Exploratory Analysis of the Effects of Celecoxib on Cognitive Function in Vortioxetine-Treated Patients With Major Depressive Disorder in the PREDDICT Study:

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Abstract

Objective: Major depressive disorder (MDD) remains difficult to treat, with many patients resistant to existing treatments or experiencing relapse. Cognitive dysfunction is associated with more severe clinical outcomes. Vortioxetine has shown efficacy in remediating depression-associated cognitive impairment. Anti-inflammatory augmentation of antidepressants is a new strategy in treating depression and has not previously been assessed for effects on cognition in depression.

Methods: Exploratory analyses were performed on secondary outcome cognitive data from the PREDDICT parallel-group, randomized, double-blind, placebo-controlled trial at the University of Adelaide (Australia). Participants (N = 119) with MDD (validated with Mini-International Neuropsychiatric Interview for *DSM-IV*) were treated with vortioxetine and celecoxib or vortioxetine and placebo for 6 weeks between December 2017 and April 2020. Measures included objective cognition composite scores (Choice Reaction Time, N-Back, Digit Symbol Substitution Test, Trail Making Task Part B), subjective cognition scores (Perceived Deficits Questionnaire), and global cognition composite scores (combined objective and subjective scores) derived from the THINC integrated tool (THINC-it). High-sensitivity C-reactive protein (hsCRP) measured at baseline and week 6 was tested for a predictive relationship with cognitive outcomes.

Results: Cognition composite scores demonstrated improvement by week 6 in both treatment groups. However, there was no significant interaction between change over time and treatment group. HsCRP did not have a significant relationship with any tested cognition measures.

Conclusions: Both treatment groups showed a reduction in depression-associated cognitive impairment. No superior clinical effect was reported for the add-on celecoxib group. HsCRP was modulated by neither vortioxetine nor add-on celecoxib.

Trial Registration: ANZCTR identifier: ACTRN12617000527369

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Depressive disorders cause significant personal and societal burden of disease, affecting 322 million people globally per year, and are the single largest contributor to non-fatal health loss.[1] Major depressive disorder (MDD) is characterized by impaired affect, cognitive dysfunction, and significant psychosocial impairment that persists from weeks to years.[2] Disruption to cognitive abilities may impair an individual's ability to maintain autonomy, relationships, employment, and other aspects of independent psychosocial functioning.[3–5] Multiple cognitive domains may be impacted,[6,7] and cognitive dysfunction can persist following symptomatic remission.[8] Residual cognitive deficits may contribute to ongoing occupational and social dysfunction and promote suicidal ideation.[9] Moreover, patients with MDD-associated cognitive dysfunction are more likely to experience a more severe course of illness, including greater likelihood of experiencing suicidal ideation.[10,11]

Clinical Points

- Persistent or severe major depressive disorder (MDD)-associated cognitive impairments are common in MDD patients with chronic low-grade inflammation.
- Anti-inflammatory treatment of MDD is a novel strategy, and this is the largest known trial to augment an antidepressant with an anti-inflammatory or placebo.
- The present randomized controlled trial does not support the use of anti-inflammatory augmentation to remediate cognitive symptoms of MDD.

Cognitive impairment may be a risk factor for or predictive marker of MDD development, or a consequence of the disorder, highlighting the need for MDD treatments that prioritize restoration of cognitive function.[12]

MDD may be difficult to treat, with only approximately one-third of patients responding to the first antidepressant medication trialled and one-third of patients failing to respond to multiple trials of medication,[13] likely due to the clinical and biological heterogeneity of MDD. One potential subtype of MDD is characterized by chronic low-grade inflammation.[14] Patients with this MDD feature may experience more frequent or severe cognitive impairment as well as a more severe overall presentation of MDD.[15] Furthermore, administration of a proinflammatory agent has previously been demonstrated to induce symptoms of MDD and cognitive impairment, introducing that, conversely, reducing inflammation may attenuate symptoms of MDD and cognitive impairment.[16,17] Various strategies involving anti-inflammatory treatment have been investigated to remediate MDD, either alone or in addition to conventional antidepressants. A meta-analysis[18] found celecoxib superior to placebo in treatment of depression or depressive symptoms across 10 studies, and celecoxib specifically used as add-on treatment rather than monotherapy showed a large effect size across 4 studies.[19–22]

Strategies for treating the cognitive aspects of MDD are wide-ranging,[15] including antidepressants such as vortioxetine that have demonstrated efficacy for the treatment of cognitive dysfunction in MDD in randomized controlled trials (RCTs).[23] However, treating MDD-associated cognitive impairment with anti-inflammatory medication is a newer concept and remains unexplored in clinical trials.[15,24]

In the PREDDICT study, we hypothesized that augmenting vortioxetine with celecoxib would lead to a greater reduction in MDD-associated morbidity relative to vortioxetine augmented with placebo, particularly when participants showed evidence of belonging to an inflammation-associated MDD subtype. This subtype was established according to peripheral high-sensitivity C-reactive protein concentration (hsCRP) measured prior to commencement of medication.[25] As recently published, the trial found that there was no significant difference in the primary outcome of overall symptom severity rated using the Montgomery-Asberg Depression Rating Scale (MADRS) between the two treatment groups (vortioxetine plus celecoxib vs vortioxetine plus placebo), suggesting that there was no benefit of add-on celecoxib.[26] Given the overall statistically significant clinical improvement in the entire cohort treated with vortioxetine, it is worthwhile to explore the secondary study outcomes related to cognitive function in more detail. The aims of these analyses were

1. To investigate the efficacy of augmenting vortioxetine with celecoxib for treating MDD-associated cognitive dysfunction in the PREDDICT trial;
2. To investigate the change in cognition in the PREDDICT trial in treatment groups of vortioxetine augmented with celecoxib and vortioxetine augmented with placebo; and
3. To determine if baseline hsCRP and change in hsCRP concentration over time can be used to predict cognitive functioning in the PREDDICT trial.

METHODS

Study Design

Data were collected as part of the PREDDICT RCT, which has been described previously, including the full inclusion and exclusion criteria.[25] The study was a randomized, parallel, double-blind RCT with a superiority framework with a primary outcome measure of change in MADRS, conducted at the University of Adelaide, Australia, between December 2017 and April 2020. Results of the primary study outcome have been reported previously.[26] The study was approved by the Human Research Ethics Committees of the Royal Adelaide Hospital and the University of Adelaide (reference number R20170320 HREC/17/RAH/111) and registered on the Australian New Zealand Clinical Trials Registry (ACTRN12617000527369).

Participants with MDD validated with the Mini-International Neuropsychiatric Interview (version 5, for *DSM-IV*)[27] who gave written informed consent were randomized by the Clinical Trials Unit at Royal Adelaide Hospital Pharmacy, using a randomization table, to receive either 400 mg of celecoxib or placebo daily for 6 weeks, in addition to vortioxetine at a dose of 5 mg, 10 mg, or 20 mg, depending on participant tolerability, response, and group assignment.[28] Assessments were completed every 2 weeks for the duration of the 6-week RCT.

HsCRP concentration was measured in serum isolated from peripheral blood samples collected at baseline, week 6, and week 35 or final study visit in the case of early withdrawal. Determination of hsCRP

Table 1.
Components of Cognitive Composite Measures Derived From THINC-it Cognitive Battery

Composite measure[a]	Scale name	Purpose of scale	Task description and details	Score range and interpretation
Subjective cognition composite	THINC-it Perceived Deficits Questionnaire for Depression–5-item	Participant's own recollection of cognitive difficulties in the past 7 days	Participants asked to rate the frequency of experiencing difficulty related to organization, concentration, recall, or conscious awareness	0–20, where the higher the number, the greater the perceived cognitive deficit
Objective cognition composite	THINC-it Spotter (equivalent to choice reaction time[30])	Test of attention and response speed	Participants must receive and classify a stimulus by selecting the pre-specified corresponding response	Accuracy assessed by number of correct answers (range: 0–40)
				Speed assessed by mean response time in milliseconds across the 40 prompts
	THINC-it Symbol Check (equivalent to N-back [1-back][31])	Test of working memory and attention	Symbols are visible and then individually covered sequentially, with the participant having to correctly recall and input the matching response	Accuracy assessed by number of correct answers (range: 0–40)
				Speed assessed by mean response time in milliseconds across the 40 prompts
	THINC-it Codebreaker (equivalent to digit symbol substitution test[32])	Test of attention, perceptual speed, motor speed, visual scanning, and memory	Using a key relating numbers to particular symbols, participants must decode as many symbols as possible in the allocated time	Accuracy assessed by number of correct answers in 2-minute test window
				Speed assessed by mean response time in milliseconds across all prompts delivered in 2-minute test window
	THINC-it Trails (equivalent to trail making test part B[33])	Test of visual search speed, scanning, speed of processing, mental flexibility, and executive functioning	Participant draws a continuous line between circles labeled with letters and numbers and must correctly alternate between the alphabetical and numerical scales in ascending order	Accuracy assessed by number of errors made (range: 0–18)
				Speed assessed by total response time in seconds to complete the task

[a]A global cognition composite was formed using all of the scales listed.
Abbreviation: THINC-it = THINC integrated tool.

concentration used immunonephelometry on the BN II System (Siemens Healthcare GmbH, Erlangen, Germany) using the reagent N CardioPhase hsCRP (#OQIY13/10446090, Siemens Healthcare GmbH, Erlangen, Germany) at the central laboratory of the University Hospital Münster, Münster, Germany.

Outcomes

The THINC integrated tool (THINC-it) is a self-administered battery of cognitive assessments completed under the supervision of a blinded trial staff member. It includes 4 objective cognitive measures and 1 self-assessed subjective judgment of cognitive abilities in the last 7 days.[29] Further details are given in Table 1. All listed outcome measures were completed by each participant at baseline, week 2, and week 6 study visits.

The THINC-it measures were used to form composite measures of cognition; specifically, the single measure of the Perceived Deficits Questionnaire for Depression–5-item (PDQ-5-D) reports exclusively on subjective cognition, the 4 objective assessments (with accuracy and response time components measured for each) were used to form an objective cognition composite, and a global cognition composite was formed using all of the aforementioned components. The composites were formed by first reversing the scores of 3 measures (choice reaction time [CRT], N-back, and digit symbol substitution test [DSST] number correct) so that all components had the same directionality, where a lower score is associated with better cognitive performance. Then, each component of the composite was scaled using the min-max normalization method, calculated according to the formula *(observed – minimum)/(maximum – minimum)*, where minimum and maximum are the lowest and highest values respectively recorded for a variable, regardless of participants' treatment group or the time point of the observation,[34,35] using the R package tidyLPA.[36] Averages of min-max–normalized components were used for final analysis, giving each composite a minimum value of 0 and a maximum value of 1, with a lower score indicating better cognitive performance. When only subjective cognition was reported, no data transformation was made.

Statistical Tests

Data from the baseline to week 6 assessments were included to evaluate the efficacy of the treatment over the RCT period. Four participants from the intention-to-treat population did not complete the THINC-it battery at any time point due to technical difficulties.

Table 2.

Baseline Characteristics of the Study Population With Data Available for Analysis[a]

Characteristic	All	Vortioxetine + placebo	Vortioxetine + celecoxib	Group difference, F_{df} or OR (95% CI)	*P*
Total participants, PREDDICT	N = 119	n = 60	n = 59		
Total participants included in present analyses	N = 115	n = 59	n = 56		
Age, y, median (IQR)	47 (32, 57)	47 (30, 57)	46 (33.75, 57)	$0.003_{1,113}$	.957
Sex, n (%)					
Male	48 (42)	23 (39)	25 (45)	0.794 (0.353 to 1.777)	.574
Female	67 (58)	36 (61)	31 (55)		
hsCRP, mg/L, median (IQR)	1.5 (0.6, 5.1)	1.2 (0.6, 4.5)	1.7 (0.675, 6.2)	$0.107_{1,113}$	.744
Body mass index, median (IQR)	28.88 (24.84, 33.62)	28.81 (24.64, 34.73)	29.42 (24.89, 33.23)	$0.002_{1,113}$	.961
Education, y, median (IQR)	14 (12.5, 16)	14 (12.75, 16.75)	14 (12.38, 16)	$0.003_{1,113}$	.953
National Adult Reading Test					
Number correct, median (IQR)	34 (29, 38)	33 (28.5, 37.5)	36 (29, 38)	$0.030_{1,113}$	.862
Projected full-scale IQ, median (IQR)	110.8 (104.6, 115.7)	109.5 (103.9, 115.1)	113.2 (104.6, 115.7)	$0.030_{1,113}$	.862
Treatment resistant depression, yes, n (%)	88 (77)	45 (76)	43 (77)	1.029 (0.397 to 2.681)	1.000
Smoking history, yes, n (%)	57 (50)	33 (56)	24 (43)	0.594 (0.264 to 1.317)	.193
Alcohol consumption, standard drinks/wk, median (IQR)	2 (0, 6.5)	2 (0, 6)	1.75 (0, 7.75)	$0.227_{1,113}$	.634
Global cognition composite, median (IQR)	0.31 (0.24, 0.38)	0.30 (0.23, 0.37)	0.31 (0.27, 0.37)	$0.359_{1,113}$	.550
Objective cognition composite, median (IQR)	0.28 (0.20, 0.36)	0.27 (0.19, 0.38)	0.29 (0.24, 0.35)	$0.067_{1,113}$	.797
Subjective cognition score (PDQ-5-D), mean (SD)	11.31 (4.36)	10.66 (4.22)	12.00 (4.44)	$2.754_{1,113}$	.100
MADRS score, median (IQR)					
Baseline	27 (22.5, 32.5)	26 (21, 30)	28 (24, 34.25)	$5.244_{1,113}$	.024
Week 6	19 (11, 27.8)	19 (11, 25)	19 (10.5, 29)	$0.709_{1,96}$	.402

[a]Adapted from Baune et al 2021[26]; modified to include participant summaries for those with cognitive data available at baseline. Data are expressed in n (%), mean (SD) for normally distributed data, and median (IQR) for data non-normally distributed in at least 1 measured group at baseline. Group differences calculated with linear models for continuous variables and Fisher exact tests for binomial variables. Treatment resistant depression recorded if participant had 2 or more failed trials of MDD treatment that were of adequate dosage and duration.

Abbreviations: CI = confidence interval, hsCRP = high sensitivity C-reactive protein, IQR = interquartile range, MADRS = Montgomery-Asberg Depression Rating Scale, OR = odds ratio, PDQ-5-D = Perceived Deficits Questionnaire for Depression–5-item, SD = standard deviation.

Data for 1 participant were excluded from the analysis of 2 outcomes (Trail Making Task number of errors and Trail Making Task total response time) only, due to incorrectly completing THINC-it Trails at all time points. All other relevant available data were included.

As the presented analyses are secondary outcome measures of the PREDDICT RCT, they are considered exploratory only. Post hoc statistical power is not reported.[37] All analyses were run in R (version 4.2.1, R Foundation for Statistical Computing). Missing data due to early withdrawal were balanced between treatment groups and considered "missing at random" and therefore appropriate for analysis with linear mixed effects models, which allow for retention of available observations in the analysis despite other observations' absence, with no multiple imputation required.[38] The effects of treatment group, time, and interaction of treatment group allocation with time on each outcome measure were assessed using linear mixed effects models for repeated measures (MMRM) with random intercept using the package lmerTest, which extends the lme4 package.[39,40] In adjusted models, age, sex, education, log of baseline hsCRP, and change in log of hsCRP from baseline to week 6 were included as covariates where specified. Alternatively, standard linear regressions have been included where specified. Standard mean differences (SMD) were calculated to represent the magnitude of change between observations. Education was rated based upon the Australian Qualifications Framework to determine relative years spent in formal education.[41]

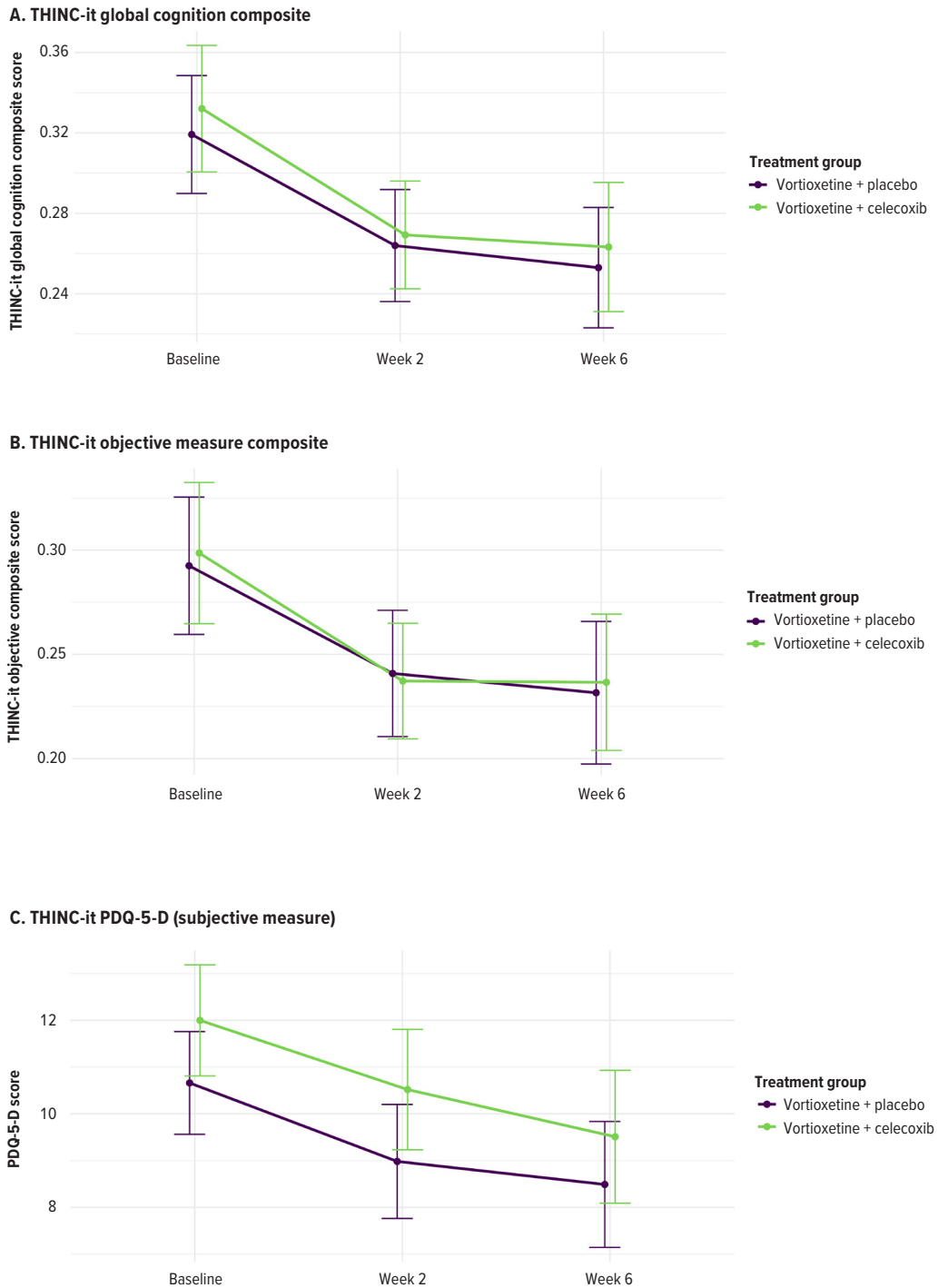
RESULTS

Descriptive statistics for sociodemographic characteristics of participants and summaries for each outcome's observations are recorded in Table 2. There were no significant differences between the treatment groups at baseline in any of the cognition composite values. Number of participants with full data for the present analysis was N = 115 at baseline, N = 107 at week 2, and N = 98 at week 6.

The global, objective, and subjective composite cognitive measure scores changed significantly over the RCT period in both individual treatment groups of vortioxetine plus celecoxib or vortioxetine plus placebo (Figure 1, Table 3). In all cases, the cognitive scores reduced over time, indicating improvement in cognitive functioning during the first 6 weeks of the RCT. However, there was no significant difference in any cognitive measure between the two treatment groups over time; hence, the improvement over time in the vortioxetine and celecoxib group did not exceed that of the vortioxetine and placebo group, or vice versa (Table 3). Changes in individual THINC-it cognitive measures are reported in Supplementary Table 1, Supplementary Figure 1, and Supplementary Appendix 1.

Figure 1.

Change Over Time in THINC-it–Derived Cognition Composite Scores[a]



[a]Mean vortioxetine + placebo and vortioxetine + celecoxib scores at baseline, week 2, and week 6 time points. Error bars indicate 95% CI.
Abbreviations: CI = confidence interval, PDQ-5-D = Perceived Deficits Questionnaire for Depression–5-item, THINC-it = THINC integrated tool.

Table 3.

Change in THINC-it Cognition Composite Score Estimates Over Time (Adjusted Model) for Vortioxetine + Placebo and Vortioxetine + Celecoxib Treatment Groups in PREDDICT Study

		SMD (95% CI)	Estimate (95% CI)	*P* value
THINC-it global cognition composite score	Time by treatment group interaction			.846[a]
	Vortioxetine + placebo	−0.613 (−1.004 to −0.220)	−0.062 (−0.078 to −0.047)	<.001
	Vortioxetine + celecoxib	−0.593 (−0.980 to −0.204)	−0.068 (−0.084 to −0.053)	<.001
THINC-it objective cognition composite score	Time by treatment group interaction			.901[a]
	Vortioxetine + placebo	−0.499 (−0.887 to −0.109)	−0.057 (−0.074 to −0.040)	<.001
	Vortioxetine + celecoxib	−0.509 (−0.894 to −0.122)	−0.063 (−0.079 to −0.046)	<.001
THINC-it PDQ-5-D (subjective cognition) score	Time by treatment group interaction			.581[a]
	Vortioxetine + placebo	−0.495 (−0.883 to −0.105)	−2.089 (−3.066 to −1.113)	<.001
	Vortioxetine + celecoxib	−0.525 (−0.910 to −0.138)	−2.297 (−3.259 to −1.335)	<.001

[a]*P* values refer to time by treatment group interaction. "Time" variable includes baseline, week 2, and week 6 observations for composite scores. Estimates are differences in means. SMDs, estimates, and *P* values refer to the difference between baseline and week 6. Covariates include participant age, sex, and education level. SMDs are calculated on raw means for selected groups and time points, not estimated model means.

Abbreviations: CI = confidence interval, PDQ-5-D = Perceived Deficits Questionnaire for Depression–5-item, SMD = standardized mean difference, THINC-it = THINC integrated tool.

Moreover, there was no significant relationship between log hsCRP at baseline and change in the cognitive measures between baseline and week 6, which indicates that baseline hsCRP levels were not associated with or predictive of change in any of the cognitive measures (Table 4). Change in log hsCRP between baseline and week 6 of the RCT was also not related to change in cognitive performance during the RCT (Table 4).

DISCUSSION

With this analysis in the double-blind PREDDICT RCT, we sought to determine if the combined administration of vortioxetine and celecoxib was more effective in treating cognitive dysfunction in participants with MDD compared to vortioxetine plus placebo, and if any observed changes in cognitive outcomes were related to corresponding changes in hsCRP over the treatment period. There was a significant improvement in cognitive function for both treatment groups receiving vortioxetine over the course of treatment; however, there was no additional effect of add-on celecoxib. The improvement over the RCT might be explained by vortioxetine treatment, which was taken by both treatment groups and has been associated with better cognitive function than placebo or other antidepressants in other trials.[32] However, as there was no group in the present RCT who did not receive vortioxetine, we cannot assess the causality of the observed change. The SMDs in this study indicated medium effect sizes for improvement the 3 cognition composite scores. This is comparable to the findings of previous clinical trials into vortioxetine's efficacy in treating MDD-associated cognitive dysfunction. In a meta-analysis, an SMD of 0.34 was found for effect on psychomotor speed, 0.26 for effect on executive function, and 0.24 for effect on delayed recall, across at least 500 vortioxetine-treated participants in 2 or more studies.[23] More recently, a meta-analysis calculated an SMD of 0.34 for effect of vortioxetine on global-executive functioning across 5 studies.[42]

Many antidepressants, including vortioxetine, exert their therapeutic effects via binding to serotonin (5-HT) receptors. However, vortioxetine has a unique binding profile, including inhibiting the 5-HT transporter (SERT), acting as agonist at 5-HT_{1A}, a partial agonist at 5-HT_{1B}, and an antagonist at 5-HT_{1D}, 5-HT_{3}, and 5-HT_{7} receptors.[43] These targets were selected due to evidence of their relevance in remediating both cognitive impairment and mood symptoms.[43] Binding at these receptor sites appears to reduce GABAergic transmission from interneurons, resulting in increased glutamatergic signaling, long-term potentiation, and neuroplasticity.[44,45] These downstream consequences of serotonergic receptor binding may be responsible for the therapeutic effects of vortioxetine. Postmortem and neuroimaging studies of patients with MDD have shown volumetric reductions and reductions in neuronal and glial cellular sizes and counts.[46,47] These changes may be a result of a neurotoxic environment caused by release of proinflammatory cytokines by glial cells into the brain parenchyma.[48] The glial cells are likely stimulated to undergo structural and functional changes into proinflammatory and neurotoxic configurations.[49,50] Induction of glial cells to proinflammatory states prevents

Table 4.
Effect of log hsCRP on THINC-it Cognition Composite Scores Across the PREDDICT Randomized Controlled Trial[a]

	Effect of log baseline hsCRP on composite scores over time (adjusted MMRM model)		Relationship between hsCRP change score and composite measures' change scores (standard linear regression)	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
THINC-it global cognition composite score	−0.005 (−0.017 to 0.007)	.390	−0.002 (−0.014 to 0.011)	.806
THINC-it objective cognition composite score	−0.003 (−0.015 to 0.009)	.600	−0.003 (−0.016 to 0.011)	.704
THINC-it PDQ-5-D (subjective cognition) score	−0.409 (−1.029 to 0.211)	.193	0.110 (−0.704 to 0.924)	.788

[a]Adjusted MMRM models include covariates of participant age, sex, education level, and log of baseline hsCRP, with "time" variable including baseline, week 2 and week 6 observations for global, objective and subjective cognition scores. Estimates and *P* values refer to the estimated change in cognitive measure per unit change of log hsCRP on the adjusted MMRM model. For standard linear regressions, estimates and *P* values refer to change in cognitive measure score from baseline to week 6 vs change in log hsCRP from baseline to week 6 and includes covariates of participant age, sex, and education level, as well as baseline cognitive measure score and baseline log hsCRP score, to control for regression-to-the-mean effects.

Abbreviations: CI = confidence interval, hsCRP = high sensitivity C-reactive protein, MMRM = mixed effects models for repeated measures, PDQ-5-D = Perceived Deficits Questionnaire for Depression–5-item, THINC-it = THINC integrated tool.

these cells from performing homeostatic maintenance, including release of factors supporting cellular growth.[49,50] Meanwhile, vortioxetine has been demonstrated to have immunomodulatory effects via antioxidant and anti-inflammatory action on human monocytes.[51] Vortioxetine may exert therapeutic effects by reverting glial cells to protective phenotypes; however, this has currently only been recorded on human cells in vitro, and it is unknown if the effect would be clinically meaningful in patients.[51]

However, our study results do not support the addition of celecoxib to vortioxetine as a clinical treatment strategy for MDD-associated cognitive dysfunction, as there were no significant differences in overall effect on any included measure between the vortioxetine plus celecoxib and vortioxetine plus placebo treatment groups. Previous studies showed a large effect size for celecoxib add-on treatment on overall antidepressant effect,[18] but this broad antidepressant effect of celecoxib was not replicated in our previously published investigation on overall MDD treatment in the PREDDICT cohort.[26] To our knowledge, no other published studies have trialled anti-inflammatory treatment of MDD-associated cognitive dysfunction at this time. Importantly, as this is an exploratory investigation based on secondary measures, we cannot definitively state that there is no benefit of such a strategy for any patient with MDD-associated cognitive dysfunction. Given the repeated findings in the literature of an association between MDD, cognitive impairment, and neuroinflammation, it is possible that a different anti-inflammatory agent may have an effect, and this area should continue to be explored.[52] Furthermore, as vortioxetine itself has demonstrated anti-inflammatory properties,[51] if this is the mechanism by which participants improved, it is possible that no additional benefit via this pathway was possible from celecoxib administration.

Additionally, hsCRP measurements from baseline or baseline to week 6 change were not useful as predictors of cognitive functional response to treatment between baseline and week 6. This result is consistent with other previously published PREDDICT study findings, which also did not find any associations between pre-treatment hsCRP and global measures of MDD symptoms and severity.[26] However, the majority of the cohort had a screening hsCRP level ≤ 3 mg/L and were designated as "depression without inflammation" cases, which may indicate that there was not enough variation in the values to detect change. Alternatively, celecoxib may not have a proportional relationship between dose and peripheral hsCRP concentration specifically. Celecoxib's anti-inflammatory mechanism of action is as a selective cyclooxygenase (COX)-2 inhibitor, favoring COX-2 potency 30-fold to COX-1 potency in vitro.[53] A study in patients with ankylosing spondylitis found that hsCRP concentration decreased following celecoxib administration, but a larger decrease was found at a dose of 200 mg rather than 400 mg celecoxib.[54] While this is only 1 study, it may be indicative of either a ceiling effect on celecoxib coadministration or a nonlinear dose-response relationship, in which higher doses induce additional changes that negate the therapeutic impact. Additionally, celecoxib is capable of binding to other targets, albeit at concentrations above the therapeutic range.[55] These secondary actions may have

undermined the anti-inflammatory effect. Furthermore, it has been demonstrated that COX-2 inhibitors including celecoxib can exacerbate certain inflammatory disorders via mechanisms such as T helper 1 activation, oxidative and nitrosative stress, and mitochondrial function.[56] These pathways have also been demonstrated to be impaired in MDD.[56] A duplicative effect on these pathways by endogenous MDD and administered COX-2 inhibitors may lead to increased inflammation. Similarly, hsCRP may not be appropriate for distinguishing changes in inflammatory state due to vortioxetine. A study demonstrated improvement in cognitive measures among patients with MDD treated with the antidepressants fluoxetine or venlafaxine and also demonstrated a relationship between cognitive measures and hsCRP, with higher baseline or week 6 hsCRP concentration correlated with worse cognitive functioning.[57] However, while they found a significant change over time in hsCRP concentration, the levels increased rather than decreased over 6 weeks of treatment.[57] Findings of this study, supported by additional examples from the literature, show that the use of hsCRP as a biomarker is challenged by results that do not generalize well across patients, likely due to high heterogeneity of phenotypes.

Strengths of the study include the novelty of testing anti-inflammatory medication as an antidepressant-adjunctive treatment strategy in MDD-associated cognitive dysfunction; the significantly larger number of participants than in previous celecoxib add-on trials; the validated discipline-specific cognitive assessment tools utilized in the study, including both objective and subjective measures[8,29]; and the robust statistical methodology accounting for differences in baseline observations or missing data from early study withdrawal.[58] However, these analyses also have limitations. First, these are secondary analyses and require replication, and additional studies with cognition as a primary outcome of anti-inflammatory treatment are required. Second, as both groups consisted of the same treatment, namely vortioxetine, there is no placebo-only group. However, our approach mirrors common clinical practice of antidepressant treatment in moderately to severely affected patients with MDD. Meanwhile, all measured variables had to be scaled to the same range to form the composite scores, and while min-max normalization is an effective method of doing so, any transformation of a variable from its raw value will result in a loss of information.[34,35] Additionally, although all participants were guided through a visual tutorial of THINC-it tasks by blinded trial staff, their first actual attempt was during the baseline appointment, and so practice effects may have influenced scores of the individual objective measures at the week 2 and week 6 assessments, rather than the administered treatments. However, as the magnitude of change in the objective assessments was similar to that seen for the PDQ-5-D subjective measure of cognition, which is not affected by test-retest conditions, we consider these findings appropriate for discussion. Finally, while more nuanced aspects of cognitive function may be examined by interpreting individual components of the THINC-it battery in isolation, we reduced the likelihood of family-wise errors by creating composite scores.

In conclusion, participants in the PREDDICT study showed improvements in subjective, objective, and overall measures of cognition. These changes were clinically similar to findings of other studies involving treatment of cognitive dysfunction with antidepressants, especially vortioxetine. However, there was no evidence that the addition of celecoxib to vortioxetine led to any additional clinical benefit. We further showed that hsCRP measured at baseline was not associated with and could not be used as a predictor of clinical cognitive improvement resulting from this treatment. Further studies are needed to understand the relationship between inflammation and cognitive symptoms of MDD, and if different therapeutic agents targeting these pathways can lead to better outcomes in patients. Additional research is also necessary to identify biomarkers, inflammatory or otherwise, to predict MDD trajectory and treatment responses.

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Supplementary Material

Article Title: Exploratory Analysis of the Effects of Celecoxib on Cognitive Function in Vortioxetine-Treated Patients With Major Depressive Disorder in the PREDDICT Study: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Figure 1** Graphs of Change of Individual Cognitive Outcome Measures Over Time for Vortioxetine + Placebo and Vortioxetine + Celecoxib Participants
2. **Table 1** Change in THINC-it Individual Cognition Objective Measure Estimates Over Time (Adjusted Model) for Vortioxetine + Placebo and Vortioxetine + Celecoxib Treatment Groups in the PREDDICT Study
3. **Appendix 1** Summary of Supplementary Results

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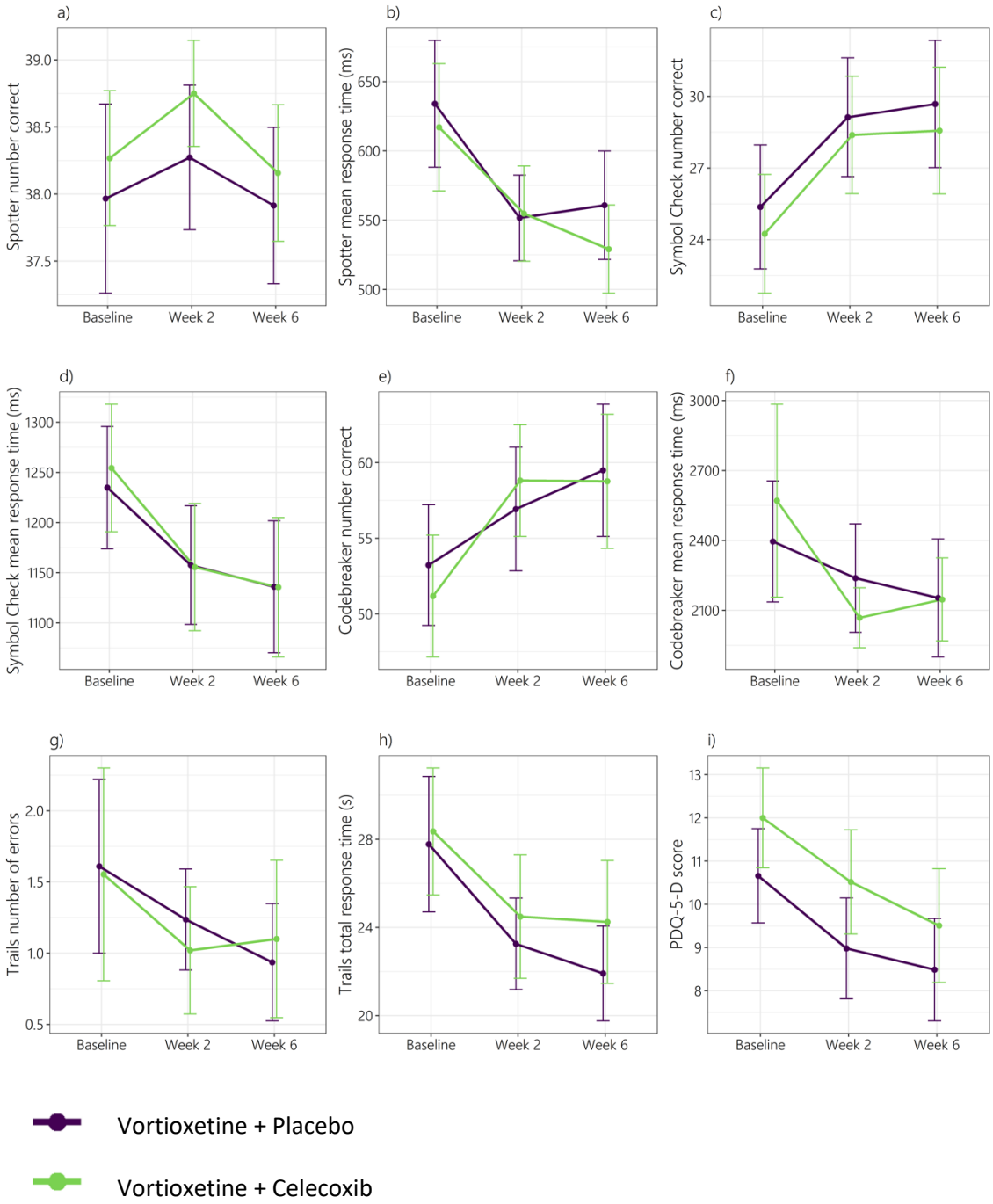
Supplementary Figure 1: Graphs of change of individual cognitive outcome measures over time for vortioxetine + placebo and vortioxetine + celecoxib participants



*Plots of the mean of vortioxetine + placebo and vortioxetine + celecoxib scores at baseline, week 2, and week 6 time points for THINC-it tasks **a** Spotter number correct, **b** Spotter mean response time, **c** Symbol Check number correct, **d** Symbol Check mean response time, **e** Codebreaker number correct, **f** Codebreaker mean response time, **g** Trails number of errors, **h** Trails total response time, **i** PDQ-5-D score. Error bars represent 95% confidence interval.*

Supplementary Table 1: Change in THINC-it individual cognition objective measure estimates over time (adjusted model) for Vortioxetine + Placebo and Vortioxetine + Celecoxib treatment groups in the PREDDICT study

			SMD (95% CI)	Estimate (95% CI) change (baseline to week 6)	p value
THINC-it Spotter *Choice reaction time (CRT)*	number correct[a]	Time by treatment group interaction			0.875^
		Vortioxetine + Placebo	-0.020 (-0.403, 0.363)	0.03 (-0.64, 0.69)	0.935
		Vortioxetine + Celecoxib	-0.057 (-0.436, 0.322)	-0.12 (-0.77, 0.54)	0.727
	mean response time	Time by treatment group interaction			0.137^
		Vortioxetine + Placebo	-0.440 (-0.827, -0.052)	-67.36 (-98.49, -36.23)	<0.001
		Vortioxetine + Celecoxib	-0.576 (-0.961, -0.187)	-83.48 (-114.16, -52.79)	<0.001
THINC-it Symbol Check *N-back*	number correct[a]	Time by treatment group interaction			0.937^
		Vortioxetine + Placebo	0.424 (0.035, 0.810)	3.85 (1.87, 5.83)	<0.001
		Vortioxetine + Celecoxib	0.438 (0.053, 0.821)	4.34 (2.39, 6.29)	<0.001
	mean response time	Time by treatment group interaction			0.721^
		Vortioxetine + Placebo	-0.405 (-0.791, -0.017)	-84.70 (-129.40, -40.01)	<0.001
		Vortioxetine + Celecoxib	-0.466 (-0.850, -0.080)	-110.46 (-154.50, -66.42)	<0.001
THINC-it Codebreaker *Digit Symbol Substitution Test (DSST)*	number correct[a]	Time by treatment group interaction			0.322^
		Vortioxetine + Placebo	0.389 (0.002, 0.775)	5.82 (2.89, 8.76)	<0.001
		Vortioxetine + Celecoxib	0.468 (0.082, 0.851)	7.46 (4.57, 10.35)	<0.001
	mean response time	Time by treatment group interaction			0.221^
		Vortioxetine + Placebo	-0.244 (-0.628, 0.142)	-226.32 (-479.34, 26.71)	0.079
		Vortioxetine + Celecoxib	-0.341 (-0.722, 0.042)	-418.67 (-668.16, -169.18)	0.001
THINC-it Trails *Trail making test part B (TMT-B)*	number of errors	Time by treatment group interaction			0.755^
		Vortioxetine + Placebo	-0.327 (-0.712, 0.059)	-0.70 (-1.41, 0.00)	0.050
		Vortioxetine + Celecoxib	-0.178 (-0.560, 0.204)	-0.47 (-1.17, 0.23)	0.187
	total response time	Time by treatment group interaction			0.679^
		Vortioxetine + Placebo	-0.560 (-0.949, -0.168)	-5.54 (-8.27, -2.81)	<0.001
		Vortioxetine + Celecoxib	-0.377 (-0.761, 0.008)	-3.95 (-6.65, -1.25)	0.004

[a] "number correct" measures have opposite directionality to all others, where a higher score indicates better performance. "Time" variable includes baseline, week 2 and week 6 observations for composite scores. Estimates are differences in means. P values refer to the difference between baseline and week 6. Covariates include participant age, sex, and education level. SMD calculated using package MBESS[33] where Group 1 = week 6 and Group 2 = baseline. Abbreviations: CI = confidence interval, SMD = standard mean difference.

Appendix 1: Summary of supplementary results

The majority of the individual THINC-it cognition measures showed a significant change between baseline and week 6. The directionality of each significant change indicates improvement in performance. Magnitudes of the significant changes over the RCT ranged from small (smallest SMD = -0.341 [DSST mean response time, vortioxetine + celecoxib group]) to medium (largest SMD = -0.576 [CRT mean response time, vortioxetine + celecoxib group].