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LETTER TO THE EDITOR

# Future directions for the investigation of intranasal oxytocin and pain

## Comment on: Oxytocin nasal spray in fibromyalgic patients (Rheumatol Int. E-pub ahead of print. doi: 10.1007/s00296-014-2953-y)

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It is with great interest that we read the article "Oxytocin nasal spray in fibromyalgic patients" published in Rheumatology International. Mameli et al. [1] conducted a placebo-controlled, double-blind crossover trial and reported that daily administration of 80 IU intranasal oxytocin over the course of 3 weeks did not result in adverse side effects or lower reports of pain among 14 women with fibromyalgia. We commend the authors for conducting an innovative trial using daily intranasal oxytocin administration. Several points can be advanced from this article to improve future trials assessing oxytocin and pain associations.

The provision of additional information is important to place the results of this investigation in the context of the current literature and to provide heuristic for future trials. First, the procedure for patient self-administration of intranasal oxytocin was not explicitly described by Mameli et al. [1]. Importantly, rapid and successive sniffs may result in a higher concentration of the drug being swallowed and a lower availability for absorption. Second, the compositions of the oxytocin and placebo nasal sprays were not clearly described, and no formal assessment of expectation or blinding was reported. Thus, it is difficult to determine what influence expectation effects had on the reported results, an important point to consider given recent evidence that intranasal oxytocin may enhance placebo analgesia [2]. Third, the precise timing of intranasal oxytocin administration and subsequent pain ratings was not indicated. Many aspects of the oxytocin–pain association are not yet well understood. For instance, it is unclear whether elevations in plasma and/or central oxytocin levels have analgesic properties (see [3]), which pain modalities are most responsive to oxytocin (e.g., acute, intermittent, chronic), or the duration of effects (e.g., minutes to hours). Careful documentation of administration procedures may provide insight into answering these important questions.

Mameli et al. [1] suggest that future trials use a dose of oxytocin that exceeds 80 IU. Caution is warranted as most research assessing intranasal oxytocin has used doses ranging between 16 and 48 IU, and lower doses may yield more fruitful results. For example, stronger effects of a 24-IU dose of intranasal oxytocin on the cortisol response to intense exercise were reported than for a 48-IU dose [4]. There may exist a dose threshold above which no further intranasal oxytocin can be absorbed. For instance, a 16-IU dose of intranasal oxytocin resulted in similar salivary concentrations following a 7-h duration as did a 24-IU dose [5]. Dose–response investigations are needed to determine dose optimization.

This trial was powered to detect large effects, and the results are inconclusive. A minimum detectable Cohen's $d$ effect size of 0.81 would be needed in a trial using paired-samples $t$ tests, two-tailed hypothesis testing, power at 80 %, $\alpha$ at .05, and a sample size of 14 [6]. Our laboratory observed medium effect sizes for the administration of 40 IU intranasal oxytocin on acute cold pressor pain in healthy young adults using a placebo-controlled, double-blind, within-subject crossover design [7]. It may be optimistic to suspect that intranasal oxytocin used as an adjuvant treatment would result in larger pain reductions among patients who are on a complex pain regimen than it would in otherwise healthy adults.

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We believe that this is a highly significant area of future investigation. Animal and human research suggests that oxytocin administration and elevated peripheral and central oxytocin concentration are associated with lower pain perception [3]. Further, biologically plausible mechanisms exist to support an association between oxytocin and pain (see [3]). Results reported by Mameli et al. [1] are important in suggesting that intranasal oxytocin is safe and well tolerated in a clinical sample of fibromyalgic patients (see also [8] for a review on side effects). Additional methodologically rigorous trials are needed with larger sample sizes to assess the viability of using intranasal oxytocin as an adjuvant pharmacotherapy in chronic pain populations.

**Conflict of interest** None.

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