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Treatment of depression related to recurrence: 10-year follow-up in general practice

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SUMMARY

Objectives: To study outcomes related to long-term treatment of depression and differences in treatments for first episodes of depression in patients with and without recurrences.

Methods: A historic cohort design study with 222 general practice patients who had been followed up for 10 years after being diagnosed of depression. Prescriptions for antidepressants, psychotropics and referrals over the period of 10 years following the first diagnosis of depression were studied.

Results: Over the 10-year period, the length of treatment with antidepressants and the doses prescribed were low compared to what is known to be efficacious in depression. This was also true for treatment during the first episode. Patients with a recurrent type of illness were more often treated with antidepressants and other psychotropics during their first episode than patients with only one episode of depression, but they were not referred any more often.

Conclusions: Even though treatment was not as recommended for depression, the majority of the patients did not have recurrences. Future prospective research is needed to study causal relationships between treatment of depression and long-term outcome.

INTRODUCTION

From the literature we know that in general practice, patients with depression often do not get the treatment regarded as therapeutic. Most studies have shown that if antidepressants are prescribed at all, the doses are often too low and the length of the prescriptions too short when compared with what is recommended for depression (1–4). However, we do not know how patients with depression are treated long-term and the exact relationship between lack of 'adequate medication' and long-term outcome is not clear, particularly in primary care (5). In a study we performed on course and long-term outcome of depression in general practice, 60% of the patients did not have any recurrence in a follow-up of 10 years after the first diagnosis (6). Medication and referrals were items that had been checked during the data collection for this study. Therefore, it was possible with the same database to describe all treatment during this 10-year period. The treatment during the first episode of depression was studied with the following questions in mind: how frequently had antidepressants been prescribed? Were dosage and length of treatment prescribed 'adequate' and could differences in treatment of the first episode be found between patients with one, two or more than two episodes of depression?

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MATERIAL AND METHODS

Database

The material for this study was collected from the Continuous Morbidity Registry (CMR) of the Department of General Practice and Social Medicine of the University of Nijmegen (7, 8). It is a network of four practices (total of 12 000 patients) in the Nijmegen region, in which all morbidity is recorded on an ongoing basis since 1971. The following demographics are recorded: age, gender and social class. Diagnoses of all new episodes of illness are registered according to the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2) (until 1984 according to

the criteria for classification of the Dutch translation of the British E-list) (9, 10). Although the diagnosis of depression of the patients in this study could not be assessed retrospectively, a recent study showed a high accordance of the diagnosis of depression by general practitioners in the CMR with the criteria of Major Depressive Disorder (MDD) in psychiatry (11). Because in the Dutch health care system the general practitioner has a fixed list of patients and is also gate-keeper of access to specialist medical-care, long-term data are available for nearly all patients and it is possible to study treatment related to outcome over a long period of time.

Patient data

For the study on long-term course and outcome of depression mentioned earlier, the charts of 222 patients coded with a first depression (ICHPPC-2 criteria) before 1985 had been studied in detail in the practices. Table 1 shows age, gender and social class of the 222 patients, who could be followed up for 10 years starting on the day that the diagnosis of depression was made for the first time. Table 2 shows the distribution of the number of depressive episodes of these 222 patients over the 10-year follow-up period. In 134 patients (60% of 222) only one episode of depression had occurred in the 10 years of follow-up, while 12% had more than three episodes. For the medication study, 10 full years on the charts were screened for prescriptions with antidepressants and other psychotropic drugs starting on the date of first diagnosis of depression. Referrals within primary care and to secondary care were also registered.

Table 1. Demographics of the 222 patients coded for depression

Age	< 45	50%
	45–64	43%
	> 65	6%
Gender	Male	39%
	Female	61%
Social class	Low	63%
	Middle	32%
	High	4%

Table 2. Number of episodes with depressive illness. Number of patients = 222

Number of episodes	Percentage of patients
1	60
2	16
3	12
4	6
5	4
> 6	3

Drug data: classification, unit of comparison and episodes

Antidepressant drugs were registered according to the Anatomical Therapeutical Classification methodology as recommended by the WHO Drug Utilization Research Group (12). As a unit of comparison the ratio of Prescribed Daily Dose to Defined Daily Dose (PDD/DDD) was used (13). To compare the effect of drugs a measure of equipotency must be determined. Therefore, all daily doses were standardized by using the PDD, the dose prescribed by the physician for the individual patient. The PDD equals the actual daily dose. The DDD is the assumed average effective daily dose for the drug used for its main indication in adults and is expressed in amount of the active substance. DDD values are assigned by the World Health Organization (WHO) Collaborating Centre for Drugs Statistics Methodology and Nordic Council on medicines and are published in *Guidelines for Daily Doses*, a publication based on dose documentations per drug as prepared by WHO Oslo, based on international textbooks, journals and documentation approved by drug control authorities. These documentations are available on request from Oslo. Table 3 shows the published DDD of antidepressants prescribed to the patients in our study.

A medication-episode was defined as an uninterrupted period with antidepressant medication. Changes in type or dose of the antidepressant drug are allowed in such a medication-episode. The rationale for summing PDD/DDD ratios for different antidepressants is found in the definition of DDD as the average maintenance dose of a particular drug for its main indication in adults.

Table 3. DDD for antidepressants as published by WHO, 1996 (12)

Antidepressants	DDD (mg)
Tricyclic derivates	
Desipramine	100
Imipramine	100
Imipramine oxide	100
Clomopramine	100
Opipramol	150
Trimipramine	150
Lofepramine	105
Dibenzepin	300
Amitriptyline	75
Nortriptyline	75
Protriptyline	30
Doxepin	50
Butriptyline	75
Dosulepin	150
Tetracyclic derivates	
Maprotiline	100
Mianserin	60
Modified cyclic derivates	
Nomifensine	150
Trazodone	300

DDD, defined daily dose; WHO, World Health Organization

In these practices a 'first prescription' was never given for more than 2 weeks, as is the rule nowadays in The Netherlands. Antidepressant medication is not effective within such a short time. Therefore, if only one prescription had been registered on the chart without a clear definition of the length this was considered by us as a no medication-episode.

Prescriptions for other psychotropic drugs were registered as follows: if they had been prescribed, the type and frequency of the prescription was recorded. A distinction was made between just incidentally (not more than two prescriptions a year), chronically (for more than 6 months a year), or in between.

The first episode of all patients was studied in detail to see if differences could be found in treatment between those patients who eventually had only one, two or more than two episodes of depression.

Statistical analysis

Differences between groups are tested with Chi square (χ^2) statistics and χ^2 for linear trends. The differences in length and ratio of antidepressant medication between the patients with and without recurrent illness were calculated with the Wilcoxon test.

RESULTS

Long-term treatment with antidepressants, other psychotropic medication and referrals

A total of 441 medication-episodes with antidepressants had been registered on the patient charts during the 10-year follow-up period (148 during the first episode). The doctor's notes allowed the assessment of length of treatment in 80% and dosage in 54% of these medication-episodes (of the first episode 84% and 62%). Sixty-two (28%) patients did not have a medication-episode. Almost all of these patients belonged to the group who had only one episode of depression (57 of 62). Of the 88 patients with recurrences, 94% received prescriptions for antidepressants sometime during the 10-year follow-up period.

The tricyclic antidepressants amitriptyline and imipramine were prescribed most frequently. New generation antidepressant medications did not appear during our study period. Of the 222 patients, 17 received medication with lithium in addition to their medication with antidepressants. Twenty-four percent of the registered medication-episodes for antidepressants were shorter than 28 days, 21% of these episodes had a length of more than 6 months. PDD/DDD ratios were low, 78% of these ratios had a value of less than 1.

A total of 191 patients (86% of 222) received one or more prescriptions for other psychotropic drugs at a certain point during the 10-year follow-up period, mainly benzodiazepines (175 patients, 79% at least one prescription for a benzodiazepine). Twenty-six of the 134 patients with single episode depression and five of the 88 patients with recurrent depression never received prescriptions with other psychotropic medication during the 10-year follow-up period (19% and 6%, respectively). This difference was significant ($P = 0{\cdot}004$).

Other psychotropic drugs were prescribed mostly during the year following the first diagnosis of depression (in 78% of the 222 patients). After this the percentage dropped, but in every subsequent year around 35% of the patients received at least one prescription for these drugs. Thirty-four

patients (15%) were referred to secondary care (psychiatrist, neurologist) and 19 patients (9%) within primary care (psychologist, social worker or ambulatory psychiatric care facility).

Relationship between treatment during first episode and recurrence

To compare the management of first episodes of depression, the 222 patients were divided into three categories: patients who during the first 10 years after the diagnosis had experienced one ($n = 134$), two ($n = 36$) or more than two ($n = 52$) episodes of depression. No significant differences were found in patient demographics between the categories in age, gender and social class. Treatment during the first episode was different for the three categories. Patients who later had recurrences had received more treatment. Table 4 shows the differences in treatment between the three categories. A significant trend in treatment approach could be found. Of the 134 patients who did not have any recurrence of depression, 67 (50%) received antidepressant medication during their first and only episode of depression. For the category with two episodes this was 26 (72%) and for the category with more than two episodes 41 (79%). Doses and length of the prescriptions with antidepressants were low, with no significant differences between the three categories. For other psychotropic drugs the percentages in the three groups were 62%, 69% and 79%, respectively. The combination of antidepressants and other psychotropics in the first year after diagnosis also showed a significant trend. Although higher for patients with more episodes, the differences were not significant for referral and other combinations.

DISCUSSION

The results of this study are consistent with those of other studies, which show that patients prescriptions for antidepressants were for shorter and smaller doses than recommended in guidelines (14, 15). We found differences in treatment of the first episode of depression in patients with one, two or more than two episodes of depression. Although more patients who later had recurrences received prescriptions with antidepressants during their first episode than patients without recurrences, the doses were also low and length of the medication episodes short, with no significant differences between the categories. We also found high prescription rates for minor tranquillisers, mostly benzodiazepines, just as in other studies, for example, a study with depressed outpatients (16). Although sleep disturbance and comorbidity with anxiety could have been reasons for prescribing this kind of medication, this was not mentioned consistently on the patient records, nor could we find other reasons for the 'lack of adequate medication'. Even though the treatment was 'inadequate by psychiatric standard', the majority of the patients in our study had a favourable outcome

Table 4. Treatment during first depressive episode related to number of depressive episodes. Percentages of treated patients per episode

	Number of episodes (number of patients)			
	1 ($n = 134$)	2 ($n = 36$)	>2 ($n = 52$)	Significance (P)
Antidepressants*	50	72	79	< 0·001
Psychotropics in first year*	62	69	79	0·03
Referral	16	17	23	0·3
Antidepressants + psychotropics*	33	56	63	< 0·001
Antidepressant + referral	9	14	17	0·1
Psychotropics + referral	12	17	21	0·1
Antidepressants + psychotropics + referral	13	14	17	0·07

Referral = referral to primary or secondary care
*Significant with Chi square for linear trend

without recurrences. With this study design we could not establish a causal relationship between treatment and the outcome. Our results do offer support for a view that depression in primary care may be different from depression seen in psychiatry and may require a different treatment (17). As has been pointed out in other studies, a diagnosis does not necessarily mean a need for treatment (18). Even when a diagnosis of Major Depressive Disorder has been made, spontaneous recovery should be considered for a number of cases in general practice and watchful waiting could prove worthwhile. At least one study has demonstrated that patients in general practice receiving antidepressant treatment as recommended in guidelines had higher rates of relapse than those receiving no therapy (19). Others found patients receiving either placebo or active intervention in mild to moderately severe MDD responding equally (20). Our results point in the same direction for long-term outcome, no adequate treatment and a low recurrence rate. It could also mean, as has been suggested in other studies, that perhaps antidepressants in a lower dose and with a shorter length of prescriptions are effective for a number of patients with depression in general practice (21–23).

The strength of this study is the long follow-up period of 10 years and the possibility of relating treatment to outcome. However, a causal relationship cannot be established from our results. Another limitation of this study is that the data on the charts concerning length and doses of the prescriptions for antidepressants were not complete. Even though bias in information recording and retrieval was unlikely, it is still possible and care is required in drawing conclusions from these data. The fact that the results in our study only concern prescriptions with tricyclics could lead to the comment that the value of our conclusions are limited and the results do not reflect the progress made with selective serotonin reuptake inhibitors (SSRIs). There were two obvious reasons for the fact that our results only concern tricyclics: the study period (first depressive episode before 1985) and the fact that in the Dutch guidelines for depression published in 1994, tricyclics are still the antidepressants of first choice (15). Although SSRIs are used more and more frequently, a number of patients still receive prescriptions for tricyclics and for this group our conclusions are still valid. The questions we raised about appropriate treatment for depression in general practice will have to be answered for treatment with SSRIs as well. Lack of knowledge about the severity of the depression, comorbidity and of other confounders is a limitation of this study that should also be mentioned. Finally, an aspect that was not taken into account in most studies, including ours, but that should be remembered when discussing treatment related to outcome, is the fact that prescribing medication does not necessarily mean that patients really use these drugs. A study (24) on primary non-compliance with prescribed medication in primary care shows that the percentage of non-redemption of prescriptions is high (14.5%). This should be kept in mind when discussing the results of treatment and should be considered in future studies. Prospective studies concerning long-term course and outcome of depression in general practice, relating treatment to outcome and taking into account other confounders are necessary so that sounder recommendations for treatment of depression in general practice can be made.

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