

Brief Commentary

e The Successful Treatment of Opioid Withdrawal-Induced Refractory Muscle Spasms with 5-HTP in a Patient Intolerant to Clonidine

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Instituting drug holidays for chronic opioid using patients is becoming commonplace for pain practitioners initiating procedures such as intrathecal pump or spinal cord stimulator trials. As such, pain practitioners need to be adept in their management of acute opioid withdrawal. Successfully weaning an opioid dependent patient off of chronic opioids requires a thorough knowledge of the available adjuvants to assist in this process. However, that selection can become exhausted by adjuvant side effects or by ineffective attenuation of opioid withdrawal symptoms. In that case, novel drugs, or novel application of currently available medications must be sought after to assist in the drug holiday. We present a case in which refractory muscle spasms secondary to opioid withdrawal were successfully treated with an over-the-counter supplement that is not typically used for the attenuation of opioid withdrawal symptoms. In a patient intolerant to the side effects of clonidine, we were able to successfully wean chronic opiates by treating refractory muscle spasms with the serotonin precursor, 5-hydroxytryptophan (5-HTP). We hypothesize that our success with this medication gives further credence to the role of serotonin in opioid withdrawal somatic symptomatology, and supports the need for future research to clarify the role of serotonin precursors or serotonin modulating drugs as potential alternatives in those unable to follow standard treatment protocols.

Key words: 5-hydroxytryptophan (5-HTP), opioid withdrawal, muscle spasms, serotonin, drug holiday, chronic pain

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Thousands of opioid-dependent patients undergo either gradual reduction or abrupt discontinuation of opioids for a variety of reasons. The withdrawal symptomatology is well described – early symptoms include anxiety and drug craving followed by sweating, chills, muscle and joint pain, spasms, tremors, rhinorrhea, tachycardia, hypertension, nausea, vomiting, diarrhea, restlessness, and insomnia (1). The severity of symptoms varies depending on the duration of opioid use and the severity of dependence (2). Symptoms of opioid withdrawal are oftentimes unbearable for the patient to successfully cease all use and subsequently lead to opioid relapse. Standard treatment protocols designed to alleviate withdrawal symptomatology typically employ an alpha-2 agonist in conjunction with other

agents targeted for symptomatic relief of common withdrawal symptoms.

Although mechanisms of opioid withdrawal are complex and not entirely understood, it is largely thought to be secondary to a hyperadrenergic state primarily mediated by high norepinephrine (NE) levels in the locus coeruleus of the anterior pons caused by upregulation of cAMP-mediated pathways (other sites such as the periaqueductal gray matter, nucleus raphe magnus, and nucleus accumbens also play a role in the neurobiology of withdrawal) (3-5). It is hypothesized that alpha-2 agonists, such as clonidine exert their effects by decreasing sympathetic outflow to counteract the hyperadrenergic state. Given this finding, clonidine has long been used as a cornerstone of opioid weaning, though side effects of hypotension,

bradycardia, and sedation oftentimes preclude its use in some populations. In addition, clonidine is also not particularly effective at reducing the muscle aches, insomnia, and drug cravings that are prominent sequelae of withdrawal (6). Currently there are no effective non-opioid outpatient alternatives to clonidine when this therapy fails.

The role of the serotonergic system in opioid withdrawal has long been a topic of widespread interest. As there are multiple publications showing the role of serotonin in opioid withdrawal (4,6-9), so too are studies that try to disprove its significance (10). Although 5-hydroxytryptophan (5-HTP) has not been studied in direct relation to relieving opioid withdrawal-induced muscle spasms, it has been shown to be an effective treatment of serotonin depletion and muscle spasms caused by withdrawal from 3,4-methylenedioxymethamphetamine (MDMA) (12-13). Reflecting on the possible link between a depleted serotonin state and the occurrence of muscle spasms, we hypothesized that our patient may benefit from a serotonin modulating drug. Given the relative safety profile, non-addictive potential, lack of contraindications and minimal side effects (Table 1), 5-HTP appeared to be an appropriate adjunct to try in this patient.

We present a 53 year-old woman with a history of restless leg syndrome and severe lumbosacral spondylosis with debilitating chronic back pain that was managed with chronic opioid therapy. After years of treatment with decreasing utility, we proceeded with the evaluation for a potential intrathecal drug delivery system. Prior to evaluation, her medication regimen consisted of the following medications: clonazepam, fentanyl patch, hydrocodone/acetaminophen, zolpidem, and ropinirole. Prior to the intrathecal opioid trial, the patient was completely weaned off all narcotics for a duration of 4 weeks. Clonidine patches were

prescribed for anticipated withdrawal symptoms.

Four days after the cessation of opioids, the patient reported extreme insomnia secondary to incessant muscle spasms in her arms and legs. She was unable to tolerate clonidine due to unbearable "mental fog-giness." Traditional muscle relaxants did not decrease the severity of her symptoms. At this point, it was suggested to try a trial of over-the-counter 5-HTP supplement at a loading dose of 200 mg the first night and 100 mg nightly thereafter until symptoms subsided. She noted great improvement in both her muscle spasms and insomnia. She discontinued its use without consequence after approximately 2 weeks of therapy. During this time and subsequently thereafter, the patient remained symptom free and successfully refrained from using further narcotics while she successfully underwent the intrathecal opioid trial and ultimately went on to permanent implantation.

DISCUSSION

5-HTP is a naturally occurring intermediate metabolite in the production of serotonin from the essential amino acid, L-tryptophan. Because serotonin cannot cross the blood brain barrier, central serotonin production is dependent on either L-tryptophan or 5-HTP. Unlike L-tryptophan, which requires a transport molecule to cross the blood brain barrier, 5-HTP does not. In addition, one of the key benefits of using 5-HTP directly is that it bypasses the rate-limiting step in serotonin synthesis of L-tryptophan to 5-HTP by tryptophan hydroxylase, which can be inhibited by numerous factors including stress, insulin resistance, vitamin B6 deficiency, and low levels of magnesium (13). 5-HTP can increase levels of serotonin, melatonin, dopamine, norepinephrine, and beta-endorphin (13-15). Although the majority of evidence for its clinical use is not strong, 5-HTP has been well regarded as a safe alternative in in-

Table 1. Adverse side effects and contraindications of 5-HTP.

Adverse Side Effects	Contraindications
nausea* diarrhea loss of appetite difficulty breathing dilation of pupils exaggerated reflexes loss of muscle coordination blurry vision cardiac dysrhythmias	Carcinoid tumors Use with MAOIs, SSRIs, TCAs, serotonin syndrome Use with 5-HT ₁ receptor agonists (sumatriptan, naratriptan, and zolmitriptan) Patients with ischemic heart disease or coronary artery spasm Patients with uncontrolled hypertension Pregnant or nursing mothers Caution with use with carbidopa, scleroderma-like skin changes

*most common. Adapted from 5-HTP. United States National Library of Medicine: Toxicology Data Network (15)

somnia, depression, appetite suppression, fibromyalgia, and reducing the discomfort experienced in those with chronic pain (7,13,14,16).

Over the past 40 years, researchers have been trying to elucidate the exact mechanisms underlying opioid withdrawal in the hopes of directly targeting drug therapy at the source of the symptoms (4). There is not a single mechanism or cerebral site involved with drug withdrawal but instead a complex interplay of multiple neurotransmitter systems likely acting on multiple different sites in both the central and peripheral nervous systems (5). In the struggle to map such pathways, there has been extensive research in delineating what role the serotonergic system plays in this system (5,10).

There have been conflicting studies comparing whether low levels (9) or increased levels (6-8) of 5-HT transmission attenuate opioid withdrawal. Chronic exposure to opioids results in a dramatic decrease in dopamine and 5-HT neurotransmission, causative factors thought to be potentially responsible for the somatic symptoms of opioid withdrawal (6-8). In 2005, researchers were able to prove that bupirone was as effective as a methadone taper in alleviating the withdrawal symptoms of heroin addicts after accounting for its slightly slower onset (6). Although bupirone acts on multiple receptors, its primary clinical effect is thought to be mediated through increasing 5-HT transmission.

We relied on extrapolated data from the wide use of 5-HTP among MDMA users for post-MDMA-use symptomatology including muscle spasms, cramps, jaw clenching, depression, fatigue, anxiety, insomnia, and GI disturbances (17,18). Chronic MDMA use depletes 5-HT levels which is a major contributing factor to the neurotoxicity experienced with its use (11,12). We hypothesized that our patient would benefit from a fast-acting, low dose serotonin agonist such as 5-HTP.

Herein we presented a case in which a patient either intolerant or refractory to multiple medications used in the treatment of opioid withdrawal was successfully treated with 5-HTP. In light of previous research supporting the role of serotonergic systems in the opioid withdrawal syndrome, 5-HTP was chosen and proved effective in the alleviation of our patient's refractory muscle spasms. As mechanisms underlying opioid withdrawal remain complex and still largely unknown, we believe that our case further suggests the important role that serotonin modulation may play in withdrawal symptomatology, most notably a state of serotonin depletion. Further research needs to be conducted to elucidate the appropriate use of serotonin-modulating drugs in the treatment of opioid withdrawal that are either used in conjunction with, or when indicated in place of alpha-2 agonists.

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