Depression Severity and Cognitive Symptoms are Independent Predictors of Functioning in Patients with Depression

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Background
Major depressive disorder (MDD) is a common and debilitating condition characterized by emotional, somatic and cognitive symptoms that significantly affect patient functioning.1 Functional impairment imposes a significant burden in MDD and can persist even after remission of mood symptoms / preventing a full return to social and professional life.

PERFORM (Prospective Epidemiological Research on Functioning Outcomes Related to Major depressive disorder) is a European prospective observational cohort study undertaken to better understand the course of a depressive episode and its impact on patient functioning over a 2-year period in outpatients with MDD who were either initiating or undergoing their first switch of antidepressant monotherapy.1 In this study, functional impairment in patients with MDD was found to be not only associated with severity of depressive symptoms, but also independently associated with severity of cognitive symptoms consistently throughout the 2 years of follow-up.2

This post-hoc analysis was undertaken to further investigate the interrelationship of depression severity, cognitive symptoms and functioning in patients treated for MDD in the PERFORM study using the structural equations model (SEM) approach; this statistical method allows estimation of direct and indirect associations between groups of variables, permitting elucidation of potential causal relationships.

Methods
PERFORM study design
- Multicenter, prospective, non-interventional cohort study in five European countries: France, Germany, Spain, Sweden and the UK.
- Setting: general practitioners or psychiatrist outpatient practices (260 sites).
- Study assessments: during routine visits at baseline and 2, 6, 12, 18 and 24 months.
- Follow-up: 2-year follow-up, with study assessments during routine visits at baseline and 2, 6, 12, 18 and 24 months.
- Treatment: patients were treated with antidepressant monotherapy or an antidepressant switch, according to the treating clinician.
- Data collection: outcome and co-occurring factors were recorded in a standardized and structured format.

Statistical analysis
SEMs were used to explore the temporal association between the three outcomes of interest (Fig. 1A).3
- The SEM is a series of multivariate linear regressions modelled in one analysis.
- The arrows in Fig. 1A represent the effects (regression coefficients) that are estimated in the SEM.
- The three outcome measures were allowed to depend on the scores of each outcome at the most recent prior visit, but not at any earlier visits. Outcome measures from the same visit were allowed to be correlated.
- Statistical tests were used for general goodness-of-fit and for testing of standardized regression coefficients (SRC), used to evaluate the interaction between PHQ-9, PDQ-5 and SDS scores over time.
- G-computation was used as a sensitivity analysis to the SEM (Fig. 1B).4,5

Results
Study population
- 1402 patients were enrolled in the study, 1000 (77.7%) of whom had at least two consecutive assessments and thus provided data for this analysis.
- A gradual decrease in mean scores over time was seen for all three outcome measures, suggesting general improvement in all variables over the 2 years of follow-up (Fig. 2).
- A slower rate of change was observed for cognitive symptoms (PDQ-5 score) than for the other outcomes.

Relationship between depression severity, cognitive symptoms and functional impairment (SEM analysis)
- Patient-rated depression severity (PHQ-9), cognitive symptoms (PDQ-5) and functional impairment (SDS total score) depended moderately to strongly on the value of the previous assessment on the same scale.
- Standardized regression coefficients were 0.38–0.71 for PHQ-9, 0.60–0.71 for PDQ-5, and 0.44–0.50 for SDS total score (all p<0.001).
- At the significance level of 0.001 (Fig. 3):  
  - Depression severity at Month 2, 6 and 12 predicted the degree of functional impairment at Month 6, 12 and 18, respectively (SRC: 0.17, 0.25 and 0.22).
  - Severity of cognitive symptoms at baseline and Month 18 predicted depression severity at Month 2 and 24, respectively (SRC: 0.19 and 0.22).
  - Severity of cognitive symptoms at baseline, Month 2 and Month 18 predicted the degree of functional impairment at Month 2, 6 and 24, respectively (SRC: 0.18, 0.15 and 0.22).
- The degree of functional impairment did not significantly predict depression severity or the severity of cognitive symptoms at any time point.
- Depression severity did not predict the severity of cognitive symptoms at any time point.

Conclusions
General improvements in depressive symptoms, cognitive symptoms and functioning were observed over the 2 years of follow-up.
- Using SEM methods, patient-reported depression severity was found to be a major predictor of functional impairment at the subsequent visit, for the 2 years of follow-up.
- The severity of patient-reported cognitive symptoms was an independent and important predictor of later functional impairment, and generally predicted depression severity at subsequent visits.
- The degree of functional impairment was not found to predict depression severity on severity of cognitive symptoms at any subsequent visit at the 0.001 significance level. Similarly, depression severity was not found to significantly predict the severity of cognitive symptoms at any subsequent visit at this significance level.
- The results of the SEM analysis were confirmed using g-computation in a causal inference model as a sensitivity analysis.

Beyond confirming that patient-reported depression severity is a major predictor of functional impairment in patients with MDD, this analysis shows that the severity of patient-reported cognitive symptoms is also an independent and important predictor of later functional impairment.
- These findings suggest that treating impaired functioning in patients with MDD may be a consequence of the persistence of cognitive symptoms and highlight the importance of recognizing cognitive symptoms in patients with MDD in daily practice. Treatment interventions targeting both depression and cognitive symptoms could improve 0.19 annual recovery in this population.

References
5. G-computation was used as a sensitivity analysis to the SEM (Fig. 1B).4,5
6. Statistical analysis SEMs were used to explore the temporal association between the three outcomes of interest (Fig. 1A).3
7. The SEM is a series of multivariate linear regressions modelled in one analysis.
8. The arrows in Fig. 1A represent the effects (regression coefficients) that are estimated in the SEM.
9. The three outcome measures were allowed to depend on the scores of each outcome at the most recent prior visit, but not at any earlier visits. Outcome measures from the same visit were allowed to be correlated.
10. Statistical tests were used for general goodness-of-fit and for testing of standardized regression coefficients (SRC), used to evaluate the interaction between PHQ-9, PDQ-5 and SDS scores over time.
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Figure 1. Illustration of the SEM (A) and the model for the g-computation (B)

Figure 2. Distribution of depression severity (PHQ-9 score, range 0–27), functional impairment (SDS total score, range 0–100) and cognitive symptoms (PDQ-5 score, range 0–27) at each visit

Figure 3. Significant regression coefficients based on the SEM standardized by time point

Figure 4. Significant causal effect sizes from g-computation standardized by time point

Figure 5. Regression coefficients from the SEM versus g-computed effect estimates

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- Beyond confirming that patient-reported depression severity is a major predictor of functional impairment in patients with MDD, this analysis shows that the severity of patient-reported cognitive symptoms is also an independent and important predictor of later functional impairment.
- These findings suggest that treating impaired functioning in patients with MDD may be a consequence of the persistence of cognitive symptoms and highlight the importance of recognizing cognitive symptoms in patients with MDD in daily practice. Treatment interventions targeting both depression and cognitive symptoms could improve 0.19 annual recovery in this population.