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Targeting Treatments to Improve Cognitive Function in Mood Disorder:
Suggestions From Trials Using Erythropoietin

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ABSTRACT

Objective: There is no established efficacious treatment for cognitive dysfunction in unipolar and bipolar disorder. This may be partially due to lack of consensus regarding the need to screen for cognitive impairment in cognition trials or which screening criteria to use. We have demonstrated in 2 randomized placebo-controlled trials that 8 weeks of erythropoietin (EPO) treatment has beneficial effects on verbal memory across unipolar and bipolar disorder, with 58% of EPO-treated patients displaying a clinically relevant memory improvement as compared to 15% of those treated with placebo.

Methods: We reassessed the data from our 2 EPO trials conducted between September 2009 and October 2012 to determine whether *objective* performance-based memory impairment or *subjective* self-rated cognitive impairment at baseline was related to the effect of EPO on cognitive function as assessed by Rey Auditory Verbal Learning Test (RAVLT) total recall with multiple logistic regression adjusted for diagnosis, age, gender, symptom severity, and education levels.

Results: We included 79 patients with an *ICD-10* diagnosis of unipolar or bipolar disorder, of whom 39 received EPO and 40 received placebo (saline). For EPO-treated patients with objective memory dysfunction at baseline (n = 16) (defined as RAVLT total recall ≤ 43), the odds of a clinically relevant memory improvement were increased by a factor of 290.6 (95% CI, 2.7–31,316.4; $P = .02$) compared to patients with no baseline impairment (n = 23). Subjective cognitive complaints (measured with the Cognitive and Physical Functioning Questionnaire) and longer illness duration were associated with small increases in patients' chances of treatment efficacy on memory (53% and 16% increase, respectively; $P \leq .04$). Diagnosis, gender, age, baseline depression severity, and number of mood episodes did not significantly change the chances of EPO treatment success ($P \geq .06$). In the placebo-treated group, the odds of memory improvement were not significantly different for patients with or without objectively defined memory dysfunction ($P \geq .59$) or subjective complaints at baseline ($P \geq .06$).

Conclusions: Baseline objectively assessed memory impairments and—to a lesser degree—subjective cognitive complaints increased the chances of treatment efficacy on cognition in unipolar and bipolar disorder.

Trial Registration: ClinicalTrials.gov identifier: NCT00916552

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Cognitive dysfunction is common in unipolar (UD) and bipolar disorders (BD), with deficits in verbal memory and executive function being most pronounced.[1,2] Cognitive deficits are associated with poor prognosis and reduced socio-occupational capacity.[3,4] However, there is no established effective treatment for persistent cognitive dysfunction in mood disorders[1,5] despite intensive research into new pharmacologic and psychological treatments.[6–9]

Patients with schizophrenia generally display severe global cognitive deficits with effect sizes > 1.[10] In contrast, patients with mood disorders show less pronounced cognitive deficits,[11,12] with only 20% of UD and 30% of BD patients exhibiting severe dysfunction across multiple domains[13] despite highly prevalent subjective cognitive complaints.[14–16] This introduces a great risk of including "cognitively intact" UD and BD patients in cognition trials, which increases the frequency of type II error. For example, it was demonstrated in a negative trial in BD that baseline cognition correlated with the magnitude of treatment-related cognitive improvement, suggesting that patients in this trial were not sufficiently impaired for detection of treatment efficacy.[17] This finding is consistent with the observation that functional remediation, a new psychological intervention for functional and cognitive impairment in BD, had no cognitive efficacy in a combined group of cognitively intact and impaired patients[18] but improved memory in a subgroup with cognitive deficits.[19]

Nevertheless, the importance of baseline cognitive deficits in participants of cognition trials is not well established. There is no consensus regarding the need to screen for cognitive impairment in these trials or which screening criteria to implement. In particular, whether we can rely on patients' subjective cognitive complaints or require objective neuropsychological tools to demonstrate sufficient cognitive dysfunction to enter the trial is unclear. While no trials used objective screening for cognitive impairment, subjective cognitive difficulties have been used as an inclusion criterion in a few trials.[7,18,20,21] However, subjective cognitive difficulties may be suboptimal since subjective and objective measures of cognition are not closely related.[14–16,22]

In 2 randomized, double-blind placebo-controlled trials, we found that 8 weeks of weekly EPO infusions

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Clinical Points

- There is a lack of consensus regarding *whether* and *how* to screen for cognitive impairment in patients with mood disorders, which has implications for success rates of new treatment strategies targeting cognition.
- If a patient presents with subjective cognitive complaints, screening for cognitive dysfunction with a brief neuropsychological test may be useful before commencing a cognition treatment to increase the odds of treatment success.

resulted in mood-independent improvement of verbal memory in UD[23] and a trend toward improvement in BD,[21] which was associated with reversal of left hippocampal volume loss across both diagnostic groups.[24] The studies were inspired by preclinical and clinical findings that both endogenous brain-derived EPO and systemically administered EPO exert neuroprotective effects, enhance neuroplasticity, and improve cognition under diseased and normal conditions.[25–27] Of the EPO-treated patients, 58% (n = 23) showed a "clinically relevant" memory improvement, defined a priori as ≥ 4 points greater than the saline group,[28] ie, ≥ 6 points, as compared to 15% (n = 6) of those treated with placebo.

This report used the data from these trials to determine whether various baseline patient characteristics affected the chances of detecting clinically relevant memory improvement in response to EPO. Specifically, we addressed the following questions: (1) Is memory dysfunction at baseline, indexed by RAVLT total recall, associated with greater chances of achieving a clinically relevant EPO-associated memory improvement? (2) Are more subjective cognitive difficulties at baseline associated with greater chances of achieving a clinically relevant EPO-associated memory improvement? (3) Is objective memory dysfunction or subjective cognitive difficulties at baseline the best predictor of the chances of a clinically relevant memory improvement in response to EPO? (4) Is an association between memory impairment at baseline and chances of achieving a clinically relevant memory improvement *specific* to EPO (ie, not present in the saline group)? Answers to these questions may inform future cognition trials in mood disorders on whether screening for cognitive impairment can increase the chances to reveal efficacy of novel treatments.

METHODS

Study Participants

A detailed description of the 2 double-blind, placebo-controlled studies of EPO can be found elsewhere.[21,23] In brief, participants were recruited through the Copenhagen Clinic for Affective Disorders and by advertisement on relevant websites between September 2009 and October 2012. Participants were screened with Schedules for Clinical Assessment in Neuropsychiatry. Included patients had an *ICD-10* diagnosis of unipolar depression that met criteria for treatment resistance based on the Treatment Response to Antidepressant Questionnaire[29] outcome with moderate depression (Hamilton Depression Rating Scale 17-items [HDRS-17][30] score ≥ 17) or BD in partial remission (HDRS-17 and Young Mania Rating Scale [YMRS][31] scores ≤ 14) with subjective cognitive difficulties according to the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) (a score of ≥ 4 on ≥ 2 items).[32] No statistical differences were observed between the EPO- or saline-treated participants in diagnosis, mood symptoms, age, gender, education, or illness load.[21,23]

Procedures

Patients were randomized to receive 8 weekly intravenous infusions of EPO (Eprex; 40,000 IU; Janssen-Cilag) or saline (NaCl 0.9%) in addition to their antidepressant or mood-stabilizing medication in a double-blind manner. The high EPO dose was chosen because only 1% of the peripherally injected EPO enters the brain under conditions of an intact blood-brain barrier, leading to concentrations in brain tissue comparable to the optimal concentrations for neuroprotection in neuron cultures.[33–36] Blood tests and blood pressure were taken weekly during the treatment period with the examiners being blind to the results. Screening, safety precautions, and blinding procedures are reported elsewhere.[21,23]

Cognitive function was assessed at week 1 (baseline), 9 (1 week post-treatment), and 14 (6 weeks follow-up) with a neuropsychological test battery including the Rey Auditory Verbal Learning Test (RAVLT)[37] and with the CPFQ. Change in verbal memory indexed by RAVLT total recall from weeks 1 to 9 was the primary outcome measure in the BD study[21] and was assessed in the UD study as tertiary outcome (with mood symptoms as primary and secondary outcomes).[23] To minimize learning effects, 3 equivalent alternate versions of the RAVLT were administered at weeks 1, 9, and 14 in a counter-balanced fashion.[21,23] Mood symptoms were assessed with the HDRS-17, Beck Depression Inventory (BDI),[38] and YMRS at weeks 1, 5, 9, and 14. Whole-brain fMRI was performed at weeks 1 and 14. Outcome assessors were blinded to patients' treatment allocation throughout the study period and data analysis (see details in Miskowiak et al[21,23]).

The study was carried out in accordance with the latest version of the Declaration of Helsinki; was approved by the local ethics committee, Danish Medicines Agency, and Danish Data Agency; and was registered at ClinicalTrials.gov (NCT00916552). After complete description of the study, written informed consent was obtained from all participants.

Endpoint

The "clinically relevant" verbal memory change in response to EPO was defined a priori to be ≥ 4 points compared with saline, that is, halfway to normal function.[28] Given a mean of 2 points improvement in the saline-treated group, we here define the clinically relevant

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treatment-associated improvement as a change of ≥ 6 points in RAVLT total recall from weeks 1 to 9.

Predictors

Objective memory performance at baseline was quantified by RAVLT total recall score. Baseline RAVLT total recall was analyzed as a continuous variable. It was also dichotomized at cutoff score of 43, corresponding to 1 standard deviation below the meta-norms for healthy, age-matched individuals,[39] where scores ≤ 43 were considered "memory dysfunction" and scores > 43 were considered "normal" memory function. Subjective cognitive difficulties were quantified by the total score of CPFQ cognitive items *d* through *g,* spanning attention, memory, word finding, and mental sharpness (range, 4–24 points with higher scores indicating greater difficulties). Other baseline variables (see Statistical Methods) were also evaluated for their effect on the chances of detecting a therapeutic effect on cognition.

Statistical Methods

Analyses regarding questions 1, 2, and 3 were performed using the data from EPO-treated patients. Analysis regarding question 4 combines data from EPO-treated and saline-treated control patients. Multiple logistic regression was implemented to associate objective and subjective baseline memory function with clinically relevant memory improvement. All analyses were adjusted for age, gender, years of education (on continuous scale), diagnosis (BD/UD), baseline depression severity indexed by the HDRS-17 score (on continuous scale), total number of (hypo)manic and depressive episodes, and years of illness. Variables with outliers were log transformed. Likelihood ratio tests were used to test if the effects of RAVLT on clinically relevant memory improvement were modified by length of education (dichotomized) and CPFQ, respectively.

The discriminative abilities of objective and subjective baseline memory function were compared based on the predicted personalized chances of a clinically relevant memory improvement. The personalized chances were obtained for each patient from multiple logistic regression including objective memory dysfunction and other variables (objective prediction) and from multiple logistic regression including subjective cognitive difficulties and other variables (subjective prediction). Changes in the predicted chances of clinically relevant memory improvement when switching from the objective to the subjective prediction were assessed graphically with reclassification diagrams and overall by differences of the corresponding AUC (area under the receiver operating characteristic [ROC] curves).[40] The ROC was based on the outcome yes/no for clinically relevant memory improvement and the personalized predicted chance by multiple logistic regression as a marker. The AUC has the following retrospective interpretation: in a random pair of treated patients where one has treatment success and the other does not, the AUC is the probability that the higher chance was predicted to the patient who has treatment success. The differences between the AUC of the objective and subjective predictions were tested with the Long de Long tests.[41] All analyses were performed with R version 3.1.1.[42] (http://www.R-project.org).

Table 1. Demographic and Clinical Variables (EPO Group)[a]

Variable	Normal Baseline Memory (n = 23)	Baseline Memory Dysfunction (n = 16)	Total (N = 39)	*P* Value
Age				
20–35 y	10 (43.5)	2 (12.5)	12 (30.8)	
35–50 y	9 (39.1)	9 (56.2)	18 (46.2)	
50–70 y	4 (17.4)	5 (31.2)	9 (23.1)	.11
Gender				
Male	5 (21.7)	8 (50.0)	13 (33.3)	
Female	18 (78.3)	8 (50.0)	26 (66.7)	.13
Diagnosis				
Unipolar	10 (43.5)	7 (43.8)	17 (43.6)	
Bipolar	13 (56.5)	9 (56.2)	22 (56.4)	1.00
Years of education				
≥ 15	18 (78.3)	9 (56.2)	27 (69.2)	
< 15	5 (21.7)	7 (43.8)	12 (30.8)	.27
Baseline HDRS-17 rating				
Complete remission	3 (13.0)	3 (18.8)	6 (15.4)	
Partial remission	9 (39.1)	6 (37.5)	15 (38.5)	
Symptomatic	11 (47.8)	7 (43.8)	18 (46.2)	.89
Illness duration				
0–10 y	8 (34.8)	4 (25.0)	12 (30.8)	
11–20 y	8 (34.8)	5 (31.2)	13 (33.3)	
21–30 y	5 (21.7)	3 (18.8)	8 (20.5)	
> 30 y	2 (8.7)	4 (25.0)	6 (15.4)	.57
No. of mood episodes				
0–10	14 (60.9)	10 (62.5)	24 (61.5)	
11–20	4 (17.4)	6 (37.5)	10 (25.6)	
>20	5 (21.7)	0 (0.0)	5 (12.8)	.08

[a]Values shown as n (%).
Abbreviations: CI = confidence interval, HDRS-17 = Hamilton Depression Rating Scale 17-items.

RESULTS

Patient Flow and Characteristics

Table 1 displays the characteristics of EPO-treated patients with memory dysfunction and normal memory at baseline. For characteristics of the entire cohort, please refer to Supplementary eTables 1 and 2.

Of the 84 patients randomized to EPO (n = 42) or saline (n = 42), 1 patient (EPO) withdrew at baseline, and 1 (saline) chose to terminate the trial in week 5. RAVLT data were missing for 2 patients (1 EPO, 1 saline). One patient (EPO) was removed due to missing information on length of education. Logistic regression analyses for questions 1 through 3 therefore included 39 EPO-treated participants and 79 participants in the entire cohort for question 4.

Logistic Regression Analyses

1. Is memory dysfunction at baseline associated with greater chances of achieving a clinically relevant EPO-associated memory improvement? Logistic regression analysis with memory dysfunction indexed by RAVLT total recall ≤ 43 as the predictor variable showed that the odds of achieving success of EPO treatment were increased by a factor of 290.6 (95% CI, 2.7–31,316.4; $P = .02$) for patients with baseline memory dysfunction (n = 16) compared to

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patients with normal baseline memory (n = 23) (Table 2 and Figure 1). In contrast, there was no impact of educational level, diagnosis, gender, age, baseline depression severity, number of mood episodes, or length of illness on the likelihood of improving cognitive function defined as ≥ 6 points' improvement in RAVLT total recall ($P \geq .06$) (Table 2).

Logistic regression analysis using patients' baseline RAVLT total recall scores showed that the odds of a successful EPO treatment on memory function were increased by increased by 86% (95% CI, 0%–346%; $P = .049$) for each unit *decrease* in baseline RAVLT total recall scores (Table 2).

2. Are more subjective cognitive difficulties at baseline (as assessed by the CPFQ) associated with greater chances of achieving a clinically relevant EPO-associated memory improvement? Logistic regression analysis using the baseline CPFQ cognition items total score as the predictor revealed a small increase in the chances of EPO treatment success in patients with more cognitive complaints (OR = 1.53; 95% CI, 1.04–2.25; $P = .03$; Table 3), which were further increased with more years of illness (OR = 1.16; 95% CI, 1%–33%; $P = .04$).

3. Is baseline objective memory dysfunction as assessed by the RAVLT total recall score or baseline subjective cognitive difficulties as assessed by the CPFQ the best predictor of the chances of a clinically relevant memory improvement in response to EPO? Based on multiple logistic regression, the personalized predicted chances of a clinically relevant memory improvement in response to EPO were obtained with CPFQ and RAVLT. Figure 2 shows that in most patients who achieved the clinically relevant memory improvement (green triangles), the predicted chances based on RAVLT were higher than those based on CPFQ, and in most patients who did not achieve success (red triangles), the predicted chances based on RAVLT were lower than those based on CPFQ. This indicates that RAVLT is a better predictor than CPFQ.

Figure 3 displays the ROC curves and corresponding areas under the curve for predicted chances of clinically relevant memory improvement based on logistic regression including either RAVLT total recall or the CPFQ cognition items score. Both models were adjusted for age, gender, length of education, diagnosis, and baseline depression severity. As evident from the ROC curves, the discriminative ability of the logistic regression using baseline RAVLT was higher than that using CPFQ, although this difference was not statistically significant ($P = .29$).

4. Is an association between cognitive impairment at baseline and chances of achieving a clinically relevant memory improvement specific to EPO? Likelihood ratio tests were applied in all data (combined EPO and control) to test if the effects of baseline memory dysfunction and of subjective cognitive complaints on the odds of achieving clinically relevant memory improvement were modified by EPO treatment. The effect of baseline memory dysfunction on chances of treatment success was significantly different between patients treated with EPO and patients in the saline control arm (likelihood ratio test: $P = .04$), indicating this effect was specific to the active intervention group. In contrast, the effect of more subjective cognitive complaints at baseline was not significantly different between EPO- and saline-treated patients (likelihood ratio test: $P = .45$).

Table 2. Objectively Assessed Baseline Memory Dysfunction as Predictor of Clinically Relevant EPO-Associated Memory Improvement

Variable	Odds Ratio (95% CI)	*P* Value
Baseline memory dysfunction (RAVLT total recall ≤ or > 43)		
BL RAVLT		
>43	1.0 (1.0–1.0)	1.00
≤43	290.58 (2.70–31,316.36)	.02*
Education	1.72 (0.98–3.01)	.06
BL HDRS-17	1.18 (0.89–1.55)	.24
Gender		
Male	1.0 (1.0–1.0)	1.00
Female	3.21 (0.21–49.87)	.40
Age	1.04 (0.93–1.16)	.52
Diagnosis		
Unipolar	1.00 (1.00–1.00)	1.00
Bipolar	2.28 (0.07–79.95)	.65
Years of illness	1.16 (0.97–1.40)	.11
Log (number of mood episodes)	0.56 (0.10–3.04)	.50
RAVLT total recall score (continuous)		
BL RAVLT (negative)	1.86 (1.00–3.46)	.049*
Education	3.14 (0.92–10.77)	.07
BL HDRS-17	1.15 (0.82–1.62)	.41
Gender		
Male	1.00 (1.00–1.00)	1.00
Female	2.17 (0.13–36.62)	.59
Age	0.86 (0.70–1.08)	.19
Diagnosis		
Unipolar	1.00 (1.00–1.00)	1.00
Bipolar	0.19 (0.00–20.26)	.49
Years of illness	1.49 (0.95–2.31)	.08
Log (number of mood episodes)	0.49 (0.06–3.86)	.49

*$P < .05$.
Abbreviations: BL = baseline, CI = confidence interval, EPO = erythropoietin, HDRS-17 = Hamilton Depression Rating Scale 17-items, RAVLT = Rey Auditory Verbal Learning Test.

Using all data (EPO and saline), the odds in the EPO group for successful treatment effect were 34.1 higher in patients with baseline memory dysfunction compared to patients with normal baseline memory dysfunction (95% CI, 3.3–349.1; $P = .003$). Again using all data, patients with more subjective cognitive complaints at baseline had a 62% increase in chances for treatment success (OR = 1.62; 95% CI, 1.17–2.24; $P = .004$).

In the saline control arm, the odds for clinically relevant memory improvement were not significantly different between patients with baseline memory dysfunction compared to patients with normal baseline memory ($P = .59$) (Figure 1). There was a trend toward greater chances for memory improvement in saline-treated patients with more baseline cognitive complaints ($P = .06$).

DISCUSSION

This secondary data analysis, aimed to determine which baseline characteristics increased patients' chances of achieving a clinically relevant memory improvement in response to EPO treatment. Patients with objective memory

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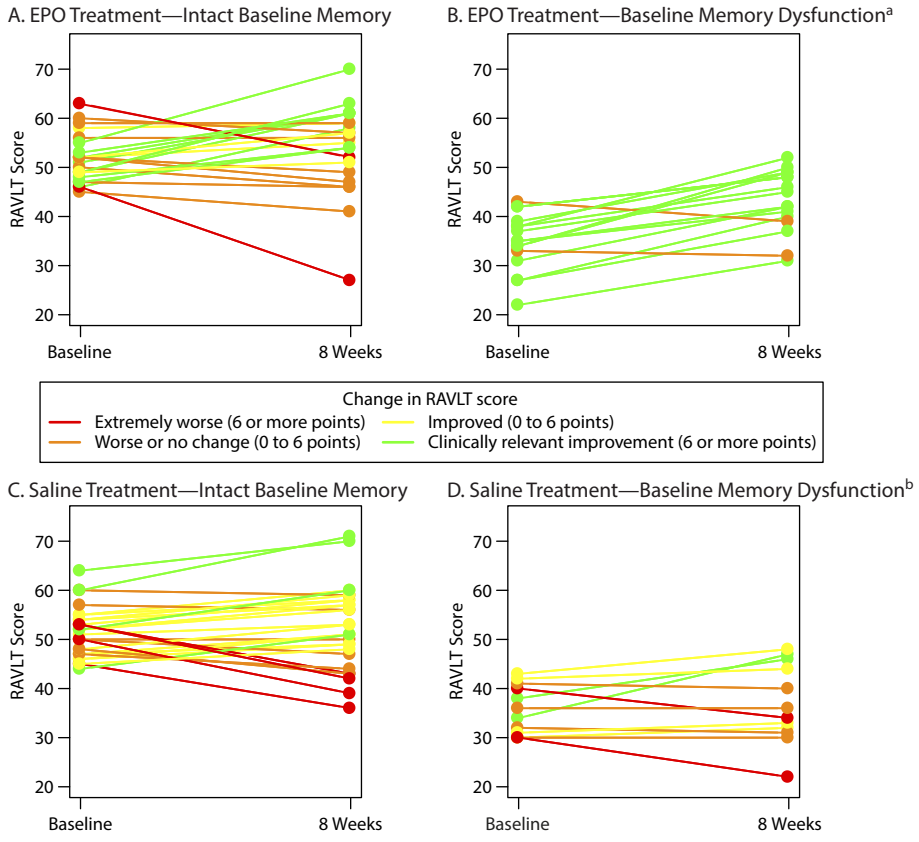
Figure 1. Change in Memory Performance for Erythropoietin (EPO)-Treated and Saline-Treated Patients With Intact Baseline Memory (RAVLT total recall scores > 43) and Baseline Memory Dysfunction (RAVLT total recall scores ≤ 43)



[a]The odds of a successful EPO treatment were increased by a factor of 290.6 (95% CI, 2.7–31,316.4; $P = .02$) for patients with baseline memory dysfunction compared to patients with normal baseline memory.
[b]With saline treatment, there were no differences in the odds of achieving a clinically relevant memory improvement between those with normal memory and those with memory dysfunction at baseline.
Abbreviation: RAVLT = Rey Auditory Verbal Learning Test.

dysfunction at baseline, defined as a RAVLT total recall score ≤ 43, were 290.6 times (95% CI, 2.7–31,316.4; $P = .02$) more likely to achieve EPO treatment success than patients with normal baseline memory. Greater baseline subjective cognitive difficulties, as measured by the CPFQ cognitive items, and more years of illness were associated with 53% (95% CI, 4%–225%; $P = .03$) and 16% (95% CI, 1%–33%; $P = .04$) increase in the chances of treatment efficacy, respectively. The effect of objectively measured baseline memory dysfunction on the odds of treatment success was specific for the EPO group, while the smaller effect of baseline subjective cognitive complaints was not significantly different between EPO and saline treated patients.

These results suggest that objective baseline memory dysfunction must be sufficiently poor for a treatment effect to be seen, if the findings from EPO are generalizable to other cognitive enhancing interventions. These results are consistent with other reports.[17,19] Other factors may also affect the chances of finding a pro-cognitive effect. For example, post hoc analysis of our negative trial of cognitive remediation in BD revealed *no* efficacy in the subgroup of

Table 3. Subjective Cognitive Function at Baseline as Predictor of Clinically Relevant EPO-Associated Memory Improvement

Variable	Odds Ratio (95% CI)	*P* Value
CPFQ	1.53 (1.04–2.25)	.03*
Education	1.01 (0.74–1.37)	.97
BL HDRS-17	0.96 (0.74–1.23)	.73
Gender		
Male	1.00 (1.00–1.00)	1.00
Female	0.36 (0.05–2.45)	.30
Age	1.05 (0.94–1.16)	.39
Diagnosis		
Unipolar	1.00 (1.00–1.00)	1.00
Bipolar	1.38 (0.06–31.91)	.84
Years of illness	1.16 (1.01–1.33)	.04*
Log (number of mood episodes)	1.11 (0.32–3.91)	.87

*$P < .05$.
Abbreviations: CI = confidence interval, CPFQ = Cognitive and Physical Function Questionnaire, EPO = erythropoietin, HDRS-17 = Hamilton Depression Rating Scale 17-items.

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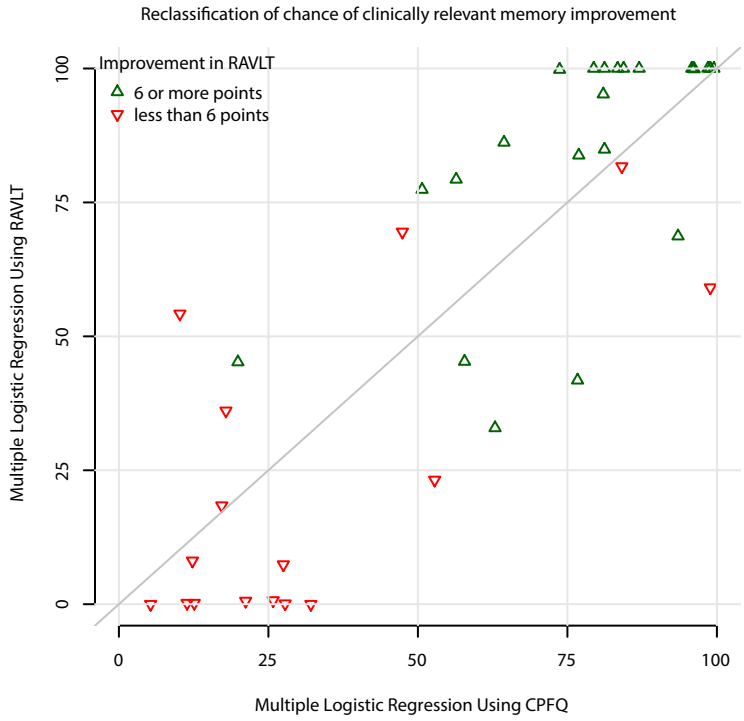
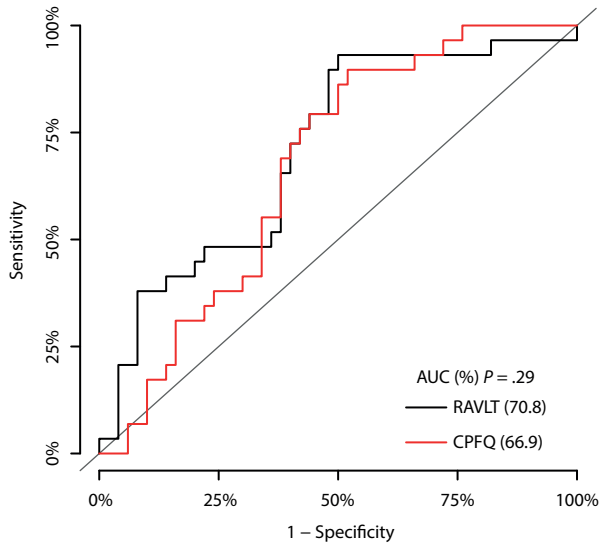
Figure 2. Reclassification Diagram[a]



[a]In most patients who achieved a clinically relevant memory improvement (green triangles), the predicted chances based on the RAVLT total score were higher than those based on CPFQ, and in most patients who did not achieve success, the predicted chances based on the RAVLT were lower than those based on CPFQ. This indicates that RAVLT is a better predictor than CPFQ.
Abbreviations: CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, RAVLT = Rey Auditory Verbal Learning Test.

Figure 3. ROC Curve



Abbreviations: AUC = area under the curve, CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, RAVLT = Rey Auditory Verbal Learning Test, ROC = receiver operating characteristic.

patients with cognitive deficits.[7] Negative findings in trials that target cognition therefore cannot exclusively be explained by the absence of cognitive impairment in study participants. Nevertheless, given the remarkably greater odds of treatment efficacy in patients with baseline memory deficits, systematic objective screening for cognitive dysfunction in future cognition trials in mood disorders may avoid the inclusion of participants with little scope for cognitive improvement.

It was an unexpected finding that more *subjective* cognitive complaints at baseline increased patients' chances of treatment efficacy on objective cognition since subjective and objective measures of cognition correlate poorly.[14,15] This discrepancy could be related to cognitive reserve. Hence, if patients had better than normal cognitive capacity before their illness, objective tests may not pick up the cognitive decline *after* illness onset where their performance could be "merely" within normal range.[43] The subjective measures may better capture such cognitive decline. Since EPO may *restore* lost cognitive capacity rather than *enhance* cognition beyond the habitual level,[25] this could explain the greater chances of EPO treatment success in patients with greater cognitive complaints. However, this cannot fully account for the phenomenon, since *objective* cognitive improvement is not always accompanied by decrease in *subjective* difficulties.[21] This highlights the role of other factors, such as depressive

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symptoms, in the poor correlation between objective and subjective measures of cognition.[14–16] Further, the small effect of baseline subjective cognitive complaints on the chances of memory improvement was not *specific* for the EPO intervention. It may therefore be useful to implement a brief, feasible *objective* screening tool for cognitive impairment in cognition trials such as the Screen for Cognitive Impairment in Psychiatry,[44] which we found to have high sensitivity and specificity for cognitive dysfunction in BD and UD.[15,16] This may be particularly relevant in EPO trials to ensure that only patients with high scope for treatment efficacy are enrolled, given the risk of blood clotting and need for intensive safety monitoring during EPO treatment. However, objective screening criteria should not stand alone; patients must also *experience* cognitive difficulties for the treatment to be clinically meaningful and to ensure that patients are motivated for taking part in the trial.

Interestingly, the observed additional small (16%) incremental increase in the odds for EPO treatment success with for every year of illness suggests that treatment for cognitive deficits may work better in patients at later stages. This finding is in line with the staging model of affective illness[45] and warrants further investigation of EPO to target cognitive and functional impairments in patients at chronic illness stages.

A key limitation is that our definition of a "clinically relevant" memory improvement of ≥ 6 points in RAVLT total recall was somewhat arbitrary. Nevertheless, verbal memory impairment has been consistently associated with functional disability in BD,[46,47] suggesting that improvement in this aspect of cognition may translate into increased functional capacity long-term. The heterogeneous group of UD and BD patients with different depression symptom severity could have impacted on the association between baseline memory dysfunction and treatment success. However, we observed no difference in diagnoses or symptoms between patients with and without memory dysfunction, and logistic regression analyses revealed no impact of diagnosis or depression severity on EPO treatment success. The modest sample size of EPO-treated patients (n = 39) resulted in wide confidence intervals of the estimated odds ratios and could have introduced type II errors. The present analyses should therefore only be considered *hypothesis-generating*. Further, the CPFQ is one of several self-rate measures of cognitive impairment, and other tools could be better. Similarly, the RAVLT is one of numerous neuropsychological tests, of which others may be better for assessment of baseline cognition. It is a limitation that we had not estimated the IQ of patients in the EPO trials since this could have provided additional information about EPO treatment success. It is also a limitation that all the effects are related to EPO treatment, since the associations might be different with other pro-cognitive interventions. Finally, this is a *secondary* analysis of our original EPO trials, which limits certainty without replication in a new prospectively planned study. A strength is that the analyses were based on some of the few randomized, controlled trials that demonstrated treatment-associated cognitive improvement. The cohort was therefore uniquely suited for investigation of baseline predictors of treatment efficacy on cognition.

In conclusion, objectively assessed cognitive impairment at baseline was a strong predictor of EPO treatment success. Subjective cognitive difficulties and longer illness duration were also associated with a small increase in the chances for EPO efficacy. Although the present findings warrant replication, they indicate that screening for objective cognitive dysfunction and subjective cognitive difficulties may be useful in future cognition trials.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Targeting Treatments to Improve Cognitive Function in Mood Disorder: Suggestions From Trials Using Erythropoietin

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List of Supplementary Material for the article

1. **eTable 1** Descriptives
2. **eTable 2** Likelihood of clinically relevant memory improvement in EPO and saline groups

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Supplementary eTable 1. **Descriptives (all).**

Variable	Unit	Normal baseline memory (n=51)	Baseline memory dysfunction (n=28)	Total (n=79)	p-value
Treatment, n (%)	EPO	23 (45.1)	16 (57.1)	39 (49.4)	
	Saline	28 (54.9)	12 (42.9)	40 (50.6)	0.43
Age in years, n (%)	20-35	22 (43.1)	5 (17.9)	27 (34.2)	
	35-50	17 (33.3)	12 (42.9)	29 (36.7)	
	50-70	12 (23.5)	11 (39.3)	23 (29.1)	0.07
Gender, n (%)	Male	12 (23.5)	15 (53.6)	27 (34.2)	
	Female	39 (76.5)	13 (46.4)	52 (65.8)	0.01
Diagnosis, n (%)	Unipolar	22 (43.1)	15 (53.6)	37 (46.8)	
	Bipolar	29 (56.9)	13 (46.4)	42 (53.2)	0.51
Years of education, n (%)	>=15	30 (58.8)	18 (64.3)	48 (60.8)	
	<15	21 (41.2)	10 (35.7)	31 (39.2)	0.81
BL HDRS-17, n (%)	Complete remission	10 (19.6)	3 (10.7)	13 (16.5)	
	Partial remission	18 (35.3)	11 (39.3)	29 (36.7)	
	Symptomatic	23 (45.1)	14 (50.0)	37 (46.8)	0.60
Years of illness, n (%)	0-10	12 (23.5)	6 (21.4)	18 (22.8)	
	11-20	21 (41.2)	10 (35.7)	31 (39.2)	

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Variable	Unit	Normal baseline memory (n=51)	Baseline memory dysfunction (n=28)	Total (n=79)	p-value
	21-30	12 (23.5)	5 (17.9)	17 (21.5)	
	>30	6 (11.8)	7 (25.0)	13 (16.5)	0.50
Number of mood episodes, n (%)	0-10	37 (72.5)	19 (67.9)	56 (70.9)	
	11-20	8 (15.7)	8 (28.6)	16 (20.3)	
	>20	6 (11.8)	1 (3.6)	7 (8.9)	0.23

Abbreviations: BL: baseline; CI: confidence interval; EPO: erythropoietin; HDRS-17: Hamilton Depression Rating Scale 17-items; n: number.

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Supplementary eTable 2. **Likelihood of clinically relevant memory improvement in EPO and saline groups.** Using all data (EPO and saline), objective memory dysfunction and subjective cognitive complaints at baseline were both associated with increased chances of treatment efficacy on memory in EPO-treated patients (p=0.003 and p=0.004, respectively). The effect of baseline RAVLT on chances of clinically relevant memory improvement was significantly *different* between patients treated with EPO and patients in the saline control arm (EPO: OR=34.1, saline: OR=1.80; likelihood ratio test: p=0.04). In contrast, the effect of higher baseline CPFQ on chances of clinically relevant memory improvement was *not* significantly different between EPO and saline treated patients (EPO: OR=1.62, saline: OR=1.39; likelihood ratio test: p=0.45).

Variable	Units	Odds Ratio	95% CI	p-value
Objective memory dysfunction				
Treatment (EPO): RAVLT_baseline (<=43 vs >43)		34.06	[3.32 - 349.10]	0.003*
Treatment (Saline): RAVLT_baseline (<=43 vs >43)		1.80	[0.21 - 15.27]	0.59
Subjective cognitive complaints				
Treatment (EPO): CPFQ		1.62	[1.17 - 2.24]	0.004*
Treatment (Saline): CPFQ		1.39	[0.98 - 1.96]	0.06

Abbreviations: CI: confidence interval; CPFQ: Cognitive and Physical Functioning Questionnaire; EPO: erythropoietin; RAVLT: Rey Auditory Verbal Learning Test.

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