Eur J Clin Pharmacol (2005) 61: 303–307
DOI 10.1007/s00228-005-0921-x

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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Discontinuation symptoms in users of selective serotonin reuptake inhibitors in clinical practice: tapering versus abrupt discontinuation

Received: 26 November 2004 / Accepted: 7 March 2005 / Published online: 20 May 2005

Abstract *Objective*: Tapering of selective serotonin reuptake inhibitor (SSRI) therapy, as opposed to abrupt discontinuation, has been recommended by several guidelines and in the literature in order to diminish the occurrence of discontinuation symptoms. However, the evidence of a favourable effect of tapering is limited, and it is unclear how patients ought to discontinue SSRIs in daily life. The aim of this study was to examine the way in which patients discontinue SSRI therapy in clinical practice and to compare the effect of tapering with that of abrupt discontinuation on the occurrence of discontinuation symptoms.
Methods: Patients ($n = 74$) who recently discontinued SSRI therapy completed a questionnaire containing questions about discontinuation symptoms (DESS events), the prescribed SSRI, reasons for discontinuation, way of discontinuation, knowledge of discontinuation symptoms, impact on daily life and patient counseling and education. The number of DESS events was compared among groups (abrupt discontinuation versus tapering; age; male versus female; paroxetine versus other SSRIs; knowledge of discontinuation symptoms at start of therapy versus lack of knowledge).
Results: A total of 66 patients were eligible for analysis. Of all patients ending SSRI therapy, 21% abruptly discontinued therapy. There was a significant difference in the number of DESS events between abrupt discontinuation and tapering of SSRI therapy (12.0 versus 5.9). There was also a tendency for an adverse effect of lack of knowledge of discontinuation symptoms at the start of therapy on the number of DESS events (8.9 versus 5.5).
Conclusion: One in five patients abruptly discontinued their SSRI therapy in clinical practice. Abrupt discontinuation caused a larger increase in the number of discontinuation symptoms than tapering. We therefore advise tapering SSRI therapy in clinical practice to prevent unnecessary adverse effects of discontinuation.

Keywords SSRI · Discontinuation symptoms · Tapering

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Introduction

In about one-third of the patients who stop therapy with selective serotonin reuptake inhibitors (SSRIs) discontinuation symptoms occur, which can be bothersome, have an adverse effect on patients' quality of life and may lead to unnecessary renewed antidepressant use [1, 2]. In some patients, these discontinuation symptoms can even cause considerable morbidity, can be misdiagnosed leading to inappropriate treatment and can adversely affect future antidepressant compliance [3, 4]. Although the exact mechanism of the occurrence of these discontinuation symptoms is still unclear, the symptoms are probably due to an abrupt decrease in available synaptic serotonin in the face of downregulated serotonin receptors [5]. Findings that the reintroduction of a SSRI suppresses discontinuation symptoms within hours and that SSRIs with a shorter half-life cause discontinuation symptoms more frequently than those with an extended half-life, support this hypothesis [6–8]. Tapering SSRI therapy, therefore, as opposed to abrupt discontinuation, has been recommended as part of routine practice in several guidelines and in the literature [1, 9, 10]. However, there are, to our knowledge, no observational or experimental direct comparative studies to support the tapering

recommendation. Besides the lack of evidence of a favourable effect of tapering, it is unclear how patients ought to discontinue SSRI therapy in routine practice. The GPs may not be confidently aware of adverse events associated with SSRI discontinuation [11]. In addition, patients may not always inform their physician about stopping SSRI medication [12] and discrepancies between instructions on the use of SSRIs and what patients remember being told have also been shown [13].

The aim of this study was therefore to examine the way in which patients discontinue SSRI therapy in clinical practice and to compare the effect of tapering with that of abrupt discontinuation on the occurrence of discontinuation symptoms.

Methods

Setting and design

Patients were included at 16 community pharmacies in The Netherlands between 1 December 2002 and 31 January 2003. The inclusion criteria for participation in the study were: male or female aged over 18 years, prescription duration of paroxetine, fluoxetine, fluvoxamine or citalopram of at least 2 months during the past half year and last dose of antidepressant between 2 weeks and 3 months prior to inclusion. Based on these inclusion criteria, potential patients were selected through the pharmacy information and administration systems. These patients were contacted by phone to check for inclusion criteria and willingness to participate. Eligible patients received a pretested questionnaire and were asked to complete and return it within 1 week to the study coordinator. After 1 week, patients were telephoned once to check for any problems in completing the questionnaire. Ethics committee approval at this time was not required in The Netherlands for this type of study. Because there was no information available about the number of patients abruptly discontinuing therapy in daily life, it was not feasible to make a consideration of sample size. Therefore, the number of patients was based on and limited by the potentials of the participating pharmacies.

Outcome measures

Primary outcome measure was the number of discontinuation symptoms. The occurrence of discontinuation symptoms was assessed by means of a Dutch translation of the Discontinuation-Emergent Signs and Symptoms (DESS) checklist [14]. This 43-item DESS checklist was developed by Rosenbaum et al. based on an evaluation of signs and symptoms associated with discontinuation or interruption of SSRI treatment, as reported in the available literature. Patients were asked whether they had experienced one of the listed signs or symptoms during the first week after they had discontinued antidepressant therapy, but not during antidepressant use (i.e. newly occurring DESS events). In addition, patients were asked to indicate whether the specified sign or symptom was already present during the last 2 weeks of treatment (i.e. intra-individual change in the number of DESS events). Secondary outcome measure was the occurrence of a ''discontinuation syndrome''. Patients were classified as having experienced a ''discontinuation syndrome'' if the number of reported DESS events increased by four or more from during treatment to the week after discontinuation of treatment [14]. Other questions were about reasons for discontinuation, impact on daily life, and patient counseling and education. Patients were asked to indicate the reason for discontinuation (''side effects'', ''no need for antidepressants'', ''feeling better'', ''ineffectiveness'', ''antidepressant used up'', ''forgotten and discontinued'', ''advice from others'' or ''other reasons''). Three questions were used to assess the impact on daily life. Patients were asked to rate on a 4-point scale whether discontinuation caused problems in their relationships with family or friends, with other people or in daily life and job activities (''no problems'', ''minimal problems'', ''moderate problems'', or ''severe problems''). Patients were also asked to rate their general functioning after discontinuing therapy on a 4-point scale (''excellent'', ''good'', ''reasonable'' or ''bad''). Finally, patients were asked to indicate whether they had received information about discontinuation symptoms at the start of therapy and whether they perceived this information as adequate or inadequate.

Determinants

The primary determinant of interest was the method of discontinuation SSRI therapy; abrupt discontinuation versus tapering. Patients were asked to indicate the way in which they discontinued their antidepressant: abruptly, using a self-made tapering schedule, using a GP-made schedule, using a psychiatrist-made schedule or using a schedule made by the pharmacist. Other determinants were gender, type of SSRI, age and knowledge of symptoms at the start of therapy.

Data analysis

The independent-samples *t*-test was used to compare the number of newly occurring DESS events and the intra-individual change in number of DESS events among groups of variables (abrupt discontinuation versus tapering, male versus female, paroxetine versus other SSRIs and knowledge of discontinuation symptoms at start of therapy versus lack of knowledge). The one-way analysis of variance (ANOVA) test was used to compare the number of DESS events between groups of age. The presence or absence of the discontinuation syndrome was treated as a binominal variable. Relative magnitudes of association between abrupt discontinuation

versus tapering therapy and the presence of the discontinuation syndrome is expressed as a relative risk (RR) and 95% CI. The impact on daily life variables regarding problems in relationships and contact with other people were dichotomised as ''problems'' (moderate or severe) versus ''no problems'' (no or minimal). General functioning was dichotomised as ''negative'' (reasonable or bad) versus ''positive'' (excellent or good). All statistical analyses were performed using SPSS 10.0.

Results

To check for inclusion criteria and willingness to participate in the study, a total of 105 patients were contacted. Of these, 20 could not be included: 6 were unreachable by phone, 12 were not willing or able to participate and 2 never actually started taking the antidepressant. Therefore, 85 patients fulfilled the inclusion criteria and were willing to participate—74 (87%) of these patients completed and returned the questionnaire, of which 66 (78%) patients were eligible for analysis. Mean (±SD) age of the eligible patients was 46.3 ± 14.0 years and 50 (76%) patients were female. Paroxetine was used by 46.3 (70%) patients, 7 (11%) used fluoxetine, 7 (11%) fluvoxamine and 6 (9%) citalopram. Median daily doses were 20 mg for paroxetine, 20 mg for fluoxetine, 100 mg for fluoxetine and 20 mg for citalopram. Of all patients, 14 (21%) abruptly discontinued their antidepressant, 28 (42%) used a self-made tapering schedule, 20 (30%) a GP-made schedule and 4 (6%) a tapering schedule made by a psychiatrist. The periods of tapering varied from 2 weeks to 4 months.

Table 1 lists the intraindividual change in number of DESS events after discontinuation and the number of newly occurring DESS events after discontinuation for different groups. Patients who abruptly discontinued therapy experienced significantly more DESS events than patients who tapered therapy. There is a trend for a significant adverse effect in patients who report a lack of knowledge of discontinuation symptoms at the start of therapy. No differences were shown for age, gender and prescribed SSRI. In 39 (59%) of all the patients, the ''discontinuation syndrome'' occurred. Abrupt discontinuation of antidepressant therapy has an adverse effect on the occurrence of the discontinuation syndrome (86% versus 52%; RR 1.6; 95% CI 1.2–2.3).

The most frequently reported discontinuation symptoms included nervousness or anxiety, irritability, bouts of crying or tearfulness, dizziness or lightheadedness. Trouble sleeping, dizziness, confusion or trouble concentrating, headache, nausea and vomiting were the symptoms patients experienced as most serious.

Main reasons for discontinuing antidepressant therapy were feeling better (45%), side effects (24%), no need for antidepressant (15%) and ineffectiveness (8%). More than one reason for discontinuation was indicated by 36% of all patients. Of all patients, 38% had discontinued antidepressant therapy once before. Most patients discontinued therapy on their own initiative (83%) and/or on advice of their general practitioner (27%). Patients' social environments and pharmacists hardly played a role in this. Of all patients,

Table 1 Symptoms following discontinuation of selective serotonin reuptake inhibitor (SSRI) therapy

	Number of patients	Intra-individual change in number of DESS events[a]	*P*-value[c]	Number of newly occurring DESS events[b]	*P*-value[c]
		Mean (SEM)		Mean (SEM)	
Overall	66	6.5 (1.0)		7.2 (0.9)	
Way of discontinuation					
Tapering	52	5.1 (0.9)	0.004	5.9 (0.9)	0.006
Abrupt discontinuation	14	11.7 (2.7)		12.0 (2.6)	
Gender					
Male	16	5.8 (2.3)	0.67	6.4 (2.1)	0.60
Female	50	6.7 (1.1)		7.5 (1.0)	
Age (years)					
< 40	20	4.6 (1.7)	0.28	5.5 (1.6)	0.30
40–54	30	8.1 (1.7)		8.7 (1.6)	
≥55	16	5.9 (1.3)		6.6 (1.2)	
SSRI					
Paroxetine	46	6.8 (1.2)	0.62	7.8 (1.1)	0.38
Others	20	5.8 (1.8)		6.0 (1.8)	
Knowledge of symptoms at start of therapy[d]					
Yes	25	4.9 (1.2)	0.14	5.5 (1.0)	0.08
No	35	8.0 (1.6)		8.9 (1.5)	

[a] Intra-individual change in number of DESS events from treatment phase to discontinuation phase

[b] Number of newly occurring DESS events following SSRI discontinuation

[c] *P* values assessed using one-way ANOVA for comparing the number of DESS events among groups of age and independent-samples *t*-test for comparing among groups for the other parameters

[d] Totals are less than 66 due to missing data

9% restarted their antidepressant and 27% considered restarting.

Of all patients, 38% were informed about the possible occurrence of discontinuation symptoms before starting their therapy: 27% received this information from the general practitioner, 5% were informed by the psychiatrist and 5% by the pharmacist. Knowledge of discontinuation symptoms influenced the way patients discontinued their antidepressant. Of the patients who were informed about discontinuation symptoms, 12% abruptly discontinued therapy, while in the group that was not informed 26% discontinued therapy abruptly. Of all patients, 49% perceived the information about discontinuation symptoms as inadequate.

An adverse effect on general functioning after discontinuation therapy was indicated by 83% of the patients abruptly discontinuing therapy and by 48% of the patients tapering therapy. Discontinuation influenced both daily and job activities: 45% of the patients abruptly discontinuing therapy and 26% of the patients tapering therapy experienced problems. Problems in relationships with family and friends were indicated by 29% of the patients abruptly discontinuing and by 24% of the patients who tapered their cessation. Finally, 33% of the patients who abruptly discontinued therapy and 16% of those tapering therapy experienced problems in contact with other people.

Discussion

Although guidelines recommend to taper SSRI therapy when discontinuing, this study shows that one in five patients abruptly discontinued their SSRI in clinical practice. Abrupt discontinuation of SSRI therapy caused a larger increase in discontinuation symptoms than tapering. This study also shows that abrupt discontinuation had an adverse effect on daily life activities and social functioning. An adverse effect of discontinuation has also been seen in other studies [4, 7]. Discontinuation symptoms may be misdiagnosed, leading to alternative pharmacological therapy or re-instatement of the antidepressant [4]. In our study, several patients indeed restarted their therapy. Misdiagnoses may also lead to unnecessary diagnostics and accompanying costs [6, 8, 15]. We suggest that knowledge of discontinuation symptoms and tapering strategies by both patients and professionals can be an important factor in preventing the occurrence of discontinuation symptoms. In this study, patients who reported a lack of knowledge of discontinuation symptoms at the start of their antidepressant experienced a larger increase in symptoms after discontinuation. Only one-third of all patients was informed about the possible occurrence of these symptoms.

We have used three different outcome measures to assess the effect of discontinuation: intra-individual change in number of DESS events, number of newly occurring DESS events and the occurrence of the discontinuation syndrome. The number of patients having a discontinuation syndrome, an increase of DESS events by four or more after discontinuation, represents those patients who experienced a substantial negative effect of discontinuation. However, the discontinuation syndrome is a binominal measure and therefore less sensitive for changes, whereas the intra-individual change in number of DESS events and the number of newly occurring DESS events are continuous measures. The intra-individual change in number of DESS events reflects an overall effect of discontinuation, including positive effects of discontinuation, such as the disappearance of side effects. The number of newly occurring DESS events, however, reflects the effect of discontinuation itself. Therefore, the latter approach may be more appropriate with respect to the aim of our study, comparing the effect of tapering with abrupt discontinuation. Overall, the outcome measures we used appeared to be feasible and sensitive for changes in therapy. A doubling of symptoms between tapering and abrupt discontinuation has been shown, resulting in a convincing significant and clinical effect.

We would also like to touch on some limitations of our study. Patients were interviewed retrospectively, which may have introduced a recall bias. However, the negative effect of abrupt discontinuation is strikingly large, and it is not expected that patients who abruptly discontinued their SSRI would recall more symptoms than patients who taper therapy. Selection of patients may have also introduced a bias. In view of the large number of patients willing to participate and completing and returning the questionnaire, and the characteristics of the patients, we think a selection bias is unlikely. There are no reasons to believe that the non-participating patients would differ from the participating patients in the number of discontinuation symptoms occurring. Finally, the numbers of patients using the various SSRIs were too small to show any difference among the different types of SSRIs.

One major strength of our study is that we used data from patients directly. Therefore, we were able to show how patients discontinue therapy in real life. To our knowledge, this is the first study that shows a remarkable number of patients discontinuing therapy abruptly, resulting in a rather adverse effect on patients' daily lives. Although a prospective study would be of value in studying the effect of discontinuation with respect to indication, type of SSRI and cumulative dose, the results of our study may not be undervalued. In conclusion, therefore, we urge to taper SSRI therapy in clinical practice to prevent unnecessary adverse effects of discontinuation. Patients' knowledge of discontinuation symptoms and how to discontinue SSRI therapy must therefore be improved.

Acknowledgements We would like to thank the participating pharmacists for including patients and Olga van Vemde en Chantal Fleers for collecting the data.

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