



## **BIOLOGIC AND CLINICAL RATIONALE FOR THE USE OF PSILOCYBIN FOR NOCIPLASTIC PAIN INDICATIONS**

### BACKGROUND

Psychedelics have been used in many cultures for thousands of years, and recently there has been a resurgence of interest in using them to treat psychiatric conditions. These substances have a generally favorable safety profile, especially when compared with opioid analgesics and many categories of psychiatric drugs. Clinical evidence to date for their use for chronic pain is limited; however, several studies and reports over the past 50 years have shown potential analgesic benefit in cancer pain, phantom limb pain and cluster headaches (24). While the mechanisms by which the classic psychedelics may provide analgesia are unclear, several possibilities exist given the similarity between 5-HT<sub>2A</sub> activation pathways of psychedelics and the nociceptive modulation pathways in humans.

Psychedelics extend local functional connections to become more global with many additional brain regions. After the normal organization is disrupted, there is emergence of strong, topologically long-range functional connections that are not present in the normal state. Nicholl et al. hypothesized that after the psychedelic-induced brain network disruption, the formation of long-range functional connections may be solidified through local anti-inflammatory effects to allow “healthy” reconnections as the acute effects of the drug dissipate (16).

Additionally, the durable alterations in functional connectivity (FC) in brain networks seen with psychedelic use (27) suggest a way that these agents could help reverse the pathologic changes in neural connections seen in chronic pain states. Given the current state of the opioid epidemic and limited efficacy of non-opioid analgesics, it is time to consider further research on psychedelics as analgesics to improve the lives of patients with chronic pain conditions, particularly nociplastic pain. Nociplastic pain is defined by the International Association for the Study of Pain as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the

somatosensory system causing the pain" (28). Nociceptive pain includes fibromyalgia, which is of interest in this study.

## MOLECULAR MECHANISM OF ACTION FOR PSYCHEDELICS IN NOCICEPTIVE PAIN

The primary mechanism of action of psychedelics is via activation of the serotonin 5-HT<sub>2A</sub> receptor, which is a G protein-coupled receptor encoded by the HTR2A gene (1). Phenethylamine hallucinogens (e.g. mescaline) are typically selective for 5-HT<sub>2</sub> subtypes, including 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> sites. Tryptamine hallucinogens, including psilocybin, bind non-selectively to most 5-HT receptors and may also bind to the  $\sigma$ <sub>1</sub> receptor, the trace amine receptor and the 5-HT transporter (SERT). Ergolines (e.g. LSD), by contrast, display high affinity for most 5-HT, dopaminergic and adrenergic receptors (1).

Normally, descending inhibitory 5-HT pathways help to modulate the transmission of pain signals in the spinal cord and decrease the sensitivity of spinal dorsal horn neurons by inhibiting the c-fiber responses of wide dynamic range neurons (2,3). It has been suggested that malfunction of these descending inhibitory pathways plays a role in the development of hyperalgesia and allodynia (4,5).

In rat models, the descending inhibitory effects of 5-HT are mediated by activation of 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors; but after nerve ligation, only activation of the 5-HT<sub>2A</sub> subtype resulted in persisting 5-HT descending inhibition, suggesting a role for the latter receptor in pain caused by nerve injury. The 5-HT<sub>2A</sub> receptor may play a role in hyperalgesia and neuropathic pain. 5-HT<sub>2A</sub> mRNA are expressed by dorsal root ganglia (DRG) neurons (6). DRG neurons are depolarized by 5-HT<sub>2A</sub>, and 5-HT<sub>2A</sub> receptors in the DRG have been shown to potentiate inflammatory pain.

## NEURAL IMAGING ADVANCES FOR UNDERSTANDING NOCICEPTIVE PAIN

Recent advances in brain imaging technology have allowed the mapping of neural connectivity within the brain. The identification of connections referred to as resting-state networks and the temporal connection between anatomically separate areas designated as FC has helped show how brain regions are connected as well as the patterns of connection that are associated with neuropathology or psychological phenomena. These brain network dynamics are revealed through functional magnetic resonance imaging (fMRI) resting state FC analysis. This work has identified brain connectivity networks that are essential for integration of information for complex cognitive function. Healthy brain networks have a characteristically efficient organization.

There is growing evidence that disruption of these efficient networks is associated with several neurological conditions, including but not limited to depression, anxiety, trauma, addiction, as well as many chronic pain states such as somatoform pain disorder, fibromyalgia, rheumatoid arthritis, centralized pain, chronic pelvic pain, lumbar back pain and phantom limb pain (7,8,9).

In evaluating the FC changes between healthy volunteers and subjects with chronic pain conditions, the common pathological reorganization was in the extent of the association between prefrontal cortex and the insula. The extent of this reorganization was a function of the intensity of the chronic pain and its duration (8,9). Several imaging studies have demonstrated that psychedelics alter established patterns of connectivity within the brain by reducing the stability and integrity of established brain networks and by increasing the global integration between established brain networks (27). In patients with phantom limb pain, mental imagery exercises have been shown to decrease pain as well as reduce cortical reorganization, as seen on fMRI (11). An fMRI study of mirror visual feedback (MVF) therapy in patients with phantom limb pain found that reduction in phantom pain after MVF therapy was associated with increased activity in the prefrontal cortex. In a recent case report, a patient who combined MVF therapy and psilocybin had a profound and beneficial pain response compared with the use of MVF alone, suggesting possible synergistic effects (25). A possible explanation for this response was provided in studies performed in the Carhart-Harris labs. In analyzing a series of fMRI studies involving psilocybin, Carhart-Harris, et al. proposed that psychedelics “disintegrate” brain networks while increasing the “repertoire of connectivity motifs” that form and fragment within a network. They suggest that psychedelics may have therapeutic potential in psychiatric conditions by disrupting spatiotemporal patterns of brain activity but that these drug-induced changes may need to be mediated by other therapeutic processes such as co-administered psychotherapy (12).

## THE RATIONALE FOR USING PSYCHEDELICS TO ADDRESS NOCIPLASTIC PAIN INCLUDING FIBROMYALGIA

The literature on classic psychedelics and chronic pain is limited but does include several indicators that these agents have analgesic potential. There are several articles including case reports, case series, retrospective surveys and prospective non-randomized trials of either psilocybin or LSD in chronic pain conditions. The earliest published studies on psychedelics and analgesia are works from Dr. Eric Kast in the mid-1960s on analgesic response to LSD for cancer pain. In these studies, LSD not only acutely outperformed 2 mg of PO hydromorphone or 100 mg of PO meperidine but also produced analgesia that persisted for an average of 3 weeks after LSD administration (29).

More recently, two retrospective cross-sectional surveys of patients with cluster headaches showed that the use of hallucinogens such as LSD and psilocybin was associated with a reduction in headache severity and an extension of remission periods (23, 30). Psilocybin was reported to be roughly as effective as high flow oxygen in aborting cluster headaches and was more effective than oral or intranasal triptan administration (but less effective than triptan administration by the subcutaneous route). Psilocybin was also used to prevent cluster headaches and was determined by users to be more effective than conventional pharmaceutical agents including verapamil, prednisone, topiramate and melatonin. In contrast to psychedelics, the authors found highly variable reports of efficacy when cannabis was self-administered as a treatment, worsening symptoms in some patients and improving symptoms in others.

The mechanisms by which chronic pain develops are not completely understood but likely involve a complex interplay between somatic and visceral afferent input, peripheral and central sensitization, emotional state, behavior and cognition (24). Distraction and changes in mood can have a powerful effect on the perception of pain (14). Recent randomized, double-blind trials demonstrated that psilocybin can relieve anxiety and depression in patients with life-threatening cancer (15, 19). There is also evidence that specific 5-HT<sub>2A</sub> gene polymorphisms are associated with fibromyalgia, chronic widespread pain and pelvic pain, further demonstrating a significant role of the 5-HT<sub>2A</sub> receptor in pain perception (16).

There are several mechanisms whereby psychedelic drugs could potentially produce antinociceptive effects in chronic pain states. First, 5-HT<sub>2A</sub> receptor activation causes upregulation of genes associated with neuroplasticity and suppresses TNF- $\alpha$ -induced inflammation. Moreover, treatment with psychedelic drugs causes downregulation of 5-HT<sub>2A</sub> receptor binding sites (17). Agonist-induced downregulation of the 5-HT<sub>2A</sub> receptor is not linked to changes in the level of 5-HT<sub>2A</sub> mRNA, but rather likely occurs due to redistribution of the receptor from the cell surface to intracellular compartments. To date, studies have not examined whether psychedelic drugs induce 5-HT<sub>2A</sub> internalization in dorsal horn neurons. Such an effect could potentially counteract the sensitization of spinal nociceptive responses in neuropathic pain states.

The transition from acute pain to chronic pain, especially in patients with nociplastic pain, has been shown to involve neuroplasticity or other changes in nervous system structure and function. These neuroplastic changes have been detected at multiple levels of the central nervous system, ranging from the spinal cord to the cortex (18). Given the accumulating evidence of altered brain FC in chronic pain states, the ability of psychedelics to disrupt established brain connection patterns is the most intriguing potential analgesic mechanism for psychedelics. Should this prove to be the case, combining psychedelics with more traditional therapeutic modalities could result in synergistic therapeutic benefits. Potential psychedelic co-therapeutic modalities include

MVF therapy, physical therapy, nerve blocks, neuromodulation techniques, psychotherapy, or others with the goal of reversing some of the neuroplastic changes that resulted in the chronic pain state.

## FIBROMYALGIA CLINICAL STUDY RATIONALE

Fibromyalgia is a chronic syndrome that affects 2% to 4% of the population and is characterized by widespread musculoskeletal pain that often manifests with a cluster of co-occurring symptoms including sleep disturbances, fatigue, cognitive dysfunction, and mood disorders (e.g., anxiety and depression). The administration of TRP-8802, an oral formulation of synthetic psilocybin, in concert with psychotherapy may be a potentially safe and effective treatment for symptoms associated with fibromyalgia. The pressing need for effective fibromyalgia treatments, known safety of psilocybin therapy, and mechanistic plausibility for potential benefit provide a backdrop for investigating TRP-8802 as a treatment for fibromyalgia.

Current treatments for fibromyalgia are inadequate, and there is an unmet need for treatment. Fibromyalgia treatment is challenging: many nonpharmacological therapies are inaccessible due to cost and lack of treatment providers, and most pharmacological therapies are only modestly effective while causing a significant side-effect burden. Some researchers have proposed that psychedelic drugs such as psilocybin may have potential therapeutic value for treating fibromyalgia and chronic pain. Much of this interest has been generated by the results from small clinical trials using psilocybin among individuals with psychiatric disorders such as anxiety, depression and addiction (19,20,21,22, 26), which show remarkable improvements in otherwise seemingly intractable conditions.

Studies with modern neuroimaging techniques (e.g., fMRI) have shown that psilocybin dramatically alters maladaptive patterns of connectivity between different brain regions, which in combination with psychotherapy may promote improved clinical symptoms. Basic science research has identified the serotonin 5-HT<sub>2A</sub> receptor as the primary target for psychedelics – a finding of interest given that polymorphisms in the encoding 5-HT<sub>2A</sub> gene are associated with fibromyalgia and chronic widespread pain (16).

While case series and retrospective surveys suggest that psychedelic use may improve chronic pain due to cluster headaches/migraine (23, 30), phantom limb pain (25), and neuropathic pain (24), no studies to date have examined the potential role of psychedelics in fibromyalgia.

## PLANNED STUDY IN FIBROMYALGIA USING TRP-8802

To better understand the potential benefits of psilocybin in chronic pain management, Tryp Therapeutics is planning to perform an open-label, Phase 2a clinical trial to assess the clinical utility of TRP-8802 in concert with psychotherapy to treat chronic pain symptoms in patients with fibromyalgia. Participants will undergo an initial pain phenotyping assessment (which includes a series of validated instruments for assessing pain and related fibromyalgia symptomatology), fMRI, and EEG. TRP-8802-psychotherapy intervention, the structure of which has been used in previous psilocybin-based clinical trials (26), will begin with initial meetings between the patient and the therapist followed by two drug dosing sessions and then integration sessions following drug dosing. Rigorous post-treatment evaluations will assess the clinical effects of TRP-8802 as measured by changes from baseline in the parameters of the deep phenotyping assessment, as well as in fMRI and EEG, through 6 months of observation. Safety of TRP-8802 in this novel treatment population will include close monitoring of subjects during the dosing sessions and gathering of adverse events reported during the trial.

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