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Could intranasal oxytocin be used to enhance relationships? Research imperatives, clinical policy, and ethical considerations

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Abstract

Purpose of review—Well-functioning romantic relationships are important for long-term health and well-being, but they are often difficult to sustain. This difficulty arises (in part) because of an underlying tension between our psychobiological natures, culture/environment, and modern love and relationship goals. One possible solution to this predicament is to intervene at the level of psychobiology, enhancing partners' interpersonal connection through neurochemical modulation. This article focuses on a single, promising biobehavioral subsystem for such intervention: the attachment system, based largely upon the expression of the neuropeptide oxytocin. Could the exogenous administration of oxytocin—under the right conditions—be used to facilitate relational or marital well-being?

Recent findings—If so, it would require considerable forethought. Recent research complicates the popular image of oxytocin as a universal social enhancer or 'love hormone' and shows that it may exert a variety of different effects, at different dosages, on different people, under different circumstances. Accordingly, we discuss what is known about oxytocin, including its "good" and "bad" effects on human behavior and on higher-order functional processes.

Summary—Building upon animal-model, human preclinical, and clinical findings, we outline a proposal for the use of oxytocin in the therapeutic neuroenhancement of contemporary romantic relationships. Highlighting key targets for future research along the way, we then conclude by discussing some of the clinical and ethical considerations that would pertain to the implementation of this knowledge in applied settings.

Keywords

oxytocin; neuroenhancement; couple therapy; marriage; love drugs

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Introduction

In a recent publication, Earp, Sandberg, and Savulescu [1*] argued that the well-documented fragility of modern marriages may trace (in large part) to a set of deeply-rooted disparities: between human psychobiology, the modern environment, and widespread cultural and ethical ideals concerning love and relationships. Natural selection did not shape our basic mating strategies—nor our underlying brain chemistry—to foster life-long, monogamous matrimony in the modern world, but rather to promote the reproductive success of our progenitors in the environment of the Pleistocene [2, 3]. Just as with pair bonding in other species, it has been suggested that the human mating system evolved to sustain relationships only as long as would have been required to raise ancestral offspring during their period of peak vulnerability [4]. Unqualified sexual exclusivity—rare or nonexistent in the rest of the animal kingdom—is unlikely to have evolved in *homo sapiens* either, as evolutionary theory predicts, and as a preponderance of evidence confirms [5, 6].

Nevertheless, many contemporary, especially Western, societies promote a model of long-lasting, sexually exclusive love as the moral and relational ideal, and as important for or even central to human thriving. This discrepancy between the blind goals of natural selection and the conscious values of modern couples—and the societies in which they conduct their relationships—results in a serious tension. This tension is very often “resolved” with our evolved biobehavioural dispositions trumping our considered values. Evidence of this phenomenon includes frequent incidences of infidelity in married couples and growing divorce rates across the globe. It is now estimated that at least 20% (and up to 72%) of husbands and at least 10% (and up to 54%) of wives commit adultery [7, 8]; and that half or more of marriages end in divorce [1*, 9, 10]. Despite the earnest desire of a majority of individuals to enter into life-long relationships [11], marital dissatisfaction is common, and positive, healthy relationships are often difficult to sustain.

Yet remaining in a good marriage can bring a range of important benefits. These include resilience against the negative effects of life stressors [12, 13], higher self-ratings of health and well-being [14], lower rates of diagnosed psychological disorders [13], greater life expectancy [14], fewer diagnosable health problems [15], improved coping with major illnesses [16], greater career achievement [17], and fewer financial problems [18]. In contrast, relationship discord has been found to be the most frequent cause of emotional distress [19] with outright relationship failure (in the form of break up or divorce) often resulting in prolonged periods of depression [20], permanent damage to life satisfaction [21], and long-lasting collateral harm to children when they are involved as well [22, 23]. While achieving relationship satisfaction is a primary goal for most individuals, only 37% of couples claim to be very happy in their marriage [24].

How might this situation be addressed? Typically, couples experiencing difficulties desire to improve their relationship and for many of them it is beneficial to do so. In addition to the general health and well-being advantages of building a well-functioning relationship, individuals often have hedonic, economic, religious, cultural, and/or social reasons to enhance their love [2]. There are several methods that couples might employ to ameliorate their marriage or relationship. These include focusing on the positive aspects of the relationship, nurturing commitment, and prioritizing sex and intimacy [25]. When these methods fail, couples might try marital therapy or relationship counseling.

Meta-analyses and systematic reviews indicate that a range of common therapies can indeed be effective in relieving couple distress in many situations [26, 27]. However, “research also indicates that a sizeable percentage of couples fail to achieve significant gains from couple therapy or show significant deterioration afterward” [28, p. 317]. As the fecund field of

relationship counselling approaches its first centenary [29], therefore, there is reason to ask whether standard therapeutic strategies might be improved and/or productively complemented going forward.

Given the hypothesized tension between our inherent psychobiology and our conscious marriage/relationship goals, it has recently been suggested that direct intervention on the biochemical side of the equation might be a promising avenue to explore [1*, 2]. Savulescu and Sandberg [2] argued that pharmacological administrations—based on existing and near-future developments in neuroscience and biotechnology—could be used to improve relationship health and satisfaction. Specifically, they suggested that the chemical modulation of love- and bonding-related neural systems, under the guidance of trained professionals such as clinicians or marriage therapists, could be used to overcome, at least partially, the evolved limitations of marital well-being. These neurochemical enhancers would be used in *conjunction* with counseling and/or other controlled activities to facilitate communication and the pursuit of joint goals and ideals between couples experiencing conflict.

Prior work on this topic has considered the possibility of neurochemical relationship enhancement using broad, conceptual strokes [1*, 2]. This paper, by contrast, attempts a finer level of scientific and practical detail. Our particular focus will be on the brain-level *attachment system* [30], maintained (in large part) by the neuropeptides oxytocin and vasopressin [31, 32]. Specifically, we wish to explore the ways in which synthetic oxytocin may be used to improve the quality of romantic relationships using existing means of administration, and drawing upon recent evidence from published clinical and pre-clinical studies. Building upon the work of other researchers [33], we shall postulate that oxytocin—by acting on the neural substrates of attachment—could serve as an adjunctive therapeutic agent in marriage counseling, so long as certain ethical and clinical-policy considerations are taken into account.

In the following sections we review what is known about oxytocin, the effects of oxytocin on the brain and behavior, and develop our rationale for using it to enhance relationships. We then identify a number of urgent research targets before outlining an applied program for the use of oxytocin in therapeutic settings. Finally, we address some of the most pressing ethical considerations that would necessarily arise in any attempt to “treat” interpersonal relationships via drug-based methods.

Oxytocin as a modulator of social attachment in humans and other animals

The neuropeptide oxytocin is present in a large number of animal species from reptiles—in the form of vasotocin, an evolutionary precursor—to mammals, encompassing the primates, and is intimately associated with social, sexual, and reproductive behaviors including mating and childbirth. Produced by the hypothalamus, oxytocin plays a dual role in modulating a wide range of essential processes: it acts as a hormone when released into the peripheral bloodstream, controlling functions such as milk letdown, uterine contraction, and cervical dilation during parturition in females; and it acts as a neurotransmitter when released into the central nervous system, influencing social, behavioral, and motivational states in both sexes through the stimulation of its neuroreceptor targets in the hippocampus, amygdala, and nucleus accumbens as well as elsewhere throughout the brain and in the spinal cord [34].

Animal model research points to a strong relationship between socially monogamous attachment behaviors and the expression of oxytocin within the brain—along with that of an affiliated peptide, vasopressin, and a suite of auxiliary hormones and neurotransmitters including dopamine. Notably, anatomical investigations into the mating patterns of two

closely-related species of vole—the monogamous prairie vole (*Microtus ochrogaster*) and the polygamous montane vole (*Microtus montanus*)—suggest that their dissimilar bonding strategies may turn upon systematic differences in the distribution of oxytocin and vasopressin receptor neurons in their brains [35]. In one study, implanting a vasopressin receptor gene into the ventral forebrain of a sample of typically promiscuous male voles caused them to behave much like their monogamous cousins [36], while another critical experiment [37] involved manipulating hormone levels *within* the monogamous prairie vole species. Infusing oxytocin into the brains of the females, and vasopressin into the brains of the males, significantly enhanced pair-bonding even in the absence of actual mating.

Based upon these and similar findings, Young and Wang [38] developed a neurobiological model of rodent pair bonding. They argued that the concurrent activation of oxytocin, vasopressin, and dopamine receptor neurons during mating activities results in the formation of a conditioned partner preference. Specifically, oxytocin and vasopressin facilitate the processing of social cues necessary for partner recognition while dopamine plays a reinforcing role by signalling reward. “The convergence of mechanisms underlying reward, conditioning, and the neural processing of social cues,” they write, “seems to result in the motivation to maintain selective contact with one’s partner” [38, p. 1053].

It has not yet been shown conclusively that human attachment relies on the same hormonal machinery as that seen in voles, but several researchers have argued that natural selection would favor conservation of so fitness-relevant a biochemical system [39, 40]. Neuroimaging studies in humans have largely substantiated this view. Mothers who observe photographs of their own infants compared against matched controls show heightened activation in brain areas rich in oxytocin, vasopressin, and dopamine neuroreceptors [41, 42]. This effect is amplified for mothers who exhibit a secure attachment style compared to those who are insecurely attached, and correlates with oxytocin levels in the blood [43]. Finally, analogous activation patterns are seen in adults who are exposed to images of their romantic partner—with whom they report being “intensely in love”—as opposed to images of a platonic acquaintance [44]. While none of these findings demonstrate that elevated oxytocin levels in humans directly induce greater feelings of love or interpersonal attachment—whether in the maternal-infant or adult-romantic case [45]—they do point to a clear association between oxytocin and attachment that seems to mirror what has been observed in other species.

Recent experiments have gone still further, and have attempted to investigate a potential *causal* relationship between the administration of oxytocin and various phenomena associated with social attachment. Using a simple nasal spray to deliver oxytocin directly into the brain—albeit in a diffuse and not entirely well-understood manner [46**]—key studies to date have employed a double-blind, placebo-controlled experimental design. These foundational studies have yielded a range of important discoveries. As we discuss in the following section, the latest evidence suggests that endogenously boosting oxytocin levels may result in prosocial, bond-enhancing outcomes for *some* individuals (or couples) under the right set of circumstances; but it may also lead to antisocial, adverse outcomes if certain dispositional and situational considerations are not taken into account.

Oxytocin as a therapeutic relationship enhancer: promise and peril

How might oxytocin work as a therapeutic relationship enhancer? Given its central role in modulating attachment between individuals, at least in voles, and quite plausibly in humans as well, it seems reasonable to ask whether artificial oxytocin supplementation might be useful for maintaining or even improving romantic relationships. Theoretically, at least, there is good reason to think that it could. As Carter [47, p. 782] has summarized the effects

of oxytocin on social behavior in animals: “Oxytocin ... may serve to inhibit defensive behaviors associated with stress, anxiety or fear, and allow positive social interactions and the development of bonds.”

In fact, oxytocin nasal spray is already being trialed as a possible treatment for specific clinical conditions that involve *disrupted* attachment and other problems in social processing [48]. For example, in the case of autism—a disorder known for its symptomatic social deficits—oxytocin administration increases eye-contact [49], emotion understanding [50], and the effectiveness of decision-making in social contexts [49]. Initial clinical studies have also shown that oxytocin administration may be useful as an adjunctive treatment for depression, anxiety, and schizophrenia, although further research is needed to confirm the reliability of these preliminary findings [51*]. Crucially, to the extent that individual-level symptoms associated with any of these disorders may impair relationship health or general functioning, their amelioration (via oxytocin administration or other means) would likely yield interpersonal, relational, or marital benefits as well.

Oxytocin administration has also been investigated with healthy populations. The last decade has seen a plethora of preclinical studies demonstrating prosocial effects of oxytocin in such individuals, suggesting that oxytocin-based relationship counseling may indeed be a fruitful avenue to explore. In the following sub-sections we discuss the specific domains in which oxytocin-based therapy seems likeliest to yield relationship-level benefits, and then we turn to our analysis of potential anti-social outcomes and other complicating risk factors.

Fostering pro-relationship mindsets and behaviours

Oxytocin administration holds promise for acting in areas that are central to relationship health and functioning. Specifically, oxytocin has been shown to reduce anxiety and stress [52-54]; boost trust [55-57**], eye-contact [58], mind-reading [59], and empathy [60]; heighten the availability of positive relationship memories [61, 62]; and improve social attention, recognition, and appraisals, as well as the encoding and retrieval of memories with social content [63**]. In a relationship context, these effects could (1) increase partner approachability and cooperativeness [56, 64*], (2) increase mutual understanding and perspective-taking, thereby enhancing interpersonal learning in the therapeutic process, and (3) increase positive relationship reflections, which are likely to be associated with successful therapy outcomes [65, 66].

Moreover, in one study, oxytocin-primed male participants who were in a committed heterosexual relationship—but not single males—kept themselves at a significantly greater distance from an attractive female experimenter during an initial personal encounter. Such males also showed a decreased reflexive approach response when exposed to erotic images of beautiful women as measured by computerized approach-avoidance paradigm [67*]. These findings suggest that intranasal oxytocin may help to promote fidelity toward one’s current partner by contributing to the ongoing maintenance of an existing monogamous pair bond.

Enhancing processing of bonding cues

A focus on pair bonding and is also captured by the evolutionary-biological perspective on oxytocin, which emphasizes its role in facilitating the processing of cues related to bonding and reproductive behavior [61]. In line with this view, a study by Unkelbach, Guastella, and Forgas [68] showed that male participants were quicker to identify positively-valenced stimuli associated with bonding and relationships when operating under the influence of oxytocin compared to a placebo. Since oxytocin can strengthen the encoding of positive social stimuli to make them more salient, it might facilitate interpersonal intimacy by

making the encoding of positive social cues more rewarding and memorable [69]. As Striepens *et al.* [51*, p. 445] have suggested: “by acting as a neuroplasticity agent, oxytocin may help rewire neural systems, so that specific cues from individuals with whom bonds are formed are more likely to elicit recognition and pleasure in the future.”

Facilitating improved communication

A final means by which oxytocin administration may be able to enhance the effectiveness of standard therapeutic modalities is via improved communication, allowing couples to learn about each other more effectively and develop joint decisions. In a seminal study, Ditzen *et al.* [70] showed that oxytocin can facilitate positive communication—and reduce stress levels—in romantic couples engaged in an argument. In this double-blind, placebo-controlled study, heterosexual couples received oxytocin (versus placebo) before engaging in a conversation about a chronic source of conflict. Interactions were videotaped and coded for verbal and nonverbal communication behaviors, and salivary cortisol measures were collected. Oxytocin increased the ratio of positive to negative communication behaviors and facilitated a more rapid reduction in cortisol levels after the conflict. Importantly, couples’ therapy—when it *is* effective—is believed to work best by enhancing partners’ communication skills [71*]; and Gottman [72] has demonstrated that the ratio of positive to negative communication behaviors is strongly predictive of long-term relationship survival [73, 74].

Risk factors and side-effects

These positive effects of oxytocin administration, however, constitute only part of the recent trend in research. In tension with the early wave of pro-social findings associated with oxytocin (see Table 1 for a selective summary), more recent studies have pointed to a potential “dark side” as well [75*, 76]. Indeed, more troubling consequences of oxytocin administration are increasingly being uncovered, showing that oxytocin can have a range of different effects, on different people, under different circumstances. For example, Shamay-Tsoory and colleagues [77] have shown that in addition to promoting empathy and generosity, oxytocin can increase feelings of envy and *schadenfreude*. DeClerck, Boone, and Kiyonari [78] found that people behave more cooperatively under the influence of oxytocin when interacting with familiar targets, but *less* cooperatively if the target is a stranger. And DeDreu *et al.* [79] demonstrated that oxytocin can increase in-group favoritism (ethnocentrism) while at the same time potentially magnifying out-group prejudice. These results suggest that oxytocin may ultimately turn out to be “double-edged sword” – capable of “promoting bonds with familiar individuals, but promoting unfriendly behavior toward strangers” [75*, p. 269].

By the same token, distinct personality traits have recently been associated with negative effects of oxytocin on behavior. Bartz *et al.* [80], for example, showed that patients with borderline personality disorder may exhibit *decreased* trust and cooperativeness under the influence of oxytocin. In addition, individuals who are anxiously attached have been shown to be likelier to remember their own mothers as being less close and caring [81]. And oxytocin seems to improve empathic accuracy only in less-socially proficient individuals, whereas it has no effect for those who are already well-attuned to social information [69]. These and other newer findings complicate the notion that oxytocin can serve as a universal ‘enhancer’ of social-cognitive behaviors. Indeed, as Bartz, Zaki, Bolger, and Ochsner [82*, p. 301] argue in a seminal review, when it comes to social effects of oxytocin in humans: “context and person matter.”

Research implications and clinical policy considerations

What do these considerations entail for our question about the potential use of oxytocin as a relationship enhancer, whether employed in a clinical or a counseling setting? As Miller [75*, p. 269] notes: “Going forward, the success or failure of oxytocin as a psychiatric drug may hinge on figuring out which disorders and which people respond positively to the hormone ... and in what context.” Similarly, Guastella and MacLeod [63**, p. 416] have recently stated: “The investigation of individual differences in reactivity to oxytocin is likely to be of profound importance ... key markers [are needed] that can index variation in the degree to which people are affected by the spray, and how this variation is associated with changes in underlying circuitry.”

Significant work is needed, therefore, to create an anthology of both benefit- and risk factors (Table 2) that would mitigate either in favor of or *against* the prescribed use of oxytocin. These might include certain personality traits (i.e., bipolar disorder, borderline personality disorder, insecure attachment styles), genetic profiles (including genes that control for the distribution of oxytocin and vasopressin receptors within the brain), and relevant situational factors. Couples would need to be screened for any complicating variables prior to oxytocin administration, and any individuals who were at a high risk for outcomes that were either predominantly or severely unfavorable might need to be excluded from oxytocin-based treatment plans.

At the same time, however, it would be premature to conclude that oxytocin should *never* be administered in such “problematic” cases. Rather, the existence of possible risk factors for certain individuals suggests that greater initial effort may be required to determine what sort of *psychotherapeutic contexts* and *treatment paradigms* would have to be used to ensure that oxytocin administration resulted in net benefits rather than net harms. In other words, the possibility that oxytocin could prove advantageous (on balance) even for individuals with “risky” profiles—by, e.g., facilitating the development of healthier relationship schemas with the guidance of a counselor or therapist—must not be ruled out in advance of attempting the necessary research.

Indeed, the potential for negative effects of oxytocin administration in general should be considered in a proper context. With regard to findings that oxytocin may increase feelings of envy (or decrease cooperation) during interactions with unfamiliar targets, for instance, it must be remembered that romantic partners are not strangers to *each other*. Hence, it seems reasonable to hypothesize, at least *these* types of problematic out-group or stranger-driven effects would be unlikely to occur in a counseling setting. Furthermore, even if oxytocin administration does turn out to promote such troubling phenomena as in-group favoritism (at the expense of more altruistic out-group judgments), two further conditions would have to be met before these sorts of effects would count against the desirability of attempting oxytocin-based therapy.

First, it would have to be shown that any out-group negativity extended *beyond* the time-frame of the counseling session in which the “in-group” therapeutic effects were being harnessed or explored. Second, it would need to be shown that such “bad” effects were *stronger* when oxytocin is administered exogenously (i.e., through a nasal spray) than when it is released endogenously by the hypothalamus. This is because couples who were trying to improve their relationship through an increased pursuit of intimate activities, such as mutual touching or engaging in sexual intercourse—both of which trigger the endogenous release of oxytocin—should not be expected to refrain from these activities simply because they might inspire a transitory in-group bias.

These considerations show how important it will be, going forward, to study the effects of oxytocin on human judgment and behavior “outside of the lab.” In other words, the effects of a single dose of oxytocin on highly sensitive, quick-to-follow dependent measures—such as is typical for current research—need to be systematically compared against the effects of more ecologically valid drug administrations. Such a comparison would require the investigation of chronic (therapeutic) applications on longer-term attitudinal and behavioral tendencies, as well as the careful examination of any “natural” effects of fluctuating oxytocin levels stemming from ordinary activities and behaviors.

Additional gaps

There are number of additional gaps in our current understanding as well. If any large-scale therapeutic programs are to be attempted, we suggest, these gaps will need urgently to be filled (see Table 3). First, future studies should carefully evaluate the effects of oxytocin administration on both *women and men*. A majority of studies to date have been restricted to males [33] and it will be important to investigate how and to what extent any positive outcomes might generalize to both sexes, particularly in a relationship context. Second, much more work is needed to uncover the *means* by which oxytocin exerts its various effects [83]. As Young (quoted in Miller [75*, p. 296]) has stated: “If we want to move beyond this initial investigatory era and get more sophisticated and potent effects, we need to understand the mechanisms.”

Third, *dosing* and *safety* guidelines need to be established. For example, it will be important to determine whether oxytocin might have addictive properties, particularly at high doses. While there is no evidence to date that oxytocin does have such properties, there could be a potential problem with “demand characteristics” – i.e., the *expectation* that that a drug is having some effect, leading one to do things that one would otherwise not do. At the same time, however, several studies have reported that individuals who are given intranasal oxytocin do *not* report feelings of euphoria or any sort of conscious knowledge of being administered the drug as compared to a placebo [84]. Regarding dosages, these range (in current research) from 18 to 40 IU, and from single instances of administration to up to 182. Yet “the dose that has been most widely used (24 IU) [was] chosen for historical reasons, [and] it remains unclear whether another optimal dose exists or whether someone who does not respond to lower doses of oxytocin nasal spray may subsequently respond to a higher dose” [63**, p. 417].

Fourth, *long term* administration needs to be studied. As McDonald and colleagues [84, p. 11] state: “In order to safeguard further clinical applications of oxytocin, research should direct attention to the impact of intranasal oxytocin when applied in higher-dosage[s] [as well as] longer-term.” Fifth, *larger samples* and *experimental designs* need to be more consistently used. Many recent studies “involve small numbers of patients and are simply correlative. Going forward it is important that ... research involves sufficient patient numbers and employs experimental designs that rigorously test [oxytocin’s] therapeutic potential” [51*, p. 436].

Sixth, oxytocin administration needs to be studied in *conjunction* with psychological and behavioral therapies, as well as with other pharmacological agents, rather than exclusively in isolation [46**, 51*]. This will be especially important for determining whether oxytocin might be useful for “problematic” cases such as those described above. And seventh, *ecological validity* needs to be investigated. As we noted earlier, many of the current findings—both “promising” and “perilous”—stem from single administrations of oxytocin in a laboratory setting. Very little is known about long-term effects of such administration in the “real world” of either individuals’ or couples’ lives.

Practical considerations

What about more practical concerns about the use of oxytocin in applied settings? Even as the numerous extant research-gaps begin to be addressed, it will be essential for couples seeking to improve their relationships with adjunct oxytocin-based treatments to do so under the guidance of a *trained professional*. This professional should be responsible for undertaking any *pre-screening* requirements as noted above, and should ensure that careful monitoring of the relationship takes place at regular intervals [66]. Finally, it would be imperative to confirm that *both* partners had given their informed consent to undertake drug-based relationship treatment and that treatment could be stopped at the request of either partner.

Ethical implications of oxytocin-based relationship therapy

In addition to policy considerations concerning research aims and clinical practice, the prospect of using an endogenously-administered chemical substance to “treat” or even “enhance” an interpersonal relationship raises a number of pressing ethical questions as well. First, a caution must be raised regarding the specific role of oxytocin in modulating both *trust* and *aversion to betrayal* in the context of romantic relationships. In a seminal study, Kosfeld and colleagues [55] demonstrated that intra-nasally administered oxytocin can increase an individual’s willingness to “accept social risks arising through interpersonal interactions.” In addition, DeDreu [85] recently showed that oxytocin can promote cooperation in some individuals by *reducing* their aversion to being betrayed. Yet within certain partnerships, an instinctive unwillingness to suffer repeated betrayals of trust could be vital for protecting the health and well-being of the individual so betrayed. In this situation, oxytocin-administration might diminish one’s ability to recognize the *risks* associated with trusting one’s partner, who might then go on to break one’s trust again.

This consideration highlights the importance of being able to determine what sorts of factors should be considered constitutive of healthy vs. unhealthy relationships in the first instance — i.e., those worth sustaining or even enhancing (through therapeutic interventions or by other means), and those in need of re-evaluation or even termination. While couples have typically been encouraged to find their own answers to these difficult questions, we suggest that the imminent prospect of *neurochemical modulation* of human relationships calls for the development of more general ethical guidelines concerning when and how to deploy these potentially potent new technologies. We have argued elsewhere that such guidelines should be tied to a robust account of personal and interpersonal well-being [86], and should be sensitive to potential harms that may impact upon the lives of children and other vulnerable parties [1*].

Within the context of these more general principles, however, any oxytocin-based treatment plan will have to take into consideration the specific contextual factors that apply to the unique situation of each individual couple. While some couples may *benefit* from trust-enhancing interventions, for example, other couples may be put at risk as we noted above. In addition, although we elected to exclude problematic “stranger” or “out-group” effects from our exploratory list of potential risks associated with oxytocin administration in Table 2, it is conceivable that some couples’ relationships will have deteriorated to such a degree that the individuals involved do indeed “feel like strangers” to each other. Future research should attempt to determine whether oxytocin may have positive or negative effects in situations such as these. Yet while the existence of negative effects in early trials may simply point to the need to develop complementary administration paradigms that could moderate or even reverse these “bad” effects in applied settings, the importance of pre-screening and the close involvement of a trained professional in any therapeutic program cannot be overstated.

Serious care must also be taken to avoid any form of coercion. A particularly problematic situation might arise if one of the partners in a relationship sought to cajole the other partner into remaining in the relationship against his or her wishes, whether by pursuing oxytocin-based therapy or otherwise. Additionally, partners might disagree on the extent to which they believe that the relationship is worth strengthening. These kinds of worries can be allayed by the conditions indicated earlier: (1) oxytocin administration should *only* be pursued if both partners autonomously agree to the treatment; and (2) oxytocin should *only* be administered when it is based on sound ethical reflection, in the context of a structured treatment plan, with the careful guidance of a professional trained in counseling.

Conclusion

Positive interpersonal relationships are healthy. They may even be as important for the promotion of health and well-being as any number of more widely-discussed public health priorities. Indeed, a recent meta-analysis showed that well-functioning social relationships are as essential to good health as exercising and refraining from smoking [87]. By contrast, relationship dysfunction as well as social isolation and outright loneliness are *threatening* to health, and can lead to such outcomes as depression, illness, elevated levels of latent herpes virus reactivation, and even inflamed immune responses. Research has shown that this type of inflammation may contribute to such ills as coronary heart disease, Type 2 diabetes, arthritis, and Alzheimer's disease [88, 89]. If relationship dysfunction, therefore, turns out to be at the "root" of such serious problems as heart disease or arthritis, then treatment modalities aimed at addressing relationship functionality in the first instance would seem to be well worth investigating.

Toward this end, however, neurochemical interventions designed to promote interpersonal health and well-being as a complement to existing therapeutic strategies have gone largely unexplored. Accordingly, we have reviewed a range of preliminary studies that show that the exogenous administration of oxytocin may confer a number of pro-social outcomes, and we have argued that these could serve to enhance at least some romantic relationships. Large-scale, carefully-controlled clinical trials are needed to determine which people (including which couples), under which specific conditions, will be most likely to benefit from oxytocin-based treatments; and a detailed profile of risk factors and contra-indications needs to be compiled as well. Such efforts will inevitably raise a number of clinical, policy, and ethical considerations that must be addressed in tandem with any progress made on scientific and theoretical fronts. By anticipating some of these considerations, we hope to have contributed our part to this exciting new area of research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- * Intranasal oxytocin may hold promise for the therapeutic neuroenhancement of modern relationships. Oxytocin has “good” and “bad” effects, however, that may be different for different individuals and couples depending upon a range of personal, interpersonal, and contextual factors.
- * Large-scale clinical trials with adequate sample sizes, and that include both males and females, are needed to fill in a range of “gaps” in existing knowledge. Chronic administrations and ecologically valid study designs should be top research priorities.
- * The imminent prospect of neurochemical modulation of interpersonal relationships should inspire the development of general ethical guidelines for the responsible use of such technology. These guidelines should emphasize autonomy, consent, and personal and interpersonal well-being.
- * As is the case with any new area of biomedical research, practical, moral, and clinical-policy considerations must be addressed in tandem with any progress made on scientific and theoretical fronts.

Table 1
Selective summary of possible enhancing effects of oxytocin on relationships

Effect:	Reference:
Anxiety and stress-reduction	Heinrichs <i>et al.</i> [52] Kirsch <i>et al.</i> [53] Domes <i>et al.</i> [54]
Trust	Kosfeld <i>et al.</i> [55] Declerck <i>et al.</i> [56] Van IJzendoorn <i>et al.</i> [57**]
Eye gazing	Guastella <i>et al.</i> [58]
Mind-reading	Domes <i>et al.</i> [59]
Empathy	Hurlemann <i>et al.</i> [60]
Positive relationship memories	Heinrichs <i>et al.</i> [61] Guastella <i>et al.</i> [62]
Social attention, recognition, and appraisals	Guastella & Macleod [63**]
Cooperation	Arueti <i>et al.</i> [64*] Declerck <i>et al.</i> [56]
Fidelity	Scheele <i>et al.</i> [67*]
Processing of bonding cues	Heinrichs <i>et al.</i> [61] Unchelbach <i>et al.</i> [68]
Emotion detection and recognition	Bartz <i>et al.</i> [69] Hurlemann <i>et al.</i> [60] Guastella <i>et al.</i> [50]
Positive communication behavior	Ditzen <i>et al.</i> [70]

Table 2
Selective summary of the possible negative effects of oxytocin administration and associated risk factors

Negative Effect	Risk Factor	Reference
Decreased trust and cooperativeness	Borderline personality disorder / highly rejection sensitive individuals	Bartz <i>et al.</i> [80]
Negative attachment memories	Anxious attachment style	Bartz <i>et al.</i> [81]
Social cue overload	Hypersensitivity to social cues	Bartz <i>et al.</i> [82*]

Table 3
Targets for future research and clinical policy recommendations

Targets for future research

- 1 Create anthology of benefit- and risk factors: personality, situational, genetic
- 2 Study males and females
- 3 Investigate mechanisms of action
- 4 Establish dosing and safety guidelines
- 5 Study long-term administration
- 6 Use larger samples
- 7 Use experimental designs
- 8 Study effects in conjunction with therapies and other chemical agents
- 9 Assess ecological validity ... "outside the lab"

Clinical policy recommendations

- 1 Develop pre-screening protocols based on risk factors
- 2 Ensure that oxytocin is administered with trained professional guidance
- 3 Both partners must autonomously agree to treatment
- 4 Either partner can terminate treatment