Prospective Epidemiological Research on Functioning Outcomes Related to Major depressive disorder

PERFORM

Residual Patient-Reported Cognitive Dysfunction: A Potential Predictor for Relapse in MDD?

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ABSTRACT *

Objective: PERFORM (Prospective Epidemiological Research on Functioning Outcomes Related to Major depressive disorder) is a European 2-year prospective observational cohort study. It included 1457 patients treated for major depressive disorder (MDD). This analysis aims to identify predictors of relapse and to determine if residual patient-reported cognitive dysfunction (PRCD) is one of the predictors.

Methods: Inclusion criteria were: outpatients from primary and secondary care practices, DSM-IV-TR diagnosis of MDD, age 18–65 years, initiating or switching to an antidepressant treatment in monotherapy. Patients with co-morbid psychiatric disorders or neurodegenerative diseases were excluded. Relapse status was assessed at 6 months in patients in remission at 2 months, based on either treatment change due to lack of efficacy or an increase in MDD symptoms shown by a Patient Health Questionnaire 9-item (PHQ-9) score ≥10 or Montgomery-Åsberg Depression Rating Scale score ≥22; or a Clinical Global Impression-Severity scale score ≥4 if neither of the previous scales were assessed. Quality of life (12-item Short-Form Health Survey [SF-12]) and PRCD (Perceived Deficit Questionnaire 5-item [PDQ-5]) were collected among other variables. Using an interim 6-month dataset, clinically relevant factors identified from a literature review were tested in univariate logistic regression analyses; factors with p<0.20 were then combined in a multiple logistic regression followed by backward variables selection with p<0.05. Four factors were forced into the model as being expected predictors of relapse: country, age, sex and PHQ-9 score at 2 months. Sensitivity analyses consisted of forward selection method or alternative outcome definitions. Data are presented as odds ratio (OR) and [95% confidence interval].

Results: Among the 296 remitters at 2 months, 19.3% had relapsed at 6 months. Mean 2-month PDQ-5 score was 8.8 in relapsers and 6.5 in non-relapsers; in multivariate analysis, one additional unit of PDQ-5 at 2 months was associated with a 16% increase in risk of relapse at 6 months (OR = 1.16 [1.04-1.30]). Other significant risk factors of relapse were male sex (OR = 2.74 [1.15-6.54]) and a low score on the SF-12 physical component (OR = 0.95 [0.91-1.00]). The results from the sensitivity analysis using the forward selection method were consistent for the PDQ-5 (OR = 1.16 [1.04-1.30]) and most of the other factors. The SF-12 physical component was replaced with chronic pain/fibromyalgia, which covers similar concepts. The OR of PDQ-5 was consistent across all other sensitivity analyses (between 1.12 and 1.18).

Conclusion: Residual PRCD measured with PDQ-5 in remitted MDD patients appears to be a potential predictor of relapse. The extensive control for known predictors of relapse in the model and the consistent estimates for different definitions of relapse demonstrate the robustness of this finding. These results need to be confirmed in further studies.

***Updated data, using the final 24-month dataset, are presented in the poster.**

BACKGROUND

Major depressive disorder (MDD) is a chronic and recurring condition that affects more than 120 million people worldwide[1] and is one of the top ten causes of disability.[2]

As each depressive episode evolves, individuals with MDD present different degrees of functional impairment and thus variations in disease-related costs. Such costs comprise direct (treatment) costs and even greater indirect costs (arising from productivity loss).[3] In particular, relapse after remission of symptoms is potentially associated with a high functional and economic burden. Despite therapeutic advances, not all patients achieve stable remission, and limited evidence exists to aid clinical decision-making regarding the risk of relapse.[4]

PERFORM (**P**rospective **E**pidemiological **R**esearch on **F**unctioning **O**utcomes **R**elated to **M**ajor depressive disorder) is a prospective, observational cohort study undertaken to monitor the functioning of patients with MDD over a 2-year period in routine clinical practice in five European countries.

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OBJECTIVE

This analysis was undertaken to identify predictors of relapse by Month 6 for patients in remission at Month 2 in the PERFORM study, and to determine if residual patient-reported cognitive dysfunction (PRCD) was one of these predictors.

METHODS

PERFORM study design[5]

- Multicenter, prospective, non-interventional cohort study in five European countries: France, UK, Spain, Germany and Sweden.
- Setting: general practitioners' or psychiatrists' outpatient practices (260 sites).
- Patients with MDD initiating antidepressant monotherapy or undergoing their first switch of treatment (Table 1).
- Two-year follow-up period (visits at 2, 6, 12, 18, and 24 months; Table 2).

Table 1. Patient selection criteria

INCLUSION	EXCLUSION
• Outpatients **18–65** years old	• Schizophrenia or other psychotic disorders, bipolar disorder, substance dependence, dementia or other neurodegenerative disease significantly impacting cognitive functioning
• With a current or new **diagnosis of Major Depressive Episode** according to DSM-IV-TR	• Mood disorder due to a general medical condition or substances
• **Starting an antidepressant treatment in monotherapy at baseline** (treatment initiation or first treatment switch) as decided by the physician	• Pregnant women or women 6 months post-partum
	• Acute suicidality
	• Residential instability with an expected loss of follow-up in the coming 2 years (eg, change of address)

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision.

Table 2. Study assessments

			VISITS 1–4 (baseline, ~2, ~6, and ~12 months)[a]	VISITS 5 AND 6 (~18 and ~24 months)[a]
All physicians		Patient characteristics	x	x
		History of MDD/clinical characteristics	x	x
		MDD management + resource use	x	x
		CGI-S	x	x
Psychiatrists only		MADRS	x	x
		HAM-A	x	x
Patient-reported outcomes	Disease severity	PHQ-9	x	x
	Functioning	SDS	x	x
		WPAI-SHP	x	x
		DFFS[b]	x	
	Quality of life	SF-12	x	
		EQ-5D (UK)	x	x
	Sexual dysfunction	ASEX	x	
	Adherence	MMAS-4[b]	x	
	Subjective cognitive symptoms	PDQ-5[b]	x	x
		Important life events	x	x

[a]Month 2: ±3 weeks; Month 6: ±1 month; Months 12, 18, and 24: ±2 months. [b]In some countries only.

ASEX: Arizona Sexual Experiences Scale; CGI-S: Clinical Global Impression – Severity scale; DFFS: Depression and Family Functioning Scale; EQ-5D: EuroQol 5-Dimensions Questionnaire; HAM-A: Hamilton Anxiety Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder; MMAS-4: Morisky Medication Adherence Scale-4 items; PDQ-5: Perceived Deficit Questionnaire-5 items; PHQ-9: Patient Health Questionnaire-9 items; SDS: Sheehan Disability Scale; SF-12: Medical Outcomes Study Short-Form (12-item) Health Survey; WPAI-SHP: Work Productivity and Activity Impairment Questionnaire-Specific Health Problem.

Assessment of predictors for relapse

Using the final (24-month) dataset, factors recorded at baseline and Month 2 were analyzed as potential predictors of relapse by Month 6 in patients who were in remission at Month 2.

Remission

Remission at the 2-month visit was defined according to the following algorithm, based on published literature and expert opinion:
- PHQ-9 total score ≤9
- If PHQ-9 is missing, then MADRS total score ≤10
- If MADRS is missing, then CGI-S score ≤2.

Relapse

For patients in remission at 2 months, relapse at the 6-month visit was defined as:
- Treatment modification (switch or combination) for lack of efficacy
OR
- PHQ-9 score ≥10, or MADRS score ≥22, or CGI-S score ≥4.

Patient-reported cognitive dysfunction

PRCD was assessed by the 5-item Perceived Deficit Questionnaire (PDQ-5), which measures the frequency during the previous 4 weeks of subjective cognitive symptoms (memory, concentration, and executive function).[6,7] Total score range is 0–20, higher scores reflect higher impairment.

Statistical analysis

Clinically relevant factors identified from a literature review were tested in univariate logistic regression analyses (Table 3).

Factors with p<0.20 were then combined in a multiple logistic regression followed by backward variable selection (i.e., sequential removal of the least significant variable from the model and recomputation of the model until all remaining variables have p<0.05).

Four factors were forced into the model as adjustment variables: country, age, sex, and PHQ-9 score at 2 months.

Results are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs).

By default, ORs for assessment scales and continuous outcomes are given per additional unit. To account for the differences in metrics between scales, ORs for assessment scales were also estimated per additional half standard deviation (0.5*SD).

Sensitivity analyses included replacing the backward selection process by a forward selection process and the use of alternative definitions for remission and relapse.

Table 3. Variables selected for univariate and multivariate analyses

TYPE OF VARIABLE	VARIABLES TESTED IN UNIVARIATE ANALYSES	VARIABLES SELECTED FOR MULTIVARIATE ANALYSES (p<0.20 in univariate analyses)
Sociodemographic factors	Country *(BL)* Age *(BL)* Sex *(BL)* Tobacco use *(BL)* Educational level *(BL)* Body mass index *(M2)* Marital status *(M2)* Employment status *(M2)* At least one important life event *(M2)*	Country *(BL)*[a] Age *(BL)*[a] Sex *(BL)*[a] Marital status *(M2)*
Patient history	Previous episode *(BL)*	
Comorbidities	At least one concomitant mental disorder *(BL)* At least one chronic medical condition *(BL)* Chronic pain or fibromyalgia *(BL)* At least one anxiety symptom/disorder *(M2)*	
Resource use and treatment patterns	Physician specialty *(BL)* Previous or current psychotherapy *(BL)* Treatment stopped between baseline and Month 2 Sick leave *(PreM2)* Hospitalization for depression *(PreM2)* Switch of antidepressant *(PreM2)* MMAS-4 score *(M2)* Treatment line *(M2)*	 Switch of antidepressant *(PreM2)*
Disease severity	Suicide attempt *(PreM2)* PHQ-9 total score *(M2)* CGI-S score *(M2)* PDQ-5 total score *(M2)* WPAI-SHP score *(M2)* SF-12 – PCS score *(M2)* SF-12 – MCS score *(M2)* ASEX score *(M2)*	Suicide attempt *(PreM2)* PHQ-9 total score *(M2)*[a] CGI-S score *(M2)* PDQ-5 total score *(M2)* WPAI-SHP score *(M2)* SF-12 – PCS score *(M2)* SF-12 – MCS score *(M2)*

[a]Factors forced in the model.
BL: at baseline; *M2*: at Month 2; *MCS*: mental component summary; *PCS*: physical component summary; *PreM2*: prior and up to Month 2 (anytime before baseline, at baseline, or between baseline and Month 2).

RESULTS

Population

1402 patients were enrolled in the study, 1159 of whom provided analyzable data. The analyzable population comprised all patients who met study inclusion and exclusion criteria and for whom at least one post-baseline assessment was recorded. Of the 300 patients with known relapse status who were in remission at Month 2, 59 (19.7%) had relapsed by Month 6.

- Mean (±SD) 2-month PDQ-5 score was 8.8 (±4.8) in relapsers and 6.5 (±4.0) in non-relapsers (p<0.001; Student's *t* test).

Risk factors for relapse

Results of the multivariate analysis for risk factors of relapse at Month 6 in patients in remission at Month 2 are shown in Table 4.

- Each additional unit of PDQ-5 total score (range 0–20) at 2 months was associated with a 12% increase in the odds of relapse at 6 months (p=0.042).
- Each additional unit of PHQ-9 total score (range 0–27) at 2 months was associated with a 27% increase in the odds of relapse at 6 months (p=0.030).
- An additional 0.5*SD in PDQ-5 total score (2.16 units) and in PHQ-9 total score (1.18 units) at 2 months was associated with a similar increase in the odds ratio of relapse at 6 months:
  - PHQ-9 total score: OR 1.33 (95% CI: [1.03, 1.72])
  - PDQ-5 total score: OR 1.28 (95% CI: [1.01, 1.62]).
- Other significant risk factors for increasing the risk of relapse were being male, and being married or living as a couple.

The results from the sensitivity analysis using a forward selection process were identical to those obtained using the backward selection process (base case analysis). The same factors were retained by both selection processes, including PDQ-5 and PHQ-9 (Figs. 1 and 2).

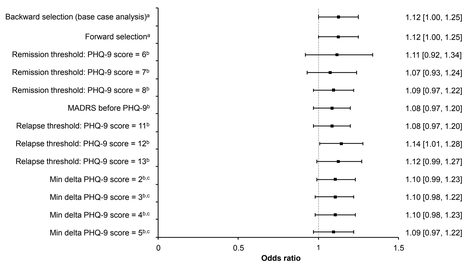
- The ORs for PDQ-5 and PHQ-9 were consistent across all other sensitivity analyses (ranging from 1.07 to 1.14 and 1.08 to 1.33, respectively).

Table 4. Multivariate logistic regression model for the analysis of risk factors of relapse at Month 6 in patients in remission at Month 2 (backward selection)

Variable	Categories	n/N (%)	Odds ratio (95% CI)	p-value
Country[a]	France	11/59 (18.6)	1	
	Spain	5/27 (18.5)	0.79 (0.22, 2.82)	0.719
	UK	15/65 (23.1)	0.97 (0.36, 2.64)	0.952
	Sweden	3/9 (33.3)	2.15 (0.40, 11.49)	0.371
	Germany	3/26 (11.5)	0.51 (0.12, 2.22)	0.367
Age	Per additional year	—	0.99 (0.96, 1.03)	0.765
Sex	Female	21/131 (16.0)	1	
	Male	16/55 (29.1)	2.47 (1.05, 5.80)	**0.037**
Marital status (M2)	Single or divorced/separated or widowed	8/66 (12.1)	1	
	Married or living as a couple	29/120 (24.2)	2.73 (1.05, 7.12)	**0.040**
PHQ-9 total score (M2)	Per additional unit	—	1.27 (1.02, 1.59)	**0.030**
PDQ-5 total score (M2)	Per additional unit	—	1.12 (1.00, 1.25)	**0.042**

[a]Global p-value = 0.703.

Fig. 1. Summary of sensitivity analyses of PDQ-5 effect (odds ratio [95% CI]) on relapse at Month 6



[a]Computed for patients with complete values on all candidate variables (n=186).
[b]Computed for patients with complete values on all variables in the final model (n=193).
[c]Additional criterion for relapse definition: minimum change in PHQ-9 total score between Month 2 and Month 6.

Fig. 2. Summary of sensitivity analyses of PHQ-9 effect (odds ratio [95% CI]) on relapse at Month 6

[a]Computed for patients with complete values on all candidate variables (n=186).
[b]Computed for patients with complete values on all variables in the final model (n=193).
[c]Additional criterion for relapse definition: minimum change in PHQ-9 total score between Month 2 and Month 6.

CONCLUSIONS

- This analysis has shown that there are a variety of predictors of relapse in patients with MDD.
- Residual patient-reported cognitive dysfunction at Month 2 measured with PDQ-5 appears to be a predictor of relapse at Month 6 in patients with MDD in remission.
- Other predictors were PHQ-9 total score at Month 2, being male, and being married or living as a couple.
- The magnitude of effect for residual patient-reported cognitive dysfunction at Month 2 is comparable to that of depressive symptoms at Month 2.
- The extensive control for known predictors of relapse in the model and the sensitivity analyses demonstrate the consistency of these findings.
- Early identification of patients at risk of relapse may improve clinical decision-making and long-term outcomes in patients with MDD.

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