Dose-Dependent Effect of Lithium on Cognition in Mild Cognitive Impairment

To the Editor: Miskowiak et al[1] showed that recombinant human erythropoietin (rhEPO) has the potential to treat cognitive dysfunction in bipolar disorder patients. Specifically, they found that rhEPO enhanced both sustained attention and speed of complex information processing across learning, attention, and executive function in bipolar disorder patients with moderate to severe cognitive problems. However, an important potential confound was not considered: patients were allowed to continue taking antidepressant or mood-stabilizing drugs.[2]

The mood-stabilizing drug lithium has dose-dependent effects on cognition in amnestic mild cognitive impairment from 150 mg to 600 mg.[3] These effects may be due to activation of a critical pathway involving mammalian target of rapamycin (mTOR) and brain-derived neurotrophic factor (BDNF), as demonstrated in animal models.[4] This pathway mediates brain plasticity, including hippocampal-dependent learning and memory. By contrast, doses >1 g/d may have neurotoxic effects, including cognitive slowing and decreased astrogliogenesis, via inhibition of signal transducer and activator of transcription 3 (STAT3).[5] This cognitive slowing can be observed in working memory tasks, including executive attention and short-term memory.

In addition to its effects in bipolar disorder patients, rhEPO could improve cognitive ability in patients with neurodegenerative disease[6–8] via the mTOR/BDNF signaling pathway[9,10] and could protect astroglia[11] via the Janus kinase 2 (JAK2)/STAT3 pathway.[12,13] Thus, lithium and rhEPO would have similar effects through mTOR/BDNF, but would exert opposing effects on STAT3 because rhEPO protects astroglia while lithium inhibits astrogliogenesis. Consequently, inclusion of lithium-treated patients could be a confounder in studies of rhEPO for cognitive dysfunction in bipolar disorder patients.

It is important to consider whether the results obtained by Miskowiak et al may have been affected by exposure of patients to lithium salts prior to or during the study. Explicit data regarding lithium exposure should be reported for each study group, including regimen and treatment duration. Analysis of these data would determine whether rhEPO and lithium have independent effects in bipolar disorder or whether the beneficial effect attributed to rhEPO may be at least partially due to lithium or an interaction between rhEPO and lithium.

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Dr Miskowiak and Colleagues Reply

To the Editor: We thank Dr Lozano and colleagues for their comments on our study "Recombinant Human Erythropoietin to Target Cognitive Dysfunction in Bipolar Disorder: A Double-Blind, Randomized, Placebo-Controlled Phase 2 Trial,"[1] which give us the opportunity to address some conceptually important points regarding the effects of erythropoietin (EPO) on cognition.

Lozano et al note that it is a potential confound that patients remained on their mood-stabilizing treatment including lithium for the duration of the study for 2 reasons: first, lithium has dose-dependent procognitive effects in patients with amnestic mild cognitive impairment in doses from 150 mg to 600 mg[2] but harmful effects on cognition at doses ≥1 g; second, lithium and EPO may activate similar signaling pathways[3,4] and thus exert synergistic actions on neuroplasticity. Lozano et al point out that the EPO-associated improvement of cognition could have therefore been influenced by patients' lithium treatment during or prior to the study and request (1) explicit data regarding lithium exposure for each study group and (2) analysis of whether EPO and lithium have independent cognitive effects, or whether the beneficial effects attributed to EPO could be partially due to lithium or an interaction between EPO and lithium.

In response to point 1, we have included information about lithium treatment doses (which remained unchanged throughout the trial), duration of lithium treatment, and baseline plasma lithium levels for each study group in Table 1. As mentioned in the original article,[1] there was a higher number of lithium-treated patients in the EPO vs saline groups (n = 12 vs n = 5; $P = .05$). However, within the lithium-treated patients (n = 17), there was no difference in the lithium dose, treatment duration, or plasma lithium level between the EPO and saline groups (P values ≥ 0.12).

In response to point 2, we have conducted the following analyses:

a. We reanalyzed the effects of EPO on speed of complex cognitive processing across attention, memory, and executive function (cognitive composite score) and on sustained attention (Rapid Visual Processing [RVP] speed

Table 1. Lithium Treatment Specifications

	EPO Group (n = 23)	Saline Group (n = 21)	*P* Value
Lithium-treated patients, n (%)	12 (52)	5 (24)	.05
Product specifications—patients treated with Lithiumcarbonat (OBA Pharma ApS)/Litarex (Actavis A/S), n/n	8/4	4/1	
Lithium dose, mg, mean (SD)	487 (509)	251 (460)	.12
Plasma lithium level, mmol/L, mean (SD)	0.73 (0.20)	0.71 (0.15)	.82
Lithium treatment duration, mo, mean (SD)	5 (9)	3 (8)	.45

Abbreviation: EPO = erythropoietin.

for correct responses and accuracy) with repeated-measures analysis of covariance (ANCOVA) including the following covariates: lithium dose (mg) and lithium treatment duration (months) in addition to mania and depression symptoms at week 9, measured with the Hamilton Depression Rating Scale 17-items (HDRS-17) and the Young Mania Rating Scale (YMRS) (for original analyses, see Miskowiak et al[1]). This analysis showed that the beneficial effects of EPO versus saline on cognition remained significant (cognitive composite: $F_{1,37} = 4.96$, $P = .03$; RVP speed: $F_{1,34} = 9.76$, $P = .004$), also at the week 14 follow-up assessment (cognitive composite: $F_{1,37} = 4.59$, $P = .04$; RVP speed: $F_{1,34} = 7.17$, $P = .01$; RVP accuracy: $F_{1,34} = 7.78$, $P = .009$). In additional analyses in which plasma lithium level was entered as a covariate in addition to HDRS-17 and YMRS scores, the effect of EPO on cognition also prevailed at both week 9 (cognitive composite: $F_{1,35} = 4.57$, $P = .04$; RVP speed: $F_{1,33} = 7.52$, $P = .01$) and week 14 (cognitive composite: $F_{1,36} = 3.99$, $P = .05$; RVP speed: $F_{1,33} = 5.39$, $P = .03$; RVP accuracy: $F_{1,33} = 6.33$, $P = .02$).

b. We performed an additional exploratory analysis in the subgroup of patients who were *not* receiving lithium treatment (N = 26; EPO: n = 11, saline: n = 15), of course expecting a loss of statistical power due to the substantial reduction in numbers of patients. This subgroup analysis showed a strong trend toward cognitive improvement in EPO- versus saline-treated patients despite the reduced statistical power (cognitive composite: $F_{1,22} = 3.58$, $P = .07$; RVP speed: $F_{1,20} = 2.98$, $P = .10$).

c. Finally, we assessed any potential interaction effects of lithium and EPO on cognition using 2-way ANCOVA with group (EPO/saline) and lithium treatment (yes/no) as fixed factors, cognitive change from baseline to week 9 as the dependent variable, and HDRS-17 and YMRS scores at week 9 as covariates. This analysis revealed no significant 2-way interactions between group and lithium treatment on cognitive change (cognitive composite: $F_{1,37} = 0.24$, $P = .63$; RVP speed: $F_{1,34} = 0.33$, $P = .57$).

In conclusion, the beneficial effects of EPO on cognition in bipolar disorder demonstrated by Miskowiak et al[1] were independent of lithium treatment and cannot be attributed to lithium or to an interaction between EPO and lithium.

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