Intranasal Oxytocin for Adults with Anorexia Nervosa

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1. Background

Anorexia nervosa (AN) is characterised by anxious preoccupation with food, shape and weight,[1,2] but includes socioemotional features that are potentially 'undertargeted' by current treatment options.[3] These include difficulty expressing emotion or understanding the emotional expression of others, avoidance of emotional stimuli, relationship difficulties, and social withdrawal.[3,4,5]

AN is a dangerous condition in which fewer than 50% of people make a full recovery.[2,3] NICE recommends family therapy as a front-line treatment for AN in young people,[6] but only recommends which psychological therapies clinicians should *consider*: cognitive behavioural therapy for eating disorder, the Maudsley Model of AN Treatment for Adults, or specialist support clinical management.[6] Often, nutritional rehabilitation (NR) (supervised refeeding) is the only support provided.[2,7]

NICE advises against medication as the sole treatment for AN.[6] Atypical antipsychotics are frequently used to reduce obsessions and increase weight,[3] and antidepressants are commonly used for the affective features of AN.[5]

Oxytocin (OT) is a neuropeptide and hormone that plays a well-recognized role in labour, breastfeeding and bonding.[7,8] It is also understood to contribute to regulation of interpersonal interactions and sociability, emotional reactivity, and feeding behavior.[2,7,8] These factors have raised interest in OT as an adjunct treatment for AN.[7,8]

2. Investigations

Four studies on the impact of OT on AN have had their results published. These are outlined in the table below. The outcomes measured were either socioemotional or food-focused elements of AN.

Study	Groups & results	Outcome measures
Russell et al. 2018 (2)	NR + OT (n=16), NR + placebo (n=17), all with AN. OT group showed improvements on: • eating concern (EDE-Q), • cognitive flexibility, • salivary cortisol.	• Weight gain (Body Mass Index) • Core eating disorder psychopathology (EDE-Q) (eating concern, restraint, weight concern, shape concern, global score) • Autism spectrum features (Autism Quotient) (social skill, attention switching, attention to detail, communication, imagination, total score) • Social anxiety (Liebowitz Social Anxiety Scale) (fear/anxiety, avoidance) • Identification of emotional expression (RMET) • Obsessive-compulsive features (OCI-R) • Motivation to change (ANSOCQ) • Stage of illness (CASIAN) • Cognitive flexibility (WCST) • Salivary cortisol • Response to high energy snack (STAI)
Leppanen et al. 2017 (1,4)	AN (n=30), healthy control (n=29). Comparing OT to placebo, AN group had: • lower salivary cortisol, • more typical attention to food stimuli. HC group no change.	• Attentional bias (VPDT) to: • Food stimuli • Smoothie consumption (mL) • Anxiety in response to smoothie (VAS) • Salivary cortisol • RMET • Emotional response to film clips (PANAS)
Kim et al. 2015 (5)	AN (n=35), bulimia nervosa (n=34), healthy control (n=33). Comparing OT to placebo, BN group improved on: • food intake, • sad identification. HC group improved on: • sad identification. AN group no change.	• Fruit juice consumption (mL) • Food intake over 24 hours (kcal) • Emotional intensity identification (DFMT) (sad, fear, angry, happy, total)

Kim et al. 2014 (9,10)	AN (n=31),
	healthy control (n=33).
	Comparing OT to placebo,
	AN group improved on:
	• eating stimuli,
	• negative shape stimuli,
	• angry stimuli.
	HC group improved on:
	• disgust stimuli.
		• Attentional bias (MDPT) to:
		  • Eating stimuli
		  • Weight stimuli
		  • Shape stimuli (positive, neutral, negative)
		  • Emotion stimuli (happy, angry, disgust)
		• Fruit juice consumption (mL)

EDE-Q, Eating Disorders Examination; RMET, Reading Eyes in Mind Test; OCI-R, Obsessive Compulsive Inventory; ANSOCQ, AN Stage of Change Questionnaire; CASIAN, Clinical Administered Staging Instrument for AN; WCST, Wisconsin Card Sort Test; STAI, State-Trait Anxiety Inventory; VPDT, visual probe detection task; VAS, visual analogue scale; PANAS, Positive and Negative Affect Schedule; DFMT, dynamic facial morphing task; MDPT, modified dot probe task

3. Evidence for Oxytocin

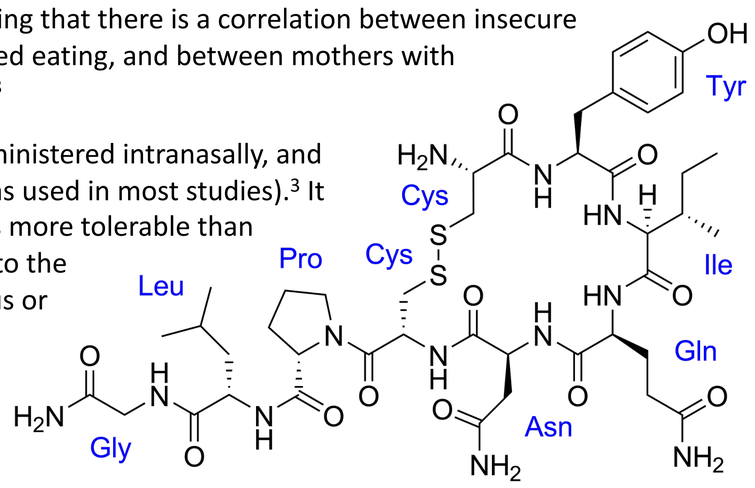
OT has been found to reduce cognitive rigidity and increase interpersonal trust in adults with autism spectrum disorder (ASD),[2] traits that are shared with AN – there is a high rate of comorbidity between AN and ASD.[7,9] There is also evidence that OT can improve sociability and decrease anxiety, inflexible cognitions and repetitive behaviour (as seen in depression, anxiety, social phobia and obsessive-compulsive disorder), although the evidence is not as strong as for ASD.[3,7]

There is good evidence for OT's anxiolytic effect.[5,8] People with AN have been found to have high salivary and plasma cortisol, which can be reduced by OT.[1,2] A similar effect of OT on cortisol has been found in depression, emotionally unstable personality disorder (EUPD), Fragile X syndrome, and substance misuse.[1] Cortisol is a marker of neurobiological stress, and potentially increases attentional bias to food, shape and weight stimuli in AN.[1] Findings from animal studies suggest OT can moderate the influence of stress and anxiety on eating.[1]

A finding that has carried from animal studies to humans is that OT can increase trust in strangers[3]: this could help overcome barriers to familial and therapeutic relationship-forming that are commonly experienced with AN patients.[7] Other animal studies suggest that OT plays a role in eating dysfunction, e.g. by mediating leptin.[8]

There is clear evidence that the oxytocinergic system is disrupted in AN,[8] including low OT in the cerebrospinal fluid and plasma of people with AN.[2,5,10] Primate studies suggest low OT could contribute to the social withdrawal seen in AN.[10] Given OT's established role in attachment formation, it is therefore unsurprising that there is a correlation between insecure maternal attachment and disordered eating, and between mothers with eating disorder and child bonding.[8]

Practically, OT is almost always administered intranasally, and has been found safe for 18-40 IU (as used in most studies).[3] It has a low side effect profile,[8] and is more tolerable than the alternatives for gaining access to the central nervous system: intravenous or intracranial administration.[7]



Oxytocin with labels. 2009. Accessed 3 April 2020 from https://commons.wikimedia.org/wiki/File:Oxytocin_with_labels.png

4. Limitations

These four studies of OT for AN have small and specific samples:[3,8] participants are exclusively female, and mostly inpatients (between 50%[1,4] and 100%[2,5]).

Many participants were using psychotropic medication, rendering the benefit of OT unclear. Between 9%[5] and 59%[2] took antidepressants and up to 66%[2] took antipsychotics. Serotonin increases OT concentration,[8] and may impact socioemotional processing.[4]

OT is clearly involved in feeding,[2,7,8] but its prevalence in trials for obesity and Prader-Willi syndrome (due to the anorexigenic effect of OT)[8] suggests that there is complexity that requires further investigation. There is a risk that OT could lead to reduced food intake in people with AN.[9]

Some studies suggest that low OT in AN is a result of the malnourished state and not a cause[7] – it correlates with low body fat and low bone density.[2,7] Epigenetic findings of high methylation of oxytocin receptor genes in AN suggest that low OT is a result of early trauma, which may itself lead to maladaptive coping like disordered eating.[8]

Although fertility is affected by AN, pregnancy is not impossible. Given OT's role in pregnancy, the risks of OT as a treatment option for pregnant women with AN have not been explored, and pregnant women were excluded from these studies.[2,5]

Animal studies suggest that chronic OT use may negatively impact social behavior.[8] Most studies above only administered one dose,[1,4,5,9,10] or administered longer term but ran no follow up[2].

5. Conclusions

While it is difficult to draw broad conclusions about the clinical utility of OT in AN as most studies use different outcome measures,[3] OT was shown to improve eating concern,[2] cognitive flexibility,[2] and attentional bias to food stimuli,[1] eating stimuli[9], negative shape stimuli[9] and emotional anger stimuli.[10] This is promising, and contributes to existing research.

Of the two studies that measured it, salivary cortisol reduction was statistically significant in both.[1,2] Given the link between cortisol and attentional bias,[1,9] it may be useful to consider OT as a pro re nata (PRN) medication in AN to reduce anxiety around mealtimes. OT did not increase calorie intake, but disruption of factors that maintain AN, like neurobiological stress and information processing biases,[1] could contribute to recovery through conditioning or fear extinction.[9]

Future research would do well to explore the effects of OT as an adjunct to psychological therapies for AN.[6] While OT has been correlated to many elements of AN (e.g. maternal relationship,[8] malnutrition,[7] childhood trauma[8]), the direction of causality remains to be established. OT's lack of impact on outcomes measuring social cognition in the studies above suggests that AN features OT disturbance beyond simply deficit, which needs to be further explored.[8]

6. Relevance

The patient who inspired this poster was a young woman with an AN diagnosis. She experienced increasing social isolation at home and school, and showed attentional bias to weight, shape and eating after being called 'fat' as a child. She had difficulty expressing emotion to her family and healthcare professionals. She especially struggled at mealtimes, from arguing with her parents at home, to refusing meals in hospital, to ripping out her nasogastric feeding tube. She displayed many anxious fixations and socioemotional dysfunctions typical of AN that OT is being explored as a treatment for. This patient could have benefit from PRN OT before meals to reduce stress and anxiety, particularly as she had to wait for treatment due to service availability.

7. References

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