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Consequences of a benzodiazepine discontinuation programme in family practice on psychotropic medication prescription to the participants

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Gorgels WJMJ, Oude Voshaar RC, Mol AJJ, van de Lisdonk EH, Mulder J, van den Hoogen H, van Balkom AJLM, Breteler MHM and Zitman FG. Consequences of a benzodiazepine discontinuation programme in family practice on psychotropic medication prescription to the participants. *Family Practice* 2007; **24**: 504–510.

Background. Whether long-term benzodiazepine users who participate in a family practice-based benzodiazepine discontinuation programme substitute benzodiazepines by other psychotropics is not clear.

Objective. To evaluate the impact of a benzodiazepine discontinuation programme on non-benzodiazepine psychotropic prescription in family practice.

Methods. In family practices in the Netherlands, 2425 long-term benzodiazepine users participated in a two-step benzodiazepine discontinuation programme. The programme started with a discontinuation letter (Step 1). Subjects unable to stop ($N = 1707$) were offered participation in Step 2, a three-group randomized trial with a taper procedure with group psychotherapy, a taper without psychotherapy and usual care. Only 156 subjects agreed to participate. The comparison group consisted of 1821 long-term users from family practices not participating in the programme. The main outcome was the change in prescription of non-benzodiazepine psychotropic medication from baseline (3 months before the start of the programme) till 21 months after the start of the programme. Four logistic regression models were performed concerning antidepressant prescription in the follow-up.

Results. Only antidepressants were prescribed in relevant numbers. The prescription of antidepressants was not related to the programme. (P -value of experimental versus control group varied between 0.18 and 0.85 in the four models). The most important predictor of antidepressant prescription in follow-up was baseline antidepressant prescription [odds ratio (OR): 67.2; 95% confidence interval (95% CI): 49.8–90.7]. Subjects, of whom the prescription of benzodiazepines had been discontinued completely, had been prescribed less antidepressants (OR: 0.8; 95% CI: 0.6–1.0).

Conclusion. An effective benzodiazepine reduction programme was not accompanied by a substitute use of other psychotropics.

Keywords. Family medicine, mental health, prescribing, substance misuse.

Introduction

Benzodiazepines are effective drugs in the short-term treatment of insomnia and anxiety.¹ The clinical efficacy

of long-term benzodiazepine use, however, has not been established satisfactorily.² Above that, long-term benzodiazepine use is associated with benzodiazepine dependence, increase of fall-risk and impairment of cognitive

Received 14 December 2006; Revised 12 April 2007; Accepted 17 June 2007.

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function.^{1,2} Therefore, interventions to decrease long-term use in the large population of users in family practice are sensible. Several benzodiazepine discontinuation programmes have shown to be successful in decreasing the number of long-term benzodiazepine users.³⁻⁹ Up till now, however, it is not clear whether benzodiazepine discontinuation programmes lead to changes in the prescription of other psychotropic medications. Data of psychotropic use after benzodiazepine discontinuation are scarce. Evaluations of the New York State triplicate prescription regulation suggested a possible increase of prescription of other, more harmful, psychotropics when benzodiazepine prescription decreased.¹⁰ Initiation of other psychotropics after benzodiazepine discontinuation may be expected for several reasons such as psychiatric co-morbidity, patient pressure and treatment of benzodiazepine withdrawal symptoms.

As these agents may carry comparable side effects as benzodiazepines, like increased fall-risk,¹¹ it is important to know whether discontinuation of benzodiazepines leads to changes in prescription of these other psychotropics. This may provide a more adequate risk-benefit estimation of benzodiazepine discontinuation programmes.

Recently, the current authors carried out a stepwise programme to reduce long-term benzodiazepine use in a large family practice-based population (the Benzoredux programme). An intention to treat analysis was performed comparing the effectiveness of the benzodiazepine discontinuation programme in long-term benzodiazepine users in family practices, to which the programme was offered, with usual care control practices. Both intervention steps, a discontinuation letter (Step 1) and a subsequent, family practitioner guided, taper scheme (Step 2), were effective in discontinuation of benzodiazepine use, although additional group psychotherapy (in Step 2) did not improve this outcome.^{5,8} Factors associated with benzodiazepine abstinence in the programme were as follows: amount and duration of initial benzodiazepine use, gender (Step 1) and benzodiazepine dependence severity, as measured by the Benzodiazepine Dependence Self-Report Questionnaire, amount of initial benzodiazepine use and alcohol use (Step 2).^{8,12} Relapse in benzodiazepine use (meaning restart of family practitioner prescription) was related to initial use of multiple benzodiazepines, use of antidepressants and initial benzodiazepine type.¹²

In the present study, we evaluated the consequences of the benzodiazepine discontinuation programme on the prescription of non-benzodiazepine psychotropics to the participants of the Benzoredux programme.

Materials and methods

Design

The Benzoredux programme was a prospective, controlled, stepped-care and intervention programme in

family practice, aimed to reduce long-term benzodiazepine use.^{5,8} The study was carried out between August 1998 and December 2001. The intervention consisted of a discontinuation letter, followed by an evaluation consultation after 3 months. At this consultation, persistent users were asked to participate in step two: a three-group Randomized Controlled Trial with a taper scheme by the family practitioner, with (group A) or without group psychotherapy (group B) and a usual care control condition (group C). (The usual care controls did not receive any help with benzodiazepine reduction and were informed about the randomization result by letter).

Study population

Subjects were regarded as long-term benzodiazepine users when they fulfilled two conditions: (i) they had received prescriptions for benzodiazepines for more than 3 months and (ii) they had used an amount of benzodiazepines sufficient for 60 days of use according to the family practitioner prescription rules within the last 3 months before inclusion in the programme. Baseline values were obtained of 2425 subjects from 27 family practices.⁵ Seven hundred and eighteen subjects, of these 2425, were excluded for the intervention due to exclusion criteria formulated by the researchers' ($N = 467$) and family practitioners considerations [$N = 251$ (=10%; the range per practice was 2–28% of all includable subjects)] (Fig. 1). The discontinuation letter was sent to the remaining 1707 subjects, of which subsequently 156 (9%) were motivated for the second intervention step after they had failed to discontinue due to the discontinuation letter alone.⁸

From a National Information Network of family practices (LINH), at the end of the 21 months follow-up, baseline and follow-up data were obtained from 1821 long-term benzodiazepine users from 16 regular care control practices (Fig. 1). The LINH network is a valid sample of all Dutch family practices.¹³ We included all practices that used the same electronic medical dossier (EMD) as in the experimental group and with a complete registration period covering the study period up to and including 1 year before the start of the study. The practices corresponded on average with the experimental practices regarding location and organizational type.⁵

Measurements

All practices had an EMD at the minimum for basic patient administration and drug prescription. In total, four different EMD systems were used by the participating practices. All prescription data of study participants were automatically extracted from the EMD in the practice anonymously. An intervention starting date was assigned to each subject being the date of mailing the discontinuation letter. The subjects in the experimental practices that were excluded for the

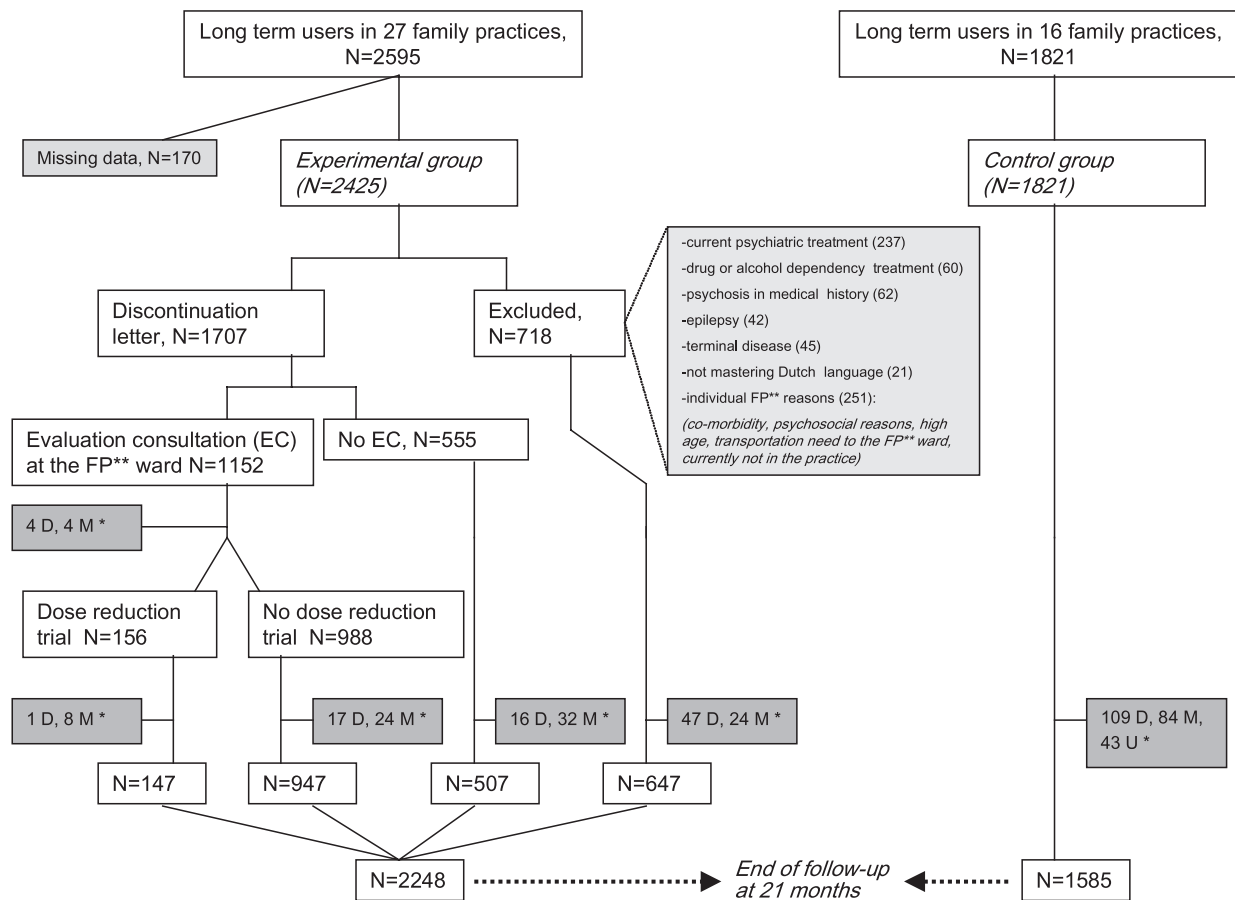


FIGURE 1 Study profile. *Lost to follow-up abbreviations: D = death, M = moved from the FP practice, U = reason unknown. **FP = family practitioner

discontinuation letter and all subjects from the control group received an equivalent time point as intervention starting date. The study period was divided into 3-month periods where each period in fact consisted of 91 days exactly. By this, the baseline period was defined as the 3-month time period prior to the intervention starting date and the 21 months follow-up after the baseline period was divided into seven periods of 3 months.

The following data and definitions were used.

1. Basic characteristics: gender, age and health insurance status [private or National Health Service].
2. Baseline benzodiazepine use: the amount of benzodiazepine use in the baseline period was expressed as the average prescribed daily dose (PDD), using benzodiazepine equivalence rules by Zitman *et al.*⁹ (for instance, a PDD of 1 is equivalent with prescription for average daily use of 10 mg diazepam).
3. Definition of a prescription: a prescription of a psychotropic agent in a 3-month period was defined as any prescript of the agent issued by the family practitioner within the concerning 3-month time period. With the psychotropic prescriptions two variables

were constructed: (i) the total number of prescriptions in the concerning 3-month period and (ii) a dichotomous variable indicating either none (0) or at least one prescription (1) of the specific agent in the concerning 3-month period (prescription prevalence).

4. Definition of short-term benzodiazepine discontinuation: the discontinuation letter suggested discontinuation of benzodiazepine use by gradually bringing down the use. We therefore recorded discontinuation after a period of 3 months and not immediately after the sending of the letter. Short-term discontinuation was thus defined as the absence of any benzodiazepine prescription in the second 3-month period (i.e. four up to and including 6 months) after mailing the letter. Persistent users were defined as subjects receiving at least one benzodiazepine prescription in the second 3-month period after the mailing of the letter.

Analysis

We first performed a descriptive analysis of the course of non-benzodiazepine psychotropic medications in the experimental group and the control group. The

following subgroups of psychotropic agents (anatomical therapeutic codes) were defined: antidepressants (N06A), antipsychotics (N05A), non-benzodiazepine hypnotics [i.e. zolpidem (N05CG01) and zopiclone (N05CF01)], barbiturates (N05CA), anti-epileptics (N03), hydroxyzine (N05BB01), meprobamate (N05BC01) and buspirone (N05BE01).¹⁴ It appeared that only antidepressants were prescribed in relevant quantities (see Results). Therefore, the differences in mean number of prescriptions of antidepressants per period were statistically tested between the experimental group and the control group. The analysis was restricted to 21-month study completers (experimental group: $N = 2248$ and control group: $N = 1585$). Statistical comparisons within and between groups were performed with chi-square tests and t -tests, at a two-sided significance level of 0.05.

Logistic regression was performed to study the influence of several variables on the prescription of antidepressants in the follow-up. We used the following independent variables: study group (experimental/control), short-term discontinuation of benzodiazepine prescription (yes/no), prescription of an antidepressant in the baseline period (yes/no), baseline benzodiazepine prescription (PDD, continuous), gender, age (three categories: <50 , 50 to <75 , ≥ 75 years) and health insurance status. These variables were entered in four explanatory multivariate models with the following dependent variables: (i) Model A: prescription of an antidepressant in every 3-month period in the follow-up (yes/no); (ii) Model B: no prescription of an antidepressant in any 3-month period in the follow-up (yes/no); (iii) Model C: at least one prescription of an antidepressant in at least one 3-month period in the follow-up (yes/no) and (iv) Model D: at least one prescription of an antidepressant in each of two consecutive 3-month periods in the follow-up (yes/no). (This last model was chosen as a minimal treatment period of a depression is considered to be 6 months)

Results

Table 1 shows baseline characteristics of the two study groups. No statistically significant differences were observed between the experimental and the control group, except for baseline prescription of anti-epileptics, which was higher in the experimental group ($P = 0.002$).

No statistical differences were observed in the baseline level of antidepressant prescription or in the follow-up period between the experimental and control group (Table 2).

With the dichotomous variable 'prescription prevalence' per period, we studied patterns of use during the follow-up. Those who used antidepressants in the baseline period had a high chance of using them in all

TABLE 1 Baseline characteristics of study subjects

	Control ($N = 1585$)	Experimental ($N = 2248$)
Number of practices	16	27
Age (years) [mean (SD)]	63.9 (15.2)	61.8 (14.7)
Gender (% female)	73.1	71.0
Health insurance (% NHS)	80.5	80.0
Baseline benzodiazepine prescription [average daily PDD (SD)]	0.8 (0.8)	0.9 (1.0)
Baseline prescription ^a		
Overall (all medications)	8.2 (6.8)	9.0 (9.8)
Overall, except benzodiazepines	5.39 (5.93)	5.95 (8.38)
Benzodiazepines	2.81 (2.03)	3.07 (2.45)
Anti-depressants	0.48 (1.21)	0.52 (1.26)
Non-benzodiazepine hypnotics ^b	0.04 (0.38)	0.04 (0.34)
Anti-psychotics	0.17 (0.85)	0.13 (0.75)
Anti-epileptics	0.05 (0.35)	0.12 (0.89)
Hydroxyzine	0.002	0.004
Buspirone	0.002	0.002
Meprobamate	0	0.001
Barbiturates	0.001	0.003

NHS = National Health Service.

^aAverage number of prescriptions (SD) per subject in 3-month baseline period.

^bZolpidem (N05CG01) + zopiclone (N05CF01).

subsequent seven follow-up periods [experimental group: $N = 240$ (53%) of a total of 452; control group: $N = 167$ (52%) of a total of 319]. Furthermore, those who did not have a prescription of an antidepressant at baseline had a high chance of remaining abstinent of antidepressant prescription during all seven follow-up periods [experimental group: $N = 1535$ (85%) of a total of 1796; control group: $N = 1063$ (84%) of a total of 1266].

The number of subjects that had a change in antidepressant prescription status, compared with baseline period status, in at least one follow-up period was comparable for the experimental and control groups [$N = 473$ (21%) in the experimental group and $N = 355$ (22%) in the control group], ($P = 0.32$). The patterns of prevalences of prescription in the periods in these subjects appeared to be very diverse and not systematic.

Table 3 shows the results of the logistic regression analysis in four explanatory models for antidepressant prescription in the follow-up. Study group was no predictor of antidepressant prescription in any model. In all models, baseline antidepressant prescription status was the strongest predictor. Furthermore, in all models, discontinuation of benzodiazepine prescription at short term was statistically related to receiving less antidepressant prescriptions. Also, age was significantly related in all four models, showing that a higher age was related with less antidepressant prescription.

In both the experimental and the control groups, the number of prescriptions of non-benzodiazepine

hypnotics [zolpidem (N05CG01) and zopiclon (N05CF01)] was low.

No significant changes in prescription were observed in the follow-up (Table 2).

Prescriptions of meprobamaat (N05BC01), buspirone (N05BE01), hydroxyzine (N05BB01) and barbiturates (N05CA) were not separately analysed due to very low prevalences. No new users of these substances were observed.

The prevalence of use of anti-psychotics (N05A) and anti-epileptics (N03) was low (Table 1). No significant changes were observed in the number of prescriptions of these classes during the follow-up for the experimental and control groups.

Discussion

The main finding of this study was that an effective benzodiazepine reduction programme in primary care did not increase the prescription of other psychotropic medication. Participation in this programme did not alter the group prevalence of antidepressant use.

Apart from the follow-up of the New York State triplicate prescription programme (TPP), in the 90s, data on consequences of benzodiazepine discontinuation programmes are scarce. In the TPP programme, complication of benzodiazepine prescription by governmental rules might have increased prescriptions of other psychotropics, like meprobamaat, hydroxyzine

TABLE 2 Mean number of prescriptions (SD) per subject per 3 months of antidepressants (ATC: N06A) and non-benzodiazepine hypnotics [zolpidem (ATC: N05CG01) + zopiclone (ATC: N05CF01)] in the experimental group (N = 2248) and control group (N = 1585)

Category		Baseline		3-month periods in follow-up					
		-3 to 0 months	0-3 months	4-6 months	7-9 months	10-12 months	13-15 months	16-18 months	19-21 months
Antidepressants	Experimental	0.52 (1.26)	0.54 (1.35)	0.53 (1.33)	0.51 (1.28)	0.52 (1.28)	0.53 (1.29)	0.54 (1.33)	0.52 (1.28)
	Control	0.48 (1.21)	0.49 (1.25)	0.45 (1.14)	0.45 (1.13)	0.46 (1.12)	0.48 (1.14)	0.51 (1.20)	0.48 (1.12)
Non-benzodiazepine hypnotics	Experimental	0.04 (0.34)	0.04 (0.34)	0.04 (0.33)	0.04 (0.42)	0.03 (0.36)	0.03 (0.31)	0.03 (0.31)	0.03 (0.35)
	Control	0.04 (0.38)	0.04 (0.37)	0.04 (0.39)	0.04 (0.35)	0.04 (0.35)	0.04 (0.35)	0.05 (0.42)	0.04 (0.37)

ATC, anatomical therapeutical code

TABLE 3 Adjusted ORs (95% CIs) of four multivariate logistic regression models in all subjects (N = 3833) explaining antidepressant use in the follow-up

Dependent variable	Model A			Model B			Model C			Model D		
	OR	(95% CI)	P-value	OR	(95% CI)	P-value	OR	(95% CI)	P-value	OR	(95% CI)	P-value
Study group (experimental = 1, control = 0)	1.0	(0.8-1.4)	0.79	1.1	(0.9-1.4)	0.18	0.9	(0.7-1.1)	0.18	1.0	(0.8-1.2)	0.85
Benzodiazepine prescription discontinuation (yes/no)	0.7	(0.5-1.0)	0.04	1.3	(1.0-1.7)	0.04	0.8	(0.6-1.0)	0.04	0.7	(0.5-0.9)	0.01
Baseline prescription of AD (yes/no)	98.7	(67.0-145.2)	<0.001	0.02	(0.01-0.02)	<0.001	67.2	(49.8-90.7)	<0.001	50.8	(39.9-64.6)	<0.001
Baseline prescription of benzodiazepine (PDD)	1.0	(0.9-1.1)	0.99	1.0	(0.9-1.1)	0.83	1.0	(0.9-1.1)	0.83	1.0	(0.9-1.1)	0.97
Gender (female = 1, male = 0)	1.0	(0.7-1.4)	0.98	1.1	(0.9-1.4)	0.26	0.9	(0.7-1.1)	0.26	0.8	(0.6-1.0)	0.11
Age (years)												
<50 (reference)	—			—			—			—		
50 to <75	0.9	(0.6-1.2)	0.34	1.7	(1.3-2.1)	<0.001	0.6	(0.5-0.7)	<0.001	0.6	(0.5-0.7)	<0.001
≥75	0.5	(0.3-0.8)	0.001	2.2	(1.7-3.0)	<0.001	0.4	(0.3-0.6)	<0.001	0.4	(0.3-0.5)	<0.001
Health insurance (private = 1, NHS = 0)	0.8	(0.6-1.2)	0.23	1.0	(0.8-1.3)	0.94	1.0	(0.8-1.3)	0.94	1.1	(0.9-1.5)	0.37

AD, antidepressant agent; NHS, National Health Service.

and barbiturates.¹⁰ There was hardly any prescription of these substances in our study groups which indicates that prescription of these substances in this primary care group of long-term benzodiazepine users has been virtually abandoned. Furthermore, the TPP studies were performed in a different time span in which for instance many of the modern antidepressant agents were not available. Moreover, comparison with the TPP programme fails as their intervention was mainly directed towards the prescriber and the present programme was mainly directed towards the user.

This study has several strengths that improve the external validation and thus generalizability. A large sample of subjects was included that was adequately monitored by the family practitioner. Furthermore, an intention to treat analysis was performed, in which those subjects from the experimental practices that were excluded for the discontinuation programme were included in the analysis. By doing so, selection bias was avoided in the comparison with the control group. Another advantage of this study is that we adjusted for possible seasonal differences by choosing similar starting dates of the intervention for the control and experimental groups.

Our a priori hypothesis was that quitting benzodiazepines could initiate new prescriptions of other psychotropics. The baseline prescription of antidepressants was high in this group of long-term benzodiazepine users with an average of about 50 prescriptions per 3 months in 100 subjects. Prediction analysis in the Benzoredux study already showed that subjects who use both an antidepressant and a benzodiazepine do not have a higher chance of quitting benzodiazepines, but when subjects succeed in quitting benzodiazepines, they are more capable of maintaining benzodiazepine abstinence when being already on an antidepressant.¹² In the present study, no changes in prescription of antidepressant agents were observed between the experimental and the control groups. However, the multivariate analysis showed that discontinuation of prescription of benzodiazepines was associated with a lower chance to receive an antidepressant prescription in the follow-up compared with persistent users. Whether this observation has clinical significance is not clear. Psychiatric co-morbidity like depression and generalized anxiety disorder may be more present among the persistent users compared to those who are able to discontinue benzodiazepine prescription. Unfortunately, we were not able to study this more in-depth as we did not have clinical diagnosis data. The present study in any case suggests that quitting benzodiazepines as a result of this programme in general does not initiate new antidepressant prescriptions. This was supported by the observation of a high level of consistency in antidepressant using status from baseline till end of follow-up. The absence of initiation of new psychotropics in long-term benzodiazepine users that were able to discontinue their

benzodiazepine prescription in this large study may suggest that successfully discontinuing benzodiazepines characterizes subjects that suffer less psychopathology.

Finally, the baseline prevalence of prescription of the more recently developed hypnotic agents zolpidem and zopiclone was low, probably due to the fact that it is not rational to have both a benzodiazepine and one of the two other hypnotics prescribed (the agent zaleplone is not available in the Netherlands). National prescription data from Dutch pharmacies show an increase of the prescription of zopiclone and zolpidem in the period from 2001 till 2005 of 20% to 1.1 million prescriptions in 2005. In this period, a decrease of prescriptions of nitrazepam (18% to 0.5 million prescriptions in 2005) was observed.¹⁵ This may suggest that family practitioners in the Netherlands in general more often prescribe zolpidem or zopiclone, in favour of a long-acting benzodiazepine hypnotic. The important finding in the present study was that no substitute use with these hypnotics was observed in the follow-up of this benzodiazepine discontinuation programme.

As both 'epilepsy' and 'psychosis in medical history' were exclusion criteria, the prevalence of use of anti-psychotics (N05A) and anti-epileptics (N03) was low among those receiving the actual intervention and no significant changes were observed in the number of prescriptions of these classes.

We conclude with the most important finding that a benzodiazepine reduction programme in primary care does not lead to substantial changes in prescription of non-benzodiazepine psychotropic agents. Our results thus indicate a pure advantage of preventing complications when quitting benzodiazepines, as no substitute use with associated risks was observed.

Declaration

Funding: Dutch Health Care Insurance Council (OG97-015).

Ethical approval: The study was approved by the Committee on Research involving Human Subjects (currently known as CMO Arnhem/Nijmegen).

Conflicts of interest: none.

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