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# VENLAFAXINE AND TREATMENT-RESISTANT DEPRESSION

Michael E. Thase, M.D.,* Edward S. Friedman, M.D., and Robert H. Howland, M.D.

***Treatment-resistant depression (TRD) is an important clinical problem. This paper briefly reviews the definition of TRD and summarizes methodological issues that pertain to treatment research. Recent studies of venlafaxine treatment for TRD also are reviewed. It is concluded that venlafaxine at higher doses is a reasonably well-tolerated and an effective alternative for patients with TRD and typically should be used before tricyclic antidepressants or monoamine oxidase inhibitors. Further research is needed to confirm the prediction that switching a SSRI nonresponder to venlafaxine is a more effective strategy than switching to a second SSRI. The relative merits of switching from a SSRI to venlafaxine versus adding a norepinephrine reuptake inhibitor also warrant careful study. Depression and Anxiety, Volume 12, Supplement 1:55–62, 2000.*** *© 2000 Wiley-Liss, Inc.*

**Key words:** *venlafaxine; treatment resistance; refractory depression; depression; antidepressants*

## INTRODUCTION

Depression is an important public health problem and, among those who receive appropriate antidepressant therapy, 10–20% will remain persistently depressed despite multiple treatment trials. These patients, often described as treatment resistant or refractory, require a disproportionately large amount of mental health services and have manifold disabilities at home and in the workplace. Therefore, identification of effective therapies that work after others have failed has great importance not only for our patients and their families but also for society at large. This article will briefly review the methodology of research studies on treatment-resistant depression (TRD) and specifically focus on studies of venlafaxine (VLX) conducted with antidepressant nonresponders.

## UNDERSTANDING TRD: OVERVIEW

There are about as many review papers on TRD as there are well-controlled clinical trials of this important problem [Thase and Rush, 1995]. This directly reflects how difficult the topic is to study.

TRD is a description of a particular type of clinical course, not a diagnosis [Dyck, 1994]. There are many reasons that people do not respond to antidepressant pharmacotherapy [Fava and Davidson, 1996; Thase and Rush, 1995]. Heterogeneity of samples with TRD is the rule, not the exception. Critical factors that influence the probability of response to antidepressants include nonadherence, misdiagnosis of the principal (Axis I) disorder, and failure to recognize a general medical disorder or medication toxicity that can prolong depression [Fava and Davidson, 1996; Thase and Kupfer, 1987]. Other important factors that can increase the likelihood of nonresponse include an antidepressant trial of insufficient dose and/or inadequate duration, ongoing alcohol or substance abuse, or other Axis I or Axis II co-morbidities, lack of social support, and marked ongoing stressors [Fava and Davidson, 1996; Thase and Howland, 1994; Thase and Kupfer, 1987]. Several subtypes of depression also respond differentially to various antidepressants. For example, psychotic depressions often do not respond to antidepressant monotherapy, reverse neurovegetative features may reduce the probability of response to some antidepressants (but not others), and recognition of past hypomanias or dysphoric mixed states may result in emphasizing mood stabilizers ahead of further trials of antidepressants [Schatzberg and Rothschild, 1992; Stewart et al., 1993; Sachs, 1996]. In practice, the "art" of treating TRD patients is one part perseverance and one part the ability to sift through the myriad factors that may have contributed to each patient's particular treatment history.

If all things were equal, which of course they never are, algorithm-guided care of antidepressant nonresponders might suffice. For example, Thase and Rush

**University of Pittsburgh School of Medicine, Department of Psychiatry, Pittsburgh, Pennsylvania**

*Correspondence to Dr. Michael E. Thase, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213-2593. E-mail: thaseme@msx.upmc.edu

[1997] illustrated that a competently administered sequence of five different strategies could be expected to deliver a 95% cumulative response rate. In practice, however, the proportion of people who develop chronic depression during prospective follow-up is three or four times larger than expected from a simple accumulation of the probabilities of responding to sequential strategies [Coryell et al., 1990]. Sequential treatment algorithms also are less helpful when it is necessary to pick between several diverse but apparently comparably useful alternatives or when there are no data, only divergent opinions about subsequent options. Treatment algorithms thus provide only a template than can guide selection of more or less appropriate options.

Thase and Rush [1995, 1997] have suggested that, after careful evaluation of each patient's risk factors for nonresponse and history of various treatments, the clinical course of TRD can be staged according to prior treatment history. Use of this staging system, summarized in Table 1, helps to ensure that each patient will receive the best-documented treatments in a logical order. By specifying nonresponse to tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs), and electroconvulsive therapy (ECT) to define several classes of newer antidepressants, stages of TRD, the approach described by Thase and Rush [1995, 1997] also takes into account the side effect burden and/or complexity of the alternate strategies. Furthermore, we suggest that the term "refractory depression" not be used until a patient has not responded to a series of up to five treatment trials, culminating with bilateral ECT. We will use this approach to staging TRD to describe the samples of studies included in this review.

## MEASURING OUTCOME IN TRD

The standard randomized clinical trial approach used to test the efficacy of novel antidepressants is not well-suited for studies of TD. One the one hand, comparative studies of active treatments require large sample sizes, which essentially prevent adequately powered studies to be conducted at a single site. On the other hand, the standard control condition of smaller clinical trials, double blind placebo, is increasingly under scrutiny for studies of uncomplicated groups of depressed patients [Rothman and Michaels, 1994], let alone for studies of patients who have failed to respond to several medication trials [Thase and Rush, 1997]. As a result, virtually no randomized, double blind placebo-controlled trials have been conducted with samples of patients in more advanced stages of TRD.

**TABLE 1. A simple system for staging antidepressant resistance**

| | |
|---|---|
| Stage I: | failure of at least one adequate trial of one major class of antidepressants |
| Stage II: | failure of at least two adequate trials of at least two distinctly different classes of antidepressant |
| Stage III: | Stage II resistance plus failure of an adequate trial of a TCA or MAOI |
| Stage IV: | Stage III resistance plus failure of an adequate trial of a MAOI and TCA |
| Stage V: | Stage IV resistance plus failure of a course of bilateral ECT |

There are, however, several alternate designs to consider. Random assignment to continue to take the most recent, ineffective antidepressant may be preferable to a placebo condition, particularly if the antidepressant has not been taken for longer than 6 weeks. There is evidence, for example, that more chronically depressed patients benefit from longer medication trials [Thase et al., 1996; Keller et al., 1998] and about 20% of the patients studied by Thase et al. [1989] responded between the 12th and 18th week of treatment with the combination of imipramine and interpersonal psychotherapy. Nevertheless, unless there is some experimental manipulation, such as adding a placebo to the ongoing treatment, patients in a continued treatment control condition will not have the same expectation for improvement as those who receive a different form of treatment. Adding a placebo to an ongoing course of antidepressant therapy would equate expectancies if the study included an active augmentation strategy. The handful of such studies that have been completed suggest that low placebo response rates can be expected, on the order of 10–20% [see Thase and Rush, 1995]. However, a placebo augmentation response rate of 47% was reported in a recent study in which a minimum antidepressant trial of only 4 weeks was required [Landén et al., 1998].

For studies of alternate monotherapies (i.e., switch studies), an active control group can be used. If an augmentation strategy is chosen as the comparator, which one should be considered as the standard? Augmentation with lithium salts is clearly the best studied, followed by augmentation with thyroid hormone, pindolol, and buspirone [Aronson et al., 1996; Thase et al., 1998; Nelson, 1998]. As the latter two strategies have not yet been established definitively as effective, we would recommend using lithium or thyroid augmentation as a basis of comparison. These strategies can be expected to yield 30 to 50% response rates [Aronson et al., 1996; Thase and Rush, 1995].

Another strategy that could permit the ethical use of a placebo would capitalize on the role of psychotherapy in TRD [Thase, 1997; Fava et al., 1997]. Psychotherapy is highly valued by most depressed patients [Seligman, 1995] and there have been a sufficient number of clinical case series in TRD to justify it as a reasonable intervention [Thase and Howland, 1994; Fava et al., 1997]. To utilize psychotherapy as a control condition, a protocol might have patients begin a focused, time-limited therapy before discontinuing the ineffective antidepressant. Patients might then enter the double-blind medication trial only if they are not experiencing significant symptom relief at the end of 6 to 8 addi-

tional weeks of therapy. Random assignment to an antidepressant or placebo could then be implemented in concert with completion of an additional 6 to 8 weeks of therapy.

More commonly, switch studies of TRD are essentially open label case series. Response rates in these studies vary from as low as 0% to as high as 80% [see Thase and Rush, 1995]. We suspect that the wide variation in response rates is more reflective of the heterogeneous past treatment histories of the patients groups, rather than the potency of the interventions being tested. Open label switch studies thus convey only the most coarse estimate of the promise of a novel strategy. Randomization and, when feasible, double blind administration of an active comparator and the novel are ultimately necessary to accurately gauge the safety and utility of these strategies.

For Stage I treatment resistance, a switch "within-class" has become a relevant option [Thase and Rush, 1997]. A number of open label studies have examined the tolerability and response to a second SSRI after failure of an initial trial. Most of these studies have reported response rates of 50% or higher, indicating that the within-class switch is a credible alternative for SSRI nonresponders [Brown and Harrison, 1995; Joffe et al., 1996; Thase et al., 1997]. However, the adequacy of the prior treatment trial usually was not confirmed prospectively and, in the single inpatient trial of a highly comorbid patient group, a much lower response rate was observed [Zarate et al., 1996]. Thus, the relative efficacy of the within-class switch is still in doubt. Future studies of novel interventions for SSRI nonresponders thus could utilize randomization to double-blind therapy with a second SSRI trial as an ethically acceptable. From this perspective, the novel intervention would have to be superior to the second SSRI to be a clinically meaningful strategy.

For patients who have failed at least two SSRIs, one of the most critical questions centers around whether it is better to switch to another newer antidepressant (i.e., bupropion, VLX, nefazodone, mirtazapine, moclobemide, or reboxetine) or to rely upon an older standard, such as a TCA or a nonselective, irreversible MAOI. Although there is compelling evidence that the MAOIs are useful treatments for antidepressant nonresponders [e.g., Nolen et al., 1988; Thase et al., 1995], problems with tolerability and concerns about the need for dietary adherence to prevent hypertensive crises have greatly limited their application. One possible strategy could delimit use of MAOIs to studies of patients with antidepressant-resistant bipolar depression [Thase et al., 1992a; Ketter et al., 1995] or prominent reverse vegetative features [Thase et al., 1992b], for whom the MAOIs may be truly the preferred treatment of "next choice." Conversely, TCAs could be reserved for studies of patient groups with more typical features. In this way, the tolerability and efficacy of newer strategies could be evaluated against appropriately chosen older standards.

For the small number of TRD patients who have failed both TCAs and MAOIs, ECT is the only strong basis of comparison. One can expect an ECT response rate of 50% to 60% in Stage IV TRD [Prudic et al., 1990], and it is likely that no other treatment currently available has this chance of success [Thase and Rush, 1997]. A design utilizing random assignment to ECT versus a novel intervention thus represents the best strategy for patients with more advanced stages of resistance. Beyond efficacy, factors such as cost, risk of memory impairment and relapse risk after successful initial treatment provide important secondary considerations when ECT is the comparator. For example, a novel pharmacologic treatment may be significantly less effective than ECT at day 28 and yet have offsetting advantages in terms of lower cost, less memory impairment, and a lower risk relapse.

## WHY VENLAFAXINE? PRACTICAL AND CONCEPTUAL RATIONALES

Among the various options available for SSRI nonresponders, switching to VLX has received considerable attention. There are several reasons that shaped the initial experiences with VLX as a second- or third-line strategy. First, when the immediate-release (IR) formulation of VLX was introduced in the United States in 1995, there were already three SSRIs on the market. When compared to fluoxetine, sertraline, and paroxetine, VLX-IR therapy necessitated twice daily dosing, could result in decimalized doses (e.g., 37.5 mg or 112.5 mg), and often required more dosage titration, with efficacy at daily doses as low as 75 mg and as high as 375 mg. Second, unlike the SSRIs, higher dose VLX-IR therapy was associated with an increased risk of blood pressure elevations, necessitating regular monitoring [Thase, 1998]. Third, despite overall comparability of side-effect profiles, nausea early in therapy was more problematic with VLX-IR than the SSRIs [Preskorn, 1995]. Although slower dosage titration and symptomatic treatment of nausea could lessen this side effect, such problems tended to reinforce early clinical impressions that VLX-IR was a more difficult medication to prescribe than the SSRIs. Finally, there was early evidence that VLX-IR at higher doses may have greater efficacy than SSRIs [Clerc et al., 1994; Dierick et al., 1996], which provided further impetus for use of VLX when SSRIs fail.

A subsequent review of published studies [Thase, 2000a] confirmed that, at doses of 150 mg/day or higher, VLX therapy was associated with a 10% advantage in remission rates when compared to SSRIs. This finding parallels the results of earlier meta-analyses comparing tertiary amine TCAs and SSRIs [Anderson and Tomenson, 1995; Anderson, 1998]. Such differences in efficacy have been presumed to be the result of the capacity of VLX and tertiary amine TCAs

such as clomipramine to inhibit reuptake of both serotonin and norepinephrine [Anderson, 1998; Thase, 2000a]. This characteristic, often referred to as "dual reuptake" mechanism of action, appears to be more pronounced at higher doses of VLX doses of 150 mg and higher [Harvey et al., 2000]. Although a causal relationship between increasing potency of norepinephrine reuptake inhibition and stronger clinical effects has not been proven, available evidence supports such a relationship. For example, the clinical relevance of this observation is bolstered by evidence of dose-response relationships with respect to both symptom reduction [Rudolph et al., 1998] and increased blood pressure [Thase, 1998]. It is the combination of empirical evidence of greater efficacy, a coherent conceptual basis for predicting differential response, and greater simplicity and safety versus alternatives (i.e., clomipramine or TCA + SSRI combinations) that has justified the continued interest in the VLX molecule for TRD.

## STUDIES OF VENLAFAXINE IN TRD

There are four published studies of VLX therapy in TRD [Nierenberg et al., 1994; de Montigny et al., 1999; Poirer and Boyer, 1999; Mitchell et al., in press]. Three reports describe prospective open label case series, ranging in size from 70 to 312 patients. The fourth [Poirer and Boyer, 1999] reports a randomized, double blind trial comparing VLX and paroxetine. All four studies utilized the IR formulation of VLX. A fifth study, which compares response to lower and higher doses of the extended release (XR) formulation in SSRI nonresponders, should be completed by the end of the year 2000. The four completed studies are summarized on Table 2 and are described below.

The first report of the VLX-IR therapy in TRD was published in 1994. Nierenberg et al. [1994] treated 70 patients with nonbipolar depression for up to 12 weeks. Past treatment histories were carefully documented and all patients had failed at least three different treatment strategies, including a TCA. A subgroup of patients (n = 15) also had failed to respond to ECT. Thus, the study group consisted of patients with Stage III, Stage IV, or Stage V TRD. In addition to their advanced degree of treatment resistance, the study group was quite chronically depressed with an average episode duration of 4.2 years at the start of VLX treatment.

Patients were treated with a fixed-flexible dose protocol initiated at 25 mg of VLX-IR on day 1, 50 mg on days 2–4, 75 mg on days 5–7, and 150 mg on days 8–14. Thereafter, the dose could be increased by 75 mg/day per week, if tolerated, to a maximum of 450 mg/day. The mean dose of VLX-IR received during the protocol was 245 (s.d. = 99) mg/day. Concomitant

**TABLE 2. Summary of published studies of venlafaxine-IR treatment of antidepressant nonresponders**

| Study | TRD stages | Comparator | n | Weeks of treatment | Dose (SD) | Response rate (%) | Remission rate (%) | Comments |
|---|---|---|---|---|---|---|---|---|
| Nierenberg et al. [1994] | IV and V | None | 70 | 12 | 245 (99) | 33 | 16 | Only 2 of 15 (13%) ECT nonresponders responded to VLX-IR. 23/55 (41%) Stage IV TRD patients responded; 54% of responders may have relapsed by month 6. |
| de Montigny et al. [1999] | I through IV | None | 152 | 8 | 260 (98) | 58 | 28 | Responders not evaluated in relatioin to past treatment history. |
| Mitchell et al. [2000] | I through IV | None | 312 | 8 | 201 (NA) | 53 | 41 | Response not evaluated in relation to stage of resistance. Poorer outcomes in patients with comorbid disorders and among those who failed to respond to a maximal trial of a TCA. |
| Poierer and Boyer [1999] | Mostly II | Paroxetine | 60<br>62 | 4 | 269 (47)<br>36 (5) | 45<br>36 | 37<br>18 | Difference in remission rate is statistically significant. However, differences on HAM-D and CGI response rates and HAM-D mean symptom improvement scores were not significant. |

therapy with lorazepam (up to 3 mg/day) was permitted during the first 3 weeks of treatment.

Among the final sample of 70, four patients (5.7%) withdrew from the study during the first 6 weeks because of side effects. Four other patients subsequently withdrew because of side effects. Five additional patients (7%) were withdrawn early because of lack of efficacy, including one patient who completed suicide.

Outcomes were assessed with the HAM-D, MÅDRS, and CGI. At week 8, mean HAM-D scores had improved by 42% and MÅDRS scores fell by an average of 38.7%. Categorical response rates appeared to peak at week 8, although several additional patients responded by week 12. Final response rates ranged from 30% (MÅDRS definition) to 40% (CGI score of 1 or 2); about one half of responders were fully remitted. Of note is that only 2 (13%) of the 15 patients who had failed to respond to ECT responded to VLX therapy.

Nierenberg et al. [1994] reported several other trends associated with response to VLX. Nonresponders tended to have a younger age of onset, longer duration of illness, and higher HAM-D severity score at baseline. However, with the exception of nonresponse to ECT, none of these associations was sufficiently robust to guide treatment selection.

Responders were permitted to remain on VLX-IR for up to 3 years. Although a formal analysis of longer term outcomes was not presented, Nierenberg et al. [1994] reported that 46% of responders at week 12 sustained their response at week 24, which suggests that up to 54% of the responders had relapsed. If this is accurate, the high risk of relapse observed among patients with advanced stages of treatment resistance after successful initial therapy with VLX undermines the apparent utility of this strategy, at least as a monotherapy. Further longitudinal studies of the clinical course of TRD patients are clearly needed.

The second open-label case series was reported by de Montigny and colleagues [1999]. Their study, a Canadian multicenter trial, required that patients had failed to respond to at least one 8 week trial of antidepressant therapy at standard doses of imipramine (e.g., ≥ 150 mg/day) or fluoxetine (40 mg/day). A total of 158 patients began treatment with VLX-IR. Approximately 40% of the study group had been depressed for 2 years or longer. The study group had failed to respond to between one and eight antidepressants; 45% of the patients had not responded to three or more antidepressants. This means that at least one half of the study group would be classified as Stage I or Stage II TRD, with the remainder at Stage III or more advanced. It was not reported if any of the patients had failed to respond to ECT.

de Montigny and colleagues [1999] treated patients for up to 8 weeks. The VLX-IR dose was initiated at 37.5 mg b.i.d. and could be titrated up to 375 mg/day during the next 4 weeks of therapy. Twelve patients (8%) withdrew from the study because of tolerability problems. By day 56, the average daily dose of VLX-IR was 260 (s.d. = 98) mg/day. Average HAM-$D_{21}$ scores had decreased at 55% by week 8, with 88 (58%) responders among the 152 patients included in the ITT sample. Forty-two patients (28%) achieved a 75% reduction in HAM-D scores, the definition of remission.

The authors did not report outcomes across stages of TRD. However, in their discussion of the results they stated that 7 of the 10 patients who had failed to respond to lithium augmentation responded to VLX, as did 8 of the 12 patients who had not benefited from the combination of desipramine and a SSRI. The latter observation is noteworthy because the combination of desipramine and a SSRI would be expected to have the same "dual reuptake" inhibition mechanism of action as VLX.

The third open-label series [Mitchell et al., 2000] was conducted at 40 centers in Australia. This study required that patients had failed to respond to a minimum 4 week trial at minimum adequate doses of standard antidepressants (e.g., 150 mg/day of imipramine, 20 mg/day of fluoxetine, 50 mg/day of sertraline, or 300 mg/day of moclobemide). Patients who had not responded to a single maximal trial of any antidepressant were considered to have an "absolute" level of resistance, whereas those who had received only minimally adequate trials were said to have "relative" resistance.

The 8 week acute phase trial was initiated with VLX-IR, 37.5 mg b.i.d., for 14 days. Thereafter, daily dose could be increased by 75 mg/day on a weekly basis, up to a maximum dose of 300 mg/day. The mean final dose of VLX-IR was 201 mg/day (s.d. not reported); 28% of the sample received the maximum 300 mg/day dose.

Among an initial enrollment of 456 patients, 312 met criteria for resistance to at least one antidepressant, of which 71% (n = 220) were considered to have absolute resistance. Overall, patients had failed an average of 2.7 (1.8) "absolute" trials and 1.8 (1.3) "relative" trials, resulting in an average of nearly 5 failed trials per patient. As only 31 patients (10%) had failed a nonselective MAOI, the study group was compromised predominantly of patients at TRD Stages II and III. Twenty-six patients (8%) had received ECT, although it was not reported how many had failed to respond to ECT in the current episode versus the number that had relapsed. The patient group was chronically ill [episode duration $\bar{x}$ = 3.0 (s.d. = 5.1) years].

During acute phase treatment, MÅDRS scores decreased from 33.2 to 17.9 ($\bar{x}$ = 46% improvement). A 53% response rate was observed on the MÅDRS, with about 80% of responders achieving a final score of ≤ 11, which the investigators considered a full remission.

Fifty-seven (18%) patients withdrew from the ITT sample before week 8. The exact number of TRD cases discontinued because of intolerable side effects was not reported, but it was stated that 11% of the larger sample could not tolerate one or more adverse events.

The authors reported that Axis I comorbidity and absolute resistance to at least one prior trial predicted a poorer chance of response to VLX. Failing to respond to an "absolute" trial of TCA, for example, lowered the probability of response to VLX from about 65% to 45%. They also observed that patients who obtained at least 20% improvement during the first 2 weeks of therapy were much more likely to respond to VLX therapy than patients who showed little initial improvement (final response rates: 73% versus 18%). It would appear that the combination of failure to respond to a maximal trial of another antidepressant, the presence of significant Axis I comorbidity, and lack of early improvement would be a particularly ominous prognostic constellation for VLX treatment.

The fourth study of VLX therapy in TRD utilized a more rigorous design. Poirer and Boyer [1999] treated 122 TRD patients in a 4 week, randomized, double blind clinical trial comparing venlafaxine [up to 300 mg/day; $\bar{x}$ = 269 [(47) mg/day] and paroxetine [up to 40 mg/day; $\bar{x}$ = 36 (5) mg/day]. In terms of the "equity" of dosing, the average patient in the VLX- IR group received 71% of the United States F.D.A. approved maximum dosage (i.e., 269/375), whereas the average paroxetine-treated patient received 72% (i.e., 36/50) of maximum dosage. All of the patients had failed to respond to at least two minimally adequate antidepressant trials (e.g., ≥ 4 weeks of clomipramine therapy at ≥ 100 mg/day). About 70% of the sample had failed an initial TCA trial and about 65% had not responded to a SSRI. With a few exceptions, the study group had Stage II TRD.

Intent-to-treat analyses of the HAM-$D_{17}$ documented a 45% (27/60) response rate with VLX-IR and a 33% (18/62) response rate with paroxetine. Remission, defined by a final HAM-D score ≤ 10, was achieved by 37% and 18% of the respective treatment groups. Despite these clinically and, with respect to remission rates, statistically significant differences, the groups obtained comparable mean improvements on the HAM-D. The groups also had similar response rates on the CGI (VLX: 33/60; PAR: 36/62). These findings would suggest that the real advantage of VLX relative to paroxetine was the greater proportion of responders who achieved full remission. Because the trial lasted only 4 weeks, it is not possible to ascertain if this difference was simply attributable to a more rapid onset of therapeutic action of VLX [cf. Rickels et al., 1995] or greater overall therapeutic activity [Thase, 2000a].

## CONCLUSIONS, CLINICAL CONSIDERATIONS, AND FUTURE DIRECTIONS

The results of these four reports indicate that 40–55% of patients with TRD stages I to IV will respond to 8 weeks of treatment with VLX in doses of 150 to 375 mg/day. Between 50% and 80% of these responders will remit completely during the same time frame. Although it is not possible to conclude that switching antidepressant monotherapy nonresponders to VLX will result in superior outcomes when compared with relevant alternatives [e.g., lithium augmentation, adding a noradrenergic TCA, (or bupropion or reboxetine) to the ineffective SSRI, switching SSRIs, or switching to an of antidepressant from yet another class], the double-blind study of Poirer and Boyer [1999] did find an advantage favoring VLX-IR over paroxetine at comparable doses.

The results of these studies place the expected utility of VLX therapy for more advanced stages of TRD in the same range of response as observed with the TCAs and, for unselected populations, nonselective MAOIs [see Thase and Rush, 1995]. For most patients, VLX therapy will be better tolerated and safer than either of these older alternatives. Therefore, VLX is a very appropriate option for TRD patients at the I, II, or III stages of resistance.

There were several limitations of VLX therapy of TRD revealed in this review. First, Nierenberg et al. [1994] observed a low response rate (13%) among patients who had failed ECT during the index episode of depression. Although other relevant antidepressant monotherapies may have yielded comparably low response rates, the search for reasonable alternatives for ECT nonresponders must continue. Nierenberg et al. [1994] also presented preliminary data that suggested that more than half of the TRD patients at Stages IV or V who responded to VLX relapsed within 3 months, apparently despite continued therapy. If this finding is confirmed, it might indicate that such highly resistant patients could have a better chance of sustained recovery if lithium or another mood stabilizer were also prescribed. We have observed a parallel finding in a study of patients who responded to ECT [see Thase, 2000b].

Tolerability was generally not a problem in these studies, even though all four studies used the IR formulation of VLX. Available data comparing the tolerability of the IR and XR formulations of VLX would suggest that use of the extended release formulation will improve the tolerability of VLX and, perhaps, result in better outcomes [Cunningham et al., 1997]. However, it must be noted that single daily dosing with the XR formulation has not been studied extensively at doses above 225 mg/day and regular blood pressure monitoring is certainly indicated when higher doses of either formulation of VLX are prescribed [Thase, 1998].

In practice, the major dose-limiting side effects of VLX-IR therapy are nausea and other gastrointestinal side effects during the first few weeks of treatment. Slower titration, dose reduction, and, if necessary, symptomatic treatment with 5-$HT_3$ antagonists (i.e., ondansetron or mirtazapine) can usually remedy this problem. Similarly, treatment emergent anxiety, agitation, or insomnia can usually be managed with concomitant benzodiazepines or, for selected patients, atypical neuroleptics or mirtazapine. About 5% of pa-

tients treated with VLX at the FDA maximum dose may require concomitant therapy with an antihypertensive. Some experts prefer calcium channel blockers or the β-blocker pindolol (more renowned for its 5-$HT_{1A}$ blockade) for this purpose, because of putative antidepressant effects, although there is no clinical evidence that the theoretical benefits of these strategies actually result in better antidepressant responses.

Another caveat is that resistance and intolerance are commonly intermingled in practice. There is no reason to suspect that patients who cannot tolerate a therapeutic trial of a SSRI will be particularly well suited for VLX therapy. Nevertheless, several studies have demonstrated that patients who cannot tolerate fluoxetine or sertraline can benefit from other SSRIs [Brown and Harrison, 1995; Thase et al., 1997], so use of VLX for such patients should not be considered contraindicated. However, SSR intolerant patients may have a better chance of tolerating an alternate newer medication, such as bupropion, nefazodone, mirtazapine, moclobemide, or reboxetine.

There is not an extensive data base on the use of various augmentation strategies with VLX nonresponders. In our experience, VLX nonresponders can be augmented with lithium salts, buspirone, thyroid hormone, stimulants, or atypical antipsychotics, with results comparable to what is observed with SSRIs or TCAs. Likewise, combining VLX with bupropion or mirtazapine is sometimes effective when simpler strategies have failed.

Most of the decisions concerning "What's next?" for patients with advanced stages of TRD must be made without the benefit of extensive empirical evidence. Beyond recommending ECT for patients with melancholic or psychotic features or a MAOI for someone with prominent reverse neurovegetative features, the relative merits of switching, augmenting, or combining various antidepressants must be weighed on a case-by-case basis. In this context, VLX is an effective and well-tolerated antidepressant that can be distinguished from the SSRIs by norepinephrine reuptake inhibitory effects at higher dosages [Harvey et al., 2000]. We predict that this proposed second mechanism of action will result in superior response (when compared to a second SSRI trial) in Stage I TRD, although it must be recognized that this prediction is not proven. However, until definitive data are available, a theoretical rationale, coupled with evidence of a 10% advantage in remission rates relative to SSRIs [Thase, 2000a], provide a strong case for selection of VLX ahead of alternate monotherapies for TRD.

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