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Insights on the cognitive enhancement effect of desvenlafaxine in major depressive disorder

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Abstract

Background Desvenlafaxine, a serotonin-norepinephrine reuptake inhibitor, has demonstrated efficacy in improving affective symptoms of Major Depressive Disorder (MDD); however, its effects on associated cognitive and functional difficulties remain underexplored. This study seeks to assess the antidepressant effects of desvenlafaxine in patients with SSRI-resistant MDD, its impact on both objective and subjective cognitive performance, where cognitive improvements occur independently of clinical recovery or not, and its influence on psychosocial functioning.

Methods An observational case-control prospective study with 66 participants was conducted, including 26 patients with a current MDD episode, with an inadequate SSRI response, and with the prescription of desvenlafaxine as the next antidepressant therapeutic option, and 40 healthy controls. Sociodemographic, clinical, cognitive, and functional assessments were conducted both before and after a 12-week treatment period. Changes were analyzed using two tailed paired-samples t-tests, with Cohen's d for effect sizes. Cognitive improvements were compared between the patients who achieved remission and those who did not.

Results Patients showed significant improvements in depressive and anxiety symptoms, attention/working memory and processing speed, self-perceived cognitive difficulties and psychosocial functioning. Highlighting the fact these cognitive enhancements occurred independently of patients' clinical improvement.

Conclusions The findings of this study focus on the therapeutic potential of desvenlafaxine, demonstrating its efficacy not only in ameliorating clinical and functional symptoms but also in addressing specific cognitive impairments in patients with depression. Further research is needed to elucidate the mechanisms underlying desvenlafaxine's effects and optimize treatment strategies for individuals with MDD.

Trial registration number NCT03432221 (clinical.trials.gov). Registration date: 08-01-2018.

Keywords Desvenlafaxine, Major depressive disorder, Cognition, Psychosocial functioning

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Background

Cognitive symptoms in Major Depressive Disorder (MDD) encompass a wide range of difficulties, including impairments in attention, processing speed, memory, and executive function [1–5]. These cognitive difficulties are not secondary to clinical symptoms of depression [6], and they play a central role in the psychosocial functioning impairments experienced by individuals with depression ranging from hampered performance in occupational and educational contexts to disruptions in social interactions [7–10]. Consequently, cognitive difficulties significantly contribute to diminished quality of life and even to heighten the vulnerability to relapse in affected individuals [3, 8, 11]. Understanding the intricate interplay between cognitive symptoms and functional impairments is essential for the development of comprehensive pharmacological treatment approaches that address both the clinical and cognitive dimensions of depression, in order to achieve a full recovery from depressive episodes [12]. In this sense, it is crucial to discern whether antidepressant medications solely alleviate clinical depressive symptoms, or they also enhance specific cognitive domains [13]. This distinction is critical for guiding the selection of antidepressants based on their differential effects on cognitive functions.

Desvenlafaxine, a Serotonin-Norepinephrine Reuptake Inhibitor (SNRI), has garnered attention not only for its efficacy in relieving depressive symptoms and its promising functional outcomes [14–18], but also for its potential positive impact on the cognitive performance of patients with MDD. Results from a previous study indicate that desvenlafaxine is likely to show beneficial effects beyond mood regulation, displaying a significant improvement in working memory [19]. Along the same lines, Lam and colleagues proposed the use of desvenlafaxine as a relevant pharmacological strategy to address cognitive symptomatology in depression, proving efficacy in the cognitive domains of attention, cognitive and psychomotor processing speed, and in the executive function of cognitive flexibility [20]. By modulating neurotransmitter levels, particularly serotonin and norepinephrine, desvenlafaxine seems to be able to activate cognitive processing and to promote better cognitive performance in individuals struggling with MDD. Along with objective improvements in cognitive function, patients also reported a notable enhancement in self-perceived cognitive abilities after desvenlafaxine treatment [20]. Other research findings suggest that subjective cognitive performance has a direct impact on functional improvement, and on the overall capacity for full recovery from depressive episodes [12, 21]. Therefore, desvenlafaxine's capacity to target both depressive symptoms and cognitive dysfunction suggests a broader therapeutic potential, offering hope for the improvement of cognitive outcomes alongside mood stabilization in MDD patients. However, there are very few studies that consider the cognitive effects of desvenlafaxine, and even fewer that comprehensively evaluate its clinical, cognitive, and functional impact.

The aims of the present study are: (i) to describe the antidepressant effect of desvenlafaxine in those MDD patients who did not achieve clinically significant improvement when treated with Selective Serotonin Reuptake Inhibitor (SSRI) in an appropriate dose and for the adequate time, (ii) to investigate the efficacy of treatment with desvenlafaxine on objective and subjective cognitive performance, (iii) to determine whether observed cognitive improvements are uniquely attributable to clinical recovery, and (iv) to examine any potential benefits of desvenlafaxine in psychosocial functioning.

Methods

Participants

A sample of 26 patients between the age of 18 and 60 years old was recruited from the Outpatient Psychiatry Service of Corporació Sanitària Parc Taulí in Sabadell, Catalonia (Spain). All patients fulfilled the inclusion criteria of a current MDD episode (according to the DSM-5 criteria) with a score of 18 points or higher in the 17-item Hamilton Depression Rating Scale (HDRS-17) [22, 23], along with a non-response or incomplete response to SSRI in an appropriate dose and for the adequate time, and with the prescription of desvenlafaxine as the next antidepressant therapeutic option. Patients were assessed by experienced psychiatrists, and the exclusion criteria considered for all participants were the following: (i) meeting criteria or having a history of posttraumatic stress disorder, obsessive-compulsive disorder, psychotic, bipolar, or substance use disorders, (ii) having any current or past central nervous system diseases, (iii) showing clinically significant unstable medical illness or clinically significant abnormal vital signs as determined by the expert clinical team, (iv) being pregnant or oral contraceptive users. Forty healthy controls (HC) were recruited using hospital brochures ensuring the same sociodemographic environment as patients with neither history of psychiatric disorders nor family history of mood disorders.

This investigation received the official approval of the Research Ethics Committee at Corporació Sanitària Parc Taulí. Every participant voluntarily provided a written informed consent after a comprehensive explanation of the study's aims and procedures. The study also strictly complied with current data protection laws, adhering rigorously to the ethical guidelines outlined in the Declaration of Helsinki and following the principles of Good Clinical Practice. Furthermore, it was registered on

clinical.trials.gov with the identifier NCT03432221 (Registration date: 08-01-2018).

Study design

The study is a 12-week observational case-control prospective study. After providing written informed consent, participants underwent a baseline psychiatric assessment, which included sociodemographic, clinical and psychosocial functioning characteristics. Experienced clinical neuropsychologists also administered an extensive neurocognitive battery. These assessments were repeated after 12-week treatment period. The prescribing psychiatrist determined the dosage of desvenlafaxine, starting at 50 mg/day and adjusting it up to a maximum of 150 mg/day after the fourth week of treatment. Every two weeks, psychiatrists made regular follow-up visits, making decisions regarding medication dosage or discontinuation based on their clinical judgement.

Sociodemographic and clinical assessment

Sociodemographic and clinical variables were obtained during a semi-structured interview, which covered age, sex, years of schooling, estimated intelligence quotient (IQ), age at illness onset, number of depressive episodes, duration of the current episode and the baseline medication prescription. The estimated IQ was determined using the Vocabulary subtest from the Wechsler Adult Intelligence Scale, fourth edition (WAIS-IV) [24]. Depressive symptomatology was assessed using the HDRS-17 [22, 23] where scores of 18 or higher indicate a moderate to severe level of depression. Symptom severity was assessed using the Clinical Global Impression scale (CGI) [25], which employs a graded scale ranging from 1 (normal) to 7 (most severely ill). Participants also completed the Remission from Depression Questionnaire (RDQ) [26], which provides insights into patients' perception of their clinical remission status, including not only aspects such as mood but also other areas like a positive mental health or a general sense of wellbeing. In order to gauge the severity of anxiety symptoms, the Hamilton Anxiety Rating Scale (HARS) [27, 28] was additionally administered.

Objective and subjective cognitive assessment

Objective cognitive function was measured with a battery of neuropsychological tests covering key cognitive domains associated with MDD, including memory, attention, working memory, processing speed and executive function: the Digit forward and backward (WAIS-IV) [24]; the Rey Auditory Verbal Learning Test (RAVLT) [29, 35], the Trail Making test Part A (TMT-A) and Part B (TMT-B) [30], the Digit Symbol Substitution Subtest (DSST, WAIS-IV) [24], the Phonemic Verbal Fluency FAS test, adapted for Spanish speaking population as PMR [31, 32], and the Wisconsin Card Sorting Test (WCST) [33]. The patients' appraisal of their own cognitive functioning, referred as subjective cognition, was assessed through the Perceived Deficit Questionnaire – Depression 5-item (PDQ-D-5) [34]. PDQ-D-5 is a brief screening self-report measure of cognitive dysfunction that assesses attention, retrospective memory, prospective memory, and planning and organization. Each item is rated from 0 (never) to 4 (almost always); so higher scores indicate a higher perception of suffering from cognitive deficits.

Psychosocial functioning assessment

The Functioning Assessment Short Test (FAST) [35] was employed to evaluate the patients' psychosocial functioning, encompassing six different subscales: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. Scores equal to or greater than 12 represent a mild to severe functional impairment. Higher scores indicate a greater degree of disability [36]. Another instrument used as part of the functional assessment was the Sheehan Disability Scale (SDS) [37], which is a 3-item self-report instrument designed to evaluate disability across three domains: occupational functioning, social life and leisure activities, and family life and household responsibilities. Scores range from absence of impairment (0) to extreme impairment (30). Scores equal to or below 6 suggest functional remission.

Statistical analyses

The raw scores derived from neuropsychological assessments underwent a conversion into T-scores through the application of standardized and demographically corrected normative data. To reduce the number of objective cognitive variables, four cognitive domains were computed: (i) Attention/Working Memory (Digit forward and backward, WAIS-IV); (ii) Verbal Memory (Immediate recall–sum of trials 1–5 – and delayed recall of the RAVLT); (iii) Processing Speed (TMT-A and DSST); and (iv) Executive Function (TMT–B, PMR and number of completed categories of the WCST). Baseline differences between MDD patients (whole sample, $n = 26$) and HC ($n = 40$) were assessed via Student's t-test for independent samples and chi-square analyses, depending on the continuous or categorical nature of each sociodemographic, clinical, cognitive, and functional variables.

Potential changes in clinical scales from baseline to 12-week intervention (follow-up) were examined using two tailed paired-samples t-tests, with effect sizes determined by Cohen's d. The clinical course of the antidepressant drug response was also categorized into three ad-hoc constructs: clinical response (a reduction of more than 50% on the follow-up HDRS-17 scale score

compared with the baseline HDRS-17 score); partial response (25–50% of HDRS-17 score reduction); and no clinical response (less than 25% score on the HDRS-17). Additionally, the percentage of patients who achieved clinical remission, being understood as a score less than or equal to 7 on the HDRS-17 scale at the follow-up assessment, was also calculated. Changes in both objective (Attention/Working Memory, Verbal Memory, Processing Speed, and Executive Function) and subjective cognitive performance from baseline to follow-up were also examined using the same statistic approach, with Cohen's d used to quantify effect sizes. In order to examine whether the use of desvenlafaxine triggers any functional improvement, paired samples t-tests were conducted to assess potential changes in psychosocial functioning scales. The minimal clinically important difference on the FAST scale, defined as a reduction of 7 to 9 points in total FAST score [38], was calculated as well.

Additionally, to address concerns about potential selection bias in the final sample, a comparison was conducted between the baseline sociodemographic, clinical, functional and cognitive characteristics of the final analyzed sample (Completers) and those of the patients who dropped out of the study (Lost to follow-up).

Subsequent analyses aimed to establish whether the observed cognitive improvements were specifically linked to clinical remission. To this end, cognitive changes were quantified exclusively for the cognitive domains that exhibited significant differences between assessments by subtracting baseline scores from follow-up scores. Finally, these significant cognitive changes – both objective and subjective – were compared between patients who achieved complete clinical remission and those who did not (non-clinical remission). Statistical analyses of the clinical trial were carried out using the Statistical Package for Social Sciences (SPSS, IL, Chicago, version 29) and statistical significance was set at $p < .05$.

Results

Baseline whole sample's characteristics

Table 1 shows the sociodemographic, clinical, cognitive and functional characteristics of the total sample, which includes 26 MDD patients and 40 HC. There were no significant differences between MDD and HC in age or sex. Although MDD patients had lower estimated IQ scores

Table 1 Mean scores (standard deviation) for sociodemographic, clinical, cognitive and functional baseline characteristics across groups

	GROUPS		STATISTICS	
	MDD ($n = 26$)	HC ($n = 40$)	F or χ^2	*p-value*
Age, *years*	48.8 (9.2)	45.93 (7.6)	1.85	0.178
Sex, n *female (%)*	17 (65.4)	22 (55)	0.7	0.402
Years of schooling, *n*	10 (3.4)	13.18 (3.4)	13.11	0.001
Estimated IQ, *T-score*	52 (14.6)	57.9 (8.3)	4.44	0.039
Age at illness onset, *years*	42.5 (12.1)			
Depressive episodes, *n*	1.8 (1.1)			
Duration of the current episode, *n*	40.6 (26.82)			
Baseline medication, *n (%)**				
Sertraline	9 (34.6)			
Fluoxetine	3 (11.5)			
Paroxetine	7 (26.9)			
Citalopram	5 (19.2)			
Escitalopram	2 (7.7)			
HDRS-17, *total score*	23.1 (3.3)	2.5 (2.8)	735.05	< 0.001
CGI Severity, *total score*	4.1 (0.4)			
RDQ, *total score*	56.5 (10.9)			
HARS, *total score*	25.1 (5.5)	3.1 (3.5)	369.17	< 0.001
Attention/Working Memory, *T-score*	42.1 (6.6)	49.9 (10.6)	11.27	0.001
Verbal Memory, *T-score*	40.9 (8.7)	48.1 (9.4)	9.91	0.003
Processing Speed, *T-score*	48.2 (8.4)	53.9 (7.1)	8.52	0.005
Executive Function, *T-score*	43.4 (7 – 4)	49.7 (5.9)	14.30	< 0.001
PDQ-D-5, *total score*	12 (3.3)	4.3 (2.4)	114.53	< 0.001
FAST, *total score*	45.6 (12)	9.2 (7.9)	218.55	< 0.001
SDS, *total score*	23.6 (4.6)			

MDD: Major Depressive Disorder, HC: Healthy Controls, IQ: Intelligence Quotient, HDRS-17: 17-item Hamilton Depression Rating Scale, CGI: Clinical Global Impression, RDQ: Remission from Depression Questionnaire, PDQ-D-5: Perceived Deficit Questionnaire-Depression 5-item, FAST: Functioning Assessment Short Test, SDS: Sheehan Disability Scale. *Baseline medication prior to desvenlafaxine.

Table 2 Clinical, functional and cognitive characteristics at baseline and 12-week intervention

	MDD ($n=20$)		STATISTICS		
	BASELINE	**FOLLOW-UP**	**Paired-samples t-test**	***p-value***	**Cohen's d**
Clinical outcomes:					
HDRS-17, *total score*	22.8 (3.5)	9.3 (5.5)	10.9	< 0.001	2.32
CGI Severity, *total score*	4.1 (0.3)	2.6 (1.1)	5.2	< 0.001	1.3
RDQ, *total score*	55.8 (10.4)	51.8 (15.9)	1.12	0.278	0.26
HARS, *total score*	25.1 (5.6)	10.8 (8.2)	7.23	< 0.001	1.81
Cognitive outcomes:					
Attention/Working Memory, *T-score*	43.2 (6.4)	46 (6.7)	-2.24	0.037	0.50
Verbal Memory, *T-score*	41.1 (8.4)	43.9 (7.5)	-1.63	0.120	0.36
Processing Speed, *T-score*	47.9 (8.7)	50 (8.2)	-2.73	0.014	0.63
Executive Function, *T-score*	43.8 (8.3)	45.4 (8.5)	-1.14	0.270	0.26
PDQ-D-5, *total score*	11.7 (2.8)	4.8 (4.1)	7.07	< 0.001	1.67
Functional outcomes:					
FAST, *total score*	44.5 (9.3)	38.7 (13.1)	2.12	0.047	0.47
SDS, *total score*	23.1 (4.5)	20.8 (8)	1.27	0.218	0.29

MDD: Major Depressive Disorder, HDRS-17: 17-item Hamilton Depression Rating Scale, CGI: Clinical Global Impression, RDQ: Remission from Depression Questionnaire, FAST: Functioning Assessment Short Test, SDS: Sheehan Disability Scale, PDQ-D-5: Perceived Deficit Questionnaire-Depression 5-item.

compared to HC group, the scores from both groups fell well within the range of clinical normality (± 1 standard deviation from the population mean). Also, MDD patients exhibited fewer years of schooling than the HC group. Regarding clinical measures, significant differences were observed in HDRS-17 compared to HC, with MDD patients being moderately to severely depressed at baseline as expected. According to the CGI scale, participants enrolled in the study presented a moderate level of illness. Furthermore, MDD patients displayed severe levels of anxiety and a self-perception of not being in clinical remission. Significant differences were observed between MDD patients and HC on cognitive measures, showing worse baseline performance in Attention/Working Memory, Verbal Memory, Processing Speed, and Executive Function in MDD. Lastly, MDD patients reported greater subjective cognitive deficits than HC in baseline assessment. Likewise, scores on psychosocial functioning scales (FAST and SDS) among depressive patients indicated a greater degree of functional impairment in comparison to the HC group.

Potential changes from baseline to 12-week intervention

Out of the 26 with MDD individuals enrolled in the study, 20 participants (77%) successfully completed the 12-week treatment regimen and underwent both baseline and follow-up assessments. Six patients (23%) withdrew during the follow-up study period citing personal reasons or non-compliance with scheduled study visits. At post-assessment, 65% ($n=13$) of patients were prescribed a daily dose of 100 mg of desvenlafaxine, 20% ($n=4$) received 150 mg/day, and the remaining patients (15%, $n=3$) were given 50 mg/day. During the follow-up assessments, notable enhancements were observed in clinical, cognitive and functional outcomes. Clinical, cognitive and functional changes between baseline and follow-up assessments are shown in Table 2. Additionally, no differences were found between the final analyzed sample (Completers, $n=20$) and the group of patients who did not follow the treatment (Lost to follow-up, $n=6$). Supplementary Table 1 includes comparisons for sociodemographic, clinical, functional and cognitive baseline characteristics between those latter two groups.

Clinical outcomes

A noteworthy improvement in depressive symptomatology was evidenced ($p<.001$) by a shift from a moderate-severe to mild severity of illness. To be precise, among the MDD patients, 16 individuals (80%) attained a clinical response, whereas 3 participants (15%) achieved a partial response, and only one individual did not respond to the antidepressant treatment with desvenlafaxine. Specifically, of the participants with clinical response, 8 of them (40%) achieved a clinical remission, denoted by a HDRS-17 score of 7 or lower. In line with the clinical improvement, the impression of severity scale (CGI) switched to a doubtfully ill status ($p<.001$). Anxiety symptomatology also improved ($p<.001$), with scores falling within the range of mild severity. Conversely, no significant differences were observed in self-perceived clinical remission ($p<.278$).

Cognitive outcomes

Concerning cognitive performance, statistically significant improvements were observed in Attention/Working Memory ($p=.037$) and Processing Speed ($p=.014$). On the contrary, no significant changes were noted in Verbal Memory ($p=.120$) nor in Executive Function ($p=.270$). Scores on PDQ-D-5 decreased substantially ($p<.001$),

leading to an improvement of the patients' appraisal of their own cognitive functioning.

Functional outcomes

Finally, changes in functional assessments were observed in FAST scale (p =.047), but not in SDS scale (p =.218). Specifically, 8 participants (40%) achieved minimal clinical improvement in the FAST total score.

The potential influence of clinical improvement on cognitive changes

Cognitive changes in Attention/Working Memory (F = 2.131, p =.162) and Processing Speed (F = 1.718, p =.207) did not vary between patients who achieve (n = 8) or did not achieve clinical remission (n = 12) after a 12-week treatment with desvenlafaxine. Similarly, the change in self-perception of cognitive difficulties (PDQ-D-5) did not differ based on clinical remission status (F = 2.872, p =.114).

Discussion

The present study provides robust scientific evidence supporting the use of desvenlafaxine as an effective antidepressant demonstrating significant clinical improvements not only in reducing depressive symptoms but also in alleviating anxiety after 12 weeks of treatment. Notably, the desvenlafaxine treatment also yields significant cognitive enhancements in attention/working memory and processing speed, independently of overall clinical improvement. Furthermore, these clinical and cognitive benefits are accompanied by an enhanced psychosocial functioning, highlighting desvenlafaxine's potential to facilitate a more comprehensive recovery from depressive episodes. Importantly, this study focuses on a population that had not responded to previous SSRI treatment, thereby addressing more challenging depressive and cognitive symptoms.

The 12-week desvenlafaxine treatment demonstrated significant clinical improvements, consistent with numerous prior trials that have established its efficacy in improving depressive and anxiety symptoms in depression, both in the short and long term [16, 39–41]. This study focused on patients with SSRI-resistant depression shows that depressive and anxiety symptoms were reduced to mild severity after only 12 weeks, with clinical assessments indicating that most patients were barely symptomatic. These findings add valuable insights into the potential of desvenlafaxine as a reliable therapeutic option in routine clinical practice.

The cognitive benefits observed in this study, particularly in attention/working memory and processing speed, are consistent with previous research [19, 20], further underscoring the desvenlafaxine's positive impact on cognitive recovery. Improvements in attention and processing speed are often the first cognitive benefits to emerge after starting antidepressant treatment [42–44]. While working memory tends to improve concurrently [44], its enhancement is generally less pronounced compared to the gains seen in attention and processing speed. Conversely, cognitive domains like verbal memory and executive function may exhibit greater resistance to treatment [43, 45, 46], persisting difficulties even during clinical remission phase or in periods of greater clinical stability [47]. To date, no studies have demonstrated significant improvements in learning and verbal memory attributable to desvenlafaxine use [13]. And even though one previous eight-weeks of open-label study reported some improvement in executive function improvement, specifically in cognitive flexibility [43], the present findings do not replicate this observation. Addressing these latest cognitive challenges may require prolonged use of antidepressants or additional targeted interventions such as cognitive remediation therapies [48, 49]. Therefore, while desvenlafaxine promises to benefit some specific cognitive functions, comprehensive treatment strategies need to be tailored to address the varied cognitive complexities experienced by MDD patients.

One potential rationale for these cognitive enhancements stems from the serotonergic and noradrenergic effects induced by the medication. Desvenlafaxine primarily ameliorates depressive symptoms by modulating serotonin and norepinephrine levels. However, in addition to its role in mood regulation, desvenlafaxine may exert cognitive benefits by promoting neuroplasticity in areas of the brain involved in cognition [50] such as the prefrontal cortex and hippocampus [51, 52]. These changes are thought to be mediated by the upregulation of brain-derived neurotrophic factor [53], which supports synaptogenesis and neurogenesis, thereby improving cognitive functions like such as attention, working memory and processing speed [13]. Furthermore, antidepressants like desvenlafaxine modulate functional connectivity within cognitive networks, particularly the central executive network and fronto-striatal pathways. Importantly, cognitive improvements have been observed to occur independently of mood improvements, suggesting that the mechanisms underlying cognitive recovery are distinct from those that drive mood remission [54]. This mechanistic of action supports using antidepressants with broad mechanisms to target both cognitive and affective symptoms in MDD for more comprehensive treatment outcomes.

Desvenlafaxine treatment not only improves objective cognitive function, but also improves self-perceived cognitive difficulties. A study from Lam and colleagues similarly found that patients treated with desvenlafaxine achieved a significant improvement in self-perceived cognitive functioning [20]. Indeed, it is well established

that the enhancement in the perception of cognitive difficulties may be mediated by the alleviation of affective symptoms. Specifically, desvenlafaxine through the reduction of anxious and depressive symptoms may indirectly enhance subjective cognitive function, because this alleviation reduces patients' distress and mitigates negative self-perceptions regarding cognitive performance.

In the present study, achieving clinical remission does not seem to be cognitively beneficial. There were no significant differences in either objective or subjective cognitive improvements between the group that achieved clinical remission, defined as a HDRS-17 score of 7 or less, and the group that did not reach this threshold at the follow-up assessment. This suggests that cognitive benefits from desvenlafaxine may occur independently of clinical remission. Interestingly, evidence from studies on other antidepressant treatments, such as duloxetine and vortioxetine, similarly indicates that the effects of antidepressants on cognitive functions are largely independent of their effects on mood symptoms [55, 56]. Furthermore, research in this field highlights that cognitive difficulties in depression are not mood-dependent as they often persist even during clinical remission [57, 58]. Therefore, the present results reinforce the notion that cognitive impairments represent a distinct symptom domain of depression that should be specifically targeted in treatment strategies [50, 59, 60].

Understanding the potential impact of desvenlafaxine on psychosocial functioning in depressed patients is also crucial [15, 20]. The current study demonstrates significant advancements in daily functioning, as assessed by the FAST scale after 12 weeks of treatment. This improvement denotes a shift from severe impairment to a markedly improved state, underscoring desvenlafaxine's potential for improving functional outcomes. Interestingly, while there was a substantial improvement in FAST scores, SDS scores did not show significant change, indicating that different aspects of psychosocial functioning may respond differently to treatment. This discrepancy can primarily be attributed to the differences in the content and structure of the scales, including the number of items and the scope of domains assessed. The FAST test is a comprehensive instrument with 24 items across six domains, whereas the SDS is a shorter, more general scale with only three items, making these scales not directly comparable. A recent study by Christensen and colleagues emphasizes that the FAST scale provides a more detailed assessment of patient functioning than SDS [38]. Some studies in other clinical populations have shown small to moderate correlations between corresponding subscales of the FAST and SDS, which helps contextualize the observed discrepancy in the current study [61]. Additional longitudinal studies exploring prolonged treatment effects and potential predictors of functional response are a must.

The main limitation of the present study is the relatively small sample size because a substantial part of the study coincided with the COVID-19 pandemic. The pandemic significantly impacted participant recruitment and adherence to study protocols, with restrictions on in-person visits, heightened health concerns, and logistical difficulties in conducting assessments under pandemic conditions. These factors severely limited the ability to recruit and retain participants. Additionally, a relocation of the principal investigator to a different hospital during the study further disrupted recruitment efforts and continuity in follow-up management. These unforeseen circumstances collectively contributed to a smaller-than-anticipated sample size, which affected the overall scale of the study and may have limited the study's statistical power. The small sample size may also constrain the generalizability of the results to other populations, such as those with different clinical characteristics or from other geographic areas. Furthermore, the short-term follow-up period limits the assessment of long-term cognitive outcomes and treatment duration. Future research should address these limitations by including larger samples with extended follow-up periods to evaluate the sustained effects of desvenlafaxine on cognitive function in MDD. Additionally, employing other study designs, such as randomized controlled trials (RCTs), could help better clarify the effects of desvenlafaxine on cognitive and functional domains.

Conclusions

The findings of this study provide valuable insights into the potential therapeutic advantages of desvenlafaxine, extending beyond clinical symptom relief to include its efficacy in mitigating specific cognitive impairments in individuals with depression who did not respond to previous SSRI treatment. Additionally, the desvenlafaxine treatment demonstrated a positive impact on enhancing psychosocial functioning in these patients. Further research is warranted to explore the underlying mechanisms responsible for the effects of desvenlafaxine, with the aim of fully delineating its therapeutic potential and refining treatment strategies for individuals suffering from MDD.

Abbreviations

MDD	Major Depressive Disorder
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
HDRS-17	17-item Hamilton Depression Rating Scale
HC	Healthy Controls
WAIS-IV	Wechsler Adult Intelligence Scale, fourth edition
CGI	Clinical Global Impression scale
RDQ	Remission from Depression Questionnaire
HARS	Hamilton Anxiety Rating Scale
RAVLT	Rey Auditory Verbal Learning Test

TMT-A	Trail Making test Part A
TMT-B	Trail Making test Part B
DSST	Digit Symbol Substitution Subtest
WCST	Wisconsin Card Sorting Test
PDQ-D-5	Perceived Deficit Questionnaire – Depression 5-item
FAST	Functioning Assessment Short Test
SDS	Sheehan Disability Scale
SPSS	Statistical Package for Social Sciences

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Author contributions
NC conceived the idea, designed the study and obtained the funding. SC and NC performed the selection of the patients. MVG, MSB and GN did the data collection. MVG, JT and NC carried out the statistical analysis. TS, CLM and MJP helped in the interpretation of the results. MVG wrote the original article draft. All authors contributed and have approved the final version of the manuscript.

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

Declarations

Ethics approval and consent to participate
This investigation received the official approval of the Research Ethics Committee at Corporació Sanitària Parc Taulí (Sabadell, Catalonia, Spain). Every participant voluntarily provided a written informed consent after a comprehensive explanation of the study's aims and procedures. The study also strictly complied with current data protection laws, adhering rigorously to the ethical guidelines outlined in the Declaration of Helsinki and following the principles of Good Clinical Practice.

Consent for publication
Not applicable.

Competing interests
Over the past five years, NC has received research grants and/or honorary fees as a consultant or speaker from various organizations, including Adamed, Angelini, Content Ed Net Communications, Elsevier, Esteve, Exeltis, Janssen, Lundbeck, Pfizer, Servier, Viatris, Fundació la Caixa, Carlos III Health Institute, ERA-NET Neuron, the Spanish Ministry of Science and Innovation (CIBERSAM), and Health Research and Innovation Strategic Plan (PERIS) 2016-2020, Marató TV3. The other authors declare no competing interests in the present study.

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