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Management Of Neuropathic Pain Through Unani System Of Medicine

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Abstract
Neuropathic pain is associated with impaired quality of life, and is often poorly managed. Around 7–8% of adults have pain with neuropathic characteristics. A quarter of people with diabetes and 35% of people with HIV have neuropathic pain. The management of neuropathic pain can be challenging and, as with all pain, should be approached with a bio psychosocial framework. There are several options for drug treatment as part of an overall approach to improve patients' quality of life and function. Through this paper an effort has been made to focus on how Unani system of medicine can overcome this condition.
Keywords: Neuralgia, Neuropathic, Management

Abbreviations- NMDA: N-methyl-D-aspartate; CNS: central nervous system; PNS: peripheral nervous system; STZ: streptozotocin; ROS: reactive oxygen species; CIPN: chemotherapy drugs that induce peripheral neuropathy; HAE-AC: hydroalcoholic extract of A. calamus; MPO: myeloperoxidase; TST: tibial and sural nerve transection; CCI: chronic constriction injury; TBARS: thiobarbituric acid reactive substances; GSH: glutathione; PDPN: painful diabetic polyneuropathy; 6-OHDA: 6-Hydroxydopamine; PCPA: p-chlorophenylalanine; COX-2: cyclooxygenase 2; MDA: malondialdehyde; SNL: spinal nerve ligation; NOS: nitric oxide synthase; PSNL: partial sciatic nerve ligation; EEPp: ethanolic extract from P. pubescens fruits; THC/CBD, A9-Tetrahydrocannabinol/Cannabidiol; DRG: dorsal root ganglion; 3α-HSOR: 3α-Hydroxysteroidoxidoreductase; SOD: superoxide dismutase

Introduction

Waja is an Arabic word which is used for pain. Synonym of *Waja* is alam/aalam. *Waja* (Pain) is a perception of incongruity in the body. In Unani System of Medicine, there are two main causes of pain. (a) Sudden or irregular abnormality of Temperament (*Su'-i-Mizaj Mukhtalif*). (b) Breach of continuity (*Tafarruq-i-Ittisal*). Irregular abnormality of temperament means the normal balance of temperament becomes disturbed, the newly developed temperament becomes hot or cold contrary to the original. According to *Jalinus* (Galen) loss of continuity is the only real cause of pain. Thus if heat produces pain, it is through a breach of continuity. Similarly, cold acts by shrinking and retracting tissue particles and thus dislocating these from their original positions. [1, 2, 3, 4]

Pain is a manifestation of the loss of the harmony of an area of the body, which is and it is important for the topographic localization of the suffering tissue or organ and the detection of the causative factor of the disease. [5]

Concept of Neuropathic pain in Unani System of Medicine

Neuropathic pain is supposed to be a post-renaissance described medical entity. It is often believed that John Fothergill (1712-1780) who provided the first description of this condition in 1773 [7]. Fact is that the Unani physicians were very much familiar to Neuropathic Pain and the term they used for Neuropathic Pain was *Waja al Asab*.

The term *"Waja al Asab"* (Nerve-Originated Pain) was used as a term in the classical Unani literature for describing pain syndromes which etiologically originated from nerves rather than the tissues and organs.

The term "*Khadar*" (Abnormal sensation) was also used by Persian scholars to explain abnormal sensations such as numbness, tingling sensation, or piercing needles because of nervous anatomic or functional pathology [8, 9, 10]

Zakariyā Rāzī (865-925 AD) classified various pains according to their point of origin and believed that the nerve were the potential originating site of pain contiguous to the viscera, bone, fascia, muscle and blood vessels. Additionally, he described the differentiating properties of the nerve originated pain in his book *"Liber Continens"* [8].

Majusi (982 AD) explained that pain is mostly caused by nerves and described *khadar* as a sensation that is analogous to tingling over a body part and numbness when needles penetrate it. [9]

Avicenna introduced other kinds of pain such as toxic and induced snake bite ones. He also suggested natural electrical injury due to touch of the electric fish as another cause of nerve originated pain. [8]

"The characteristic of *Khadar* is that the patient sense like the tingling sensation or penetrating needle in his organ, with the defect in his sensation quality and motor dysfunction. The condition is similar to that happens in the foots when anyone sit on them or be compressed by other thing for a long time." *Khadar may be due to poisoning, snake or scorpion bite, touch of an electrical fish called Nagher, and opium overdose.* [9, 11, 12]

Traumatic nerve pain is another concept of nerve-originated pain that is discussed by *Jurjani*. Iatrogenic nerve injuries were prevalent in medieval Persia as a complication of bloodletting by venesection. *Jurjani* believed that nerve injury is more painful than other tissue injuries due to functional and anatomic connection between nerves and brain. He also considered sciatica (*Irq al Nisa*) as a nerve-originated pain that could lead to motor dysfunction. [8,14]

Avicenna, based on the site, classified the causes of nerve-originated pain into brain, total spinal cord, specific level of spinal cord, and peripheral nerve damage. He also noted the coincidence of nerve-originated pain with stroke, epilepsy, meningitis and tetanus. *Avicenna* believed that motor neurons

are less sensitive than sensory neurons in pathologic conditions, so chronicity of sensory neuropathies may lead to motor dysfunctions. He also made a description of trigeminal neuralgia [13].

Pathophysiology

Majoosi discussed regarding pathophysiology of nerve originated pain. He proposed nerve compression at different spinal levels and sensory nerves as the potential etiology for nerve-originated pain. According to him, excessive temperatures and physical cold stimuli on nerve could be the causal agent. His observations on the mentioned pathological conditions were associated with impairment in the nerve conduction leading to an abnormal sensory function. He also theorized a possible motor dysfunction with nerve-originated pains as in the case of sensory and motor innervations of an organ by a single nerve. [8]

•***Waja' Khadari*** **(Neuropathic pain):** A neuropathic nature of pain, characterized by pain with paresthesia caused by the blockage of sensory nerve endings due to extreme cold, congestion or other reason.

Principle of Treatment

Principal of treatment will be disease specific and based on three basics temperament change matter dissolving drugs and anaesthetics basic therapeutic strategies will be adopted which mention *Ibn e Sina* but in case of the severity, *musakkinat* will first principle which will priority. Change of the condition of an organ from cold to hot or vice versa and other factors that affecting temperament included changes in food, climate, rest, exercise, sleep and emotions. An example of Avicenna's temperament change protocol was 'walking a long distance, listening to nice music which induces sleep or engaging in pleasurable experience can be powerful analgesics' [4]

Ilaj e Asli **(Primary Treatment)**

1. *Izalae sabab* (Removal of the cause)

Actual and foremost treatment of pain is removal of cause such as application or administration of heteropathic regimens in case of *sue mizaj sada*, diversion and evacuation of morbid matter in case of *sue mizaj maddi* and *tafarruq e ittesal*.

2. *Imalae Mawad (Diversion of morbid matter):*

The Diversion of morbid matter from the affected site to the other is called *Imalae Mawad*. It is done by increasing the flow of humours/circulation towards a specific site by various modes. The purpose of diversion is to reduce irritation, to reduce inflammation and ultimately to relive pain.

3. *Tanqiya Mawad (Evacuation of morbid matter):*

Elimination of morbid matter is called as *Tanqiya Mawad* by which the causative or acrid humour is removed. The various methods of *tanqiya mawad* are:

Ilaj e Saanawi (Secondary Treatment)

When the pain is intolerable, use of *Qawi musakkinat* (potent analgesics) and *Muklhadderat* (anaesthetics) are recommended. [17,46]

The management of pain in Unani system is based on the concept of *Ilaj bil zid* with administration of drugs of opposite property of the disease. The analgesics used are either *Moaddelat* (moderators) or *Mohallilat* (resolvents) or *Mukhadderat* (anaesthetics). The *moaddelat* and *mohalillat* relieve the pain by normalizing the cause of *sue mizaj* and *tafarruqe ittesal*, while anaesthetics relieve pain by desensitizing the nerve endings.[3, 6,11]. Based on aetiology of pain, Avicenna advocated the mode of

action of pain relievers. They exert their action as *Moaddelat* (temperament modulator), *Mohalillat* (Resolvent drugs) or *Mukhadderat* (anaesthetics).
First two types of analgesics are beneficial for s*ue-mizaj* and *tafarruq e ittesal* while *mukhadderat* are beneficial for desensitizing the local nerve which carry impulse of pain.[3,11]

1. *Moaddelat (Modulator or Moderate Analgesics)*

These analgesics act due to their contrary property. Therefore the relief of pain may depend upon altering the temperament of painful area. In *Sue mizaj sada* alter the temperamental condition of an organ from hot to cold or vice versa by using shibt (*Antheum graveolance*), katan (*Linum usitatissimum)*, made into a poultice and applied over the painful area.

2. *Muhallilat (Resolvent)*

These analgesics act by dispersing the matter which produces pain, therefore in the treatment of *Sue Mizaj maddi* or *tafarruq e ittesal*, resolvent analgesics are recommended, Further he stated that *mohalillat* (Matter dissolving drugs) act as relaxants or softeners, eg: *Baboona* (*Anthimis nobilis*), dill (*Antheum graveolens*), linseed (*Linum usitatissimum*), melilot (*Melilotus sp.*), celery seed (*Apium graveolens*), bitter almond (*Prunus amygdalus*), Nakhoona (*Trigonella uncata*). [2,4,6]

3. *Mukhadderat (Anaesthetics)*

They act by diminishing sensation in the concerned part. In fact *mukhadderat* (anaesthetics) are beneficial for desensitizing the local nerve which carry impulse of pain [4,11]. As per Unani Concept "His" (sensation) is mainly composed of *hararat* and *rutubat* (hot and moist) which perceive pain and unpleasant feeling in pathological condition. Hence, *mukhadderat* which are *barid wa yabis* (cold and dry) in temperament, hampers the transmission of *rooh e nafsani* or feeling of pain at particular organ due to their contrast property. Further due to *barid* temperament of *mukhadderat,* nerve fibre density decreases which may lead to greater reduction in conduction velocity of *rooh e nafsani* (neurotransmission for pain) [16].
Mukhadderat were widely used since time immemorial. *Al-Razi* (Rhazes 835-925 A.D.) used *Afiyun* (*Papaver somniferum*) as a *mukhaddir* (anaesthetic) in surgical procedures, Avicenna too used some opium formulations as analgesic and anaesthetics prior to surgery. He mentioned the analgesic, anaesthetic and hypnotic action of some herbs including Afiyun (*Papaver somniferum*) BizrulBanj (*Hyocyasmus albus*), shokran (*Conium maculatum)* mandragora or nightshade (*Mandragora officinarum*) and also advocated the use of ice as *Mukhaddir* (anaesthetic). He was well aware of the potency and toxicity of some of these formulations and differentiated between sleep inducing drugs and those that impair the sensation. Furthermore, he also stated that one of the impediment of pain management depends upon the mode of action of drug. If the drug is slow acting, patient may not tolerate the pain for prolonged period and if fast acting such as *advia mukhaddira*, it produces adverse effects. Therefore, the treatment entirely depends on the intelligence of physician.[2, 6,11]
There are plenty of single as well as compound Unani formulations mentioned in classical literature for the management of neuropathic pain. The efficacy of these drugs have been proved by using scientific parameters through various research. Few classical single Unani medicines used for the management of neuropathic pain along with their mechanism of action are listed below.

1. Waj Turki *(Acorus calamus)*

A. calamus, belongs to Araceae family, it has been used for the management of several inflammatory disorders in Indian traditional medicine [18]. The *hydroalcoholic extract* of *A. calamus* (HAE-AC) has been shown to significantly attenuate thermal hyperalgesia, thermal allodynia and mechanical hyperalgesia on neuropathic pain induced by tibial and sural nerve transection (TST) in rats. Moreover, a significant decrement in the superoxide anion, total calcium levels and myeloperoxidase (MPO) activity were also observed [19]. Furthermore, HAE-AC decreased superoxide anion, total calcium levels and MPO activity in sciatic nerve chronic constriction injury (CCI). It also attenuated CCI induced development of painful behavioural changes including: thermal, radiant, mechanical hyperalgesia and thermal, chemical, tactile allodynia in rats [20]. In other study, HAE-AC attenuated the development of painful behavioural (thermal and mechanical hyperalgesia and mechanical allodynia), biochemical (rises in the levels of superoxide anion, total calcium and myeloperoxidase activity) and histological changes in vincristine-induced neuropathy in rats [21]. In a further study saponin rich extract of *A. calamus* (20 and 40 mg/kg) significantly improved CCI-induced nociceptive pain threshold, sciatic functional and electro-physiological changes in rats [22]. These effects may have been exerted probably by multiple mechanisms containing antioxidative, anti-inflammatory, calcium inhibitory activity and neuroprotective actions [19-20].

2. Zafran *(Crocus sativus)*

C. sativus commonly known as Saffron belongs to the Iridaceae family and extensively cultivated in Iran and other countries such as India and Greece [22, 24]. It is used traditionally as food and remedy for several disorders including bronchospasm, insomnia, asthma, menstruation problems, pain relief and cardiovascular disorders [25]. Chemical studies have shown that most important bioactive constituents of *C. sativus* are crocin, crocetin, safranal and picrocrocin [25, 26]**.** The ethanolic and aqueous extracts of saffron as well as safranal attenuated the behavioural symptoms of neuropathic pain in CCI model in rats [27]. Besides, the ethanolic and aqueous extracts of *C. sativus* attenuated malondialdehyde (MDA) and increased GSH levels in CCI animals[28]. Safranal showed an anti-nociceptive effect in chemical (formalin and acid acetic tests) methods of nociception in mice [29]. Stigma extracts of *C. sativus* exerted anti-inflammatory effects[30]. A recent study showed that saffron and crocin (30 mg/kg) reduced thermal hyperalgesia and mechanical allodynia, but crocin at lower dose (15 mg/kg) was ineffective to produce protective effects [31]. Ethanolic and aqueous extracts of *C. sativus* as well as safranal diminished allodynia and hyperalgesia induced by (CCI) of the sciatic nerve, besides *C. sativus* extracts significantly decreased the lumbar spinal cord contents of MDA and proinflammatory cytokines (TNFα, IL-1β, IL-6) [32]. A more recent study showed that, saffron as an adjunctive therapy in combination with amitriptyline lead to improvement of the therapeutic outcome in the management of neuropathic pain [33].

3. Qinnab (*Cannabis sativa*)

A9-Tetrahydrocannabinol/Cannabidiol (THC/CBD) *Cannabis sativa* has a long history of use as a medicinal agent [34]. THC/CBD is derived from strains of *C. sativa* plant developed to produce high and reproducible yields of THC and CBD, with trace quantities of other cannabinoids and terpenes in a solution having ethanol, propylene glycol, and peppermint oil flavoring. THC and CBD contain ≥ 90% of the total cannabinoid content of the extracts [19]. THC/CBD display many pharmacologic effects such as anti-inflammatory, appetite stimulant and anti-emetic effects [34]. THC/CBD has been approved in Canada as adjunctive treatment for the symptomatic improve of neuropathic pain in multiple sclerosis (MS) in adults [19]. The standardized extract of *C. sativa* evoked a total relief of

thermal hyperalgesia, in CCI model in rat that was mediated by vanilloid receptors TRPV1 [34]**.** A phase-II randomized clinical trial study showed that administration of active cannabis ranging in potency between 1 and 8% D-9-tetrahydrocannabinol significantly reduced neuropathic pain intensity in HIV-associated distal sensory predominant polyneuropathy (DSPN). These results showed that cannabinoid therapy may be an effective choice for pain relief in patients with medically intractable pain due to HIV-associated DSPN with mild and self-limited side effects [18]. Moreover, in randomized controlled trials THC/CBD was effective in patients with central neuropathic pain and MS who completed -2 years of treatment with no evidence of tolerance [19]. Also Johnson *et al*. in a double-blind, randomized, placebo-controlled, parallel-group trial study showed that THC/CBD is a useful adjunctive treatment for relief of pain in patients with intractable cancer-related pain who experience inadequate analgesia despite chronic opoid therapy [20]. Same authors in an open-label extension study showed that long-term use of THC/CBD spray relieved cancer-related pain and generally well tolerated in advanced cancer patients. Moreover, patients who kept using the study medication did not seek to increase their dose of THC/CBD spray over time [21]. Recently, in a double-blind, randomized, placebo-controlled, parallel group study administration of THC/CBD oromucosal spray in patients with peripheral neuropathic pain clinically improved their pain, sleep quality and global impression of change in the severity of their condition [22]. More recently in a multi-center, open-label, follow-on study THC/CBD spray was beneficial for the majority of patients that have peripheral neuropathic pain associated with diabetes or allodynia. THC/CBD spray was well tolerated during the study period and also patients did not seek to increase their dose over time, with no new safety concerns arising from long-term use [23].

Table 1. Mechanisms of actions of Unani medicines against neuropathic pain in animal models

Unani drug	Animal model	Mechanisms of actions	Study
1. Amla *(Emblica officinalis)*	Streptozotocin (STZ)-induced diabetes in rat	Modulation of oxidative–nitrosative stress	(40)
2. Majeeth (*Rubia cordifolia)*	Paclitaxel-induced neuropathic pain in rat	Involvement of GABA or antioxidant mechanism	(41)
3. Raihan **(***Ocimum sanctum)*	Vincristine-induced neuropathic pain in rat	Decrement of oxidative stress and calcium levels	(42)
4. Waj Turki (*Acorus calamus)*	a) Tibial and sural nerve transection (TST) in rat) Chronic constriction injury (CCI) in rat	a) Anti-inflammatory, antioxidant, and neuroprotective actions b) Anti-oxidative, anti-inflammatory, neuroprotective and calcium inhibitory	(19) (20)

Unani drug	Animal model	Mechanisms of actions	Study
	c) Vincristine-induced neuropathic pain in rat	c) Anti-oxidative, anti-inflammatory, neuroprotective and calcium inhibitory actions	(21)
5. Zard Chob (Curcumin)	a) CCI in mice b) CCI in rat	a) Descending monoamine system (coupled with spinal β2-adrenoceptor and 5-HT1A receptor) b) Decrement the serum level of COX-2	(43) (44)
6. Qinnab (*Cannabis sativa)*	CCI in rat	Mediated by vanilloid receptors TRPV1.	(45)
7. Zafran (Saffron's extracts and safranal)	CCI in rat	Antioxidant effects.	(27)

Conclusion

This paper reveals that Unani System of Medicine has potential in the management of Neuropathic pain. Various single plants have shown promising results in relieving this type of pain. Further investigations are needed to isolate the various phyto constituents present to get a clear idea of the mechanism of action of the plants and Unani compound formulations for the management of neuropathic pain.

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