



# Objective: remission of depression in primary care The Oreon Study

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## KEYWORDS

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## Abstract

**Objective:** Treatment of depression should result in the absence of symptoms, i.e. remission, in order to restore the functional status of the patient and reduce the risk for relapse. The study assessed the current remission rates in primary care and determined the influencing factors.

**Methods:** 10 consecutive depressive patients treated by antidepressants for at least 3 months and not more than 12 months were screened by each investigator. Remission rates were defined using the Hamilton-Depression scale 7 items (score of 3 or less) as well as the Carroll self rating scale (score of 7 or less). In addition, patients completed the Sheehan Disability Scale (SDS). Initial severity of depression, type of treatment and socio-economic factors were collected.

**Results:** 292 general practitioners screened a total of 2630 patients. Results indicated low remission rates: 28.3% according to the clinician and 17.1% according to the patient. Absence of remission was associated with higher impairment in work, social and family life. The most frequently reported residual symptoms in nonremitters were general somatic symptoms (92%), depressed mood (92%), psychic anxiety (91%) and impaired work and activities (89%). No differences were observed in remission rates between men and women. Remission rates were significantly lower in patients living alone as compared to those living in couple or family (25.1% vs 30.2%,  $p=0.03$ ), in patients with lower education (21.3% vs 32.3%,  $p<0.001$ ), in patients speaking French as compared to Dutch (24.0% vs 34.0%  $p<0.001$ ), and unemployed patients compared to patients having an occupation (17.1% vs 39.0%,  $p<0.001$ ). Higher initial severity and number of previous episodes decreased remission rates ( $p<0.001$ ).

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*Conclusion:* This study shows low remission rates in depressed patients treated in general practice. The absence of remission is associated with impairment in work, social and family life. Special attention should be given to identify patients who do not reach remission.

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## 1. Introduction

Depression is a major concern in public health. Indeed, according to the World Health Organization (WHO), depression currently represents the second cause of disability in developed countries (World Health Organization, 2001). Over the last years, much effort has been devoted to improve the diagnosis and treatment of the illness. In particular, the different phases of the treatment have been better defined as well as the duration of antidepressant therapy. Several treatment guidelines have been developed by national or international societies (American Psychiatric Association, 2000; Anderson et al., 2000; Ellis, 2004; Bauer et al., 2002; Canadian Psychiatric Association, 2001).

The vast majority of depressive patients are seen in primary care. In epidemiological studies, the prevalence of major depression in general practice was often higher than 10%, e.g. 11.5% in the US (Spitzer et al., 1994) and 13.9% in Belgium (Anseau et al., 2004, 2005).

There is a unanimity among guidelines to consider that the goal in the treatment of depression is to reach remission, i.e., the absence of symptoms. Indeed, the lack of remission increases the risk for relapse (Pintor et al., 2003, 2004), more chronic depressive episodes (Judd et al., 2000) and shorter intervals between episodes (Judd et al., 2000) and continuing impairment in work, relationship, and overall quality of life (Keller, 2003; Miller et al., 1998; Murphy et al., 1987). A recent study in general practice showed that patients non reaching remission after 3 months of treatment were nearly 3 times more likely to present a relapse at long-term follow-up (Simon, 2000).

The remission rates obtained in clinical trials of antidepressants were generally found as rather low, between 25 and 35% (Nierenberg et al., 1999a,b). However, the duration of such trials is generally too short to reach optimal antidepressant efficacy. Little is presently known about the rate of remission among depressive patients treated in natural settings. A recent study found a remission rate of 27.5% in patients treated with citalopram for up to 14 weeks in "real world" settings (Trivedi et al., 2006). Therefore, the objective of the present study was to assess the actual remission rates of depressive patients treated in primary care and to determine the influencing factors.

## 2. Methods

### 2.1. Selection of investigators and patients

Two hundred and ninety-two general practitioners (GPs) participated to the study. In order to have representative samples of patients consulting primary care in Belgium and Luxembourg, the investigators were geographically distributed over the territory, with medium to large size practices.

Each investigator was requested to select 10 consecutive depressive outpatients aged of at least 18 years treated by antidepressants for at least 3 months and not more than 12 months.

The study was performed according to the standards of Good Clinical Practice. The protocol was approved by the Ethical Committee of the University of Liège Medical School and all patients gave their written consent.

### 2.2. Assessments

First, the investigator collected demographic information concerning his/her patients as well as the method of diagnosis the initial severity of depression, the number of previous episodes and the current antidepressant treatment. In addition, the investigator rated the severity of depression using the shortened 7-item version of the Hamilton Depression Scale (HAMD-7) (Hamilton, 1960; McIntyre et al., 2002, 2005). This abbreviated HAMD-7 was recently demonstrated as equivalent to the HAMD-17 in assessing remission in patients with a major depressive disorder undergoing drug therapy (McIntyre et al., 2005). Patients completed the Carroll Depression Self-Rating Scale (Carroll et al., 1981; Feinberg et al., 1981; Smouse et al., 1981; Charles et al., 1986) as well as the Sheehan Disability Scale (Sheehan, 1983; Leon et al., 1997). The Carroll Depression Scale is a self-rating instrument built to provide scores equivalent to the 17-item Hamilton Depression Scale; the Sheehan Disability Scale rates the level of impairment caused by the patient's psychiatric condition from 0 to 10 on 3 main fields: work, social, and family life.

Remission rates were defined by a score of 3 or less on the 7-item Hamilton Depression Scale and 7 or less on the Carroll Scale (Frank et al., 1991; McIntyre et al., 2002, 2005).

### 2.3. Data analysis

The statistical analysis was both descriptive and inferential. For the quantitative variables, the descriptive statistics consisted of the mean, median, standard deviation, and 95% confidence intervals on the mean; for the categorical variables, frequencies and percentages. Statistical tests were performed two-tailed, at the 5% level of significance.

Logistic regression was used to investigate the effect of potential prognostic factors on the occurrence of remission. First each factor was compared for patients with and without remission using chi-square test for the categorical variables, Mann-Whitney test for ordinal variables and *T* test for continuous variables.

Subsequently, logistic regression models were applied using a stepwise approach: all above covariates and two-by-two interactions were included one by one into the model and those reaching the 5% level of significance were retained. In that case, odds ratios were estimated comparing the probability of remission between two levels of the covariate with an odds ratio >1 corresponding to a higher probability of remission for the first level compared to the next one.

Since, in case of a significant interaction between two covariates, odds ratios could no longer be calculated, an additional model without interaction terms was applied. However, it should be noted that these odds ratios should be considered as only indicative.

## 3. Results

### 3.1. Characteristics of the sample

A total of 2630 patients were included in the study. Their socio-demographic and clinical characteristics are given in Table 1.

The initial diagnosis of depression was made by the GP in 85% of the cases and by a psychiatrist in 10%. Duration of antidepressant treatment was 6.9 months.

### 3.2. Remission rates

Remission rates were 28.3% according to the clinicians (HAMD-7 $\leq$ 3) and 17.1% according to the patients (Carroll rating scale $\leq$ 7).

The frequency of residual symptoms, as assessed by the patients using the Carroll rating scale is provided in Fig. 1. The most frequently reported residual symptoms were general somatic symptoms (92%), depressed mood (92%), psychic anxiety (91%) and impaired work and activities (89%). All residual symptoms were significantly more frequent in nonremitted as compared to remitted depressive patients.

### 3.3. Correlates of remission

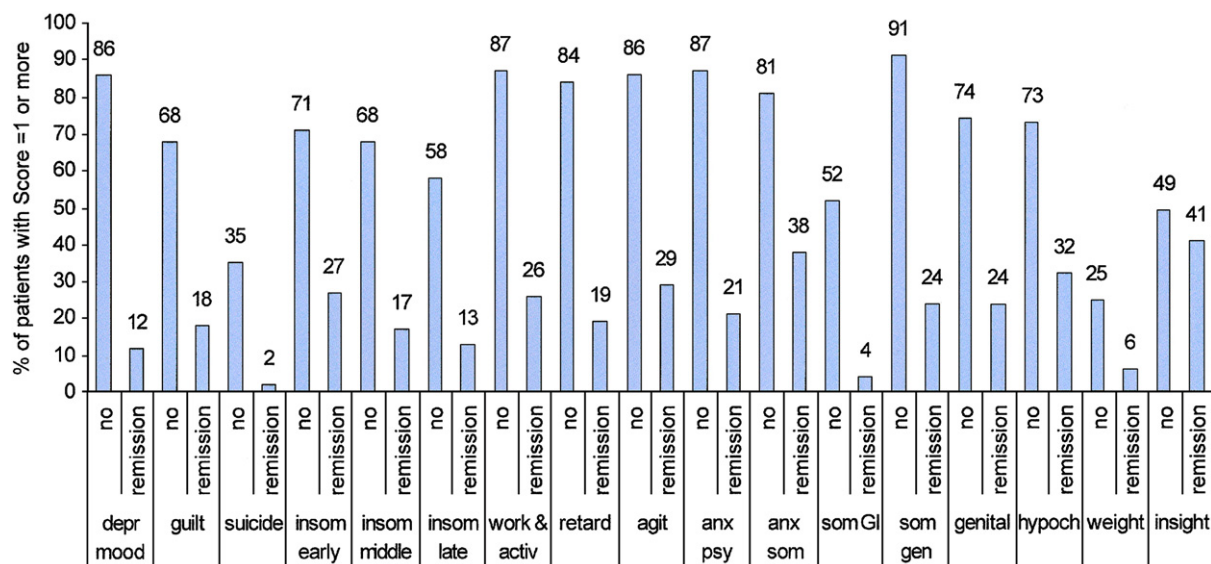
Mean age was identical in remitter and nonremitter depressive patients. Comparison of socio-economic factors between the two groups is provided in Table 2. Living alone, unemployment, lower education and French language were significantly more frequent in nonremitter depressive patients. Higher initial severity of the depressive symptomatology decreased the remission rate with 21.2% for severe level, 27.2% for moderate level and 41.2% for mild level ( $p<0.001$ ). In addition, the presence of previous depressive episodes was associated with lower remission rate: 39.8% of remission in patients without any previous episode, 29.2% for patients with one previous episode, 21.0% for two previous episodes and 13.9% for more than two episodes ( $p<0.001$ ).

Using logistic regression, two factors were significant in the model with interaction: number of previous episodes and initial severity (Table 3): the presence of previous depressive episodes and higher initial severity of the symptomatology were associated with lower remission rates. Significant interactions were found between professional status and duration of treatment ( $p=0.004$ ) on the one hand and between language and education ( $p=0.0036$ ) on the other hand. Therefore, since in case of a significant interaction between two covariates, odds ratios could no longer be calculated, an additional model without interaction was applied showing the influence of professional status, duration of treatment, language and education on remission rates. Concerning professional status, employees presented remission rates higher than workers but lower than middle managers and unemployees. A duration of treatment of 6 months or more was also a positive factor for remission. Concerning language, speaking Dutch was indicative of better remission and concerning education, a higher secondary degree was associated with lower remission rate than a lack of degree. However, it should be noted that these odds ratios should be considered as only indicative (Table 3).

Regarding treatment duration, a period longer than 6 months was associated with higher remission rates than a shorter period (33.2% vs 24.8%,  $p<0.001$ ). Multivariate analyses showed a significant improvement in remission rate between 3 and 6 months ( $p<0.001$ ) but no further improvement for the remaining of the study period ( $p=0.928$ ) (Fig. 2).

**Table 1** Demographical and clinical characteristics of the sample

	<i>n</i>	%
Number of patients	2630	
Age (mean)	49.7	
<i>Gender</i>		
Male	734	28
Female	1889	72
<i>Language</i>		
French	1962	52
Dutch	1268	48
<i>Family situation</i>		
Alone	698	27
Couple/family	1869	71
Group	57	2
<i>Professional status</i>		
Without income	285	11
Unemployed/replacement income	437	17
Self-employed	150	6
Worker	331	13
Employee	655	25
Middle management	83	3
Senior executive	50	2
Retired	621	24
<i>Educational level</i>		
No degree	117	4
Primary education	286	11
Lower secondary/vocational	818	31
Higher secondary	688	26
Higher non-university	528	20
University	166	6
<i>Initial severity of depression</i>		
Mild	565	22
Moderate	1495	58
Severe	529	20
<i>Prior depressive episodes</i>		
0	901	36
1	712	29
2	354	14
>2	592	20
<i>Current antidepressant treatment</i>		
Tricyclics	71	3
SSRI	1544	61
Citalopram	284	19
Escitalopram	249	17
Fluoxetine	188	12
Paroxetine	422	28
Sertraline	336	22
SNRI	792	31
Others	230	9
Associated anxiolytic	678	26
Associated hypnotic	288	11



**Figure 1** Comparison of the frequency of residual symptoms, as assessed by the Carroll Depression Scale in remitted and nonremitted depressive patients.

On the Sheehan Disability Scale, the absence of remission was associated with significantly higher impairment in work (5.0 vs 1.6), social life (5.0 vs 1.5) and family life (4.9 vs 1.4) ( $p < 0.001$ ).

#### 4. Discussion

This study shows a very low remission rate for depressive patients receiving antidepressants for 3 to 12 months in general practice: 28.3% according to the GP and 17.1% according to the patient. However, these results confirm data obtained in clinical trials with only 25 to 35% of remission rates (Nierenberg et al., 1999a,b). Interestingly, Trivedi et al. (2006) recently found nearly identical remission rates (27.5%) among depressive patients treated with citalopram in primary and psychiatric care settings using similar definitions. In this study, patients received flexible doses of citalopram for up to 14 weeks. Like Trivedi's findings, our study was performed in the "real world" care settings but differed in several aspects, particularly regarding its cross-sectional design, the longer duration of the antidepressant treatment (3 to 12 months) and the inclusion of all types of antidepressants.

Many explanations can be raised for these poor levels (Nierenberg et al., 2003). Depressed patients could be satisfied with partial relief of target symptoms such as sleep and/or appetite disturbances and therefore not particularly willing to pursue remission as the objective of treatment. Also, patients may not tolerate or may be unwilling to accept the side-effects associated with the optimal dosages of their medications. In addition, general practitioners may be uncomfortable or unfamiliar with recommended optimal dosages of antidepressants and may not feel confident pushing dosages to these levels because of the risk of side-effects. Patients may also underestimate the severity of their depression and not pursue treatment.

The lower remission rate according to the evaluation of the patients as compared to the GPs could depend on methodological biases. Indeed, the definition of remission

was based on the 7-item Hamilton Depression Scale for the GPs and on the Carroll Rating Scale for the patients themselves. The Carroll Rating Scale was developed as a self-rating instrument for depression, closely matching the information content and specific items of the 17-item Hamilton Depression Scale (Carroll et al., 1981; Feinberg et al., 1981; Smouse et al., 1981; Nasr et al., 1984). Comparisons of the two instruments found strong correlation but some differences: Carroll scores increased more rapidly than Hamilton scores with increasing severity of depression (Carroll et al., 1981) and the factor analyses of the two instruments did not strictly correspond (Smouse et al.,

**Table 2** Comparison of remission rates according to socio-economic factors

Factor	% remission	<i>p</i>
<i>Gender</i>		
Man	30	0.529
Woman	28.5	
<i>Living condition</i>		
Alone	25.1	0.028
Couple/group	30.2	
<i>Professional status</i>		
Unemployment	15.9	<0.001
All others	30.6	
<i>Education</i>		
No/lower education	21.3	<0.001
Higher education	32.3	
<i>Language</i>		
French	24	<0.001
Dutch	34	



**Table 3** Factors associated with remission (stepwise logistic regression)

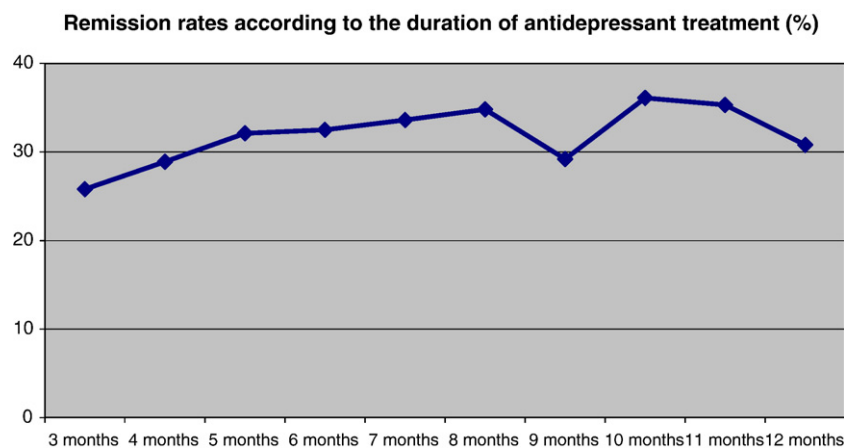
Factors	p-value	Odds ratios [95% Confidence Intervals ]
Model with interaction		
Number of previous episodes	$p < 0.001$	>2 episodes vs none: 0.300 [0.215–0.418] 2 episodes vs none: 0.441 [0.316 - -0.615] 1 episode vs none: 0.698 [0.548 - -0.888]
Initial severity	$p < 0.001$	Severe vs mild: 0.470 [0.337 - -0.655] Moderate vs mild: 0.600 [0.468 - -0.768]
Model without interaction		
Professional status	$p = 0.001$	Employee vs: Retired: 1.266 [0.928–1.728], NS Senior executive: 1.003 [0.467 - -2.155], NS Middle management: 0.415 [0.208 - -0.825] Worker: 1.459 [1.011–2.105] Self-employed: 1.055 [0.667–1.670], NS Unemployee: 0.627 [0.430–0.913] Without any income: 1.323 [0.904 - -1.937], NS $\geq 6$ months vs <6 months: 1.731 [1.395–2.104]
Duration of treatment	$p < 0.001$	Dutch vs French: 1.541 [1.257 - -1.888]
Language	$p < 0.001$	Higher secondary vs: University: 1.174 [0.737–1.871], NS Higher non-university: 1.294 [0.962–1.742], NS Lower secondary/vocational: 0.881 [0.667–1.162], NS Primary: 0.848 [0.572–1.256], NS No degree: 0.274 [0.130–0.579]
Education	$p = 0.003$	

Stepwise logistic regression: all covariates and two-by-two interactions were included one by one in the model with interaction and those reaching the 5% level of significance were retained. In that case, odds ratios were estimated comparing the probability of remission between two levels of the covariate. An odds ratio >1 correspond to a higher probability of remission. Confidence intervals including the number 1 are non significant (NS). In case of a significant interaction between two covariates, odds ratios could no longer be calculated and an additional model without interaction terms was applied. However, these odds ratios should be considered as only indicative.

1981). Alternatively, this finding could reflect a general trend of depressive patients to rate their symptoms as more severe as compared to observer's ratings. Several studies support this hypothesis (Tondo et al., 1988), particularly in nonendogenous depressive patients (Domken et al., 1994; Ueki et al., 2002, White et al., 1984; Enns et al., 2000). Rush et al., 1987 suggested that "anxious, atypical, somaticizing depressives view themselves as more severely depressed than do clinicians". In addition, clinicians' assessments were generally found as more sensitive to change than self-ratings (Corruble et al., 1999).

The concept and operationalization of remission need to be discussed. Clinically, remission phase is characterized by

resolution of the depressive symptoms. In 1991, Frank et al. proposed operational criteria for remission based on scores of standardized assessment tools, such as a score of 7 or less on the 17-item Hamilton Depression Scale or of 8 or less on the Beck Depression Inventory during at least 2 weeks. More recently, McIntyre et al. (2002, 2005) validated a shortened version of the HAM-D comprising 7 items, the Toronto HAM-D 7 scale. A score of 3 or less on the Toronto HAM-D was found to correlate with a 17-items HAM-D definition of full remission. A score for defining full remission (10 or less) has also been validated on the Montgomery and Asberg Depression Rating Scale (Zimmerman et al., 2004a). A self-report questionnaire, the clinically useful depression outcome scale, was recently

**Figure 2** Remission rates according to the duration of antidepressant treatment.

proposed by Zimmerman et al. (2004b). In addition, a survey of the patients opinion found that the 3 factors that were the most frequently judged to be very important in determining remission were the presence of features of positive mental health such as optimism and self-confidence; a return to one's usual, normal self; and a return to usual level of functioning (Zimmerman et al., 2006).

The use of a minimal score on depression scales such as HAM-D has been criticised since those instruments contain a large number of nonspecific symptoms of depression. In addition, the cutoff score of 7 on the Hamilton Depression Scale has been questioned by several clinicians who have suggested that this cutoff score is too high (Nierenberg et al., 1999a; Judd et al., 2000). Such a cutoff allows for the presence of residual symptoms and some patients even qualify for a depressive disorder diagnosis (Nierenberg et al., 1999b). In a recent study, Zimmerman et al. (2005) proposed a 17-item HAM cutoff score of 2 or less. The application of such a cutoff in our sample using the Carroll scale would have reduced further the number of remitted depressive patients (4.1%). However, median HAM-D scores in the general population were found of 2 compared to 20 in patients with major depressive disorder with a cutoff of 7 providing the best differentiation between depressed and nondepressed persons (Thase, 2002; Thase et al., 2002).

The lack of remission is associated with significantly more impairment in work, social life and family life, confirming previous report showing a poor quality of life in nonremitted depressive patients (Murphy et al., 1987). This finding stresses the importance of achieving remission.

In our study, several factors appear to play a significant role in the rate of remission. First, a higher initial severity and a higher number of previous episodes decrease the remission rates. Those two factors have long been considered as associated with poorer prognosis (Hirschfeld et al., 1998, 2002; Swindle et al., 1998; Simon, 2000; Trivedi et al., 2006). On the socio-economic level, four factors were associated to lower remission rates: living alone, unemployment, lower education and speaking French. Living with a spouse or partner and a higher educational level have already been demonstrated as predictor of treatment response to antidepressants (Joyce and Paykel, 1989; Hirschfeld et al., 1998; Szadoczky et al., 2004; Swindle et al., 1998; Trivedi et al., 2006). Similarly, the beneficial role of a professional activity in the outcome of depression has already been reported previously (de Graaf et al., 2002; Trivedi et al., 2006). These findings show that the remission of a depressive episode is dependent on the socio-economic context. The pharmacological intervention can be insufficient to modify a pathological environment.

Our finding of a significant difference between French and Dutch speaking depressive patients in their remission rates need some clarifications. Belgium is composed of 2 main communities, speaking Dutch in the north (the Flanders) and French in the south (Wallonia); Brussels, the capital of the country is mainly composed of French-speaking citizens. The economic situation of the Dutch-speaking region is currently much better than the French-speaking areas; for instance, the percentage of unemployment is 16.7% in Wallonia, 20.3% in Brussels and 7.5% in Flanders (Belgian Government, 2005). However, there are data possibly pointing to socio-cultural rather than to socio-economic factors and more precisely to the attitude toward

suffering. Northern countries exhibit a more stoicist attitude toward adversity than their southern counterparts. This is indirectly demonstrated by the much more frequent recourse to anxiolytic drugs in French speaking countries. For example, according to Pelissolo et al. (1996), 25–30% of the French general population are occasional or regular users of anxiolytic and hypnotic drugs with between 5 and 7% chronic users, corresponding to 2 to 3 times superior to most industrialized countries. In the survey by Ohayon and Lader (2002), France has the highest proportion of anxiolytic users (9.0%) followed by Italy (5.8%); the rate is only 0.7% in Germany and 0.6% in the U.K.

In contrast, gender does not appear to play a significant role in remission rates, confirming previous reports (Zlotnick et al., 1996; Szadoczky et al., 2004). A recent report, however, found that female patients presented higher remission rates than male subjects (Trivedi et al., 2006).

Several limitations in the design of this study should be acknowledged and discussed. First, no systematic diagnostic procedure was imposed. Patients were included if they were initially diagnosed as depressives and treated by antidepressants. Despite its limitations, this method corresponds better to the treatment procedure applied in general practice where due to time limitations systematic diagnostic procedures are very rarely used. Second, the study uses a cross-sectional design which does not enable us to follow the evolution of the treated patients over time. In addition, the sample could have been somewhat biased since only those patients reconsulting their GP between 3 and 12 months of antidepressant therapy were included. Therefore, patients who did not reconsult their practitioner due to either rapid or complete recovery or on the opposite lack of any improvement and even worsening leading to referral to a specialist or hospitalisation are not evaluated.

It would have been of real interest to perform similar study among patients seen by psychiatrists to evaluate if their therapeutic results are better than those of GPs. Several reports seem to indicate that psychiatrists could obtain higher remission rates than primary care physicians (Gruen et al., 2004). A recent study, however, found comparable remission rates in primary and psychiatric care for depressive patients treated with citalopram (26.6% vs 28.0%) (Trivedi et al., 2006).

In total, the findings of this study show that much progress has still to be made for improving the treatment of depression in primary care. A recent review shows that strategy which revealed effective in improving patient outcome generally are those with complex interventions that incorporated clinician education and a greater degree of integration, between primary and secondary care (Gilbody et al., 2003). This is clearly a challenge for the future.

## Role of the funding source

The funding source (Wyeth Belgium) was only involved with the collection of the data.

## Contributors

Marc Anseau was associated with the elaboration of the protocol and the analysis and discussion of data and wrote the manuscript;

Koen Demyttenaere was associated with the elaboration of the protocol and the analysis and discussion of the data; Jan Heyrman was associated with the elaboration of the protocol and the analysis and discussion of the data; André Migeotte was associated with the elaboration of the protocol and the analysis and discussion of the data; Sophie Leyman was associated with the elaboration of the protocol and the analysis and discussion of the data; and Annick Mignon was associated with the elaboration of the protocol and the analysis and discussion of the data.

## Conflict of interest

None.

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