The role of oxytocin as an indicator of outcome and therapeutic alliance

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ABSTRACT

Oxytocin is a neuropeptide produced by the hypothalamus and involved in numerous functions, such as labor and breastfeeding. The literature has highlighted the critical role of this hormone in interpersonal relationships – particularly in mother-child and sentimental relationships – implicating it in attachment bonds. Several recent studies have examined the activation of oxytocin in the psychotherapeutic relationship. This narrative review article describes the modulation of the oxytocinergic axis in patients and therapists, based on a review of papers identified through searches of PsycINFO, PubMed, and RivistaWeb, from January 2015 to May 2024. The results of this literature review support the hypothesis that changes in oxytocin levels during interactions between a therapist and patient are associated with the therapeutic process by activating the attachment system. Furthermore, this mechanism does not appear to be influenced by the therapist's theoretical model of reference but rather by their ability to empathize with the patient. In conclusion, this mini-review highlights the significant function of oxytocin as a potential biomarker for assessing the patient-therapist relationship, identifying a biological substrate of the therapeutic alliance.

Key words: oxytocin, therapeutic alliance, depression, psychotherapy, attachment, neurobiology.

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Citation: Durante, C., Di Vincenzo, G., Minutoli, A., Nicolais, G., Carola, V., (2025). The role of oxytocin as an indicator of outcome and therapeutic alliance. *Research in Psychotherapy: Psychopathology, Process and Outcome, 28*(2), 842. doi: 10.4081/ripppo.2025.842

Contributions: CD, GDV, and AM, article search and selection, and writing – original draft; VC and GN, conceptualization, funding acquisition, supervision, and writing – review & editing. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: not required.

Consent for publication: not required.

Availability of data and materials: the data reported in this manuscript have been presented only in this study and will be made available upon reasonable request.

Funding: this work was supported by Sapienza University of Rome through research grants to VC and GN.

Received: 19 November 2024.
Accepted: 11 April 2025.

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Research in Psychotherapy:
Psychopathology, Process and Outcome 2025; 28:842
doi:10.4081/ripppo.2025.842

Introduction

Oxytocin (OT) is a neuropeptide produced by the hypothalamus that mediates numerous bodily functions. Such activities include the stimulation of labor and lactation, as well as protection against and prevention of certain organic diseases (Patin *et al.*, 2017). Patin *et al.* (2017) believe that OT is involved in recognizing emotions and empathy, as well as in promoting social synchrony and cooperation between individuals. Several studies have confirmed these elements that have implicated OT in social interactions, from mother-child relationships to romantic interactions (Grebe *et al.*, 2017; Scatliffe *et al.*, 2019).

In humans, pathological and dysfunctional relationships correlate with OT levels. For example, patients with borderline personality disorder (BPD), a disorder characterized in part by disorganized representations of attachment and an inability to form stable interpersonal relationships, harbor lower plasma OT levels (Jobst *et al.*, 2016). Furthermore, OT has been shown to be involved in the formation of attachment bonds. Maternal sensitivity, when accompanied by an increase in maternal OT during interactions with a child, promotes secure attachment in the child (Kohlhoff *et al.*, 2022).

Epigenetic modification of genes that regulate OT pathways and endogenous OT levels has been associated with how people form and maintain intimate social relationships with others, as ev-

idenced by the link between low methylation of the oxytocin receptor gene promoter and high plasma levels in young adults with better social outcomes and thus less anxious attachment (Ebner *et al.*, 2019).

Given the function of OT in interpersonal relationships and the factors that can play a crucial role in the development of psychopathology, recent research efforts have focused on determining the role of endocrine hormones in therapist-patient interactions, primarily based on the theoretical framework of attachment theory. Such studies have hypothesized that OT is a biomarker for assessing the therapeutic relationship (Zilcha-Mano *et al.*, 2018). Consequently, these models identify a biological substrate of the therapeutic alliance and provide evidence for theoretical models that consider therapy an emotional reactivator of the parent-child relationship (Zilcha-Mano *et al.*, 2020). Diverse theoretical models consider the patient's manner of engaging with the therapist as modalities acquired during childhood, which are organized in representations and expectations about oneself, others, and interpersonal relationships (Bowlby, 1973; Weiss *et al.*, 1986). Thus, arising from studies that highlighted the importance of the oxytocinergic system in the formation of attachment bonds with parents and subsequently with significant figures in adulthood (Scatliffe *et al.*, 2019), the literature has examined the role of OT in therapeutic interactions as a potential process marker, identifying the synchronization of OT levels between patient and therapist as an indicator of the strength of the therapeutic alliance (Zilcha-Mano *et al.*, 2020).

Because the therapeutic alliance is one of the most predictive non-specific factors of a positive treatment outcome, some studies have also viewed OT as a potential marker of outcome – *i.e.*, a sign of symptomatic improvement following therapeutic treatment (Atzil-Slonim *et al.*, 2022; Fischer *et al.*, 2023; Jobst *et al.*, 2018).

Most studies on the function of OT in the therapeutic process have included patients who have been diagnosed with major depressive disorder (MDD) as an experimental sample. Studies on OT in MDD have yielded heterogeneous results, suggesting that alterations in OT in this condition are influenced by other factors. It can be assumed, among various hypotheses, that lower OT levels in MDD patients depend on the presence of emotionally traumatic experiences (Fischer & Zilcha-Mano, 2022). In these cases, subjects develop impairments in social skills and synchronization, benefiting less from therapeutic treatment (Fischer & Zilcha-Mano, 2022). Further, it cannot be excluded that differences in the literature may be related to individual aspects: according to the social salience hypothesis, OT is assumed to increase the salience of social stimuli and, thus, depending on subjective characteristics, to have pro-social or anti-social effects (Engel *et al.*, 2022; Shamay-Tsoory & Abu-Akel, 2016).

A recent systematic review by Hohl *et al.* (2024), which considered different forms of psychotherapy in various classes of psychiatric patients, found that OT levels were significantly associated with treatment outcomes only in MDD patients. These data could be explained by the impairment of the attachment system found in depressive syndromes (Fischer & Zilcha-Mano, 2022). This work (Hohl *et al.*, 2024) is valuable because it also suggests that the association between OT levels and treatment outcomes of depressive symptoms is not due to the psychotherapeutic method applied but to the therapeutic alliance.

In light of these data, this review has the primary objective of investigating, through an analysis of recent literature, whether OT levels measured in patients and/or therapists can serve as a biomarker of psychotherapeutic treatment success. In particular, we focused on treating patients with MDD and BPD, two disorders in which impairment of the attachment system has been described (Fischer & Zilcha-Mano, 2022; Jobst *et al.*, 2016). The evidence that biological substrates underlying the etiopathogenesis of different psychopathologies might involve the oxytocinergic system differently supports our decision to focus only on these two disorders.

A second objective is to evaluate to what extent the biological synchronization of OT between patient and therapist is related to the construction of the therapeutic alliance. Since it is well known that this alliance represents a non-specific therapeutic factor, we included in our review studies on this topic using different therapeutic approaches.

Materials and Methods

Literature search

This is a narrative review of the current literature in PsychInfo, PubMed, and Rivisteweb, covering publications from January 2015 to May 2024. This timeframe was selected to ensure the inclusion of studies that utilized the most recent and reliable biological protocols for OT detection analysis, thereby enhancing the validity of the reviewed findings. The search strategy utilized a combination of the following key words and terms: oxytocin, therapeutic alliance, depression, oxytocin dysregulation, counseling, psychotherapy, attachment, and biomarkers.

The articles included in this study met the following criteria: i) Participants had a diagnosis of either MDD or BPD; ii) the studies focused on adults, since the oxytocinergic system and attachment processes during development are not comparable to those of the adult; iii) face-to-face individual psychotherapy was employed, given the limited evidence supporting the equivalence of online and in-person therapy in terms of therapist-patient biological synchronization; iv) the studies were either empirical investigations or case studies; v) and they were available in English.

As a result, 15 articles were included, considering both descriptive and experimental articles. All articles that involved intranasal administration of OT were excluded.

Results

OT as an outcome indicator in psychotherapy

Several studies have proposed OT as a marker of changes in the therapy and treatment efficacy (Jobst *et al.*, 2018; Zilcha-Mano *et al.*, 2021). Overall, treatment outcomes appear to be associated with the following factors: a) the patient's OT levels (Atzil-Slonim *et al.*, 2022; Fischer & Zilcha-Mano, 2022; Jobst *et al.*, 2018); b) OT levels in the therapist (Fischer *et al.*, 2023); and c) the synchronization of OT levels between the therapist and patient (Tal *et al.*, 2023; Zilcha-Mano *et al.*, 2021).

Plasma OT levels in MDD patients can predict the outcome of psychotherapy. Higher levels of OT correlate with a greater ability to build therapeutic relationships (Jobst *et al.*, 2018) and thus better enjoy and internalize the emotional experience with the therapist. Conversely, MDD patients with more significant impairments in social skills and an anxious attachment style benefit less from treatment (Fischer & Zilcha-Mano, 2022), which is related to basal neuropeptide levels and the reactivity of the OT system in interactions (Atzil-Slonim *et al.*, 2022). In patients with

increased OT reactivity, psychotherapeutic treatment has a more significant effect in reducing depressive symptoms (Atzil-Slonim *et al.*, 2022). Thus, OT reactivity appears to be an important biomarker of success in the treatment of MDD, consistent with studies that implicate OT as a biological substrate for resilience, of which reactivity is theorized to be a core principle (Atzil-Slonim *et al.*, 2022; Feldman, 2020).

Evidence for this prognostic marker has been provided by research that has assessed OT levels in BPD patients, which has noted lower basal plasma OT levels and difficulties in OT system activation and hormonal modulation, likely related to histories of early trauma in these patients (Ebert *et al.*, 2017). In this respect, the dysregulation of OT could be involved in the disorder's etiology, especially regarding dysfunctional relationships (Jobst *et al*., 2018). Reflecting on data showing that this disorder is often characterized by early relational trauma that compromises the formation of secure attachment bonds, it could be hypothesized that the biological ability of the system to modulate and regulate itself in the face of social stimuli – rather than basal OT levels – is what undermines the therapeutic alliance and treatment outcomes (Jobst *et al.*, 2018).

Notably, in addition to the patient's OT levels, those of the therapist predict treatment outcomes. Fischer *et al.* (2023) showed that an increase in the therapist's OT levels from the beginning to the end of a session during interviews in which patients reported experiencing more negative emotions predicted lower depressive symptoms in subsequent sessions. The authors hypothesized that this rise in therapists' OT levels in response to patients' negative emotions reflects activation of the therapists' caregiving system, signaling the emergence of a good and healthy interaction. Thus, OT levels in the therapist and patient seem to react to the activation of the attachment system, as confirmed by studies on the synchronization of OT levels between the therapist and patient and their association with therapeutic improvement.

OT as an indicator of the therapeutic alliance

In addition to treatment outcomes, OT appears to be a biomarker of therapeutic alliance building. The construct of 'working alliance' or 'therapeutic alliance' (Greenson, 1965; Zetzel, 1956), initially derived from the psychoanalytic literature, refers to the relational and cooperative aspects between the patient and therapist. The bonding dimension that is characterized by positive reciprocal feelings in this dyad is considered one of the most critical aspects of the concept of the alliance, precisely because of its similarity to attachment relationships (Baldoni & Campailla, 2017). Such interactions are established in all forms of therapy and are influenced by the complementarity of the patient's attachment style with that of the therapist (Baldoni & Campailla, 2017). In this respect, the most significant factor in alliance building is the repair of relational ruptures (Zilcha-Mano *et al.*, 2020), of which two types can be defined: withdrawal, in which the patient denies, intellectualizes, or changes the topic, and confrontation, wherein the patient questions the therapy and therapeutic effects.

Specific instruments have been developed to assess the therapeutic alliance and determine its correlation with treatment outcomes, dropout rates, and instances of rupture and resolution during treatment (Colli *et al.*, 2017). The synchronization of OT levels between therapist and patient appears to be associated with relational ruptures and repairs (Tal *et al.*, 2023; Zilcha-Mano *et al.*, 2020). Based on a standard protocol that was used by Zilcha-Mano *et al.* (2020), a patient with major MDD underwent a short psychodynamic therapy of 16 sessions. In sessions 4, 8, 12, and 16, the patient and therapist were asked for a saliva sample to measure OT levels before and after the session. In addition, both completed the Working Alliance Inventory after each session. The results of the study, replicated in subsequent research (Tal *et al.*, 2023; Zilcha-Mano *et al.*, 2022), demonstrated synchronization in OT levels between the patient and therapist in all but the eighth session, during which an inconsistency in the dyad's hormone levels was evident. Specifically, the patient's OT levels were significantly higher than those of the therapist. The authors attributed this phenomenon to the presence of numerous withdrawal breaks that activated the patient's attachment system, causing OT levels to spike. Their study replicated the results of a previous report (Zilcha-Mano *et al.*, 2018), in which the patient's trait OT, as well as state OT, increased throughout sessions, indicating the creation of a more secure attachment (Zilcha-Mano *et al.*, 2020).

In a study by Tal and colleagues (2023), a decline in the therapist's OT was associated with more cases of withdrawal ruptures, which were more prevalent in sessions with subjects with an anxious attachment orientation. In these cases, incongruence in the OT levels between the therapist and patient was not present, validating the hypothesis that higher content of this neuropeptide correlates with activation of the attachment system under conditions that stress the individual; when this system is compromised, oxytocinergic reactivity is similarly impaired (Tal *et al.*, 2023).

This indicates impaired activation of the attachment system, characterized in this case by overactivation that does not allow OT levels to modulate and synchronize with the therapist, resulting in lower relational responsiveness and decreased symptomatology (*ibidem*). Patients with lower levels of trait OT before the start of treatment have worse expectations of the efficacy of psychotherapy. In contrast, those with high concentrations of OT before treatment have reported greater expectations of improvement and are more successful at all stages of psychotherapy, experiencing less fear of change in the early phase of therapy (Engel *et al.*, 2022).

Patients and therapists are more synchronized in the most effective treatments. Impaired synchrony is a biological mechanism through which compromised social functioning undermines treatment outcomes: it can be suggested that dyads that include patients with better interpersonal skills are more likely to be synchronized biologically, translating into more effective working relationships between patients and therapists, thus effecting better treatment outcomes (Zilcha-Mano *et al.*, 2021). In fact, in MDD patients with impaired social skills – and thus, presumably impaired regulation of OT – lower hormonal synchronization between the patient and therapist during dynamic psychotherapy results in a poorer reduction of distress (Fischer & Zilcha-Mano, 2022; Zilcha-Mano *et al.*, 2021). Thus, it is possible that poorer social functioning before the start of therapy predicts lower levels of therapist-patient synchrony in changes in OT throughout treatment, which in turn predicts less mitigation of depressive symptoms during treatment (Zilcha-Mano *et al.*, 2021).

Overall, these studies demonstrate the potential of OT as a predictor of therapeutic improvement and as a marker of the therapeutic alliance, suggesting critical clinical implications. According to Zilcha-Mano and colleagues (2021), interventions could be implemented to improve biological synchrony between patients and therapists in cases of patients with social dysfunction by training therapists in the development of synchronized relationships; alternatively, intranasal OT could be administered to the patient to reactivate oxytocinergic mechanisms and increase treatment efficacy. Table 1 presents a summary of the literature review.

Table 1. Experimental studies investigating the role of OT as an outcome indicator in psychotherapy and/or indicator of therapeutic alliance.

Reference	Patients	Therapist	Gender (patients)	Gender (therapists)	Mean age	Intervention	Impact
Zilcha-Mano *et al.*, 2018	22 MDD	Number not specified	14 Females 8 Males	Not specified	30.22±7.30*	Short-term psychodynamic psychotherapy	An increase in OT was associated with an impediment in forming the attachment bond
Zilcha-Mano *et al.*, 2020	1 MDD	Number not specified	Male	Not specified	30	Short-term psychodynamic psychotherapy; Working Alliance Inventory	The discrepancy between patient and therapist OT levels during withdrawal ruptures during treatment is associated with the activation of the attachment system in the patient
Zilcha-Mano *et al.*, 2021	37 MDD	Number not specified	22 Females 15 Males	Not specified	31.54±9.63	Short-term psychodynamic psychotherapy	OT synchrony between patients and therapists was associated with effective treatment
Tal *et al.*, 2023	53 MDD	6	35 Females 18 Males	3 Females 3 Males	31.9±8.52	Short-term psychodynamic psychotherapy	Withdrawal ruptures increased with higher patient OT than therapist OT, but only when anxious attachment was low
Jobst *et al.*, 2016	21 BPD; 20 HCs	Number not specified	Females	Not specified	BPD: 30.0±7.95 HCs 29.71±10.26	Adult Attachment Projective Picture System	Disorganized attachment representations show lower plasma OT levels
Jobst *et al.*, 2018	16 MDD	Number not specified	Not specified	Not specified	Not specified	Cognitive Behavioral Analysis System of Psychotherapy	Lower OT plasma levels at baseline correlated with smaller changes in BDI-II scores
Ebert *et al.*, 2017	57 BPD; 43 HCs	Number not specified	Females	Not specified	BPD 24.8±4.7 HCs 23.4±3.3	Fears of Compassion Questionnaire; Recalled Parental Rearing Behavior Questionnaire	BPD patients had significantly lower OT plasma levels than HCs; OT levels seem to be linked with the tolerance of compassionate feelings and early experiences with caregivers
Atzil-Slonim *et al.*, 2022	30 MDD	5	11 Females 19 Males	Females	34.63±9.27	Brief supportive–expressive psychodynamic psychotherapy	The reactivity of the OT system, regardless of the direction of change, is a biomarker of success in the treatment of MDD

MDD, major depressive disorder; BPD, borderline personality disorder; HCs, healthy controls; DSM-5, Diagnostic and Statistical Manual of Mental Disorders; BDI-II, Beck Depression Inventory; OT, oxytocin; *mean ± standard deviation.

Discussion and Conclusions

The existing literature has primarily examined the role of OT in interpersonal contexts and attachment bonds. Some studies have already analyzed the role of hormones and OT in the therapeutic relationship (Fischer & Zilcha-Mano, 2022; Hohl *et al.*, 2024). In particular, the recent review by Hohl and collaborators (2024) pointed out that OT plays a significant role in association with treatment outcomes in the case of MDD but not in other psychopathological disorders. Our research confirms these results and then integrates them with an analysis of OT as a process marker in constructing the therapeutic relationship. Precisely for this reason, contrary to the work of Hohl *et al.* (2024), articles that involved the administration of OT were not included in our review. We aimed to focus our analysis on the natural processes of synchronization of OT levels between the therapist and patient as a possible indicator of the reactivation of the attachment system, identifying the therapeutic relationship as a key determinant in treatment outcomes. To this end, our study highlights the possible functioning of this hormone in the psychotherapeutic relationship. By reviewing the literature, we could glean the modulation of the OT axis in the therapist, as well as in the patient, demonstrating the potential of OT as a valid biomarker of the therapeutic alliance and an indicator of the outcome of psychotherapy. This result can be deduced from comparing research investigating this aspect through different psychotherapeutic methods. The achievement of similar results in the application of different types of psychotherapy, which has also been confirmed by other work (Hohl *et al.*, 2024), is a finding that supports the importance of the therapeutic alliance as a nonspecific promoter of change. This branch of research is exciting, as it provides the opportunity to cross-sectionally investigate various aspects of psychotherapy, regardless of the approach, diagnosis, or technique, shedding light on such constructs as the therapeutic alliance and related mechanisms of rupture-repair, emotional attunement of the patient-therapist dyad, and countertransference management and supervision. Moreover, attachment theory, in this sense, emerges as an effective paradigm for reading and operationalizing these phenomena, and the studies we have considered confirm the involvement of OT as a biological activation factor of this motivational system within each psychotherapeutic dyad.

In conclusion, based on our review, such elements become measurable variables even for less manualized and codified psychotherapies, such as expressive-psychodynamic modalities, and for broader diagnostic categories involving samples of clinical patients that differ from those examined here, considering various age groups. It would be desirable to explore these implications further through longitudinal studies, especially in psychodynamically oriented psychotherapies, to elucidate the intersubjective mechanisms involved in therapeutic co-construction. The preponderance of studies included in our analysis employed a psychodynamic approach, suggesting that this therapeutic approach might work by reactivating old relational patterns, similar to those of early caregivers. In line with this, it would be useful to replicate these studies by exploring the association between therapeutic alliance, OT levels, and therapy efficacy through different therapeutic approaches.

Finally, studies should focus on the association between OT and the therapist's gender to determine the modulatory effects of the latter factor on neurobiological levels and activation of the attachment system, depending on the patient's age.

In summary, the role of OT in psychotherapy is a promising field of research aimed at broadening our understanding of the patient-therapist relationship, which may be associated with the psychological well-being of the dyad and the efficacy of therapies.

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