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1 **Intranasal oxytocin: myths and delusions**

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37

38 **Abstract**

39         Despite widespread reports that intranasal application of oxytocin has an exuberant  
40 variety of behavioural effects, very little of the huge amounts applied intranasally appears to  
41 reach the CSF. However, peripheral concentrations are raised to supraphysiological levels,  
42 with likely effects on diverse targets including the gastrointestinal tract, heart and  
43 reproductive tract. The wish to believe in the effectiveness of intranasal oxytocin appears to  
44 be widespread, and needs to be guarded against with scepticism and rigor. Pre-registering  
45 trials, declaring primary and secondary outcomes in advance, specifying the statistical  
46 methods to be applied, and making all data openly available should minimise problems of  
47 publication bias and questionable post hoc analyses. Effects of intranasal oxytocin also need  
48 proper dose-response studies, and need to include controls for peripheral effects, by  
49 administering oxytocin peripherally and by blocking peripheral actions with antagonists.  
50 Reports in the literature of oxytocin measurements include many that have been made with  
51 discredited methodology. Claims that peripheral measurements of oxytocin reflect central  
52 release are questionable at best.

53

54 **Introduction**

55         More than 100 neuropeptides are expressed in different neuronal subpopulations.  
56 Whereas neurotransmitters are packaged in abundant small vesicles targeted to nerve endings,  
57 peptides are packaged in large vesicles that are relatively sparse, and which can be released  
58 from all compartments of a neuron. These vesicles carry a large cargo (~85,000 molecules of  
59 oxytocin) and peptides act at receptors with nanomolar affinity (1). Often, receptors are  
60 densely expressed at sites innervated by few fibres that contain the peptide ligand, indicating  
61 that neuropeptides are more like hormones than neurotransmitters, acting at sites distant from  
62 their point of release, with organisational and activational roles rather than roles in  
63 information processing *per se* (2).

64         Some neuropeptides have a startling ability to evoke particular behaviours. Central  
65 injections of oxytocin trigger satiety and enhance sexual behaviour in animal models; in rats  
66 and sheep they can trigger maternal behaviour (3,4), in monogamous voles they facilitate pair  
67 bonding (5), and oxytocin-receptor deficient mice show disturbances in social behaviour.

68         Recently, there has been a deluge of reports that oxytocin affects social behavior in  
69 humans when delivered as a nasal spray, and in some studies when delivered peripherally (6).  
70 Such effects have several possible explanations. Oxytocin might enter the CNS, mimicking

71 “neurohormonal” oxytocin release (2), or might act peripherally to indirectly affect  
72 behaviour, either via oxytocin receptors or vasopressin receptors activated at high  
73 concentrations of oxytocin. Other possibilities are that reported effects reflect methodological  
74 weaknesses, and post-hoc interpretation of outcomes with minimal statistical rigor.

75

## 76 **Oxytocin and the blood-brain barrier**

77 Most of the body’s oxytocin is stored in the posterior pituitary, which, in the adult rat,  
78 contains 0.5-1 $\mu$ g oxytocin and similar amounts of vasopressin. This gland contains the nerve  
79 endings of magnocellular neurons whose cell bodies lie in the hypothalamus, but it lies  
80 outside the blood-brain barrier, so peptide released from these endings readily enters the  
81 blood. The rat pituitary contains enough vasopressin to maintain the normal plasma  
82 concentration of 1pg/ml for 30 days, and a concentration of 10pg/ml, as seen during water  
83 deprivation, for three days (1).

84 Between the blood and interstitial fluid of the body there is no barrier to the passage  
85 of peptides, so the distribution volume for oxytocin is much larger than the plasma volume  
86 (7). Oxytocin is stable in plasma (except in pregnancy, when oxytocinase is abundant), and is  
87 cleared from the blood via the kidneys and liver. In the rat, at i.v. doses of up to 500ng/kg,  
88 oxytocin disappears from the blood with a half-life of 3-8min (8). The half-life in CSF is  
89 longer: 28min in guinea pig (9), and 19min in rat (10). Oxytocin is thought to be cleared from  
90 CSF by a combination of flow into the subarachnoid space (11), and active transport into  
91 blood (12).

92 In man, the pituitary oxytocin content (estimated by bioassay) is ~14IU (28 $\mu$ g) (13).  
93 Circulating concentrations are (as in the rat) ~1-10pg/ml, and the pharmacokinetics after i.v.  
94 injection fit a two-compartment model, with a distribution volume of ~33L, a distribution  
95 half-life of ~3min and an elimination half-life of ~20min (14). As in the rat, ~1% of oxytocin  
96 is excreted in urine (15).

97 After entering the blood, oxytocin rapidly penetrates extravascular fluid, but does not  
98 cross the blood-brain barrier in appreciable amounts. In an early study, Ermisch *et al.* gave  
99 rats intracarotid injections of radiolabelled oxytocin: brain areas without an effective blood-  
100 brain barrier extracted up to 30-fold more peptide than other brain regions, but oxytocin  
101 failed to penetrate deeper into the brain (16). Brain areas that lack a blood-brain barrier are  
102 encapsulated by glial and endothelial cells that form tight junctions, preventing passage of  
103 peptides both to deeper brain regions and from them.

104 The effectiveness of the blood-brain barrier for oxytocin was measured by Mens *et*  
105 *al.*, who injected 5µg subcutaneously in rats, increasing plasma concentrations 500-fold to  
106 ~38,600pg/ml (10). Increases in CSF were modest; concentrations increased from ~40pg/ml  
107 to ~150pg/ml. The authors calculated that just 0.002% of the injected oxytocin had reached  
108 the CNS after 10min, when CSF concentrations were maximal.

109

### 110 **Oxytocin penetration of the brain after intranasal administration**

111 Two routes have been proposed for the passage of peptides from nose to brain. The  
112 first postulates internalization of peptide into olfactory or trigeminal neurons, followed by  
113 axonal transport and exocytosis. There is doubt about whether peptides survive  
114 internalisation, and Born *et al.* dismissed this as requiring hours for substances to reach the  
115 brain by axonal transport (17). Oxytocin might pass through intercellular clefts into the  
116 subarachnoid space, but transport across the arachnoid membrane is not an important route  
117 for the entry of solutes into brain (18). The arachnoid is a multi-layered epithelium with tight  
118 junctions between cells of the inner layer that form an effective seal; valve-like villi project  
119 into the sagittal sinus through the dura and only allow CSF movement from the brain to  
120 blood. However, if vast amounts of peptide accumulate in the subarachnoid space, the  
121 concentration difference across the blood-brain barrier might support non-specific passage.  
122 The slow disappearance of oxytocin from blood after intranasal application suggests that  
123 large amounts reach an extravascular pool from which it slowly leaches into the circulation.

124 Ang and Jenkins studied the brain penetration of radiolabelled vasopressin given i.v.,  
125 and, importantly, measured how much label was still associated with intact peptide (19).  
126 Vasopressin, like oxytocin, is a nonapeptide with a sulphur bridge, differing in just two  
127 amino acids, and has similar bioavailability. Plasma vasopressin disappeared with the  
128 expected bi-exponential decay, while CSF levels of the label were maximal after 50min; this  
129 peak was <1% of that in plasma, and none of the label in CSF was associated with intact  
130 peptide. They also gave labelled vasopressin intranasally, sampling CSF and plasma 40min  
131 later. The concentration of label in CSF was ~5% of that in plasma, but whereas 16.5% of the  
132 label in plasma was associated with intact peptide, *none* of the label recovered from CSF was.

133 Since then, six studies have measured CSF levels of oxytocin or vasopressin  
134 following intranasal application. Born *et al.* reported that, after giving 40IU (80µg) in man,  
135 CSF levels rose within 10min from ~5pg/ml to ~10pg/ml, increasing to ~20pg/ml at 60min  
136 (17). They administered, as a bolus, more than twice the pituitary vasopressin content,  
137 justifying this dose on the basis that most probably passes through the nose without being

138 absorbed. Estimating the CSF volume as 300ml, it seems that ~4.5ng of vasopressin reached  
139 the CSF: 0.005% of the given dose – assuming that the rise was due to administered peptide  
140 and not endogenous release triggered indirectly.

141 Striepens *et al.*(20) measured CSF oxytocin in 11 patients given 24IU oxytocin  
142 intranasally. Whereas Born *et al.* saw an increase after 10min (albeit with vasopressin, at a  
143 larger dose) (17), Striepens *et al.* saw no increase at 45 or 60min. However, three patients  
144 sampled at 75min had CSF levels 64% higher than controls (at ~30pg/ml). In the same  
145 month, the authors submitted a paper on fMRI changes in subjects tested 30min after  
146 intranasal oxytocin (21). That paper does not cite the CSF data, or the fact that the fMRI  
147 measurements were made at times when CSF oxytocin was unchanged.

148 Neumann *et al.* gave 20µg of oxytocin intranasally to rats (20 times the pituitary  
149 content) and found no change in CSF oxytocin after 45min (22). However, they found a  
150 doubling of oxytocin levels in microdialysates of brain regions collected at 30-60min,  
151 correlated with a four-fold rise in plasma. Intracranial microdialysis inevitably ruptures blood  
152 vessels around the probe, so these measurements might reflect local passage into the brain  
153 from damaged vessels.

154 Dal Monte *et al.* gave 48IU oxytocin (~10µg/kg body weight) intranasally to  
155 macaques, using either a spray or nebuliser (23). These increased CSF oxytocin from  
156 ~35pg/ml to ~90pg/ml after 40min. On the (very) conservative assumption that the CSF/ECF  
157 volume in the macaque is 40ml, then the additional content at this time is 2.2ng, 0.002% of  
158 the administered dose.

159 Chang *et al.* gave 25IU oxytocin to two macaques, and reported a rise in CSF from  
160 ~20 to ~50pg/ml at 35min (24). In a larger study, Modi *et al.* gave 24IU oxytocin (~5µg/kg  
161 body weight) to macaques by spray or aerosol; only the aerosol produced a significant  
162 increase in CSF (from ~20 to ~60pg/ml) (25). Again assuming a CSF volume of 40ml, the  
163 additional content at this time is 1.6ng - 0.003% of the administered dose. Both spray and  
164 aerosol raised plasma oxytocin levels. Intravenous administration of the same dose raised  
165 plasma levels to ~60,000pg/ml with no increase in CSF.

166 All seven studies administered enormous amounts of peptide intranasally – in every  
167 case more than the pituitary content as a bolus – yet found only modest rises in CSF: two  
168 found no rise. At most, 0.005% of intranasally injected oxytocin reaches the CSF within an  
169 hour. Intranasal application achieves higher concentrations of peptide in blood than in CSF,  
170 and, as basal concentrations in plasma are lower than in CSF, the proportional change in  
171 blood is much greater.

172

173 **How much oxytocin must enter the brain for a behavioral effect?**

174 Although intranasal application seems inefficient, doses of oxytocin that have become  
175 conventional in human studies all exceed the pituitary content of oxytocin. Thus, given that  
176 enormous amounts are given, the tiny rate of penetration might still allow biologically  
177 relevant amounts of peptide to enter the brain. If 24IU oxytocin were delivered as a bolus  
178 intravenously, the peak plasma concentration would exceed 1,400pg/ml, three orders of  
179 magnitude higher than physiological concentrations.

180 Are these enormous intranasal doses enough to deliver effective concentrations of  
181 oxytocin into the brain? In lactating rats, suckling evokes bursts of action potentials in  
182 oxytocin cells that result in pulsatile oxytocin secretion, and this bursting is facilitated by 1-  
183 2ng oxytocin i.c.v. (26). Effects on maternal behavior in the rat need much higher doses  
184 (~400ng) (4). Partner preference effects in voles require infusions of oxytocin at 10-100ng/h  
185 (5), and, to stimulate maternal behavior in sheep, it seems necessary to deliver 5µg i.c.v. (3).

186 It is unsurprising that higher concentrations of oxytocin are needed for behavioral  
187 effects than for peripheral effects. As in most G protein-coupled receptors, agonist  
188 stimulation of oxytocin receptors leads to desensitization (27). Receptors at peripheral sites  
189 are exposed to much lower concentrations of oxytocin (1-10pg/ml), than receptors in the  
190 brain (1), so will be more sensitive to it.

191 Thus 1ng oxytocin is the lowest i.c.v. dose shown to elicit a behavioural effect in  
192 animal studies, and 2ng induces expression of the immediate-early gene *c-fos* in rat brain  
193 regions where oxytocin receptors are expressed, including in the amygdala and  
194 hypothalamus. By contrast, intranasal application of 1µg oxytocin in rats produced no  
195 activation at these or any other sites in the forebrain (28) - and no activation in the olfactory  
196 bulb, the postulated primary target of interneuronal transfer of oxytocin. Maejima *et al.*  
197 reported that intranasal administration of a higher dose of oxytocin (10µg) activated Fos  
198 expression at the paraventricular nucleus, the area postrema and the dorsal motor nucleus of  
199 the vagus (29). The area postrema is outside the blood-brain barrier, and should not be  
200 accessible to oxytocin from the CSF. These same areas were also activated by oxytocin given  
201 systemically.

202

203 **Peripheral consequences of intranasal oxytocin**

204 Although intranasal applications deliver only modest rises in CSF concentrations,  
205 they produce large and prolonged increases in circulating oxytocin, to levels far above those

206 needed for physiological effects. Oxytocin receptors are widely distributed in the periphery:  
207 their presence on mammary tissue and uterus is well known, but there are many other sites of  
208 expression (30). Fifty years ago, intranasal oxytocin was commonly used to augment labor,  
209 using doses much lower than used lately, despite the high levels of pregnancy oxytocinase  
210 that must be overcome for oxytocin to exert a uterotonic effect. Hoover studied 1,806 women  
211 who had been given intranasal oxytocin during childbirth (31). Labor was stimulated by 1-4  
212 doses of 0.4-0.8IU given at 20-min intervals - a total of, at most, 3.2IU. Equivalent effects  
213 were achieved by intravenous infusion of 1-2mU/min, giving rise to the estimate that ~1% of  
214 intranasally-applied oxytocin enters the circulation (32).

215 Intranasal application of oxytocin or vasopressin, at doses currently used, delivers  
216 supraphysiological concentrations into the circulation. Born *et al.* achieved plasma  
217 concentrations of 20pg/ml after giving 40IU vasopressin (17). These are higher than  
218 Robertson *et al.* reported for any patient, including those with pathologically elevated  
219 vasopressin secretion; in man, maximal urine concentrating ability is achieved at a  
220 vasopressin concentration of ~5pg/ml (33). Of the above-mentioned studies, four (20,22,24,  
221 25) achieved oxytocin concentrations in excess of 20pg/ml from basal levels of <5pg/ml,  
222 while Dal Monte *et al.* reported a rise to 80pg/ml after nasal spray, but no significant rise  
223 with a nebulariser (23). Modi *et al.* reported a 100-fold increase in plasma in the macaque (to  
224 >300pg/ml), and a rise to ~60pg/ml (from 10pg/ml) after nebulariser application (25).

225

### 226 **Peripheral targets for oxytocin**

227 Oxytocin regulates feeding and metabolism at multiple sites (34,35). Its receptors are  
228 expressed throughout the gastrointestinal tract, and on gastric vagal nerve endings (36).  
229 Intranasal application in dogs increases glucagon and insulin secretion (37), and this is  
230 probably mediated peripherally as intravenous oxytocin has a similar effect in goats (38) and  
231 dogs (39). In rats, oxytocin receptors are expressed by glucagon- and insulin-secreting cells  
232 in the pancreas (40), and direct stimulation of glucagon release has been characterised *in vitro*  
233 (41). Oxytocin also affects gastric motility: it is secreted in response to food intake, and slows  
234 gastric emptying (42).

235 At the ventromedial nucleus of the hypothalamus, oxytocin promotes both satiety and  
236 sexual receptivity – enhancing the lordosis effect in female rats (43); this nucleus contains  
237 virtually no oxytocin fibres so is a likely target of dendritic secretion from magnocellular  
238 oxytocin neurons (35). Some oxytocin cells of the paraventricular nucleus project to the  
239 spinal cord, where they regulate penile erection (44). However, oxytocin is also released from

240 the pituitary during sexual arousal, and, in the male reproductive tract, oxytocin acts on the  
241 vas deferens to facilitate sperm transport (45), in the prostate gland (46) to promote  
242 ejaculation, and on the penis (47) to promote erection.

243 Oxytocin receptors are expressed in the heart, coupled to secretion of natriuretic  
244 hormone (48). Oxytocin has direct cardiac effects, and intranasal application in man increases  
245 heart rate variability (49). At the anterior pituitary, oxytocin is a releasing factor for prolactin,  
246 and has effects on other endocrine cells too (50). In man, intravenous oxytocin has been  
247 reported to inhibit ACTH release (51), although in animal models oxytocin seems to have a  
248 predominantly stimulatory effect (52). Measurements of plasma corticosterone after  
249 intranasal oxytocin have reported mixed effects; one recent study reports a rise in stress-  
250 evoked secretion (53). Oxytocin receptors are also present on bone (54) and in the thymus  
251 (55). Finally, oxytocin at moderately high concentrations is an agonist at V1 vasopressin  
252 receptors, and these are expressed at many peripheral sites (including the olfactory epithelium  
253 (56); the consequences of activating these is not known). These peripheral actions of oxytocin  
254 seem likely to have some behavioural consequences – especially those on reproductive  
255 organs, the heart and gastrointestinal tract.

256 However, it is not impossible that enormous amounts of oxytocin delivered  
257 intranasally achieve biologically significant elevations in the brain. Oxytocin is avidly  
258 degraded in brain tissue, as known from the fact that CSF concentrations of oxytocin-  
259 associated neurophysin are much higher than those of oxytocin. This neurophysin, a fraction  
260 of the peptide precursor, is secreted in equimolar amounts to oxytocin, but is not  
261 enzymatically degraded in brain. Comparing CSF levels of neurophysin and oxytocin  
262 suggests that only ~5% of the oxytocin that is released in the rat brain reaches the CSF (1).  
263 Thus, intranasally applied oxytocin *might* penetrate some brain regions yet not enter the CSF.  
264 However, it seems inappropriate to cite CSF measurements as if they demonstrate that  
265 substantial brain penetration occurs when they show minimal penetration at best, and it is  
266 disconcerting that the high levels of oxytocin achieved in the periphery are assumed to have  
267 no behavioral consequences. Effects of intranasal oxytocin need proper dose-response  
268 studies, and need to include controls for peripheral effects, by administering oxytocin  
269 peripherally and by blocking peripheral actions with antagonists.

270

### 271 **Measuring oxytocin and vasopressin**

272 Many studies have drawn conclusions from highly questionable measurements of  
273 plasma oxytocin, and others mistakenly claim that plasma measurements reliably reflect

274 oxytocin release in the brain. Validated radioimmunoassays have long converged on the  
275 conclusion that basal circulating levels of oxytocin and vasopressin in man are in the range 1-  
276 10pg/ml, confirmed recently by combined LC/mass spectrometry (57). However, assays of  
277 unextracted plasma mainly measure immunoreactivity that is chemically and physiologically  
278 unrelated to vasopressin or oxytocin, and mainly contained in high molecular weight  
279 fractions. Robertson *et al.* showed that two radioimmunoassays for vasopressin yielded  
280 measurements in unextracted plasma that were at least two orders of magnitude greater than  
281 those inferred from other evidence, and which did not fluctuate in parallel with endogenous  
282 authentic vasopressin (33,58). Eliminating high molecular weight elements by extraction  
283 subsequently became standard in labs measuring oxytocin or vasopressin in plasma.

284 However, many papers have used an ELISA on unextracted plasma, yielding values  
285 of >300pg/ml (59-65). In response to caustic criticism (66), the manufacturers “strongly  
286 recommended” that plasma samples should be extracted to avoid matrix interference (67), a  
287 recommendation reinforced by Christensen *et al.* (68), but this advice is still being ignored.  
288 Any hope that the measured levels correlate with authentic oxytocin levels seems vain. Three  
289 studies have compared ELISA oxytocin measurements of the same samples with and without  
290 extraction (69-71): all reported no correlations.

291 One of those papers concludes that adolescent exposure to oxytocin increases plasma  
292 oxytocin in adulthood, and it might be expected that this conclusion was drawn from data on  
293 extracted plasma (70). Not so: the data from extracted samples showed no differences  
294 between groups: instead, the authors built their interpretation on the measurements of  
295 unextracted plasma.

296 The discrepancy between measurements in unextracted and extracted plasma is two  
297 orders of magnitude, but when Wismer Fries *et al.* reported that urinary excretion of oxytocin  
298 and vasopressin in orphans was affected by early neglect, they reported levels that were, for  
299 both peptides, nearly a million fold too high, after applying a method that was neither  
300 sensitive enough or selective enough to measure either peptide in urine (72), a report that  
301 attracted pointed criticism (73,74). The authors have since improved their methodology, and  
302 in subsequent studies report values in line with classically validated measurements (75).

303

304 **Central and peripheral release of oxytocin**

305           The lack of access to central measures of oxytocin has led some to turn to peripheral  
306 measures of oxytocin in the belief that these are convergent. Central oxytocin derives from at  
307 least three separate systems. Some magnocellular neurons project sparsely to some other  
308 brain areas, including the amygdala and septum, but it seems likely that most of the central  
309 innervations derives from non-neuroendocrine neurons of the paraventricular nucleus (76)  
310 that do not project to the pituitary. For example, oxytocin is released from neurons that  
311 project to the caudal brainstem, regulating gastric reflexes (77), and from neurons that project  
312 to the spinal cord which are involved in penile erection (44).

313           Oxytocin *is* released into the brain in large amounts from the soma and dendrites of  
314 neurons that project to the pituitary– but this is semi-independent of axonal release, being  
315 governed in part by mobilisation of intracellular calcium, a mechanism not present at the  
316 terminals (2). In response to  $\alpha$ -melanocyte stimulating hormone (acting at MC4 receptors),  
317 oxytocin is released from dendrites of magnocellular neurons, but their electrical activity and  
318 peripheral oxytocin secretion is inhibited (78). In response to i.v. cholecystokinin, oxytocin is  
319 released into the blood and in the hypothalamus (79), but several other agents affect release  
320 differentially: for instance, in dogs, opioids stimulate peripheral secretion but suppress central  
321 secretion (80). Hyperosmotic stimuli increase oxytocin release from both dendrites and nerve  
322 terminals in rats, but on different time scales; dendritic release is increased as plasma  
323 concentrations fall (2).

324           Appetite-related stimuli and some reproductive stimuli activate both central and  
325 peripheral oxytocin release, but the timings and extent of these actions differ, and differences  
326 are exaggerated by the different pharmacokinetics in the two compartments. Oxytocin is  
327 released into blood and brain during parturition, but in sheep (81), plasma concentrations  
328 were only elevated for 15min postpartum whereas those in CSF were increased for >120min.

329           Stress affects both central and peripheral secretion of oxytocin– but while swim stress  
330 in rats increases oxytocin release in the hypothalamus and into plasma (82), novelty stress  
331 increases CSF but not plasma concentrations (83). In lactating rats, oxytocin is released in the  
332 hypothalamus in response to suckling *before* any peripheral secretion (84), but in guinea pigs,  
333 simultaneous measurements revealed a large increase in plasma during suckling but no  
334 change in CSF (85), leading the authors to conclude that CSF levels reflect secretion from  
335 centrally projecting neurons that are functionally independent of the magnocellular  
336 neurosecretory neurons.

337           In lactating rhesus monkeys, Amico *et al.* (86) found that “variations in the  
338 concentrations of oxytocin in CSF were independent of the suckling stimulus and plasma

339 oxytocin concentrations” and noted, as others had before (87), that CSF levels but not plasma  
340 levels show a circadian variation. They concluded that “release of oxytocin into the CSF of  
341 lactating monkeys is disassociated from release into the peripheral circulation” (86).

342 Winslow *et al.* measured CSF and plasma oxytocin in rhesus monkeys in a study of  
343 the effects of rearing conditions: while CSF oxytocin correlated with social behaviour,  
344 plasma levels did not, nor did they correlate with CSF levels collected in the same session  
345 (88). CSF and plasma concentrations showed no correlation in patients with aneurysmal  
346 subarachnoid haemorrhage (89), or in either suicide attempters or healthy volunteers (90), or  
347 in non-neurological and nonpsychiatric patients under basal conditions (91), or in MDMA  
348 users (92). Carson *et al.* reported that CSF and plasma oxytocin concentrations are correlated  
349 in children, but only after correcting the data for multiple variables that led to independent  
350 release (93). Oxytocin is released into the blood at orgasm in men (94), but Kruger *et al.*  
351 found no changes in CSF at any stage of the sexual response cycle (95).

352

### 353 **Publication bias**

354 Much of the interest in intranasal oxytocin followed a report that it enhanced trust  
355 (96); extravagant data interpretations and unorthodox uses of statistics in some of these  
356 studies have been incisively criticised (97), and such defects appear to be widespread. The  
357 unreliability of small clinical trials is recognised, and attributed to a combination of  
358 publication bias, questionable statistical analysis and methodological weaknesses, and there  
359 are similar concerns about basic biological research (98). Ferguson and Heene argued that for  
360 psychological research “ the field often constructs arguments to block the publication and  
361 interpretation of null results and that null results may be extinguished through questionable  
362 researcher practices”, resulting in the promulgation of theories that are “ideologically popular  
363 but have little basis in fact” (99). A survey of researchers in psychology suggested that  
364 practices such as excluding outliers *post-hoc*, using multiple outcome measures and only  
365 reporting results that reached statistical significance, and halting data collection to test for  
366 significance and resuming if significance is not found are common (100). Simmons *et al.*  
367 warned of practices that transform null findings into positive findings by statistical  
368 adjustments or the exercise of undisclosed “researcher degrees of freedom” (101), they  
369 showed, by simulations and experiments, how easy it is to accumulate “statistically  
370 significant” evidence for a false hypothesis.

371 Pre-registering trials, declaring primary outcomes in advance, specifying statistical  
372 methods to be applied, and making data openly available should minimise these problems.

373 Several recent trials conform to some of these conditions, particularly in reporting clear  
374 primary outcomes. They show no effect of intranasal oxytocin on patients with schizophrenia  
375 or healthy volunteers (102,103); or in early psychosis (104); or on individuals with Prader-  
376 Willi syndrome (105); or in MDMA users (92); or in youths with autism spectrum disorders  
377 (106,107). Revealingly, in the last study “caregivers who believed their children received  
378 oxytocin reported greater improvements than caregivers who believed their child received  
379 placebo.” The wish to believe in the effectiveness of intranasal oxytocin appears widespread,  
380 and needs to be guarded against.

381

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