Evaluation of patient outcomes in an area where prescribing of anticholinergic antidepressants was influenced by academic detailing

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Abstract
Objective: To evaluate, on a patient level, the effect of a "physician-level intervention" that successfully reduced the incidence of anticholinergic antidepressant prescribing.
Design: Cross-sectional surveys with questionnaires sent before and after intervention.
Setting: Additional study in an RCT to reduce the prescribing of highly anticholinergic antidepresssants in the elderly in the South Holland Islands.
Participants: Elderly patients (age 60-95 years) who used antidepressants in 1995 and 1996 in our research area according to a health insurance prescription database.
Main outcome measures: Prevalence of adverse events related to antidepressant use, severity of depression and quality of life were compared in users living in the intervention and control areas.
Results: Prior to our intervention we sent 2,359 questionnaires of which we could use 827 (35%) for analysis. At baseline, there were no statistically significant differences between the intervention and control areas. After the intervention 3,375 questionnaires were sent, of which 939 (28%) could be used. The occurrence of "dry mouth" and "coughing" and the "amount of pain" were lower in the intervention area compared to the control area ($p < 0.05$).
Conclusion: We found no indications that adverse events, severity of depression or quality of life were changed in an unfavourable direction, when comparing patients inside and outside the intervention area.

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Introduction

Most programmes that intend to rationalise prescribing evaluate their effectiveness by looking at prescription volumes. There is increasing attention on the economic evaluation of treatment strategies and interventions to rationalise prescribing [1–3]. The need to include patient outcome measures has been mentioned before, but is not often practised [4–6]. Recently, the results of a randomised controlled trial were published which compared the effect of different outreach strategies on the prescribing of antidepressants in primary care [7]. The prescribing of highly anticholinergic antidepressants for the elderly was reduced. During the intervention, the prescribing of anticholinergic versus non-anticholinergic antidepressants remained a topical issue [8–10]. On the one hand, there was a consensus report published on behalf of the Dutch association of General Practitioners ("NHG-standaard") [11] in which tricyclic antidepressants were presented as first choice drugs for the treatment of depression. Conversely, there was a consensus report which was prepared by consultants of different disciplines (psychiatrists, geriatricians et cetera) ("CBO-consensus report") [12] in which serotonin re-uptake inhibitors were presented as first choice compounds. Both types of antidepressants produce different side-effects. Given the controversy on the subject, and the lack of information on how the elderly react to these drugs [13], we decided to collect data on patient outcomes as well as prescription data. This article reports on the effects on a patient level of an intervention to reduce the prescribing of highly anticholinergic antidepressants in the elderly.

Materials and methods

Setting

The project was conducted in a research area that is part of the service area of the health insurance company "OZ zorgverzekeringen" in the southwest of the Netherlands. Approximately 240,000 people (60% of the population in the research area) were insured through "OZ zorgverzekeringen" of whom 50,000 were 60 years of age or older.

Design

To measure patient outcomes, we performed two cross-sectional surveys. Questionnaires were sent to elderly antidepressant users living in the area where we performed the randomised controlled trial [14], prior to and after the performance of the trial (see box). The questionnaire was sent on only one occasion at each mailing point. Three weeks after we sent the first questionnaire, we sent a reminder letter to encourage people who had not filled in the questionnaire to still do so. This gave virtually no extra responses (seven extra). Therefore we did not send a reminder letter after the second questionnaire.

Short details of the academic detailing trial on the prescribing of antidepressants are presented in the box

Participants

During the first survey (prior to the intervention study) all elderly people (60–95 years of age) in the research area who had used an antidepressant during the year prior to the survey (1995) were invited to fill in the questionnaire. During the second survey (after the intervention) all elderly who were selected for the first survey were again asked to participate. The second survey population also included all elderly who had newly started an antidepressant during the year of the intervention study, and thus had not been asked to participate during the first survey. Thus, the

Box 1
The participants in the study were 190 general practitioners and 37 pharmacists organised in 21 Peer Review Groups in an area covering approximately 50,000 elderly between 60 and 95 years old. The 21 Peer Review Groups were equally divided into an individual intervention arm, in a group visit intervention arm and a control arm (no visits). Our intervention followed theories and experiences usually referred to as academic detailing. The focus of the study was the reduction of highly anticholinergic antidepressants in the elderly. The outcome of the study was that in both intervention arms the prescribing of highly anticholinergic antidepressants (number of new prescriptions) was reduced (26% and 45%, respectively) while the incidence of prescribing of less anticholinergic antidepressants was increased (40% and 29%, respectively) compared to the control arm. The first questionnaire was sent out in March, immediately prior to the intervention. The second questionnaire was distributed exactly one year later.

elderly who started an antidepressant in 1996 only received the second questionnaire.

Questionnaire
The questionnaire contained questions about general patient characteristics (sex, age, marital status etc.), medical state (including a list of complaints and known side-effects, related to depression and both types of antidepressants), medical consumption, and the COOP-WONCA Health Charts (a simple visual scale for quality of life validated for use in primary care) [15–19]. The complete questionnaire was pretested on elderly from another area.

Procedures
Patients who had at least one prescription of an antidepressant were identified using the reimbursement data that pharmacists send to the health insurance company. These databases do not include information on diagnosis or indication of use. Patients who had at least one prescription of an antidepressant (defined as a drug with ATC code N06A or N06CA01) reimbursed in 1995 were selected [20]. Questionnaires were sent to patients by the health insurance company with postage-paid return envelopes.

The letter stated that the aim of the study was to evaluate drug use in elderly. We emphasised that limited information was collected from experimental drug trials and the importance of surveys on the effects of drugs in the elderly in daily practice. The use of antidepressants and the prescribing intervention study were not specifically mentioned in the letter.

Analysis
Our intervention (to reduce the prescribing of highly anticholinergic antidepressants in the elderly) was directed at prescribers and pharmacists. This report focuses on patient outcome (adverse events, symptoms related to depression and general well-being) in the areas in which the intervention was performed versus the control area. We decided to perform an intention-to-treat analysis. Thus, not only the patients of the most responsive physicians were included in the analysis but all patients of all physicians in the intervention areas and control area.

The reduction of the prescribing of highly anticholinergic antidepressants, as intended by our intervention, could occur in two ways. Firstly, the reduction could occur in patients newly prescribed an antidepressant. Secondly, in patients already using highly anticholinergic antidepressants, a switch to less anticholinergic antidepressants could take place. So far, we have only evaluated the effect of our intervention on the incidence of initiating highly and less anticholinergic antidepressants and not the effect on switching of antidepressants [14]. The latter is expected to occur less or later than the effect on new starts of antidepressants.
In the light of this, and the fact that no baseline questionnaires were taken from the patients newly started on an antidepressant, we decided not to compare the change in patient outcomes (post-intervention minus baseline outcomes). We compared post-intervention patient outcomes separately for all patients in the intervention areas versus all patients in the control area and for patients newly started on an antidepressant in the intervention areas versus patients newly started on an antidepressant in the control area.

Descriptive statistics of the baseline questionnaire are presented in order to be able to evaluate whether possible post-intervention differences were already present prior to the intervention.

Dichotomous patient outcomes (e.g. the presence of adverse events) were evaluated by logistic regression. Effect estimates were adjusted for age and sex differences in the intervention versus the control groups.

Ordinal patient outcomes (scores of COOP/WONCA) were analysed by linear regression (adjusted for age and sex differences) and expressed as mean difference and 95% confidence intervals.

Results

Response
In our first survey in 1996, prior to the intervention study, we sent questionnaires to 2,359 users of antidepressants in 1995 of which 945 were returned (see table 1). Fifty-eight of these questionnaires had too many missing values and 60 were answered by persons not asked to participate (generally the spouse of the selected patient), leaving 827 (35% of 2,359) questionnaires that could be used for our data analysis.

For the second survey in March 1997, after completion of our intervention study, the patients that

Table 1 *Response rates for questionnaires*

	Pre-intervention	*Post-intervention (new starters)*
Sent	2,359	3,375 (1,016)
Returned	945	1,033 (314)
Analysed	827	939 (296)

were sent a questionnaire during the first survey (n = 2,359) and the patients that used an antidepressant in 1996 and not in 1995 (new starters of an antidepressant; n = 1,016) were sent a questionnaire (in total n = 3,375). Of these groups the response rates were 719 (30% of 2,359) and 314 (31% of 1016), respectively. For our data analysis for the post-intervention questionnaire we were able to use 939 (28% of 3,375) questionnaires. Reasons for the reduction of the 1,033 (n =719 plus n = 314) questionnaires to 939 were major omissions in the answers to the questionnaire (n = 64) and answering of the questionnaire by a family member (n = 30). To focus on the effect of the intervention on those who had commenced antidepressant therapy after the visits had actually taken place, only 101 (9.9% of 1016) questionnaires were used. The reduction of the 314 questionnaires to 101 was caused by a family member answering the questionnaire (n = 18) and the start of the antidepressant prior to the date on which the patient's general practitioner was visited for the intervention meeting (aimed to change the prescribing of antidepressants) (n = 195). In the control area patients, the mean date of the visit to general practitioners in the intervention areas was calculated and used. This was needed to create a post-intervention period in the control area.

Tables 2 and 3 show the number of adverse events and complaints related to depression and antidepressant use reported by the (former) users of antidepressants in the research area, before and after the intervention. Table 4 relates to the new starters of antidepressants in the research area. Prior to the intervention there were no statistically significant differences in baseline characteristics. After the intervention only "dry mouth", "coughing" and "amount of pain" were reported to be significantly less ($p < 0.05$) in the intervention area, as compared to the control area (Table 3, 4, and 5, respectively). Other patient outcome measures, including overall well-being and quality of life questions from the COOP/WONCA charts post-intervention, showed no significant differences between the control and intervention area (Table 5).

Discussion

Due to the low patient response rate, caution must be used in interpreting our study results.

When we assume that selection bias is absent or low, this study demonstrated that in an area in which the prescribing of antidepressants in the elderly was intentionally changed, the well-being of patients who used or recently had used antidepressants was comparable to similar patients in an area in which this prescribing intervention was not executed. Except for fewer complaints of dry mouth, coughing and amount of pain in patients in areas in which the intervention took place compared to the control area, the

Table 2 *Baseline characteristics of patients living in an area in which a randomised controlled trial was performed to reduce the prescribing of highly anticholinergic antidepressants**

N = 827 *number (female)* *Complaints*	*Control area* *296 (204)* *n (%)*	*Intervention area* *531 (368)* *n (%)*
Coughing	81 (27.4)	149 (28.1)
Dry mouth	129 (43.6)	211 (39.7)
Falling more often	19 (6.4)	44 (8.3)
Blurred vision	74 (25.0)	128 (24.1)
Nausea	27 (9.1)	70 (13.2)
Impaired concentration	62 (20.9)	111 (20.9)
Dyspepsia	70 (23.6)	111 (20.9)
Palpitations	43 (14.5)	93 (17.5)
Sleepiness	64 (21.6)	96 (18.1)
Memory problems	85 (28.7)	141 (26.6)
Sad feelings	101 (34.1)	176 (33.1)
Constipation	36 (12.2)	66 (12.4)
Diarrhoea	17 (5.7)	39 (7.3)
Feeling numb	36 (12.2)	57 (10.7)
Irritable	35 (11.8)	55 (10.4)
Anxiety	55 (18.6)	103 (19.4)
Unstable gait	99 (33.4)	180 (33.9)
Reaction time increased	51 (17.2)	83 (15.6)
Dizziness	69 (23.3)	121 (22.8)
Difficulties falling asleep	124 (41.9)	224 (42.2)
Eczema	20 (6.8)	61 (11.5)
Severe pain	91 (30.7)	155 (29.2)

* No statistically significant differences (logistic regression).

Table 3 *Outcome of patients in an area in which the prescribing of highly anticholinergic antidepressants was successfully reduced (intervention) compared to a control area (control)*

N = 939 *number (female)* *Complaints*	*Control* *337 (230)* *n (%)*	*Intervention* *602 (426)* *n (%)*
Coughing	93 (27.6)	152 (25.2)
Dry mouth *	146 (43.3)	220 (36.5)
Falling more often	20 (5.9)	44 (7.3)
Blurred vision	75 (22.3)	133 (22.1)
Nausea	45 (13.4)	62 (10.3)
Impaired concentration	56 (16.6)	122 (20.3)
Dyspepsia	66 (19.6)	105 (17.4)
Palpitations	61 (18.1)	115 (19.1)
Sleepiness	68 (20.2)	119 (19.8)
Memory problems	97 (28.8)	165 (27.4)
Sad feelings	101 (30.0)	203 (33.7)
Constipation	40 (11.9)	64 (10.6)
Diarrhoea	28 (8.3)	43 (7.1)
Feeling numb	48 (14.2)	68 (11.3)
Irritable	40 (11.9)	79 (13.1)
Anxiety	66 (19.6)	127 (21.1)
Unstable gait	114 (33.8)	203 (33.7)
Reaction time increased	62 (18.4)	96 (15.9)
Dizziness	68 (20.2)	130 (21.6)
Difficulties falling asleep	122 (36.2)	252 (41.9)
Eczema	30 (8.9)	66 (11.0)
Severe pain	111 (32.9)	168 (27.9)

* $p = 0.041$.

Table 4 *Outcome of patients who newly started an antidepressant in an area in which the prescribing of highly anticholinergic antidepressants was successfully reduced (intervention) compared to a control area (control)*

N = 101	*Control*	*Intervention*
number (female)	*35 (23)*	*66 (43)*
Complaints	*n (%)*	*n (%)*
Coughing *	13 (37.1)	11 (16.7)
Dry mouth	12 (34.3)	17 (25.8)
Falling more often	1 (2.9)	6 (9.1)
Blurred vision	12 (34.3)	18 (27.3)
Nausea	3 (8.6)	6 (9.1)
Impaired concentration	5 (14.3)	13 (19.7)
Dyspepsia	3 (8.6)	8 (12.1)
Palpitations	5 (14.3)	15 (22.7)
Sleepiness	11 (31.4)	17 (25.8)
Memory problems	9 (25.7)	21 (31.8)
Sad feelings	10 (28.6)	22 (33.3)
Constipation	5 (14.3)	6 (9.1)
Diarrhoea	3 (8.6)	9 (13.6)
Feeling numb	5 (14.3)	6 (9.1)
Irritable	5 (14.3)	10 (15.2)
Anxiety	10 (28.6)	14 (21.2)
Unstable gait	12 (34.3)	19 (28.8)
Reaction time increased	6 (17.1)	9 (13.6)
Dizziness	6 (17.1)	18 (27.3)
Difficulties falling asleep	13 (37.1)	24 (36.4)
Eczema	5 (14.3)	8 (12.1)
Severe pain	11 (31.4)	17 (25.8)

* $p = 0.024$.

occurrence of adverse events, complaints related to depression, the seriousness of depressed feelings and the scores of different domains of quality of life were comparable. This may be due to the fact that both types of antidepressants have differing side-effects.

Response rates in both surveys were low (28–35%). These rates were lower than expected when compared with similar surveys. In retrospect, there may be several reasons for low response besides the general tendency of more and more people to refuse to participate in questionnaire surveys. First, the questionnaire was relatively long, especially for an elderly group (60–95 years in our surveys). It is possible that the explanation of the total study (including our intervention study) and more information about other projects by our institute would have increased response rates; however, this information might also have influenced patient responses (information bias).

Our comparison of responders and non-responders for age, sex and antidepressant use revealed no important differences for several general patient characteristics (data not shown). Although this may reflect only minor selection bias in our study results, this interpretation is speculative. Furthermore, the relative small sample size and the uncertainty of confounding bias (not all prognostic factors of different outcomes were available) further limits the interpretation of the study results.

Although our statistically significant differences can be due to a type I error (we performed 90 statistical comparisons), an interesting finding was than in the intervention areas the occurrence of dry mouth was lower that in the control area. This finding was in accordance with the reduction in the prescribing of highly anticholinergic antidepressants in the intervention areas. This finding was statistically significant when all patients were analysed together and not when the analysis was restricted to the patients newly started on an antidepressant, although the same ten-

Table 5 *COOP/WONCA prior to and after the performance of a randomised clinical trial in which the prescribing of highly anticholinergic antidepressants was successfully reduced in the intervention area (intervention) compared to the control area (control)*

	Baseline (all patients)		*Post-intervention (all patients)*		*Post-intervention (new starters)*	
	Intervent.	*Control*	*Intervent.*	*Control*	*Intervent.*	*Control*
N	*531*	*296*	*602*	*337*	*66*	*35*
COOP/ WONCA item #	Mean (std dev)	Mean (std dev)	Mean (std dev)	Mean (std dev)	Mean (std dev)	Mean (std dev)
Physical fitness	3.79 (1.06)	3.87 (0.94)	3.79 (1.00)	3.88 (0.98)	3.64 (0.98)	3.73 (0.98)
Change in health lately	3.12 (0.82)	3.17 (0.81)	3.11 (0.77)	3.15 (0.75)	3.02 (0.84)	3.18 (0.67)
Overall health lately	3.68 (0.74)	3.68 (0.70)	3.64 (0.71)	3.74 (0.71)	3.60 (0.76)	3.94 (0.50)
Feelings of depression	2.62 (1.22)	2.73 (1.15)	2.68 (1.21)	2.64 (1.14)	2.71 (1.26)	2.66 (1.21)
Daily activities	3.00 (1.24)	3.02 (1.22)	2.98 (1.21)	3.01 (1.25)	2.89 (1.32)	3.03 (1.05)
Social activities	2.49 (1.41)	2.46 (1.34)	2.45 (1.36)	2.41 (1.33)	2.40 (1.40)	2.42 (1.30)
Amount of pain	2.85 (1.19)	2.89 (1.17)	2.83 (1.17)	3.00 (1.16)*	2.73 (1.12)	3.18 (1.16)

* Mean difference –0.178 (95%CI –0.34 to –0.02) $p = 0.028$.
\# The COOP/WONCA charts use an ordinal five-point response scale illustrated with a simple drawing from 1 (no impairment) to 5 (severe impairment).

dency (lower occurrence of dry mouth) was observed.

Our study design and the way we analysed the data show the difficulties one encounters when patient outcomes are to be evaluated in a study in which the intervention was directed at the prescribing of general practitioners. Decisions have to be made concerning intention-to-treat versus a per protocol analysis and whether or not to correct for baseline findings. Furthermore evaluation of only patients using antidepressants at baseline and post-intervention (chronic users) or also including patients that stopped using antidepressants prior to the baseline measurement. Finally, evaluating post-intervention data of only patients that newly started an antidepressant during the intervention period versus evaluation of all patients that used at baseline or had recent past use of antidepressants et cetera.

Prior to the start of the study we thought the most relevant patient data would be baseline and post-intervention data of patients that newly started an antidepressant during the intervention period. However, a simple and practical solution for the collection of the baseline questionnaire was not possible, especially in the control area in which the general practitioners and pharmacists were not contacted. We think that our evaluation of pre- and post-intervention data, which demonstrates that patient outcome was not changed in an unfavourable direction, adds valuable information to the effect of outreach programmes at a patient level.

Conclusion

This study demonstrates some of the problems that have to be overcome when including patient outcome measures in an outreach programme on quality of prescribing in a primary care setting. Although this study has methodological limitations and a low response rate, we have no indications that well-being, adverse events, severity of depressive feelings and quality of life were changed in an unfavourable direction.

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