

Supplementary Material

Appendix 1. Ethical approval

National approvals were obtained as follows.

France (102 physicians/sites)

- French National Agency for Medicines and Health Products Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé, previously called Agence Française de Sécurité Sanitaire des Produits de Santé)
- Advisory Committee on Information Processing in Material Research in the Field of Health (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé)
- French data protection agency (Commission Nationale de l'Informatique et des Libertés)
- French National Medical Council (Conseil National de l'Ordre des Médecins), Ethics Committee (CPP Ile de France II)

Germany (47 physicians/sites)

- Munich Ethics Committee
- Local Ethics Committees including Hamburg, Rheinland-Pfalz, Sachsen, and Westfalen-Lippe Ethics Committees and others

Spain (46 physicians/sites)

- Agencia Española del Medicamento y Productos Sanitarios
- Comités Éticos de Investigaciones Clínicas
- Comunidades Autónomas of 14 regions

Sweden (22 physicians/sites)

- Umeå Ethics Committee

UK (65 physicians/sites)

- Medical Research and Ethics Committee
- National Institute for Health Research
- Local submissions

Appendix 2. Overview of the scales used to assess depression severity, cognitive symptoms, and functioning

9-Item Patient Health Questionnaire (PHQ-9)

Objective	To grade depressive symptom severity
Rater	Patient
Recall period	2 weeks
Domains/items	9 items assessing different symptoms of depression
Scoring	Frequency of each symptom scored from 0 (“not at all”) to 3 (“nearly every day”) then summed to provide an overall score of 0–27. Scores of 5–9, 10–14, 15–19, and >20 represent mild, moderate, moderately severe, and severe depression, respectively
References	Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. <i>J Gen Intern Med.</i> 2001;16:606–613

5-Item Perceived Deficit Questionnaire (PDQ-5)

Objective	To assess perceived cognitive symptoms from the patient’s perspective
Rater	Patient
Recall period	4 weeks
Domains/items	5 items assessing aspects of memory, attention and concentration that may be affected by major depressive disorder
Scoring	Frequency of each symptom scored from 0 (“never”) to 4 (“almost always”) then summed to provide an overall score of 0–20, with higher scores reflecting greater severity of cognitive symptoms
References	Sullivan MJ, Edgley K, Dehoux E. A survey of multiple sclerosis. Part 1. Perceived cognitive problems and compensatory strategy use. <i>Can J Rehabil.</i> 1990;4:99–105 National Multiple Sclerosis Society. <i>Multiple Sclerosis Quality of Life Inventory: A User’s Manual.</i> New York, NY: The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee, The National Multiple Sclerosis Society; 1997

Sheehan Disability Scale (SDS)

Objective	To evaluate the extent of functional impairment occurring in work/school, social and family life
Rater	Patient
Recall period	7 days
Domains/items	3 domains assessing work/school, social life/leisure, and family life/home responsibilities
Scoring	For each domain, impairment is rated on a scale of 0–10; higher values indicate greater impairment. The individual domain scores can be summed to provide an overall functional-impairment score that ranges from 0 (unimpaired) to 30 (greatly impaired)
References	Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. <i>Int Clin Psychopharmacol.</i> 1996;11(Suppl 3):89–95 Sheehan KH, Sheehan DV. Assessing treatment effects in clinical trials with the Discan metric of the Sheehan Disability Scale. <i>Int Clin Psychopharmacol.</i> 2008;23:70–83

Appendix 3. G-computation methodology

G-computation is a method for assessing causal inference and provides estimates with causal interpretations from nonrandomized data under certain conditions, such as when unmeasured confounders may be present. In the scenario reported in this study, a specific effect of a rating at a given time point on another rating at the following time point is estimated while removing — rather than correcting for — the effect of potential confounders. Contrary to structural equation models (SEMs), the effect of each rating (“exposure”) on each dependent rating (“outcome”) is estimated separately. For example, the effect of 5-item Perceived Deficit Questionnaire (PDQ-5) at Month 2 on Sheehan Disability Scale (SDS) at Month 6 is estimated treating 9-item Patient Health Questionnaire (PHQ-9) and SDS at Month 2 as confounders and PHQ-9 and PDQ-5 as mediators (Figure 1B).

In G-computation, confounding effects are removed by creating new datasets of counterfactuals, where the “exposure” is uncorrelated with the potential confounders and then estimating the mean difference between two different exposures. Mediators should be ignored. The counterfactual outcomes were estimated in a linear regression model including main effects of the three ratings along with all three first-order interactions and the second-order interaction to ensure sufficient flexibility. The effect of the “exposure” on the “outcome” was then estimated in a linear regression of the counterfactual outcomes on “exposure”. Standard errors and *P*-values were obtained from 10,000 bootstrap samples.

Table S1 Summary of patient characteristics at baseline

Patient characteristic	Study population (N=1159)
<i>Sociodemographics</i>	
Country (n)	
France	339
Spain	270
UK	341
Sweden	45
Germany	164
Age, mean \pm SD (years)	44.3 \pm 12.0
Female (%)	73.2
Marital status (%)	
Single	21.6
Married/couple	58.5
Divorced/separated	16.7
Widowed	3.2
Education (%)	
No degree or diploma	4.5
Elementary school	24.4
High school	36.9
Non-university degree	14.0
University degree	20.2
Work status (%)	
Paid employment or self-employed	66.8
Unemployed	17.8
<i>Characteristics of current depressive episode</i>	
Treating physician (% of patient group)	
General practitioner	83.6
Psychiatrist	16.4
Duration of episode (%) ^a	
<1 week	1.6
1–2 weeks	5.9
2–4 weeks	21.3
4–8 weeks	19.8
>8 weeks	51.4
Treatment ^b	
Initiating antidepressant therapy (%)	78.7
Switching antidepressant therapy (%)	21.3
Significant symptoms of anxiety (%) ^c	62.6
Anxiety disorders (%) ^d	45.5
<i>Other current illnesses</i>	
Mental health disorders other than depression (%)	
Alcohol abuse or dependence	2.7
Other abuse disorders	1.3
Somatoform disorders	7.9
Eating disorders (anorexia, bulimia)	8.1
Other	0.6

Patient characteristic	Study population (N=1159)
Functional syndromes (%)	
Chronic pain	16.7
Chronic fatigue	16.1
Fibromyalgia	6.8
Premenstrual syndrome	3.5
Sleep disorders	28.2
Other	2.8
<i>Previous depressive episodes</i>	
History of depression (%)	
Previous episode ^e	56.6
Episode within previous 12 months if previous episode ^f	25.5
Antidepressant treatment if previous episode ^g	80.9
Previous hospitalization for depression ^f	8.9
Remission of previous episode ^f	83.2
Previous suicide attempt ^f	13.1

Notes: ^aPhysicians' response. ^bN=1157; switching/initiating status unknown for two patients. ^cThe percentage refers to patients "probably" or "definitely" presenting clinically significant symptoms of anxiety according to physician; total N=1158. ^dThe percentage refers to patients "probably" or "definitely" meeting Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) criteria for one or more of the anxiety disorders according to physician; N=1120. ^eN=1157. ^fN=655. ^gN=654.

Abbreviation: SD, standard deviation.

Table S2 Regression coefficients, variances, and correlations based on the SEM

Regression coefficients						
Effect on	Effect of	Month 2	Month 6	Month 12	Month 18	Month 24
PDQ-5	PDQ-5	0.739 (0.038) ***	0.698 (0.039) ***	0.608 (0.042) ***	0.653 (0.043) ***	0.829 (0.030) ***
	SDS total	0.014 (0.028)	0.012 (0.030)	0.038 (0.032)	0.096 (0.036) **	-0.045 (0.035)
	PHQ-9	0.021 (0.035)	0.079 (0.036) *	0.120 (0.041) **	0.008 (0.040)	0.036 (0.042)
SDS total	PDQ-5	0.308 (0.080) ***	0.264 (0.078) ***	0.070 (0.078)	0.012 (0.084)	0.343 (0.080) ***
	SDS total	0.531 (0.054) ***	0.506 (0.051) ***	0.472 (0.053) ***	0.515 (0.067) ***	0.416 (0.062) ***
	PHQ-9	0.024 (0.071)	0.233 (0.064) ***	0.308 (0.071) ***	0.272 (0.076) ***	0.160 (0.079) *
PHQ-9	PDQ-5	0.256 (0.062) ***	0.189 (0.058) **	-0.007 (0.059)	0.151 (0.062) *	0.274 (0.055) ***
	SDS total	0.047 (0.044)	-0.005 (0.039)	0.015 (0.042)	0.044 (0.051)	-0.014 (0.045)
	PHQ-9	0.429 (0.055) ***	0.626 (0.047) ***	0.726 (0.053) ***	0.597 (0.055) ***	0.584 (0.054) ***
Residual variances and correlations						
	Variable(s)	Month 2	Month 6	Month 12	Month 18	Month 24
Residual variance	PDQ-5	10.7	12.2	12.1	11.3	8.7
	SDS total	41.5	38.0	34.7	38.2	29.2
	PHQ-9	28.0	23.3	22.7	23.2	16.6
Residual correlation	PDQ-5/SDS total	0.52	0.57	0.61	0.62	0.53
	SDS total/ PHQ-9	0.66	0.73	0.73	0.75	0.70
	PHQ-9/ PDQ-5	0.56	0.61	0.60	0.66	0.54
Standardized regression coefficients						
Effect on	Effect of	Month 2	Month 6	Month 12	Month 18	Month 24
PDQ-5	PDQ-5	0.706 (0.036) ***	0.656 (0.039) ***	0.597 (0.042) ***	0.646 (0.042) ***	0.835 (0.040) ***
	SDS total	0.020 (0.040)	0.019 (0.047)	0.064 (0.053)	0.150 (0.056) **	-0.075 (0.057)
	PHQ-9	0.023 (0.039)	0.097 (0.045) *	0.154 (0.053) **	0.010 (0.052)	0.047 (0.055)
SDS total	PDQ-5	0.177 (0.046) ***	0.145 (0.043) ***	0.043 (0.048)	0.007 (0.051)	0.221 (0.051) ***
	SDS total	0.452 (0.046) ***	0.464 (0.047) ***	0.499 (0.056) ***	0.496 (0.064) ***	0.436 (0.065) ***
	PHQ-9	0.016 (0.048)	0.168 (0.046) ***	0.250 (0.057) ***	0.217 (0.061) ***	0.135 (0.067) *
PHQ-9	PDQ-5	0.187 (0.045) ***	0.136 (0.042) **	-0.005 (0.044)	0.114 (0.047) *	0.217 (0.044) ***
	SDS total	0.050 (0.048)	-0.006 (0.047)	0.020 (0.053)	0.053 (0.061)	-0.018 (0.058)
	PHQ-9	0.365 (0.047) ***	0.588 (0.044) ***	0.711 (0.052) ***	0.591 (0.054) ***	0.606 (0.057) ***

Notes: Standard deviations for path coefficients are in parentheses. *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$

Abbreviations: PDQ-5, 5-item Perceived Deficit Questionnaire; PHQ-9, 9-item Patient Health Questionnaire; SDS, Sheehan Disability Scale; SEM, structural equation model.

Figure S1 Regression coefficients from the SEM versus G-computed effect estimates.

Note: The identity line is included. No systematic differences between estimates based on the two approaches, suggesting robustness of the findings. SEM, structural equation model.

