Title: Restarting antidepressant treatment following early discontinuation – a primary care database study

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Article Category: Health Services Research

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Word count 2098

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Abstract

Background

Many patients in primary care stop antidepressant treatment after only one prescription, so do not benefit from treatment. Some patients who stop initial antidepressant treatment go on to restart it, but neither the incidence of restarting, nor the probability that patients who restart treatment subsequently complete an adequate course of treatment is known.

Methods

We used a primary care database (over 1.2 million records) to study patients who commenced treatment with an eligible antidepressant between April 2007 and March 2008 and who stopped treatment for at least one month after the first prescription. We examined their subsequent antidepressant prescriptions to estimate the probability of restarting antidepressant treatment, the likelihood of continuing subsequent treatment, and the patient characteristics associated with these.

Results

6,952/24,817 (28%) patients discontinued antidepressant treatment after the first prescription. The cumulative probability of restarting treatment after early discontinuation was 8.6% (95% ci 8.0 - 9.3) after one month off treatment, and 24.1% (22.9 - 25.2) after 9 months off treatment. The probability of those who restarted treatment continuing for 6 months or more was 29.3% (26.5 -32.5).

Conclusions

Few patients who stop antidepressant treatment after the first prescription subsequently complete an adequate treatment course within the next year. Initiatives to promote adherence to appropriate antidepressant treatment should begin during the first prescription.

KEYWORDS

Antidepressant treatment, Prescribing, Depression, Primary Care, Database research

Introduction

Guidelines for treatment of depression recommend antidepressants for depression of at least moderate severity and that this treatment should be continued for ≥6 months following symptom resolution [1,2]. In routine care, much antidepressant treatment is not guideline-compliant and around a quarter of patients prescribed a new antidepressant stop after the first prescription [3-5]. There are several possible reasons for early discontinuation including disagreement between doctor and patient over the diagnosis or the appropriateness of pharmacotherapy [6-9]. Qualitative research has suggested that early discontinuation may be followed by sustained treatment, as patients "experiment" with treatment before committing to a full course [10]. However we could find no quantitative data on subsequent use of antidepressants after early discontinuation, although other studies have examined longer timescales [11]. Studies on antidepressant adherence have generally considered the first interruption in treatment as cessation of treatment and the endpoint for the study [3,4].

We carried out a primary care database study to investigate (a) how many patients who stopped an antidepressant prescription after one month went on to restart over the next 10 months, (b) how long the subgroup of patients who restarted continued their treatment, and (c) how these behaviours related to patient characteristics.

Methods

We analysed data from the Primary Care Clinical Informatics Unit Research (PCCIUR) database, comprising anonymised information from General Practices across Scotland. We extracted data on all prescriptions for included antidepressants between 1 April 2006 and 31 March 2008 and demographic details of patients who received them.

We included adults continuously registered with the same GP practice throughout the study period who began a new course of an eligible antidepressant in the months of April 2007 to March 2008 (i.e. after at least one year without antidepressant treatment). Eligible antidepressants were those

commonly used in primary care to treat depression: serotonin-specific reuptake inhibitors (SSRIs); serotonin noradrenaline reuptake inhibitors (SNRIs; except duloxetine), lofepramine and trazodone.

We excluded patients <18 years and patients whose only prescription was in the final month of the time period as it was impossible to assess discontinuation after this. We used calendar months as the unit of analysis for treatment and for each patient we categorised each month with a binary value of 1 ("on-treatment") or 0 ("off-treatment"). Patients' treatment over the two years of data could thus be summarised by a sequence of 24 binary digits. The process of condensing the detailed prescription information into this sequence began by calculating the number of days of treatment in each prescription using details of the prescriptions (date, dose, frequency and quantities). This detailed information allowed the algorithm to handle prescriptions which were shorter or longer than 28 or 30 days and to differentiate between consecutive prescriptions of the same drug (treatment days were added together) and parallel prescription of antidepressants in combination (treatment days were not added together).

We developed a categorisation algorithm to reduce raw data into binary sequences over several iterations which led to rules in the algorithm, such as for carrying forward days of treatment, described below. For each iteration we checked the output sequence against manual interpretation of the prescription data using actual dates. For example the algorithm output sequence "1001" should correspond to two periods of treatment separated by at least 60 days without treatment. This validation process was conducted on the output from the algorithm of 150 randomly selected records. The process of algorithm development and validation continued over several iterations until there was full agreement between researchers and the computer algorithm

The categorisation algorithm is shown as a flow chart in figure 1. It was run for each patient separately. For each month in sequence, its external inputs were information about days and dates of treatment and its output was a binary value indicating the status of the month as on- or off-treatment. Within each month, treatment days prescribed in the month were allocated to that month, except where treatment was initiated (i.e. not a follow-on prescription) after the 21st of a month in which case those treatment days were all allocated to the next month. If there were more treatment days allocated to a month than days in that month, the left-over treatment days were carried forward to the

next month. Months containing 4 or more days of treatment were designated on-treatment months (to prevent small carry-forward events accounting for extra months on- treatment).

For analysis, patients were split by sex, age band (18-34,35-64,65 and over) and deprivation, calculated using the Carstairs and Morris Index of Deprivation[12] and presented as quartiles (quartile 1=least deprived, quartile 4=most deprived). Patients were classed as 'early discontinuers' if their first on-treatment month was followed by one or more off-treatment months. Early discontinuers who received a subsequent prescription for an antidepressant were classed as 'restarters'. Restarters could either be returning for treatment of the index depressive episode or consulting about a new episode after a period of wellbeing. These could not be differentiated using the available data. For each restarter, we calculated the time between the initial single prescription and the restart, the duration of the restarted treatment, and the total number of discrete episodes of treatment. The maximum duration of follow up was 10 months (one year minus one month on-treatment and one month off- treatment).

We reported crude rates of restarting after early discontinuation and used odds ratios to examine the effects of sex, age and deprivation on these. We examined the time to restart and the duration of restarted treatment using survival analysis in which Cox Proportional Hazards models were adjusted for age, sex and deprivation and clustered by GP practice. All statistical analyses were performed using R-3.0.1.

Results

Treatment initiation and early discontinuation

The sample population comprised 1,280,840 patients. A new eligible course of antidepressant treatment was begun by 24,817 adult patients in the study period of whom 16,613 (66.9%) were female. 6877 (27.7%) patients were aged 18-34 years, 13,854 (55.8%) 35-64 years and 4086 (16.4%) ≥65 years; 7560 (30.4%) were in the least deprived quartile, quartile 2: 8,103 (32.7%), quartile 3: 4,345 (17.5%) and quartile 4: 4,809 (19.4%). 6952 patients prescribed a new course of antidepressant were classed as early discontinuers (28%) and of these 1459 (21%) were classed as restarters. Table 1 section A reports the associations of sex, age and deprivation on early discontinuation among all patients prescribed a new course of antidepressant.

Restarting treatment following early discontinuation

Table 1 section B reports the asoociations of sex, age and deprivation on restarting following early discontinuation. Restarting appeared to be slightly more common in patients with greater soci-economic deprivation. Most patients who restarted antidepressant treatment after early discontinuation did so after only one or two months off-treatment: the cumulative probability of restarting treatment after early discontinuation was 8.6% (95% ci 8.0 - 9.3) after one off-treatment month, 16.1% (15.2 - 17.0) after a further two months, 21.0% (19.9 – 22.0) by 6 months after initially stopping treatment and 24.1% (22.9 - 25.2) by 9 months.

Duration of restarted treatment

Survival analysis showed that persistence on restarted antidepressants was poor: only 51.5% (48.9 - 54.2) of restarters continued treatment beyond 2 months of restarted treatment , and 29.3% (26.5 - 32.5%) continued beyond 6 months of restarted treatment. Table 1 section C shows the association of duration of treatment with age, sex and deprivation: older patients who restarted treatment were most likely to continue restarted treatment and those aged under 35 least likely. Repeatedly cycling on and off antidepressants appeared to be uncommon with only 19% of restarters having more than 2 distinct periods on-treatment. However as data was available for only a maximum of 10 months after restarting, this is likely to have been under-identified and longer periods of follow up are needed to obtain acccurate assessments of the prevalence of this behaviour.

Influence of GP coding of depression

In view of the relatively low rates of restarting treatment we conducted a post-hoc analysis in which we compared those patients whose treatment initation was accompanied with a new diagnostic code for depression and those where it was not. We had previously shown that discontinuation after one prescription was slightly more common in those without a code [4]. By 6 months after the initial discontinuation 24.5% (22.3 – 26.7) of those with a code had restarted treatment compared to 18.2% (17.1 – 19.2) of those without: hazard ratio 1.41 (1.25 to 1.59). There was no difference in the duration of restarted treatment: hazard ratio 0.96 (0.82 to1.12). Data were incomplete for coding analysis in 95 cases.

Discussion

Summary of main findings

Patients who receive a single prescription for antidepressants and then discontinue treatment are unlikely to restart treatment in the following 12 months. For those who do, particularly when aged under 35, the probability of sustained, guideline-compliant, treatment is low. Repeatedly cycling on and off antidepressants is relatively uncommon in all patient groups.

Strengths and limitations

We used detailed prescription data from a large and representative database of patients and general practices in Scotland to categorise sequential months as on- or off- antidepressant treatment. This gave a measure of patient treatment times and patterns which was validated manually in a random sample. We did not limit the analysis to patients with a coded diagnosis of depression: while this means we may have included some patients with other indications for treatment we chose this approach because GPs frequently manage depression without electronically recording a diagnostic code and we have previously found that uncoded patients were only slightly more likely to discontinue treatment [4]. While most patients for whom GPs prescribe an antidepressant are appropriately treated [13], GPs over-diagnose depression in patients with emotional distress. [14,15] Although some patients with these conditions may also warrant treatment because of concurrent anxiety or a history of previous depressive episodes [15]**.** Even among patients in whom the GP recorded a code for

depression, we found that only a quarter had received further antidepressant treatment in the next 6 months after early discontinuation.

We limited any effect of prescribing for other indication by excluding antidepressants more commonly prescribed for chronic pain (amitriptyline, duloxetine) from our eligible list.

Antidepressant treatment data were available for one 12 month period only, while this means that the number of patients for whom 6 months of data after restarting were available was small, we used survival analysis to allow for different durations of follow up. Analysis took place more than 5 years after treatment. It used the period of widest coverage of the database, which subsequently reduced in size owing to GP system changes. While antidepressant prescribing volumes continue to rise, rates of new antidepressant prescribing in Scotland were relatively static around the time of this study [16] and there has been only a modest change in the incidence of depression in the UK since then. [17] The increased volume of antidepressant prescribing over time has been largely attributed to patients using these medications long term [16,18]. We are not aware of any substantial changes in rates of discontinuation of newly initiated treatment since this data was collected,

We were unable to link data on treatment discontinuation to clinical outcomes. We previously found that self-report measures of depression severity were coded in only a third of new instances of depression treatment [4].and many patients who discontinue treatment also discontinue follow up. It is not possible to say from our data what proportion of early discontinuers remained depressed.

Implications for practice

While our findings do not contradict the suggestion that some patients go through a system of trial and error in relation to antidepressant treatment to manage their depression [10], they suggest that it is relatively uncommon. Rather, most very short courses of antidepressants are not repeated, suggesting either that they were a crisis response [19] or unwanted by the patient [6,8,9]. Age, sex and deprivation had only small or no associations with restarting or continuing treatment.

Clinicians, particularly in primary care need to be aware of these patterns in antidepressant use.. For patients with clear indications for therapy, they should consider using motivational techniques [20-22], structured patient follow up [23], and assessment of treatment preferences [24], in the early stages of

treatment, to ensure patients stay on the medication for long enough to benefit. For patients where there is more uncertainty about the indications of treatment, knowledge of the low probability of completing treatment should strengthen practitioners in following guidelines to avoid or defer antidepressant prescription.

Conclusions

Few patients who stop antidepressant treatment after the first prescription subsequently complete an adequate treatment course within the next year. Initiatives to promote adherence to appropriate antidepressant treatment need to begin during the first prescription.

Declarations/ Acknowledgements:

1. This study used fully anonymised data, no specific ethical approval was necessary.

2. No external source of funding for this study.

3. The authors declare no conflict of interest

References

1. Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2000 british association for psychopharmacology guidelines. *J Psychopharmacol*. 2008;22(4):343-396.

2. National Institute for Health and,Clinical Excellence, ed. *Depression in adults (update).* London: National Institute for Health and Clinical Excellence; 2009; No. Guideline 90.

3. Demyttenaere K. Risk factors and predictors of compliance in depression. *Eur Neuropsychopharmacol*. 2003;13 Suppl 3:S69-75.

4. Burton C, Anderson N, Wilde K, Simpson CR. Factors associated with duration of new antidepressant treatment: Analysis of a large primary care database. *Br J Gen Pract*. 2012;62(595):104-e112.

5. van Geffen EC, Gardarsdottir H, van Hulten R, van Dijk L, Egberts AC, Heerdink ER. Initiation of antidepressant therapy: Do patients follow the GP's prescription? *Br J Gen Pract*. 2009;59(559):81-87.

6. Hunot VM, Horne R, Leese MN, Churchill RC. A cohort study of adherence to antidepressants in primary care: The influence of antidepressant concerns and treatment preferences. *Prim.Care Companion.J Clin.Psychiatry*. 2007;9(2):91-99.

7. Jaffray M, Cardy AH, Reid IC, Cameron IM. Why do patients discontinue antidepressant therapy early? A qualitative study. *Eur J Gen Pract*. 2014;20(3):167-173.

8. van Geffen EC, Hermsen JH, Heerdink ER, Egberts AC, Verbeek-Heida PM, van Hulten R. The decision to continue or discontinue treatment: Experiences and beliefs of users of selective serotonin-reuptake inhibitors in the initial months--a qualitative study. *Res Social Adm Pharm*. 2011;7(2):134-150.

9. Anderson C, Roy T. Patient experiences of taking antidepressants for depression: A secondary qualitative analysis. *Res Social Adm Pharm*. 2013;9(6):884-902.

10. Schofield P, Crosland A, Waheed W, et al. Patients' views of antidepressants: From first experiences to becoming expert. *Br J Gen Pract*. 2011;61(585):142-148.

11. Gardarsdottir H, van Geffen EC, Stolker JJ, Egberts TC, Heerdink ER. Does the length of the first antidepressant treatment episode influence risk and time to a second episode? *J Clin Psychopharmacol*. 2009;29(1533-712; 1):69-72.

12. Carstairs V, Morris R. Deprivation and health in scotland. *Health Bull*. 1990;48(4):162-175.

13. Cameron IM, Lawton K, Reid IC. Appropriateness of antidepressant prescribing: An observational study in a scottish primary-care setting. *Br J Gen Pract*. 2009;59(566):644-649.

14. Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: A meta-analysis. *Lancet*. 2009;374(9690):609-619.

15. Cameron IM, Lawton K, Reid IC. Recognition and subsequent treatment of patients with sub-threshold symptoms of depression in primary care. *J Affect Disord*. 2011;130(1-2):99-105.

16. Lockhart P, Guthrie B. Trends in primary care antidepressant prescribing 1995-2007: A longitudinal population database analysis 1. *Br J Gen Pract*. 2011;61(590):565-e572.

17. Kendrick T, Stuart B, Newell C, Geraghty AW, Moore M. Changes in rates of recorded depression in english primary care 2003-2013: Time trend analyses of effects of the economic recession, and the GP contract quality outcomes framework (QOF). *J Affect Disord*. 2015;180:68-78.

18. Moore M, Yuen HM, Dunn N, Mullee MA, Maskell J, Kendrick T. Explaining the rise in antidepressant prescribing: A descriptive study using the general practice research database. *BMJ*. 2009;339(0959-535):3999.

19. Macdonald S, Morrison J, Maxwell M, et al. 'A coal face option': GPs' perspectives on the rise in antidepressant prescribing. *Br J Gen Pract*. 2009;59(566):299-e307.

20. Balan IC, Moyers TB, Lewis-Fernandez R. Motivational pharmacotherapy: Combining motivational interviewing and antidepressant therapy to improve treatment adherence. *Psychiatry*. 2013;76(3):203-209.

21. Interian A, Lewis-Fernandez R, Gara MA, Escobar JI. A randomized-controlled trial of an intervention to improve antidepressant adherence among latinos with depression. *Depress Anxiety*. 2013;30(7):688-696.

22. Keeley RD, Burke BL, Brody D, et al. Training to use motivational interviewing techniques for depression: A cluster randomized trial. *J Am Board Fam Med*. 2014;27(5):621-636.

23. Burton C, Cameron I, Anderson N. Explaining the variation between practices in the duration of new antidepressant treatment: A database cohort study in primary care. *Br J Gen Pract*. 2015;65(631):e114-20.

24. Wouters H, Van Dijk L, Van Geffen EC, Gardarsdottir H, Stiggelbout AM, Bouvy ML. Primary-care patients' trade-off preferences with regard to antidepressants. *Psychol Med*. 2014:1-8.

Table 1:Influences of patient sex, age and deprivation on probabilities of early discontinuation, restarting treatment and continuing with restarted antidepressant treatment during 12 months of follow up in a primary care database population

Patient Characteristics	A. Number and probability of stopping after first prescription			B. Number and probability of restarting after discontinuation			C. Probability of continuing restarted treatment	
	N (%)	OR[b]	95% CI	N (%)	HR[c]	95% CI	HR[d]	95%CI
Sex								
Female	4,647 (28.0)	--- [a]		979 (21.1)	--- [a]		--- [a]	
Male	2,305 (28.1)	1.01	0.95 - 1.07	480 (20.8)	1.01	0.90 - 1.12	0.99	0.86 - 1.14
Age band								
18 – 34	2,263 (32.9)	--- [a]		467 (20.6)	--- [a]		--- [a]	
35 – 64	3,480 (25.1)	0.68	0.64 - 0.73	731 (21.0)	1.02	0.90 - 1.41	1.30	1.12 - 1.50
65 and older	1,209 (29.5)	0.86	0.79 - 0.93	261 (21.5)	1.06	0.91 - 1.23	1.67	1.35 - 2.06
Deprivation[e]								
Quartile 1	1,908 (25.2)	--- [a]		383 (20.1)	--- [a]		--- [a]	
Quartile 2	2,322 (25.2)	1.19	1.11 - 1.28	477 (20.5)	1.03	0.89 - 1.19	0.82	0.68 - 0.99
Quartile 3	1,250 (28.8)	1.20	1.10 - 1.30	253 (20.2)	1.03	0.84 - 1.18	0.81	0.66 - 1.00
Quartile 4	1,472 (30.6)	1.31	1.21 - 1.42	346 (23.5)	1.19	1.02 - 1.41	0.91	0.74 - 1.11
Total	6,952			1,459				

[a] First value in each patient characteristic category set as a reference value.
[b] An Odds Ratio of >1 indicates the patient is more likely to discontinue medication after a single month of treatment;
[c] HR: hazard ratio. A hazard ratio >1 indicates the patient is more likely to restart treatment after early discontinuation.
[d] HR: hazard ratio. A hazard ratio >1 indicates the patient is more likely to remain on treatment after restart
e Deprivation quartiles: 1= least deprived, 4 = most deprived