproteases in the early-and late-phase development of neuropathic pain. Nature medicine 2008;14:331–336.
45. Inoue K, Tsuda M, Koizumi S: ATP receptors in pain sensation: involvement of spinal microglia and P2X4 receptors. Purinergic signalling 2005;1:95–100.
46. Tsuda M, Inoue K, Salter MW: Neuropathic pain and spinal microglia: a big problem from molecules in 'small'glia. Trends in neurosciences 2005;28:101–107.
47. Tsuda M, Shigemoto-Mogami Y, Koizumi S, Mizokoshi A, Kohsaka S, Salter MW, Inoue K: P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury. Nature 2003;424:778–783.
48. Hama A, Sagen J: Behavioral characterization and effect of clinical drugs in a rat model of pain following spinal cord compression. Brain research 2007;1185:117–128.
49. Kinsey SG, Long JZ, O'Neal ST, Abdullah RA, Poklis JL, Boger DL, Cravatt BF, Lichtman AH: Blockade of endocannabinoid-degrading enzymes attenuates neuropathic pain. Journal of Pharmacology and Experimental Therapeutics 2009;330:902–910.
50. DomBourian MG, Turner NA, Gerovac TA, Vemuganti R, Miranpuri GS, Türeyen K, Satriotomo I, Miletic V, Resnick DK: B1 and TRPV-1 receptor genes and their relationship to hyperalgesia following spinal cord injury. Spine 2006;31:2778–2782.
51. Wu J, Renn CL, Faden AI, Dorsey SG: TrkB. T1 contributes to neuropathic pain after spinal cord injury through regulation of cell cycle pathways. The Journal of Neuroscience 2013;33:12447–12463.
52. Ji R-R, Berta T, Nedergaard M: Glia and pain: is chronic pain a gliopathy? PAIN® 2013;154:S10-S28.
53. Zhang Z-J, Cao D-L, Zhang X, Ji R-R, Gao Y-J: Chemokine contribution to neuropathic pain: respective induction of CXCL1 and CXCR2 in spinal cord astrocytes and neurons. PAIN® 2013;154:2185–2197.
54. Gao Y-J, Ji R-R: Chemokines, neuronal–glial interactions, and central processing of neuropathic pain. Pharmacology & therapeutics 2010;126:56–68.
55. Chen G, Park C-K, Xie R-G, Berta T, Nedergaard M, Ji R-R: Connexin-43 induces chemokine release from spinal cord astrocytes to maintain late-phase neuropathic pain in mice. Brain 2014;137:2193–2209.
56. Sorkin L, Svensson CI, Jones-Cordero TL, Hefferan MP, Campana WM: Spinal p38 mitogen-activated protein kinase mediates allodynia induced by first-degree burn in the rat. Journal of neuroscience research 2009;87:948–955.
57. Tan Y-H, Li K, Chen X-Y, Cao Y, Light AR, Fu K-Y: Activation of Src family kinases in spinal microglia contributes to formalin-induced persistent

pain state through p38 pathway. The Journal of Pain 2012;13: 1008–1015.
58. Weisshaar CL, Dong L, Bowman AS, Perez FM, Guarino BB, Sweitzer SM, Winkelstein BA: Metabotropic glutamate receptor-5 and protein kinase C-epsilon increase in dorsal root ganglion neurons and spinal glial activation in an adolescent rat model of painful neck injury. Journal of neurotrauma 2010;27:2261–2271.
59. Villemure C, Čeko M, Cotton VA, Bushnell MC: Insular cortex mediates increased pain tolerance in yoga practitioners. Cerebral cortex 2013:bht124.
60. Lee M, Moon W, Kim J: Effect of yoga on pain, brain-derived neurotrophic factor, and serotonin in premenopausal women with chronic low back pain. Evidence-Based Complementary and Alternative Medicine 2014;2014
61. Curtis K, Osadchuk A, Katz J: An eight-week yoga intervention is associated with improvements in pain, psychological functioning and mindfulness, and changes in cortisol levels in women with fibromyalgia. 2011
62. Vallath N: Perspectives on Yoga inputs in the management of chronic pain. Indian journal of palliative care 2010;16:1.
63. Kim S-S, Min W-K, Kim J-H, Lee B-H: The effects of VR-based Wii Fit Yoga on physical function in middle-aged female LBP patients. Journal of physical therapy science 2014;26:549–552.
64. Bushnell MC, Čeko M, Low LA: Cognitive and emotional control of pain and its disruption in chronic pain. Nature Reviews Neuroscience 2013;14:502–511.
65. Zhang N, Yin Y, Xu S-J, Wu Y-P, Chen W-S: Inflammation & apoptosis in spinal cord injury. The Indian journal of medical research 2012;135:287.
66. Smith EN, Boser A: Yoga, vertebral fractures, and osteoporosis: Research and recommendations. International journal of yoga therapy 2013;23:17–23.
67. Zwick D, Dunn M: Integrating Iyengar yoga into rehabilitation. Nursing2016 2007;37:10–12.
68. Balasubramaniam M, Telles S, Doraiswamy PM: Yoga on our minds: a systematic review of yoga for neuropsychiatric disorders. Frontiers in PSYCHIATRY 2013;3:117.
69. Büssing A, Ostermann T, Lüdtke R, Michalsen A: Effects of yoga interventions on pain and pain-associated disability: a meta-analysis. The Journal of Pain 2012;13:1–9.
70. Chiesa A, Serretti A: Mindfulness-based interventions for chronic pain: a systematic review of the evidence. The Journal of Alternative and Complementary Medicine 2011;17:83–93.
71. Kennedy P, Duff J: Post traumatic stress disorder and spinal cord injuries. Spinal Cord 2001;39:1–10.
72. Telles S, Naveen K, Dash M: Yoga reduces symptoms of distress in tsunami survivors in the andaman islands. Evidence-based complementary and alternative medicine 2007;4:503–509.
73. Descilo T, Vedamurtachar A, Gerbarg P, Nagaraja D, Gangadhar B, Damodaran B, Adelson B, Braslow L, Marcus S, Brown R: Effects of a yoga breath intervention alone and in combination with an exposure therapy for post-traumatic stress disorder and depression in survivors of the 2004 South-East Asia tsunami. Acta Psychiatrica Scandinavica 2010;121:289–300.
74. Kjaer TW, Bertelsen C, Piccini P, Brooks D, Alving J, Lou HC: Increased dopamine tone during meditation-induced change of consciousness. Cognitive Brain Research 2002;13:255–259.
75. Streeter CC, Whitfield TH, Owen L, Rein T, Karri SK, Yakhkind A, Perlmutter R, Prescot A, Renshaw PF, Ciraulo DA: Effects of yoga versus walking on mood, anxiety, and brain GABA levels: a randomized controlled MRS study. The Journal of Alternative and Complementary Medicine 2010;16:1145–1152.
76. Pal R, Singh SN, Chatterjee A, Saha M: Age-related changes in cardiovascular system, autonomic functions, and levels of BDNF of healthy active males: role of yogic practice. Age 2014;36:1–17.
77. Murthy PNV, Gangadhar B, Janakiramaiah N, Subbakrishna D: Normalization of P300 amplitude following treatment in dysthymia. Biological Psychiatry 1997;42:740–743.
78. Kjellgren A, Bood SÅ, Axelsson K, Norlander T, Saatcioglu F: Wellness through a comprehensive Yogic breathing program–A controlled pilot trial. BMC complementary and alternative medicine 2007;7:1.
79. Naveen G, Thirthalli J, Rao M, Varambally S, Christopher R, Gangadhar B: Positive therapeutic and neurotropic effects of yoga in depression: A comparative study. Indian journal of psychiatry 2013;55:400.
80. Tilbrook HE, Cox H, Hewitt CE, Kang'ombe AR, Chuang L-H, Jayakody S, Aplin JD, Semlyen A, Trewhela A, Watt I: Yoga for chronic low back pain: a randomized trial. Annals of internal medicine 2011;155:569–578.
81. Sherman KJ, Cherkin DC, Wellman RD, Cook AJ, Hawkes RJ, Delaney K, Deyo RA: A randomized trial comparing yoga, stretching, and a self-care book for chronic low back pain. Archives of internal medicine 2011;171:2019–2026.
82. Frank JW, Bair MJ, Becker WC, Krebs EE, Liebschutz JM, Alford DP: Update in pain medicine for primary care providers: a narrative review, 2010–2012. Pain medicine 2014;15:425–431.
83. Wren AA, Wright MA, Carson JW, Keefe FJ: Yoga for persistent pain: new findings and directions for an ancient practice. Pain 2011;152:477.
84. Hill JC, Whitehurst DG, Lewis M, Bryan S, Dunn KM, Foster NE, Konstantinou K, Main CJ, Mason E, Somerville S: Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. The Lancet 2011;378:1560–1571.
85. Tekur P, Chametcha S, Hongasandra RN, Raghuram N: Effect of yoga on quality of life of CLBP patients: A randomized control study. International journal of yoga 2010;3:10.
86. Sanford M: January 2007
87. Iyengar BKS: Light on yoga. 1965
88. Schütze R, Rees C, Preece M, Schütze M: Low mindfulness predicts pain catastrophizing in a fear-avoidance model of chronic pain. Pain 2010;148:120–127.
89. Urtikova N, Berson N, Van Steenwinckel J, Doly S, Truchetto J, Maroteaux L, Pohl M, Conrath M: Antinociceptive effect of peripheral serotonin 5-HT 2B receptor activation on neuropathic pain. Pain 2012;153:1320–1331.
90. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, Wernicke JF: A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Medicine 2005;6:346–356.
91. Zope SA, Zope RA: Sudarshan kriya yoga: Breathing for health. International journal of yoga 2013;6:4.
92. Lim S-A, Cheong K-J: Regular Yoga Practice Improves Antioxidant Status, Immune Function, and Stress Hormone Releases in Young Healthy People: A Randomized, Double-Blind, Controlled Pilot Study. The Journal of Alternative and Complementary Medicine 2015;21:530–538.
93. Kumar N, Bhatnagar S, Velpandian T, Patnaik S, Menon G, Mehta M, Kashyap K, Singh V: Randomized controlled trial in advance stage breast cancer patients for the effectiveness on stress marker and pain through Sudarshan Kriya and Pranayam. Indian journal of palliative care 2013;19:180.
94. Shree N, Bhonde RR: Can yoga therapy stimulate stem cell trafficking from bone marrow? Journal of Ayurveda and integrative medicine 2016;7:181–184.
95. Malshe PC: Nisshesha rechaka pranayama offers benefits through brief intermittent hypoxia. AYU (An international quarterly journal of research in Ayurveda) 2011;32:451.
96. Vera FM, Manzaneque JM, Maldonado EF, Carranque GA, Rodriguez FM, Blanca MJ, Morell M: Subjective sleep quality and hormonal modulation in long-term yoga practitioners. Biological psychology 2009;81:164–168.
97. Michalsen A, Grossman P, Acil A, Langhorst J, Lüdtke R, Esch T, Stefano G, Dobos G: Rapid stress reduction and anxiolysis among distressed women as a consequenceof a three-month intensive yoga program. Medical Science Monitor 2005;11:CR555-CR561.
98. Sutar R, Yadav S, Desai G: Yoga intervention and functional pain syndromes: a selective review. International Review of Psychiatry 2016;28:316–322.