

Invited Review

Cite this article: Kazdin AE *et al* (2024). Patterns, predictors, and patient-reported reasons for antidepressant discontinuation in the WHO World Mental Health Surveys. *Psychological Medicine* **54**, 67–78. <https://doi.org/10.1017/S0033291723002507>

Received: 29 March 2023
Revised: 25 July 2023
Accepted: 1 August 2023
First published online: 14 September 2023


Keywords:

antidepressants; major depressive disorder; medication discontinuation

Corresponding author:

Ronald C. Kessler;
Email: kessler@hcp.med.harvard.edu

Patterns, predictors, and patient-reported reasons for antidepressant discontinuation in the WHO World Mental Health Surveys

Alan E. Kazdin¹, Meredith G. Harris^{2,3}, Irving Hwang⁴, Nancy A. Sampson⁴, Dan J. Stein^{5,6}, Maria Carmen Viana⁷, Daniel V. Vigo^{8,9}, Chi-Shin Wu¹⁰, Sergio Aguilar-Gaxiola¹¹, Jordi Alonso^{12,13,14}, Corina Benjet¹⁵, Ronny Bruffaerts¹⁶, José Miguel Caldas-Almeida¹⁷, Graça Cardoso¹⁷, Elisa Caselani¹⁸, Stephanie Chardoul¹⁹, Alfredo Cía²⁰, Peter de Jonge^{21,22}, Oye Gureje²³, Josep Maria Haro^{24,25,26}, Elie G. Karam^{27,28,29}, Viviane Kovess-Masfety³⁰, Fernando Navarro-Mateu^{31,32,33}, Marina Piazza^{34,35}, José Posada-Villa³⁶, Kate M. Scott³⁷, Juan Carlos Stagnaro³⁸, Margreet ten Have³⁹, Yolanda Torres⁴⁰, Cristian Vladescu⁴¹, Ronald C. Kessler⁴  and on behalf of the WHO World Mental Health Survey collaborators¹

Abstract

Background. Despite their documented efficacy, substantial proportions of patients discontinue antidepressant medication (ADM) without a doctor's recommendation. The current report integrates data on patient-reported reasons into an investigation of patterns and predictors of ADM discontinuation.

Methods. Face-to-face interviews with community samples from 13 countries ($n = 30\,697$) in the World Mental Health (WMH) Surveys included $n = 1890$ respondents who used ADMs within the past 12 months.

Results. 10.9% of 12-month ADM users reported discontinuation based on recommendation of the prescriber while 15.7% discontinued in the absence of prescriber recommendation. The main patient-reported reason for discontinuation was feeling better (46.6%), which was reported by a higher proportion of patients who discontinued within the first 2 weeks of treatment than later. Perceived ineffectiveness (18.5%), predisposing factors (e.g. fear of dependence) (20.0%), and enabling factors (e.g. inability to afford treatment cost) (5.0%) were much less commonly reported reasons. Discontinuation in the absence of prescriber recommendation was associated with low country income level, being employed, and having above average personal income. Age, prior history of psychotropic medication use, and being prescribed treatment from a psychiatrist rather than from a general medical practitioner, in comparison, were associated with a lower probability of this type of discontinuation. However, these predictors varied substantially depending on patient-reported reasons for discontinuation.

Conclusion. Dropping out early is not necessarily negative with almost half of individuals noting they felt better. The study underscores the diverse reasons given for dropping out and the need to evaluate how and whether dropping out influences short- or long-term functioning.

Introduction

Major depressive disorder (MDD) is among the most common mental disorders, affecting an estimated 4.4 percent of the world's population each year (Cipriani *et al.*, 2018; World Health Organization, 2017). Depression increases morbidity and mortality (Goldstein *et al.*, 2020; Lépine & Briley, 2011; Wang *et al.*, 2020) and is one of the larger contributors to disability worldwide (GBD, 2017 DALYs & HALE Collaborators, 2018). The economic costs of major depression are enormous (Chisholm *et al.*, 2016; Chiu, Lebebaum, Cheng, de Oliveira, & Kurdyak, 2017; Kessler, 2012; Tanner *et al.*, 2020; Yamabe, Liebert, Flores, & Pashos, 2019).

Several effective treatments for MDD exist, including a wide range of antidepressant medications (ADMs), psychological therapies, brain stimulation therapies (e.g. transcranial magnetic stimulation, electroconvulsive therapy, deep brain stimulations) and others (Barth *et al.*, 2016; Cipriani *et al.*, 2018; Moshe *et al.*, 2021). ADMs are by far the most frequently used of these treatments given their low cost and ease of administration (Brody & Gu,

2020; Cipriani et al., 2018; Herrman et al., 2019). ADM use for treatment of MDD has increased in recent years (Mojtabai & Olfson, 2014; Scholten, Batelaan, & Van Balkom, 2020). In addition, ADMs are often prescribed for anxiety as well as for other mental and physical conditions (e.g. headache, pain, insomnia, gastrointestinal disorders) (Gardarsdottir, Heerdink, van Dijk, & Egberts, 2007; Wu et al., 2012). Among the reasons for the widespread use of ADMs are the empirical support for their positive effects, their low-cost relative to other treatments, and their accessibility in countries where access to other treatments is limited.

Despite their demonstrated efficacy, an estimated 33–60 percent of patients who begin ADMs discontinue even when this is not recommended by their treatment provider (Fornaro et al., 2023; Wells, Clerkin, Ellis, & Beevers, 2014). Discontinuation usually occurs within the first 3 months of beginning treatment even though recommendations are for continued use over much longer durations (6–9 months) (American Psychiatric Association, 2010; National Institute for Health and Care Excellence [NICE], 2009; Olfson, Marcus, Tedeschi, & Wan, 2006). As might be expected, discontinuation is associated with an increased likelihood of relapse and risk of suicide (Liu et al., 2021; Sirey et al., 2017; Van Leeuwen et al., 2021). In some patients there can be a wide range of symptoms often referred to as part of the ‘antidepressant withdrawal syndrome’ (e.g. flu-like symptoms, dizziness, shaking, fatigue, electric shock sensations, anxiety, emotional lability, lowering of mood, irritability, and bouts of crying) (Clarke et al., 2022; Fornaro et al., 2023; Gastaldon et al., 2022; Sørensen, Jørgensen, & Munkholm, 2022). Many of these symptoms can be enduring (Davies, Pauli-Jones, & Montagu, 2018).

The focus on ADM discontinuation has long been recognized as important for treatment planning. Findings from multiple studies have suggested that disorder severity, low income, lack of insurance, public *v.* private insurance, ethnic minority status, younger age, and comorbid anxiety and/substance use are associated with discontinuation (Akincigil et al., 2007; Bambauer, Soumerai, Adams, Zhang, & Ross-Degnan, 2007; Ji & Hong, 2020; Samples & Mojtabai, 2015; Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). However, the great majority of prior studies were characterized by either small samples, investigation of single clinical settings or geographical locales, evaluation of only one or two ADMs, or drawing on prescriber, electronic, or pharmacy records to infer actual use *v.* discontinuation. Little attention has been accorded reports by individuals themselves who are taking ADMs in community contexts (Kato et al., 2021; Samples & Mojtabai, 2015). Direct reports are critical to understanding who has continued or discontinued medication, the reasons for discontinuation, the timing of discontinuation over the course of treatment, and whether the decision to discontinue was based on the patient or the prescriber. Moreover, not everyone who discontinues fails to respond to treatment. Consequently, it is important to evaluate when and for whom discontinuation is ill advised. Thus, it is important to work with broadly defined samples and to look more directly than in prior studies at use reported by individuals themselves, the reasons for discontinuation, and evaluation of clinical status.

The purpose of the current report was to present the results of a study of ADM discontinuation in samples of the general population across many countries in the World Mental Health (WMH) surveys. We evaluated the diagnoses of the people who use ADMs with special attention to depression and anxiety and, importantly, we examined patient-reported reasons for discontinuing ADMs.

Methods

Sample

The World Health Organization’s (WHO) World Mental Health (WMH) surveys are a coordinated set of community epidemiological surveys administered to probability samples of adults in the non-institutionalized household population in countries throughout the world (Scott, de Jonge, Stein, & Kessler, 2018). Data for the current report are from 15 WMH surveys in 13 countries. Four of the countries were low- or middle-income countries (LMICs) as per the World Bank’s classification (Fantom & Serajuddin, 2016): Colombia (2 surveys), Mexico, Peru and Romania. The other nine were high-income countries (HICs): Argentina, Belgium, France, Germany, Italy, Netherlands, Portugal, Spain (two surveys), and the United States. It should be noted that a larger number of WMH surveys asked about 12-month medication use, but only the 15 considered here included the question series about reasons for use. All samples were based on multi-stage clustered area probability household designs; they were nationally representative in nine surveys, representative of all urbanized areas in two others, and representative of selected regions or Metropolitan areas in the others (online Supplementary Table S1). Average response rate weighted by sample size was 69.6%.

Measures

The interview

Interviews were administered face-to-face in respondents’ homes after obtaining informed consent. Local ethics or institutional review committees at each site reviewed and approved the protocol to ensure protection of human subjects, in line with appropriate international and local guidelines. Interviews were in two parts to reduce respondent burden. Part I assessed core mental disorders and was administered to all respondents. Part II assessed additional disorders and correlates and was administered to 100% of Part I respondents with any disorder, plus a probability subsample of other respondents. Part II data were weighted to adjust for the under-sampling of Part I non-cases, with the resulting weighted Part II prevalence estimates being equivalent to Part I estimates (Heeringa et al., 2008). Of the 30 697 Part II respondents, we focused on the 1890 who were users of ADMs in the past 12 months but who had no evidence of bipolar disorder (i.e. neither met criteria for lifetime bipolar disorder in the diagnostic assessment nor reported bipolar disorder as a reason for their ADM use). Each of these individuals was asked about up to three medications (and up to five in some surveys). In the few cases where a patient reported using more than this number of medications, we sampled this maximum number randomly from those used and weighted the respondent’s data to adjust for the under-sampling. A total of 2139 ADM uses were included among the sampled medications for these 1890 respondents. These are the cases considered in the current report.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Diagnoses

The survey instrument was the WHO Composite International Diagnostic Interview (CIDI) Version 3.0 (Kessler & Üstün, 2004), a fully structured interview generating diagnoses of lifetime

and 12-month DSM-IV disorders. The disorders considered here are MDD and a series of anxiety disorders that include agoraphobia, generalized anxiety disorder, panic disorder, post-traumatic stress disorder, social phobia and specific phobia. Diagnoses based on the CIDI had good concordance with diagnoses based on blinded clinical reappraisal interviews using the Structured Clinical Interview for DSM-IV (SCID; [First, Spitzer, Gibbon, and Williams, 2002]) as the gold standard (Haro *et al.* 2006). We categorized respondents into four MDD categories: threshold 12-month prevalence (12 M MDD), lifetime but not 12-month prevalence (LT MDD), 12-month subthreshold MDD in the absence of LT MDD (Partial MDD), and none of the above. The same four categories were used to define anxiety disorders hierarchically (i.e. 12 M anxiety includes respondents who met full criteria for at least one anxiety disorder; LT anxiety includes other respondents who met lifetime criteria for at least one anxiety disorder; partial anxiety includes other respondents who met 12-month subthreshold criteria for at least one anxiety disorder, and other respondents had none of these disorders). We also created a four-category hierarchical variable that combined scores on the separate four-category MDD and anxiety variables.

Antidepressant use

ADM use was defined as taking an ADM at any time in the past 12 months. Information on use was captured by presenting respondents with a list of psychotropic medications using both generic and trade names and asking about use in the past 12 months for 'problems with your emotions, nerves, mental health, substance use, energy, concentration, sleep, or ability to cope with stress'. The medication list included ADMs, anxiolytics, hypnotics, antipsychotics, mood stabilizers, and other psychotropic agents. Respondents were instructed to include 'medications even if you took them only once'. Because drug administration policies vary across countries, the medication list was modified for each country. We asked about a total of 41 ADMs, which were categorized for analysis into SSRIs (selective serotonin reuptake inhibitors), other new-generation ADMs (those marketed after fluoxetine, 1986), TCAs (tricyclic ADMs), and other older ADMs (e.g. monoamine oxidase inhibitors, St. John's Wort, trazodone, and unspecified). Two clinical psychiatrists with expertise in global public health (DV, CW) independently reviewed responses about medications used in the past 12 months (which involved selecting from country-specific lists including generic and brand names) and classified ADMs into the four categories. Discrepancies were reconciled by consensus.

For each psychotropic medication used in the past 12 months, the type and duration of use were recorded. In addition, medication-specific follow-up questions were asked separately for up to five psychotropic medications in six European countries (Belgium, France, Germany, Italy, Netherlands, Spain) and up to three in other countries. These numbers captured well over 90% of ADM uses in each survey. One of these questions was: 'What problems did you take (NAME OF MEDICATION) for?' Both structured and open-ended responses were recorded and classified into the categories (i) depression (sadness/depression/ crying or suicidal thoughts), (ii) anxiety (nerves/anxiety or panic), (iii) poor sleep, (iv) other physical problems (low energy, poor appetite or physical pain), and (v) other reasons, such as little or no sexual functioning, marital problems, not getting along with others, poor work performance, alcohol or drug problems, poor concentration, and poor memory. Multiple reasons could be reported, which is important because some of the 'other' reasons

are also symptoms of MDD and anxiety disorders. Respondents were then asked if they were still taking each medication; if not, whether they discontinued on their own or based on the recommendation of their prescribing health professional. A series of follow-up questions asked about reasons for ADM discontinuation (see online Supplementary Table S2 for the interview questions).

Data analysis

Weights were applied within surveys to adjust for differences in within-household probabilities of selection and to calibrate the data to match Census population distributions on socio-demographic and geographic variables. Part II data were then weighted to adjust for differential probabilities of selection into Part II. Cross-tabulations were used to examine gross associations between ADM discontinuation and clinical variables as well as patient-reported reasons for discontinuation. The time-to-discontinuation distribution by week and the projected cumulative probability of discontinuation by 1 year (52 weeks) were estimated using the two-part actuarial survival curve method implemented in SAS 9.4 (SAS Institute Inc, 2013). Given the sparseness of the data on discontinuation after the first 6 weeks, the survival curves in subsequent weeks were smoothed using a 4-week moving average. Discrete-time survival analysis with person-week the unit of analysis was then used to examine predictors of discontinuation (Hosmer, Lemeshow, & May, 2008). These models had a probit link function with robust standard errors (Tabatabai *et al.*, 2014). This was done both for discontinuation overall and for discontinuation due to specific types of reasons. Coefficients and coefficients ± 2 of their design-based SEs were then exponentiated to create risk ratios (RRs) and 95% confidence intervals (CIs). Significance of RR sets defining a single categorical variable (e.g. the dummy variables defining ADM classes) was evaluated with Wald χ^2 tests based on design-corrected coefficient variance – covariance matrices. Statistical significance was evaluated consistently using two-sided design based 0.05-level tests. All statistical analyses were carried out using the Taylor-series linearization method (Wolter, 1985), a design-based method implemented in SAS 9.4 program (SAS Institute Inc, 2013) that adjusts estimates of SEs and CIs for the weighting and clustering of observations in the WMH surveys.

Results

Sample characteristics

The great majority of observations in the sample came from HICs (87.1%) (Table 1). Median (inter-quartile range) age was 49 (37–59). 72.8% were female, 62.6% were married and 22.1% previously married. The distribution of education using pooled within-country categories was 22.6% high, 25.6% high-average, 23.9% low-average, and 20.8% low. The distribution of family income using pooled within-country categories was 23.2% high, 27.2% high-average, 23.4% low-average, and 26.2% low.

Clinical characteristics by treatment status

73.3% ($n = 1573$) of ADMs were still being used at the time of interview compared to 10.9% ($n = 238$) discontinued based on prescriber's advice and 15.7% ($n = 328$) discontinued by the patient in the absence of prescriber advice (henceforth referred to as discontinuation 'by the patient'). Table 2 provides

Table 1. Sample characteristics of 12-month person-ADM users in the analysis

	Total Est ^a	Current user Est ^a	Discontinued by prescriber Est ^a	Discontinued by patient Est ^a
Country income group				
HIC	87.1	89.0	85.4	79.4
LMIC	12.9	11.0	14.6	20.6
Age				
Median	48.7	50.9	41.4	41.9
IQR	37.4	40.3	33.0	31.8
Sex (%)				
Male	27.2	26.6	31.1	27.0
Female	72.8	73.4	68.9	73.0
Marital status (%)				
Married	62.6	63.4	60.5	60.1
Previously married ^b	22.1	22.5	18.7	22.4
Never married	15.4	14.1	20.8	17.4
Education ^c				
High	22.6	22.5	20.3	24.6
High-average	25.6	23.3	29.4	33.3
Low-average	23.9	24.0	22.8	24.1
Low	20.8	23.1	18.5	11.7
Family income ^d				
High	23.2	22.1	24.0	27.8
High-average	27.2	26.2	27.4	31.9
Low-average	23.4	25.1	22.8	15.6
Low	26.2	26.6	25.8	24.7
(n)	(2139)	(1573)	(238)	(328)

Abbreviations: Total, the total number of observations in the sample, where patients who reported using two or more ADMs were treated as separate observational records; Current, observations of patients still taking their ADM at the time of interview; Discontinued based on patients who terminated on their own verses those terminated by the prescriber; HICs, high-income countries; LMICs, low-and-middle-income countries; IQR, inter-quartile range (i.e. 25th to 75th percentiles of the distribution).

^aEstimate treats row variable as numerator and column variable as denominator. For example, the estimate for HIC (87.1%) is the % among the Total. The Est value for age is the Median/IQR, and is % for all the other rows.

^bIncluding separated, divorced, and widowed.

^cIn quartiles defined by country-specific distributions (see Evans-Lacko et al., 2018 for details).

^dLow was defined as less than 50% of the country-specific median, low-average as between low and the country-specific median, high-average as between low-average and twice the country-specific median, and high as more than twice the country-specific median.

information on clinical characteristics of the sample by ADM treatment status (currently using, discontinued on prescriber's advice, discontinued by patient). Significantly higher proportions of the first two subgroups than the third were from HICs (89.0–85.4% *v.* 79.4%, $\chi^2_2 = 14.4$, $p < 0.001$). The three subgroups also differed significantly in duration of use, with much higher proportions of those who discontinued than those still using having durations of 1–2 weeks (27.7–27.4% *v.* 4.7%) or 3–6 weeks (23.1–21.9% *v.* 7.1%). Durations of 7+ weeks were much more common among patients who were still using than those who discontinued on their own or discontinued on prescriber's advice (88.2% *v.* 49.2–50.7%; $\chi^2_4 = 225.6$, $p < 0.001$).

The three subgroups did not differ significantly in the other clinical characteristics considered in Table 2. Most patients in all three subgroups used SSRIs (56.5–59.9%) rather than in either older (28.7–31.3%) or newer (8.8–14.8%) ADMs. The plurality across subgroups had diagnoses of 12-month threshold MDE

and/or anxiety disorder (41.4–47.6%) followed by either subthreshold 12-month MDE and/or anxiety disorder either in the absence (23.4–28.3%) or presence (19.4–22.2%) of lifetime MDE and/or anxiety disorder. Patient-reported reasons for ADM use were also comparable across subgroups, with depression-only (33.1–38.4%) and anxiety-only (20.7–26.1%) the most common reasons.

Time to discontinuation

Survival analysis was used to estimate conditional hazards of discontinuation by the patient as a function of number of weeks of use as well as the cumulative probability of such discontinuation by weeks of use. Curves were smoothed because of the relatively small sample size (Fig. 1). A projected 19.0% (s.e. = 0.1%) of patients would be expected to discontinue after 1 year, with a significantly lower proportion in HICs (17.7%, s.e. = 0.1%) than

Table 2. Clinical characteristics by ADM treatment status

	Total		Current user		Discontinued by prescriber		Discontinued by patient		χ^2 ^b	df
	% ^a	(s.e.)	% ^a	(s.e.)	% ^a	(s.e.)	% ^a	(s.e.)		
Country income group										
HIC	87.1	(1.1)	89.0	(1.3)	85.4	(2.1)	79.4	(2.7)	14.4*	2
LMIC	12.9	(1.1)	11.0	(1.3)	14.6	(2.1)	20.6	(2.7)		
ADM class										
SSRI	58.5	(1.4)	58.8	(1.6)	59.9	(3.6)	56.5	(3.5)	4.5	6
Newer ADMs	12.5	(0.8)	12.6	(1.0)	8.8	(1.7)	14.8	(2.3)		
TCA	19.6	(1.0)	19.1	(1.1)	23.6	(3.1)	18.8	(2.6)		
Other older ADMs	9.4	(1.1)	9.6	(1.4)	7.7	(1.7)	9.9	(2.6)		
Diagnosis										
12-month threshold	42.9	(1.4)	41.4	(1.5)	47.6	(3.9)	46.6	(3.5)	6.6	6
LT threshold	20.4	(1.2)	20.4	(1.3)	22.2	(3.4)	19.4	(2.7)		
12-month subthreshold	27.7	(1.4)	28.3	(1.6)	23.4	(4.3)	27.6	(4.0)		
Other	9.0	(1.1)	9.9	(1.5)	6.8	(1.5)	6.3	(1.7)		
Duration of ADM use										
1–2 weeks	10.8	(0.8)	4.7	(0.7)	27.7	(3.7)	27.4	(2.9)	225.6*	4
3–6 weeks	11.2	(0.8)	7.1	(0.8)	23.1	(3.6)	21.9	(2.7)		
7+ weeks	78.1	(1.1)	88.2	(1.0)	49.2	(3.7)	50.7	(3.3)		
Patient-reported reasons for ADM use										
Depression	34.6	(1.1)	34.0	(1.3)	33.1	(3.7)	38.4	(3.1)	9.9	10
Anxiety	23.1	(1.2)	23.2	(1.4)	26.1	(3.5)	20.7	(3.4)		
Poor sleep	4.4	(0.5)	4.2	(0.6)	3.1	(0.8)	6.2	(1.3)		
Other physical	10.4	(1.2)	11.0	(1.5)	8.3	(1.6)	9.0	(1.5)		
Any other single reason ^c	7.9	(0.8)	8.2	(0.9)	10.6	(3.0)	4.8	(1.5)		
Multiple reasons ^d	19.6	(1.0)	19.4	(1.2)	18.8	(3.0)	21.0	(2.8)		
(n)	(2139)		(1573)		(238)		(328)			

Abbreviations: Total, the total number of observations in the sample, where patients who reported using two or more ADMs were treated as separate observational records; Current, observations of patients still taking their ADM at the time of interview; Discontinued based on patients who terminated on their own versus those terminated by the prescriber; HICs, high-income countries; LMICs, low-and-middle-income countries; IQR, inter-quartile range (i.e. 25th to 75th percentiles of the distribution).

^aEstimate treats row variable as numerator and column variable as denominator. For example, the % of SSRI (58.5%) is the % among the Total.

^b χ^2 tests evaluate the significance of differences in distributions across subgroups defined by the columns.

^cIncluding little or no sexual functioning, sexual problems, not getting along with others, poor work performance, alcohol or drug problems, poor concentration, poor memory, and any other as single reasons.

^dTwo or more reasons, multiple reasons from the 'Any other single reason category' (i.e. both alcohol/drug and cognition) also counts as multiple.

*Significant at the 0.05 level, two-sided design-based test.

LMICs (28.5%, s.e. = 0.4%; $\chi^2_1 = 13.3$, $p < 0.001$). The highest hazard of discontinuation was after 1 week of use (1.5%) and was again significantly lower in HICs (1.3%, s.e. = 0.1%) than LMICs (3.8%, s.e. = 0.9%; $\chi^2_1 = 396.3$, $p < 0.001$).

Reasons for discontinuation

Reported reasons for discontinuation by the patient were categorized rationally into four broad categories based on previous conceptual frameworks: (Henshaw & Freedman-Doan, 2009; Magaard, Seeralan, Schulz, & Brütt, 2017) lack of continued need, perceived treatment ineffectiveness, enabling factors (pressure to quit from friends or family; inability to afford treatment), and predisposing factors (fear of dependence; wanting to solve the

problem on one's own). The most commonly reported reason for discontinuation was lack of continued need, largely due to feeling better (46.6%) (Table 3). Strikingly, a significantly higher proportion of patients who discontinued after 1–2 weeks (51.4%) than either 3–6 weeks (32.8%) or 7+ weeks (50.0%; $\chi^2_2 = 7.6$, $p = 0.022$) reported feeling better as a reason for discontinuation despite it typically taking longer than 2 weeks for ADM effects to be felt. More detailed analyses found that lack of continued need was reported by equal proportions of users of SSRIs and TCAs (48.4% v. 49.6%), but a lower proportion of patients using newer ADMs (32.2%) and a considerably higher proportion of patients using other (than TCAs) older ADMs (70.8%; $\chi^2_3 = 9.0$, $p = 0.029$) (online Supplementary Table S3). Disorder status was also associated negatively with lack of continued need as a reason

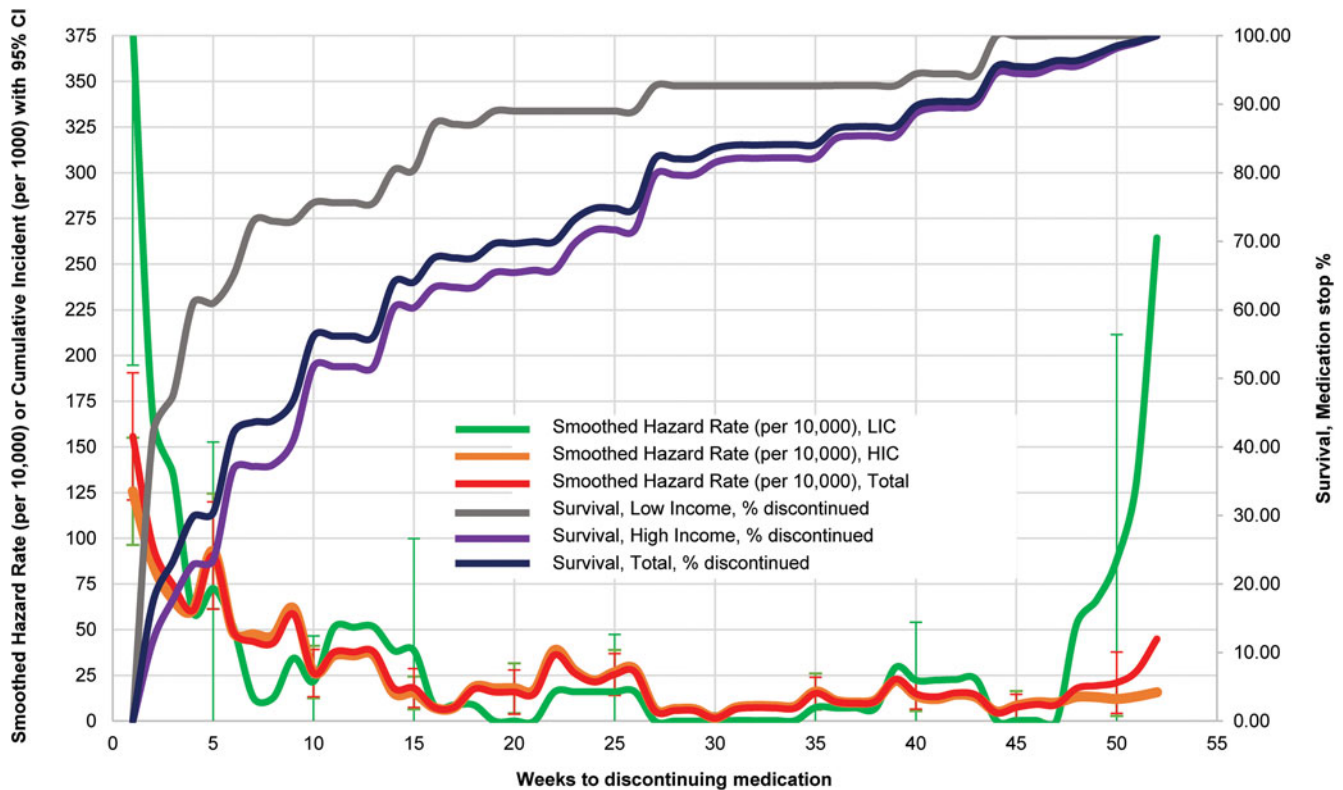


Figure 1. Projected morbid risk of stopping medication at the end of 12 months is 19.0% (s.e. = 0.1) for the total sample, 17.71% (s.e. = 0.1) for high income countries, 28.54% (s.e. = 0.4) for low-income countries. Hazard rate is the rate of the outcome occurrence at the given time period. Survival curve shows the cumulative % with the outcome occurrence at the given time period. Discontinuing is referring to discontinuation by the patient.

for discontinuation ($\chi^2_3 = 13.6$, $p = 0.003$) due to a much higher proportion among patients with subthreshold disorder (65.8%) and lower among other patients (38.8%) than among patients with threshold (12-month or lifetime) disorders (40.8–45.2%) (online Supplementary Table S3). Lack of continued need as a reason for discontinuation was also significantly associated with reason for ADM use ($\chi^2_5 = 18.5$, $p = 0.002$) due to lower proportions of discontinued among patients who used for other (than sleep) physical reasons or other single reasons (than depression, anxiety, or sleep) (31.8–25.0%) than those who used for depression, anxiety, or sleep (47.4–57.0%) (online Supplementary Table S3).

Predisposing factors were the next most common reasons for discontinuation (20.0%) (Table 3). Probability of reporting these reasons was not related to time to discontinuation ($\chi^2_2 = 3.8$, $p = 0.15$). However, more detailed analyses found that predisposing factors were more common among users of SSRIs and newer ADMs (22.8–30.4%) than TCAs and other older ADMs (10.7–5.7%; $\chi^2_3 = 16.1$, $p = 0.001$) and much lower among patients without a mental disorder or 12-month subthreshold problems (0.0) and those using for poor sleep (4.9%) than others (14.3–33.8%; $\chi^2_3 = 156.1$, $p < 0.001$) (online Supplementary Table S3).

Perceived ineffectiveness was the next most common reason for discontinuation (18.5%) (Table 3) due to a combination of reports that the medication was not working (14.3%) and that the patient experienced side-effects (5.1%). Perceived ineffectiveness was less likely to be reported as a reason among patients who discontinued after 1–2 weeks (14.3%) than after 3 or more weeks, but this difference was not significant (21.0–19.8%, $\chi^2_2 = 5.2$, $p = 0.08$). More detailed analyses not reported in Table 3

found that ineffectiveness was less likely to be reported as a reason for discontinuation among patients with 12-month subthreshold diagnoses (7.8%) than others (18.7–24.3%; $\chi^2_3 = 12.2$, $p = 0.007$), and by patients who used ADMs for sleep, other physical problems, or multiple problems (11.9–13.1%) than other single reasons (20.6–28.6%; $\chi^2_5 = 22.4$, $p < 0.001$) (online Supplementary Table S3). Enabling (5.0%) and other (14.2%) reasons for discontinuation were less common (Table 3).

Predictors of discontinuation

Survival analysis found that country income group was the only predictor of discontinuation by the patient that varied in importance by time of discontinuation ($\chi^2_2 = 10.8$, $p = 0.005$). The other predictors had RRs that were consistent across person-weeks in univariable analyses (online Supplementary Table S4). The subset of the latter predictors that had significant univariable associations pooled across person-weeks was included in a multivariable model (Table 4). RR of discontinuation in that model was highest in weeks 1–2 (RR = 7.4) and intermediate in weeks 3–6 (RR = 3.9) relative to weeks 7+ (RR = 1.0). RR was four-fold as high in LMICs as HICs in weeks 1–2, two-fold as high in LMICs as HICs in weeks 3–6, and equal in LMICs compared to HICs between 7–52 weeks. In addition, being employed and having high/high-average family income were associated with elevated RR of discontinuation (RR = 1.4), whereas age, history of prior psychotropic medication use, and receiving the ADM prescription from a mental health professional rather than from a general medical practitioner were all associated with significant reduced RRs of discontinuation (RR = 0.6–0.8). Finally, patient education

Table 3. Reasons for discontinuation by patient

	Weeks used before discontinuation by patient								χ^2 ^b	df
	Total		1–2		3–6		7+			
	% ^a	(s.e.)	% ^a	(s.e.)	% ^a	(s.e.)	% ^a	(s.e.)		
Lack of continued need										
Felt better	46.6	(2.8)	51.4	(4.6)	32.8	(5.0)	50.0	(4.1)	7.6*	2
No longer needed ^c	1.8	(0.6)	0.0	(0.0)	2.0	(1.5)	2.7	(1.1)	0.0	1 ^d
Total	48.4	(2.8)	51.4	(4.6)	34.9	(5.0)	52.7	(3.9)	7.3*	2
Treatment ineffectiveness										
Medication not working	14.3	(1.2)	13.0	(2.1)	17.3	(3.1)	13.7	(1.8)	1.8	2
Side effects	5.1	(1.0)	2.1	(0.7)	6.5	(3.2)	6.1	(1.3)	7.2*	2
Total	18.5	(1.3)	14.3	(2.2)	21.0	(3.4)	19.8	(1.9)	5.2	2
Predisposing factors ^e										
Fear of dependence	15.3	(1.5)	23.2	(3.7)	12.1	(3.7)	12.5	(1.6)	9.4*	2
Wanted to solve problem on own	7.1	(1.4)	6.8	(1.3)	8.8	(3.9)	6.5	(1.4)	0.6	2
Total	20.0	(2.0)	25.0	(3.5)	20.9	(4.9)	16.9	(2.3)	3.8	2
Enabling factors										
Pressured to quit ^f	4.2	(0.8)	4.3	(0.5)	2.6	(1.6)	4.8	(1.6)	0.8	2
Couldn't afford treatment	1.0	(0.4)	2.5	(1.3)	0.0	(0.0)	0.5	(0.0)	12.7*	1 ^d
Total	5.0	(0.9)	6.2	(1.4)	2.6	(1.6)	5.4	(1.6)	1.7	2
Other reasons										
Any other reason	14.2	(1.9)	8.9	(4.6)	26.4	(4.6)	11.9	(1.5)	12.6	2
(n)	(328)		(87)		(67)		(174)			

*Significant at the 0.05 level, two-sides design-based test.

^aEstimate treats row variable as numerator and column variable as denominator. For example, the % or 'Felt Better' (46.6%) is the % of those that stopped medication because they felt better among the Total.

^b χ^2 tests evaluate the significance of differences in distributions across subgroups defined by the columns.

^cBelieved problem would get better without medication.

^d1 df test leaving out 0 cell.

^eWe also asked about embarrassment, but no patient reported this as a reason for discontinuation.

^fSomeone in personal life pressured the patient to quit.

and disorder severity, both of which had significantly elevated univariable RRs with discontinuation, were nonsignificant in the multivariable model (RR = 1.3).

These multivariable predictors of discontinuation were then decomposed through reported reasons by estimating the model separately for the four broad types of reasons considered here (Table 4). Time to discontinuation, although related to all four types of reasons, was most strongly related to predisposing reasons and least strongly related to enabling reasons. The higher discontinuation rates of LMICs than HICs as a function of time to discontinuation were exclusive to need and enabling factors for discontinuation in weeks 1–2 and enabling factors for discontinuation in weeks 3–6. Socio-economic predictors were consistently related to continued need, with education also related to enabling factors. Age, in comparison, was related only to treatment ineffectiveness and predisposing factors. Prior psychotropic medication use and disorder severity, in comparison, were related exclusively to discontinuation due to enabling factors. Receiving the prescription from a mental health professional rather than a primary care treatment provider was related exclusively to discontinuation due to predisposing factors.

Discussion

The study provided information on ADM discontinuation among 1890 individuals spanning 13 countries. SSRIs were the most frequently used ADM, encompassing more than half the sample. Depression and anxiety were the primary reasons for taking ADMs. Reasons for using ADMs did not vary by type of medication. Treatment was discontinued in 10.9% of cases based on the recommendation of the prescriber and an additional 15.7% of patients discontinued on their own. Discontinuing by either criterion was higher in LMICs than HICs within the first several weeks of treatment. Discontinuation did not vary systematically as a function of the initial reason for taking ADMs. Patients were less likely to discontinue on their own if the ADM had been prescribed by a psychiatrist in contrast to a general medical practitioner.

Among the noteworthy findings is that roughly half of discontinuation, whether based on the prescriber or the patient's own decision, occurred because the patient felt better. It is noteworthy, though, that this reason for discontinuation was more common among patients who discontinued within 1–2 weeks of initiating

Table 4. Multivariable predictors of discontinuation by patient

	Total		Need		Ineffective		Predisposing		Enabling	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Person-weeks										
1–2	7.4*	(5.0–10.9)	5.7*	(3.1–10.7)	7.2*	(3.5–15.0)	15.6*	(7.6–31.7)	6.3*	(1.8–22.4)
3–7	3.9*	(2.6–6.0)	2.5*	(1.1–5.6)	4.6*	(1.9–11.1)	5.4*	(2.5–11.5)	1.0	(0.1–8.1)
7–52 (REF)										
χ^2_2	116.1*		31.2*		33.0*		58.9*		8.4*	
County income level										
LMIC 1–2 weeks	4.0*	(2.2–7.5)	7.2*	(3.1–16.8)	0.7	(0.1–4.0)	0.4	(0.1–2.1)	8.5*	(1.8–40.3)
LMIC 3–6 weeks	2.0	(0.8–4.7)	2.3	(0.5–11.3)	0.6	(0.1–3.3)	0.7	(0.2–2.4)	12.6*	(1.1–142.7)
LMIC 7–52 weeks	0.9	(0.4–1.7)	0.9	(0.4–2.3)	0.3	(0.0–1.8)	0.5	(0.1–2.2)	1.0	(0.1–8.1)
χ^2_3	20.9*		21.3*		2.3		2.1		10.7*	
Socio-economic status										
Employed	1.4*	(1.0–1.9)	2.0*	(1.2–3.3)	0.7	(0.1–1.4)	1.0	(0.6–1.9)	1.6	(0.5–4.8)
High/low-average education ^a	1.3	(0.8–2.2)	3.7*	(1.8–7.4)	1.6	(0.7–3.7)	1.3	(0.6–2.8)	8.5*	(1.8–40.2)
High/high-average income	1.4*	(1.0–1.9)	1.7*	(1.0–2.9)	1.1	(0.6–1.9)	1.4	(0.8–2.6)	0.7	(0.3–1.9)
Other										
Age (in decades)	0.8*	(0.7–0.9)	0.9	(0.8–1.0)	0.8*	(0.6–0.9)	0.7*	(0.5–0.8)	0.9	(0.7–1.2)
Prior psychotropic use ^b	0.6*	(0.5–0.9)	0.7	(0.4–1.2)	0.8	(0.4–1.6)	0.6	(0.3–1.1)	0.2*	(0.1–0.5)
Disorder severity ^c	1.3	(0.9–1.7)	1.0	(0.7–1.6)	1.6	(0.9–2.8)	1.2	(0.6–2.1)	3.6*	(1.2–10.9)
Rx by MH professional	0.6*	(0.4–0.9)	0.6	(0.3–1.0)	0.9	(0.5–1.6)	0.4*	(0.2–0.8)	0.5	(0.1–1.9)
(n) ^d	(98 685)		(98 685)		(98 685)		(98 685)		(98 685)	

Abbreviations: RR, relative risk; 95% CI, 95% confidence interval of RR.

^aHigh, high-average, and low-average education were Coded 1; low education was Coded 0.

^bIn past 2 years.

^cSevere/moderate (Coded 1) v. mild/none (Coded 0).

^dNumber of person-weeks in the analysis, noting that all person-weeks of patients who did not report lack of continued need as a reason for discontinuation were coded to NO on dropout in the 'Need' model, all person-weeks of patients who did not report treatment ineffectiveness as a reason for discontinuation were coded to NO on dropout from the 'Ineffective' model, etc.

*Significant at the 0.05 level, two-sided design-based test.

treatment, which is before the time ADMs effects are typically found to exist, indicating that the term 'feeling better' might mean something other than episode remission. There is no way to evaluate this issue objectively with the WMH data, though, as information was not collected about symptom profiles at the time of discontinuation.

Interestingly, ADM discontinuation as a function of type of prescriber due to a lower rate of discontinuation among individuals whose prescriber was a psychiatrist than a general practitioner. Of course, patients are not randomly assigned to type of prescriber, so conclusions about the basis of this difference cannot be determined here. Even so, this difference warrants further research in case there are differences in prescribing practices that can be identified and that would help reduce rates of discontinuation more generally and specialty for general practitioners.

That early discontinuation often occurred because patients felt better could mean that patients improved in ways that affected their daily lives even if not their symptoms. It could also mean that the expectations of these patients were low and that even a minimal improvement was seen as feeling better. The latter is

the interpretation typically made in clinical research (Anderson, Bautista, & Hope, 2019; Bai, Yang, Chen, & Gao, 2020; Cuijpers, Noma, Karyotaki, Cipriani, & Furukawa, 2019; Kullgard, Holmqvist, & Andersson, 2022). However, our result suggests that this assumption deserves more careful consideration. The patient perspective is critically important and warrants more serious investigation in future research to clarify the relationships among acceptability of treatment, termination that is genuinely premature, and satisfactory improvement from the perspective of the patient (Montoya et al., 2016).

Although feeling better was by far the most frequent reason given for discontinuation, 20.0% of the patients who discontinued treatment on their own reported predisposing factors (e.g. fear of dependence, wanting to resolve problems on one's own) as reasons and 18.5% reported ineffectiveness of treatment. We evaluated whether discontinuation by the patient could be predicted and found several reliable predictors, including low country income level, being employed, and having above average personal income. Age, prior history of psychotropic medication use, and being prescribed treatment from a mental health professional

rather than from a general medical practitioner, in comparison, were associated with low probability of discontinuation. Importantly, we found that most of these predictors differed in importance as a function of the reasons for discontinuation. This is critical to note for future research as well as for efforts to develop pre-treatment risk models to target preventive interventions. There are important clinical implications of this variation both for predicting discontinuation and different for predicting outcomes with which discontinuation can be associated. For example, it is possible that discontinuing because treatment was ineffective might influence the likelihood of seeking further treatment. Improved understanding of the outcomes of those who discontinue would also be an important line of research.

Limitations

The study has several noteworthy limitations. First, data were based on retrospective respondent self-reports about medication use and treatment discontinuation over the past 12 months. Self-reports are subject to recall bias. However, prior research has found good agreement between self-reports of medication use and objective data such as pharmacy and prescription records (e.g. Boudreau *et al.* 2004; Cotterchio, Kreiger, Darlington, & Steingart, 1999; Kwon *et al.* 2003).

Second, information of key characteristics of the ADMs used was not collected, such as ADM dose. Nor did we evaluate the timeline of taking ADMs in relation to the occurrence of symptoms or reports of ADM effectiveness. The latter is important because evaluations of ADM effectiveness at the time of interview might be different than evaluations at the time of terminating ADM use. Nor did we obtain information about symptom profiles either at the beginning of treatment or at the time of treatment discontinuation, which could have been used to confirm patient reports about feeling better as a reason for discontinuation.

Third, although we made comparisons across different conditions (e.g. anxiety, depression), between patients whose prescriptions came from mental health specialists *v.* primary care treatment providers, and by ADM class, we could not draw any causal inferences about these factors, as none of them was randomized. Instead, results involving these correlates should be interpreted as providing only descriptive information about patterns of discontinuation. Similarly, our comparisons across income level were limited by the relatively small sample size of the same in LMICs.

Conclusions

We conducted a large-scale study of ADM discontinuation based on general population samples in 13 countries. We examined reasons for discontinuation, timing of discontinuation, and descriptive correlates. The findings convey the importance of evaluating discontinuation in a finer-grained fashion than is usually the case given that approximately half of the patients who discontinued on their own did so because, based on their own self-reports, they felt better. These data have important implications for understanding patterns and predictors of ADM discontinuation that recognize variation in reasons for discontinuing aimed at guiding preventive interventions. Attention to those at risk for discontinuing and not improving could lead to better strategies to improve clinical care.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291723002507>

Acknowledgements. None.

Authors' contributions. The World Mental Health Survey collaborators are: Ali Al-Hamzawi, MD; Yasmin A. Altwajiri, PhD; Laura Helena Andrade, MD, PhD; Lukoye Atwoli, MD, PhD; Corina Benjet, PhD; Guilherme Borges, ScD; Evelyn J. Bromet, PhD; Brendan Bunting, PhD; Somnath Chatterji, MD; Louisa Degenhardt, PhD; Hristo Hinkov, MD, PhD; Chi-yi Hu, MD, PhD; Aimee Nasser Karam, PhD; Georges Karam, MD; Norito Kawakami, MD, DMSc; Salma Khaled, PhD; Andrzej Kiejna, MD, PhD; John J. McGrath, MD, PhD; Jacek Moskalewicz, PhD; Daisuke Nishi, MD, PhD; David R. Williams, MPH, PhD; Bogdan Wojtyniak, ScD; Peter Woodruff, MBBS, PhD, FRCPsych; Miguel Xavier, MD, PhD; Alan M. Zaslavsky, PhD.

Funding statement. The World Health Organization World Mental Health (WMH) Survey Initiative is supported by the United States National Institute of Mental Health (NIMH; R01 MH070884), the John D. and Catherine T. MacArthur Foundation, the Pfizer Foundation, the United States Public Health Service (R13-MH066849, R01-MH069864, and R01 DA016558), the Fogarty International Center (FIRCA R03-TW006481), the Pan American Health Organization, Eli Lilly and Company, Ortho-McNeil Pharmaceutical Inc., GlaxoSmithKline, and Bristol-Myers Squibb. We thank the staff of the WMH Data Collection and Data Analysis Coordination Centres for assistance with instrumentation, fieldwork, and consultation on data analysis. None of the funders had any role in the design, analysis, interpretation of results, or preparation of this paper. The views and opinions expressed in this report are those of the authors and should not be construed to represent the views of the World Health Organization, other sponsoring organizations, agencies, or governments.

The Argentina survey – Estudio Argentino de Epidemiología en Salud Mental (EASM) – was supported by a grant from the Argentinian Ministry of Health (Ministerio de Salud de la Nación) – (Grant Number 2002-17270/13-5). The Colombian National Study of Mental Health (NSMH) is supported by the Ministry of Social Protection. The Mental Health Study Medellín – Colombia was carried out and supported jointly by the Center for Excellence on Research in Mental Health (CES University) and the Secretary of Health of Medellín. The ESEMeD project is funded by the European Commission (Contracts QL5-1999-01042; SANCO 2004123, and EAHC 20081308), the Piedmont Region (Italy), Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, Spain (FIS 00/0028), Ministerio de Ciencia y Tecnología, Spain (SAF 2000-158-CE), Generalitat de Catalunya (2017 SGR 452; 2014 SGR 748), Instituto de Salud Carlos III (CIBER CB06/02/0046, RETICS RD06/0011 REM-TAP), and other local agencies and by an unrestricted educational grant from GlaxoSmithKline. The Mexican National Comorbidity Survey (MNCS) is supported by The National Institute of Psychiatry Ramon de la Fuente (INPRFMDIES 4280) and by the National Council on Science and Technology (CONACyT-G30544-H) with supplemental support from the Pan American Health Organization (PAHO). The Peruvian World Mental Health Study was funded by the National Institute of Health of the Ministry of Health of Peru. The Portuguese Mental Health Study was carried out by the Department of Mental Health, Faculty of Medical Sciences, NOVA University of Lisbon, with collaboration of the Portuguese Catholic University, and was funded by Champalimaud Foundation, Gulbenkian Foundation, Foundation for Science and Technology (FCT) and Ministry of Health. The Romania WMH study projects 'Policies in Mental Health Area' and 'National Study regarding Mental Health and Services Use' were carried out by National School of Public Health & Health Services Management (former National Institute for Research & Development in Health), with technical support of Metro Media Transilvania, the National Institute of Statistics-National Centre for Training in Statistics, SC Cheyenne Services SRL, Statistics Netherlands and were funded by Ministry of Public Health (former Ministry of Health) with supplemental support of Eli Lilly Romania SRL. The Psychiatric Enquiry to General Population in Southeast Spain – Murcia (PEGASUS-Murcia) Project has been financed by the Regional Health Authorities of Murcia (Servicio Murciano de Salud and Consejería de Sanidad y Política Social) and Fundación para la Formación e Investigación Sanitarias (FFIS) of Murcia. The US National Comorbidity Survey Replication (NCS-R) is supported by the National Institute of Mental Health (NIMH; U01-MH60220) with supplemental

support from the National Institute of Drug Abuse (NIDA), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Robert Wood Johnson Foundation (RWJF; Grant 044708), and the John W. Alden Trust. Dr Stein is supported by the Medical Research Council of South Africa (MRC). A complete list of all within-country and cross-national WMH publications can be found at <http://www.hcp.med.harvard.edu/wmh/>.

Competing interest. In the past 3 years, Dr Kessler was a consultant for Cambridge Health Alliance, Canandaigua VA Medical Center, Holmusk, Partners Healthcare, Inc., RallyPoint Networks, Inc., and Sage Therapeutics. He has stock options in Cerebral Inc., Mirah, PYM, Roga Sciences and Verisense Health. Dr Navarro-Mateu reports non-financial support from Otsuka outside the submitted work. In the past 3 years, Dr Harris has received personal fees from RAND Corporation outside the submitted work. In the past 3 years, Dr Stein has received honoraria from Discovery Vitality, Johnson & Johnson, Kanna, L'Oreal, Lundbeck, Orion, Sanofi, Servier, Takeda, and Vistagen. All other authors declare no conflict of interest.

Disclaimer. None of the funders had any role in the design, analysis, interpretation of results, or preparation of this paper. The views and opinions expressed in this report are those of the authors and should not be construed to represent the views of the World Health Organization, other sponsoring organizations, agencies, or governments.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

¹Department of Psychology, Yale University, New Haven, CT, USA; ²School of Public Health, The University of Queensland, Herston, QLD 4006, Australia; ³Queensland Centre for Mental Health Research, The Park Centre for Mental Health, QLD 4072, Australia; ⁴Department of Health Care Policy, Harvard Medical School, Boston, MA, USA; ⁵Department of Psychiatry & Mental Health and South African Medical Council Research Unit on Risk and Resilience in Mental Disorders, University of Cape Town, Cape Town, South Africa; ⁶Groote Schuur Hospital, Cape Town, South Africa; ⁷Department of Social Medicine, Postgraduate Program in Public Health, Federal University of Espírito Santo, Vitoria, Brazil; ⁸Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada; ⁹Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA; ¹⁰National Center for Geriatrics and Welfare Research, National Health Research Institutes, Zhunan Town, Taiwan; ¹¹Center for Reducing Health Disparities, UC Davis Health System, Sacramento, CA, USA; ¹²Health Services Research Unit, IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain; ¹³Department of Medicine and Life Sciences, Pompeu Fabra University (UPF), Barcelona, Spain; ¹⁴CIBER en Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain; ¹⁵National Institute of Psychiatry Ramón de la Fuente Muñiz, Mexico City, Mexico; ¹⁶Universitair Psychiatrisch Centrum – Katholieke Universiteit Leuven (UPC-KUL), Campus Gasthuisberg, Leuven, Belgium; ¹⁷Lisbon Institute of Global Mental Health and Comprehensive Health Research Centre, NOVA Medical School, Universidade Nova de Lisboa, Lisbon, Portugal; ¹⁸Unit of Epidemiological and Evaluation Psychiatry, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy; ¹⁹Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI, USA; ²⁰Anxiety Disorders Research Center, Buenos Aires, Argentina; ²¹Department of Developmental Psychology, University of Groningen, Groningen, The Netherlands; ²²Interdisciplinary Center Psychopathology and Emotion Regulation, University Medical Center Groningen, Groningen, The Netherlands; ²³Department of Psychiatry, University College Hospital, Ibadan, Nigeria; ²⁴Research, Teaching and Innovation Unit, Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain; ²⁵Centre for Biomedical Research on Mental Health (CIBERSAM), Madrid, Spain; ²⁶Departament de Medicina, Universitat de Barcelona, Barcelona, Spain; ²⁷Department of Psychiatry and Clinical Psychology, Faculty of Medicine, Balamand University, Beirut, Lebanon; ²⁸Department of Psychiatry and Clinical Psychology, St George Hospital University Medical Center, Beirut, Lebanon; ²⁹Institute for Development

Research Advocacy and Applied Care (IDRAAC), Beirut, Lebanon; ³⁰Institut de Psychologie, EA 4057, Université Paris Cité, Paris, France; ³¹Unidad de Docencia, Investigación y Formación en Salud Mental (UDIF-SM), Gerencia Salud Mental, Servicio Murciano de Salud, Murcia, Spain; ³²Murcia Biomedical Research Institute (IMIB-Arixaca), Murcia, Spain; ³³CIBER Epidemiology and Public Health-Murcia (CIBERESP-Murcia), Murcia, Spain; ³⁴Instituto Nacional de Salud, Lima, Peru; ³⁵Universidad Cayetano Heredia, Lima, Peru; ³⁶Faculty of Social Sciences, Colegio Mayor de Cundinamarca University, Bogota, Colombia; ³⁷Department of Psychological Medicine, University of Otago, Dunedin, Otago, New Zealand; ³⁸Departamento de Psiquiatría y Salud Mental, Facultad de Medicina, Universidad de Buenos Aires, Argentina; ³⁹Trimbos-Instituut, Netherlands Institute of Mental Health and Addiction, Utrecht, Netherlands; ⁴⁰Center for Excellence on Research in Mental Health, CES University, Medellin, Colombia and ⁴¹National Institute for Health Services Management, Bucharest, Romania

References

- Akincigil, A., Bowblis, J. R., Levin, C., Walkup, J. T., Jan, S., & Crystal, S. (2007). Adherence to antidepressant treatment among privately insured patients diagnosed with depression. *Medical Care*, 45(4), 363–369. doi: 10.1097/01.mlr.0000254574.23418.f6
- American Psychiatric Association. (2010). Practice guideline for the treatment of patients with major depressive disorder. Retrieved from https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf
- Anderson, K. N., Bautista, C. L., & Hope, D. A. (2019). Therapeutic alliance, cultural competence and minority status in premature termination of psychotherapy. *The American Journal of Orthopsychiatry*, 89(1), 104–114. doi: 10.1037/ort0000342
- Bai, Y., Yang, H., Chen, G., & Gao, K. (2020). Acceptability of acute and maintenance pharmacotherapy of bipolar disorder: A systematic review of randomized, double-blind, placebo-controlled clinical trials. *Journal of Clinical Psychopharmacology*, 40(2), 167–179. doi: 10.1097/jcp.0000000000001169
- Bambauer, K. Z., Soumerai, S. B., Adams, A. S., Zhang, F., & Ross-Degnan, D. (2007). Provider and patient characteristics associated with antidepressant nonadherence: The impact of provider specialty. *The Journal of Clinical Psychiatry*, 68(6), 867–873. doi: 10.4088/jcp.v68n0607
- Barth, J., Munder, T., Gerger, H., Nüeschen, E., Trelle, S., Znoj, H., ... Cuijpers, P. (2016). Comparative efficacy of seven psychotherapeutic interventions for patients with depression: A network meta-analysis. *Focus (American Psychiatric Publishing)*, 14(2), 229–243. doi: 10.1176/appi.focus.140201
- Boudreau, D. M., Daling, J. R., Malone, K. E., Gardner, J. S., Blough, D. K., & Heckbert, S. R. (2004). A validation study of patient interview data and pharmacy records for antihypertensive, statin, and antidepressant medication use among older women. *American Journal of Epidemiology*, 159(3), 308–317. doi: 10.1093/aje/kwh038
- Brody, D. J., & Gu, Q. (2020). Antidepressant use among adults: United States, 2015–2018. Retrieved from <https://www.cdc.gov/nchs/products/databriefs/db377.htm>
- Chisholm, D., Sweeny, K., Sheehan, P., Rasmussen, B., Smit, F., Cuijpers, P., & Saxena, S. (2016). Scaling-up treatment of depression and anxiety: A global return on investment analysis. *The Lancet Psychiatry*, 3(5), 415–424. doi: 10.1016/s2215-0366(16)30024-4
- Chiu, M., Lebebaum, M., Cheng, J., de Oliveira, C., & Kurdyak, P. (2017). The direct healthcare costs associated with psychological distress and major depression: A population-based cohort study in Ontario, Canada. *PLOS One*, 12(9), e0184268. doi: 10.1371/journal.pone.0184268
- Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., ... Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *The Lancet*, 391(10128), 1357–1366. doi: 10.1016/s0140-6736(17)32802-7
- Clarke, C. S., Duffy, L., Lewis, G., Freemantle, N., Gilbody, S., Kendrick, T., ... Hunter, R. M. (2022). Cost-utility analysis of discontinuing antidepressants in England primary care patients compared with long-term maintenance: The ANTLER study. *Applied Health Economics and Health Policy*, 20, 269–282. doi: 10.1007/s40258-021-00693-x

- Cotterchio, M., Kreiger, N., Darlington, G., & Steingart, A. (1999). Comparison of self-reported and physician-reported antidepressant medication use. *Annals of Epidemiology*, 9(5), 283–289. doi: 10.1016/S1047-2797(98)00072-6
- Cuijpers, P., Noma, H., Karyotaki, E., Cipriani, A., & Furukawa, T. A. (2019). Effectiveness and acceptability of cognitive behavior therapy delivery formats in adults with depression: A network meta-analysis. *JAMA Psychiatry*, 76(7), 700–707. doi: 10.1001/jamapsychiatry.2019.0268
- Davies, J., Pauli-Jones, R., & Montagu, L. (2018). Antidepressant withdrawal: A survey of patients' experience by the all-party parliamentary group for prescribed drug dependence. Retrieved from <https://www.drugsandalcohol.ie/29794/7/APPG-PDD-Survey-of-antidepressant-withdrawal-experiences.pdf>
- Evans-Lacko, S., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Benjet, C., Bruffaerts, R., ... Thornicroft, G. (2018). Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: Results from the WHO World Mental Health (WMH) surveys. *Psychological Medicine*, 48(9), 1560–1571. doi: 10.1017/S0033291717003336
- Fantom, N. J., & Serajuddin, U. (2016). The World Bank's classification of countries by income. *World Bank Policy Research Working Paper 7528*. Retrieved from <https://openknowledge.worldbank.org/entities/publication/336a7f99-b73f-5b16-b36b-6dc49321e971>
- First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). *Structured clinical interview for DSM-IV-TR axis I disorders, research version, non-patient edition*. New York, NY: New York State Psychiatric Institute.
- Fornaro, M., Cattaneo, C. I., De Berardis, D., Ressico, F. V., Martinotti, G., & Vieta, E. (2023). Antidepressant discontinuation syndrome: A state-of-the-art clinical review. *European Neuropsychopharmacology*, 66, 1–10. doi: 10.1016/j.euroneuro.2022.10.005
- Gardarsdottir, H., Heerdink, E. R., van Dijk, L., & Egberts, A. C. (2007). Indications for antidepressant drug prescribing in general practice in the Netherlands. *The Journal of Affective Disorders*, 98(1–2), 109–115. doi: 10.1016/j.jad.2006.07.003
- Gastaldon, C., Schoretsanitis, G., Arzenton, E., Raschi, E., Papola, D., Ostuzzi, G., ... Barbui, C. (2022). Withdrawal syndrome following discontinuation of 28 antidepressants: Pharmacovigilance analysis of 31688 reports from the WHO spontaneous reporting database. *Drug Safety*, 45(12), 1539–1549. doi: 10.1007/s40264-022-01246-4
- GBD 2017 DALYs and HALE Collaborators. (2018). Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, 392(10159), 1859–1922. doi: 10.1016/S0140-6736(18)32335-3
- Goldstein, B. I., Baune, B. T., Bond, D. J., Chen, P. H., Eyler, L., Fagiolini, A., ... Fiedorowicz, J. G. (2020). Call to action regarding the vascular-bipolar link: A report from the vascular task force of the international society for bipolar disorders. *Bipolar Disorders*, 22(5), 440–460. doi: 10.1111/bdi.12921
- Haro, J. M., Arbabzadeh-Bouchez, S., Brugha, T. S., de Girolamo, G., Guyer, M. E., Jin, R., ... Kessler, R. C. (2006). Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. *International Journal of Methods in Psychiatric Research*, 15(4), 167–180. doi: 10.1002/mpr.196
- Heeringa, S., Wells, J., Hubbard, F., Mneimneh, Z., Chiu, W., Sampson, N., & Berglund, P. (2008). Sample designs and sampling procedures. In R. Kessler & T. Ustun (Eds.), *The WHO world mental health surveys: Global perspectives on the epidemiology of mental disorders* (pp. 14–32). Cambridge, England: Cambridge University Press.
- Henshaw, E. J., & Freedman-Doan, C. R. (2009). Conceptualizing mental health care utilization using the health belief model. *Clinical Psychology: Science and Practice*, 16(4), 420–439. doi: 10.1111/j.1468-2850.2009.01181.x
- Herrman, H., Kieling, C., McGorry, P., Horton, R., Sargent, J., & Patel, V. (2019). Reducing the global burden of depression: A Lancet-world psychiatric association commission. *Lancet (London, England)*, 393(10189), e42–e43. doi: 10.1016/S0140-6736(18)32408-5
- Hosmer Jr., D. W., Lemeshow, S., & May, S. (2008). *Applied survival analysis: Regression modeling of time-to-event data* (2nd ed.). Hoboken, NJ: Wiley.
- Ji, N. J., & Hong, Y. P. (2020). Effect of income level on adherence to antidepressant treatment in first onset depression outpatients. *PLOS One*, 15(9), e0238623. doi: 10.1371/journal.pone.0238623
- Kato, M., Hori, H., Inoue, T., Iga, J., Iwata, M., Inagaki, T., ... Tajika, A. (2021). Discontinuation of antidepressants after remission with antidepressant medication in major depressive disorder: A systematic review and meta-analysis. *Molecular Psychiatry*, 26, 118–133. doi: 10.1038/s41380-020-0843-0
- Kessler, R. C. (2012). The costs of depression. *Psychiatric Clinics of North America*, 35(1), 1–14. doi: 10.1016/j.psc.2011.11.005
- Kessler, R. C., & Üstün, T. B. (2004). The World Mental Health (WMH) Survey Initiative version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *International Journal of Methods in Psychiatric Research*, 13(2), 93–121. doi: 10.1002/mpr.168
- Kullgard, N., Holmqvist, R., & Andersson, G. (2022). Premature dropout from psychotherapy: Prevalence, perceived reasons and consequences as rated by clinicians. *The Journal Clinical Psychology in Europe*, 4(2), e6695. doi: 10.32872/cpe.6695
- Kwon, A., Bungay, K. M., Pei, Y., Rogers, W. H., Wilson, I. B., Zhou, Q., & Adler, D. A. (2003). Antidepressant use: Concordance between self-report and claims records. *Medical Care*, 41(3), 368–374. doi: 10.1097/01.Mlr.0000053019.79054.B6
- Lépine, J. P., & Briley, M. (2011). The increasing burden of depression. *Neuropsychiatric Disease and Treatment*, 7(Suppl 1), 3–7. doi: 10.2147/ndt.S19617
- Liu, X., Momen, N. C., Molenaar, N., Rommel, A. S., Bergink, V., & Munk-Olsen, T. (2021). Discontinuation of antidepressants: Is there a minimum time on treatment that will reduce relapse risk? *The Journal of Affective Disorders*, 290, 254–260. doi: 10.1016/j.jad.2021.04.045
- Magaard, J. L., Seeralan, T., Schulz, H., & Brütt, A. L. (2017). Factors associated with help-seeking behaviour among individuals with major depression: A systematic review. *PLOS One*, 12(5), e0176730. doi: 10.1371/journal.pone.0176730
- Mojtabai, R., & Olfson, M. (2014). National trends in long-term use of antidepressant medications: Results from the U.S. National Health and Nutrition Examination Survey. *The Journal of Clinical Psychiatry*, 75(2), 169–177. doi: 10.4088/JCP.13m08443
- Montoya, A., Lebec, J., Keane, K. M., Fregenal, I., Ciudad, A., Morínigo, Á., ... Zimmerman, M. (2016). Broader conceptualization of remission assessed by the remission from depression questionnaire and its association with symptomatic remission: A prospective, multicenter, observational study. *BMC Psychiatry*, 16, 352. doi: 10.1186/s12888-016-1067-3
- Moshe, I., Terhorst, Y., Philippi, P., Domhardt, M., Cuijpers, P., Cristea, I., ... Sander, L. B. (2021). Digital interventions for the treatment of depression: A meta-analytic review. *Psychological Bulletin*, 147(8), 749–786. doi: 10.1037/bul0000334
- National Institute for Health and Care Excellence (NICE). (2009). Depression in adults: Recognition and management. Retrieved from <https://www.nice.org.uk/guidance/cg90>
- Olfson, M., Marcus, S. C., Tedeschi, M., & Wan, G. J. (2006). Continuity of antidepressant treatment for adults with depression in the United States. *American Journal of Psychiatry*, 163(1), 101–108. doi: 10.1176/appi.ajp.163.1.101
- Samples, H., & Mojtabai, R. (2015). Antidepressant self-discontinuation: Results from the collaborative psychiatric epidemiology surveys. *Psychiatric Services*, 66(5), 455–462. doi: 10.1176/appi.ps.201400021
- SAS Institute Inc (2013). *SAS software* (9.4 ed.). Cary, NC: SAS Institute Inc.
- Scholten, W., Batealan, N., & Van Balkom, A. (2020). Barriers to discontinuing antidepressants in patients with depressive and anxiety disorders: A review of the literature and clinical recommendations. *Therapeutic Advances in Psychopharmacology*, 10, 1–10. doi: 10.1177/2045125320933404
- Scott, K. M., de Jonge, P., Stein, D. J., & Kessler, R. C. (2018). *Mental disorders around the world: Facts and figures from the WHO world mental health surveys*. Cambridge, England: Cambridge University Press.
- Sirey, J. A., Banerjee, S., Marino, P., Bruce, M. L., Halkett, A., Turnwald, M., ... Kales, H. C. (2017). Adherence to depression treatment in primary care: A randomized clinical trial. *JAMA Psychiatry*, 74(11), 1129–1135. doi: 10.1001/jamapsychiatry.2017.3047

- Sørensen, A., Jørgensen, K. J., & Munkholm, K. (2022). Description of antidepressant withdrawal symptoms in clinical practice guidelines on depression: A systematic review. *The Journal of Affective Disorders*, 316, 177–186. doi: 10.1016/j.jad.2022.08.011
- Tabatabai, M. A., Li, H., Eby, W. M., Kengwoung-Keumo, J. J., Manne, U., Bae, S., ... Singh, K. P. (2014). Robust logistic and probit methods for binary and multinomial regression. *Journal of Biometrics & Biostatistics*, 5(4), 202. doi: 10.4172/2155-6180.1000202
- Tanner, J. A., Hensel, J., Davies, P. E., Brown, L. C., Dechairo, B. M., & Mulsant, B. H. (2020). Economic burden of depression and associated resource use in Manitoba, Canada. *The Canadian Journal of Psychiatry*, 65(5), 338–346. doi: 10.1177/0706743719895342
- Van Leeuwen, E., van Driel, M. L., Horowitz, M. A., Kendrick, T., Donald, M., De Sutter, A. I., ... Christiaens, T. (2021). Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults. *Cochrane Database of Systematic Reviews* (4), CD013495. doi: 10.1002/14651858.CD013495.pub2
- Wang, Y. H., Li, J. Q., Shi, J. F., Que, J. Y., Liu, J. J., Lappin, J. M., ... Bao, Y. P. (2020). Depression and anxiety in relation to cancer incidence and mortality: A systematic review and meta-analysis of cohort studies. *Molecular Psychiatry*, 25(7), 1487–1499. doi: 10.1038/s41380-019-0595-x
- Warden, D., Rush, A. J., Trivedi, M. H., Fava, M., & Wisniewski, S. R. (2007). The STAR*D project results: A comprehensive review of findings. *Current Psychiatry Reports*, 9(6), 449–459. doi: 10.1007/s11920-007-0061-3
- Wells, T. T., Clerkin, E. M., Ellis, A. J., & Beevers, C. G. (2014). Effect of antidepressant medication use on emotional information processing in major depression. *American Journal of Psychiatry*, 171(2), 195–200. doi: 10.1176/appi.ajp.2013.12091243
- Wolter, K. (1985). *Introduction to variance estimation*. New York, NY: Springer-Verlag.
- World Health Organization. (2017). Depression and other common mental disorders: Global health estimates. Retrieved from <https://apps.who.int/iris/handle/10665/254610>
- Wu, C. S., Shau, W. Y., Chan, H. Y., Lee, Y. C., Lai, Y. J., & Lai, M. S. (2012). Utilization of antidepressants in Taiwan: A nationwide population-based survey from 2000 to 2009. *Pharmacoeconomics and Drug Safety*, 21(9), 980–988. doi: 10.1002/pds.3255
- Yamabe, K., Liebert, R., Flores, N., & Pashos, C. L. (2019). Health-related quality of life outcomes, economic burden, and associated costs among diagnosed and undiagnosed depression patients in Japan. *ClinicoEconomics and Outcomes Research*, 11, 233–243. doi: 10.2147/ceor.S179901