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Published in:
INTERNATIONAL CLINICAL PSYCHOPHARMACOLOGY

DOI:
10.1097/YIC.0000000000000384

Publication date:
2022

OPEN

Social withdrawal as a trans-diagnostic predictor of short-term remission: a meta-analysis of five clinical cohorts

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Social withdrawal is an early manifestation of several neuropsychiatric disorders, and it is characterised by a gradual disengagement from social interactions, potentially leading to complete isolation. This study investigated the association between social withdrawal at baseline and short-term symptom remission in five independent cohorts, including patients with major depressive disorder (MDD), bipolar spectrum disorders, and schizophrenia. Measures of social withdrawal were derived in each study, and clinical remission was estimated based on the psychopathological severity assessed after short-term psychopharmacological treatment (12 weeks). Logistic regression was performed in each sample, adjusting for age and baseline psychopathological severity residualised for social withdrawal. Results were then meta-analysed across samples within a random-effect framework. A total of 4461 patients were included in the analyses (3195 patients with MDD, 655 with bipolar spectrum disorders and 611 with schizophrenia). The meta-analysis showed that higher baseline levels of social withdrawal were associated with a decreased likelihood of short-term remission ($OR_{adj}=0.67$, 95% CI, 0.58–0.79, $P=5.28\times10^{-7}$), with the strongest effect in patients with schizophrenia. Overall, our study highlighted the need to address social withdrawal in the early phases of the disease to promote symptom remission in patients with major psychiatric disorders. Understanding the neurobiology underlying social withdrawal may aid the development of medications that can specifically reverse social impairment, thereby fostering clinical remission. ***Int Clin Psychopharmacol*** **37: 38–45 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.**

International Clinical Psychopharmacology 2022, **37**:38–45

Keywords: bipolar disorder, major depressive disorder, psychopharmacology, remission, social withdrawal, schizophrenia, transdiagnostic

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Received 15 October 2021 **Accepted** 9 November 2021

Introduction

Social withdrawal is defined as a progressive retreat from social interactions that a person establishes in the family, at the workplace, and in friendship circles, potentially leading up to total isolation (Kas *et al*., 2019). It represents a multi-determined complex behaviour that may be considered as a neuropsychiatric trans-diagnostic symptom domain (Gur and Gur, 2016; Cotter *et al*., 2018). Indeed, social withdrawal has been reported as part of the cluster of negative symptoms since the first descriptions of schizophrenia (Addington and Addington, 2008; Green *et al*., 2015), and it is also a common early manifestation of mood disorders (Van Rheenen and Rossell, 2014; Kupferberg *et al*., 2016).

Social withdrawal is sustained by pathogenic processes affecting the so-called 'social brain', a term used for describing the complex network of brain regions underpinning social functioning. Interestingly, the brain structures and neurotransmitters associated with social withdrawal are transdiagnostically the same in neuropsychiatric disorders (Cacioppo *et al*., 2014; Porcelli *et al*., 2019; Saris *et al*., 2021). Moreover, patients often show an impairment of social

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.intclinpsychopharm.com.

0268-1315 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. DOI: 10.1097/YIC.0000000000000384

functioning before other symptoms arise, and social withdrawal may persist after remission (Feldman *et al.*, 2004; Dominguez *et al.*, 2010; Porcelli *et al.*, 2020). Therefore, social withdrawal may be considered as an independent behavioural trait with a specific underlying biological substrate (Porcelli *et al.*, 2019), related to but not completely explained by psychopathological severity, comorbid medical diseases or medication exposure (Heinssen *et al.*, 2000; Reichman and Negron, 2001; Arango *et al.*, 2004; Bellack *et al.*, 2004; Porcelli *et al.*, 2020). Social withdrawal results from a combination of genetic and environmental influences. Both family and twin studies have provided evidence for a heritable component of social anxiety/avoidance (Hudson and Rapee, 2000). In general, social functioning is considered a continuously distributed trait in the population (Reeb-Sutherland *et al.*, 2012), and it has a single-nucleotide polymorphism-based heritability of 6% (Bralten *et al.*, 2021). Social functioning is also influenced by socio-demographic factors, including age, education level, employment and marital status, but also clinical (e.g. medical comorbidities and smoking) and psychological factors (e.g. temperament and impairments in other cognitive domains) (Fett *et al.*, 2011; Green *et al.*, 2015; Gur and Gur, 2016; van der Wee *et al.*, 2019; Porcelli *et al.*, 2020).

Of note, negative symptoms of schizophrenia, including 'passive/apathetic social withdrawal', were shown to be negatively correlated with global functioning more than positive symptoms (Rabinowitz *et al.*, 2012), and social functioning was found to be correlated with subjective life satisfaction (Fitzgerald *et al.*, 2001). Moreover, social functioning is relevant to physical health, as there is considerable evidence that social relationships are pivotal for human wellbeing and survival (Eisenberger and Cole, 2012). Indeed, low social engagement has been associated with poorer health outcomes, increased risk of cardiovascular diseases and mortality rates, with a greater effect than smoking, alcohol use or obesity (Holt-Lunstad *et al.*, 2010; Eisenberger and Cole, 2012; Cacioppo *et al.*, 2015).

In this context, social withdrawal has been identified as an important dimension to be evaluated and studied in patients with neuropsychiatric disorders, independently from their diagnosis, because of its impact on individuals/society and the evidence of biological determinants that makes social withdrawal a target for possible innovative treatments (Kas *et al.*, 2019).

The present study aims to investigate the association between social withdrawal and short-term symptom remission in five independent clinical cohorts, including patients with major depressive disorder (MDD), bipolar spectrum disorder and schizophrenia.

Material and methods

Study samples

Clinical Antipsychotic Trials of Intervention Effectiveness

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study is a large, National Institute of Mental Health-funded, randomised controlled trial including 1600 patients with schizophrenia. This trial was designed to determine the long-term effectiveness and tolerability of one conventional and four second-generation antipsychotic medications. Eligible participants were randomised to olanzapine, risperidone, ziprasidone, quetiapine or perphenazine in a double-blind manner and received treatments for up to 18 months or until treatment was discontinued for any reason. At baseline, socio-demographic, psychosocial and clinical information was collected, the Positive and Negative Syndrome Scale (PANSS) was used to assess psychopathological severity and the Quality-of-Life Scale (QOLS) for various aspects of interpersonal and social experience (Kay *et al.*, 1987; Swartz *et al.*, 2003). The QOLS is a 21-item scale, in which each item is rated on a 7-point scale, from 0 (highest impairment) to 6 (almost normal) (Heinrichs *et al.*, 1984). The QOLS item 8 ('social withdrawal') was selected as an indicator of social withdrawal in our study. This item rates the degree to which the person actively avoids social interaction due to discomfort or disinterest. For the present study, baseline and third-month (12 weeks) follow-up data were considered. Further details about CATIE design and population are available elsewhere (Stroup *et al.*, 2003).

Combining Medications to Enhance Depression Outcomes

The Combining Medications to Enhance Depression Outcomes (CO-MED) study is a 7-month, single-blind, randomised trial designed to compare the efficacy of three different initial medications in the short-term (12 weeks) and longer-term (28 weeks) treatment of nonpsychotic MDD. Participants were recruited from six primary care and nine psychiatric care sites across the USA. Each patient received either a combination of two antidepressants (bupropion + escitalopram or venlafaxine + mirtazapine) or an antidepressant (escitalopram) plus placebo. At baseline, clinical and demographic information was collected. The psychopathological severity was assessed using the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C) (Trivedi *et al.*, 2004) at baseline and follow-up. The Work and Social Adjustment Scale (WSAS) was selected to derive an indicator of social withdrawal for our analyses. The WSAS is a self-reported five-items scale that assesses work and social functioning on a nine-point range, from 0 (no impairment) to 8 (very severe impairment) (Mundt *et al.*, 2002). For the present study, we combined item 3

[impairment in social activities: 'Because of my depression, my social leisure activities (with other people, such as parties, bars, clubs, outings, visits, dating, home entertainment) are impaired'] and item 5 (impairment in close relationships: 'Because of my depression, my ability to form and maintain close relationships with others, including those I live with is impaired'), By combining items 3 and 5, we obtained a measure of social withdrawal ranging from 0 (unimpaired) to 16 (highly impaired). More information about the study design and population is detailed elsewhere (Rush *et al.*, 2011). For the present study, baseline and third month (12 weeks) follow-up data were considered.

European Group for the Study of Resistant Depression

This is a European multicentre cross-sectional study that aimed to investigate the clinical and biological correlates of resistant MDD. The study design and population were described in detail elsewhere (Dold *et al.*, 2018). Briefly, subjects of age 18 years and older, who met the DSM-IV-TR criteria for MDD, were recruited in 10 specialist referral centres between 2011 and 2016. Subjects must have received at least one adequate antidepressant trial for the current episode. Sociodemographic and clinical information was collected through a comprehensive clinical interview conducted by trained psychiatrists. Current psychopathological severity was evaluated through the Montgomery and Asberg Depression Rating Scale (cMADRS) (Montgomery and Asberg, 1979). Symptom severity at the onset of the current depressive episode was estimated according to patient's statements and information obtained from medical records (retrospective MADRS, rMADRS). For our analyses, data at study entry and retrospective data were considered. Item 8 of the rMADRS ('Have you lost your feelings for friends and acquaintances?') was identified as the best proxy of social withdrawal in this study. This item specifically rates the subjective experience of reduced interest in the surroundings or activities that normally give pleasure, as well as the ability to react with adequate emotion to circumstances or people, with a score from 0 (almost normal) to 6 (highest impairment).

Sequenced Treatment Alternatives to Relieve Depression

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study was performed to assess the efficacy and tolerability of different antidepressants through four sequential treatment levels. Detailed information about the study design and population can be found elsewhere (Howland, 2008). In brief, patients with nonpsychotic MDD (DSM-IV criteria) were enrolled from primary care or psychiatric outpatient clinics. At baseline, clinical and demographic information was collected. Psychopathological severity was assessed using the 16-item QIDS-C (Trivedi *et al.*, 2004) at baseline and follow-up. A detailed assessment of overall functioning was carried out through the WSAS (Mundt *et al.*, 2002), from which a social withdrawal indicator was derived as explained for the CO-MED study. For our analyses, baseline and third month (week 12) follow-up data were considered.

Systematic Treatment Enhancement Program for Bipolar Disorder

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study is a prospective clinical trial performed to expand the knowledge on the management, treatment, and longitudinal outcome of bipolar disorder. STEP-BD applied a hybrid design to collect longitudinal data as patients transitioned between naturalistic treatment phases and randomized clinical trials. Description of the study design and population are detailed elsewhere (Sachs *et al.*, 2003). In brief, patients older than 15 years, affected by bipolar disorder type I or II, cyclothymia, bipolar disorder not otherwise specified, or schizoaffective disorder, bipolar subtype, were recruited. Depressive symptoms were evaluated through the MADRS (Montgomery and Asberg, 1979), and symptoms of mania were evaluated by the Young Mania Rating Scale (Young *et al.*, 1978). The Life-Range of Impaired Functioning Tool (LRIFT) was selected to derive an indicator of social withdrawal. The LRIFT is a clinician-administered scale that was specifically developed to assess, on a five-point scale, functional impairment in different areas, such as work and interpersonal relations, as well as satisfaction and recreation (Leon *et al.*, 1999). For the present study, we combined item 2c ('Interpersonal relations with other relatives') and item 2d ('Interpersonal relations with friends') scores into a unique measure of social withdrawal, ranging from 2 (unimpaired) to 10 points (highly impaired). Only baseline and third month (12 weeks) follow-up data of patients with a major depressive episode at the study entry were considered for our analyses. Patients in a (hypo)manic or mixed phase were not considered, as these groups usually show an abnormal expansion/elation of mood.

Clinical outcome

We considered symptom remission, defined as follows: in CATIE, as a PANSS score ≤60 (Opler *et al.*, 2007), in STAR*D and CO-MED as a QIDS-C score ≤5 (Trivedi *et al.*, 2006), in European Group for the Study of Resistant Depression (GSRD) and STEP-BD as a MADRS score ≤9 (Zimmerman *et al.*, 2004). In all samples, remission was considered after 12 weeks of treatment, except for GSRD that was a cross-sectional study, and treatment outcome was evaluated after at least 6 weeks of treatment with an antidepressant prescribed at an adequate dose.

Statistical analyses

Only subjects with a follow-up assessment of psychopathological severity at week 12 (or at study entry for GSRD) were included in the analyses. Socio-demographic and clinical characteristics were compared between remitters and nonremitters in each sample using Chi-square statistics for categorical variables and Student's *t* statistics for continuous variables. Univariate logistic regression analyses were carried out to investigate the crude associations between baseline social withdrawal and short-term remission as the dichotomous dependent variable. Odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated to assess the significance of each association. Multivariate analyses were then performed in each sample, adjusting for age and baseline psychopathological severity residualised for social withdrawal. These covariates were chosen because they are modulators of remission (Lambert *et al.*, 2010; Novick *et al.*, 2015; Bukh *et al.*, 2016; Kelly and Mezuk, 2017; Chae *et al.*, 2019); we residualised baseline psychopathological severity to subtract the effect of social withdrawal. Coefficients of regression analyses were standardised.

Finally, results were meta-analysed across samples using a random-effect model, as the included studies were assumed to vary in methodology, designs and population characteristics. The Paule–Mandel estimation method was used, as the effect sizes were based on a dichotomous outcome and there was no extreme variation of sample size between included studies (Paule and Mandel, 1982; Langan *et al.*, 2019). Heterogeneity between studies was assessed by χ^2 test of fit (Cochrane *Q* test) and I^2 statistic. A χ^2 statistic having $P<0.05$ and I^2 statistic >50% were considered suggestive of heterogeneity (Higgins *et al.*, 2003). Descriptive and regression analyses were performed using IBM SPSS for Macintosh, version 24.0 (IBM, 2016), while the meta-analysis was conducted through the metafor R-package (Viechtbauer, 2010). Results were considered statistically significant if $P<0.05$.

Results

In total, 611 patients with schizophrenia from CATIE, 352 patients with MDD from CO-MED, 1397 patients with MDD from GSRD, 1446 patients with MDD from STAR*D, and 655 patients with bipolar spectrum disorders and a current depressive episode from STEP-BD were included in the analyses. Socio-demographic and psychopathological characteristics of nonremitter and remitter patients in each included sample are reported in Supplementary Tables 1–5, Supplemental digital content 1, http://links.lww.com/ICP/A90.

Associations between baseline levels of social withdrawal and short-term clinical remission

Univariate analyses showed an association between higher baseline social withdrawal and reduced rates of short-term remission in CATIE ($OR_c=0.627$; 95% CI, 0.530–0.740; $P=4.07\times10^{-8}$), GRSD ($OR_c=0.689$; 95% CI, 0.586–0.809; $P=6\times10^{-6}$) and STAR*D ($OR_c=0.701$; 95% CI, 0.627–0.784; $P=5.6\times10^{-10}$). A similar trend of association was observed, in the same direction, in CO-MED ($OR_c=0.832$; 95% CI, 0.673–1.028; $P=0.089$) and STEP-BD ($OR_c=0.803$; 95% CI, 0.645–1.001; $P=0.051$), although results did not reach statistical significance. After adjusting for age and baseline psychopathological severity residualised for social withdrawal, the associations found in univariate analyses were overall confirmed, with the addition of a statistically significant association in the STEP-BD sample (Table 1).

Meta-analysis of results

A total of 4461 patients with mood disorders and schizophrenia were included in the meta-analysis.

The meta-analysis of the crude ORs resulting from univariate logistic regression analyses showed that higher baseline social withdrawal was significantly associated with decreased odds of short-term remission ($OR_c=0.713$; 95% CI, 0.650–0.783; $P=9.89\times10^{-13}$). No heterogeneity between studies was detected ($Q=5.69$, $P=0.22$ and $I^2=36.01\%$).

In the meta-analysis of results from the multivariate analyses, we confirmed that higher baseline levels of social withdrawal were significantly associated with decreased odds of short-term remission ($OR=0.672$; 95% CI, 0.576–0.785; $P=5.28\times10^{-7}$; Fig. 1), with medium heterogeneity between studies ($Q=10.98$, $P=0.03$ and $I^2=69.60\%$).

Discussion

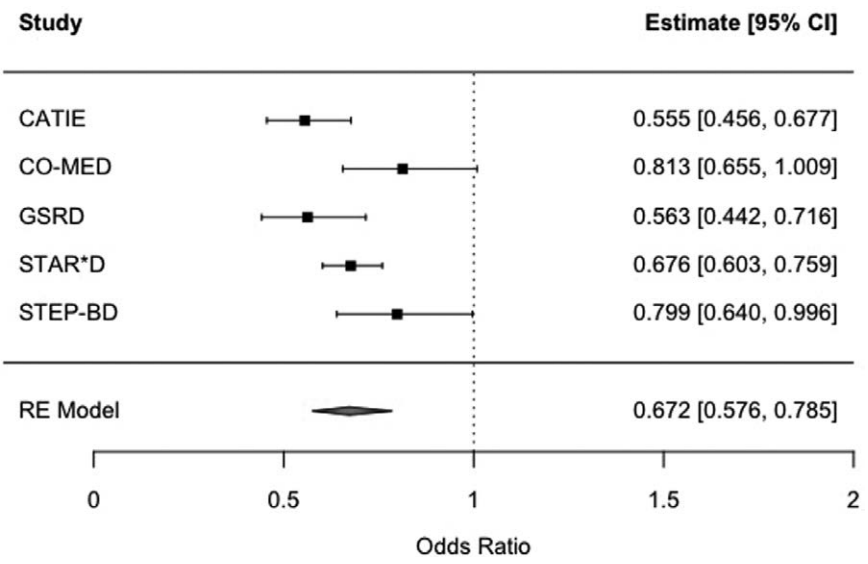
To the best of our knowledge, this is the largest study investigating social withdrawal as a potential predictor of short-term clinical remission in a total of 4461 patients with MDD, bipolar spectrum disorders or schizophrenia. Results from our meta-analysis showed a significant association between higher social withdrawal at baseline and reduced probability of short-term remission.

Table 1 Association between baseline social withdrawal and short-term clinical remission

Individual samples	OR	95% CI	*P*
CATIE	0.555	0.456–0.677	5.42×10^{-9}**
CO-MED	0.813	0.655–1.009	0.059
GSRD	0.563	0.442–0.716	3×10^{-6}**
STAR*D	0.676	0.603–0.759	4.13×10^{-11}**
STEP-BD	0.799	0.640–0.997	0.046**

Analyses were adjusted for age and baseline psychopathological severity residualised for social withdrawal.
CI, confidence intervals; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; CO-MED, Combining Medications to Enhance Depression Outcomes; GSRD, European Group for the Study of Resistant Depression; OR, odds ratio; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder.
**Statistically significant result ($P<0.05$).

Fig. 1



Forest plot showing the association between social withdrawal at baseline and short-term clinical remission across the five included cohorts. Analyses were adjusted for age and baseline psychopathological severity residualised for social withdrawal. Odds ratios and 95% confidence intervals (CI) are shown for each of the included samples.

The strongest effect was found among patients with schizophrenia, in line with previous findings indicating that negative symptoms, particularly blunted affect and social withdrawal, are major obstacles for remission in patients with schizophrenia (Schennach-Wolff *et al*., 2011). Significant associations between higher social withdrawal at baseline and short-term remission were found in two out of the three MDD samples (i.e. GSRD and STAR*D), although a trend of association in the same direction was also observed in CO-MED. The smaller sample size of CO-MED was likely the reason for the lack of statistical significance and wider confidence intervals for the association estimate in this sample. In patients with bipolar disorder, our results confirmed the findings of other samples and were in line with previous evidence showing that impairment in work functioning and social relationships is associated with lower remission and recovery rates in bipolar disorder (Haro *et al*., 2011).

Overall, our findings emphasise the importance of social withdrawal as a transdiagnostic symptom domain that clinicians should carefully address to achieve full remission in patients with major psychiatric disorders; psychopharmacological research should be directed at better targeting this domain. The amount of evidence gathered about social brain allows drafting an initial picture of the complex interplay between different neurotransmitter systems in several aspects of social stimuli processing, suggesting possible targets for pharmacological action. In particular, dopaminergic neurons, which are modulated amongst others by oxytocin, play a role in social perception, social reward, as well as in the formation and maintenance of relationships. The opioid and dopaminergic system cooperates in regulating the hedonics aspects of social reward, as well as the feelings of social distress, while the oxytocin system has key excitatory effects on brain areas involved in regulating emotions related to social stimuli. Other neurotransmitter systems, most notably the γ-aminobutyric acid (GABA) system, also mediate the oxytocin effects (Porcelli *et al*., 2019). Nevertheless, no medications have yet been developed for specifically treating social withdrawal. It is unknown whether antidepressants improve social functioning by acting directly on the mechanisms that determine it, or indirectly by improving depressive and anxiety symptoms. Some evidence suggests that antidepressants acting on noradrenergic neurotransmission may improve social functioning more rapidly and significantly than those acting exclusively on serotonergic neurotransmission, pointing to a major role for norepinephrine over serotonin on social withdrawal and drugs such as venlafaxine, duloxetine, milnacipran and reboxetine as best suited for the treatment of social withdrawal (Keller, 2001; Briley and Moret, 2010). Even considering social withdrawal as part of negative symptoms of schizophrenia, we currently lack convincing evidence about the efficacy of existing treatments (Aleman *et al*., 2017; Veerman *et al*., 2017), with the possible exception of the novel antipsychotic cariprazine (Corponi *et al*., 2019). Interestingly, the benefit of cariprazine on negative symptoms was at least partially independent from improvements in positive symptoms and extrapyramidal symptoms (Earley *et al*., 2019). This may

suggest that cariprazine's unique D3-greater-than-D2 dopamine receptor affinity could underlie its efficacy on negative symptoms. This evidence represents only a starting point on the way of developing new treatments specific for social withdrawal, but new knowledge on the neurobiological underpinnings of social withdrawal is needed.

This study comes with some strengths and limitations. In addition to the large pooled study sample, our metanalytical and trans-diagnostic approach makes our results robust and generalizable to a broad group of patients with different psychiatric disorders (MDD, bipolar spectrum disorders and schizophrenia). Among limitations, the use of proxy indicators of social withdrawal might be questionable. Indeed, social functioning can be studied using various psychodiagnostic scales, but little consensus exists on which is the best strategy (Teo *et al.*, 2013). The majority of previous studies lack a specific measure of social functioning/dysfunction (Hirschfeld *et al.*, 2000; De Silva *et al.*, 2013), and specific measures were not available in the datasets included in the present study. Nonetheless, we selected different items from different psychodiagnostic scales able to assess the interactions with relatives, friends, and other people, as the validity of the use of these proxies has been previously reported (Porcelli *et al.*, 2020). Second, we only evaluated remission as treatment outcome, but not the improvement in specific symptom domains that may be relevant for patients' quality of life (e.g. cognitive symptoms), and we considered a relatively short-term follow-up. Third, the GRSD sample was different from the others due to its cross-sectional design, and baseline levels of social withdrawal were derived from a retrospective evaluation of MADRS.

Conclusion

In conclusion, our meta-analysis found that higher baseline levels of social withdrawal are associated with lower rates of remission in treated patients with MDD, bipolar spectrum disorders and schizophrenia. This association was independent of age and residuals of baseline psychopathological severity. Overall, our findings suggest that clinicians should concentrate their efforts on reducing social disengagement symptoms in order to facilitate patients with mood disorders and schizophrenia in achieving remission. A deeper knowledge of the neurobiological underpinnings of social withdrawal will be needed in order to develop novel specific treatments that can ultimately result in improved rates of clinical remission.

Acknowledgements

We thank the US National Institute of Mental Health (NIMH) for providing access to data on the STAR*D, STEP-BD, CO-MED and CATIE samples. We also thank the authors of previous publications in these datasets, and foremost, we thank the patients and their families who agreed to be enrolled in the studies. Data were obtained from the limited access datasets distributed from the NIH-supported STAR*D (NIMH Contract No. N01MH90003, ClinicalTrials.gov identifier is NCT00021528), STEP-BD (NIMH Contract No. N01MH8001), CO-MED (NIMH Contract No. N01MH90003) and CATIE (NIMH Contract No. N01MH900001). We thank the European Group for the Study of Resistant Depression (GRSD) for providing access to the dataset they collected. C.F. was supported by Fondazione Umberto Veronesi (https://www.fondazioneveronesi.it).

The PRISM project (www.prism-project.eu) leading to this application has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115916. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. This publication reflects only the authors' views neither IMI JU nor EFPIA nor the European Commission are liable for any use that may be made of the information contained therein. The European Group for the Study of Resistant Depression (GRSD) was supported by an unrestricted grant from Lundbeck that had no further role in the study design, data collection, analysis, and interpretation, as well as in writing and submitting of the article for publication. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

S.K. received grants/research support, consulting fees and/or honoraria within the last three years from Angelini, AOP Orphan Pharmaceuticals AG, AstraZeneca, Eli Lilly, Janssen, KRKA-Pharma, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe and Servier. S.M. is a member of the board of the Lundbeck International Neuroscience Foundation and of the advisory board of Servier. S.M. has received grant/research support from Lundbeck. A.S. is or has been a consultant/speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi and Servier. D.S. has received grant/research support from GlaxoSmithKline and Lundbeck, and he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Lundbeck. J.Z. has received grant/research support from Lundbeck, Servier and Pfizer; he has served as a consultant on the advisory boards for Servier, Pfizer, Solvay and Actelion; and he has served on speakers' bureaus for Lundbeck, GSK, Jazz and Solvay. M.J.K. has received (nonrelated) research funding from Novartis. C.F. was a speaker for Janssen. For the remaining authors, there are no conflicts of interest.

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