

Night Pain – Vital Functions (Sleep & Pain) Interact: Use of a *California poppy* agent to improve restorative sleep

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The severity of chronic pain can be mild to severe and it can be episodic or continuous. In some cases the pain partially affects the patient's well-being, level of function, and quality of life and in others it is completely incapacitating. The goal of pain management is to rapidly provide relief and improve the quality of life, including the ability to participate in day-to-day activities. Analgesics and other medications are commonly used in the treatment of chronic pain but many of these medications effect sleep and/or sleep quality. Clinical trials have shown decreases in total sleep time, decreases in rapid eye movement (REM) sleep, and decreases or increases in Stage 1, 2, 3 or 4¹⁻⁶. Sleep has been shown to be negatively affected by NSAIDs, opioids and other pain medications. But what about the inter-relation of pain with

sleep? It is a bidirectional relationship where poor sleep enhances pain and enhanced pain further disturbs sleep.

According to the medical literature, 50% to 89% of chronic pain patients complain of poor sleep and/or feeling unrefreshed upon awakening⁷. Sleep has an essential function especially for recovery in chronic pain conditions. Lower sleep efficiencies and fragmented sleep were observed in a polysomnographic study of patients with diabetic and postherpetic neuropathy⁸.

In patients with fibromyalgia, the amount of slow sleep, REM sleep, and total sleep time were reduced relative to age-matched controls⁸. A prospective study in this patient population demonstrated that nights with poor sleep tended to be followed by days with greater pain and days with greater pain lead to nights with greater sleep

disturbance⁸. This type of sleep disturbance is reported in many other types of chronic pain conditions.

According to the majority of the studies, sleep deprivation produces hyperalgesic changes in patients⁹⁻¹⁰. According to some studies, the hours of reported sleep on the previous night was a highly significant predictor of the current day's pain frequency¹¹. In addition, these studies showed that night-to-night changes in sleep affect pain report.

The body of evidence demonstrates the importance of considering sleep when assessing and treating pain. These two vital functions sleep and pain are also inter-related with anxiety and depression. In fact, insomnia, anxiety or depression are frequent co-morbidities associated with chronic pain. Disrupted sleep and rest patterns and poor sleep quality were positively correlated with depression and pain-related disability¹².

California poppy (*Eschscholzia californica*), has a long traditional use history as an analgesic, anxiolytic and sedative. According to the historical use, when used as a sleep aid, the time it takes to fall asleep is reduced and sleep quality is improved¹³. There are no reported cases of addiction or physical dependence to California poppy making this herb an interesting candidate for the management of chronic pain.

The pharmacological mechanism of action of California poppy is complex. Its potential use as an analgesic or co-analgesic and sedative is supported by the pharmacological properties of the herb. Dose-dependent sedative properties as well as anxiolytic effects were shown in mice¹⁴⁻¹⁵. The anxiolytic effects occurred at lower doses than the sedative effects. In a subsequent study, using a 5:1 herb extract, Rolland et al¹⁴⁻¹⁵ confirmed the sedative and anxiolytic properties of the herb in mice using two behavioural tests. Flumazenil® is a benzodiazepine antagonist and was used to partially antagonize the sedative and anxiolytic effects. The mouse study also demonstrated that the herb had no antihistaminic effects which have been associated with sedative effects of some drugs. This led the researchers to suggest that benzodiazepine receptors may be implicated in the sedative and anxiolytic properties of the herb. Contrary to the typical pharmacological properties of a benzodiazepine, California poppy did not exhibit any anticonvulsant properties against pentetyletetrazole. Similarly, the mouse study also showed that the herb lacked muscle relaxant and antipsychotic properties which are common with benzodiazepines and antidepressants. The herb also lacked antidepressant-like properties in the animal model. A dose-dependent peripheral analgesic effect was

demonstrated using the writhing test. The herb only had effects in the hot plate test at higher dosages but no dose-response was demonstrated. The sedative effect clearly shows a central effect of the herb but the absence of central analgesic effect at lower doses is part of its complex pharmacology.

Gafner et al¹⁶ demonstrated that a 70% ethanol extract of California poppy (*Eschscholzia californica*) was able to bind to 5-HT_{1A} and 5-HT₇ receptors. The activity on the 5-HT_{1A} receptor was at least partly due to the presence of one of the aporphine alkaloids. The dose-dependent antidepressant-like effects of protopine were demonstrated in animal models¹⁷. Protopine was shown to be an inhibitor of both serotonin transporter and noradrenaline transporter *in vitro*. However, it would require about 4 grams of the standardized extract (5:1 extract ratio) to obtain a dose level of protopine that is sufficient to observe an antidepressant like effect. This would explain the absence of this type of an effect in human subjects.

Based on the *in vivo* experimental studies conducted by Rolland et al¹⁴⁻¹⁵, the sedative and anxiolytic effects of California poppy are dose-dependent with the anxiolytic effects occurring at lower doses than the sedative effects. Chamberland¹⁸ described that sedation and analgesia were dose-dependent in humans. As

with any pharmacologically-active ingredient, side effects were also dose-dependent. The observed side effects included insomnia (excitation), drowsiness and altered dreaming.

The insomnia effect was described as an excitation subsequent to consuming California poppy and is consistent with the pharmacology of the alkaloids present in the herb. The effect on dreaming was described as pleasant dreams or bizarre dreams (fantastic dreaming). This is not euphoria or hallucination but a physiological effect on dreaming.

Herbalists traditionally use tinctures of California poppy to treat nightmares in children. Some herbalist believed that the benefit in children was derived from the anxiolytic and sedative properties of the herb. Anxiety and sleep are inter-related. It was originally believed that the herb provided benefit through its anxiolytic effect on the child (i.e., calming the child before sleep onset). Based on our understanding of sleep and the inter-relationship between sleep and anxiety, the herb probably improved sleep quality in these patients by directly influencing sleep physiology.

The investigations performed by Chamberland¹⁸ lead to the use of concentrated, standardized, extracts of this herb for use as an adjuvant to pain medications in the treatment of chronic pain. An open-label clinical trial (approved by a central ethics review

board) was performed in patients with moderate-to-severe uncontrolled chronic pain¹⁹. The patients suffered from back pain, joint pain, arthritis, cervical pain, and fibromyalgia with or without myofascial syndrome. The severity of pain ranged from moderate, moderate-severe to severe. In every case, the research product was used as an adjuvant to standard of care.

Approximately 50% of the study patients had a significant clinical benefit in pain relief or sleep. This is a clinically significant result since the patient population consisted of patients with uncontrolled pain despite receiving standard of care for many years. A change in the Visual Analog Scale (VAS) of 1.0 or less was classified as a no response to the treatment. The average delta-VAS for these patients was 2.4.

In some patients, the herbal agent was added to the standard of care only for the management of pain-related insomnia. The majority of these patients obtained a significant improvement in sleep and some described that they had pleasant dreams.

The study results showed that the California poppy extract product could be used to provide additional analgesia to the patient and for the management of night pain and insomnia. Although it possess both analgesic and sedative-hypnotic properties, our research and experience with these standardized

extracts has lead us to believe that this herbal agent provides its main benefits to patients because of its effects on sleep quality.

Its effect on dreams is believed to be associated with the herbs effect on sleep. It has been shown to induce pleasant or strange dreams (fantastic dreams) in patients¹⁸. Dreaming is part of a very complex physiology. There are studies that have associated dreaming with rapid eye movement (REM) sleep²⁰. We have postulated that this effect on dreaming occurs because of the agent's effect on sleep quality. These herbal agents help improve the poor quality sleep in patients with chronic pain. This herbal agent will effectively improve sleep and over time the patient's health will globally improve. This overall improvement is a result of the improved quality of sleep (i.e. restorative sleep).

Many references provide dosage information for the use of California poppy but this information is based on historical use and not clinical trial evidence. The clinical results discussed in this article were obtained in patients using a standardized concentrated herb extract. The content of the isoquinoline alkaloids is critical for clinical benefit. The use of this type of a herbal agent should be considered for any patient suffering from chronic pain with disrupted sleep (i.e., insomnia as a co-morbidity).

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