It is illegal to post this copyrighted PDF on any website. Current and Remitted Depression and Anxiety Disorders as Risk Factors for Medication Nonadherence

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ABSTRACT

Objective: To investigate the impact of current and remitted depression and anxiety disorders and sociodemographic and other related factors on medication nonadherence in a large cohort study.

Method: The Medication Adherence Rating Scale was used to assess medication nonadherence of 1,890 medication users in the 4-year follow-up assessment of the Netherlands Study of Depression and Anxiety, which was conducted between 2008 and 2011. Psychiatric diagnoses according to the *DSM-IV*, sociodemographic and clinical characteristics, and medication use were determined. *Medication nonadherence* was defined by the tendency to forget a dose, change the dose, stop for a while, skip 1 dose, or take a smaller dosage than prescribed.

Results: Overall medication nonadherence was 44%. In multivariate analyses, all current and remitted depression and anxiety diagnoses were risk factors for medication nonadherence as compared to subjects never having had a depressive or anxiety diagnosis (P < .05). Age (OR=0.85, P < .001) and antidepressant use (OR=0.66, P = .001) were associated with less medication nonadherence. Alcohol dependence (OR=1.67, P = .05) and the number of dietary supplements (OR=1.18, P = .02) proved risk factors for medication nonadherence were mainly driven by depression diagnosis.

Conclusions: All current and remitted depression and anxiety disorders were risk factors for medication nonadherence. Since these disorders are highly comorbid with other medical conditions, health care workers should address medication nonadherence in patients with depression and/or anxiety disorders, even in those who are in symptomatic remission.

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*Corresponding author: Pierre M. Bet, PharmD, Department of Clinical Pharmacology and Pharmacy, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands (pm.bet@vumc.nl). In 2003, the World Health Organization (WHO) published an evidence-based guide to emphasize the importance and the magnitude of medication nonadherence.¹ Medication nonadherence, defined as the extent to which a person's behavior on taking medication does not correspond with instructions from a health care provider, accounts for substantial worsening of disease and increased hospital admissions, health care costs, and death.²⁻⁷ Of all medication-related general hospital admissions in the United States, 33% to 69% are due to medication nonadherence.⁷ In developed countries, medication nonadherence rates of chronic therapy are about 50%.¹ Despite advances made in the field of adherence research during the last decades, nonadherence rates have remained roughly unchanged.⁸

The identification of nonadherence in clinical practice is difficult. When nonadherence is assessed by the treating physician, patients are tempted to give subjective and socially desired answers and tend to overestimate correct medication intake.⁷ Obtaining data using objective measures, like biological markers or drug blood levels, is expensive and not always feasible in clinical practice. Therefore, insight into risk factors of medication nonadherence in a naturalistic setting is important because it allows clinicians to focus attention on patients at risk of nonadherence and optimize therapy.

Depression is a well-established risk factor for medication nonadherence.^{1,7,9-11} Depressive disorders may compromise the ability of the patient to adhere to medication regimens, dietary instructions, or lifestyle instructions that are important in successfully managing chronic disease conditions.^{10–12} About 50% of the patients with depression also have an anxiety disorder.¹³ Similar to depression, anxiety disorders also occur frequently in conjunction with other somatic conditions.¹⁴ However, as compared to depression, the impact of anxiety disorders on medication nonadherence is scarcely documented and the available evidence is inconclusive. A meta-analysis¹⁰ of a limited number of smaller studies reported small and inconsistent effect sizes. Larger studies assessing medication nonadherence in both anxiety disorders and depression in concert have not been conducted. Data on the association between medication nonadherence and remitted depression or anxiety are also lacking.¹⁵

Sociodemographic factors, like gender, age, income, and education, have been inconsistently associated with medication nonadherence.^{1,16-18} As associations of these risk factors for medication nonadherence may vary among age groups and conditions studied, they have to be taken into account.¹ The present study aims to obtain insight into the relationship between medication nonadherence and current and remitted depression and anxiety disorders, sociodemographic characteristics, and other related risk factors in a large study population in a naturalistic setting.

It is illegal to post this copyrighted PDF on any website. Likert scale, from always (1) to never (5), providing a 5 to 25

- All current and remitted depression and anxiety disorders are risk factors for medication nonadherence.
- Given the high somatic comorbidity, health care workers should address medication nonadherence, even when patients are in symptomatic remission.
- Anxiety diagnosis as a risk factor for medication nonadherence is mainly driven by depression.

METHOD

Clinical Points

Study Sample

The Netherlands Study of Depression and Anxiety (NESDA) is a large, ongoing longitudinal cohort study designed to investigate the course and consequences of depressive and anxiety disorders. The NESDA recruited 2,981 depressed or anxious subjects aged 18 to 65 years from the entire range of settings (from mental health care organizations to primary care and community settings) and stages of psychopathology as well as healthy controls. Healthy controls were recruited from the general population (n = 138), with parents with a depressive and/or anxiety disorder) and primary care (n = 514, of whom 141 subjects had subthreshold symptoms), and at baseline measurement, the absence of depression and anxiety disorders was confirmed. Subjects with psychotic disorder, obsessivecompulsive disorder, bipolar disorder, or severe addiction disorder were not included. The NESDA, its rationale, and its objectives have been described elsewhere in more detail.¹⁹ The study protocol was approved centrally by the ethics review board of the VU University Medical Center (Amsterdam, the Netherlands) and subsequently by local review boards of each participating center. For the present study, a medication adherence questionnaire was introduced in the 4-year follow-up assessment of NESDA, which was conducted between 2008 and 2011. The 4-year follow-up assessment was completed by 2,402 subjects aged 22 to 69 years (81% of baseline sample). Nonresponse (n = 579) was significantly higher among those with lower education and a depressive or an anxiety disorder, but was not associated with age or gender. For the present analyses, all medication users with a complete psychiatric diagnosis at the 4-year follow-up (n = 1,890) were included, of whom 312 had no history of depressive or anxiety disorders, 921 had a remitted disorder, and 657 had a current disorder.

Medication Nonadherence

Medication adherence was assessed using the Medication Adherence Rating Scale (MARS),²⁰ a questionnaire measuring a range of nonadherent behavior. The MARS is well validated and has been used for a range of chronic diseases in various settings and different countries.4,21-28 Medication nonadherence is defined by the tendency to forget a dose, change the dose, stop for a while, skip 1 dose, or take a smaller dosage than prescribed. Subjects were asked in a nonjudgmental way to score these 5 MARS items on a 5-point

score. Higher scores are indicative of a better adherence to prescribed therapy. In the present study, MARS scores of 24 and 25 were defined as adherent and scores of 23 or lower were defined as nonadherent. This MARS cutoff value was chosen in order to equally divide all medication users in 2 groups to optimize identification of risk factors.

Risk Factors

Possible risk factors for medication nonadherence include a variety of sociodemographic variables, psychiatric status, medication variables, and comorbid somatic conditions, and these factors were selected on the basis of literature data on medication nonadherence.1,7,10-12,15,29

Sociodemographic Variables

Age, sex, education level, employment status (yes/no), partner status (yes/no), social network size, and net household income were assessed by interview or questionnaire. Education level was expressed by years of education. Social network size was categorized in 2 groups: 0-5 and 6 or more persons aged 18 years or older, with regular and meaningful contact and not being a member of the subject's household. Net household income was assessed as a continuous indicator based on 24 categories of net monthly household income: less than €600 (US \$870), 22 categories with a €200 (US \$290) range (eg, €601–€800, €801–€1,000), and more than €5,000 (approximately US \$7,250) per month.

Psychiatric Status

The presence of a depressive disorder (major depressive disorder and dysthymia) or an anxiety disorder (panic disorder, social phobia, generalized anxiety disorder, and agoraphobia) was established using the WHO Composite International Diagnostic Interview (CIDI), version 2.1.³⁰ The CIDI establishes diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), criteria and is a highly accurate and validated instrument for assessing depressive and anxiety disorders.³⁰ We categorized all subjects to obtain 1 "depression and/or anxiety" variable with 5 groups: no lifetime depression or anxiety diagnosis, remitted depression and/or a remitted anxiety disorder, a current (6-month recency) pure depression diagnosis, a current pure anxiety diagnosis, or a current diagnosis of both depression and an anxiety disorder. For 5 subtypes of anxiety diagnosis (generalized anxiety disorder, agoraphobia, panic, panic with agoraphobia, and social phobia), subjects were categorized into no lifetime, past, and current (6-month recency) subtype anxiety diagnosis. Depressive symptom severity was assessed with the 30-item Inventory of Depressive Symptomatology (IDS).³¹ IDS scores were categorized in 5 groups: normal (0-13), mild (14-25), moderate (26-38), severe (39-48), and very severe (49 and higher) symptomatology. Anxiety symptom severity was assessed with the 21-item Beck Anxiety Index (BAI).² BAI scores were categorized in 4 groups: normal (0-9), mild (10-18), moderate (19-29), and severe (30 and higher)



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It is illegal to post this col Table 1. Baseline Characteristics of Medication Users

(n = 1.900)

(11=1,000)		
Variable	n	Value
Sociodemographic characteristics		
Female gender, % Age, mean (SD), y Education level, mean (SD), y Marital status (husband, wife, or partner), % Social network > 5 persons, % Employed, % Income level per mo, mean (SD) Euro	1,791 1,792 1,803 1,861	68 47 (13) 12 (3.3) 73 49 63 €2.550 (€1.270)
US dollar		\$3,700 (\$1,840)
Psychiatric status		
Depression and/or anxiety diagnosis, n (%) No lifetime depression or anxiety diagnosis Remitted depression and/or anxiety diagnosis Current pure depression diagnosis Current depression and anxiety diagnosis Disease severity, mean (SD) IDS score BAI score Psychotropic medication, n (%) Antidepressant use Anxiolytic use Alcohol diagnoses, n (%) Alcohol dependence, n (%) Alcohol abuse, n (%)	1,830 1,828	312 (16.5) 921 (48.7) 190 (10.1) 249 (13.2) 218 (11.5) 16.5 (12.2) 8.7 (8.6) 482 (25.5) 73 (3.9) 130 (6.9) 82 (4.3) 97 (5.1)
Other characteristics		
No. of comorbid conditions, median (IQR) ^a No. of medications per subject, median (IQR) ^a Dietary supplements including vitamins, median (IQR) ^a		1 (0–2) 3 (1–4) 0 (0–0)
^a Interquartile range is 25%–75%.	Inventor	of Doprossivo

Abbreviations: BAI = Beck Anxiety Inventory, IDS = Inventory of Depressive Symptomatology, IQR = interquartile range.

symptomatology. Alcohol dependence and alcohol abuse was also assessed with the CIDI.

Medication Variables

Medication use, including name, dose, and daily amount of both psychotropic and nonpsychotropic medication, was assessed using each subjects' medication boxes and bottles. Medication was classified by using the WHO Anatomical Therapeutic Chemical (ATC) system.³² Antidepressant and anxiolytic medication were identified by ATC codes N06A and N05B/C, respectively. Dietary supplements, including vitamins, were not considered medications and were treated as a separate group.

Comorbid Somatic Conditions

All subjects were asked about the presence of 11 major chronic somatic conditions: lung disease, heart disease, diabetes, stroke, arthritis, rheumatism, cancer, hypertension, gastrointestinal ulcers, allergy, and thyroid disease.

Statistical Analysis

Logistic regression was used to test all selected variables univariately for association with medication nonadherence, and odds ratios (ORs) with 95% confidence intervals (CIs) were obtained. In multivariate models 1A, 1B, and Figure 1. Distribution of Medication Adherence Rating Scale (MARS) Score (n = 1,890)^a

n



Nonadherent subjects: MARS score 23 and lower (n = 827 [44%]); adherent subjects: MARS score 24 and higher (n = 1,063 [56%]).

1C, all sociodemographic, psychiatric, and other variables, respectively, were included. A final composite multivariate model included gender and all variables with P values < .10 in univariate analysis. Because no clear MARS cutoff point for nonadherence has been defined in the literature, we conducted sensitivity analyses on the final multivariate model using different MARS cutoff values ranging from 19 to 24. All subtypes of anxiety diagnoses were analyzed univariately as well as corrected for depression diagnosis. All analyses were conducted with Statistical Package for the Social Sciences (SPSS) software, version 20 (International Business Machines Corporation; Armonk, New York). P values < .05 were considered statistically significant.

RESULTS

In the present sample, 68% of the subjects were women, and the mean age was 47 years. Sociodemographic, psychiatric, and medication characteristics are listed in Table 1. The distribution of the MARS score is presented in Figure 1. When a cutoff score of 23 was used, the percentage of medication nonadherence was 44%. The maximum score of 25, indicating high adherence, was reached by 34% of subjects. The odds for medication nonadherence within the depression and anxiety symptom severity groups are presented in Figures 2 and 3, respectively. Depression and anxiety symptomatology were found to be risk factors for medication nonadherence. While in the depression group odds gradually increased with symptom severity, in subjects with severe anxiety symptomatology, no increased risk of medication nonadherence was observed.

In the univariate analysis (see Table 2, left column), older age (OR=0.85; P<.001), social support (>5 persons) (OR=0.81; P=.03), and antidepressant use (OR=0.76; P=.01) were associated with less medication nonadherence, while employment (OR=1.23; P=.03) and the number of dietary supplements, including vitamins (OR=1.14; P=.05), were associated with medication nonadherence. All psychiatric

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Figure 2. Odds Ratios (95% CI) of Medication Nonadherence According to Depression Symptom Severity (n = 1,830)



Abbreviation: IDS = Inventory of Depressive Symptomatology, OR = odds

ratio

Figure 3. Odds Ratios (95% CI) of Medication Nonadherence According to Anxiety Symptom Severity (n = 1,828)



Abbreviation: BAI = Beck Anxiety Index, OR = odds ratio.

Table 2. Odds Ratios of Medication Nonadherence as Measured by the Medication Adherence Rating Scale (MARS) Score (n = 1,890)

	Uni	variate Mode	a	Mult	tivariate Mod	el ^b	Multivariate Model 2 ^c		
Variable	OR	95% CI	P Value	OR	95% Cl	P Value	OR	95% CI	P Value
Sociodemographic characteristics					Model 1A				
Male gender (vs female)	1.13	0.93–1.37	.23	1.16	0.94–1.43	.16	1.19	0.96-1.48	.11
Age (per 10 years)	0.85	0.80-0.92	<.001	0.86	0.80-0.94	<.001	0.85	0.79-0.93	<.001
Years of education (per year)	1.01	0.99-1.04	.38	1.01	0.98-1.05	.41			
Partner	0.86	0.70-1.06	.15	0.95	0.75-1.20	.65			
Social support (> 5 persons)	0.81	0.67-0.98	.03	0.81	0.66-0.98	.03	0.83	0.68-1.01	.06 ^d
Employment	1.23	1.02-1.50	.03	1.17	0.93-1.47	.17	1.13	0.91-1.41	.27
Income (classification 24 categories)	0.99	0.98-1.01	.20	0.99	0.97-1.01	.14			
Psychiatric status					Model 1B				
Depression and/or anxiety diagnosis									
No lifetime depression or anxiety diagnosis	Reference			Reference			Reference		
Remitted depression or anxiety diagnosis	1.52	1.17–1.99	.002	1.65	1.25-2.16	<.001	1.58	1.18-2.10	.002
Current depression diagnosis	1.79	1.24-2.58	.002	1.99	1.36-2.90	<.001	1.79	1.18–2.70	.006
Current anxiety diagnosis	1.50	1.07-2.11	.02	1.63	1.15-2.32	.006	1.50	1.03-2.18	.04
Current depression and anxiety diagnosis	1.58	1.11-2.25	.01	1.72	1.19-2.50	.004	1.56	1.04-2.33	.03
Alcohol diagnoses									
Alcohol dependence	1.68	1.08-2.63	.02	1.83	1.07-3.13	.03	1.67	1.01-2.75	.05
Alcohol abuse	1.22	0.81-1.84	.34	0.86	0.52-1.40	.54			
Psychotropic medication									
Antidepressant medication	0.76	0.62-0.94	.01	0.66	0.53-0.82	<.001	0.66	0.52-0.84	.001
Anxiolytic medication	1.59	0.99–2.54	.05	1.46	0.90-2.35	.12	1.56	0.95-2.57	.08 ^e
Other characteristics					Model 1C				
No. of comorbid conditions	0.98	0.91-1.05	.50	0.98	0.90-1.06	.58			
No. of medications	0.99	0.95-1.03	.68	1.00	0.95-1.05	.93			
No. of dietary supplements	1.14	1.00-1.30	.05	1.14	1.00-1.30	.05	1.18	1.02–1.36	.02

^aBased on univariate logistic regression.

^bBased on multivariate logistic regression with all sociodemographic (model 1A), psychiatric (model 1B), and other (model 1C) characteristics in a model. ^cBased on multivariate logistic regression with all variables with *P* < .10 in univariate analysis and gender in a model (model 2).

dStatistically significant in sensitivity analysis (see Supplementary eTable1) at MARS cutoff value 22: OR = 0.79 (95% CI, 0.64–0.98), P = .04.

eStatistically significant in sensitivity analysis (see Supplementary eTable1) at MARS cutoff value 22: OR= 2.22 (95% CI, 1.34–3.66), P=.002.

diagnoses were associated with medication nonadherence as compared to no lifetime depression or anxiety diagnosis. Alcohol dependence (OR = 1.68; P = .02), and not alcohol abuse (OR = 1.22; P = .34), was associated with medication nonadherence. The total numbers of comorbid somatic conditions (OR = 0.98; P = .50) and medications (OR = 0.99; P = .68) per subject were not associated with medication nonadherence. The number of dietary supplements, including vitamins, per subject was borderline associated with medication nonadherence (OR = 1.14; P = .05). Univariate analyses of subtypes of anxiety diagnoses and medication nonadherence showed a positive association in subjects with a history of agoraphobia (OR = 1.32; P = .04) as compared to subject with no lifetime agoraphobia, while past anxiety

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It is illegal anv website. Table 3. Odds Ratios of Medication Nonadherence According to Anxiety Diagnosis and Its Subtypes, Both Univariate and Multivariate Adjusted for Depression Diagnosis

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		I	Jnivariate ^a		Multivariate ^b			
Variable	n	OR	95% CI	P Value	OR	95% CI	P Value	
Anxiety diagnosis								
No lifetime anxiety disorder	607	Reference			Reference			
Past anxiety disorder	806	1.23	0.99-1.52	.06	1.09	0.87-1.37	.46	
Current anxiety disorder	467	1.22	0.95-1.55	.11	1.04	0.79–1.36	.79	
Anxiety diagnosis subtype								
No lifetime generalized anxiety disorder	1,188	Reference			Reference			
Past generalized anxiety disorder	551	1.11	0.91–1.36	.31	1.01	0.81-1.24	.96	
Current generalized anxiety disorder	120	1.02	0.70-1.50	.90	0.88	0.59-1.31	.53	
No lifetime agoraphobia	1,497	Reference			Reference			
Past agoraphobia	242	1.32	1.01–1.74	.04	1.27	0.96-1.67	.09	
Current agoraphobia	105	0.90	0.60-1.34	.60	0.85	0.56-1.27	.42	
No lifetime panic	1,440	Reference			Reference			
Past panic	320	1.03	0.81-1.32	.79	0.96	0.75-1.23	.75	
Current panic	87	0.75	0,48–1.18	.22	0.68	0,43-1.07	.10	
No lifetime panic with agoraphobia	1,455	Reference			Reference			
Past panic with agoraphobia	319	0.97	0.76-1.24	.83	0.91	0.71-1.16	.44	
Current panic with agoraphobia	76	1.46	0.92-2.31	.11	1.33	0.82-2.14	.24	
No lifetime social phobia	1,119	Reference			Reference			
Past social phobia	532	1.15	0.94-1.42	.18	1.06	0.85-1.31	.62	
Current social phobia	215	1.25	0.93-1.67	.14	1.21	0.83-1.53	.45	

^aBased on univariate logistic regression.

^bBased on multivariate logistic regression adjusted for depression diagnosis (no lifetime [n=483], past [n=993], current [n = 408]).

diagnosis (OR = 1.23; P = .06) and current anxiety diagnosis (OR = 1.22; P = .11) showed borderline significance. When data were adjusted for depression diagnosis, no significant associations remained (Table 3).

In the multivariate analysis of all sociodemographic characteristics (see Table 2, model 1A, middle column), employment was no longer significantly associated, and in the multivariate analysis of all psychiatric variables (see Table 2, model 1B, middle column), no changes occurred as compared to the univariate analysis. In the multivariate analysis of all variables (see Table 2, model 2, right column), older age (OR = 0.85; P < .001) remained associated with less medication nonadherence. All current and remitted depression and anxiety diagnosis were risk factors for medication nonadherence as compared to no lifetime depression or anxiety diagnosis. Antidepressant use was associated with less medication nonadherence (OR = 0.66; P = .001). Alcohol dependence (OR = 1.67; P = .05) and the number of dietary supplements (OR = 1.18; P = .02) remained associated with medication nonadherence.

In a sensitivity analysis, all directions of the associations of the multivariate analysis remained unchanged when the cutoff value for the MARS scores for medication nonadherence varied between values of 19 and 24 (see Supplementary eTable 1 at Psychiatrist.com). At cutoff values between 20 and 22, the associations of anxiolytic use and social support with medication nonadherence were statistically significant (P < .05), while these associations were not at the cutoff value of 23 that we used in the initial analysis.

DISCUSSION

All current and remitted depression and anxiety disorders were found to be risk factors for medication nonadherence.

Since these disorders are highly comorbid with other medical conditions, health care workers should address medication nonadherence in patients with depression and/or anxiety disorders, even those who are in symptomatic remission. In this sample, alcohol dependence, use of anxiolytics, and use of dietary supplement were risk factors for medication nonadherence, while older age, more social support, and antidepressant use were associated with less medication nonadherence.

All current diagnoses of pure depression, pure anxiety, and concurrent depression and anxiety were independent risk factors for medication nonadherence, as compared to subjects without a history of depression or anxiety diagnosis. Depression diagnosis and depression symptom severity are well-established risk factors for medication nonadherence and have been studied in many somatic diseases.^{9–11,16,33–35} In contrast, data on the association between anxiety disorders and medication nonadherence have been inconclusive.^{10,33,34} A meta-analysis of 13 studies on anxiety disorders and medication adherence by DiMatteo et al¹⁰ reports small and nonsignificant associations. In a recent meta-analysis³⁴ of 17 studies in patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), anxiety disorder was a risk factor for nonadherence with antiretroviral medication. The inconsistent results for anxiety disorders could be due to the variety of populations studied in terms of somatic disease, the low number of subjects with an anxiety disorder, and the heterogeneity of definitions of medication adherence, depression and anxiety disorders, and assessment methods. However, in the present study, many of these limitations were addressed, whereas 2 large groups of subjects with pure current anxiety diagnosis (n = 249) and controls (n = 312) were evaluated. For patients with an anxiety diagnosis, there was a large, 50% higher risk

It is illegal to post this copy of medication nonadherence as compared to patients with no history of depression or anxiety disorder. These results are in line with those of a recent large population-based survey³⁵ showing a 60% increase in subjects with anxiety symptomatology as compared to subjects without symptoms. Fear of potential adverse drug reactions was an important reason for medication nonadherence.^{35,36} While clinically an anxiety diagnosis is a risk factor and a reason to address medication nonadherence, our analyses of anxiety diagnosis and its subtypes, univariately and adjusted for depression diagnosis, show that the association of anxiety diagnoses with medication nonadherence is mainly driven by depression. Although results of recent studies^{35,37} suggest higher odds for combined depression and anxiety symptomatology, concurrent depression and anxiety diagnoses did not show higher odds for medication nonadherence as compared to pure depression and pure anxiety diagnosis.

We consequently found an association of remitted depression and/or anxiety diagnosis with medication nonadherence. This finding suggests that both disorders continue to be associated with nonadherence, even when patients are in symptomatic remission. To our knowledge, the association between remitted depression or anxiety disorder and medication nonadherence has not been studied previously. Wagner et al³⁸ found an association between remitted depression and worse self-management in 153 diabetic women without reporting on medication adherence or anxiety symptom severity. Two small studies^{15,39} investigated antidepressant nonadherence of subjects with remitted depression, but these did not report on remitted depression as a risk factor for nonadherence. Our findings are of particular interest given the large numbers of patients who are in remission of depression and/or anxiety disorder and the high somatic comorbidity in this population.

Alcohol use disorders have been associated with medication nonadherence and poor outcomes in HIV,⁴⁰ while alcohol consumption has been inconsistently associated with medication nonadherence in several other diseases.⁴¹ Although at baseline severe addiction disorders were excluded, at the 4-year follow-up approximately 7% of the subjects had an alcohol diagnosis. Alcohol dependence, but not alcohol abuse, was associated with medication nonadherence. When replicated, this is an important clinical finding.

The association of antidepressant use with less medication nonadherence seems a causative relation, as was also seen in a large group of HIV-infected depressed patients, whose medication adherence improved after initiation of antidepressant use.⁴² The positive effect of antidepressants on medication adherence could be due to the relief of depression and anxiety symptoms, the result of a positive medication experience, or a training effect of physicians and pharmacists instructing patients to take antidepressant medication on a regular basis. Although in our cross-sectional cohort study, we cannot exclude a selection bias because patients accepting antidepressants as a treatment might be more medication adherent as compared to patients in favor of psychotherapy. **a contrast with the effect of antidepressants, anxiolytic** medication, which is often prescribed as needed, was associated with medication nonadherence. In this sample with a low percentage of anxiolytic users, the association was significant in the sensitivity analysis, when MARS cutoff values were lowered to scores between 20 and 22 points and medication nonadherence was defined as being more deviant from the perfect score of 25 points. However, this finding could be due to the misinterpretation of the MARS questions by subjects in relation to medication prescribed as needed and therefore needs further research and replication.

Sociodemographic factors have not been consistently associated with nonadherence.^{1,7,15-17} Poor economic status and education level are factors commonly associated with nonadherence.^{1,15,18} However, in the present study, there was no significant association between economic status or education level and medication nonadherence. This might be explained by the Dutch situation in which health care insurance is obligatory and medication is generally provided without direct payment by the patient. Under these conditions, there is no economic driver of nonadherence. Since education level and economic status are usually well correlated, this might explain our negative findings on both factors. While we assume that older patients are more likely to be more nonadherent than younger patients because of more medications and complex dosing regimens, this relationship has not been fully established.^{1,16,17} Recent reports fuel the discussion, because we and others^{18,37} report less nonadherence, while Sundbom and Bingefors³⁵ report more nonadherence with older age. We feel that age, like gender, should always be included in risk factor analysis, but in multivariate analysis, their associations with medication nonadherence should ideally become nonsignificant by the inclusion of enough discriminative risk factors. Further research on medication nonadherence could focus on more defined age groups to find the relevant risk factors within age groups.

In this large epidemiologic study, we used a self-report method to assess medication nonadherence. Assessment of medication nonadherence by a self-report questionnaire is a simple and inexpensive method to gather information and is generally considered to be reliable.^{15,43,44} When compared with the microprocessor-based Medication Event Monitoring System, which is considered the gold standard in medication adherence research, self-report questionnaires were moderately correlated in a meta-analysis that covered many different diseases.⁴⁵ In depression, the self-report questionnaires showed acceptable reliability⁴⁶ and were useful for identifying noncompliant patients.47 Since adherence measured by self-report provides a current or short-term estimate of nonadherence, it has been purported that this method is more accurate in crosssectional research.^{7,11} Although self-report usually tends to underestimate nonadherence, in the present study this is not relevant because the primary objective was not to quantify nonadherence but to investigate risk factors. Moreover, the MARS used to estimate adherence has no clear cutoff

t is illegal to post this cop point,⁺ and the use of the score of 23 as a cutoff resulte from the distribution of MARS scores in the present sample, which was similar to the distribution found in many other studies.^{22,24–26} Indicative for the robust result, the direction of the association of all variables did not change for cutoff values between 19 and 24 points.

Major strengths of the present study are the size of the study group in a naturalistic setting, which has high external validity to clinical practice, and the use of the CIDI diagnostic interview. As compared to many frequently used symptom severity scales, this diagnostic tool is highly sensitive and specific.⁴⁸ Since depression and anxiety disorders are highly comorbid, they need to be analyzed in concert, because the discriminative ability of symptom severity scales is insufficient.⁴⁸ We also looked beyond a current diagnosis of depression or anxiety and included subjects with remitted disease.

Several limitations of the present study need to be discussed. We have used a limited number of known risk factors and, for instance, did not have data on side effects and treatment complexity. In order to avoid overloading the multivariate model and the risk of multicollinearity, we have preselected variables based on P values <.10 in univariate association. To test the robustness of this approach, we have entered variables with P < .20 in univariate analysis in the multivariate model, and this did not change the

ghted PDF on any website. statistical significance of the associations. By using the 4-year follow-up data of an ongoing cohort study, we have selected medication users who were adherent to the study, which might have biased medication adherence assessments. Our cross-sectional analyses are able to detect associations and not causal relationships. The number of healthy controls was small compared to the large number of depressed and anxious subjects. Furthermore, we do not know whether the antidepressant and anxiolytic medication, included in the analyses as a risk factor, was appropriate treatment for the subjects' specific psychiatric condition. Finally, because we used the MARS for a global assessment of adherence to all medications, a methodological issue could be the misinterpretation of the MARS questions by subjects in relation to medication prescribed as needed. While changing the dose for antidepressant medication is considered nonadherent behavior, this is not the case for as-needed anxiolytic medication or nonprescription dietary supplements taken as desired by the subjects.

In conclusion, all current and remitted depression and anxiety disorders were risk factors for medication nonadherence. Since these disorders are highly comorbid with other medical conditions, health care workers should address medication nonadherence in patients with depression and/or anxiety disorders, even in those who are in symptomatic remission.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.



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Supplementary Material

- Article Title: Current and Remitted Depression and Anxiety Disorders as Risk Factors for Medication Nonadherence
- Authors: Pierre M. Bet, PharmD; Brenda W. J. H. Penninx, PhD; Stag D. van Laer, PharmD; Witte J. G. Hoogendijk, MD, PhD; and Jacqueline G. Hugtenburg, PharmD, PhD
- **DOI Number:** 10.4008/JCP.14m09001

List of Supplementary Material for the article

1. <u>eTable 1</u> Odds ratios of multivariate analyses at different cut off values for medication nonadherence as measured with the Medication Adherence Rating Scale (MARS) (n=1890)

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Supplementary eTable 1. Odds ratios of multivariate analyses^a at different cut off values for medication non-adherence as measured with the Medication Adherence Rating Scale (MARS) (n=1890).

Cut off value:	24 and lower				23 and lowe	r	22 and lower			
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	
Socio-demographic characteristics			-			-			•	
Male gender (vs female)	1.21	0.97-1.51	0.10	1.19	0.96-1.48	0.11	1.17	0.93-1.47	0.18	
Age (per 10 years)	0.82	0.75-0.90	<0.001	0.85	0.79-0.93	<0.001	0.85	0.78-0.93	<0.001	
Social Support (>5 persons)	0.91	0.74-1.12	0.39	0.83	0.68-1.01	0.06	0.79	0.64-0.98	0.04	
Employment	1.06	0.84-1.33	0.62	1.13	0.91-1.41	0.27	1.7	0.84-1.36	0.57	
Psychiatric status										
Depression and/or anxiety diagnosis										
No Lifetime Depression or Anxiety	ref	-	-	ref	-	-	ref	-	-	
diagnosis										
Remitted Depression or Anxiety	1.69	1.27-2.25	<0.001	1.58	1.18-2.10	0.002	1.63	1.17-2.25	0.003	
diagnosis										
Current Depression diagnosis	2.07	1.34-3.17	0.001	1.79	1.18-2.70	0.006	2.15	1.38-3.36	0.001	
Current Anxiety diagnosis	1.42	0.97-2.07	0.07	1.50	1.03-2.18	0.04	1.59	1.05-2.41	0.03	
Current Depression & Anxiety	1.49	0.99-2.23	0.06	1.56	1.04-2.33	0.03	1.95	1.26-3.02	0.003	
diagnosis										
Alcohol diagnosis										
Alcohol dependency	1.71	0.96-3.05	0.07	1.67	1.01-2.75	0.05	1.54	0.92-2.58	0.10	
Psychotropic medication										
Antidepressant medication	0.86	0.67-1.09	0.21	0.66	0.52-0.84	0.001	0.58	0.45-0.76	<0.001	
Anxiolytic medication	1.12	0.66-1.91	0.67	1.56	0.95-2.57	0.08	2.22	1.34-3.66	0.002	
Other characteristics										
Number of dietary supplements	1.06	0.92-1.23	0.42	1.18	1.02-1.36	0.02	1.19	1.03-1.38	0.02	

^a Based on multivariate logistic regression with all presented variables in one model.

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Supplementary eTable 1 continued.

Cut off value:		21 and lower			20 and lowe	r	19 and lower		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Socio-demographic characteristics			•			-			•
Male gender (vs female)	1.11	0.87-1.42	0.40	1.12	0.85-1.47	0.42	1.06	0.78-1.43	0.73
Age (per 10 years)	0.90	0.82-0.99	0.03	0.89	0.80-0.99	0.03	0.89	0.79-1.00	0.05
Social Support (>5 persons)	0.75	0.60-0.95	0.02	0.74	0.57-0.96	0.02	0.80	0.60-1.06	0.12
Employment	1.12	0.87-1.44	0.38	1.07	0.81-1.41	0.65	1.01	0.74-1.38	0.94
Psychiatric status									
Depression and/or anxiety diagnosis									
No Lifetime Depression or Anxiety	ref	-	-	ref	-	-	ref	-	-
diagnosis									
Remitted Depression or Anxiety	1.65	1.16-2.33	0.005	1.80	1.21-2.68	0.004	1.74	1.12-2.72	0.01
diagnosis									
Current Depression diagnosis	2.07	1.30-3.33	0.003	2.42	1.43-4.10	0.001	2.18	1.21-3.91	0.009
Current Anxiety diagnosis	1.48	0.95-2.33	0.09	1.54	0.92-2.57	0.010	1.61	0.91-2.83	0.10
Current Depression & Anxiety	2.00	1.25-3.19	0.004	2.12	1.25-3.59	0.005	2.07	1.16-3.70	0.01
diagnosis									
Alcohol diagnosis									
Alcohol dependency	1.33	0.77-2.30	0.31	1.57	0.87-2.82	0.13	1.90	1.03-3.50	0.04
Psychotropic medication									
Antidepressant medication	0.52	0.39-0.70	<0.001	0.43	0.31-0.60	<0.001	0.42	0.29-0.61	<0.001
Anxiolytic medication	2.23	1.34-3.72	0.002	2.74	1.62-4.64	<0.001	2.45	1.40-4.31	0.002
Other characteristics									
Number of dietary supplements	1.16	1.00-1.34	0.05	1.20	1.03-1.40	0.02	1.19	1.01-1.41	0.04

^a Based on multivariate logistic regression with all presented variables in one model.

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