Postprint: Study on the Predictive Value of a Risk Prediction Model for Venlafaxine Plasma Concentrations Exceeding Alert Thresholds

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Abstract

Background: Venlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant widely used for the treatment of major depression, generalized anxiety disorder, and depression comorbidities. The Chinese Expert Consensus on the Clinical Application of Therapeutic Drug Monitoring in Psychiatry (2022 Edition) proposes that therapeutic drug monitoring of venlafaxine can be performed during treatment to avoid usage exceeding the warning concentration, which may lead to adverse reactions or suboptimal therapeutic outcomes. However, the influence of patient physiology, genetic polymorphisms, and other factors on venlafaxine plasma concentrations exceeding the warning value remains controversial.

Objective: To explore the influencing factors of venlafaxine plasma concentration exceeding the warning value in depressed patients and to construct a risk prediction model for venlafaxine plasma concentration exceeding the warning value, providing a reference for individualized venlafaxine dosing.

Methods: A retrospective analysis was conducted on the clinical data of hospitalized patients who received venlafaxine treatment and therapeutic drug monitoring at the First Hospital of Hebei Medical University from January 2021 to August 2024. Included patients were divided into a target group (plasma concentration 100~400 ng/mL) and a warning-exceeding group (plasma concentration >800 ng/mL) based on venlafaxine plasma concentration monitoring values. Data on gender, age, BMI, daily dosage, plasma albumin, concomitant medications, and hepatic and renal function were collected for both groups. Logistic regression analysis was used to screen for independent influencing factors of venlafaxine plasma concentration exceeding the warning value. A nomogram prediction model was constructed based on the selected independent influencing factors and validated.

Results: This study included a total of 590 patients, comprising 203 males (34.4%) and 387 females (65.6%), with a mean age of (51.9±16.4) years. Among the 590 patients, 516 cases (87.5%) were in the target group and 74 cases (12.5%) in the warning-exceeding group. Logistic regression analysis revealed that daily dosage 225 mg (OR=26.628, 95%CI=12.912~54.916, P<0.001), renal impairment (OR=2.429, 95%CI=1.215~4.854, P=0.012), and concomitant use of CYP2D6 inhibitors (OR=5.232, 95%CI=2.781~9.844, P<0.001) were risk factors for venlafaxine plasma concentration exceeding the warning value. Based on the selected independent influencing factors, a nomogram prediction model for venlafaxine plasma concentration exceeding the warning value was established. The model demonstrated an AUC of 0.899 (95%CI=0.864~0.935), sensitivity of 48.65%, specificity of 95.74%, positive predictive value of 62.07%, and negative predictive value of 92.86%. Bootstrap validation showed good consistency between the calibration curve and the actual curve (Brier score=0.072). Hosmer-Lemeshow test results indicated good calibration of the nomogram prediction model (2=3.160, P=0.531). Clinical decision curve analysis (DCA) demonstrated that the nomogram model had good clinical utility when the threshold ranged from 0.05~0.80.

Conclusion: Daily dosage 225 mg, presence of renal impairment, and concomitant use of CYP2D6 inhibitors are independent risk factors for plasma concentration exceeding the warning value. The nomogram model constructed based on these factors can effectively predict the risk of venlafaxine plasma concentration exceeding the warning value in patients and holds high clinical application value.

Full Text

Study on the Predictive Value of a Risk Prediction Model for Venlafaxine Plasma Concentration Exceeding the Safety Threshold

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Abstract

Background: Venlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant widely used in the treatment of major depression, generalized anxiety disorder, and depressive comorbidities. China' s Expert Consensus on Clinical Application of Psychiatric Therapeutic Drug Monitoring (2022 edition) recommends monitoring venlafaxine plasma concentrations during treatment to avoid exceeding safety thresholds, which can lead to adverse reactions or suboptimal therapeutic outcomes. However, the influence of patient physiology, genetic polymorphisms, and other factors on supra-therapeutic concentrations remains controversial.

Objective: To investigate the factors influencing venlafaxine plasma concentration exceeding the alert threshold in patients with depression and to develop a risk prediction model for elevated venlafaxine concentrations, providing a reference for individualized venlafaxine therapy.

Methods: A retrospective analysis was conducted on clinical data from hospitalized patients who received venlafaxine treatment and underwent therapeutic drug monitoring (TDM) at the First Hospital of Hebei Medical University between January 2021 and August 2024. Patients were categorized into a target concentration group (100–400 ng/mL) and an above-alert group (>800 ng/mL) based on their venlafaxine plasma concentrations. Data collected included sex, age, BMI, average daily dose, plasma albumin, concomitant medications, and liver and kidney function. Logistic regression analysis was performed to identify independent risk factors associated with venlafaxine concentrations exceeding the alert threshold. A nomogram prediction model was constructed based on these factors and subsequently validated.

Results: A total of 590 patients were included, comprising 203 males (34.4%) and 387 females (65.6%) with a mean age of (51.9±16.4) years. Among them, 516 patients (87.5%) were in the target group and 74 (12.5%) in the above-alert group. Logistic regression analysis revealed that an average daily dose 225 mg (OR=26.628, 95%CI=12.912–54.916, P<0.001), renal impairment (OR=2.429, 95%CI=1.215–4.854, P=0.012), and concomitant use of CYP2D6 inhibitors (OR=5.232, 95%CI=2.781–9.844, P<0.001) were independent risk factors for venlafaxine concentrations exceeding the alert threshold. The nomogram model demonstrated an AUC of 0.899 (95%CI=0.864–0.935), sensitivity of 48.65%, specificity of 95.74%, positive predictive value of 62.07%, and negative predictive value of 92.86%. Bootstrap validation showed good consistency between the corrected and actual curves (Brier score=0.072). The Hosmer-Lemeshow test indicated good calibration (^{2}=3.160, P=0.531). Decision curve analysis demonstrated clinical utility for threshold probabilities of 0.05–0.80.

Conclusion: An average daily dose 225 mg, renal impairment, and concomitant use of CYP2D6 inhibitors are independent risk factors for venlafaxine plasma concentrations exceeding the alert threshold. The developed nomogram model effectively predicts the risk of supra-therapeutic venlafaxine concentrations and holds significant clinical application value.

Keywords: Venlafaxine; Plasma concentration; Therapeutic drug monitoring; Influencing factors; Nomogram; Forecasting; Exceeding the safety threshold

Introduction

Venlafaxine is an antidepressant that effectively antagonizes the reuptake of both serotonin and norepinephrine. Since 1995, it has been used to treat major depressive disorder, generalized anxiety disorder, and panic disorder. Its favorable safety and efficacy profile have made it one of the most commonly prescribed antidepressants worldwide. Venlafaxine is primarily metabolized by cytochrome P450 (CYP) 2D6 to its active metabolite O-desmethylvenlafaxine. At steady state, O-desmethylvenlafaxine levels are 2–3 times higher than those of the parent drug. Dose adjustments are recommended in cases of hepatic or renal dysfunction, as both sex and age can influence plasma concentrations at equivalent doses. Overall, high interindividual variability means that patients receiving identical doses exhibit substantial differences in drug exposure, with excessive exposure potentially leading to poor clinical outcomes and increased adverse event risk. Consequently, therapeutic drug monitoring (TDM) guidelines recommend TDM for patients receiving venlafaxine, with a recommended implementation level of II.

Previous studies have primarily focused on factors influencing venlafaxine plasma concentrations, though findings across studies show considerable discrepancies, and research on patients exceeding safety thresholds remains limited. Nomograms, based on multivariate regression analysis, use multiple clinical indicators or biological attributes with scaled line segments to visually demonstrate the impact of different predictive factors on outcomes, and have been widely applied in clinical event prediction. Therefore, this study employed logistic regression analysis to identify independent factors associated with supra-therapeutic venlafaxine concentrations and constructed a nomogram prediction model to enable early identification of at-risk patients and provide a scientific basis for the safe clinical use of venlafaxine.

Methods

Study Population

This retrospective study included 590 hospitalized patients diagnosed with depression who received venlafaxine treatment and underwent TDM at the First Hospital of Hebei Medical University between January 2021 and August 2024. The study was approved by the Clinical Research Ethics Committee of the First Hospital of Hebei Medical University (approval number: 20220936). Due to the use of anonymized retrospective data and minimal risk, informed consent was waived.

Inclusion Criteria

1. Met diagnostic criteria for depression according to the International Classification of Diseases, 10th Revision (ICD-10)
2. Age 18 years
3. Received venlafaxine treatment with TDM performed at steady-state concentration, defined as at least 3 days of fixed-dose therapy with blood sampling 30 minutes before the next dose

Exclusion Criteria

1. Severe cardiac, pulmonary, or other organ dysfunction
2. Patients undergoing hemodialysis
3. Patients with plasma concentrations between 400–800 ng/mL
4. Patients with incomplete clinical data

Data Collection

Patients who had received a fixed venlafaxine dose for at least 3 days underwent venous blood collection (3–5 mL) 30 minutes before the next dose once steady-state concentration was achieved. Samples were centrifuged to separate serum, which was processed using protein precipitation. Steady-state trough concentrations were quantified using an ACQUITY-X ultra-high-performance liquid chromatography-tandem mass spectrometer (Waters Corporation, USA). Patient information collected included sex, age, height, weight, BMI, plasma concentration results, plasma albumin, alanine aminotransferase, aspartate aminotransferase, plasma creatinine, creatinine clearance, and concomitant use of CYP2D6 inhibitors.

Definitions and Grouping

According to the *Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017*, the reference therapeutic range for venlafaxine is 100–400 ng/mL, with concentrations >800 ng/mL defined as exceeding the safety threshold. Patients were divided into a target concentration

group (100–400 ng/mL) and an above-alert group (>800 ng/mL) based on their venlafaxine plasma concentrations.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software. Normally distributed continuous variables were expressed as (mean±SD) and compared between groups using independent samples t-tests. Categorical variables were expressed as frequencies (percentages) and compared using ^{2} tests. Variables showing clinical significance and statistical difference in univariate analysis were included in multivariate logistic regression analysis to explore their association with supra-therapeutic venlafaxine concentrations and identify independent risk factors. Based on these factors, a nomogram prediction model was constructed using the RMS package in R software (version 3.6.1). Internal validation was performed using the bootstrap method. Model predictive performance was evaluated using receiver operating characteristic (ROC) curve analysis, calibration curve testing, and decision curve analysis (DCA). A P-value <0.05 was considered statistically significant.

Results

Comparison of Clinical Characteristics Between Groups

The study included 590 patients (203 males [34.4%] and 387 females [65.6%]) with a mean age of (51.9±16.4) years. Among these, 516 patients (87.5%) were in the target group and 74 (12.5%) in the above-alert group. Significant differences between groups were observed for sex, BMI, average daily dose, and concomitant CYP2D6 inhibitor use (P<0.05). No significant differences were found for age, plasma albumin, alanine aminotransferase, aspartate aminotransferase, or plasma creatinine (P>0.05) .

Logistic Regression Analysis of Factors Influencing Supra-Therapeutic Venlafaxine Concentrations

Using supra-therapeutic venlafaxine concentration as the dependent variable (no=0, yes=1) and statistically significant factors from clinical data analysis as independent variables—sex (female=0, male=1), BMI (<24 kg/m²=0, 24 kg/m²=1), average daily dose (<225 mg=0, 225 mg=1), renal impairment (no=0, yes=1), and CYP2D6 inhibitor use (no=0, yes=1)—multivariate logistic regression analysis revealed that an average daily dose 225 mg (OR=26.628, 95%CI=12.912–54.916, P<0.001), renal impairment (OR=2.429, 95%CI=1.215–4.854, P=0.012), and concomitant CYP2D6 inhibitor use (OR=5.232, 95%CI=2.781–9.844, P<0.001) were independent risk factors for venlafaxine concentrations exceeding the alert threshold .

Construction of the Nomogram Prediction Model

Based on multivariate logistic regression results, a nomogram prediction model was developed for assessing the risk of supra-therapeutic venlafaxine concentrations in patients with depression. The model assigned scores of 100, 30, and 51 points for the three risk factors (average daily dose 225 mg, renal impairment, and concomitant CYP2D6 inhibitor use, respectively). The sum of these scores yielded a total score of 181 points. By drawing a vertical line from the total score downward, the predicted probability of venlafaxine concentration exceeding the safety threshold could be determined [Figure 1: see original paper].

Model Performance Evaluation

Discrimination The nomogram prediction model demonstrated strong discriminative ability with an AUC of 0.899 (95%CI=0.864-0.935), sensitivity of 48.65%, specificity of 95.74%, positive predictive value of 62.07%, and negative predictive value of 92.86% [Figure 2: see original paper].

Calibration Bootstrap validation showed good consistency between the corrected and actual curves (Brier score=0.072). The Hosmer-Lemeshow test indicated good calibration (^{2}=3.160, P=0.531) [Figure 3: see original paper].

Clinical Utility Decision curve analysis demonstrated that when the threshold probability ranged from 0.05 to 0.80, using the nomogram model to predict the risk of supra-therapeutic venlafaxine concentrations provided greater net benefit than either "treat all" or "treat none" strategies, indicating good clinical utility [Figure 4: see original paper].

Discussion

Venlafaxine exhibits substantial interindividual variability in plasma concentrations due to multiple factors including patient age, sex, pathophysiological status, dosage, and drug-drug interactions, which can interfere with disease control. Early assessment of the risk of exceeding safety thresholds is clinically significant, as previous studies have shown a close relationship between supra-therapeutic concentrations and adverse events. Nomogram models visually predict the risk of exceeding safety thresholds, enabling clinicians to conveniently identify high-risk patients and inform preventive strategies, thereby improving patient outcomes and reducing adverse event rates.

The present nomogram prediction model achieved an AUC of 0.899, sensitivity of 48.65%, specificity of 95.74%, positive predictive value of 62.07%, and negative predictive value of 92.86%. Bootstrap validation demonstrated good consistency (Brier score=0.072), and the Hosmer-Lemeshow test confirmed good calibration (^{2}=3.160, P=0.531). These results are consistent with previous studies on risk

prediction models for supra-therapeutic drug concentrations, suggesting that our model has good predictive performance for identifying patients at risk of exceeding venlafaxine safety thresholds.

Logistic regression analysis identified three independent risk factors: average daily dose 225 mg, renal impairment, and concomitant CYP2D6 inhibitor use. The dose-dependent relationship and optimal target dose for venlafaxine remain uncertain, with clinical practice guidelines from different countries providing contradictory recommendations. Swedish healthcare institutions suggest no established dose-dependency within the therapeutic range, while the American Psychiatric Association guidelines recommend titrating to maximum tolerated doses. A comprehensive dose-response analysis by Furukawa et al. found that venlafaxine' s clinical efficacy increases substantially up to approximately 75–150 mg, with further gradual increases up to 151–375 mg, possibly related to the more pronounced norepinephrine reuptake blockade at higher doses (225 mg and 375 mg daily). Studies have demonstrated a statistically significant linear relationship between daily venlafaxine dose and serum concentrations of venlafaxine, O-desmethylvenlafaxine, and their sum, with high-dose users more likely to exceed safety thresholds. In our study, 85.1% of patients in the above-alert group received daily doses 225 mg, consistent with previous research and highlighting the need for close monitoring in this population.

Venlafaxine and its metabolites are primarily excreted renally, with chronic kidney disease potentially altering renal clearance. Renal impairment can reduce elimination of venlafaxine and its metabolites by approximately 55% and significantly prolong elimination half-life, necessitating dose adjustments in patients with creatinine clearance <30 mL/min. Xie et al. found that venlafaxine plasma concentrations differed across creatinine clearance levels (<80, 80–120, >120 mL/min), with concentrations decreasing as clearance increased. Our study defined renal impairment as abnormal creatinine clearance and found a significantly higher prevalence of renal impairment in the above-alert group compared to the target group ($P<0.05$), confirming that renal function is an important factor influencing supra-therapeutic concentrations.

The impact of drug-drug interactions on venlafaxine concentrations remains controversial. Venlafaxine is metabolized by multiple hepatic enzymes including CYP3A4, CYP2D6, and CYP2C19. Previous studies have shown significant differences in venlafaxine plasma concentrations between CYP2D6 normal and poor metabolizer phenotypes, and the CYP2D6*10 allele significantly alters venlafaxine pharmacokinetics in Japanese and Korean populations. However, some reports have found no statistically significant differences in drug concentrations across CYP2D6 genotype groups. In our study, 59.5% of patients in the above-alert group used CYP2D6 inhibitors, significantly higher than the 24.2% in the target group ($P<0.05$). The nomogram model showed that increased scores for CYP2D6 inhibitor use raised the total score and consequently the predicted risk of exceeding safety thresholds.

This study has several limitations. First, as a single-center retrospective study,

it has a homogeneous population and relatively small sample size, and cost constraints limited our ability to evaluate the role of genetic polymorphisms in predicting supra-therapeutic concentrations, which may limit generalizability. Future studies should expand sample sizes to validate these findings. Second, methods for controlling unknown confounding variables are limited and may introduce bias. Third, the limited sample size may affect statistical power and limit external validity. Fourth, external validation using data from other institutions was not performed; our research group plans to incorporate multi-center data for external validation to improve model accuracy and generalizability.

In summary, average daily dose 225 mg, renal impairment, and concomitant CYP2D6 inhibitor use are independent risk factors for supra-therapeutic venlafaxine concentrations. Through comprehensive analysis, this study provides a solid scientific foundation for understanding factors influencing venlafaxine safety thresholds and for risk prediction model assessment. The developed nomogram model demonstrates good predictive performance and clinical utility, enabling quantitative risk assessment for supra-therapeutic venlafaxine concentrations. However, as this model was developed from single-center data, further validation through multi-center, prospective, large-scale studies is needed.

Author Contributions: ZHANG Yanjing conceived and designed the study, analyzed feasibility, and drafted and revised the manuscript. YU Jing supervised quality control and was responsible for overall manuscript supervision. ZHANG Yanjing, LI Xiaodong, LIU Yan, and WANG Jing collected, organized, and analyzed data. ZHANG Yanjing, ZHOU Chunhua, and YU Jing interpreted results.

Conflict of Interest: The authors declare no conflict of interest.

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References

[1] WANG Xin, WU Guodong, AN Ming, et al. Research progress on PK-PD relationships and influencing factors of venlafaxine[J]. Chinese Journal of Clinical Pharmacology and Therapeutics, 2023, 28(7): 825-833.

[2] COUDERC S, MORY C, DARNAUD L, et al. Therapeutic drug monitoring of antidepressants: Why venlafaxine is the most monitored drug? A review of literature[J]. Therapies, 2021, 76(6): 725-733. DOI: 10.1016/j.therap.2021.01.052.

[3] WANG Z Z, DENG S H, LU H Y, et al. Effect of venlafaxine steady state dose-corrected concentrations of venlafaxine and O-desmethylvenlafaxine: a retrospective analysis of therapeutic drug monitoring data in a Chinese population[J]. Human Psychopharmacology, 2020, 35(3): e2733. DOI: 10.1002/hup.2733.

[4] LENSE X M, HIEMKE C, FUNK C M, et al. Venlafaxine's therapeutic reference range in the treatment of depression revised: a systematic review and meta-

analysis[J]. Psychopharmacology, 2024, 241(2): 275-289. DOI: 10.1007/s00213-023-06484-7.

[5] HIEMKE C, BERGEMANN N, CLEMENT H W, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017[J]. Pharmacopsychiatry, 2018, 51(1/2): 9-62. DOI: 10.1055/s-0043-116492.

[6] LIANG Hai, XIA Runan, WU Wei, et al. Research progress on factors influencing venlafaxine plasma concentration[J]. Chinese Journal of Hospital Pharmacy, 2023, 43(15): 1758-1763.

[7] XIE Huanshan, CHEN Huanzhen, WANG Zhanzhang, et al. Pharmacokinetic and safety evaluation of venlafaxine based on cytochrome P450 genetic polymorphisms[J]. Chinese Journal of Clinical Pharmacology, 2019, 35(19): 2426-2429, 2438. DOI: 10.13699/j.cnki.1001-6821.2019.19.061.

[8] LI Zeng, YIN Zhao, DU Shuzhang. Establishment and validation of a risk prediction model for subtherapeutic tacrolimus blood concentration[J]. Chinese Pharmaceutical Journal, 2024, 59(10): 945-950. DOI: 10.11669/cpj.2024.10.012.

[9] SCHRADER K. International statistical classification of diseases and related health problems (ICD-10)[M]//Applied Lymphology. Berlin, Heidelberg: Springer Berlin Heidelberg, 2023: 757-763. DOI: 10.1007/978-3-662-61452-5_49.

[10] SIGURDSSON H P, HEFNER G, BEN-OMAR N, et al. Steady-state serum concentrations of venlafaxine in patients with late-life depression: Impact of age, sex and BMI[J]. Journal of Neural Transmission, 2015, 122(5): 721-729. DOI: 10.1007/s00702-014-1317-9.

[11] PAULZEN M, HAEN E, HIEMKE C, et al. Antidepressant polypharmacy and the potential of pharmacokinetic interactions: Doxepin but not mirtazapine causes clinically relevant changes in venlafaxine metabolism[J]. Journal of Affective Disorders, 2018, 227: 506-511. DOI: 10.1016/j.jad.2017.11.046.

[12] ZHANG Yanjing, YU Jing, WANG Jing, et al. Analysis of laboratory alert concentrations of olanzapine in therapeutic drug monitoring[J]. China Pharmaceuticals, 2023, 32(15): 113-117. DOI: 10.3969/j.issn.1006-4931.2023.15.025.

[13] LI Jing, DUAN Zihan, SHEN Bingxiang, et al. Establishment and evaluation of a risk prediction model for digoxin plasma concentration exceeding safety limits[J]. Chinese Journal of Hospital Pharmacy, 2021, 41(13): 1332-1336. DOI: 10.13286/j.1001-5213.2021.13.11.

[14] ZHOU Juxiang, LI Yanfei, LÜ Fangjun, et al. Construction of a risk prediction model for high voriconazole plasma concentration[J]. Chinese Journal of Clinical Pharmacology and Therapeutics, 2024, 29(6): 713-720.

[15] NHS Evidence. Depression: Evidence Update April 2012[J/OL]. [2024-11-03]. https://www.mendeley.com/catalogue/768a7457-6251-3dbf-91c2-1db04a7a229d/.

[16] Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association[J]. American Journal of Psychiatry, 2000, 157(4 Suppl): 1-45.

[17] FURUKAWA T A, CIPRIANI A, COWEN P J, et al. Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression: a systematic review and dose-response meta-analysis[J]. Lancet Psychiatry, 2019, 6(7): 601-609. DOI: 10.1016/S2215-0366(19)30217-2.

[18] TROY S M, SCHULTZ R W, PARKER V D, et al. The effect of renal disease on the disposition of venlafaxine[J]. Clinical Pharmacology and Therapeutics, 1994, 56(1): 14-21. DOI: 10.1038/clpt.1994.95.

[19] XIE Huanshan, HUANG Yi, HUANG Shanqing, et al. Analysis of influencing factors for O-desmethylvenlafaxine to venlafaxine concentration ratio based on therapeutic drug monitoring[J]. Chinese Journal of Clinical Pharmacology, 2022, 38(20): 2419-2422. DOI: 10.13699/j.cnki.1001-6821.2022.20.008.

[20] CHO C K, KANG P, JANG C G, et al. PBPK modeling to predict the pharmacokinetics of venlafaxine and its active metabolite in different CYP2D6 genotypes and drug-drug interactions with clarithromycin and paroxetine[J]. Archives of Pharmacal Research, 2024, 47(5): 481-504. DOI: 10.1007/s12272-024-01495-0.

[21] WEI Longjing, CHEN Yu, GENG Jiting, et al. Correlation between CYP2D6 gene polymorphism and venlafaxine metabolism in patients with depression[J]. Chinese Journal of Hospital Pharmacy, 2019, 39(5): 497-501. DOI: 10.13286/j.cnki.chinhosppharmacyj.2019.05.14.

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Note: Figure translations are in progress. See original paper for figures.