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REVIEW

Sociodemographic and clinical predictors of compliance with antidepressants for depressive disorders: systematic review of observational studies

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Background: The literature shows that compliance with antidepressant treatment is unsatisfactory. Several personal and disease-related variables have been shown to be related to compliance behavior. The objective of this study was to review the literature about sociodemographic and clinical predictors of compliance in patients with depressive disorders.

Methods: The Medline, Embase, Cochrane Central, PsycInfo, and Cinahl databases were searched until May 2012. Studies that analyzed sociodemographic and clinical predictors or correlates of compliance in patients with depressive disorder were included. A quantitative synthesis was not performed because of the heterogeneity and availability of the data reported. For similar reasons, the results were not classified according to the different phases of treatment. The search was limited to studies published in English and Spanish.

Results: Thirty-two studies fulfilled the inclusion criteria. The most consistent associations with compliance were found for age (older patients showed more compliance) and race (white patients were more likely to adhere to treatment than minority ethnic groups). Few studies assessed clinical factors, and the most plausible predictors of compliance were certain comorbidities and substance abuse. Severity of depression did not play an important role in predicting compliance.

Conclusion: The impact of the variables studied on compliance behavior appeared to be inconsistent. Identifying potential predictors of compliance with antidepressant treatment is important, both for the routine practice of the mental health professional and for refining interventions to enhance adherence and target them to specific populations at risk of noncompliance.

Keywords: adherence, antidepressants, compliance, depression, predictors

Introduction

Depressive disorders have become a priority public health concern because of their high prevalence and global disease burden, mainly as a result of the disability caused. The total number of people with depression in Europe reached 21 million in the year 2004,[1] and the World Health Organization estimates that, by the year 2020, depression will become the second most important cause of disability worldwide.[2] Despite the availability of effective drugs for the treatment of depression, a significant percentage of patients do not achieve full remission of symptoms.[3] Furthermore, approximately 50% of patients experience recurrence, and the probability of another depressive episode increases with each case of recurrence.[4] Therefore, for many patients, depression presents as a chronic disorder that requires lifelong antidepressant treatment to

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prevent recurrences. For these reasons, most national guidelines recommend continuing treatment for 4–9 months after the current episode has remitted.[5]

In this context, compliance with antidepressant treatment becomes a crucial factor in order to reach the desired outcomes of treatment. Compliance has been defined as the extent to which a person's behavior, in terms of taking medication, following diets, or executing lifestyle changes, coincides with medical or health advice.[6] It has been discussed whether the term "adherence" reflects a less paternalistic relationship towards patients than "compliance", or even if both terms should be replaced by concepts such as alliance or concordance, which implicitly represent a more patient-centered approach.[7] This discussion is beyond the scope of this article, and therefore the terms "compliance" and "adherence" will be considered synonymous. It is accepted that nonadherence may refer to several distinct aspects of medication-taking behaviors, ie, failure to attend an initial appointment, failure to have the prescription filled, having the prescription filled but failing to take the medication, not following the frequency or dose instructions of the prescription, errors of purpose, or use of inadvertent combinations.[8] For the purposes of this work, we will refer to "nonadherence" as partial compliance (missed doses) and to "discontinuation" as definitely discontinuing the medication.

It has been argued that if guideline recommendations about antidepressant treatment were followed exactly, the overall burden of depression (measured by disability-adjusted life-years) could be reduced by approximately 28%.[9] However, several clinical studies have shown that patient adherence with antidepressants is quite unsatisfactory, specifically with regard to long-term maintenance treatment. Up to 42% of patients discontinue treatment after 12 weeks,[5] and partial compliance has been estimated to be 45%.[10] Reasons for noncompliance include a wide range of factors, related to patient or treatment characteristics, as well as to patient-physician interaction.[11,12] Adverse effects of medications have been shown to play an important role in treatment discontinuation and adherence, although the introduction of new-generation antidepressants with fewer side effects has, to some extent, overcome this problem. Other variables that have been related to nonadherence are perceived lack of efficacy, poor instructions, lack of information about the condition and its treatment, "polyprescribing", or a difficult dosing regimen.[13] In the case of mental disorders, factors related to the effect of the illness, such as lack of awareness of the disease and depressed mood or cognitive impairment, may act as additional barriers for adequate adherence to treatment.

One of the more important difficulties in research on adherence is its measurement. Several methods have been used, including patient self-report, physician rating, pill count, prescription fills count, drug/metabolite plasma concentration, or the Medication Event Monitoring System. Patient and physician reports are subject to reliability problems, while the other techniques are expensive or not acceptable to all patients because of their invasiveness. Studies that have analyzed the concordance between these different methods of assessing adherence have reported acceptable correlations between them.[14–16]

As part of a wider review concerning predictors of compliance with antidepressant medications, the aim of this study was to review the literature on sociodemographic and clinical (disease-related) predictors or correlates of compliance with antidepressants in patients with depressive disorders.

Materials and methods

The Medline, Embase, Cochrane Central, PsycInfo, and Cinahl databases were searched from January 1990 to May 2012, and two of the authors independently selected all relevant English and Spanish language publications. References were first selected by title and abstract and then obtained in full text. In addition to this search strategy, references lists were searched manually. Once the selection process was finished, discrepancies between authors were discussed and resolved by consensus.

To be included in the review, studies had to be observational and include adult and/or elderly patients diagnosed with a depressive disorder by a health care provider or the researchers of the study. They had to analyze, either by retrospective, cross-sectional, or prospective design, some of the following predictors or correlates of compliance with antidepressant medications: age, gender, race, education, living situation/marital status, income, employment status, diagnosis subtype, severity of depression, previous episodes, psychiatric and medical comorbidities, cognitive impairment, and perceived health or health-related quality of life. Studies were excluded if they included patients with bipolar or psychotic disorders, if they only included patients with depression along with a medical illness, or if participants were taking antidepressants but the diagnosis was not reported (or only assessed by participant self-report).

Data on the study sample, design, predictor variables, follow-up duration, definition and method of assessing compliance, and statistical methods were extracted. Results of multivariate analyses will be commented on, unless only bivariate analyses were reported in the study. We classified

the results into two types of noncompliance behavior, ie, discontinuation (stopping taking the medication) and nonadherence (intermittent or partial compliance).

Results

After eliminating duplicates, 1690 references were obtained. One hundred and twenty were selected by title/abstract, and 34 were finally included, comprising 32 studies (one study was reported in two references,[17,18] and another[19] used a subsample of the parent study[20]). Twenty-one additional references obtained by hand searching were examined, but none fulfilled the inclusion criteria. Among the excluded studies that assessed predictors or correlates of compliance, the most common reason for exclusion was that a formal diagnosis of depression was not required, but only the use of antidepressants.

Table 1 shows the characteristics of the studies included. Twenty-three studies were performed in the United States,[20–42] two in Canada,[43,44] two in Spain,[45,46] two in Taiwan,[47,48] one in the United Kingdom,[49] one in Belgium,[17,18] and one in New Zealand.[50] Sample sizes were less than 100 in eight studies, 100–600 in eleven studies, and more than 2000 in 12 studies. Given that the two studies[29,30] with the smallest sample sizes (30 and 22 subjects) did not yield statistically significant results for any of the variables analyzed, they are not considered in the counting of results, in order to limit the exposition to a group of studies with acceptable statistical power. Tables 2 and 3 show the results obtained.

Predictors of treatment discontinuation

Seven studies offered data about treatment discontinuation. Three used a retrospective design,[36,37,42] one was a cross-sectional study,[24] and three used a prospective design.[17,18,41,47] To assess discontinuation, four studies used self-report measures,[17,18,24,36,41] two used prescription fills data,[37,42] and one considered discontinuation as not attending follow-up visits.[47] Two studies assessed discontinuation at 3 months,[36,41] three at 6 months,[17,18,37,47] and one at 12 months.[42]

Sociodemographic predictors

Potential sociodemographic predictors investigated were age, gender, race, educational level, living situation/marital status, income, and employment status. All studies assessed the effect of age on treatment discontinuation, and three of them obtained significant results.[37,41,42] Older age was associated with both lower rates[41] and a longer time[42] to discontinuation. Sanglier et al found an interaction between age and antidepressant dispensing year, in that before 2006, older adults were more likely to discontinue than younger ones, but the opposite was found after that year.[37]

Six studies offered data about gender differences for discontinuation.[17,18,24,36,41,42] Only Woolley et al found a significant effect, with men being significantly more likely to discontinue with treatment.[41] Demyttenaere et al found an interaction between gender and functional improvement, in that the risk of discontinuation for women related to improvement in family functioning, while in men it was related to improvements in occupational, social, and family functioning.[18]

Four studies analyzed the effect of race.[24,36,41,42] Olfson et al found that Hispanic patients (but not black or other minorities) showed higher discontinuation rates than white patients.[36] Further, Wu et al reported a longer time to discontinuation in Caucasians versus African-American patients.[42]

Four studies assessed the effect of educational level on discontinuation,[24,36,41,47] and only Olfson et al found a significant result, ie, individuals with 12 years of education or less showed higher rates of discontinuation than those with more than 12 years.[36]

Bull et al found that separate or divorced patients and those whose spouses had died discontinued significantly more often than married patients.[24] The remaining two studies that assessed living situation and/or marital status of the participants did not obtain statistically significant results.[36,41]

Only Olfson et al assessed income status and found that patients with low incomes discontinued significantly more often than those with high incomes.[36] None of the four studies that included employment status as a potential predictor of discontinuation found significant results.[24,36,41,47]

Clinical predictors

Potential clinical predictors investigated were diagnostic subtype, severity of depression, previous episodes, comorbidities, cognitive impairment, and perceived health status/health-related quality of life. Hung et al found that individuals with chronic depression showed lower rates of discontinuation than those without the condition.[47] The three studies that assessed severity did not find statistically significant associations with discontinuation of treatment.[24,41,47] Bull et al found that it was improvement, and not level of depression, that predicted an adequate treatment duration.[24] Only Sanglier et al examined the role of history of previous depressive episodes and did not find statistically significant associations with discontinuation.[37] The two studies that assessed psychiatric and medical comorbidities did not find statistically significant associations.[42,47] Olfson et al is the only study that assessed

Table 1 Characteristics of the studies included

Reference and country	Aim/design/setting	Inclusion criteria/sample size	Follow-up	Adherence measure	Adherence criteria
Discontinuation studies					
Bull et al[24] USA	Predictors of discontinuation Cross-sectional Hospitals/outpatient clinics	Age 18–75 years MDD or depressive disorder (ICD-9 codes 296.2, 311) n = 401		Self-report	Continue with medication
Demyttenaere et al[17,18] Belgium	Effect of gender and impairment on adherence Prospective Primary care	Age ≥ 18 years MDD (DSM-IV) n = 272	6 months	Self-report	Continue with medication
Hung et al[47] Taiwan	Predictors of discontinuation Prospective Psychiatric hospital	Age 18–65 years MDD (DSM-IV-TR) n = 135	6 months	Attending follow-up appointments	Attending follow-up appointments
Keeley et al[29] USA	Effect of somatoform symptoms on adherence Prospective Family medicine clinic	Age ≥ 18 years Depression n = 30	14 weeks	Self-report	Continue with medication
Olfson et al[36] USA	Predictors of discontinuation Retrospective Medical Expenditure Panel Survey (1996–2001)	Age ≥ 18 years Depression (ICD-9 codes 296.2, 296.3, 300.4, or 311) n = 390	2.5 years (3 months for adherence)	Self-report	Continue with medication
Woolley et al[41] US	Predictors of discontinuation Prospective Psychiatric hospital	Age 18–75 years MDD (ICD-9 codes 296.2, 296.3) n = 403	3 months	Self-report	Continue with medication
Nonadherence studies					
Aikens et al[21] USA	Effect of beliefs about AD Cross-sectional Family medicine clinic	Age ≥ 18 years ≥12 weeks of continued AD prescriptions for treating depression n = 95		Self-report: Brief Med Questionnaire (BMQ), Morisky Compliance Scale (MCS)	Recent (BMQ): number of days adherent/14 (continuous measure) General: MCS (continuous measure)
Akincigil et al[22] USA	Predictors of adherence Retrospective Private insurance health plan database (January 2003 to January 2005)	Age ≥ 18 years Newly MDD n = 4312	33 weeks	Prescription records	Acute: MPR ≥ 75% of the time during the first 16 weeks Continuation: MPR ≥ 75% of the time during weeks 17–33
Ayalon et al[23] USA	Adherence in elderly black and Latino patients Cross-sectional University of California San Francisco patient registry system	Age ≥ 55 years MDD n = 101		Self-report	Intentional and nonintentional (both dichotomized)

Burra et al[43] Canada	Predictors of adherence Cross-sectional General hospital outpatient psychiatric practice/community outpatient psychiatric practice/general hospital-based mood disorders clinic	Age ≥ 18 years Unipolar depression n = 80		Self-report	Taken as prescribed ≥ 80% of time
Chen et al[25] USA	Predictors of guide-line concordant use Retrospective National health plan database (newly diagnosed July 2000 to December 2002)	Age ≥ 18 years MDD (ICD-9-CM codes 296.20–296.24) n = 4102	9 months	Prescription records	Both MPR = days of supply/total days ≥ 80% (adherence) AND no gaps of more than half of the days of supply since the end of the last supply (persistence)
Cohen et al[44] Canada	Effect of personality on adherence Prospective Depression clinic	Age ≥ 18 years MDE not suffering from psychosis n = 65	14 weeks	MEMS	Once daily: (days with at least one opening/total days) × 100 (continuous measure) Twice daily: (days with at least 2 openings/total days) × 100 (continuous measure)
Crown et al[26] USA	Impact of adherence on long-term costs of treatment Retrospective MarketScan database (1993–1996)	Age ≥ 18 years MDD, neurotic depression, brief or prolonged depressive reaction, depression not elsewhere classified n = 2.030	24 months (6 months for adherence)	Prescription records	At least 4 prescriptions filled in the first 6 months
Donohue et al[27] USA	Effect of pharmaceutical promotion on treatment continuation Retrospective MarketScan database (July 1997 to June 2000)	Age 18–64 years Depressive disorders (ICD-9 codes 296.2×, 296.3×, 311×, 300.4×) n = 11,306	6 months	Prescription records	Prescriptions filled for at least 4 months
Granger et al[28] USA	Preferences and adherence to treatment with Wellbutrin SR Cross-sectional Online panel Internet survey	Age ≥ 18 years Depression n = 527		Self-report	As many times per day as prescribed
Lin et al[31] USA	Adherence and health care expenditure Retrospective Medical Expenditure Panel Survey database (2004–2007)	Age ≥ 18 years MDD (ICD-9 codes 296.2, 296.3) n = 2,111,615 (weighted number)	12 months	Prescription records	Proportion of days covered = ((number of days with drug on hand)/365) × 100 (continuous measure)
Madsen et al[32] USA	Provider collaboration and patient reactance in the prediction of adherence Prospective Psychiatry clinics	Age ≥ 18 years MDD n = 50	12 weeks	Self-report	Proportion of days adherent = (number of self-reported days of not taking medication/number of days since baseline) − 1 (continuous measure)

(*Continued*)

Table 1 (*Continued*)

Reference and country	Aim/design/setting	Inclusion criteria/sample size	Follow-up	Adherence measure	Adherence criteria
Maidment et al[49] UK	Predictors of adherence in older adults Cross-sectional Primary care	Age ≥ 65 years Depression n = 67		Self-report (score range: 1–5)	Continuous measure
McLaughlin et al[33] USA	Difference on adherence between once-daily versus twice-daily bupropion Retrospective NDC Health's Intelligent Health Repository (September 2003 to February 2004)	Age ≥ 18 years Depression (ICD-9 codes 296.2, 296.3, 300.4, or 311) n = 3138	9 months	Prescription records	MPR = (days supplied/total days) > 70%
Merrick et al[34] USA	Customization and adherence Retrospective Medicaid claims for prescription drugs and medical services from the US states of Michigan and Indiana (2000–2003)	Age ≥ 18 years Depressive disorders (ICD-9 codes 296.20–296.25, 296.30–296.35, 298.0, 300.4, 309.1 and 311) n = 383	4 months	Prescription records	At least 84 days during the 114-day post-index observation period
Oller-Canet et al[46] Spain	Adherence to treatment Cross-sectional Primary care	Age ≥ 18 years Depressive disorders (depressive episodes; recurrent depressive disorder; dysthymia; mixed anxious depressive disorder; adaptive disorder) n = 212		Prescription records	(Number of prescriptions prescribed – number of prescriptions dispensed) < 3
Pfeiffer et al[35] USA	Effect of taking benzodiazepines on adherence to AD Retrospective VA National Registry for Depression (October 2006 to September 2007)	Depressive disorders (MDD, dysthymia, depression not otherwise specified, adjustment disorder with depressed mood) n = 43,915	12 months	Prescription records	MPR ≥ 72 of 90 days
Roca et al[45] Spain	Predictors of adherence Cross-sectional Psychiatric practice	Age ≥ 18 years Nonpsychotic MDD (DSM-IV) N = 3606		Physician-rated: simplified medication adherence questionnaire	Adherent (yes/no)
Russell et al[50] New Zealand	Effect of beliefs about AD on adherence Cross-sectional Primary care	Age 18–65 years MDD (DSM-IV-R) n = 85		Self-report: medication adherence report scale	Continuous measure
Sher et al[19] (subsample of Sirey et al)[20] USA	Effect of caregivers' perceived stigma and causal beliefs on patients' adherence Prospective Outpatient mental health clinic	Age 18–65 years Unipolar MDD (DSM-IV) n = 50	3 months	Self-report (score range 1–6)	Score of 6
Sirey et al[20] USA	Effect of perceived stigma and self-rated severity on adherence Prospective Outpatient mental health clinic	Age 18–65 years Unipolar MDD (DSM-IV) n = 134	3 months	Self-report (score range 1–6)	Score of 6

Stang et al[38] USA	To compare difference in adherence between once-daily versus twice-daily bupropion Retrospective Integrated health care Information services National managed care Benchmark database	Age 18–64 years Depressive disorders (ICD-9-CM codes 296.2, 296.3, 300.4, or 311) n = 2291	9 months	Prescription records	MPR = days supplied/total days (>70%)
Voils et al[39] USA	Social support and locus of control as predictor of adherence Prospective University psychiatric service	Age ≥ 59 years CES-D ≥ 16 or major depression n = 85	12 months	Self-report: Morisky compliance scale	Continuous measure
White et al[40] USA	Economic impact of patient adherence Retrospective	Age ≥ 18 years Depression n = 14,190	6 months	Prescription records	MPR = days supplied/total days (>70%)
Yeh et al[48] Taiwan	Predictors of adherence Cross-sectional Outpatient services at a department of psychiatry	Age ≥ 18 years MDD and dysthymic disorder (DSM-IV) n = 181		Self-report	Continuous measure
Discontinuation/nonadherence studies					
Keeley et al[30] USA	Association between responses to neutral facial expressions and adherence Prospective Primary care	Age ≥ 18 years Depression n = 22	3 months	Self-report Pharmacy records	Continue with medication Continuous medication availability = (days supplied/ total days) × 100
Sanglier et al[37] USA	Adherence in older and younger adults Retrospective IMS LifeLink Healthplan database (2002–2007)	Age ≥ 18 years Depressive disorders (ICD-9-CM codes 296.2, 296.3, 300.4, or 311) n = 6460	6 months	Pharmacy records	Nonpersistence: no prescription filled within twice the period covered by the latest prescription fill Adherence: derivation of the MPR = number of days covered by any antidepressant dispensing/180 (<0.20, poor; 0.20–0.79, intermediate; ≥0.80, good)
Wu et al[42] USA	Race, anxiety, and AD adherence Retrospective MarketScan database (2003–2007)	Age 18–64 years MDD (ICD-9-CM codes 296.2, or 296.3) n = 3083	12 months	Prescription records	MPR modified = days supplied/total days (>80%) Persistence = number of days from the date of the first antidepressant filled to the cessation of antidepressant use

Abbreviations: AD, antidepressant; CES-D, Center for Epidemiologic Studies Depression Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Text Revision; MDD, major depressive disorder; MDE, major depressive episode; MPR, medication possession ratio; MEMS, Medication Event Monitoring System; BMQ, Beliefs about Medicines Questionnaire; MCS, multiple chemical sensitivity; VA, Veterans Administration.

Table 2 Results of studies included (sociodemographic predictors)

	Age	Gender	Race
Discontinuation			
Bull et al[24] USA	NS	NS	NS
Demyttenaere et al[17,18] Belgium	NS	NS Significant interaction with type of impairment	
Hung et al[47] Taiwan	NS	NS	
Keeley et al[29] USA	NS	NS	NS
Olfson et al[36] USA	NS	NS	Hispanic patients continue less than white (OR 0.58; 95% CI 0.36–0.94)
Woolley et al[41] USA	Increases in age relate to less discontinuation (OR 0.98; 95% CI 0.96–1.00)	Males discontinue more (OR 2.02; 95% CI 1.16–3.49)	NS
Keeley et al[30] USA	NS	NS	NS
Sanglier et al[37] France	Interaction with dispensing year		
Wu et al[42] USA	Age 51–60 years more persistent than those aged 18–30 years (HR 0.61; 95% CI 0.51–0.74)	NS	African-Americans less persistent than Caucasians (HR 1.47; 95% CI 1.30–1.65)
Nonadherence			
Aikens et al[21] USA	NS	NS	
Akincigil et al[22] USA	Acute phase: Ages 40–49 years (OR 1.71; 95% CI 1.36–2.15), 50–64 years (OR 2.48; 95% CI 1.94–3.15), and ≥ 65 years (OR 1.96; 95% CI 1.34–2.85) more adherent than 18–25 years	NS	
Ayalon et al[23] USA	NS		NS
Burra et al[43] Canada	NS	Females are less nonadherent than males (OR 5.12; 95% CI 1.09–24.1)	
Chen et al[25] USA	Acute phase: age 35–49 years (OR 1.38; 95% CI 1.19–1.60), 50–64 years (OR 1.39; 95% CI 1.15–1.68), and ≥65 years (OR 2.77; 95% CI 1.67–4.58) more adherent than 18–34 years Continuation phase: age 35–49 years (OR 1.40; 95% CI 1.12–1.74) and 50–64 years (OR 1.81; 95% CI 1.36–2.39), more adherent than 18–34 years	NS	
Cohen et al[44] Canada	NS	NS	
Crown et al[26] USA	Increases in age relate to better adherence (t = 2.868; $P < 0.01$)	Females adhere more than males (t = 2.831; $P < 0.01$)	

Education	Living situation/marital status	Income	Employment
NS	Separated, divorced, or widowed subjects discontinued more than married people (OR 2.83; 95% CI 1.49–5.39)		NS
NS			NS
Those with 12 (OR 0.53; 95% CI 0.35–0.79) or less (OR 0.64; 95% CI 0.42–0.92) years of education continue less than those with >12 years	NS	Those with low incomes continue less than those with high incomes (OR 0.64; 95% CI 0.41–0.99)	NS
NS	NS		NS
NS			NS
NS			
		Acute phase: those earning $50,000–70,000 (OR 1.22; 95% CI 1.05–1.42) and ≥$70,000 (OR 1.30; 95% CI 1.11–1.53) adhere more than those under $50,000 Continuation phase: those earning $50,000–70,000 (OR 1.25; 95% CI 1.002–1.55) adhere more than those under $50,000	
NS		NS	
Those who had not completed post-secondary education are more nonadherent than those above that educational level (OR 4.43; 95% CI 1.03–18.9)	NS		NS

(*Continued*)

Table 2 (*Continued*)

	Age	Gender	Race
Donohue et al[27] USA	Older patients more adherent (data not reported)	Women more adherent than men (data not reported)	
Granger et al[28] USA	Likelihood of nonadherence decreased with age (data not reported)	Females were nearly twice as likely as males to be nonadherent (data not reported)	
Lin et al[31] USA	NS	NS	Hispanics less adherent than non-Hispanic whites ($P < 0.05$) and other ethnicities ($P < 0.01$)
Maidment et al[49] UK	NS	NS	
McLaughlin et al[33] USA	Increased age relate to better adherence (OR 1.01; 95% Wald CI 1.008–1.012)	NS	
Merrick et al[34] USA	Age 60–74 years (OR 2.4; 95% CI 1.2–4.8) and ≥75 years (OR 2.7; 95% CI 1.4–5.4) more adherent than 45–59 years	NS	Whites more adherent than nonwhites (OR 2.4; 95% CI 1.3–4.3)
Oller-Canet et al[46] Spain	NS	NS Significant interaction with type of AD (among SSRI users, women were more adherent than men, $P = 0.015$)	
Pfeiffer et al[35] USA	Increased age related to better adherence (OR 1.01; 95% CI 1.01–1.01)	Men show less adherence (OR 0.88; 95% CI 0.83–0.94)	Blacks (OR 0.47; 95% CI 0.44–0.50) and others (OR 0.82; 95% CI 0.72–0.93) less adherent than whites. Hispanics less adherent than non-Hispanics (OR 0.66; 95% CI 0.70–0.72)
Roca et al[45] Spain		Male gender related to poor adherence (data not reported)	
Sher et al[19] (subsample of Sirey et al)[20] USA	NS	NS	
Sirey et al[20] USA	Age ≥ 60 years better adherence than <60 years (OR 2.91; 95% CI 1.03–8.24)	NS	NS
Stang et al[38] USA	Increased age related to better adherence (OR 1.026; 95% CI 1.017–1.034)	NS	
Voils et al[39] USA	NS	NS	
White et al[40] USA	Higher rate of patients < 40 years in nonadherent group ($P < 0.001$)	NS	
Yeh et al[48] Taiwan	NS	NS	
Keeley et al[30] USA	NS	NS	NS
Sanglier et al[37] USA	Interaction with dispensing year		
Wu et al[42] USA	Ages 31–40 years (OR 1.39; 95% CI 1.15–1.67), 41–50 years (OR 1.73; 95% CI 1.40–2.14), 51–60 years (OR 1.90; 95% CI 1.45–2.49) and 61–64 years (OR 1.91; 95% CI 1.05–3.46) more adherent than 18–30 years	NS	African-American less adherent than Caucasians (OR 0.60; 95% CI 0.51–0.72)

Abbreviations: CI, confidence interval; NS, no significant results; HR, hazard ratio; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

Education	Living situation/marital status	Income	Employment
			NS
NS			NS
NS		NS	
	NS		
Lower educational level related to poor adherence (data not reported)	Living alone related to poor adherence (data not reported)		Being unemployed related to poor adherence (data not reported)
NS	NS	NS	NS
	NS		
NS	NS		
NS	NS	Higher income relates to worse adherence (t = –3.054; $P < 0.01$)	NS
NS			NS

Table 3 Results of the studies included (clinical predictors)

	Diagnostic subtype	Severity	Previous episodes
Discontinuation			
Bull et al[24] USA		NSD in BDI-FS at 3 months Those improved at 3 months discontinue less (OR 0.40; 95% CI 0.20–0.82)	
Demyttenaere et al[17,18] Belgium			
Hung et al[47] Taiwan	Those with chronic depression discontinue less than those without (OR 0.40, 95% CI 0.20–0.81)	NS (HAM-D)	
Keeley et al[29] USA		NS (PAI depression subscale)	
Olfson et al[36] USA			
Woolley et al[41] USA		NS (BDI)	
Keeley et al[30] USA	NS	NS	
Sanglier et al[37] USA			NS
Wu et al[42] USA			
Nonadherence			
Aikens et al[21] USA		NS (PHQ-9)	
Akincigil et al[22] USA			
Ayalon et al[23] USA		NS (GDS)	
Burra et al[43] Canada		NS	
Chen et al[25] USA			
Cohen et al[44] Canada	NS	NS (HDRS-17)	NS
Crown et al[26] USA	MDD single episode ($t = -2.228$; $P < 0.01$), MDD recurrent episode ($t = -2.681$; $P < 0.05$) and neurotic depression ($t = -2.284$; $P < 0.01$) relate to worse adherence		
Donohue et al[27] USA	NS		NS
Lin et al[31] USA			

Comorbidities	Cognitive impairment	Perceived health status
NS (panic/agoraphobia, social phobia, specific phobia, PTSD, OCD, GAD, migraine)		
NS (number of chronic problems)		
	NS	Those with fair or poor mental health status discontinue more at 3 months than those with excellent to good mental health status (OR 1.96; 95% CI 1.21–3.19)
NS (CDS)		
NS (anxiety disorders, medical comorbidities)		
Acute phase: those with headache or migraine adhere less than those without (OR 0.82; 95% CI 0.67–0.99). Those with 2 or more CVD/diabetes conditions (OR 0.65; 95% CI 0.49–0.86) adhere less than those without. Those with alcohol (OR 0.49; 95% CI 0.36–0.68) or substance abuse (OR 0.72; 95% CI 0.56–0.93) adhere less than those without these conditions		
	Increases in cognitive impairment related to poor unintentional adherence (OR 0.43; 95% CI 0.20–0.89)	NS
Acute phase: NS (CDS, anxiety) Those with substance abuse less adherent (OR 0.62; 95% CI 0.45–0.86). Continuation phase: NS (anxiety, substance abuse) higher CDS relates to better adherence (OR 1.13; 95% CI 1.00–1.27)		
Number of nonmental health illnesses relate to worse adherence ($t = -2.382$; $P < 0.05$)		
NS		NS

(*Continued*)

Table 3 (*Continued*)

	Diagnostic subtype	Severity	Previous episodes
Madsen et al[32] USA		NS (BDI-II)	
Maidment et al[49] UK		NS (GMSS-DS)	
McLaughlin et al[33] USA			
Merrick et al[34] USA	NS		
Oller-Canet et al[46] Spain			
Pfeiffer et al[35] USA			
Roca et al[45] Spain		Nonadherent showed more severity (HDRS) ($t = 11.3$; $P < 0.001$)	NS
Russell et al[50] New Zealand		Lower severity (BDI-II) relates to better adherence (Spearman rho 0.33; $P < 0.001$)	
Sirey et al[20] USA		NS (HAM-D)	
Sher et al[19] (subsample of Sirey et al)[20] USA		NS (HAM-D)	NS
Stang et al[38] USA			
Voils et al[39] USA			NS
White et al[40] USA			
Yeh et al[48] Taiwan		NS (BDI)	
Keeley et al[30] USA	NS	NS	
Wu et al[42] USA			

Abbreviations: NS, no significant results; BDI-FS, Beck Depression Inventory (Fast Screening); CCI, Charlson Comorbidity Index; CDS, Chronic Disease Score; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; GAD, generalized anxiety disorder; GDS, Geriatric Depression Scale; GMSS-DS, Geriatric Mental State Schedule-Depression Scale; HDRS, HAM-D Hamilton Depression Rating Scale; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; OR, odds ratio; PAI, Personality Assessment Inventory; PHQ-9, Patient Health Questionnaire; PTSD, post-traumatic stress disorder.

cognitive limitations and did not obtain statistically significant results.[36] Olfson et al found that participants with fair or poor mental health status discontinued more at 3 months than those with excellent or good status.[36]

Predictors of treatment nonadherence

Twenty-five studies assessed adherence with antidepressants. Twelve used retrospective designs,[22,25–27,31,33–35,37,38,40,42] nine were cross-sectional studies,[21,23,28,43,45,46,48–50] and four used prospective designs.[20,32,39,44] Ten studies used self-report measures,[20,21,23,28,32,39,43,48–50] 13 used prescription fills data,[22,25,26,27,31,33–35,37,38,40,42,46] one used the Medication Event Monitoring System,[44] and one used a physician-rated measure.[45] Follow-up periods ranged between 3 and 12 months.

Sociodemographic predictors

Potential sociodemographic predictors investigated were age, gender, race, educational level, living situation/marital status, income, and employment status. All studies except

Comorbidities	Cognitive impairment	Perceived health status
	Higher impairment related to better adherence (beta 0.102; $P < 0.05$)	
NS (CCI, nondepression behavioral health comorbidity)		
NS (arterial hypertension, ischemic heart disease, diabetes mellitus, COPD, osteoporosis and dyslipidemia) PTSD (OR 0.95; 95% CI 0.90–0.99), and substance use disorder (OR 0.81; 95% CI 0.77–0.85) worse adherence than not having these conditions. Other anxiety disorder (OR 1.10; 95% CI 1.04–1.16) related to better adherence		
Medical comorbidities: higher rate in nonadherent ($\chi^2 = 15.9$; $P < 0.001$) Psychiatric comorbidities: NS		Nonadherence worse in mental ($P < 0.001$) and physical health ($P = 0.001$)
		NS
Adherent group higher in CDS ($P < 0.0001$)		
NS (CDS)		
Those with anxiety disorders more adherent than those without (OR 1.55; 95% CI 1.27–1.90) Those with 2 (OR 1.30; 95% CI 1.03–1.63) or ≥3 medical conditions (OR 1.34; 95% CI 1.06–1.69) more adherent than those with no comorbidities		

three[32,45,50] offered data on age, and 13 found statistically significant associations.[20,22,25–28,33–35,37,38,40,42] As in the case of discontinuation, Sanglier et al found an interaction between age and year of drug dispensing.[37] In all the remaining studies, increasing age was associated with better adherence.

Only four studies did not assess gender as a potential predictor of adherence.[23,32,37,50] For the remaining ones, five obtained statistically significant differences favoring women,[26,27,35,43,45] while in one study women were almost twice as likely as men to be nonadherent.[28] Another study also found that women were more adherent than men, but only among users of selective serotonin uptake inhibitors.[46]

Six studies analyzed race.[20,23,31,34,35,42] Four of them showed that white patients were significantly more likely to adhere to treatment.[31,34,35,42] Ayalon et al, who did not find statistically significant results, included only black and Hispanic patients.[23] When more than two ethnic categories were compared, Hispanic patients showed the worst adherence rates.[31,35]

Two of nine studies obtained statistically significant results for educational level.[20,21,23,28,31,39,43,45,48] Burra et al found

that patients who had not completed post-secondary education showed lower rates of adherence compared with those above that educational level.[43] Roca et al found that those with a lower educational level showed poor adherence, but the article did not report how this variable was measured or the numeric results.[45]

Six studies analyzed living situation/marital status,[20,39,43,45,48,49] and only Roca et al found a statistically significant association, ie, living alone was significantly related to poor adherence.[45]

Two of five studies found that income was significantly related to adherence, with opposite results.[20,22,23,31,48] Akincigil et al found that patients with an income level lower than $50,000 had a lower rate of adherence compared with those above that level.[22] Yeh et al found a statistically significant linear inverse relationship between income and adherence.[48] Only Roca et al,[45] of six studies,[20,27,28,43,45,48] obtained a statistically significant effect for employment status, with unemployed participants showing lower adherence rates, and once again, descriptive data and statistical tests were not reported.

Clinical predictors

Potential clinical predictors investigated were diagnostic subtype, severity of depression, previous episodes, comorbidities, cognitive impairment, and perceived health status/health-related quality of life. Four studies assessed diagnostic subtype,[26,27,34,44] and only Crown et al found statistically significant associations, ie, major depression disorder and neurotic depression related independently to worse adherence.[26]

Of ten studies that assessed the influence of severity of depression,[20,21,23,32,43,44,45,48–50] only Roca et al and Russell et al found that it was related to worse adherence.[45,50] None of the five studies that assessed previous history of depressive episodes found a statistically significant relationship with adherence.[20,27,39,44,45]

Ten studies assessed psychiatric and/or medical comorbidities,[22,25,26,31,34,35,40,42,45,46] and seven found significant associations with adherence.[22,25,26,35,40,42,45] Regarding medical comorbidities, the direction of the significant relationship was inconsistent across studies; three of them obtained better adherence for patients with a higher number of comorbid diseases,[25,40,42] while another three found the opposite result.[22,26,45] Regarding psychiatric comorbidities, substance abuse was a significant predictor of nonadherence in the three studies that assessed this.[22,25,35] Comorbid anxiety disorders (except post-traumatic stress disorder, which predicted worse adherence in Pfeiffer et al)[35] was significantly related to better adherence in two studies,[35,42] but another three studies did not show statistically significant results.[22,25,26,31]

Cognitive limitations were assessed in two studies, with statistically significant results, but in opposite directions. Ayalon et al, in a sample of African-American and Hispanic patients, found that cognitive limitation was related to unintentional nonadherence,[23] while Maidment et al found that higher impairment predicted better adherence.[49]

Only Roca et al,[45] out of four studies,[23,31,39,45] obtained a statistically significant relationship between perceived health status and/or health-related quality of life and adherence, with better mental and physical health in adherent patients.

Discussion

The results of this review show inconsistent associations between the predictors studied and compliance with antidepressants. Among the sociodemographic factors, age and race appear to be the variables more consistently related to adherence. Regarding age, only two studies found a statistically significant association between older age and a lower probability of (or a longer time to) discontinuation. However, in the cases of adherence (partial compliance), approximately 60% of the studies that assessed this found statistically significant relationships, showing in all cases a positive association between older age and adherence. This effect seemed to be more intense in those studies that measured age categorically than in those which included age as a continuous variable, suggesting a nonlinear association between both factors. Depression in older adults is less well understood and presents unique clinical challenges, including more comorbidities and prescribed medications, and therefore it has been argued that the complexity of their treatment regimens along with other characteristics of aging, such as cognitive impairment, might act as barriers to adequate compliance.[51,52] Alternatively, it could be argued that the higher number of comorbidities and prescribed medications could make older people more accustomed to taking them, leading to better adherence. However, none of these explanations is supported by the results obtained in this review, because the better adherence observed in older people was independent of the effect of the number of comorbidities and/or medications taken.[22,25,26,34,42] On the other hand, cognitive impairment was a significant predictor of unintentional nonadherence in Ayalon et al,[23] but the opposite was found in the study by Maidment et al, a finding that the authors explained by the more intense support that these impaired patients would receive from their caregivers.[49]

Regarding race, the results are consistent, with higher compliance by white patients, and Hispanic patients showing the poorest adherence. As has been pointed out in other medical conditions, these ethnic differences might be accounted for by different belief systems about the nature of the disease or the potential outcomes of available treatments, as well as less trust in the health system and its professionals.[53,54] It has been shown that African-American and Hispanic patients, compared with white patients, find antidepressants less acceptable, and are less likely to believe that medications are effective and that depression is biologically based, and more likely to believe that antidepressants are addictive and that counseling and prayer are effective in treating depression.[55,56]

Low educational level has been considered to be a potential risk factor for poor adherence, because individuals with less education may have more difficulty in understanding treatment regimens, medical recommendations, or the nature of the disease from which they suffer.[57,58] However, results of the studies included here suggest that this is not an important independent predictor of compliance with antidepressant treatment, although it could interact negatively with other variables, such as patient attitudes or beliefs about treatment. Regarding gender, the results indicate better adherence for women, but most studies did not find a statistically significant relationship. Nonetheless, it appears that the attribution of higher noncompliance in women as previously reported cannot be sustained.[11,59] Only one study that assessed compliance with bupropion treatment obtained a significantly worse result for women.[28]

Among clinical factors, it seems clear that severity of depression by itself is not a significant predictor of compliance behavior. Only two cross-sectional studies obtained statistically significant findings, which could be explained by an inverse causal association, ie, that better adherence leads to reduced severity of the disease. The course of symptoms, rather than the severity level at any moment during treatment, is more likely to predict nonadherence, and several studies have shown that both improvement in symptoms and lack of treatment efficacy may be responsible for poor compliance.[8,60,61]

Medical comorbidities have been shown to relate significantly to both good and poor adherence in the studies included. As commented above, living with the experience of various diseases may provide patients with greater "expertise" in managing medications, but in interaction with other variables, such as cognitive impairment, low educational level, or incomplete or inadequate physician's instructions, it could also result in a complex regimen that hinders compliance. For the rest of the clinical variables analyzed, few studies were found that enabled us to ascertain their effect on compliance behavior.

This study aimed to identify nonmodifiable factors related to compliance with antidepressant therapy in patients with depressive disorders. An important limitation is the lack of a quantitative synthesis of results, but the fact that the studies included showed considerable heterogeneity in the statistical methods used and the predictors assessed prompted us to show the results in a narrative manner. Secondly, because predictors of compliance are not the same in different treatment phases,[59] we could not classify the results according to the follow-up duration of the studies because most of them used periods longer than 3 months without differentiating between acute and continuation phases, and cross-sectional studies included patients with different time frames since the onset of treatment. Third, we have limited the analyses to observational studies because some authors have argued that compliance rates and risk factors could be different in naturalistic studies and clinical trials.[59] Finally, the bibliographic search was restricted to studies in English or Spanish.

Appropriate prescription of antidepressant drugs is a core element in the delivery of modern mental health, with antidepressants widely used not only to relieve symptoms and cure conditions but to prevent relapses in the future. In the research on variables that influence compliance with antidepressant medications, sociodemographic and disease-related variables have received less attention than more modifiable factors, such as treatment characteristics (number and frequency of doses, type of drug, or quality of follow-up care) or patient attitudes, beliefs, and preferences concerning the disease and its treatment. However, we consider that identifying all potential predictors of compliance behavior is necessary to enrich existing theoretical models about compliance behavior, so that they can explain the complexity of this phenomenon better. To attain these aims, more research is needed on mediating factors that could account for the relationships between nonmodifiable variables, such as age or race, and adherence with antidepressants. Identifying predictors of compliance behavior might also be useful in the daily practice of mental health professionals, enabling them to detect potentially noncompliant patients more accurately, and consequently targeting specific interventions to patients or populations with distinct characteristics that could lead to treatment nonadherence.

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Disclosure

The authors report no conflicts of interest in this work.

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