Can migraine patients trust the “trust drug” to heal their pain?

**A Q&A WITH DAVID C. YEOMANS, PHD**

**WHAT SHOULD NEUROLOGISTS TAKE AWAY FROM YOUR PRESENTATION?**

**WHAT’S IMPORTANT TO KNOW ABOUT TI-001?**

Neurologists take care of the majority of episodic migraine and chronic migraine patients. Current therapies for episodic migraine are quite helpful—but do not help everyone—they work in about 60 percent of patients. For chronic migraine, the only approved treatment is botulinum toxin injections. In addition, topiramate, although not FDA approved for chronic migraine, is also commonly used off-label. Unfortunately, both of these treatments have limited efficacy—with numerous studies showing no significant effect or only a small decrease in the number of headache days per month. Thus, there is a real need for another approach.

**ABOUT THE STUDY**

The Phase II study will evaluate the use of oxytocin, given as a nasal spray, for treatment of chronic migraine. It will look for the following:

**PRIMARY OUTCOME MEASURES:**
Mean reduction in migraine headache days
Baseline is the 28-day screening period before enrollment in the study

**SECONDARY OUTCOME MEASURES:**
Change in migraine pain scores measured with a 4-point verbal rating scale Time Frame: baseline (before study drug administration) and 2 hours after dosing
Measured for every migraine episode during the open-label phase that consists of 28 days of active treatment for all enrolled subjects and during the randomized, double-blind phase. Subjects are randomized to either placebo or active and treated for 28-days during the double-blind phase.
- Frequency of nausea
- Frequency of photophobia
- Frequency of phonophobia
- Frequency of migraine episodes
- Time to study discontinuation due to any cause
- Frequency and severity of adverse events

This study has an open-label phase of 28 days wherein all subjects receive active drug and dose titrate to effect. Then they are randomized to active or placebo for an additional 28 days of treatment. Therefore, safety is measured for the entire 56 days.
For strong efficacy, nasal oxytocin requires that a degree of cytokine-driven inflammation be present for at least three hours. Thus, nasal oxytocin is only minimally effective if given to migraine patients as you would a triptan—when the headache first starts. However, when tested in chronic migraineurs, who should have chronically inflamed dura, efficacy is strong. This need for inflammation also means that anti-inflammatory drugs, which block cytokine production, will have a detrimental effect on efficacy.

The final thing they should know is that oxytocin itself has been approved for injection for more than 60 years and nasal oxytocin (albeit in a lower concentration than TI-001) has been used in some countries since 1960. In both cases oxytocin has a stellar safety record.

**WHY IS IT IMPORTANT TO EXPLORE INTRANASAL PAIN THERAPY?**

There are two reasons for looking at intranasal applications for pain. The first is practical, the second scientific.

The practical reason is that many pain patients, and particularly migraine and chronic migraineurs, suffer from nausea. Thus, taking a pill while suffering a headache may not be possible.

The second reason is scientific. For oxytocin, we are directly targeting the oxytocin receptors located on tri-

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**TRUST ME?**

In addition to the Scandinavian study mentioned by Dr. Yeomans, several studies have explored whether oxytocin can increase levels of trust and sympathy. One double-blind study administered oxytocin or placebo to high hypnotizable participants (N=28), who were administered hypnotic suggestions for socially unorthodox behaviors, including swearing during the experiment, singing out loud, and dancing in response to a posthypnotic cue. Participants who received oxytocin were significantly more likely to swear and dance than those who received the placebo.¹

In a review and meta-analyses of trials involving oxytocin, researchers found that healthy participants who intranasally administered oxytocin "led to better emotion recognition and more trust in conspecifics, but the effects appear to be moderated by context (perceived threat of the 'out-group'), personality and childhood experiences."²

In 19 clinical trials that covered autism, social anxiety, postnatal depression, obsessive-compulsive problems, schizophrenia, borderline personality disorder and post-traumatic stress, the effects of OT administration were tested, with doses ranging from 15 IU to more than 7000 IU. The combined effect size was d=0.32 (N=304; 95% confidence interval (CI): 0.18-0.47; P<0.01). However, of all disorders, only studies on autism spectrum disorder showed a significant combined effect size (d=0.57; N=68; 95% CI: 0.15-0.99; P<0.01). The authors hypothesized "that for some of the other disorders, etiological factors rooted in negative childhood experiences may also have a role in the diminished effectiveness of treatment with OT."

Oxytocin, touted as a “trust drug,” is widely discussed in the media and even sold online.
Besides nasal oxytocin, companies are also selling sublingual drops and a spray that is supposed to increase trust in others when applied to one’s own body or clothes.

geminal pain-sensing neurons. We have found that nasal application of oxytocin allows for direct access to these neurons, bypassing the blood entirely. The nose is very vascular and nasal application is a great way to get small molecules into the blood rapidly. However, the half-life of most peptides, including oxytocin in the blood is very short (which is why it is typically given by infusion for labor induction). In addition, many peptides, including oxytocin, do not readily cross the blood-brain barrier, limiting their potential sites of action.

**HOW WOULD THIS DIFFER FROM THE OTC OXYTOCIN THAT IS AVAILABLE ON AMAZON AND ELSEWHERE?**

Currently, oxytocin is a prescription-only drug and is not approved for OTC use. If there is a product being sold online or elsewhere without a prescription, there are a couple of things that should be taken into consideration.

First, assuming there is oxytocin in the material, it is not clear whether the concentration in the product would be sufficient to produce any therapeutic effect. Secondly, one needs to consider what the formulation is—what else is in there? Previous formulations of prescription nasal oxytocin, even those approved in 1960, contained excipients, such as preservatives, which today are no longer approved because of safety and toxicity concerns. No one should take a chance ordering these products online because not only could it be ineffective, but it raises serious health concerns.

Another thing to consider with these products, is how oxytocin is delivered into the body. Besides nasal oxytocin, companies are also selling sublingual drops and a spray that is supposed to increase trust in others when applied to one’s own body or clothes. There has, to my knowledge, never been a demonstration that sublingual drops of oxytocin will be effective for anything—the oral environment is quite hostile to peptides.

The second “trust” product is based on a study performed at a Scandinavian University several years ago where nasal application of substantial doses of oxytocin slightly (but significantly) and temporarily increased the level of trust in college students playing a transactional game. Note that the effect was on the person who had the oxytocin sprayed in their nose and not the other player. The number of oxytocin molecules reaching someone else’s nasal mucosa after applying a spray to oneself is likely to be vanishingly small and certainly not sufficient to affect pain.

Finally, most of these products are expensive and it is likely that the co-pay for patients to buy an FDA-approved Trigemina nasal oxytocin may actually be less.

**WHAT ARE THE NEXT STEPS FOR TI-001?**

The science that Trigemina has discovered suggests that TI-001 has the potential to be helpful in a number of head pain disorders wherein that pain is chronic or semi-acute (e.g., post-procedural). Therefore, after the successful completion of our Phase II study examining the effectiveness and safety of TI-001 in chronic migraines, we plan to explore the utility of this treatment in other craniofacial pain disorders, including trigeminal neuralgia.