Dual Reuptake Inhibitors Incur Lower Rates of Tachyphylaxis Than Selective Serotonin Reuptake Inhibitors: A Retrospective Study

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Background: The notion that selective serotonin reuptake inhibitors (SSRIs) may be associated with higher relapse rates than other antidepressants during maintenance treatment (tachyphylaxis) has been discussed for years, but to date there is little or no empirical evidence confirming this phenomenon. In this study, we systematically assessed prior antidepressant treatment history in a cohort of depressed patients who presented for outpatient psychiatric treatment. Rates of tachyphylaxis were compared in venlafaxine and tricyclic antidepressants (TCAs), which act as dual reuptake inhibitors, versus SSRIs.

Method: 237 patients who presented for treatment at the Rhode Island Hospital Department of Psychiatry's outpatient practice and were diagnosed with DSM-IV major depressive disorder were interviewed with the semistructured Treatment Response to Antidepressant Questionnaire. This cohort reported having undergone 326 prior SSRI trials, 47 prior venlafaxine trials, and 35 prior trials with a TCA. Rates of tachyphylaxis as a function of antidepressant class were compared.

Results: Rates of tachyphylaxis were significantly lower ($\chi^2 = 6.77$, df = 1, p = .01) with the dual reuptake inhibitors venlafaxine and TCAs (3 [3.7%] of 82) compared to rates of tachyphylaxis with SSRIs (46 [14.1%] of 326).

Conclusion: These results provide preliminary evidence that dual reuptake inhibitors may incur lower rates of tachyphylaxis than SSRIs. By virtue of the retrospective and nonrandom design of the study, these results warrant confirmation.

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The introduction of fluoxetine in 1988 ushered in a new era of psychopharmacology. The newer generation of antidepressant agents were safer, better tolerated, and treated a broad spectrum of disorders. The next decade consequently saw a dramatic increase in antidepressant prescriptions. Although the advantages of the selective serotonin reuptake inhibitors (SSRIs) over the older generation of tricyclic antidepressants (TCAs) were almost immediately apparent, anecdotal reports soon emerged suggesting that SSRIs may be less effective than TCAs during the maintenance phase of treatment. Patients who had initially responded to SSRIs seemed to lose their response over time (i.e., experience tachyphylaxis[1–4]) more frequently than had been observed with TCAs. Although the SSRI "poop-out" effect has never empirically been confirmed, it remains well entrenched in clinical lore. Researchers have further speculated that dual reuptake inhibitors, such as venlafaxine and TCAs, may offer greater protection against tachyphylaxis since 2 neurotransmitter systems are targeted rather than 1, although this too has yet to be empirically tested.

In the present study, we sought to examine whether a differential rate of tachyphylaxis could be elicited between various classes of antidepressants by systematically examining the treatment histories of patients who presented to our outpatient psychiatric practice. Antidepressant treatment histories are systematically assessed in patients presenting to our practice with the Treatment Response to Antidepressant Questionnaire (TRAQ). The TRAQ is a semistructured instrument developed by our group with demonstrated reliability[5] and validity.[6] Based

on previous suggestions, we hypothesized that tachyphylaxis would be reported significantly less frequently in past treatment trials with venlafaxine and TCAs than in SSRI trials.

METHOD

All subjects were receiving treatment at the Rhode Island Hospital Department of Psychiatry's Outpatient Department (Providence, R.I.). As part of the Methods to Improve Diagnostic Assessment and Services (MIDAS) project,[7,8] patients who present to the practice are invited to undergo a research diagnostic evaluation prior to meeting with their treating clinician.[8] The diagnostic evaluation is most often conducted by Ph.D.-level psychologists who have undergone extensive training as described elsewhere.[7,8]

Antidepressant treatment history was elicited using the TRAQ.[5,6] The TRAQ is a semistructured instrument designed to systematically collect information regarding past antidepressant trials, trial adequacy, response history, and compliance. Once all prior antidepressant trials have been elicited in the TRAQ interview, response history is ascertained by asking patients whether the antidepressant they received helped their depression. Typically, follow-up questions are required in order to clarify answers. Raters then ask patients to confirm their response by asking such questions as "So you believe that you had an excellent response to fluoxetine?" Generally, a positive response corresponds to a 50% or more reduction in depressive symptoms. Patients and raters are instructed not to attempt to determine whether the improvement in depressive symptoms was due to the medication, but only whether or not the improvement temporally coincided with the antidepressant trial.

Tachyphylaxis was deemed to occur when patients reported having initially had a good or excellent response for a minimum of 16 weeks that was lost over time. Thus, patients who reported only partial benefit from the medication could not be rated as having had a positive but lost response. Tachyphylaxis was confirmed in a subsequent question that inquired as to why the medication trial was stopped. Some patients, for example, who reported having had a positive but lost response then stated that they stopped the medication because they were feeling better and believed they no longer needed to take it. In such instances, patients were asked to reconcile the contradiction. A tachyphylaxis rating was obtained only when patients confirmed that the medication trial was stopped because the medication was no longer believed to be working. The results of the TRAQ interviews were always confirmed, and if necessary, amended, by the treating psychiatrists. The present protocol was approved by Rhode Island Hospital Institutional Review Board, and all subjects provided informed, written consent.

The proportion of tachyphylaxis trials was established for each antidepressant or antidepressant class of interest (SSRIs were grouped together as a class, as were TCAs) by dividing the number of tachyphylaxis trials by the total number of trials that were rated as being of adequate dose and duration. The χ^2 test was used to compare rates of tachyphylaxis between the dual reuptake inhibitors venlafaxine and TCAs and the SSRIs. Statistical significance was set at $p < .05$, and all tests were 2-tailed.

RESULTS

Two hundred thirty-seven subjects with a past or present diagnosis of DSM-IV major depressive disorder (MDD) were interviewed with the TRAQ. This cohort reported having undergone a total of 487 monotherapy antidepressant trials in the past that were prescribed at or above the minimum effective dosage (e.g., fluoxetine, 20 mg/day; sertraline, 50 mg/day; paroxetine, 20 mg/day; citalopram, 20 mg/day; escitalopram, 10 mg/day; amitriptyline, clomipramine, imipramine, and desipramine, 100 mg/day; nortriptyline, 50 mg/day) and duration (4 weeks or longer) and that were prescribed specifically for MDD. Of these, 326 trials were with an SSRI (fluoxetine, 90; sertraline, 82; paroxetine or paroxetine controlled release, 89; fluvoxamine, 6; citalopram, 46; escitalopram, 13), 47 with venlafaxine, and 35 with a TCA (amitriptyline, 13; clomipramine, 2; imipramine, 8; nortriptyline, 6; desipramine, 5; other TCA, 1). Of the 326 prior SSRI trials, the response in 46 instances (14.1%) was described as having been positive but lost. By comparison, only 2 (4.3%) of 47 venlafaxine trials and 1 (2.9%) of 35 TCA trials were reported as having a positive but lost response. Rates of reported tachyphylaxis were significantly lower for the dual reuptake inhibitors (venlafaxine plus TCAs) compared to the SSRIs ($\chi^2 = 6.77$, $df = 1$, $p = .01$), although rates of tachyphylaxis just missed statistical significance when we individually compared the venlafaxine ($\chi^2 = 3.56$, $df = 1$, $p = .06$) and TCA ($\chi^2 = 3.53$, $df = 1$, $p = .06$) cohorts to the SSRI cohort.

The overall mean ± SD (67 ± 123 versus 61 ± 103 weeks) and median (24 weeks for both) trial durations were nearly identical for the dual reuptake cohort and the SSRI cohort, respectively, suggesting that differences in trial durations can not account for the differential rate of tachyphylaxis. In the 49 trials in which tachyphylaxis was described, the mean ± SD trial duration was 121 ± 168 weeks (minimum, 16 weeks; maximum, 233 weeks). The 25%, 50%, and 75% quartile durations were 69 weeks, 123 weeks, and 169 weeks, respectively.

DISCUSSION

For years, the notion of an SSRI "poop-out" effect has permeated clinical lore, and it has been suggested that

dual reuptake inhibitors may provide better protection against tachyphylaxis. To the best of our knowledge, the present report is the first to provide empirical support for this assertion. The fact that lower rates of tachyphylaxis were found in both venlafaxine and TCA trials provides independent and complementary confirmation of our results. Nevertheless, several limitations to the present study should be kept in mind. First, our study relied entirely on retrospective reports, which are obviously less reliable than prospective ratings. However, in our previous study,[6] we demonstrated that patient report using the TRAQ elicited valid information when compared to actual treatment histories. Furthermore, the limitation of retrospective reporting would not explain why a *differential* rate of tachyphylaxis was elicited between the antidepressant classes.

Another limitation is that treatment was not randomized, and patients who received venlafaxine or TCAs may have been inherently different from those who received SSRIs. However, because venlafaxine and TCAs are often reserved for more severely ill patients and those with treatment-resistant depression, one might expect even higher rates of tachyphylaxis in these cohorts. A third limitation is that raters may have been biased in their ratings if they were familiar with the notion of an SSRI "poop-out" effect. Arguing against this limitation is the fact that most ratings were collected by psychologists who do not attend psychopharmacology conferences and have minimal exposure to the psychopharmacology literature. Although all ratings were subsequently reviewed by the treating psychiatrist, modifications in ratings were by far the exception rather than the rule.

Finally, our decision to combine the TCA and venlafaxine groups into a single cohort may legitimately be questioned. After all, desipramine and nortriptyline act mostly on the noradrenergic system, while venlafaxine resembles an SSRI at lower doses[9] (11 patients in the venlafaxine cohort reported receiving a maximum dosage of 75–149 mg/day, and 12 received 150 mg/day), and paroxetine has even been shown to have noradrenergic activity.[10] Thus, the line distinguishing between monoamine and dual reuptake inhibitors is blurry. Our decision to compare TCAs as a class and venlafaxine to SSRIs was an a priori decision made to test the clinical lore that these antidepressants incur lower rates of tachyphylaxis than SSRIs. It is hypothesized, but not given, that if dual reuptake inhibitors do in fact incur lower rates of tachyphylaxis, it is this mechanism of action that is responsible. Strictly speaking, however, the present study does not test the dual reuptake inhibition hypothesis as much as it tests an antidepressant class effect.

CONCLUSION

In conclusion, the present study provides preliminary evidence that dual reuptake inhibitors may incur lower rates of tachyphylaxis than monoamine reuptake inhibitors. By virtue of the retrospective and nonrandom design of this study, these results warrant confirmation in prospective, randomized trials.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), escitalopram (Lexapro), fluoxetine (Prozac and others), imipramine (Tofranil and others), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

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