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BRIEF REPORT

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Effects of gradual discontinuation of selective serotonin reuptake inhibitors in panic disorder with agoraphobia

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Abstract

The aim of this investigation was to explore the prevalence and features of discontinuation syndromes ensuing with gradual tapering of selective serotonin reuptake inhibitors (SSRIs), in optimal clinical conditions in patients with panic disorder and agoraphobia. Twenty-six consecutive outpatients met the DSM-IV criteria for panic disorder and agoraphobia while taking SSRIs. Twenty remitted upon behavioural treatment. Antidepressant drugs were then tapered at the slowest possible pace and with appropriate patient education. Patients were assessed with the Discontinuation-Emergent Signs and Symptoms (DESS) checklist 2 wk, 1 month and 1 yr after discontinuation. Nine of the 20 patients (45%) experienced a discontinuation syndrome, which subsided within a month in all but three patients who had been taking paroxetine for a long time. Discontinuation syndromes appeared to be fairly common even when performed with slow tapering and during clinical remission. In some cases disturbances persisted for months after discontinuation.

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Key words: Antidepressive agents, discontinuation, SSRI, withdrawal.

Introduction

Discontinuation syndromes have been described with all types of antidepressant drugs (Lejoyeux and Adès, 1997), and particularly with selective serotonin reuptake inhibitors (SSRIs) (Fava, 2006b; Lejoyeux and Adès, 1997; Zajecka et al., 1997). The evidence available suggests the highest incidence of the syndrome with paroxetine and the lowest incidence of the syndrome with fluoxetine, while other SSRIs are associated with intermediate incidence (Oliver et al., 1999). Abrupt discontinuation of SSRIs has been found to cause an increase in the number of discontinuation symptoms compared to tapering (Van Geffen et al., 2005). This has led to the belief that these syndromes are unlikely to occur if physicians discontinue SSRIs in conditions of clinical remission, with slow tapering and appropriate patient education. Such a belief, however, has not been adequately tested. Further, we do not know whether onset of withdrawal symptoms from antidepressant drugs may be related to an increased vulnerability to depressive relapse or mood swings (Fava, 2003). Hypomania or mania have, in fact, been reported to develop shortly after the discontinuation of antidepressant drugs, even though they are allegedly a rare phenomenon, which has been the subject of case reports (Andrade, 2004).

The aim of this paper was to report on discontinuation syndromes ensuing in optimal clinical conditions: panic disorder with agoraphobia which remitted upon behavioural methods, slow tapering of antidepressant drugs and appropriate patient education. A 1-yr follow-up was undertaken.

Methods

The subjects were 26 consecutive outpatients who fulfilled the DSM-IV criteria for panic disorder with agoraphobia while taking SSRIs and were treated in an affective disorders programme over a period of 5 yr. The patients' diagnoses were established by a psychiatrist and a clinical psychologist independently using the Schedule for Affective Disorders and

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Table 1. Socio-demographic and clinical characteristics of patients with remitted panic disorder ($n=20$) who had SSRI discontinued[a]

Characteristics	
Age at entry, years	37.7 (13.9)
Sex, male/female	6/14
Marital status, married/unmarried	11/9
Social class, middle-upper/working[b]	15/5
Axis I, comorbidity: Yes/No	6/14
Generalized anxiety disorder	4
Hypochondriasis	2
Axis II, comorbidity: Yes/No	2/18
Dependent personality disorder	1
Obsessive–compulsive personality disorder	1
Use of antidepressant drugs: discontinuation syndromes: Yes/No	9/11
Paroxetine, 20 mg/d	5/4
Fluvoxamine, 100 mg/d	1/1
Fluvoxamine, 150 mg/d	1/0
Fluvoxamine, 200 mg/d	0/1
Fluoxetine, 20 mg/d	1/2
Citalopram, 20 mg/d	1/2
Sertraline, 50 mg/d	0/1
Duration of antidepressant drug treatment, months	29.3 (28.0)
Use of benzodiazepines: Yes/No	7/13
Alprazolam, 0.5–1.5 mg/d	4
Lorazepam, 1–3 mg/d	2
Clonazepam, 1 mg/d	1

[a] Data are given as mean (±S.D.) and number of patients.
[b] According to the classification of occupations by Goldthorpe and Hope (1974).

Schizophrenia (SADS; Endicott and Spitzer, 1978). Patients with co-occurring mood disorder and/or social phobia and/or obsessive–compulsive disorder were excluded. The project was approved by the University of Bologna ethics committee. All patients gave written informed consent after the procedures were explained to them.

After initial diagnostic evaluations, all patients were treated according to a standardized behavioural protocol by three experienced psychiatrists. Therapy was based on behavioural exposure homework only and feedback from the therapist without therapist-aided exposure (Fava et al., 2001). Treatment consisted of 12 sessions; each session lasting 30 min, once every 2 wk. Twenty patients completed treatment and 20 were panic free from both major and minor panic at the time of the post-treatment evaluation and were rated as 'much better' according to a global scale of improvement (Kellner, 1972).

The socio-demographic and clinical characteristics of the 20 patients are outlined in Table 1, as they completed treatment. Comorbidity wad assessed at the end of behavioral treatment, to minimize state-trait contaminations, using again the SADS (Endicott and Spitzer, 1978). A global assessment of the severity of panic and depressed mood concerned with the pre-treatment status was made using two 1–7 point scales of the Clinical Interview for Depression (Paykel, 1985). The two scales consist of specific anchor points and were found to yield a sensitive measurement of change upon behavioural treatment in panic disorder (Fava et al., 1994, 2001). Upon entering the study, the 20 patients were taking the antidepressant drugs detailed in Table 1 for at least 6 months. Twelve patients (4 paroxetine, 3 fluvoxamine, 3 fluoxetine, 2 citalopram) were taking benzodiazepines. In the course of behavioural treatment, according to a standardized protocol (Fava et al., 1994), benzodiazepines were tapered and, whenever possible, discontinued. In patients who had trouble tapering their benzodiazepines (mostly alprazolam and lorazepam) the psychiatrist prescribed clonazepam as a substitute. Aside from these cases, the treating physician did not prescribe any new psychotropic drugs. At the end of treatment, seven patients were still taking benzodiazepines (2 paroxetine, 2 fluvoxamine, 2 fluoxetine, 1 citalopram) even though at much lower dosages (see Table 1). These dosages were kept unchanged during the study period.

Tapering of antidepressant drugs was performed at the slowest possible pace (50 mg every other week for fluvoxamine and sertraline, 10 mg every other week for paroxetine, fluoxetine and citalopram, with 10 mg every other day in the last segment).

After 15 d from discontinuation all patients were assessed with the Discontinuation-Emergent Signs and Symptoms (DESS) checklist (Rosenbaum et al., 1998). This allowed a comprehensive collection of all manifestations of discontinuation syndrome since some may become evident only in the second week. Patients were, however, instructed to call the treating psychiatrist at any time during that period. Patients were classified as experiencing 'discontinuation syndrome' if the number of DESS checklist events reported increased by four or more from the beginning to the end of the treatment interruption period. Patients were reassessed after 1 month and 12 months. None of the 20 patients refused follow-up assessments, which consisted of an update of clinical state, including persistence of discontinuation symptoms,

any potential treatment contacts or use of medications, and occurrence of any relapse of panic disorder or onset of a new psychiatric disorder, again using the SADS (Endicott and Spitzer, 1978). Patients were instructed to call if any new symptoms appeared and were guaranteed further treatment if necessary also during the follow-up.

Differences in age, duration of drug treatment, severity of pre-treatment panic and depressed mood, use of benzodiazepines and comorbidity between patients who experienced a discontinuation syndrome and those who did not were analysed with two-tailed *t* test and Fisher's exact probability test.

Results

Nine of the 20 patients (45%) experienced a discontinuation syndrome according to specific criteria (Rosenbaum et al., 1998). There were no significant differences between the two groups in sociodemographic variables, current use of benzodiazepines, presence of comorbidity, duration of treatment and severity of pre-treatment panic and depressed mood.

All discontinuation syndromes subsided within a month in all but three patients (27%). These three patients had all been taking paroxetine and displayed alternation of worsened mood, fatigue and emotional lability with trouble sleeping, irritability and hyperactivity, meeting the DSM-IV criteria for cyclothymic disorder except for duration. The first patient (female, 32 yr), who had been taking 20 mg/d paroxetine for 18 months, after 3 months of persistence of symptoms was prescribed clonazepam 0.5 mg b.i.d. She improved considerably. Subsequent attempts to discontinue clonazepam were, however, unsuccessful, for re-emergence of symptoms. The second patient (male, 58 yr) had been taking 20 mg/d paroxetine for 84 months. Clonazepam up to 1 mg t.i.d. did not yield any improvement. Fluvoxamine (initially 50 mg/d, then 100 mg/d) was also of little help (6-wk trial). Symptoms subsided when 10 mg paroxetine was started again. The third patient (male, 39 yr) had been taking 20 mg paroxetine for 96 months. Clonazepam up to 1 mg t.i.d. was of modest help. He was offered paroxetine again but refused. Symptoms persisted unchanged for the duration of the observation period. None of these patients had a previous or family history of bipolar disorder or cyclothymia.

During the 1-yr follow-up one patient taking citalopram who had discontinuation syndrome also had a relapse of panic disorder. She was offered a new course of treatment based on exposure and became panic free at the end of such treatment. Another patient who had been treated with paroxetine and had a discontinuation syndrome developed a major depressive disorder, which responded to treatment with 20 mg/d paroxetine.

Discussion

This study has important methodological limitations. First, its naturalistic design does not allow the control of variables of a randomized control trial. Patients were treated with different SSRIs prior to the study and durations of such treatments varied considerably. Further, tapering differed according to the type of antidepressant drugs. As a result, the incidence of discontinuation syndromes cannot be compared among patients treated with different types of SSRIs. Nonetheless, the results indicate that even in optimal conditions (remission of panic disorder upon behavioural exposure, slow tapering, adequate patient education about the transient and benign nature of potential symptoms, availability of the treating physician, exclusion of patients with previous mood disorder) discontinuation syndromes were common in patients taking SSRIs. In the majority of patients these syndromes subsided within a month. However, in three patients who had been taking paroxetine for a long time symptoms persisted and had cyclothymic features, despite lack of previous bipolar spectrum features. Re-institution of paroxetine in one case, and administration of clonazepam in another were effective in improving symptoms. This latter drug was used, since it was reported to improve depressive symptoms emerging during the treatment of panic disorder with fluvoxamine (Fux et al., 1993). In another patient treated with paroxetine, a major depressive disorder ensued during the 1-yr follow-up.

These findings are consistent with the onset of manic and hypomanic symptoms after antidepressant drug discontinuation (Andrade, 2004) and with the onset of panic symptoms 1 month following abrupt paroxetine discontinuation (Bhanji et al., 2006). In this latter case, symptoms were unresponsive to citalopram and abated only when paroxetine was resumed, as was found to be the case in one of our patients. The results are also consistent with the hypothesis that long-term treatment with antidepressants may recruit processes that oppose the initial acute effects of a drug (oppositional model of tolerance). When drug treatment ends, these processes may operate unopposed, at least for some time, and increase vulnerability to mood fluctuations (Fava, 2003). Indeed, an early relapse of depression was found

to follow double-blind discontinuation of paroxetine (Montgomery and Dunbar, 1993) and fluvoxamine (Terra and Montgomery, 1998) in recurrent depression. Some individuals, either for genetic or for the combination of psychopathological and psychosocial factors may be particularly vulnerable to the persistence of discontinuation effects after antidepressant treatment. This highlights the importance of studying specific subgroups of patients when evaluating psychiatric treatment (Benazzi, 2005; Fava, 2006a).

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Statement of Interest

None.

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