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Oxytocin in clinical settings: A three-stage roadmap for responsible translation

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Studies on the modulating effects of the neuropeptide oxytocin on prosocial behavior and cognition have increased exponentially in recent decades, generating substantial interest in potential clinical applications. Oxytocin (OT) has been nominated as a potential (adjunct) therapeutic intervention for psychiatric disorders, including autism, mood disorders, and posttraumatic stress, despite some failed replications and reports of biography- and context-dependent or iatrogenic OT effects. Given the increasing interest in OT as a psychopharmacological intervention, we must now address the key questions for responsible translation before rolling out oxytocin in therapeutic contexts. Building on our work on conditions for translating scientific findings to practice (Van IJzendoorn and Bakermans-Kranenburg, 2024), we propose a three-stage roadmap for responsible translation of OT to clinical practice: 1) replicated effectiveness, 2) reflection on ethical aspects, and 3) a suitable cost-effectiveness analysis. See Fig. 1.

Step 1. Replicated effectiveness.

OT can be considered a potential therapeutic intervention only when studies demonstrating its beneficial effects on a specific behavioural and mental outcome are successfully replicated by independent research groups and supported by meta-analytical evidence based on high-quality studies. Meta-analytic evidence is particularly important, as OT effects are not always consistent within and across conditions and target groups. Several meta-analytic studies evaluated the combined effect size of OT on symptom severity in clinical groups. For example, a recent meta-analysis of 57 effect sizes derived from 25 studies showed that OT improved social outcomes but not repetitive behavior in autism (Audunsdottir et al., 2024). This suggests that the first step toward responsible clinical translation has been partially met. However, additional meta-analytic research is needed to explore contextual moderators of OT's effectiveness, as well as to identify optimal intervention strategies—such as frequency of administration, delivery method (intranasal vs. oral), and whether OT is most effective as a stand-alone treatment or in combination with other therapies. Only once there is replicated evidence providing answers to these issues can steps two and three of the roadmap for responsible translation be responsibly pursued.

As another example, the absence of meta-analytical evidence for OT effects on positive or negative symptoms of schizophrenia (Sabe et al., 2021) suggests that, at present, there is insufficient justification for its use as an effective treatment in this context. It is important to note, however, that the absence of significant effects may reflect either genuine support for the null hypothesis or limitations of the available data, such as small sample sizes, that reduce sensitivity to detect true effects. This highlights the need for alternative approaches, including Bayesian hypothesis testing or equivalence testing (Quintana, 2018), to more rigorously evaluate OT's clinical relevance for schizophrenia. Until such analyses are conducted and yield clearer conclusions, the use of oxytocin in the treatment of schizophrenia cannot be considered evidence-based.

Step 2. Reflection on ethical aspects.

To our knowledge, ethical grounding of using OT or related psychopharmacological treatments for ASD is yet to be established. Such treatments should at least have informed consent of the stakeholders involved in coping with the consequences of a disorder. For example, stakeholders in ASD are children with ASD and their parents, adults with ASD, but also their social network and society at large. The discussions

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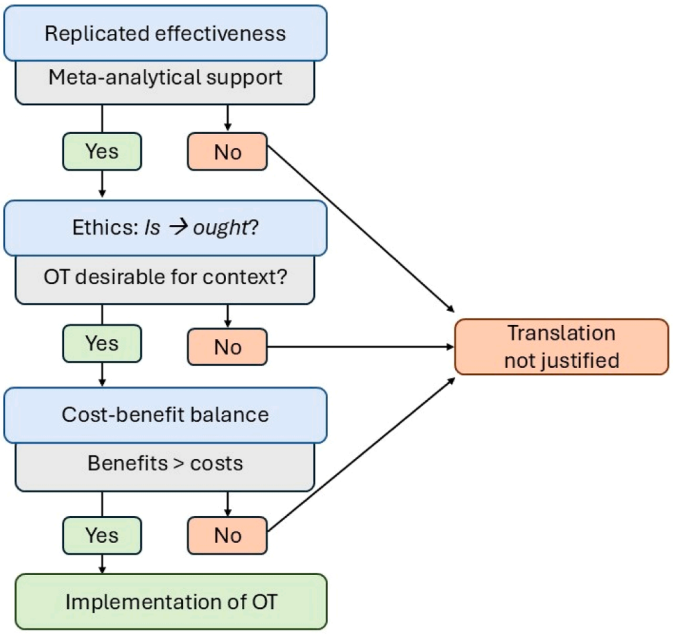

Fig. 1. A three-stage roadmap for responsible translation of oxytocin to clinical settings.

about neurodiversity shows the divergence in ideas about terminology and identity (e.g., autistic individuals versus individuals with autism) with implications for where the response to the problems should be found: adaptation of society to neurodiversity or adaptation of the individual to societal demands.

We propose a form of 'citizen assembly' as a method to build grounded consensus about the choices to be made in treatment modalities including OT (Van IJzendoorn and Bakermans-Kranenburg, 2024). A carefully stratified random selection of 100–200 stakeholders, selected to represent the population within a country, would be invited to discuss OT treatment, informed by experts in (biomedical) ethics, ASD, OT research and experts-by-experience such as policymakers, clinical professionals, social support figures, parents and individuals with autism from various ages and sociocultural backgrounds. Ideally discussions in such an assembly would result in a consensus statement about justifiable terminology, goal setting for treatment, and ethical justification of OT as (adjunct) treatment. A central aim of the assembly would be to reach a well-informed deliberated consensus, not just a (smallest) majority vote-counting decision that flatly ignores reasonable minority positions.

Step 3. Cost-benefit analysis

The third step is a suitable cost-effectiveness analysis. Integrating OT into clinical practice requires a careful balance between effect size, scalability, and costs. Effect size is a critical factor, as it helps determine whether the benefits of OT are substantial enough to justify its broader integration into clinical settings. In terms of scalability, intranasal OT would easily get the green light for dissemination, as an OT nasal spray is simple to self-administer and distribute among patients. However, the costs in terms of iatrogenic side-effects can be more sobering. Research suggests that OT effects are context-dependent, promoting prosocial behavior in safe environments (e.g., therapeutic settings) but potentially evoking adverse effects in situations of perceived threats. For instance, in mothers with postpartum depression, the distressing sound of a crying infant was perceived as more urgent but elicited a harsher intended caregiving response following intranasal OT (Mah et al., 2017). On a more encouraging note, studies in autism populations have thus far reported no significant adverse effects (DeMayo et al., 2017), suggesting that the risk of iatrogenic harm may vary across clinical groups. Therefore, cost-effectiveness analyses must be tailored to specific populations, balancing not only financial costs and therapeutic benefits but also potential unintended consequences.

That said, cost-effectiveness is not easy to determine. The metrics used in health economics are QALYs (Quality Adjusted Life-Years), where health improvement after treatment is measured in five domains: physical mobility, looking after yourself, doing usual activities, having pain or discomfort, and feeling anxious or depressed. Healthy individuals provide QALY norms for the weights assigned to improvement, based on how many years of full health they would choose over (more) years with 'some' or 'a lot' of problems in each of these domains. Although in principle this approach might enable a comparison between various treatments for a variety of disorders and illnesses, the problems are multiple: Only one of the five domains is related to mental health (minimizing QALY benefits compared to treatment of physical health issues); the effects of improvements after treatment on the social environment are not taken into account (which in case of mental health issues may be substantial); and it is debatable whether healthy individuals are in the position to decide on the weights of various health issues (Van IJzendoorn and Bakermans-Kranenburg, 2024). In some fields progress on establishing cost-effectiveness of OT versus alternative treatment may be easier, e.g., in postpartum haemorrhage (Ginnane et al., 2024). Whether OT might benefit individuals with autism and their social environment to the same extent but with economic benefits compared to alternative treatments is an open question.

1. Conclusion

Thinking about clinical applications requires addressing OT's replicated effectiveness, ethical considerations, and a comprehensive cost-benefit analysis. OT can only be applied as a therapeutic means or add-on when the three conditions for responsible translation are met. However, even at that stage, questions on the optimal dosage, treatment frequency, and type of intranasal device need to be addressed. Currently, replicated effectiveness has not been demonstrated for most psychiatric disorders that could potentially benefit from OT treatment. When the first stage of the roadmap has not yet been passed, it is premature to even think of translating OT into clinical practice.

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