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The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study

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Abstract

Twenty eight patients treated with selective serotonin reuptake inhibitors /venlafaxine were randomized to a three-day (short) or 14-day (longer) anti–depressant taper and openly assessed after a five to seven day drug-free washout, and again after seven days treatment with a new anti–depressant of the treating clinician's choice. A 'discontinuation syndrome' ($\geq$ 3 new symptoms on the Discontinuation Emergent Signs and Symptoms checklist) occurred in 46% of patients with a similar frequency in those with short (7/15) versus longer (6/13) taper. Patients initially on short half-life anti–depressants had significantly greater increases in discontinuation and depressive symptoms than those stopping fluoxetine. Four patients, all on paroxetine, developed emergent suicidal ideation after taper. These results support the importance of half-life in determining discontinuation symptoms and suggest that there is little advantage to a two-week taper over a three-day taper when switching antidepressants. Antidepressant discontinuation in depressed patients can be associated with worsening depression and increased suicidality.

Keywords

antidepressant, SSRI, fluoxetine, paroxetine, venlafaxine, discontinuation symptoms, depression, treatment, suicidality, randomised study

Introduction

Discontinuation (withdrawal) symptoms are recognized following termination or a treatment interruption of antidepressants of various classes and recent attention has focussed on the selective serotonin reuptake inhibitors (SSRIs) (Haddad *et al*., 2004). Discontinuation symptoms are usually mild and transient but in a minority of patients they can be severe and longer lasting (Haddad *et al*., 2004). Tapering the dose has been recommended to reduce discontinuation symptoms (e.g. Anderson *et al.*, 2000) but there have been no randomised trials to support this or to guide the duration of taper.

We describe a randomised naturalistic prospective study in depressed patients that investigated whether a longer (14 days) compared with a short taper (three days) decreased the incidence of SSRI/venlafaxine discontinuation symptoms.

Method

Twenty eight patients (17 female, 11 male; 26 outpatients, two inpatients) with a clinical diagnosis of major depressive disorder, treated with an SSRI or venlafaxine for $\geq$ 6 weeks and in whom the treating clinician wanted to switch antidepressant were recruited. They were assessed at baseline (T1) and then randomised to a three-day or 14-day taper of their existing antidepressant with the taper individualised according to antidepressant, dose and tablet formulation. They were reassessed five to seven days after stopping medication (T2) and then commenced a new antidepressant (excluding monoamine oxidase inhibitors (MAOIs)) of the treating clinician's choice. A final assessment (T3) occurred after one week's treatment with the new antidepressant. The study was approved by the Local Research Ethics Committee and written informed consent obtained from participants.

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Assessments consisted of the Mongomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and a modified version of the 43-item, clinician rated, Discontinuation Emergent Signs and Symptoms (DESS) checklist (Rosenbaum *et al.*, 1998). We scored each DESS item as absent (0), mild (1), moderate (2) or severe (3) and summed to give a total score. Presence of a discontinuation syndrome was defined as three or more new DESS items at T2. Planned comparisons were between (i) the three-day and 14-day taper, (ii) fluoxetine (long half-life) and shorter half-life antidepressants (other SSRIs/venlafaxine) and (iii) those switching to sameclass (SSRI or venlafaxine) versus different class (all others) antidepressants. Analysis was by repeated measures analysis of variance (ANOVA) with Huynh-Feldt correction for repeated measures and Fisher's exact tests for categorical data. Values are mean ± standard deviation.

Results

Fifteen patients were randomised to the short taper group and 13 to the longer taper group. Mean age was 39 years (SD ± 12 years) and duration of current anti–depressant treatment was 62.4 (SD ± 11.5) weeks with no statistical differences between groups. Results were available for all patients at T2 but one patient was not available for the T3 assessment. Seven were prescribed fluoxetine [four short taper (S), three longer taper (L)] and 21 other SSRIs/venlafaxine [eight paroxetine (3S, 5L), five venlafaxine (3S, 2L), five citalopram (4S, 1L), three fluvoxamine (1S, 2L)]. Fourteen switched to a same class antidepressant and 14 to a different class antidepressant.

The ANOVA showed a significant effect of time on DESS symptoms [$F(2,52) = 9.893$, $P < 0.001$] due to an increase after taper at T2, which had returned to near baseline at T3. The most common new or worsened DESS items at T2 were dizziness (42%), headache (42%), nervousness/anxiety (42%), panic/sudden anxiety (32%), agitation (32%), nausea (32%) and sudden worsening of mood (32%). Thirteen (46%) patients had a discontinuation syndrome (paroxetine 5/8, venlafaxine 3/5, citalopram 3/5, fluvoxamine 0/3, fluoxetine 2/7).

MADRS values increased significantly with discontinuation of antidepressants [time: $F(2,52) = 3.371$, $P = 0.046$], rising from 29.7 ± 8.3 at T1 to 33.8 ± 12.4 at T2, declining to 30.78 ± 12.1 at T3.

Although DESS symptoms tended to be a little higher overall in the short taper group this was not significant [$F(1,25) = 1.50$, $P = 0.232$]. The incidence of a discontinuation syndrome for patients undergoing a short taper (7/15, 47%) did not differ from those with a longer taper (6/13, 46%) ($P = 1.0$) and there was no significant taper x time interaction [$F(2,50) = 0.121$, $P = 0.878$] (Figure 1a). MADRS scores were numerically slightly higher in the short taper group at T1 and this difference increased at T2 and T3 but there was no statistically significant difference between the groups overall [$F(1,25) = 0.841$, $P = 0.368$] and no significant taper x time interaction [$F(2,50) = 0.691$, $P = 0.497$] (Figure 1c). This finding remained when patients initially prescribed fluoxetine were excluded from the analysis (data not shown).

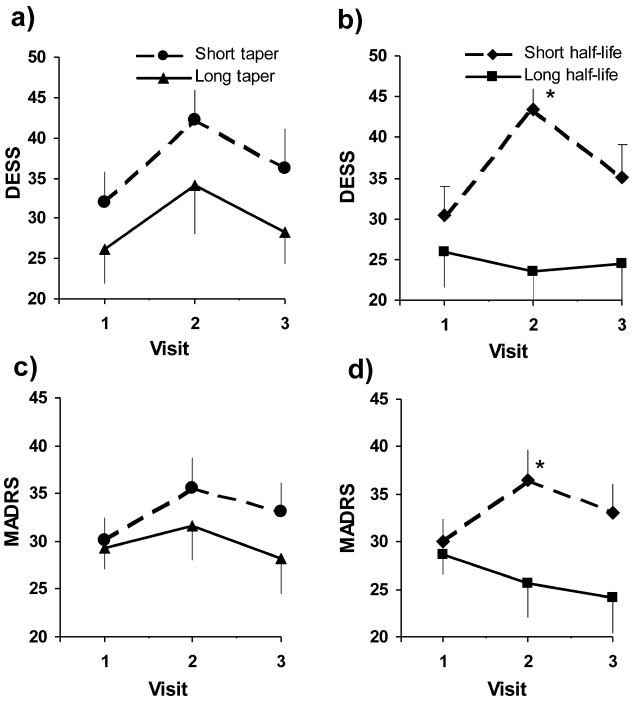

Figure 1 The effect of antidepressant half-life and rate of taper on discontinuation symptoms in depressed patients taking SSRIs/venlafaxine
a) Increase in discontinuation symptoms with drug taper [time: $F(2,52) = 9.893$, $P < 0.001$]
b) Increase in discontinuation symptoms according to drug half-life [half-life x time interaction: $F(2,50) = 6.391$, $P = 0.003$]
c) Increase in depressive symptoms with drug taper [time: $F(2,52) = 3.371$, $P = 0.046$]
d) Increase in depressive symptoms according to drug half-life [half-life x time interaction: $F(2,50) = 4.38$, $P = 0.018$]

The incidence of a discontinuation syndrome for patients on fluoxetine (2/7, 29%) was numerically but not significantly lower than for those on shorter half-life drugs (11/21, 52%) ($P = 0.40$). There were, however, significant half-life x time interactions for both the DESS [$F(2,50) = 6.391$, $P = 0.003$] (Figure 1b) and MADRS [$F(2,50) = 4.38$, $P = 0.018$] (Figure 1d) due to a large increase in symptoms at T2 with short half-life drugs but not with fluoxetine where overall values fell slightly. Separate analysis of MADRS items 1 + 2 (objective and subjective depressed mood) showed the same finding [$F(2,50) = 7.536$, $P = 0.001$]. Analysis of the MADRS suicide item did not show any overall increase during the discontinuation period [$F(2,50) = 0.138$, $P = 0.842$] but there was a trend for a half-life x time interaction [$F(2,50) = 3.270$, $P = 0.054$] due to an increase in the rating in the short half life group at T2 but a decrease in the fluoxetine group. Analysing the groups separately, in the short half-life group between T1 and T2 there was a significant increase in the suicide item rating

[$F(1,20) = 4.59$, $P = 0.045$] whereas there was a non-significant decrease with fluoxetine [$F(1,6) = 2.077$, $P = 0.20$]. Four patients, all on paroxetine, developed emergent suicidal ideation (defined as a MADRS suicide item score of two or less at T1, increasing to four or more at T2).

DESS and MADRS values decreased to near baseline at T3 with no significant difference according to class of antidepressant restarted (data not shown).

Discussion

We found that tapering over 14 days compared with three days did not reduce the incidence of discontinuation symptoms. A limitation of the study is that we do not know whether shorter (e.g. abrupt discontinuation) or longer taper duration would have revealed a difference. A study of abrupt interruption of SSRI treatment in remitted patients found a very similar incidence of a discontinuation syndrome to our findings (Rosenbaum *et al.*, 1998) although different definitions make it difficult to compare the severity of the syndrome. In clinical practice, the taper period when switching antidepressants in non-responders is likely to be within the range we chose for our study as tapering over a longer period would be impractical. We found that the increase in discontinuation symptoms was less marked with fluoxetine than other shorter half-life SSRIs and that the highest incidence of a discontinuation syndrome occurred with paroxetine. Both results are consistent with previous research (Rosenbaum *et al.*, 1998).

Case reports and intuition suggest that discontinuation symptoms are less likely when one switches between antidepressants with similar pharmacodynamic profiles. We were unable to confirm this but our study design meant that the second antidepressant was started at a time when symptoms were likely to be resolving spontaneously in any case (Haddad *et al.*, 2004). Earlier initiation of the second antidepressant may have prevented or reduced the severity of discontinuation symptoms but this needs to be investigated in an appropriately designed trial.

The increase in depressive symptoms during discontinuation is worrying, in particular the increase in suicidality, which has not previously been emphasised when stopping treatment. While depressive symptoms increased more in the short taper group than the longer taper group this was not statistically significant and overall the difference in taper length seems less important than the difference in half-life. Given the concerns about suicidality in relation to SSRIs (Cipriani *et al.*, 2005) this finding is important in highlighting the need for close monitoring when discontinuing SSRIs and venlafaxine.

The strengths in our study are the randomisation to taper length and the use of accepted instruments in determining discontinuation symptoms and mood changes. However, the study was open with small numbers and the results, therefore, need to be seen as preliminary and need replication. Nevertheless, the findings are generally consistent with previous studies and provide important additional information to clinicians faced with the common problem managing the switching of antidepressants in depressed patients. They suggest that the duration of taper is less important than the half-life of the drug (at least for tapers between 3 and 14 days) and that patients need to be warned about, and monitored for, the possibility of increased depressive and suicidal symptoms as part of the discontinuation syndrome.

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Erratum

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