

# Letters

## RESEARCH LETTER

### Effect of Oxytocin on Placebo Analgesia: A Randomized Study

Placebo responses have been shown to contribute to clinical treatment outcomes.<sup>1</sup> The pharmacological enhancement of placebo responses therefore has the potential to increase treatment benefits. The neuropeptide oxytocin may mediate processes such as empathy, trust, and social learning.<sup>2</sup> These are key elements of the patient-physician relationship, which is an important mediator of placebo responses.<sup>3</sup> We tested whether oxytocin enhances the placebo response in an experimental placebo analgesia model.

**Methods** | In January to September 2012, we recruited 80 healthy male volunteers at the University of Hamburg, Germany. Based on previous data, we expected this sample size to provide 80% power to detect an effect size of 0.35 with a 2-sided  $\alpha$  of .05. Participants were randomly assigned to the double-blind administration of 40 IU of oxytocin or saline intranasally using a simple algorithm. After 45 minutes, placebo analgesia was assessed using an established paradigm. Two identical inert ointments were applied to 2 sites on each participant's forearm, with the sites randomized across participants. The ointments were introduced by a male study physician using a script, described as an anesthetic that reduces pain (placebo) and an inert control cream (control). During the 15 minutes in which the anesthetic was believed to take effect, a calibration procedure was performed to identify the individual stimulation intensity at which a 20-second painful heat stimulus (Medoc-TSA-II; NeuroSensory Analyser) was perceived as a 60 on a visual analogue scale (VAS) (ranging from 0, no pain, to 100, unbearable pain). During the subsequent test phase, a series of 10 stimuli of the calibrated intensity was applied to each of the 2 sites in pseudorandomized order. Each stimulus lasted for 20 seconds, followed by a rating procedure and 40-second rest.

The primary outcome was the placebo analgesic response, defined as the reduction of perceived pain intensity on the placebo site compared with the control site in the oxytocin and saline groups. We also assessed the temperatures needed to induce a sensation of VAS score 60, physical and psychological adverse effects (using the multidimensional mood scale<sup>4</sup> and an open response format), and participants' treatment guess, to control for an effect of oxytocin on general pain sensitivity and blinding. Measures were analyzed using repeated-measures analysis of variance, 2-tailed 2-sample *t* tests, or  $\chi^2$  test. Statistical threshold was set at  $P < .05$ . Statistical analyses were performed using PASW Statistics version 18.0 (IBM SPSS). The study was approved by the local ethics committee, and all participants provided written informed consent.

**Results** | Data for 5 participants were excluded because of technical failure, leaving 75 participants (age, 20-38 years; oxytocin group,  $n = 37$ ). Groups did not differ significantly with regard to age, weight, anxiety, or depression scores (Table 1). Despite identical thermal stimulation on both sites, pain ratings for the placebo site were significantly lower compared with the control site across both treatment groups (Table 2). The placebo analgesic response was significantly higher in the oxytocin group compared with the saline group (oxytocin group difference, 12.84 [95% CI, 8.67-17.01]; saline group difference, 7.08 [95% CI, 3.84-10.31]) (Table 2). Temperature levels needed to induce a sensation of VAS score 60, pain ratings on the control site, adverse effects, and post hoc treatment guesses did not differ significantly between groups (Table 2), consistent with oxytocin having no analgesic effect. The dose of oxytocin induced no significant adverse effects.

**Discussion** | To our knowledge, our study provides the first experimental evidence that placebo responses can be pharmacologically enhanced by the application of intranasal oxytocin. This effect was not explained by a general effect

Table 1. Participants' Characteristics<sup>a</sup>

	Mean (95% CI)			Result	
	Oxytocin Group	Saline Group	Overall	<i>t</i>	<i>P</i> Value
Age, y	26.2 (24.9-27.6)	26.1 (24.7-27.5)	26.2 (25.3-27.1)	$t_{72} = -0.15$	.86
Weight, kg	80.4 (76.6-84.2)	81.8 (77.7-85.8)	81.1 (78.4-83.8)	$t_{71} = 0.51$	.61
Anxiety score <sup>b</sup>	33.9 (30.9-37.0)	35.2 (33.6-36.8)	34.6 (32.9-36.3)	$t_{67} = 0.78$	.44
Depression score <sup>c</sup>	6.0 (4.3-7.7)	8.1 (5.7-10.6)	7.1 (5.6-8.6)	$t_{63} = 1.46$	.15

<sup>a</sup> Participants' characteristics were compared between groups using 2-tailed 2-sample *t* tests. Groups did not differ significantly with respect to weight, age, anxiety, and depression score.

<sup>b</sup> Assessed via State-Trait Anxiety Inventory (STAI).<sup>5</sup>

<sup>c</sup> Assessed via General Depression Scale (Allgemeine Depressionskala [ADS]).<sup>6</sup>

Table 2. Primary and Exploratory Outcome Measures

	Oxytocin Group	Saline Group	Overall	Result
Pain rating during test phase, mean (95% CI), VAS score <sup>a</sup>				
Control site	59.96 (57.28 to 62.64)	58.31 (55.89 to 60.73)	59.12 (57.35 to 60.89)	Main effect of group: $F_{1,73} = 0.37$ ; $P = .54$ Main effect of condition: $F_{1,73} = 58.93$ ; $P < .001$ Interaction: $F_{1,73} = 4.93$ ; $P = .03$ Comparison control site: $t_{73} = -.93$ ; $P = .35$
Placebo site	47.11 (42.37 to 51.85)	51.23 (47.68 to 54.78)	49.20 (46.28 to 52.12)	
Placebo response (control – placebo), VAS score <sup>b</sup>				
	12.84 (8.67 to 17.01)	7.08 (3.84 to 10.31)	-5.76 (-10.93 to -0.59)	$t_{73} = 2.22$ ; $P = .03$
Adverse effects (sum score) <sup>b</sup>				
	48.88 (46.63 to 51.14)	49.30 (47.73 to 50.86)	0.40 (-2.27 to 3.09)	$t_{71} = .30$ ; $P = .76$
Temperature to induce VAS score 60 in °C <sup>b</sup>				
	46.44 (46.28 to 46.60)	46.53 (46.38 to 46.69)	0.09 (-0.12 to 0.31)	$t_{73} = .84$ ; $P = .40$
Treatment guess, % <sup>c</sup>				
Gessed oxytocin	43.30	56.70		$\chi^2_{1,73} = .73$ ; $P = .39$
Gessed placebo	53.50	46.50		

Abbreviation: VAS, visual analogue scale (range, 0-100).

<sup>a</sup> Because our study was based on a 2 × 2 factorial design with the factors group (oxytocin/saline) and condition (painful stimulation on the placebo site/painful stimulation on the control site), a repeated-measures analysis of variance was used to analyze the pain ratings during the experimental test phase. In this analysis, a difference in the primary outcome (ie, placebo analgesic response that was defined as the difference between VAS pain rating for the placebo site and the rating for the control site) between groups is reflected in the interaction of both factors.

<sup>b</sup> We also present unpaired 2-sided *t* tests to directly compare the difference measure (ie, pain rating on control site minus pain rating on placebo site) between groups. Variables with only 1 measure per group (ie, sum score of adverse effects and temperatures required to induce an intensity of VAS score 60) are also compared between groups using 2-tailed 2-sample *t* tests.

<sup>c</sup> To compare the frequency of correct treatment guesses between groups, a 2-sided  $\chi^2$  test was conducted.

of oxytocin on pain sensitivity. Such enhancement could be used to support—not replace—active treatments through placebo mechanisms. Based on its effects on trust and empathy, we hypothesize that oxytocin might have increased the believability of the instructions by the study physician. Furthermore, the potential of oxytocin to reduce stress and anxiety might have increased responsiveness to the placebo manipulation. Further studies are needed to replicate our findings in larger clinical populations, identify the underlying mechanisms, and explore moderating variables such as sex or aspects of patient-physician communication.

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**Acquisition of data:** Kessner, Sprenger.

**Analysis and interpretation of data:** Kessner, Sprenger, Wrobel, Wiech, Bingel.

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**Administrative, technical, or material support:** Kessner, Sprenger.

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## COMMENT & RESPONSE

### Contaminated Methylprednisolone Injections

**To the Editor** Dr Malani and colleagues<sup>1</sup> used a gadolinium-contrast magnetic resonance imaging (MRI) screening protocol in 172 patients who had received 1 or more spinal or paraspinal injections of highly contaminated methylprednisolone but had not presented for medical care. The authors reported abnormal MRI findings in 36 patients (21%); of these 36 patients, 35 met the definition for probable or confirmed fungal spinal or paraspinal infection.

I am concerned about the chronological sequence of MRI in relation to the last injection. The 218 study patients received at least 1 injection between August 9 and October 2, 2012, and the MRI protocol was launched on November 9, 2012, and continued until April 30, 2013. For the 35 cases of infection, the median lag time from last injection to abnormal MRI was long (87 days; range, 44-192 days). But no data were presented on the lag time for the 118 patients with normal MRIs or for the 18 patients with equivocal findings on the first and repeat MRIs.

The authors also did not indicate whether there was a predetermined time to obtain MRI after the last injection. The median lag time to normal or equivocal MRI findings might have been much shorter than the long period reported for the cases with abnormal MRIs.

Although MRI is the modality of choice for imaging early spinal or paraspinal bacterial infections, it is not without shortcomings.<sup>2</sup> In approximately 70% of cases, the typical features of bacterial spondylodiskitis are apparent on MRI within the first 4 weeks, whereas in a further 30% of cases, positive findings will be revealed only after 4 weeks.<sup>3</sup>

Moreover, in fungal spinal infections, much less is known about the time to MRI diagnosis, and it may be lower than in bacterial infections, as suggested by the findings of the authors.<sup>1</sup> In addition, in proven cases of methylprednisolone-induced spinal fungal infection in Tennessee, MRI conducted at symptom onset identified abnormalities suggestive of infection in only 46%, with a median lag time from last injection of 18 days (upper range, 56 days).<sup>4</sup>

Whether MRI should be repeated in patients with a normal initial MRI is undetermined, but might be considered if there was a significantly shorter lag time from the last injection compared with patients with an abnormal initial MRI.

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**In Reply** Dr Matuchansky raises concern about whether there was sufficient lag time between receipt of the last contaminated methylprednisolone injection and screening MRI for patients with MRI studies classified as normal or equivocal. The median time from last spinal or paraspinal injection to an abnormal MRI result was 87 days (range, 44-192 days). Matuchansky also questions whether the median lag time was shorter for patients with normal or equivocal results.

Of the 172 patients who had a screening MRI performed from November 9, 2012, through April 30, 2013, 118 were noted to have a normal MRI and 18 had an equivocal result. The median time from last spinal or paraspinal injection to a normal MRI was 101 days (range, 48-249 days) and to an equivocal MRI was 130 days (range, 75-239 days), which are both longer than the reported 87 days (range, 44-192 days) to an abnormal MRI.

Matuchansky wonders whether there was a predetermined time to obtain the MRIs after the last injection. There was not a predetermined time for screening MRI studies; however, those with pain or neuropathic symptoms at the spinal or paraspinal injection site likely underwent earlier screening MRI studies.

In addition, with regard to repeat imaging for patients with a normal MRI screening study, 18 of the 118 patients who had a normal MRI underwent repeat imaging and all 18 were read as normal.

We agree with the recent guidance from the US Centers for Disease Control and Prevention that clinicians must remain vigilant when following up patients who have received spinal or paraspinal injections of contaminated methylprednisolone.<sup>1</sup> The guidance recommends that anyone who had received such an injection and who has new or worsening symptoms at or near that site should undergo a contrast-enhanced MRI.

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