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Research Article

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Efficacy and safety of toludesvenlafaxine vs venlafaxine in depression: a multicenter, open-label, randomized controlled trial

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Abstract: Toludesvenlafaxine, a novel serotonin-norepinephrine-dopamine reuptake inhibitor, has shown promise in treating depression, yet direct comparisons with venlafaxine, a standard serotonin-norepinephrine reuptake inhibitor, remain limited, especially in the anhedonia facet. To address this gap, an 8-week multicenter, open-label, randomized controlled trial was conducted to compare toludesvenlafaxine with venlafaxine as monotherapies for major depressive disorder (MDD). Assessments were performed at baseline and weeks 2, 4 and 8, including evaluations of anhedonia (Snaith-Hamilton Pleasure Scale (SHAPS) and Dimensional Anhedonia Rating Scale (DARS)), general depressive symptoms (Montgomery-Åsberg Depression Rating Scale (MADRS), 17-item Hamilton Depression Rating Scale (HAMD-17), and Self-Rating Depression Scale (SDS)), quality of life (Satisfaction Questionnaire-Short Form (Q-LES-Q-SF)), as well as safety (Treatment Emergent Symptom Scale (TESS)) and sexual function (Arizona Sexual Experience Scale (ASEX)). The results showed that, compared with venlafaxine, toludesvenlafaxine had an earlier onset of action at week 2 in improving MADRS and HAMD-17 scores, along with alleviating anhedonia and suicidal ideation. At week 8, however, the SHAPS scores were comparable between the two groups, indicating

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their similar efficacy in treating anhedonia. In terms of safety, toludesvenlafaxine exhibited significantly lower levels of triglycerides and total bilirubin, while other indices demonstrated no significant difference. Overall, both drugs showed comparable efficacy and safety profiles for MDD over the 8-week treatment period, with toludesvenlafaxine potentially acting more rapidly.

Key words: Toludesvenlafaxine; Venlafaxine; Major depressive disorder; Antidepressants

1 Introduction

Major depressive disorder (MDD) is a globally prevalent and disabling psychiatric condition. According to the World Health Organization, approximately 280 million people worldwide suffer from varying degrees of depression (World Health Organization, 2023). The lifetime prevalence of depression in Chinese adults has reached 6.8% (Huang et al., 2019). Core symptoms such as low mood, anhedonia and suicidal ideation not only severely impact life quality but also increase the risk of comorbidities like cardiovascular diseases and metabolic syndrome, imposing a huge socioeconomic burden (Collaborators, 2022; Guo et al., 2025; Ducasse et al., 2018; Berk et al., 2023).

Despite there are effective therapies available, many patients experience residual symptoms of depression, notably anhedonia, which is closely linked to dopaminergic dysregulation. While current antidepressants primarily target serotonin and norepinephrine, emerging evidence suggests that incorporating dopaminergic modulation may improve outcomes (Tye et al., 2013; Chaudhury et al., 2013). The dopaminergic antidepressant mechanism involves multiple levels. From the perspective of neurotransmitter regulation, functional abnormalities exist in the mesolimbic dopamine system in the brains of depressed patients (Yadid and Friedman, 2008; Baik, 2020). Studies in animal models of depression have shown that dopamine release in the nucleus accumbens is reduced by approximately 19 – 32% compared with controls, which is associated with core depressive-like behaviours such as anhedonia and reduced motivation(Li et al., 2022). At the receptor level, dopamine receptors are divided into D1-like (D1, D5) and D2-like (D2, D3, D4) receptors, which have synergistic or antagonistic effects in regulating emotional and cognitive functions (Kong et al., 2023; Godino et al., 2025). Depressed patients may have an imbalance in the proportion of these two types of receptor subtypes. For example, the insufficient function of D1-like receptors may affect the executive functions (such as attention and decision-making ability) of the prefrontal cortex (Savitz and Drevets, 2013), while the excessive activation or inhibition of D2-like receptors may disrupt the balance of the reward circuit, collectively exacerbating depressive symptoms (Ott and Nieder, 2016; Terauchi et al., 2025). In the state of depression, these neural circuits are damaged and dopamine transmission is abnormal, resulting in an imbalance in emotional regulation. Some antidepressants (such as bupropion) can inhibit the function of dopamine transporters (DAT), reduce dopamine reuptake, increase the concentration of dopamine in the synaptic cleft, and enhance reward signal transmission, thereby alleviating anhedonia caused by dopamine deficiency (Rau et al., 2005; Vaishnavi et al., 2004). Thus, enhancing dopaminergic signaling potentially improves depressive symptoms compared to traditional antidepressants such as selective serotonin reuptake inhibitors, especially in terms of interest, energy and pleasure in individuals with MDD (Kong et al., 2023; Chaudhury et al., 2013).

Toludesvenlafaxine (LY03005, LPM570065, ansofaxine) is a triple reuptake inhibitor that blocks the reuptake of serotonin, norepinephrine and dopamine in the central nervous system (Charney, 1998). Preclinical animal studies have demonstrated that the acute or chronic administration of toludesvenlafaxine elevated serotonin, norepinephrine and dopamine levels in the striatum of rats (Mi et al., 2021; Zhang et al., 2014). Behavioral experiments further showed that it notably improves anhedonia symptoms in the sucrose preference test (Zhu et al., 2021). For human trials, toludesvenlafaxine has now completed phase I to III clinical trials for depression in China and was officially approved for marketing in November 2022 (H20220028, H20220029) (Pharma, March 2021.). All phase I trials conducted have shown that

toludesvenlafaxine has good tolerability and safety. Notably, sexual dysfunction induced by SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) often affects the quality of life and medication adherence of individuals (Kishi et al., 2023; Reichenpfader et al., 2014). However, preclinical studies of toludesvenlafaxine showed no changes in prolactin or testosterone levels during treatment (Li et al., 2018). The drug also exhibited limited effects on fertility and early embryonic development (Li et al., 2018; Guo et al., 2018). Phase III clinical trials have confirmed the safety and efficacy of toludesvenlafaxine in treating depression with good tolerability. According to evidence, it did not affect sexual function, had low incidences of insomnia or drowsiness, and showed no significant impact on body weight or lipid metabolism. Additionally, studies found that the acute injection of toludesvenlafaxine led to higher exposure levels than desvenlafaxine, and as expected, long-term use (up to two weeks) elevated the levels of all three monoamines, especially dopamine, more than desvenlafaxine (Zhang et al., 2014). Preclinical models of depression suggested that toludesvenlafaxine is more effective and acts more rapidly than desvenlafaxine (Zhang et al., 2014). However, head-to-head clinical data comparing toludesvenlafaxine and venlafaxine is currently lacking.

Based on prior research and clinical needs, this study designed an 8-week, open-label, randomized, head-to-head comparison of the efficacy and safety of toludesvenlafaxine hydrochloride extended-release tablets with venlafaxine hydrochloride extended-release tablets in treating individuals with MDD. We hypothesized that an additional dopaminergic mechanism of toluvenlafaxine—compared to venlafaxine—could better improve the anhedonia symptom as the primary outcome in the study, with the general efficacy and tolerability profiles examined as secondary outcomes. Thus, this study aimed to provide clinical guidance for selecting antidepressant medications.

2 Methods and materials

2.1 Trial oversight

We conducted a three-center, randomized controlled trial using a parallel group design comparing Ruoxinlin® (toludesvenlafaxine) with Bolexin® (venlafaxine) as monotherapy for the management of depressive episodes for individuals with MDD.

This study was registered (NCT06278038) and approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (IIT2023-067C). All participants understood and approved the study protocol, and signed an informed consent form before participation.

2.2 Participants

Patients with depression were recruited from the First Affiliated Hospital of Zhejiang University School of Medicine, Zhejiang Xiaoshan Hospital, and the Fourth Hospital Affiliated with Zhejiang University School of Medicine between February 22 and November 19, 2024. Eligible participants were aged 18–65 years, met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD as diagnosed by an experienced psychiatrist, and exhibited at least moderate depressive symptoms, defined as 17-item Hamilton Depression Rating Scale (HAMD-17) score $\geqslant$ 18, together with clinically significant anhedonia, indicated by Snaith-Hamilton Pleasure Scale (SHAPS) score$\geqslant$3.

Key exclusion criteria included severe suicidal risk, comorbid psychiatric disorders, substance use disorders within the previous 6 months, unstable or severe medical conditions, recent electroconvulsive or neuromodulation therapy, and pregnancy or lactation. Detailed inclusion and exclusion criteria are provided in the Supplementary Materials.

2.3 Intervention

Participants were assigned in a 1:1 ratio by central dynamic randomization to receive either

toludesvenlafaxine or venlafaxine as monotherapy for an 8-week treatment period. Toludesvenlafaxine treatment was initiated at a daily dose of 40 mg, with subsequent dose adjustments based on clinical response and tolerability, up to a maximum of 160 mg/day. In the venlafaxine group, extended-release venlafaxine was started at 75 mg/day and could be increased, when clinically indicated, to a maximum daily dose of 225 mg.

Dose modifications followed predefined clinical criteria. Short-acting hypnotics were permitted on a limited basis for severe insomnia, whereas the concomitant use of other antidepressants, antipsychotics, mood stabilizers, or neuromodulation-based interventions was not allowed. Further details regarding dose titration and concomitant medication management are provided in the Supplementary Materials.

2.4 Outcomes

Efficacy and safety assessments were conducted at baseline and at weeks 2, 4, and 8 after treatment initiation. The primary efficacy outcome was the change in anhedonia severity, measured by the SHAPS, from baseline to week 8. Secondary efficacy outcomes included SHAPS reduction rates at weeks 2, 4, and 8, calculated as the percentage change from baseline. Based on SHAPS reduction, anhedonia outcomes were categorized as recovery ($\geqslant$ 75%), marked improvement (50 – <75%), improvement (25 – <50%), or no improvement (<25%).

Depressive symptoms were additionally assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS), the HAMD-17, and the Self-Rating Depression Scale (SDS). Response was defined as a $\geqslant$ 50% reduction from baseline in MADRS or HAMD-17 scores, and remission as a MADRS score $\leqslant$ 10 or a HAMD-17 score $\leqslant$ 7. Anhedonia was further evaluated using the Dimensional Anhedonia Rating Scale (DARS), and quality of life was assessed with the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF).

Safety evaluations included the monitoring of adverse events using the Treatment Emergent Symptom Scale (TESS), assessment of sexual function with the Arizona Sexual Experience Scale (ASEX), routine laboratory tests, electrocardiography, body weight, and vital signs.

2.5 Quality control management

The study implemented comprehensive quality control measures to ensure the integrity and reliability of the trial. All investigators and raters were formally qualified and underwent thorough training before the trial, including detailed instruction on the clinical protocol and standardized use of rating scales, with inter-rater reliability checks. During the study, raters were blinded to treatment assignment, and participants' self-reported symptoms were documented objectively at the scheduled timepoints, avoiding any leading or suggestive prompts.

Medication adherence was carefully monitored through pill counts and structured interviews, supported by participant education and enhanced follow-up procedures to encourage compliance. Participants were also informed in detail about potential adverse drug reactions and the procedures for managing them. Laboratory tests were performed in accordance with standard operating procedures, with established quality control protocols for all assays. Adverse events were carefully recorded and managed according to the predefined study guidelines.

2.6 Sample size calculation

The sample size was calculated via SPSS 15, with the score changes of the SHAPS after 8 weeks of treatment as the primary outcome. According to the reference, the parameters were set as follows: mean difference in SHAPS scores between groups after 8 weeks = 2.1; standard deviation (SD) of the control group = 2.0; clinical non-inferiority margin = 0.6; α = 0.05; and power = 0.9. The calculated sample size was 32 subjects for each group. Accounting for a 20% attrition rate due to dropouts and withdrawals, the final required sample size was 40 subjects per group, resulting in a total sample size of 80 subjects.

2.7 Statistical analysis

All analyses were conducted on the modified intention-to-treat (mITT) population, which included all randomized participants who received at least one dose of study medication and had both baseline and at least one post-baseline assessment of the primary outcome. Missing values were handled using the last-observation-carried-forward (LOCF) approach.

Continuous variables were summarized as mean ± standard deviation for each treatment group at each visit. Within-group changes from baseline were compared using paired t-tests, while between-group comparisons employed analysis of variance (ANOVA) or nonparametric tests as appropriate. Least squares means for changes from baseline were calculated for each scale, and differences between groups were reported with corresponding 95% confidence intervals (95% CI). Categorical data were analyzed using chi-square tests. All statistical tests were two-sided, with P-values < 0.05 considered statistically significant. Analyses were performed using SAS version 9.2.

3 Results

3.1 Patients

Out of a total of 92 patients screened, 84 patients with MDD were enrolled and randomly assigned to receive treatment with toludesvenlafaxine or venlafaxine (42 patients in each group). The mITT population included 81 patients (40 patients in the toludesvenlafaxine group and 41 patients in the venlafaxine group). Altogether, 64 patients completed the trial, including 35 patients in the toludesvenlafaxine group and 29 patients in the venlafaxine group (**Fig. 1, Table S1**). The most common reason for withdrawal was due to adverse events (AEs). The population characteristics were recorded in **Table 1** and **Table S2**, with no significant differences in the demographic and clinical characteristics.

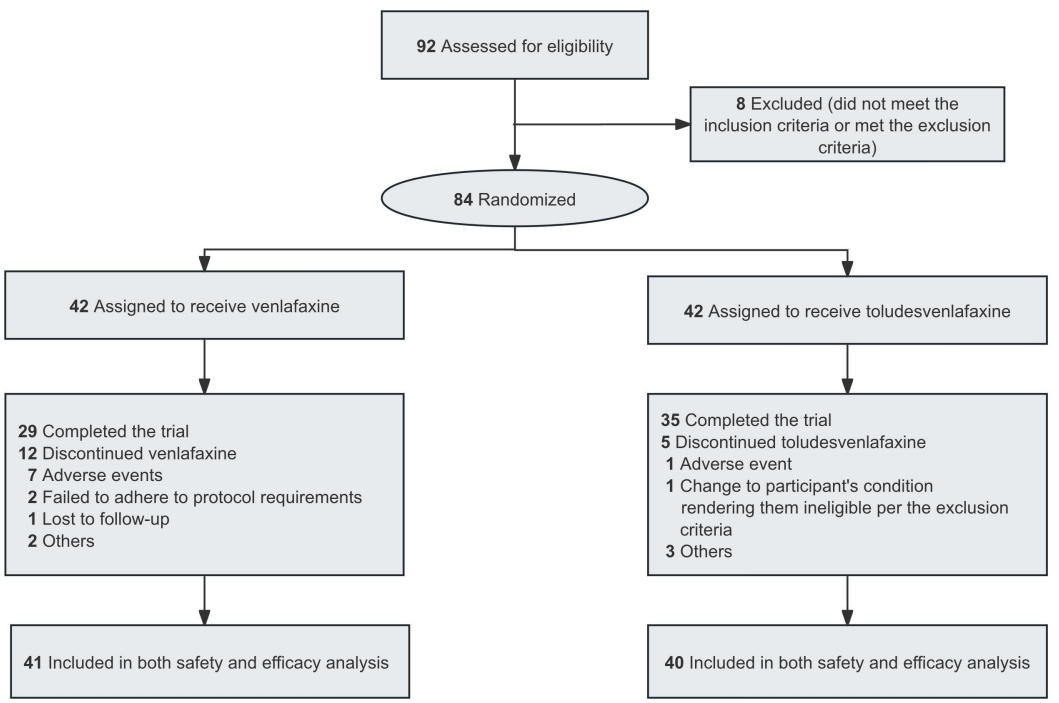

Fig. 1 Participant Allocation Flow Diagram

Table 1 General information about the subjects

		Toludesvenlafaxine group (n = 40)	Venlafaxine group (n = 41)	P value (n = 81)
Age (years)		29.8±8.6	30.6±10.8	0.7104
Sex (%)	Male	17(42.5)	16(39.0)	0.8228
	Female	23(57.5)	25(61.0)	
Nationality (%)	The Han nationality	37(92.5)	41(100.0)	0.1158
	Other	3(7.5)	0(0.0)	
Marital status (%)	Single	16(40.0)	18(43.9)	0.3320
	Divorced	2(5.0)	0(0.0)	
	In love	10(25.0)	6(14.6)	
	Married	12(30.0)	16(39.0)	
	Remarried	0(0.0)	1(2.4)	
Height (cm)		165.3±8.7	168.4±7.7	0.0951
Weight (Kg)		64.83±13.70	65.18±14.50	0.9113
BMI (kg/m^2)		23.76±4.80	22.80±3.76	0.3210
Baseline SHAPS		7.2±2.9	7.2±2.9	0.4541
Baseline MADRS		28.7±6.1	28.7±6.1	0.9479
Baseline HAMD-17		23.1±3.3	23.1±3.3	0.5340
Baseline DARS		30.5±16.0	30.5±16.0	0.2419
Baseline SDS		18.5±7.1	18.5±7.1	0.7595
Baseline Q-LES-Q-SF		31.0±7.4	31.0±7.4	0.3301

The data are expressed as mean±Standard deviation (SD) or number (percentage). BMI: body mass index; SHAPS: Snaith-Hamilton Pleasure Scale, DARS: Dimensional Anhedonia Rating Scale, MADRS Montgomery-Åsberg Depression Rating Scale, HAMD-17: 17-item Hamilton Depression Rating Scale, SDS: Sheehan Disability Scale, Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form.

3.2 Efficacy

From baseline after 8 weeks of treatment, patients in the toludesvenlafaxine group had reduced scores in SHAPS (8 weeks vs. baseline, Mean [95% CI]: −2.1 [−3.4, −0.7] vs. −0.7 [−1.7, 0.4], P=0.0044), HAMD-17 (8 weeks vs. baseline, Mean [95% CI]: −13.8 [−16.2, −11.4] vs. −8.1 [−9.8, −6.3], P<0.0001), MADRS (8 weeks vs. baseline, Mean [95% CI]: −16.4 [−19.8, −13.1] vs. −9.4 [11.6, −7.2], P<0.0001), and SDS (8 weeks vs. baseline, Mean [95% CI]: −7.4 [−10.3, −4.5] vs. −4.0 [−6.0, −1.9], P<0.0001). Similarly, the venlafaxine showed significant decreases in SHAPS (8 weeks vs. baseline, Mean [95% CI]: −2.0 [−2.9, −1.0] vs. −0.4 [−1.2, 0.4], P=0.0003), HAMD-17 (8 weeks vs. baseline, Mean [95% CI]: −13.2 [−14.8, −11.5] vs. −4.9 [−6.4, −3.4], P<0.0001), MADRS (8 weeks vs. baseline, Mean [95% CI]: −17.2 [−19.3, −15.1] vs. −5.9 [−7.7, −4.2], P<0.0001), and SDS (8 weeks vs. baseline, Mean [95% CI]: −7.3 [−10.1, −4.5] vs. −2.7 [−4.4, −1.0], P<0.0001). Both groups demonstrated significant increases in DARS scores and Q-LES-Q-SF scores (P<0.0001) compared with the baseline (**Table 2, Tables S3–S4**).

For the primary efficacy outcome, although the SHAPS scores of both groups decreased significantly

(P<0.005), no significant between-group differences in SHAPS scores were observed after 8 weeks of treatment (toludesvenlafaxine vs. venlafaxine, LS Mean [95% CI]: −1.9 [−3.0, −0.9] vs. −2.1 [−3.2, −1.1], P=0.25), indicating no anhedonia efficacy improvement for toludesvenlafaxine compared with venlafaxine **(Fig. 2)**. Meanwhile, after 8 weeks of treatment, the toludesvenlafaxine group showed neither superiority nor inferiority compared with the venlafaxine group in terms of symptom remission rate and recovery rate (95% CI: −22.5–13.7, P=0.79) (**Table 2**).

However, the toludesvenlafaxine group showed a greater advantage in the early onset of action. At the end of the second week of treatment, the changes in MADRS (P=0.022) and HAMD-17 scores (P=0.0098) from baseline in the toludesvenlafaxine group were higher than those in the venlafaxine group (**Table 3**); at this time point, the response rate (MADRS P=0.0079; HAMD-17 P=0.0285) as well as the remission rate (MADRS P=0.027) also showed significant differences between the two groups (**Tables S5–S8**). MADRS and HAMD-17 single-item score analysis showed that toludesvenlafaxine was significantly better than venlafaxine in improving depression, anhedonia, and reducing suicidal ideation at week 2. This indicated that toludesvenlafaxine rapidly alleviated the negative emotions and reduced the suicide risk for individuals with MDD (**Tables S9 and S10**).

Table 2 Changes in SHAPS scores from the baseline at the end of the 2nd, 4th, and 8th weeks

Time	Group	*n*	Change scores Mean±SD (95%CI)	Comparison within groups		LS Mean±SE (95% CI)	Comparison between groups	
				t	*P*		*F*	*P*
2nd week	Toludesvenlafaxine	40	−0.7±3.2 (−1.7,0.4)	1.28	0.2086	−0.6±0.4 (−1.5,0.3)	0.02	0.8778
	venlafaxin	41	−0.4±2.6 (−1.2,0.4)	1.03	0.3094	−0.5±0.4 (−1.4,0.4)		
4th week	Toludesvenlafaxine	40	−1.7±3.8 (−2.9,−0.5)	2.89	0.0063	−1.6±0.5 (−2.6,−0.6)	0.02	0.8880
	venlafaxin	41	−1.4±3.2 (−2.4,−0.4)	2.73	0.0095	−1.5±0.5 (−2.5,−0.5)		
8th week	Toludesvenlafaxine	40	−2.1±4.3 (−3.4,−0.7)	3.03	0.0044	−1.9±0.5 (−3.0,−0.9)	0.07	0.7958
	venlafaxin	41	−2.0±3.1 (−2.9,−1.0)	4.13	0.0002	−2.1±0.5 (−3.2,−1.1)		

Note: ANCOVA was used for the comparison between groups. The baseline values were used as covariates. The LS means of the changes in the SHAPS scores from the baseline at the end of the second week and the fourth week of medication for the two groups were calculated, as well as the difference in the adjusted means between the two groups and its 95% CI.

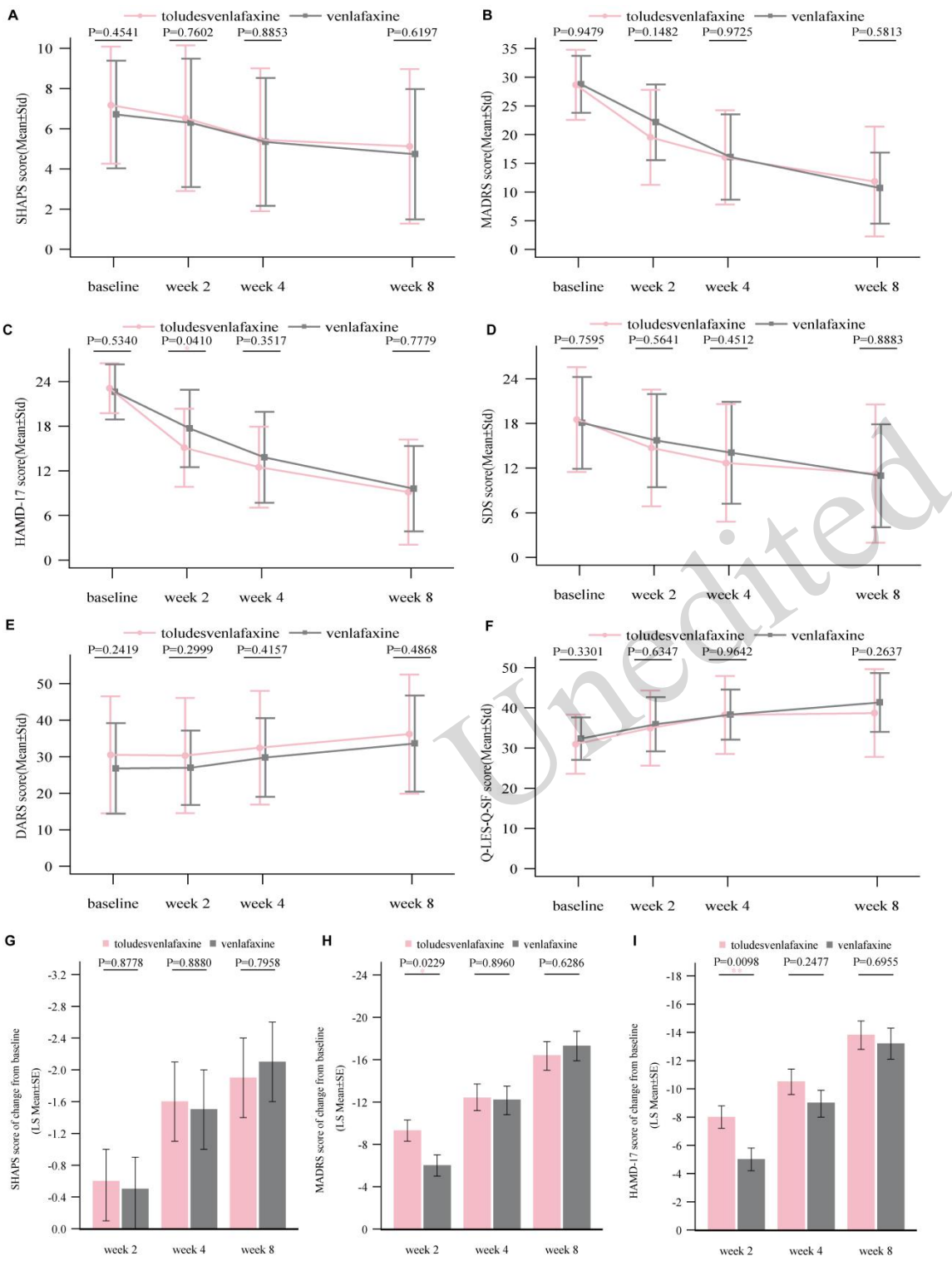

Fig. 2 Changes in different scores over time

(a-f) Mean changes in Snaith–Hamilton Pleasure Scale (SHAPS) (a), Montgomery–Åsberg Depression Rating Scale (MADRS) (b), 17-item Hamilton Depression Rating Scale (HAMD-17) (c), Sheehan Disability Scale (SDS) (d), Dimensional Anhedonia Rating Scale (DARS) (e), and Quality of Life Enjoyment and Satisfaction Questionnaire–Short Formn (Q-LES-Q-SF) (f) from baseline to endpoint. The values are expressed

as mean±standard deviation (SD). (g-i) Least-squares mean (LS Mean) change in reduction scores in SHAPS (g), MADRS (h), HAMD-17 (i) from baseline to 2 weeks, 4 weeks and 8 weeks for the toludesvenlafaxine group and the venlafaxine group. The values are expressed as LS mean±standard error of the mean (SEM). All figures have sample sizes of N=40 for the toludesvenlafaxine group and N=41 for the venlafaxine group. Statistical significance is indicated as *$P < 0.05$, **$P < 0.01$, ***$P < 0.0001$

Table 3 Changes in MADRS and HAMD-17 scores from the baseline at the end of the 2nd weeks

Time	Group	n	Change scores Mean±SD (95%CI)	Comparison within groups t	Comparison within groups P	LS Mean±SE (95% CI)	Comparison between groups F	Comparison between groups P
MADRS	Toludesvenlafaxine	38	−9.4±6.7 (−11.6,−7.2)	8.64	<0.0001	−9.3±1.0 (−11.2,−7.4)	5.42	0.0229*
	venlafaxin	33	−5.9±5.0 (−7.7,−4.2)	6.82	<0.0001	−6.0±1.0 (−8.1,−3.9)	.	.
HAMD-17	Toludesvenlafaxine	38	−8.1±5.3 (−9.8,−6.3)	9.43	<0.0001	−8.0±0.8 (−9.5,−6.5)	7.06	0.0098**
	venlafaxin	33	−4.9±4.2 (−6.4,−3.4)	6.77	<0.0001	−5.0±0.8 (−6.6,−3.4)	.	.

Note: Statistical significance is indicated as follows: *P<0.05, **P<0.01, ***P<0.0001.

3.3 Dropouts, Safety and Tolerability

A total of 17 patients dropped out of the study, corresponding to a dropout rate of 20.2%. Among them, 5 patients (11.9%) withdrew from the treatment group receiving toludesvenlafaxine, and 12 patients (28.6%) dropped out of the treatment group receiving venlafaxine. The specific dropout details are shown in **Tables S11–S12**, with a different trend found in dropout (P=0.085). Of note, drop-out for AE in the toludesvenlafaxine group showed a lower trend compared to that in the venlafaxine group (2.5% vs. 17.1%, P=0.057). Common AEs occurred in 37 (92.5%) patients of the toludesvenlafaxine group and 33 (80.5%) patients of the venlafaxine group (**Table S14**). The overall rate of study discontinuation caused by AEs was 2.5% (n=1) in the toludesvenlafaxine group and 17.1% (n=7) in the venlafaxine group (**Table 4**). The most common symptoms across groups were nausea (toludesvenlafaxine vs. venlafaxine, n=18 vs. n=12, P=0.176), mouth dryness (n=10 vs. n=14, P=0.365), and constipation (n=4 vs. n=10, P=0.140) (**Table S13**). It is worth noting that after 8 weeks of treatment, the levels of triglycerides and total bilirubin in the toludesvenlafaxine group were significantly lower than those in the venlafaxine group. However, in terms of the mean change from baseline for vital signs, ECG, hematology, most laboratory indices, and sexual function, no other clinically relevant differences were observed between the two groups (**Tables S15−S21**). The mean change in weight from baseline to end of treatment was +0.84 kg in the toludesvenlafaxine group, and −1.02 kg in the venlafaxine group. No adverse reactions caused by drug withdrawal were observed.

Table 4. Occurrence of AEs in patients during treatment

	Toludesvenlafaxine group (n=40)		Venlafaxine group (n=41)		P value
	Number of Events	Case (%)	Number of Events	Case (%)	
Adverse event (AE)	157	37 (92.5)	150	33 (80.5)	0.1935
Drug-related adverse event	133	33 (82.5)	140	32 (78.0)	0.7813
Serious adverse event (SAE)	1	1 (2.5)	0	0 (0.0)	0.4938
Serious drug-related adverse reaction	0	0 (0.0)	0	0 (0.0)	-
Adverse events leading to dose reduction	1	1 (2.5)	3	2 (4.9)	1.0000
Drug-related adverse events leading to dose reduction	1	1 (2.5)	3	2 (4.9)	1.0000
Adverse events leading to discontinuation of study participation	1	1 (2.5)	10	7 (17.1)	0.0571
Drug-related adverse events leading to study withdrawal	1	1 (2.5)	10	7 (17.1)	0.0571

Note: Adverse events refer to those that occurred after the first administration of the drug. Drug-related adverse events are defined as adverse events with a causality assessment of "definitely related," "probably related," or "possibly related" to the investigational drug.

4 Discussion

The objective of this study was to conduct a real-world head-to-head analysis of the efficacy and safety of two drugs—toludesvenlafaxine and venlafaxine—with dopamine-distinct mechanisms of action in treating MDD, especially in the anhedonia facet.

Both medications significantly improved the core depressive symptoms and comorbid anxiety, with a low incidence of serious adverse events such as sexual dysfunction, consistent with the established research consensus on the efficacy and safety of SNRI medications (Pillinger et al., 2023; Bellantuono et al., 2015; Zhou et al., 2025). Notably, compared with the venlafaxine group, the toludesvenlafaxine group showed an early action in alleviating depressive symptoms, anhedonia and suicidal ideation. This early-onset efficacy might be attributed to the pharmacological profile of toludesvenlafaxine. The active metabolite of toludesvenlafaxine, O-Desmethylvenlafaxine (ODV), exerts a stronger dual inhibitory effect on the serotonin and norepinephrine transporters, potentially facilitating a more rapid correction of monoaminergic imbalance. This mechanism may underlie its observed rapid symptom relief and reduction in suicidal ideation. In an animal study, it was demonstrated that both toludesvenlafaxine and ODV were detectable selectively in the hypothalamus and throughout brain tissue (Zhu et al., 2021). Furthermore, the early efficacy of toludesvenlafaxine in reducing suicide risk was consistent with existing research (Otto et al., 2023; Herrman et al., 2022; Wu et al., 2024; Harmer et al., 2025). Given the relatively high risk of suicide in patients with depression during the early stages of the disease, timely and effective intervention is crucial.

Importantly, no significant between-group differences were observed in the SHAPS scores at any time point, while significant improvement in the SHAPS scores in both the toludesvenlafaxine group and the venlafaxine group, compared with the baseline values, occurred at week 4. The SHAPS focuses on specific, immediate hedonic experiences and adopts strict scoring criteria. In the early stage of treatment, interventions can only alleviate the symptom of diminished interest, but patients have not yet truly experienced pleasure from specific behaviors. This finding might be attributed to the longer time required for dopaminergic (DA) effects to manifest. The restoration of nucleus accumbens D1 receptor sensitivity typically takes 2–4 weeks, while the remodeling of prefrontal-striatal circuit may take up to 6 weeks (Ventorp et al., 2022). In contrast, improvements in attention mediated by norepinephrine (NE) and mood regulation by serotonin (5-HT) can

become apparent within 1–2 weeks, which is consistent with our findings that the value of HAM-17 and MARDS decreased significantly at 2 weeks. Given that no between-group differences in SHAPS scores were observed across all time points, toludesvenlafaxine was not superior to venlafaxine in improving anhedonia. However, subsequent comparative studies between toludesvenlafaxine and venlafaxine should be designed targeting specific populations with a larger sample size and a longer follow-up time window.

In terms of safety, the majority of adverse events associated with both drugs were mild to moderate in severity, consistent with the known adverse reaction profile of SNRIs (Fava et al., 2018). However, it is noteworthy that after 8 weeks of treatment, triglyceride and total bilirubin levels were significantly lower in the toludesvenlafaxine group compared with the venlafaxine group. This observation may be related to the distinct metabolic properties of the two drugs. Venlafaxine is primarily metabolized by the CYP2D6 and CYP3A4 enzymes (Sangkuhl et al., 2014), both of which belong to the CYP450 system, whose activity is highly susceptible to genetic polymorphisms, concomitant medications, and liver function (Țieranu et al., 2018). The use of venlafaxine in patients with hepatic impairment may lead to drug accumulation due to slowed metabolism, thereby increasing the risk of adverse reactions. In contrast, toludesvenlafaxine undergoes hydrolysis primarily mediated by carboxylesterase 2 (CES2) to form its active metabolite ODV, and this process is independent of hepatic CYP450 enzymes and P-glycoprotein (Zhu et al., 2021). This characteristic confers a significantly reduced risk of drug-induced liver injury (DILI) when treating patients with liver conditions such as non-alcoholic fatty liver disease. Additionally, the lower triglyceride levels and minimal weight changes observed with toludesvenlafaxine may be attributed to its unique metabolic profile, which bypasses the CYP450 system and thus avoids related lipid metabolism disturbances. Clinically, this favorable metabolic property not only supports better long-term medication adherence but also aligns well with the frequent comorbidity of depression and metabolic disorders, offering a more suitable option for integrated mind-body care (Ducasse et al., 2018; Wang et al., 2025).

This study has the following inherent limitations: 1) The dropout rate in the venlafaxine group exceeded 20%, with most discontinuations driven by adverse events (7 cases, 16.7%), consistent with its known tolerability profile (e.g., nausea $\geqslant$25%; Drugs@FDA). Because dropout was primarily AE-related, patients who completed follow-up likely represented a more tolerant and responsive subgroup, introducing non-random attrition. This selection effect may bias efficacy estimation, while the use of a modified intention-to-treat (mITT) analysis further provides a conservative estimate. Together, these factors may affect the accurate estimation of both adverse event incidence and treatment efficacy for venlafaxine. 2) This study lacked objective biomarkers such as mature brain-derived neurotrophic factor (mBDNF), precursor brain-derived neurotrophic factor (pro-BDNF), vascular endothelial growth factor (VEGF), and plasma insulin-like growth factor-1 (IGF-1) to corroborate the findings. 3) The assessment of anhedonia and depressive mood relied solely on subjective scale ratings, without objective behavioral tasks such as the probabilistic reward task or emotion induction and experience tasks. 4) Given that this trial was designed as a real-world study, an open-label design was adopted based on pragmatic considerations. Expectation effects may have been present at week 2, and baseline scores on the Treatment Expectancy Questionnaire (TEQ) were not included as covariates in the statistical analysis. However, during the assessment process, the raters were blinded to the medication administered to the subjects. 5) The sample size was too small and should be increased, and the treatment time window should be extended.

In conclusion, both toludesvenlafaxine and venlafaxine eased depression and anxiety, but toludesvenlafaxine acted faster, cut suicidal thoughts earlier, and left triglycerides and bilirubin lower. These benefits, coupled with its CYP450-independent metabolism, position toludesvenlafaxine as a potentially preferable option. Particularly for patients with hepatic comorbidities or those requiring rapid symptom relief. However, no significant between-group differences in anhedonia improvement have been found, coupled with study limitations including high dropout rates, small sample size, and lack of objective biomarkers. Further research is still needed to help clarify the relative efficacy of these two interventions in targeting specific symptoms of MDD.

Data availability statement

All data in this study are available within the paper and its Supplementary Information.

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Author contributions

Jinyu Zhang performed the experimental research and data analysis, wrote and edited the manuscript. Xiaonan Guo was responsible for data analysis and collation, writing and editing of the manuscript. Yiheng Cui contributed to the manuscript polishing. All authors read and approved the final manuscript and, therefore, had full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

No conflicts of interest, financial or otherwise, are declared by the authors. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5). Informed consent was obtained from all patients included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

Declaration on the use of generative AI Tools

The manuscript was primarily prepared and written by the authors themselves, based on original research and analysis. Generative artificial intelligence (AI) tools were not used to create content, interpret data, or draft the main text. Any assistance from AI, if applied, was limited to language polishing or minor stylistic suggestions, and the authors carefully reviewed and verified all such content to ensure accuracy, integrity, and clarity.

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Supplementary information:
Materials and methods; Tables S1-S21