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Original article

The course of depressive symptoms and prescribing patterns of antidepressants in schizophrenia in a one-year follow-up study

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ABSTRACT

Background. – Antidepressants are frequently prescribed in patients with psychotic disorders, but little is known about their effects in routine clinical practice. The objective was to investigate the prescribing patterns of antidepressants in relation to the course of depressive symptoms in patients with psychotic disorders.
Methods. – A cohort of 214 Dutch patients with psychotic disorders received two assessments of somatic and psychiatric health, including a clinician-rated screening for depressive symptoms, as part of annual routine outcome monitoring.
Results. – Depressive symptoms were prevalent among 43% (93) of the patients. Antidepressants were prescribed for 40% (86) of the patients and the majority 83% (71) continued this therapy after one year. Multivariable analysis showed that patients with more severe psychopathology had a higher risk to develop depressive symptoms the following year (OR [95% CI] = 0.953 [0.912–0.995]). For patients with depressive symptoms at baseline, polypharmacy was a potential risk factor to keep having depressive symptoms (OR [95% CI] = 1.593 [1.123–2.261]). Antidepressant use was not an independent predictor in both analyses.
Conclusions. – Routine outcome monitoring in patients with psychotic disorders revealed a high prevalence of depressive symptoms. Antidepressants were frequently prescribed and continued in routine clinical practice.

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1. Introduction

Depressive symptoms occur in about 25% of patients with schizophrenia [10,44], but the reported prevalence may vary between 7 and 75% [15,19,20,26]. The variation is due to heterogeneous study populations, differences in study methods and differences in diagnostic criteria. Depressive symptoms may be present throughout all phases of schizophrenia [7,26]. The highest prevalence is found during acute psychotic episodes [23]. Persistent depressive symptoms during the chronic phase of illness have been associated with a higher risk for relapses [9,39]. Depressive symptoms may reflect a psychological reaction to the severe illness or 'demoralization syndrome' [34] or can partly mimic extrapyramidal side effects related to the dopamine blockade of antipsycho-

tics, known as 'akinetic depression' or dysphoria [18,20,46]. Antipsychotic-induced depressive symptoms may be treated by lowering the antipsychotic dose, switching to another (atypical) antipsychotic or adding anticholinergic medication [30,44].

Guidelines for the treatment of schizophrenia advise prescribing antidepressants for depressive symptoms [3,32,45], although there is conflicting evidence on the efficacy of antidepressants for depressive symptoms in schizophrenia from randomized controlled clinical trials [28,47]. Antidepressants are prescribed for 11 to 43% of the patients with schizophrenia [5,25,36]. They are commonly used to treat depressive symptoms, but may also be used for anxiety disorders or negative symptoms [14,38,42]. Adding antidepressants to antipsychotics increases the risk of interaction and side effects [33], and may also lead to higher medical costs.

Longitudinal observational studies describing predictors for the development or persistence of depressive symptoms in patients with schizophrenia are scarce. Moreover, longitudinal studies

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describing the course of depressive symptoms do not report details of prescribing patterns of antidepressant therapy [4,12,35,39]. It is unclear how many patients with persistent depressive symptoms continue to use antidepressants or remain untreated with antidepressants. The current naturalistic study is based on a cohort of patients with schizophrenia or related psychotic disorders, assessed during yearly routine outcome measurements. The aim is to investigate the course of depressive symptoms in relation to prescribing patterns of antidepressants in schizophrenia during one-year follow-up.

2. Methods

All patients of 18 years and older with schizophrenia or related psychotic disorders covered by a mental health care centre in a circumscribed area in The Netherlands were included in yearly routine outcome assessments of their physical and mental health as described previously [40,41]. Assessments were carried out between January 2003 and April 2006 in patients having given informed consent in accordance with the latest version of the Declaration of Helsinki. Patients were included if they completed a first (baseline) and second assessment (follow-up) within an interval of 12 months ($\pm$3 months). In-patients with an acute psychosis at first assessment were excluded from analysis. Trained nurses conducted a structured interview lasting approximately one hour to evaluate the patients' social functioning, mental and physical health status. Current medication use was retrieved from the patient's medical records and was then confirmed with the patient. A psychiatrist based the diagnosis on the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) classification system (codes 295.4–295.9, 297.1, 298.8 and 298.9) [13]. The patient's psychiatrist rated depressive and extrapyramidal symptoms on a 3-point Likert scale (absent, moderate, severe) and assessed psychosocial functioning using the Global Assessment of Functioning scales (GAF-symptoms and GAF-disability).

Patients with moderate or severe depressive symptoms were categorized as 'having depressive symptoms'. Baseline characteristics were compared (a) between patients who did not have depressive symptoms at both assessments and patients who developed depressive symptoms at second assessment ('incidence'); (b) between patients with depressive symptoms at baseline that were no longer present at second assessment ('remitted') and patients with depressive symptoms present at both assessments ('persistent').

We analyzed potential predictors of depressive symptoms at follow-up. As a first step we compared baseline characteristics between patients with and without depressive symptoms at follow-up in a univariable analysis. Categorical variables were tested using a Chi^2 test and continuous variables were not normally distributed and were therefore assessed by the non-parametric Mann-Whitney U test. Multivariable logistic regression analysis was used to identify baseline patient characteristics as independent predictors of the incidence or the persistence of depressive symptoms at follow-up. Only those baseline characteristics with a significance level of $P < 0.25$ in the univariable analysis were entered as predictors in the model. Significance levels greater than 0.05 are commonly applied to select predictors for multivariable analysis [29]. In the multivariable analysis, a probability level of $P < 0.05$ was accepted as statistically significant. All P-values are two-sided. In a more detailed description of the prescribing patterns of antidepressants, the course of depressive symptoms was compared between patients not using antidepressants at both assessments and patients who used antidepressants at both assessments by calculating the confidence intervals for these groups.

3. Results

A total of 473 patients were eligible for inclusion into the study. Of those, 34% (162) did not want to participate in a second assessment or were lost to follow-up, e.g. moved away. Twenty-one percent (97) of the patients had their second assessment not within 9 to 15 months. The remaining 45% (214) patients with a period of 11.8 months (SD 1.7) between first and second assessment were included in the study. The mean age was 38.7 years (SD 11.7; range 16–65 years) and mean duration of illness was 12.2 years (SD 9.4; range 1–44 years); 43% (92) were female, 76% (162) suffered from schizophrenia and the majority were outpatients (Table 1). Patients included in the study did not differ from the 259 not-included patients regarding age, duration of illness and prevalence of depressive symptoms at baseline. The proportion of females and outpatients was somewhat higher in the group of included patients, as was the proportion of patients using antidepressants and the average GAF-scores. Depressive symptoms were present among 43% (93) of the patients included and antidepressants were prescribed for 40% (86) patients, of whom 83% (71) continued their antidepressant therapy.

Univariable analysis showed that depressive symptoms at follow-up were potentially associated with the following baseline

Table 1
A comparison of relevant variables of the total population at baseline ($n = 473$).

	Study sample ($n = 214$)	Not included ($n = 259$)	Chi^2 or Z-value	P-value
Gender, female (%; n)	43 (92)	34 (88)	$\chi^2 = 4.04$	0.044
Age (mean; SD)	38.7 (11.7)	39.6 (12.6)	$Z = -1.14$	0.255
Duration of illness (mean; SD)	12.2 (9.4)	11.1 (9.8)	$Z = -1.25$	0.211
Diagnosis (%; n)			$\chi^2 = 1.02$	0.602
Schizophrenia	76 (162)	78 (201)		
Schizoaffective	20 (43)	17 (44)		
Psychotic disorder NOS	4 (9)	5 (14)		
Treatment status (%; n)			$\chi^2 = 7.34$	0.026
Outpatients	64 (138)	64 (167)		
Sheltered housing facilities	21 (44)	13 (34)		
Chronic in-patients	15 (32)	22 (58)		
Symptomatology (mean; SD)				
GAF-symptoms	65.6 (15.1)	59.0 (18.5)	$Z = -5.02$	0.000
GAF-disability	61.0 (16.0)	56.4 (16.4)	$Z = -4.22$	0.000
Depressive symptoms (%; n)	43 (93)	37 (97)	$\chi^2 = 1.76$	0.185
Antidepressants (%; n)	40 (86)	27 (69)	$\chi^2 = 8.89$	0.003

n: number; SD: standard deviation; NOS: not otherwise specified; GAF: global assessment of functioning. Categorical variables were analyzed by a two-sided Chi^2 test and continuous variables by a Mann-Whitney U test.

Table 2
Baseline characteristics of patients with and without depressive symptoms at follow-up ($n = 214$).

	No depressive symptoms ($n = 136$)	Depressive symptoms ($n = 78$)	Chi^2 or Z-value	P-value
Gender, female (%; n)	46 (62)	38 (30)	$\chi^2 = 1.03$	0.311
Age (mean; SD)	38.4 (12.2)	39.4 (11.0)	$Z = -0.69$	0.489
Duration of illness (mean; SD)	11.6 (9.6)	13.3 (8.9)	$Z = -1.63$	0.103
Diagnosis (%; n)			$\chi^2 = 3.04$	0.219
Schizophrenia	76 (103)	76 (59)		
Schizoaffective	18 (25)	23 (18)		
Psychotic disorder NOS	6 (8)	1 (1)		
Treatment status (%; n)			$\chi^2 = 0.56$	0.756
Outpatients	66 (90)	62 (48)		
Living in sheltered housing facilities	19 (26)	23 (18)		
Chronic in-patients	15 (20)	15 (12)		
Psychosocial status (%; n)				
No daytime activities	29 (36)	24 (18)	$\chi^2 = 0.58$	0.447
No contact with friends	31 (42)	21 (16)	$\chi^2 = 2.70$	0.100
No contact with family	12 (16)	6 (5)	$\chi^2 = 1.61$	0.205
Symptomatology (mean; SD)				
GAF-symptoms	66.9 (15.9)	63.4 (13.2)	$Z = -1.58$	0.113
GAF-disability	61.3 (16.9)	60.4 (14.3)	$Z = -0.75$	0.454
Extrapyramidal symptoms (%; n)	15 (20)	18 (14)	$\chi^2 = 0.39$	0.532
Depressive symptoms	29 (40)	68 (53)	$\chi^2 = 29.96$	0.000
Antipsychotics (%; n)			$\chi^2 = 3.29$	0.349
Atypical antipsychotics	69 (94)	62 (48)		
Typical antipsychotics	10 (14)	13 (10)		
Combination atypical + typical	10 (14)	18 (14)		
No antipsychotics	10 (14)	8 (6)		
Number of drugs prescribed (mean; SD)	2.4 (1.6)	3.3 (2.3)	$Z = -2.81$	0.005
Number of drugs prescribed; excl.antidepr.	2.0 (1.4)	2.8 (2.2)	$Z = -2.41$	0.016
Antidepressants (%; n)	35 (47)	50 (39)	$\chi^2 = 4.92$	0.027
Anticholinergics	4 (5)	9 (7)	$\chi^2 = 2.63$	0.105
Benzodiazepines	32 (43)	40 (31)	$\chi^2 = 1.45$	0.229
Moodstabilizers	13 (17)	14 (11)	$\chi^2 = 0.11$	0.738
Type of antidepressant (%; n)			$\chi^2 = 1.10$	0.576
Selective serotonin reuptake inhibitors	60 (28)	62 (24)		
Tricyclic antidepressants	17 (8)	23 (9)		
Other antidepressants	23 (11)	15 (6)		

n: number; SD: standard deviation; NOS: not otherwise specified; GAF: global assessment of functioning; excl.antidepr.: exclusive antidepressants; anticholinergics included biperiden, dexetimide and trihexyphenidyl. Categorical variables were analyzed by a two-sided Chi^2 test and continuous variables by a Mann-Whitney U test.

characteristics with a P-value < 0.25: duration of illness, diagnosis, no contact with friends or family, GAF-symptoms, depressive symptoms at baseline, antidepressant use, number of drugs other than antidepressants, use of benzodiazepines and anticholinergics (Table 2). These variables, except for use of benzodiazepines and anticholinergics being covered by the number of other drugs than antidepressants, were entered into a multivariable analysis to identify independent predictors of either the incidence or the persistence of depressive symptoms at follow-up.

Of the 121 patients without depressive symptoms at baseline, 79% (96) remained free of symptoms and 21% (25) patients newly developed depressive symptoms at second assessment (Table 3). Patients with a lower GAF-symptom score at baseline had a higher

risk of developing depressive symptoms (n = 121, odds ratio [95% confidence intervals] = 0.953 [0.912–0.995], $P < 0.030$), when adjusting for the subset of clinical and sociodemographic characteristics as mentioned above. Of the 93 patients with depressive symptoms at baseline, 43% (40) 'remitted' (i.e. were free of depressive symptoms at second assessment) and 57% (53) had 'persistent' depressive symptoms after one year. Prescription of a higher number of drugs at baseline was a risk factor to have persistent depressive symptoms at follow-up (n = 93, OR [CI] = 1.593 [1.123–2.261], $P < 0.009$).

The course of depressive symptoms in relation to antidepressant therapy is illustrated in Table 3. Of the patients without depressive symptoms at first assessment, 35% (42/121) were prescribed

Table 3
Course of depressive symptoms and antidepressant therapy between baseline and follow-up ($n = 214$).

Baseline	n	Follow-up	n	Antidepressant prescription	n
No depressive symptoms					
Antidepressants	42	No depressive symptoms	32	Discontinued	7
		Incidence of depressive symptoms	10	Discontinued	1
No antidepressants	79	No depressive symptoms	64	Started	5
		Incidence of depressive symptoms	15	Started	4
Depressive symptoms					
Antidepressants	44	Remitted from depressive symptoms	15	Discontinued	4
		Persistent depressive symptoms	29	Discontinued	3
No antidepressants	49	Remitted from depressive symptoms	25	Started	4
		Persistent depressive symptoms	24	Started	4

n = number; changes in antidepressant prescription between baseline and follow-up were indicated by 'discontinued' (patients who used antidepressants at first assessment, but discontinued their therapy before the second assessment) or 'started' (patients who did not use antidepressants at first assessment, but started before the second assessment).

antidepressants; of whom 34 continued antidepressant therapy. Of these 34 patients, 26% (9/34; CI: 12–49%) developed symptoms despite antidepressant therapy (incidence). The remaining 65% (79) patients without depressive symptoms at first assessment were prescribed no antidepressants; 70 of them did not start antidepressants between first and second assessment. The incidence rate in the latter group was 16% (11/70; CI: 7–30%). Of the patients with depressive symptoms at first assessment, 47% (44/93) were prescribed antidepressants; 37 of them continued their antidepressants at follow-up. Seventy percent (26/37; CI: 56–85%) of them had persisting depressive symptoms despite continuing antidepressants, of whom only four switched type of antidepressants at second assessment. Of the patients with depressive symptoms at first assessment, 53% (49) did not use antidepressants and 41 of them did not start antidepressants between first and second assessment. The percentage of patients with persistent depressive symptoms was 49% (20/41; CI: 33–64%).

4. Discussion

This naturalistic study showed a high prevalence rate (43%) of depressive symptoms in patients with psychotic disorders. Although the modal prevalence rate reported in the meta-analysis by Siris and Bench was 25% [44], the findings were in line with comparable studies [4,12]. Previous cross-sectional studies have shown that depressive symptoms are associated with more severe psychopathology and (related) polypharmacy [8,12,24,27,31,43]. Our longitudinal study showed that these patient characteristics are also predictors of depressive symptoms. Patients with more severe psychopathology had a higher risk to develop depressive symptoms the following year. For patients with depressive symptoms at baseline, polypharmacy was a potential risk factor to keep having depressive symptoms. Also in accordance with previous studies, depressive symptoms were not associated with age, gender, duration of illness or being institutionalized [1,2,7,8,12,31,37]. Antidepressant use at baseline was related to the presence of depressive symptoms at follow-up in univariable analysis. However, multivariable analysis indicated that antidepressant use was neither an independent predictor of remaining symptom free, nor of remitting from depressive symptoms.

Antidepressants were frequently prescribed in routine clinical practice as in previous studies [6,12,15,31]. Our study brought new insight into the prescribing patterns of antidepressants in relation to the course of depressive symptoms. The majority of antidepressants were continued once prescribed. A large proportion of patients appeared to have persistent depressive symptoms despite continuation of antidepressant treatment. Patients' symptoms may have remitted and reoccurred at second assessment or they may be non-responders. Another group continued antidepressants even though they remained free of depressive symptoms both years. Their antidepressant therapy may have served as an effective prophylaxis [16,21], for other indications such as negative symptoms or anxiety or it may indicate overprescribing. In contrast, a considerable proportion of patients did not receive antidepressants despite experiencing persistent depressive symptoms, which may suggest underprescribing.

The prescribing patterns may reflect the state of guidelines for schizophrenia. Current schizophrenia guidelines recommend to use antidepressants in patients with depressive symptoms, but do not give detailed prescribing advice, in particular about discontinuation in non-responders and duration of maintenance therapy [32,45]. Some guidelines refer for prescription of antidepressants to the depression guideline [3], although it is doubtful whether depressive symptoms in schizophrenia should be treated the same

way as major depressive disorder. One of the reasons for the lack of detail in the guidelines is the scarcity of evidence about effectiveness of antidepressants in schizophrenia [28,47], but also for depression in general [22]. More placebo-controlled research into the effectiveness of antidepressants is needed for the development and improvement of guidelines for prescription of antidepressants in schizophrenia.

Our study has the following limitations. Firstly, we cannot make firm conclusions regarding the effectiveness of antidepressants given the limitations of the naturalistic approach of the current study. This approach may give rise to 'confounding by indication' as in all observational research, i.e. patients using antidepressants may be more severely ill and thus would be more likely to have recurrent or persistent depressive symptoms. This is (partly) corrected for in our logistic regression. Other possible confounders in the apparent lack of antidepressant effect could have been poor compliance, prescription of inadequate doses in patients with antidepressants, or non-pharmacological treatments such as psychotherapy in patients without antidepressants. Secondly, depressive symptoms were clinician-rated instead of by a depression instrument validated for schizophrenia. We therefore cannot be sure whether the clinicians adequately distinguished depressive symptoms from negative symptoms. Thirdly, long-term follow-up is considered difficult in patients with schizophrenia [4,11], but we achieved a reasonable response rate of 45%. Our study sample differed from the patients who were not included in male/female ratio and level of functioning. The higher proportion of females in our study sample may explain the higher number of outpatients and the higher GAF-scores, as well as the increased use of antidepressants [6,17,31]. Despite these differences, the comparison of our findings with earlier studies as discussed above suggest that our sample is overall representative of a population with schizophrenia and related psychotic disorders. Lastly, depressive symptoms are known for their waxing and waning over time [12]. We measured symptoms once a year as part of our routine outcome monitoring, but a shorter time frame may be needed to follow patients with depressive symptoms.

In conclusion, our findings indicate that depressive symptoms occur frequently in clinical practice patients. We also found high prescription rates of antidepressants, and most patients continued their antidepressant medication once prescribed. Patients with more severe psychopathology had a higher risk to develop depressive symptoms the following year. For patients with depressive symptoms at baseline, polypharmacy was a potential risk factor to keep having depressive symptoms. We therefore would recommend close monitoring of the treatment in patients with depressive symptoms, in particular in those patients with predictors present.

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