scientific reports

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Baseline serum oxytocin and OXTR rs53576 genotype are not predictive of escitalopram response in generalized anxiety disorder

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The oxytocin system is implicated in the pathophysiology of generalized anxiety disorder (GAD). However, its utility in predicting treatment outcomes with first-line antidepressants, such as escitalopram, remains unexplored. This study aimed to investigate whether baseline serum oxytocin levels and the oxytocin receptor gene polymorphism OXTR rs53576 can predict escitalopram response in patients with first-episode GAD. This prospective cohort study enrolled 60 drug-naïve patients with first-episode GAD and 60 age- and sex-matched healthy controls. Serum oxytocin levels were measured using enzyme-linked immunosorbent assay, and the OXTR rs53576 genotype was determined using TaqMan SNP Genotyping Assays. The patients received escitalopram monotherapy (10–20 mg/day). Anxiety severity was assessed using the Hamilton Anxiety Scale at baseline and weeks 2, 4, and 8. Treatment response was defined as a ≥ 50% reduction in Hamilton Anxiety Scale score. At baseline, patients with GAD had significantly higher oxytocin levels than healthy controls (147.99 ± 99.07 pg/ml vs. 76.86 ± 96.07 pg/ml, $p < 0.001$) and a higher prevalence of OXTR rs53576 AA genotype (71.67% vs. 25.00%, $p < 0.001$). Multiple linear regression analysis revealed that both higher oxytocin levels ($p < 0.001$) and the AA genotype ($p < 0.001$) were independently associated with greater baseline anxiety severity. However, after 8 weeks of treatment, neither baseline oxytocin levels nor the OXTR rs53576 genotype predicted treatment response at any time point (all $p > 0.05$). While the oxytocin system is dysregulated in GAD, baseline serum oxytocin and OXTR rs53576 genotypes are not clinically useful biomarkers for predicting short-term responses to escitalopram. This finding refines the search for predictive tools for personalized anxiety treatment.

Keywords Generalized anxiety disorder, Oxytocin, OXTR rs53576, Escitalopram, Biomarker

Generalized anxiety disorder (GAD) is a prevalent and debilitating condition characterized by excessive and uncontrollable worry. Selective serotonin reuptake inhibitors (SSRIs) such as escitalopram represent the first-line pharmacological treatment for GAD[1]. However, treatment response is highly variable, with a substantial proportion of patients failing to achieve adequate symptom relief[2]. This response variability underscores the need for predictive biomarkers to guide treatment selection in personalized medicine.

Beyond the serotonergic system, the neuropeptide oxytocin (OT) has emerged as a key modulator of stress response, social behavior, and emotional regulation, core domains often impaired in GAD[3]. The biological activity of OT is mediated by its receptor (OXTR). A common functional polymorphism in OXTR (rs53576 A > G) has been linked to individual differences in stress reactivity and susceptibility to anxiety-related traits[4]. Although SSRIs primarily target serotonin reuptake, preclinical evidence suggests a potential interaction with the OT system, where in SSRIs may modulate OT release or signaling[5]. In particular, the OXTR rs53576 G allele (compared to the A allele) has been associated with enhanced stress resilience and more efficient oxytocinergic signaling, whereas the AA genotype is often linked to higher stress reactivity and anxiety-related traits[4,6,7]. Furthermore, peripheral OT levels in anxiety disorders have shown divergent patterns, with some studies reporting elevations, possibly reflecting a compensatory response to chronic stress[8]. This raises the possibility that individual variability in the OT system could influence the efficacy of SSRIs.

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Indeed, dysregulation of peripheral OT levels has been reported in anxiety disorders[9], and OXTR genetics are associated with disease risk. Thus, we posited that a putative "less efficient" oxytocinergic profile (e.g., AA genotype and/or dysregulated OT levels) might be associated with poorer response to SSRI treatment. Nevertheless, a critical gap remains: it is entirely unknown whether baseline assessments of OT neurobiology—specifically, peripheral OT levels and the functional OXTR rs53576 polymorphism—can predict the clinical response to an SSRI in patients with GAD. Addressing this question is crucial for evaluating the translational potential of OT biomarkers in clinical psychopharmacology.

Therefore, this prospective study aimed to directly investigate the predictive value of baseline serum OT levels and OXTR rs53576 genotype for escitalopram response in patients with first-episode medication-naive GAD. We hypothesized that if the OT system played a moderating role in SSRI efficacy, these biomarkers would be associated with differential treatment outcomes.

Methods

This prospective cohort study was conducted at Huzhou Third Municipal Hospital between June 2023 and December 2024. The study enrolled 60 medication-naive or medication-free (for ≥ 2 weeks) patients with first-episode GAD diagnosed by two psychiatrists using ICD-10 criteria. Sixty age- and sex-matched healthy controls (HCs) with no history of psychiatric disorders were recruited. All participants were of Han ethnicity, aged 18–65 years. The key exclusion criteria included comorbid Axis-I disorders, significant suicide risk, substance abuse, severe physical illness, and pregnancy/lactation. Patients received 8 weeks of escitalopram monotherapy (Lexapro®) with a fixed-dose regimen (initial 10 mg/day, which could be increased to 20 mg/day after one week). Anxiety symptoms were assessed using the 14-item Hamilton Anxiety Scale (HAMA) at baseline (for both groups) and at weeks 2, 4, and 8 of treatment (for the patients only). Assessments were performed by raters who were blinded to biomarker data. Treatment response was defined as ≥ 50% reduction from the baseline HAMA total score. Fasting blood samples were collected after an overnight fast between 8:00–10:00 AM. Serum oxytocin (OT) levels were measured using a commercial ELISA kit (Wuhan Saipai Biotechnology Co., Ltd., China) according to the manufacturer's instructions. Genomic DNA was extracted from whole blood, and OXTR rs53576 (A/G) polymorphism was genotyped using TaqMan SNP Genotyping Assays on a Bio-Rad CFX96 real-time PCR system. Genotyping accuracy was confirmed by repeated analysis of 10% random samples with 100% concordance. Due to the low frequency of the GG genotype($n = 3$ in controls, $n = 1$ in patients), and consistent with prior literature[7,8], participants were categorized as AA homozygotes or G allele carriers (AG + GG) for analysis. Data were analyzed using SPSS version 20.0 (IBM Corp., Armonk, NY). Continuous variables are presented as mean ± standard deviation or median (interquartile range) depending on their distribution. Normality was assessed using the Shapiro-Wilk test. Group comparisons for continuous variables were performed using independent t-tests or Mann-Whitney U tests, as appropriate. Categorical data were compared using χ^2 tests or Fisher's exact test when the expected cell count was < 5. Hardy-Weinberg equilibrium (HWE) was tested in the control group using the χ^2 test. Spearman correlation and multiple linear regression were used to explore the factors associated with baseline HAMA scores. Effect sizes were reported as Cohen's d for t-tests, r for Mann-Whitney U tests, and Cramér V for χ^2 tests. Statistical significance was set at a two-tailed p-value < 0.05. The study protocol was reviewed and approved by the Ethics Committee of the Huzhou Third Municipal Hospital (approval No. 2020 − 116). Written informed consent was obtained from all participants. This study was conducted in accordance with the principles of the Declaration of Helsinki. All methods were carried out in accordance with relevant guidelines and regulations.

Results

The study included 60 patients with GAD (48 females and 12 males) and 60 matched HCs. The groups were well-matched for age and sex ($p > 0.05$). At baseline, serum OT levels were significantly elevated in the GAD group compared to the HCs (147.99 ± 99.07 pg/ml vs. 76.86 ± 96.07 pg/ml, $Z = 5.196$, $p < 0.001$,**Cohen's d = 0.73**). No significant sex differences in OT levels were found in the GAD group ($p = 0.355$). The genotype distribution in the control group was in Hardy-Weinberg equilibrium ($p = 0.514$). As shown in Table 1, both the A allele and AA genotype were significantly more prevalent in patients with GAD than in HCs (allele: 80.83% vs. 53.33%, $\chi^2 = 20.549$, $p < 0.001$; genotype: 71.67% vs. 25.00%, $\chi^2 = 26.162$, $p < 0.001$).

An additional analysis revealed no significant association between OXTR rs53576 genotype (AA vs. AG + GG) and baseline serum OT levels, either in the healthy control group (Mann-Whitney $U = 307.0$, $p = 0.498$) or in the patient group ($U = 304.0$, $p = 0.171$).

Multiple linear regression revealed that the model significantly predicted baseline HAMA scores ($F = 16.234$, $p < 0.001$, adjusted $R^2 = 0.339$). As detailed in Table 2, both higher log-transformed OT levels ($\beta = 0.339$, $p < 0.001$) and the AA genotype ($\beta = -0.311$, $p < 0.001$) were independently associated with greater anxiety severity.

Response rates to escitalopram increased over time, reaching 76.7% (46/60) by week 8. Critically, as summarized in Table 3, neither baseline OT levels nor OXTR rs53576 genotype distribution differed significantly between the

Group	*n*	A allele *n*(%)	G allele *n*(%)	AA genotype *n*(%)	AG + GG genotype *n*(%)
GAD	60	97 (80.83)	23 (19.17)	43 (71.67)	17 (28.33)
HCs	60	64 (53.33)	56 (46.67)	15 (25.00)	45 (75.00)
χ^2/p		20.549/<0.001		26.162/<0.001	

Table 1. OXTR rs53576 allele and genotype frequencies.

Variable	β	t	*P*-value
Sex(Female)	0.158	2.022	0.045
Age	0.271	3.623	$p < 0.001$
Log(Oxytocin)	0.339	4.362	$p < 0.001$
rs53576Genotype	−0.311	−4.107	$p < 0.001$

Table 2. Multiple linear regression for baseline HAMA scores.

Timepoint	Comparison	Statistic	*P*-value
Week 2	OT Levels (Responders vs. Non-responders)	Z = 0.222	0.824
	Genotype (AA vs. AG + GG)	$\chi^2 = 0.185$	0.667
Week 4	OT Levels (Responders vs. Non-responders)	Z = 0.415	0.678
	Genotype (AA vs. AG + GG)	$\chi^2 = 0.287$	0.775
Week 8	OT Levels (Responders vs. Non-responders)	Z = 0.664	0.507
	Genotype (AA vs. AG + GG)	$\chi^2 = 0.490$	0.511

Table 3. Comparison of baseline biomarkers between Escitalopram responders and non-responders (Responders vs. Non-responders at week 2,Week 4 and week 8:12/48,32/28,46/14).

treatment responders and non-responders at any assessment point (weeks 2, 4, or 8; all $p > 0.05$).An exploratory subgroup analysis found no significant difference in the final response rate between patients maintained on 10 mg/day ($n = 27$) and those whose dose was increased to 20 mg/day ($n = 33$) ($p > 0.05$), suggesting that the observed lack of biomarker predictive value was not confounded by dose heterogeneity.

Discussion

This prospective study provides a clear, clinically relevant conclusion: while the oxytocin system is dysregulated in first-episode GAD, baseline serum OT levels and OXTR rs53576 genotype are not predictive of short-term response to escitalopram.

The finding of elevated OT levels in patients with GAD may seem paradoxical given the peptide's established anxiolytic properties in some contexts. This observation lends support to the 'compensatory hypothesis[8]', which posits that increased OT release may represent an endogenous, albeit insufficient, counter-regulatory response to chronic stress and anxiety. Furthermore, the strong association of the OXTR rs53576 AA genotype with both disease susceptibility and baseline symptom severity underscores its role as a genetic vulnerability factor, likely by modulating stress resilience and emotional regulation[4,10]. The multiple regression model solidifies this link, demonstrating that both the genetic and endocrine components of the OT system independently contribute to the initial clinical presentation of GAD. Our regression model also identified older age and female sex as factors independently associated with greater baseline anxiety severity. The positive association with age aligns with some clinical observations of GAD, where older adults may present with more severe or chronic worry, potentially linked to cumulative life stressors or age-related neurobiological changes. The association with female sex is consistent with the well-established epidemiological finding of a higher prevalence and often greater severity of anxiety disorders in women, which may be influenced by a combination of hormonal, psychosocial, and genetic factors. Notably, even after controlling for these demographic variables, both oxytocin levels and OXTR genotype remained strongly predictive of baseline symptom severity, underscoring the specific contribution of the oxytocin system to GAD pathophysiology.

The key finding of this study was the lack of predictive power of these baseline biomarkers for treatment outcomes. This negative result has significant implications for future translational research. This suggests that the role of the OT system in the pathophysiology of GAD may be distinct from the primary mechanism through which SSRIs such as escitalopram exert their therapeutic effects. The efficacy of escitalopram is predominantly mediated by serotonergic mechanisms, and our data indicate that the pretreatment state of the OT system does not significantly modulate this pathway in a clinically predictable way. Consequently, measuring the baseline OT or OXTR rs53576 status is unlikely to be a useful strategy for personalizing the initial selection of SSRI therapy. This finding is crucial as it helps narrow the search for clinically applicable predictors, steering future research away from these particular biomarkers for SSRI prediction.

This study had several limitations must be acknowledged. First, the sample size, although sufficient to detect large case-control differences in OT and genotype, may limit the power for subgroup analyses of treatment response, particularly for detecting small to moderate effect sizes. Second, the single-time point measurement of OT cannot capture potential dynamic changes during treatment, which might be more informative. Third, our focus on a single OXTR polymorphism cannot rule out the contribution of other genetic variants to a more complex polygenic model of treatment response. Finally, the generalizability of our findings may be limited to the Han Chinese population, and requires validation in other ethnic groups.

In conclusion, by demonstrating that the baseline OT and OXTR rs53576 genotypes are associated with disease state but not treatment outcome, our study makes a valuable contribution to the field. This provides

a clear boundary for the clinical utility of these biomarkers and refines the neurobiological models of SSRI action in GAD. Future research should prioritize longitudinal assessment of the OT system during treatment, investigate its role in predicting the response to non-SSRI interventions, and employ polygenic approaches to capture the full genetic complexity of treatment response.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 8 November 2025; Accepted: 12 January 2026
Published online: 05 February 2026

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Acknowledgements

Acknowledgements: This work was supported by the Huzhou Municipal Science and Technology Bureau (No. 2020GYB36). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions

L.X. conceived the study, secured funding, and wrote the manuscript.H.N. performed the laboratory analyses and data validation. S.X. collected and curated theclinical data and performed the formal statistical analysis. All authors reviewed and approvedthe final manuscript.

Funding

This work was supported by the Huzhou Municipal Science and Technology Bureau (No. 2020GYB36). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

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