

Research Article

Too Much or Too Little Antidepressant Medication: Difficult to Change. Two Rcts

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ABSTRACT

Background: Antidepressant use has increased exponentially in the last decades, mostly due to long continuation.

Objective: To assess the effectiveness of a tailored recommendation to cease or adjust antidepressant treatment.

Methods: Two cluster-randomized controlled trials (PANDA-study) in primary care. Long-term antidepressant users (> 9 months) were selected from GPs prescription databases. Patients were diagnosed with the Composite International Diagnostic Interview. Long-term users were split up in patients without indication for maintenance treatment (over-treatment trial) and patients undertreated despite maintenance treatment. The intervention consisted of disclosure of the current psychiatric diagnosis combined with a tailored treatment recommendation. We followed patients 12 months.

Results: We included 146 participants from 45 family practices in the over-treatment trial. Of the 70 patients in the intervention group, 34 (48%) did not comply with the advice to stop their antidepressant medication. Of the 36 (52%) patients who agreed to try, only 4 (6%) succeeded. These figures were consistent with the control group, where 6 (8%) of the 76 patients discontinued antidepressant use successfully. In terms of relapse rate, patients who were recommended to discontinue their antidepressant medication reported a higher relapse rate than the control group (36% versus 14%, p = 0.015). We included 58 patients in the under-treatment trial, with 29 patients in both the intervention and control group.

The proportion of remission was equal in both groups (n = 13, 45%).

Conclusion: Changing inappropriate long-term antidepressant use is difficult.

MeSH Headings/ Keywords: Antidepressant agents; Primary health care; Depressive disorder; Anxiety disorder; General practice; Inappropriate prescribing

Introduction

During the 1990's, antidepressants were promoted widely and general practitioners (GPs) were criticized for under-diagnosing and under-treating depressive and anxiety disorders [1-3]. Efforts were made to increase quality of care and prescription rates for antidepressants increased [4].

Now, contrary concerns are raised concerning overtreatment with antidepressants [5]. Long-term continuation contributes to the large amount of antidepressant use [6-10]. Studies suggest that many long-term users are exposed to antidepressants unnecessarily. [8,11,12] One-third of long-term antidepressant users have been found to have no identifiable justification [12]. Also, a lack of medication review during the continuation of antidepressant treatment has been suggested [8]. Clinical guidelines recommend limiting the duration of antidepressants to 6 months after remission for a first or second depressive episode or a successfully treated anxiety disorder [13-16].

Over-treatment with antidepressants is troublesome. The effectiveness is questionable: about 5 of every 6 antidepressant

users do not benefit [17]. From the GPs perspective, it is important to discuss how patients can use their own resources to cope with their problems; providing medication might be counterproductive, as medication use may diminish patient empowerment while regaining control is considered essential for recovery [18].

Under-treatment has been found to be 80% during the continuation or maintenance phase [19]. More than half of patients treated with antidepressants in primary care are prescribed doses smaller than recommended [20]. Clinical guidelines recommend subsequent treatment steps in case of no response to improve wellbeing and to prevent a chronic course [14-17].

We conclude that over-treatment with antidepressants is very prevalent, that a considerable proportion of long-term use has no clinical justification and finally that under-treatment is also very prevalent. Therefore, this study aims to reduce inappropriate long-term antidepressant use in general practice. We will evaluate the effectiveness of a patient-and-psychiatric-diagnosis tailored recommendation to cease (over-treatment) or adjust (under-treatment) antidepressant treatment.

Methods

Study design

We conducted two cluster randomised controlled trials in primary care in tandem. The study protocol is published elsewhere [21]. A summary can be found at the Nederland's Trial Register (NTR2032) (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2032). Our study was approved by the institutional ethics committee Nijmegen under registration number NL29718.091.09

Selection of study subjects

The study was conducted in 45 general practices in the Netherlands between February 2010 and March 2013. GPs identified long-term antidepressant users in their prescription database. GPs excluded patients based on the exclusion criteria below.

In- and exclusion criteria

Inclusion criteria:

a) Long-term antidepressant use (≥ 9 months). All antidepressants were included, except MAO-inhibitors.

b) Written informed consent.

Exclusion criteria:

a) Current treatment in a psychiatric in- or outpatient clinic;

b) Appropriate use of long-term antidepressants according to the Dutch guidelines for depressive and anxiety disorders (i.e. a history of recurrent depression (≥ 3 episodes) and/or a recurrent psychiatric disorder with at least two relapses after antidepressant discontinuation);

c) History of psychosis, bipolar disorder, or obsessive compulsive disorder;

d) Current diagnosis of substance use disorder excluding tobacco because of the necessity of specialized treatment.

e) Non-psychiatric indication for long-term antidepressant usage, e.g. neuropathic pain;

f) Hearing impairment and/or insufficient understanding of the Dutch language.

Informed consent procedure

Patients received an information brochure, via their GP, on the study stating the purpose of the study: to improve the treatment of patients using antidepressants long-term and to give a patient-tailored treatment recommendation. Patient could consent by filling out a return slip. We contacted consenting patients and checked in- and exclusion criteria.

Diagnostic procedures and trial-allocation

Eligible patients underwent a structured psychiatric interview by telephone using the Composite International Diagnostic Interview, version 3.0 (CIDI) conducted by trained interviewers [22-25]. Patients without a current psychiatric diagnosis or another indication for continued use (neuropathic pain, chronic pain) were allocated to the 'over-treatment' trial. Patients with a current (past 6 months) psychiatric diagnosis despite their long-term antidepressant use were allocated to the 'under-treatment' trial.

Randomisation

To prevent contamination between intervention and control group a cluster randomization was performed with the general practice as the unit of clustering. Random assignment was executed after patient recruitment was concluded per practice, i.e. a practice was either an intervention practice or a control practice.

Follow up procedures

In the course of a year, all patients were routinely followed up. After 1 year, they underwent the CIDI again. The self-report questionnaire was repeated every 3 months during a year.

Over-treatment trial

Intervention: A patient-specific letter was sent to the GP with the recommendation to discontinue the antidepressant. We provided information on antidepressant tapering and the discontinuation syndrome. We advised a gradual tapering program [21]. The GP invited the patient to discuss the recommendation. No treatment restrictions were imposed in case of a relapse or onset of a new psychiatric disorder after discontinuation. A return slip was included, to ascertain the intention to comply with the recommendation. When either the GP or the patient did not intend to comply, we asked for the reasons. In the control group, GPs were unaware which patients participated in this study and continued usual care.

Primary outcome: The proportion of participants who successfully discontinued their long-term antidepressant use after 1 year. This was defined as no antidepressant use during the preceding 6 months and the absence of a depressive or anxiety disorder during the one year follow up, as assessed by the CIDI. All medication use was collected in the follow up CIDI, as well as in self-report questionnaires. Missing and contradicting prescriptions were checked by contacting the GP.

Secondary outcome: Severity of general distress and depressive symptoms were assessed by the Brief Symptom Inventory (BSI-53) [26], and the Centre for Epidemiological Studies Depression Scale (CESD) [27], at baseline and after 3, 6, 9 and 12 months follow up. Somatic comorbidity has been assessed with the Tic-p questionnaire.

Sample size estimation: Our prospective sample size estimation aimed to provide at least 85% power for two-tailed testing with a type-1 error rate of 5 %. To account for the cluster-randomisation, we used an intra-class correlation of 0.05. Assumptions with respect to recruitment and outcomes were difficult to estimate. We expected a 20% discontinuation rate for the control and 50% for the intervention group. Spontaneous non-adherence to antidepressants is found to be 25% [28], we expected this rate to decline as treatment time elapses. The expected discontinuation rate in the intervention group is based on a primary care benzodiazepines discontinuation study [29,30]. An average Dutch general practice (2400 patients) has approximately 50-60 patients using antidepressants long-term [31], with one-third possibly inappropriately [8]. Our recruitment rate was also based on a small pilot study with three general practices being able to include three patients per practice. Assuming a dropout rate of 25%, the required sample size calculated 34 practices and 136 patients.

Statistical analyses: Analyses were conducted in IBM SPSS Statistics 20. Outcome analyses were performed on an intention-to-treat basis. Patients with an unknown primary outcome were classified as failure. The secondary outcome measures were analysed using a mixed models procedure for repeated measures, thus accounting for any missing values.

Under-treatment trial

Intervention: Disclosure of the current psychiatric diagnosis (result from the CIDI) combined with a patient-tailored treatment recommendation based on the Dutch Multidisciplinary Guidelines for the treatment of depressive disorder and of anxiety disorders [18,19]. The intention to comply with the given advice was ascertained with the return slip; unfortunately, we were unable to ascertain exactly whether they actually changed medication and/or received psychotherapy according to the advice. In the control group, GPs continued their usual care and received no information on the CIDI outcome or any treatment advice.

Primary outcome: The proportion of participants in which the depressive or anxiety disorder at baseline had remitted at one-year follow-up (based on the CIDI).

Secondary outcome: The severity of psychological symptoms, assessed by self-report questionnaires at baseline and after 3, 6, 9, and 12 months. The overall severity of psychological distress and global psychopathology was based on the Brief Symptom Inventory (BSI-53) [26]. We also included disorder specific instruments: The Centre for Epidemiological Studies Depression Scale (CES-D) [32]; the Penn State Worry Questionnaire (PSWQ) [33]; the Panic and Agoraphobic Scale (PAS) [34]; the Fear of Negative Evaluation Scale (FNES) [35].

Sample-size estimation: Assuming a success rate of 30% in the intervention group and 10% in the control group, an intra cluster correlation coefficient (ICC) of 0.05, a two-sided alpha of 0.05 and a power of 85%, we will need to include 30 clusters with 6 patients each in the under-treatment trial.

Analyses: Performed on an intention-to-treat basis, with patients lost to follow up classified as failure (for the primary outcome). Information from the self-report questionnaire at 1-year follow up was used to estimate the primary outcome when missing. Secondary outcome measures were analysed using mixed models procedure. First, the mean BSI-53 score was analysed. Secondly, disease-specific instruments were pooled, after having determined the most relevant disease-specific questionnaire for each patient based on one's primary diagnosis assessed with the CIDI at study entry, and transformed into standardized T-scores. In case of missing values, the BSI-53 score was taken.

Results

Over-treatment trial

Forty-five practices participated. In total, 6442 long-term antidepressant users were identified, of whom 2411 (37%) were deemed eligible by their GP. Three-hundred-and-fifty-eight (15%) patients consented to participate and 146 were included in this study (Figure 1).

Study population

Patient characteristics were well balanced at randomization; any differences were not statistically significant (Table 1). Figure 2 shows the distribution of patients and their outcomes.

In the intervention practices, in almost half of the cases the recommendation to discontinue was rejected (n = 34/70; 48%, 95%CI 37-60): by the patient in 14 cases (41%), the GP in one (3%) and as a shared decision in 16 (47%); in 3 cases data were missing. Reasons for rejecting the recommendation: fear of recurrence (n = 19, 56%), relapse after previous discontinuation (n = 4, 12%), presence of psychological symptoms (n = 5, 15%), wanting a second opinion (n = 4, 12%) and other reasons (unspecified) (n = 2, 6%). General distress or depressive symptoms at three months (approximately the time of consultation with GP to discuss the given recommendation) were not predictive for acceptance of the recommendation to discontinue (mean BSI 0.4, 95% CI 0.2 to 0.5; mean CESD 17, 95% CI 13-21 vs. mean BSI 0.4, 95% CI 0.2-0.6; mean CESD 15, 95% CI 11-18).

Primary outcome

In the intervention group four patients (6%, 95% CI 2-14) successfully discontinued their antidepressant, in comparison to six patients (8%, 95% CI 4-16) in the control group. When combining the intervention and control groups, we found successful discontinuation of antidepressant use in 10 patients (7%, 95% CI 4-12).

Secondary outcomes

We found a significantly higher relapse rate in the intervention group (n = 18; 36%, 95% CI 25-50) compared to the control group (n = 10; 14%, (95% CI 8-25) (p = 0.015). This difference was not associated with antidepressant discontinuation. Comparison of patients who continued their antidepressants,

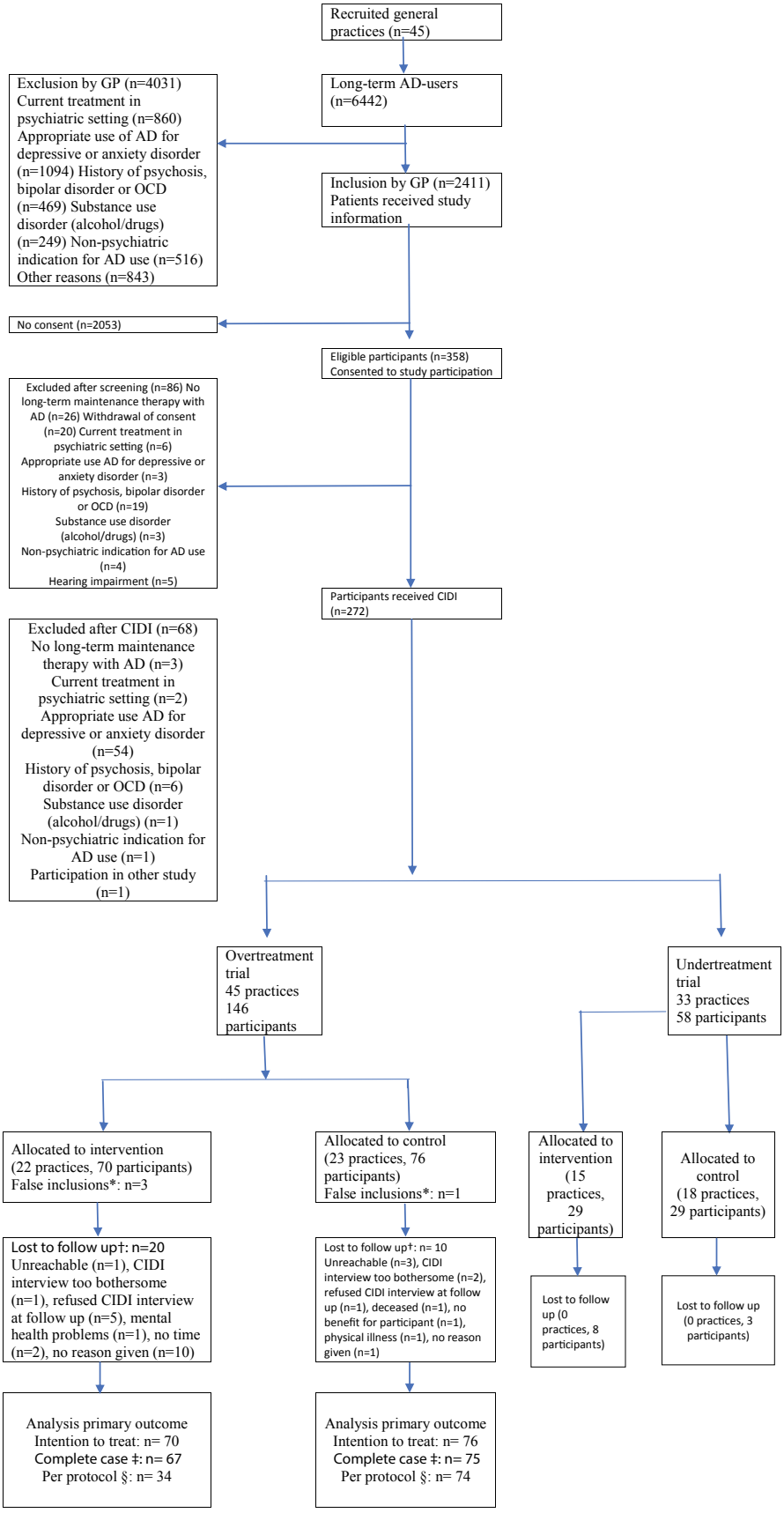

Figure 1: Flow diagram of practices and participants.
*post-randomization patients did not meet inclusion criteria (human error during inclusion process)
†patients who did not complete follow up interview
‡ patients excluded with unknown primary outcome (due to dual primary outcome, excluded cases are less than patients lost to follow up, i.e. antidepressant use known via GP prescription database)
§ intervention group restricted to patients with the intention to comply to recommendation and patients

Table 1: Baseline characteristics of participants (inappropriate long-term antidepressant users) in both the over-treatment and under-treatment trial at individual level in frequencies (percentages), unless stated otherwise. Over-treatment: > 9 months AD use, without a current indication for maintenance therapy. Under-treatment: a current psychiatric disorder despite > 9 months AD use. Patients were well balanced at randomization.

	Overtreatment trial			**Under-treatment trial**	
	Control (n=76)	Intervention (n=70)		Control (n=29)	Intervention (n=29)
Mean (SD) age (years)	56 (14.3)	56 (12.9)		53.8 (11)	55.8 (14)
Male	24 (32%)	20 (29%)		8 (28%)	8 (28%)
Marital status					
Married or living together	60 (79%)	56 (81%)		25 (86%)	22 (76%)
Separated or divorced	0 (0%)	2 (3%)		0	0
Widow/widower	7 (9%)	2 (3%)		0	0
Single	9 (12%)	9 (13%)		4 (14%)	7 (24%)
Lifetime psychiatric diagnosis			Current psychiatric diagnosis		
Any lifetime psychiatric diagnosis	48 (63%)	53 (76%)			
Depression	35 (46%)	39 (57%)	Depression	19 (66%)	16 (55%)
Panic disorder or Agoraphobia	13 (17%)	13 (19%)	Panic disorder or Agoraphobia	6 (21%)	6 (21%)
Generalized anxiety disorder	13 (17%)	22 (32%)	Generalized anxiety disorder	10 (35%)	9 (31%)
Social phobia	20 (26%)	16 (23%)	Social phobia	10 (35%)	13 (45%)
Antidepressant use					
SSRI	50 (66%)	57 (81%)		22 (76%)	25 (86%)
SNRI	11 (15%)	7 (10%)		6 (21%)	3 (10%)
Other (non-TCA)	10 (13%)	2 (3%)		0	0
TCA	5 (7%)	4 (6%)		1 (3%)	1 (3%)
Median duration of AD use at inclusion (range) in years	9.5 (1-56)	8.0 (1-48)		8 (1-33)	7 (1-30)
Somatic comorbidity					
Cardiovascular disease	7 (9%)	9 (13%)		2 (7%)	6 (21%)
Cancer	6 (8%)	8 (12%)		2 (7%)	2 (7%)
COPD/ Asthma	12 (16%)	9 (13%)		4 (14%)	4 (14%)
Diabetes Mellitus	11 (15%)	3 (4%)		4 (14%)	1 (3%)

did yield a significantly higher relapse rate in the intervention versus control group (36%, 95% CI 23-52 vs. 13%, 95% CI 6-24, p = 0.02).

Patients who successfully discontinued their antidepressant did not differ from the rest of the study population in gender, age, type of antidepressant used (SSRI, TCA or other) or psychiatric diagnosis. However, the mean duration of AD use appeared to trend toward a shorter duration in patients who successfully discontinued their AD (5.7 years; 95% CI 1.6-9.7 years vs. 9.6 years (95% CI 8.3-11.0 years), p = 0.077).

Under-treatment trial

Thirty-three practices participated in the under-treatment trial, as not all practice was able to include patients in this trial.

This resulted in the inclusion of 58 patients (Figure 1).

Study population

Fifty-eight patients were included in the under-treatment trial (Figure 1 and Table 1).

Of the 29 treatment recommendations, five (17%, 95% CI 7-36) were medication recommendations, eight (28%, 95% CI 14-46) psychological and 16 (55%, 95% CI 4-7) consisted of a choice between both. Twelve (41%, 95% CI 25-60) patients intended to comply with the recommendation. The decision to reject the recommendation was shared by the GP in nine cases (53%).

Primary and secondary outcomes

The proportion of patients achieving remission of their

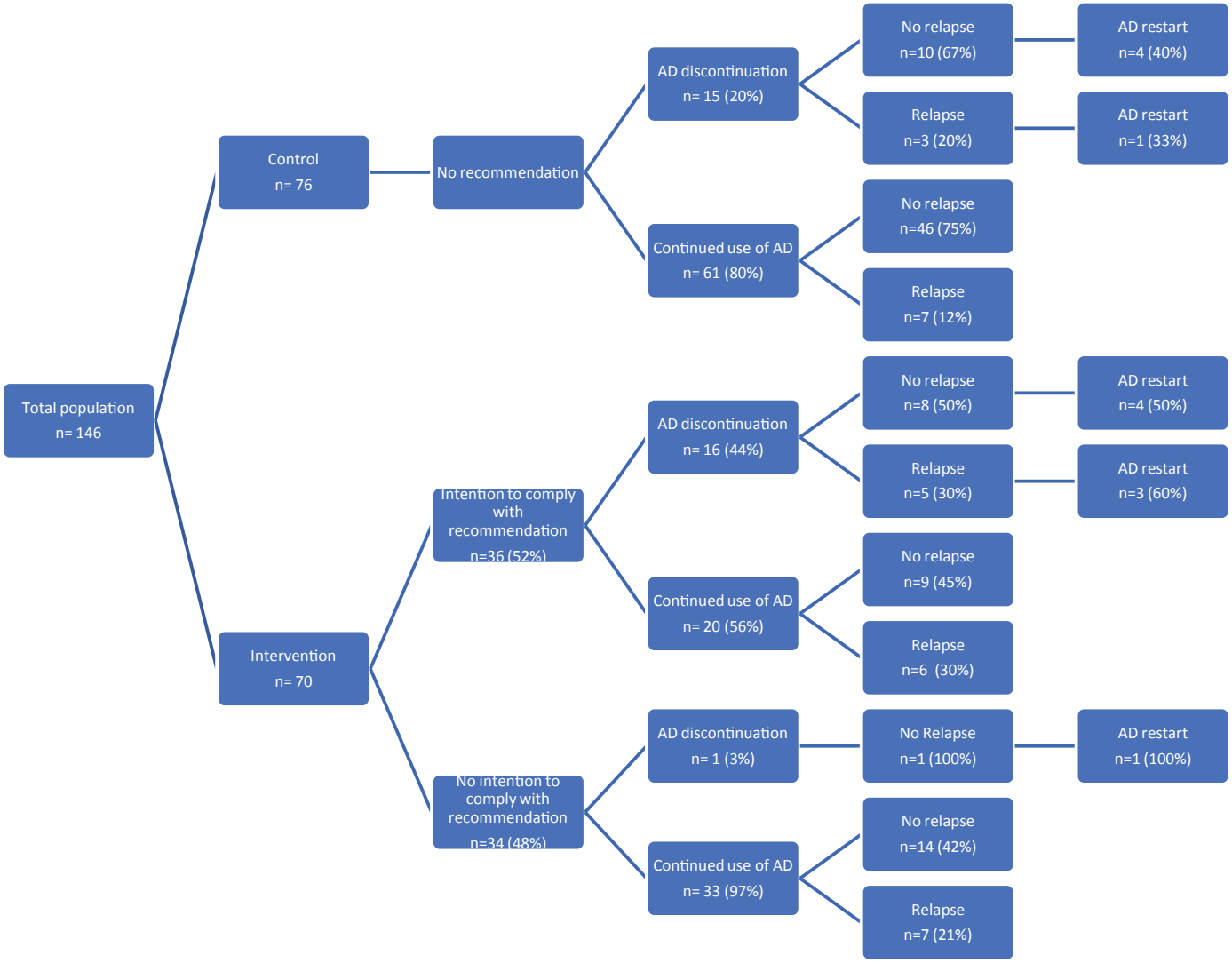

Figure 2: Patient flow and outcome in the overtreatment trial

psychiatric disorder was the same in the intervention and the control group: 45% (95% CI 28-62).

Additionally, we found no significant difference in trend on the severity of general distress between the intervention and control group in the longitudinal data during follow up, nor in the pooled T-scores for the disease specific questionnaires. There were no significant baseline differences between the two groups.

Discussion

Main findings over-treatment trial

This study shows the difficulty of discontinuing inappropriate long-term antidepressant use. Irrespective of the condition patients were allocated to, only 10 of the 146 patients with inappropriate long-term use of antidepressants not recommended by the guideline (i.e. inappropriate) were able to successfully stop in the year of the study. Half of the patients in this study rejected the recommendation to discontinue. Even when intending to comply, more than half (56%) eventually did not. Interestingly, the number of patients spontaneously discontinuing their antidepressant was similar to patients receiving the recommendation.

We found a significantly higher relapse rate in the intervention group. Strikingly, this was not associated with antidepressant discontinuation. The focus on the antidepressant use could have caused a higher risk of relapse, patients could have felt obliged to act upon this recommendation without an internal motivation, causing more anxiety for relapse and consequently, due to higher anxiety levels, a higher risk of relapse. In addition, possibly feelings of failure could arise when rejecting the recommendation.

The studied intervention was based on previous experiences with discontinuation of long-term benzodiazepine use, were a stepped care approach has been found effective [36]. A minimal intervention, consisting of an advisory letter or a consult to discuss discontinuation with the GP proved effective to discontinue benzodiazepines [37]. Apparently, the parallel with antidepressants was made too easily, with patients and GPs being hesitant to discontinue.

Main findings under-treatment trial

We found a low number of patients being under-treated amongst the participating long-term antidepressant users in primary care, in contrast with the literature [19,42,43]. This could suggest that

the prevalence is low, but could also be the result of a failed recruitment and selection bias. Even though we were unable to recruit sufficient patients for the under-treatment trial to reach adequate power [21], we feel that the results of this study are important to discuss.

The results of the under-treatment trial showed that providing GPs with a patient-tailored treatment recommendation did not have any beneficial effect on remission rates in patients suffering from a current depressive or anxiety disorder despite long-term use of antidepressant medication. Not unsurprisingly, as more than half of the patients (and their GPs) were hesitant to accept the given recommendation.

Patient preference has been emphasized to be of great importance in treating depressive disorders [44]. The hesitation to comply with the recommendation was mostly driven by an apprehension to change. Maybe for these patients there is no necessity of remission and taking long-term antidepressants is 'good enough'. Despite that studies have shown that remission is consistently associated with a better prognosis than symptomatic improvement without full remission of the disorder [45], it is conceivable that for patients the treatment goal is not remission, but merely symptom alleviation.

Interpretation and general discussion Our study showed that many patients reject a proposal to discontinue antidepressant use, that many GPs agreed with the decision not to follow the advice to discontinue and that a large number of patients [32-36] who agreed to follow the protocol, failed to do so. Clearly, there is a large gap between what guidelines say and what happens in daily practice. Although deviance from a guideline may be consistent with good care, the magnitude of non-adherence raises another possibility. We believe that apprehension to change and difficulties with discontinuation are central here. The apprehension to change was found in both patients and GPs. Qualitative research has suggested that patients attribute their wellbeing to the (continued) use of antidepressants and are more afraid of stopping than of continuing, i.e. "better safe than sorry" [38,39]. They believe their condition to be chronic and requiring life-long treatment, while feeling uncomfortable with this prospect [38-40]. Barriers GPs perceive include: concerns "not to disturb the 'equilibrium' the patient experiences", "follow the path of least resistance" and, "let patients be" [40]. GPs operate in a difficult environment where they have to deal with guidelines, their own fears, patients' opinions and fears, and the difficult process of discontinuation. Adherence to guidelines is difficult. Attempts to discontinue antidepressant use – very desirable in the light of the huge prescription rates – always have to deal with the aforementioned issues [41]?

Concerning the guidelines there is the problem that they have lately become more conservative in the prescription of antidepressant medication. It is conceivable that the GPs in the PANDA study did not agree with the guidelines, or had to get used to new insights after first complying to the notion advocated in the past that antidepressant medication should be prescribed more often. So, there certainly is an issue in the prescribing behaviour of GPs: they have to become more reluctant in prescribing and have to inform the patients that the medication will only be necessary for a limited period of time and could be discontinued after being in remission for a period of six months. In addition, patients discontinuing their antidepressant medication should receive more information, guidance and support than they receive at present. Consequently, we advocate to develop education programmes for general practitioners that give attention to the GPs' attitudes towards discontinuation, to appropriately motivate patients to discontinue antidepressant use, and to manage to process of discontinuation. This leaves alone that in our view the first, on possibly most important step to prevent inappropriate long-term use of antidepressant medication in primary care is to be more restrictive in prescribing antidepressant medication in the first place and make more use of alternative, non-pharmological treatments for depression.

Study limitations

To our knowledge, this is the first randomized controlled clinical trial focusing on long-term antidepressant use in patients in remission.

Of the large number of long-term antidepressant users, only a small portion consented to participate in this study (less than 15%). Patient recruitment is a known problem, especially in mental health research [46]. However, despite the low response rate, we did reach the prospective sample size to provide sufficient power for the overtreatment trial by approaching more practices and patients than originally anticipated. As due to privacy regulations these long-term antidepressant users remain anonymous until giving consent, unfortunately we do not know why patients decided not to participate. It is conceivable that patients not willing to participate are more reluctant to change their antidepressant treatment. This would make our findings even more concerning, as chances are that with a larger, more generalizable population, the percentage of patients successfully discontinuing their antidepressant medication might even be lower. The recruitment success of patients for participation in such an evidence-based intervention could illustrate the difference between perceived self-interest (by the patient) and perceived patient-interest (by researchers and practitioners). Further studies about antidepressant discontinuation should therefore focus on patients who are motivated for discontinuation.

Due to the pragmatic nature of this study, we did not impose our intervention on the patients and their GPs. We found a noncompliance with the given recommendation in almost half of the cases. Further qualitative research might be helpful to understand the barriers patients and GPs perceive in discontinuing inappropriate, long-term antidepressant use in patients in remission and to be able to construct a more effective intervention to reduce inappropriate long-term antidepressant use.

Conclusion

This study demonstrates the difficulty of correcting inappropriate long-term antidepressant use (according to the guidelines), fuelled by an apprehension from both patient and GP to change. A recommendation to discontinue in case of over-treatment is not effective, and maybe even counterproductive. It might be useful to forewarn patients about the difficulty to discontinue and to encourage using antidepressants for a limited period. Regular review could possibly prevent both over and under-treatment.

REFERENCES

1. Freeling P. Diagnosis and treatment of depression in general practice. *Br J Psychiatry Suppl*. 1993; 20: 14-19.
2. Freemantle N, Song F, Sheldon TA, Watson P, Mason JM, et al. Managing depression in primary care. *Qual Health Care.* 1993; 2: 58-62.
3. Paykel ES, Priest RG. Recognition and management of depression in general practice: consensus statement. *BMJ.* 1992; 305: 1198-1202.
4. Stichting Farmaceutische Kengetallen. 2013.
5. Jureidini J, Tonkin A. Overuse of antidepressant drugs for the treatment of depression. *CNS drugs.* 2006; 20: 623-632.
6. Piek E, van der Meer K, Hoogendijk WJ, Penninx BW, Nolen WA. Most antidepressant use in primary care is justified; results of the Netherlands Study of Depression and Anxiety. *PLoS One.* 2011; 6: e14784.
7. Raymond CB, Morgan SG, Caetano PA. Antidepressant utilization in British Columbia from 1996 to 2004: increasing prevalence but not incidence. *Psychiatr Serv.* 2007; 58: 79-84.
8. Petty DR, House A, Knapp P, Raynor T, Zermansky A. Prevalence, duration and indications for prescribing of antidepressants in primary care. *Age Ageing.* 2006; 35: 523-526.
9. Meijer WE, Heerdink ER, Leufkens HG, Herings RM, Egberts AC, et al. Incidence and determinants of long-term use of antidepressants. *Eur J Clin Pharmacol.* 2004; 60: 57-61.
10. Moore M, Yuen HM, Dunn N, Mullee MA, Maskell J, et al. Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. *BMJ.* 2009; 339: b3999.
11. Spijker J, de Graaf R, Bijl RV, Beekman AT, Ormel J, et al. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Br J Psychiatry.* 2002; 181: 208-213.
12. Cruickshank G, MacGillivray S, Bruce D, Mather A, Matthews K, et al. Cross-sectional survey of patients in receipt of long-term repeat prescriptions for antidepressant drugs in primary care. *Ment Health Fam Med.* 2008; 5: 105-109.
13. National Institute of Health and Clinical Excellence. Depression: the treatment and management of depression in adults (update). 2009.
14. Multi Disciplinary Guideline Anxiety Disorders. Trimbos; 2009.
15. Multi Disciplinary Guideline Depression. Trimbos; 2009.
16. Van Weel-Baumgarten EM, Grundmeijer HG, LichtStrunk E, van Marwijk HW, van Rijswijk HC, et al. The NHG guideline Depression (second revision of the NHG guideline Depressive disorder). *GP and Science.* 2012; 55: 252-259.
17. Arroll B, Macgillivray S, Ogston S, Reid I, Sullivan F, et al. Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. *Ann Fam Med.* 2005; 3: 449-456.
18. Lucassen P, van Rijswijk E, van Weel-Baumgarten E, Dowrick C. Making fewer depression diagnoses: beneficial for patients? *Ment Health Fam Med.* 2008; 5: 161-165.
19. Fujita A, Azuma H, Kitamura T, Takahashi K, Akechi T, et al. Adequacy of continuation and maintenance treatments for major depression in Japan. *J Psychopharmacol*. 2008; 22: 153-156.
20. Simon GE. Evidence review: efficacy and effectiveness of antidepressant treatment in primary care. *Gen Hosp Psychiatry.* 2002; 24: 213-224.
21. Muskens E, Eveleigh R, Lucassen P, van Weel C, Spijker J, et al. Prescribing ANtiDepressants Appropriately (PANDA): a cluster randomized controlled trial in primary care. *BMC Fam Pract.* 2013; 14: 6.
22. Haro JM, Arbabzadeh-Bouchez S, Brugha TS, de Girolamo G, Guyer ME, et al. Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health surveys. *Int J Methods Psychiatr Res.* 2006; 15: 167-180.
23. Kessler RC, Abelson J, Demler O, Escobar JI, Gibbon M, et al. Clinical calibration of DSM-IV diagnoses in the World Mental Health (WMH) version of the World Health Organization (WHO) Composite International Diagnostic Interview (WMHCIDI). *Int J Methods Psychiatr Res.* 2004; 13: 122-139.
24. Kessler RC, Ustün TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res.* 2004; 13: 93-121.
25. Kessler RC, Calabrese JR, Farley PA, Gruber MJ, Jewell MA, et al. Composite International Diagnostic Interview screening scales for DSM-IV anxiety and mood disorders. *Psychol Med.* 2012; 43: 1-13.
26. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983; 13: 595-605.
27. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Appl Psychol Med.* 1977; 1: 16.
28. Brook OH, van Hout HP, Stalman WA, de Haan M. Nontricyclic antidepressants: predictors of nonadherence. *J Clin Psychopharmacol.* 2006; 26: 643-647.
29. Voshaar ORC, Gorgels WJ, Mol AJ, van Balkom AJ, Mulder J, et al. Long-term outcome of two forms of randomised benzodiazepine discontinuation. *Br J Psychiatry.* 2006; 188: 188-189.
30. Voshaar RC, Gorgels WJ, Mol AJ, van Balkom AJ, van de Lisdonk EH, et al. Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy:

three-condition, randomised controlled trial. *Br J Psychiatry*. 2003; 182: 498-504.

31. Volkers A, Jong Ade, Bakker Dde, Dijk Lvan. Effective prescribing of antidepressants in general practice. Utrecht: NIVEL, 2005.
32. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Appl Psychol Med.* 1977; 1: 16.
33. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State Worry Questionnaire. *Behav Res Ther* 1990; 28: 487-495.
34. Bandelow B. Panic and Agoraphobia Scale (PAS). Assesment scales in depression, mania and anxiety. Seattle: Hogrefe & Huber Publishers.; 1999.
35. Watson D, Friend R. Measurement of social-evaluative anxiety. *J Consult Clin Psychol*. 1969; 33: 448-457.
36. Voshaar RC, Couvee JE, van Balkom AJ, Mulder PG, Zitman FG. Strategies for discontinuing long-term benzodiazepine use: meta-analysis. *Br J Psychiatry.* 2006; 189: 213-220.
37. Gorgels WJ, Voshaar ORC, Mol AJ, van de Lisdonk EH, van Balkom AJ, et al. Discontinuation of long-term benzodiazepine use by sending a letter to users in family practice: a prospective controlled intervention study. *Drug Alcohol Depend.* 2005; 78: 49-56.
38. Verbeek-Heida PM, Mathot EF. Better safe than sorry--why patients prefer to stop using selective serotonin reuptake inhibitor (SSRI) antidepressants but are afraid to do so: results of a qualitative study. *Chronic Illn.* 2006; 2: 133-142.
39. Leydon GM, Rodgers L, Kendrick T. A qualitative study of patient views on discontinuing long-term selective serotonin reuptake inhibitors. *Fam Pract.* 2007; 24: 570-575.
40. Dickinson R, Knapp P, House AO, Dimri V, Zermansky A, et al. Long-term prescribing of antidepressants in the older population: a qualitative study. *Br J Gen Pract.* 2010; 60: e144-e155.
41. Kendrick T. Why can't GPs follow guidelines on depression? We must question the basis of the guidelines themselves. *BMJ.* 2000; 320: 200-201.
42. Lecrubier Y. Widespread underrecognition and undertreatment of anxiety and mood disorders: results from 3 European studies. *J Clin Psychiatry.* 2007; 68: 36
43. Barkil-Oteo A. Collaborative care for depression in primary care: how psychiatry could "troubleshoot" current treatments and practices. *Yale J Biol Med.* 2013; 86: 139-146.
44. van Schaik DJ, Klijn AF, van Hout HP, van Marwijk HW, Beekman AT, et al. Patients' preferences in the treatment of depressive disorder in primary care. *Gen Hosp Psychiatry.* 2004; 26: 184-189.
45. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006; 163: 1905-1917.
46. Mason V, Shaw A, Wiles N, Mulligan J, Peters T, et al. GPs' experiences of primary care mental health research: a qualitative study of the barriers to recruitment. *Fam Pract.* 2007; 24: 518.

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