Is the Noradrenergic Symptom Cluster a Valid Construct in Adjunctive Treatment of Major Depressive Disorder?

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ABSTRACT

Objective: To identify symptoms potentially representative of a noradrenergic symptom cluster as possible predictors of response to the selective norepinephrine reuptake inhibitor (NRI) edivoxetine when used as monotherapy or adjunctive treatment in patients with *DSM-IV-TR* major depressive disorder (MDD).

Methods: Pooled data from 4 adjunctive treatment trials (selective serotonin reuptake inhibitor [SSRI] + edivoxetine 6–18 mg/d vs SSRI + placebo; N = 2,066) and data from 1 monotherapy trial (edivoxetine 6–18 mg/d versus placebo; N = 495) were used to identify predictors of response related to noradrenergic symptoms using a resampling-based ensemble tree method. The trials were conducted from 2008 to 2013.

Results: In the pooled adjunctive trials, no subgroup was identified that demonstrated a greater edivoxetine-placebo treatment difference than the overall patient cohort. In the edivoxetine monotherapy trial, no subgroup showing greater mean edivoxetine-placebo differences on the Montgomery-Asberg Depression Rating Scale versus the overall patient cohort was identified; a subgroup (67%) with high baseline Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) total score (≥ 28) showed statistically significantly ($P = .02$) greater mean edivoxetine-placebo differences on the Sheehan Disability Scale versus the overall patient cohort, and subgroups with baseline CPFQ total score ≥ 28 (65%), CPFQ cognition dimension score ≥ 16 (63%), or CPFQ physical dimension score ≥ 13 (59%) showed statistically significantly ($P \leq .025$) greater mean edivoxetine-placebo differences on the CPFQ total score versus the overall patient cohort.

Conclusions: While we could not identify symptoms predictive of response to the selective NRI edivoxetine used as adjunctive treatment, impaired cognition and physical symptoms may predict greater improvement during monotherapy.

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Recommended medications for major depressive disorder (MDD) target 1 or more monoamine neurotransmitters (eg, serotonin, norepinephrine, dopamine).[1–3] A relationship between some symptoms of MDD and individual neurotransmitter dysregulation may exist,[4] and certain symptoms of depression may respond less to serotonergic than to noradrenergic antidepressants.[3,5] Symptoms hypothesized to be part of the "noradrenergic symptom cluster" include decreased concentration, energy, and self-care as well as increased retardation, lassitude, and tiredness.[6,7] This symptom cluster suggests an interesting hypothesis: Does adding a selective norepinephrine reuptake inhibitor (NRI) improve residual symptoms of impaired cognition and fatigue and hence improve the overall depression outcome in patients with partial response to a selective serotonin reuptake inhibitor (SSRI)?

Edivoxetine hydrochloride (hereafter, edivoxetine) is a potent and highly selective NRI.[8] The efficacy of edivoxetine as adjunctive treatment for patients with MDD who were partial responders to an adequate course of treatment with an SSRI has been evaluated in one phase 2[9] and three phase 3 clinical studies.[10] No statistically significant differences between edivoxetine and placebo were observed for the primary endpoint (mean change from baseline to endpoint in Montgomery-Asberg Depression Rating Scale [MADRS] total score) in any of the phase 3 adjunctive treatment studies.[9,10] Edivoxetine monotherapy in MDD has been evaluated in 2 clinical studies, which produced mixed results. In the first study, efficacy of edivoxetine in improving depressive symptoms was not significantly different from placebo.[11] In the second study, edivoxetine significantly improved depressive symptoms more than placebo.[12]

The objective of this post hoc analysis with prespecified hypotheses was to identify subgroups among patients diagnosed with MDD presenting primarily with symptoms of the hypothesized noradrenergic symptom cluster and to determine if those subgroups show greater improvement compared with placebo after treatment with edivoxetine either as adjunctive treatment or as monotherapy compared with the full MDD sample. To address this objective, we used an MDD dataset in which partial responders to SSRIs received adjunctive treatment with edivoxetine[9,10] and a dataset in which patients with an acute episode of MDD[12] received edivoxetine monotherapy.

Table 1. Study Characteristics

Study	Authors, Year	Duration, wk	Study Design	Primary Outcome	Treatment (N)	Age, Mean, y	Female, %	Nonwhite, %	Baseline Score, Mean[a]		
									MADRS	CPFQ	SDS
LNDK	Ball et al, 2014[9]	8	Phase 2 double-blind, placebo-controlled	MADRS total score	SSRI + EDX 6–18 mg (111) SSRI + PLB (116)	45.0	69.6	37.6	EDX = 25.9 PLB = 25.9	EDX = 25.2 PLB = 25.1	EDX = 17.6 PLB = 19.0
LNBM	Ball et al, 2016[10]	8	Phase 3 double-blind, placebo-controlled	MADRS total score	SSRI + EDX 12 mg (231) SSRI + EDX 18 mg (230) SSRI + PLB (240)	45.1	64.1	28.8	EDX 12 mg = 24.7 EDX 18 mg = 25.6 PLB = 25.2	EDX 12 mg = 28.4 EDX 18 mg = 28.0 PLB = 28.6	EDX 12 mg = 18.1 EDX 18 mg = 18.1 PLB = 18.4
LNBQ	Ball et al, 2016[10]	8	Phase 3 double-blind, placebo-controlled	MADRS total score	SSRI + EDX 12–18 mg (232) SSRI + EDX 6 mg (226) SSRI + PLB (231)	47.0	66.5	19.9	EDX 12–18 mg = 24.9 EDX 6 mg = 25.3 PLB = 25.1	EDX 12–18 mg = 27.4 EDX 6 mg = 28.0 PLB = 27.4	EDX 12–18 mg = 17.2 EDX 6 mg = 18.9 PLB = 17.1
LNBR	Ball et al, 2016[10]	8	Phase 3 double-blind, placebo-controlled	MADRS total score	SSRI + EDX 12–18 mg (230) SSRI + PLB (219)	48.3	66.8	12.7	EDX = 25.2 PLB = 25.4	EDX = 28.1 PLB = 28.1	EDX = 18.5 PLB = 18.7
Pooled adjunctive treatments	NA	(See above)	(See above)	(See above)	EDX (1,260) PLB (806)	46.4	66.1	23.2[b]	EDX = 25.2 PLB = 25.3	EDX = 27.8 PLB = 27.6	EDX = 18.0 PLB = 17.8[c]
LNBI	Pangallo et al, 2011[12]	10	Phase 2/3 double-blind, placebo-controlled	MADRS total score	EDX 6–18 mg (250) PLB (245)	44.8	61.2	23.0	EDX = 29.2 PLB = 29.7	EDX = 28.7 PLB = 29.3	EDX = 18.8 PLB = 19.1

[a]Baseline values were collected before edivoxetine was added to ongoing SSRI treatment.
[b]N = 2,057.
[c]N = 805.
Abbreviations: CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, EDX = edivoxetine, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, PLB = placebo, SSRI = selective serotonin reuptake inhibitor, SDS = Sheehan Disability Scale.

Clinical Points

- A noradrenergic symptom cluster in patients with major depressive disorder (MDD) has been described, but its impact on treatment outcome is unclear. Here, subgroups within patients diagnosed with MDD presenting primarily with symptoms of the hypothesized noradrenergic symptom cluster were identified, and their responses to treatment with edivoxetine either as adjunctive treatment or monotherapy compared with the full MDD sample was assessed.
- Adjunctive treatment with edivoxetine during ongoing treatment with selective serotonin reuptake inhibitors does not result in greater treatment response in MDD patients with noradrenergic symptoms compared to the overall MDD patient population.
- Edivoxetine monotherapy resulted in greater improvement of cognitive and physical symptoms and overall functioning in MDD patients with pronounced impairments of those functions at treatment initiation compared to the overall MDD patient sample.

METHODS

Data from 4 adjunctive treatment trials (SSRI + edivoxetine 6–18 mg/d vs SSRI + placebo; N = 2,066) and 1 monotherapy trial comparing edivoxetine 6–18 mg/d and placebo (N = 495) in adult patients with MDD (*DSM-IV-TR* criteria) were used to identify predictive factors of response using variables thought to be related to noradrenergic symptoms associated with MDD. The trials were conducted from 2008 to 2013. Partial treatment response to SSRIs was defined by history using investigator opinion that the patient has experienced a minimally clinically meaningful improvement with the SSRI treatment and by ≤ 75% improvement on treatment with the current SSRI at screening based on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ).[13] Additionally, patients in all 4 adjunctive treatment studies had to have a GRID 17-Item Hamilton Depression Rating Scale (GRID-HDRS$_{17}$) total score of ≥ 16 at screening. Detailed information about the included studies is available in the primary disclosures.[9,10,12] Study protocols were reviewed and approved by the applicable organizational ethical review boards. Patients provided written informed consent before undergoing any study procedures, and the studies were conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice, and applicable laws and regulations.

Study Characteristics

Data were pooled from 4 adjunctive treatment trials[9,10] in which treatment with edivoxetine (6–18 mg/d) or placebo was added to ongoing treatment with SSRIs in adult patients with MDD who continued to present with at least moderate depressive symptoms after treatment optimization with SSRIs (Table 1). The studies were 8 weeks in duration between randomization and adjunctive treatment, utilized a placebo lead-in design of variable length, and used changes on the

MADRS total score as the primary outcome measure (Table 1). Patients had a mean age of 46.4 years, and their mean ages at onset of MDD symptoms ranged from 27 to 36 years. Patients in the adjunctive treatment trials had experienced a mean of 3 to 6 prior episodes of MDD, their current MDD episodes ranged in mean lengths from 38 and 87 weeks, and their mean baseline MADRS total score ranged from 25 to 30 (Supplementary eTable 1 at PSYCHIATRIST.COM). Patients enrolled in the adjunctive treatment trials had been taking an SSRI that had been approved for MDD at a dose within the labeling guidelines for the participating country. Patients had received SSRI treatment ≥ 6 weeks before initiation of adjunctive treatment with edivoxetine, with at least the last 2 weeks (study LNDK[9]) or 4 weeks (studies LNBM, LNBQ, and LNBR[10]) of SSRI treatment at a stable, optimized dose (which could not be adjusted during the trials; Supplementary eTable 2) as determined by the investigator.

Data from 1 edivoxetine monotherapy trial were available for analysis.[12] In this trial, adult patients with MDD received treatment with edivoxetine 6–18 mg/d versus placebo for 10 weeks (Table 1). Data from another placebo-controlled monotherapy trial examining the efficacy and safety of edivoxetine,[11] which was negative, could not be used for the current analyses because that study did not collect the needed assessments (MADRS, Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire [CPFQ],[14] and Fatigue Associated with Depression Questionnaire [FAsD]).[15]

Assessment Scales

The MADRS, CPFQ, Sheehan Disability Scale (SDS), Hospital Anxiety and Depression Scale (HADS), and FAsD were used as outcome measures and/or prespecified defined predictors in our analyses.

Consistent with the primary outcome assessment in the individual studies, baseline-to-endpoint change in MADRS total score was used as the primary global outcome measure. As a secondary global outcome measure, baseline-to-endpoint change in SDS total score was utilized. Dimensional outcome was assessed using baseline-to-endpoint change in CPFQ total score.

The MADRS[16] is a clinician-rated 10-item depression assessment scale, with each item rated on a scale of 0 (not present) to 6 (extremely bad). The MADRS total score is the sum of items 1 through 10, and the total score ranges from 0 to 60.[16]

The CPFQ[14] is a patient-rated scale assessing the patient's cognitive and physical symptoms over the previous month with 7 questions: (*a*) "How has your motivation/interest/enthusiasm been over the past month?" (*b*) "How has your wakefulness/alertness been over the past month?" (*c*) "How has your energy been over the past month?" (*d*) "How has your ability to focus/sustain attention been over the past month?" (*e*) "How has your ability to remember/recall information been over the past month?" (*f*) "How has your ability to find words been over the past month?" and (*g*) "How has your sharpness/mental acuity been over the past month?" The physical dimension subscale consists of questions *a*, *b*, and *c*, while the cognitive dimension subscale includes questions *d*, *e*, *f*, and *g*. Each question is rated on a 6-point scale (1 = greater than normal; 2 = normal; 6 = totally absent) and the total score ranges from 7 to 42.[14,17]

The SDS[18] is a patient-rated scale assessing functional impairment in 3 domains over the prior week: work/school, social life/leisure activities, and family life/home responsibilities. Patients rate their impairment in those 3 domains with a 10-point visual analog scale (0 = not at all; 10 = extremely) resulting in a total score ranging from 0 (unimpaired) to 30 (highly impaired).[18,19]

The HADS[20] is a patient-rated scale assessing both anxiety and depression with 2 independent subscales that include 14 items (7 items for each subscale) rated on a 4-point scale (0 to 3). Both the HADS anxiety and depression subscale scores range from 0 to 21, and higher scores indicate greater illness severity.[20]

The FAsD[15] is a patient-rated 13-item scale assessing fatigue in patients with MDD over the prior week. The FAsD experience subscale score is based on 6 items assessed with a 5-point Likert scale, with responses ranging from "never" to "always," and the impact subscale score is based on 7 items (5 items are rated on a 5-point Likert scale, with responses ranging from "not at all" to "very much," and 2 items require yes/no responses).[15]

Several patient baseline characteristics and disease severity measures were prespecified as potential predictors before subgroup identification analysis based on their potential associations with noradrenergic symptoms (Table 2).

Statistical Analyses

Included in the analyses were all randomized patients with baseline and at least 1 postbaseline assessment on the outcome variable, as well as baseline predictor variables available. For each outcome variable (MADRS total score, SDS total score, and CPFQ total score), a detection tool using a resampling-based ensemble tree method[22,23] was applied to search and identify patient subgroups with larger drug-placebo treatment effects compared with the overall population based on the specified predictor variables in Table 2. In this process, 400 subsamples, each having the size of 50% of the full sample, were randomly generated via sampling without replacement. Within each subsample, a recursive partitioning[24,25] algorithm was first applied to the drug-treated arm to produce an up-to 2-level decision tree, which used binary split(s) based on predictor variables to classify subjects into subgroups with differential treatment responses. The minimum subgroup size allowed was 50 patients. The subgroup showing better treatment outcome on drug treatment was extracted and compared to the outcome from the corresponding subgroup in the placebo arm. The subgroup was detected as a preliminary candidate if the observed drug-placebo relative treatment effect was significant and larger than the relative treatment effect in the overall subsample. For each detected preliminary subgroup

Table 2. Baseline Predictors Prespecified Based on Potential Association With Noradrenergic Symptoms

Scale	Item/Subscale	Cutoff Value
MADRS	Lassitude	≥ 4 and continuous
	Concentration difficulties	≥ 4 and continuous
HADS	"I still enjoy the things I used to enjoy"	Continuous
	"I feel as if I am slowed down"	Continuous
CPFQ total[17]	NA	> 25
CPFQ	Physical dimension (motivation/interest/enthusiasm, energy, wakefulness/alertness)	Continuous
CPFQ	Cognitive dimension (ability to focus/sustain attention, ability to remember/recall information, ability to find words, sharpness/mental acuity)	Continuous
FAsD	Average	Continuous
	Impact	Continuous
	Experience	Continuous
Hypotension	NA	Defined by the WHO as systolic blood pressure < 110 mm Hg in male patients and < 100 mm Hg in female patients at any baseline visit, independent of diastolic blood pressure[21]

Abbreviations: CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, HADS = Hospital Anxiety and Depression Scale, FAsD = Fatigue Associated with Depression Questionnaire, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, WHO = World Health Organization.

Table 3. Adjunctive Treatment Trials Predictor Analysis

Subgroup	Suggested Cutoff	Estimated Subgroup Size[a]	Mean Score Difference Between EDX and PLB: Subgroup	Mean Score Difference Between EDX and PLB: Overall Cohort	Adjusted *P* Value[b]
Outcome measure: MADRS total score change from baseline to endpoint				−0.66	
Low FAsD average score	< 4.1	83%	−0.79		.45
High MADRS lassitude score	≥ 3	62%	−0.66		.55
Low CPFQ cognition dimension score	< 20	87%	−0.94		.76
High MADRS lassitude and low FAsD average score	Lassitude ≥ 3 FAsD average < 4.1	49%	−0.91		.80
Outcome measure: SDS total score change from baseline to endpoint				−0.95	
High HADS item 2 (enjoy things)	≥ 2	56%	−1.33		.10
High HADS item 2 and high FAsD impact	HADS ≥ 2 FAsD > 2.5	48%	−1.18		.94

[a]Percentage of the total population.
[b]*P* values compare treatment effect in subgroup with treatment effect in overall cohort.
Abbreviations: CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, EDX = edivoxetine, FAsD = Fatigue Associated with Depression Questionnaire, HADS = Hospital Anxiety and Depression Scale, MADRS = Montgomery-Asberg Depression Rating Scale, PLB = placebo, SDS = Sheehan Disability Scale.

in a subsample, the drug-placebo difference of this subgroup in the complement subsample (remaining 50% subjects not used in preliminary detection) was also obtained to confirm the direction of treatment effect. The above detection process was repeated for all 400 random subsamples, and the most frequently detected and confirmed subgroups became top candidates. Similar subgroups were aggregated over different subsamples, and the averaged drug-placebo differences in complement subsamples provided a bias-adjusted estimate of relative treatment effect. Finally, a permutation test was also conducted to assess the statistical significance of the treatment effect in the detected subgroups against the treatment effect in the overall sample, and the reported *P* values were adjusted for multiple comparisons.

To assess the interdependence of the assessment scales used as outcome measures and predictors, Pearson correlation coefficients of baseline scores were examined and an analysis of covariance (ANCOVA) was conducted on the MADRS total score changes with baseline MADRS score, treatment, baseline CPFQ score group, and treatment-by-CPFQ group interaction terms in the model.

RESULTS

Adjunctive Treatment Trials

Using baseline-to-endpoint MADRS total score, SDS total score, or CPFQ total score changes, none of the tested predictors identified a subgroup with a significantly greater and clinically meaningful response to edivoxetine versus placebo compared with the overall study cohort (Table 3).

Monotherapy Trial

Testing of the prespecified predictors in the monotherapy trial dataset revealed subgroups defined by baseline CPFQ scores (Table 4). The difference between edivoxetine and placebo in MADRS total score change was greater in the

Table 4. Monotherapy Trial Predictor Analysis

Subgroup	Suggested Cutoff	Estimated Subgroup Size[a]	Mean Score Difference Between EDX and PLB		Adjusted *P* Value[b]
			Subgroup	Overall Cohort	
Outcome measure: MADRS total score change from baseline to endpoint				−2.47	
High CPFQ total score	≥ 28	63%	−3.32		.42
High CPFQ cognition subscale score	≥ 16	62%	−4.13		.36
Outcome measure: SDS total score change from baseline to endpoint				−1.73	
High CPFQ total score	≥ 28	67%	−2.53		.02
High CPFQ cognition subscale score	≥ 16	64%	−2.65		.28
Outcome measure: CPFQ total score change from baseline to endpoint				−1.14	
High CPFQ total score	≥ 28	65%	−2.21		.005
High CPFQ cognition subscale score	≥ 16	63%	−2.56		.005
High CPFQ total score group (> 25)	Prespecified	76%	−1.99		.005
High CPFQ physical subscale score	≥ 13	59%	−2.20		.025

[a]Percentage of the total population.
[b]*P* values compare treatment effect in subgroup with treatment effect in overall cohort.
Abbreviations: CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, EDX = edivoxetine, MADRS = Montgomery-Asberg Depression Rating Scale, PLB = placebo, SDS = Sheehan Disability Scale.

Table 5. Correlation Between MADRS Total and CPFQ Total Baseline Scores in Monotherapy Trial[a]

Variable	CPFQ Total Score	CPFQ Cognition Subscale Score	CPFQ Physical Subscale Score
MADRS total score	0.34 (< .0001)	0.29 (< .0001)	0.34 (< .0001)

[a]Values shown as Pearson Correlation Coefficient (*P* value).
Abbreviations: CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, MADRS = Montgomery-Asberg Depression Rating Scale.

identified subgroups with higher baseline severity as indicated by CPFQ scores versus the overall study cohort, but did not reach statistical significance. Treatment differences in SDS total score and CPFQ total score changes as outcome measures were statistically significantly greater in the identified CPFQ subgroups (Table 4).

Relationship of Baseline MADRS Total and Baseline CPFQ Scores in Monotherapy Trial

To assess the interdependence of the assessment scales used as outcome measures and predictors, Pearson correlation coefficients of baseline scores were examined (Table 5). Correlations between baseline MADRS total score and CPFQ total or subscale scores were weak, with coefficients ranging from 0.29 to 0.34. Hence, the patient group with higher severity in cognitive and physical impairment as assessed with CPFQ is semi-independent of the patient group with higher depression severity as assessed with the MADRS at baseline. Further, an ANCOVA was conducted on the MADRS total score changes with baseline MADRS score, treatment, baseline CPFQ score group, and treatment-by–CPFQ group interaction terms in the model. The treatment-by–CPFQ group interaction was statistically significant ($P = .002$ for CPFQ cognitive score; $P = .024$ for CPFQ total score) after adjusting for baseline MADRS score as covariate, with larger edivoxetine advantage over placebo observed in patients with higher CPFQ severity at baseline.

DISCUSSION

On the basis of differences in the mechanisms of action between SSRIs and NRIs, it should theoretically be possible to identify a MDD patient subgroup with noradrenergic symptoms receiving additional benefits from adding an NRI to its existing SSRI treatment. However, this was not the case in the current post hoc analyses—no prespecified patient subgroup within the noradrenergic symptom cluster was identified for which adjunctive treatment with edivoxetine resulted in greater improvement on the assessed outcome measures versus placebo compared with the overall patient cohort. In the overall pooled sample, edivoxetine and placebo did not significantly differ on the primary outcome measure (MADRS total score).[9,10] The 4 included studies were comparable. Additionally, the total sample size in the pooled analyses should be sufficient to identify a subgroup with noradrenergic symptoms should such a subgroup exist.

However, a patient subgroup with hypothesized noradrenergic-responsive symptoms was identified in a monotherapy trial. This subgroup had higher baseline CPFQ total and cognitive dimension scores. Symptom improvement, as reflected by SDS total score and CPFQ total score changes, during treatment with edivoxetine versus placebo was statistically significantly greater than improvement in the overall patient cohort. Between-treatment differences in MADRS total score changes were also greater in the patient subgroup with higher baseline CPFQ score, but did not reach statistical significance. However, when baseline MADRS severity was accounted for in the ANCOVA, drug-placebo treatment differences on the MADRS were significantly greater in the high CPFQ group than in overall sample. These findings regarding the effect of baseline CPFQ severity on treatment difference in depression outcome appeared to be independent of baseline MADRS total score symptom severity, as indicated by low correlations between MADRS total scores and CPFQ total and domain scores at baseline

and in the ANCOVA, an analysis of CPFQ severity effect on MADRS mean change adjusting for baseline MADRS score as covariate. Similar findings were reported for vortioxetine (10 and 20 mg/d) in a post hoc analysis of data from a placebo-controlled monotherapy trial.[17] In patients with MDD with a baseline CPFQ score >25, treatment with vortioxetine statistically significantly ($P < .05$) improved endpoint cognitive symptoms (CPFQ cognitive dimension score). Although vortioxetine also improved overall depressive symptoms in this subpopulation, path analysis demonstrated that the improvement in cognitive symptoms was a direct effect and not solely due to improvement of depressive symptoms.[17] Cognitive symptoms might be a better predictor of noradrenergic response than other symptoms thought to be norepinephrine-related.

The extent of overlap between primarily serotonergic and primarily noradrenergic symptoms is unknown, and this hypothesis has not been fully tested a priori. Studies comparing selective noradrenergic agents with selective serotonergic agents have not shown clear differences among the symptoms that are treated by either compound class.[26] The observed differences between findings with monotherapy or adjunctive therapy may be explained by the crosstalk between norepinephrine and serotonin systems and its implications for antidepressant response. For example, Blier[27] has suggested that SSRIs do affect the norepinephrine system via the inhibitory projections of serotonin neurons on norepinephrine neurons. Therefore, patients who are already on a stable dose of an SSRI before receiving adjunctive treatment with an NRI might not have as much potential for improvement during treatment with the NRI compared with patients who receive NRI monotherapy. In addition, enough overlap in SSRI and NRI mechanisms of action may exist that not enough difference remains to improve symptoms in this adjunctive treatment paradigm. Both SSRIs[28] and NRIs[29] decrease noradrenergic neuron firing, suggesting that both substance classes may have common effects on pathways involved in MDD pathophysiology. These findings suggest that the addition of norepinephrine to a system previously desensitized with ongoing serotonergic reuptake inhibition may not have the same effect on depressive symptoms compared with parallel activation of serotonergic and noradrenergic pathways.[30–32] This previous desensitization might be part of the reason why adjunctive treatment trials with edivoxetine also did not show statistically significant separation from placebo in the overall patient samples, while NRIs were effective in some monotherapy trials (eg, edivoxetine[12] and reboxetine[33,34]).

Greater improvements in SDS total scores in the identified CPFQ subgroups compared with the overall patient cohort might indicate better social functioning of this group after treatment with an NRI. These observations are consistent with findings by Dubini and colleagues,[35] who reported a significant effect of reboxetine on social functioning in patients with MDD.

Our results suggest a need for more specific scales to assess specific symptom dimensions in patients with MDD. While the MADRS and the HDRS provide reliable assessments of patients' overall depression severity, specialized scales like the CPFQ provide greater sensitivity when examining cognition and physical symptoms in patients with MDD.

The interpretation of our results is limited by the post hoc design of the analyses, the pooled dataset, and variability in edivoxetine doses among individuals. However, the individual pooled studies used very similar study designs and included comparable patient populations, and our hypotheses were prespecified. Additionally, for edivoxetine monotherapy, only data from a trial with positive results could be included in the current analyses. Prospective studies are warranted to further explore targeted treatment of patients with MDD who primarily present with symptoms representative of a noradrenergic symptom cluster. Finally, we used the resampling-based ensemble tree method because it can search for subgroups with larger treatment contrasts and provide bias-adjusted estimates as well as multiplicity adjustment. Other statistical methods, such as utilizing cluster analysis techniques, can also be adopted for subgroup identification—additional studies are warranted testing and comparing the results of other appropriate analysis approaches. One asset of the current analyses is the large sample size for the pooled adjunctive treatment dataset. The presented findings are informative for the development of compounds influencing noradrenergic signaling pathways.

CONCLUSIONS

We could not identify a subgroup of patients with MDD who had hypothesized noradrenergic symptoms more responsive to adjunctive treatment with the selective NRI edivoxetine while receiving ongoing treatment with an SSRI compared with the full patient sample. However, patients with greater cognitive impairment and physical symptoms showed greater improvements of cognitive and physical symptoms and overall functioning during edivoxetine monotherapy as compared to placebo.

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Supplementary Material

Article Title: Is the Noradrenergic Symptom Cluster a Valid Construct in Adjunctive Treatment of Major Depressive Disorder?

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List of Supplementary Material for the article

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Supplementary Material

Supplementary eTable 1. Patient's Psychiatric History

Study	Tx	Age at MDD Onset, years, mean (SD)	Number of Previous MDD Episodes, mean (SD)	Duration of Current MDD Episode, weeks, mean (SD)
LNDK	EDX (N=111)	32 (13)	6 (9)	41 (40)
	PLB (N=116)	27 (13)	6 (7)	38 (50)
LNBM	EDX 12 mg (N=231)	36 (13)	3 (4)	47 (60)
	EDX 18 mg (N=230)	35 (13)	3 (4)	49 (74)
	PLB (N=240)	33 (12)	3 (7)	48 (64)
LNBQ	EDX 12-18 mg (N=232)	36 (14)	3 (7)	61 (146)
	EDX 6 mg (N=226)	35 (14)	3 (5)	58 (118)
	PLB (N=231)	35 (14)	3 (6)	54 (119)
LNBR	EDX (N=228)	34 (14)	5 (9)	72 (118)
	PLB (N=219)	34 (14)	6 (11)	87 (161)

Abbreviations: EDX = edivoxetine; MDD = major depressive disorder; N = number of patients; PLB = placebo; SD = standard deviation; Tx = treatment.

Supplementary eTable 2. SSRI Treatments

Study	Tx[a]	Sertraline		Paroxetine		Escitalopram		Fluoxetine		Citalopram		Fluvoxamine	
		n (%)	mean dose (SD)	n (%)	mean dose (SD)	n (%)	mean dose (SD)	n (%)	mean dose (SD)	n (%)	mean dose (SD)	n (%)	mean dose (SD)
LNDK	EDX	30 (27)	108 (40)	12 (11)	28 (13)	24 (22)	16 (6)	19 (17)	34 (13)	26 (23)	25 (9)	0	-
	PLB	21 (18)	100 (42)	18 (16)	28 (12)	21 (18)	18 (7)	23 (20)	32 (15)	32 (28)	31 (11)	1 (0.9)	200
LNBM	EDX 12 mg	70 (30)	106 (50)	34 (15)	29 (10)	40 (17)	13 (5)	39 (17)	39 (16)	39 (17)	26 (10)	9 (4)	103 (40)
	EDX 18 mg	66 (29)	93 (49)	41 (18)	29 (9)	40 (17)	15 (5)	40 (17)	35 (10)	31 (13)	27 (12)	12 (5)	108 (34)
	PLB	72 (30)	90 (47)	37 (15)	28 (9)	52 (22)	15 (5)	34 (14)	35 (17)	37 (15)	26 (13)	8 (3)	78 (36)
LNBQ	EDX 12-18 mg	61 (26)	95 (45)	18 (8)	27 (11)	59 (25)	14 (5)	28 (12)	32 (13)	58 (25)	26 (10)	8 (3)	122 (41)
	EDX 6 mg	73 (32)	97 (41)	18 (8)	29 (12)	63 (28)	13 (4)	21 (9)	36 (16)	43 (19)	27 (10)	8 (4)	81 (37)
	PLB	75 (32)	97 (47)	23 (10)	26 (9)	54 (23)	14 (4)	29 (13)	30 (17)	41 (18)	25 (10)	9 (4)	111 (33)
LNBR	EDX	60 (26)	98 (41)	17 (7)	23 (6)	36 (16)	16 (5)	45 (20)	30 (12)	71 (31)	25 (9)	1 (0.4)	300
	PLB	37 (17)	109 (48)	12 (5)	28 (10)	32 (15)	17 (7)	48 (22)	27 (10)	90 (41)	27 (11)	0	-

Abbreviations: EDX = edivoxetine; n = number of patients; PLB = placebo; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor; Tx = treatment.

[a]all treatment doses are presented in mg