When at First You Don't Succeed: Sequential Strategies for Antidepressant Nonresponders

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Now, more than ever before, a wealth of options exists for depressed patients who do not benefit from treatment with standard, first-line antidepressant agents. In this paper, alternate antidepressant strategies are reviewed within the context of a five-stage strategy, ranging from lesser to greater degrees of treatment resistance. The overall strategy recommended progresses from simpler (i.e., an alternate monotherapy) to more complex strategies (i.e., combination or augmentation regimens), with the nonselective monoamine oxidase inhibitors (+/- lithium salts) and electroconvulsive therapy typically reserved for treatment of Stages III and IV of resistance, respectively. Psychotherapeutic management also is an important ingredient in the ongoing treatment of these patients, particularly to counteract the demoralization and frustration that understandably accompany the failure to respond to so many treatments. *(J Clin Psychiatry 1997;58[suppl 13]:23–29)*

Antidepressant pharmacotherapy is the cornerstone of medical treatment of the depressive disorders.[1,2] Unfortunately for our depressed patients, 10% to 20% do not tolerate an initial trial of antidepressant medication.[1,3] Moreover, 25% to 35% of those who complete an adequate trial of an approved antidepressant do not show an acceptable response.[1,3] This paper reviews the relative merits of the wide array of treatment options available to those who do not respond to an antidepressant or cannot tolerate the initial medication.

UNDERSTANDING ANTIDEPRESSANT NONRESPONSE

A number of factors may contribute, both singly and in combination, to a failed medication trial. At the simplest level, patient nonadherence with a prescribed medication is a common problem in both nonresponse and relapse after initial benefit from a particular antidepressant.[1,4] There are many reasons for not adhering to a recommended treatment, including a breakdown in collaboration between patient and physician, inadequate psychoeducation about the disorder or its treatment, and unacceptable side effects. Thus, introductory information and repeated discussions at subsequent visits are recommended to enhance adherence.

In other cases, antidepressant nonresponse is attributable to misdiagnosis, as in the case of a patient suffering from an unrecognized underlying general medical illness, or when a significant concurrent psychiatric condition, such as alcoholism or drug abuse, goes unrecognized.[5] Failure of an antidepressant trial should always trigger at least a brief reconsideration of the differential diagnosis, including both Axis I and Axis II.

Some bona fide depressive disorders are less responsive than others to standard antidepressant monotherapies. For example, a major depressive episode with psychotic features has less than one half the likelihood of responding to an antidepressant than a nonpsychotic depressive disorder.[6,7] Instead, such patients should be treated with electroconvulsive therapy (ECT) or combined neuroleptic-antidepressant regimens.[6,7] Bipolar depressive disorders, including more subtle "spectrum" presentations, similarly may be more responsive to a combination of a mood stabilizer and an antidepressant than to antidepressant monotherapy.[1,8] Depressive disorders characterized by reverse neurovegetative signs and/or prominent anxiety symptoms also may be less responsive to some classes of antidepressants than others.[3,9,10] Thus, the inadvertent selection of a less effective initial treatment accounts for another subset of antidepressant failures.

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Table 1. A Simple System for Staging Antidepressant Resistance

Stage I:	Failure of at least one adequate trial of one major class of antidepressant
Stage II:	Stage I resistance plus failure of an adequate trial of an antidepressant in a distinctly different class from that used in Stage I
Stage III:	Stage II resistance plus failure of an adequate trial of a TCA
Stage IV:	Stage III resistance plus failure of an adequate trial of an MAOI
Stage V:	Stage IV resistance plus failure of a course of bilateral ECT

In other cases, the diagnosis is correct, the patient is adherent to the recommended treatment, and the depressive disorder is potentially responsive to antidepressants, yet the treatment fails because of poor execution. Providing too low a dosage or too brief a trial are examples of such failures. Moreover, although a majority of antidepressant responders benefit from standard dosages within the first 4 weeks of treatment, some patients require higher doses for longer periods of time.[3]

CLASSIFYING ANTIDEPRESSANT NONRESPONSE

In acute depression, psychosocial support and adaptive neurophysiologic factors may serve to facilitate a recovery. In fact, in milder acute major depressive episodes it is sometimes difficult to differentiate response to an antidepressant from that to placebo.[1] However, likelihood of a placebo responsiveness or spontaneous remission dissipates after an initial antidepressant failure.[3] As a result, progressively more complex or powerful interventions are often necessary as a patient's history of antidepressant failures builds.

Thus, treatment-resistant depression is a heterogenous and often multicenter entity. In our experience, we have found it helpful to borrow the concept of illness staging from our colleagues in oncology.[3] We believe that the staging model summarized in Table 1 reflects a useful guideline for psychiatrists when a serotonin selective reuptake inhibitor (SSRI) is chosen as the first-line strategy. Following this schema, antidepressant nonresponders are classified along a continuum demarcated by five stages of resistance, with a series of sequential strategies logically suggested for each stage. We note, however, that the predictive value of this particular classification, like other contemporary treatment algorithms, has not been fully validated by empirical research.

MANAGEMENT OF ANTIDEPRESSANT NONRESPONDERS

A number of reasonable alternatives are available to treat patients who have not responded to an initial antidepressant trial (Table 2). Assuming that the patient has not responded to a 4-week trial of an SSRI in moderate dosages, the most parsimonious strategy is to provide a longer trial, at either the original or a higher dose. For fluoxetine, currently the most widely prescribed SSRI in the United States,[1] some evidence suggests that a dosage increase may not be necessary before the fifth or sixth week of therapy,[11,12] perhaps because of the relatively long time its active metabolite, norfluoxetine, takes to reach steady state. If this is true, then dosage increases of the other SSRIs, sertraline, paroxetine, and fluvoxamine, may be warranted sooner, but generally not before 4 weeks of therapy. In any event, when an initial trial of an SSRI in moderate dosages is well tolerated but ineffective, dosage increase represents a most reasonable next step. The major drawbacks of "mega-dose" SSRI therapy are cost and the potential for a dose-dependent increase in side effects.

After failure of an initial SSRI trial, many clinicians will try an alternate member of the same class. Drawing on 30 years of experience with the tricyclic antidepressants (TCAs), it might be expected that a better chance of success would be gained from switching to a different class of medication, i.e., from a TCA to a monoamine oxidase inhibitor (MAOI).[3] However, over the past 2 years, a series of studies have emerged suggesting that patients intolerant[13,14] of or not responsive[14–16] to one SSRI have a 40% to 70% chance of responding to a second "classmate" (Table 3). Pooling data across studies, the probability of response was significantly higher in the two reports including SSRI-intolerant patients (66%; 146/218) than in the two studies delimited to SSRI nonresponders (48%; 41/86) ($\chi^2 = 9.70$, df = 1, p = .002). Moreover, outcomes were significantly better in the three outpatient studies (64%; 174/273)[13–15] than in the Zarate et al.[16] inpatient study (42%; 13/31) ($\chi^2 = 5.59$, df = 1, p = .018). In addition, all

Table 2. Reasonable Treatment Strategies After Initial Antidepressant Nonresponse

Longer trial, higher dosages
Switch within same class
Switch across classes
Augmentation strategies

Table 3. Efficacy of Treatment With a Second SSRI After an Unsuccessful Initial Trial

Study	Sample[a]	First Drug	Second Drug	Response Rate to Second Drug
Brown and Harrison[13]	OP, INT	Fluoxetine	Sertraline	71% (79/112)
Zarate et al[16]	IP, NR	Fluoxetine	Sertraline	42% (13/31)
Joffe et al[15]	OP, NR	SSRI[b]	SSRI[b]	51% (28/55)
Thase et al[14]	OP, INT, and NR	Sertraline	Fluoxetine	63% (67/106)

[a]OP = outpatient; IP = inpatient; INT = intolerant to individual SSRI; NR = not responsive to initial SSRI.
[b]SSRI = one serotonin selective reuptake inhibitor followed by another, including fluvoxamine.

Table 4. Conceptual Advantages of Crossover Monotherapy Vis-à-Vis Augmentation Strategies

Lower risk of drug-drug interactions
Different potencies of neurotransmitter uptake blockade
Different dose-limiting side effects
Possibly different mechanisms of action
Usually less expensive
Heuristically pure

of these studies were conducted "open label," and none included a randomized comparison group. The evidence available is only suggestive that a second SSRI trial may be the treatment of first choice after failure to respond to one SSRI. At this time, we recommend that clinical judgment be used on a case-by-case basis to decide if a second SSRI trial is warranted before turning to alternate classes of medication, guided by preliminary observations that better outcomes have been noticed in outpatients treated with lower doses of the index SSRI.

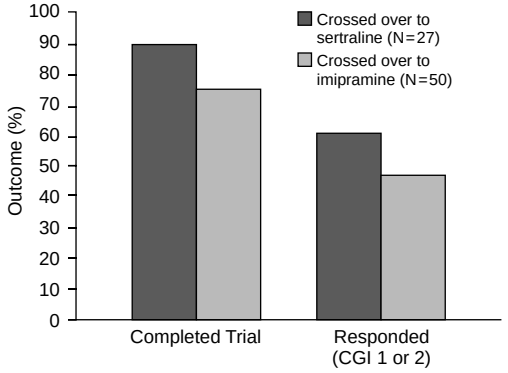
Stage I Resistance

A documented resistance or intolerance to the SSRI class warrants a change in treatment strategies. Some authorities recommend a switch or "crossover" to an alternate monotherapy, whereas others prefer to try to augment the SSRI with another agent. Prescription of an alternate class of monotherapy has several conceptual advantages relative to augmentation strategies (Table 4). However, augmentation strategies offer the practical benefit of avoiding discontinuation of initial antidepressant, which is often associated with at least a transient worsening of the patient's symptoms. Also, when effective, some augmentation strategies may offer the promise of a more rapid response. Thus, because both approaches have particular merits, it may be some time before a clear consensus emerges about whether to augment or to switch to a different class of antidepressants.

If one switches to an alternate medication class, common choices include the TCAs,[3] bupropion,[17] venlafaxine,[18] and nefazodone. For patients with so-called atypical depressions or prominent reverse-neurovegetative features, MAOIs also may be considered at this decision point.[3,10] Of course, for patients started on a TCA first, the SSRIs offer a valuable alternative, particularly for outpatients.[3]

Currently, we favor the use of alternate newer antidepressants for treatment of SSRI nonresponders. This is because agents such as venlafaxine, bupropion, and nefazodone are dissimilar enough from the SSRIs to warrant a trial, and they are both better tolerated and safer in overdose than the TCAs. There are, as of yet, no controlled data on the relative merits of these agents for treatment of Stage I–resistant depression. However, on the basis of other studies, one might favor venlafaxine for more severe cases (including hospitalized patients),[18–20]

Figure 1. Results of a 12-Week Double-Blind, Crossover Study of Chronically Depressed Outpatients Treated With Sertraline or Imipramine After Initial Failure of the Alternate Medication*



*Data from reference 27.

bupropion for anergic and bipolar spectrum patients,[21,22] and nefazodone for patients with significant anxiety[23] or insomnia.[24] Bupropion[25] and nefazodone[26] have the additional advantage of a lower risk of sexual dysfunction, which is a common side effect of SSRIs, TCAs, and MAOIs.

Stage II Resistance

Although the TCAs are in many ways rapidly becoming outmoded drugs, they may prove particularly useful for treatment of patients with Stage II–resistant depression. For example, Thase and Rush[3] reviewed the treatment literature from 1960 through 1994 and concluded that TCAs had about a 50% response rate when used following either an SSRI or MAOI failure. Results consistent with this conclusion were observed in a recently completed multicenter clinical trial comparing imipramine and sertraline as treatments of chronic depressive disorders.[27] In this study, patients who failed to respond to an initial 12-week antidepressant trial were "crossed over" to the alternate agent with the double blind maintained. As summarized in Figure 1, sertraline nonresponders had a 43% response rate to imipramine. Interestingly, imipramine nonresponders who were switched to sertraline had even better treatment completion and response rates (90% and 65%, respectively).[27]

Studies of bupropion[17] and venlafaxine[18] also have reported comparable response rates in samples of depressed patients that we would classify as having a mixture of Stage II– or Stage III–resistant depression. The importance of staging the degree of resistance is illustrated in the Nierenberg et al.[18] study of venlafaxine. Specifically, they found a venlafaxine response rate of only 13% (2/15) in patients who had failed ECT (i.e., Stage V resistance), compared to a 42% (23/55) response rate in patients with a less marked degree of treatment resistance.[18]

Table 5. Common Augmentation Strategies for Antidepressant-Resistant Depression

Lithium augmentation
Thyroid augmentation
Pindolol augmentation
Buspirone augmentation
Antidepressant augmentation
Neuroleptic augmentation

Stage III Resistance

Following our classification schema, patients with Stage III resistance have failed to respond to SSRIs, at least one other class of newer antidepressant, and a TCA. Following several such unsuccessful monotherapy trials, a stronger case can be made for augmentation strategies.

Common augmentation strategies for SSRI nonresponders are summarized in Table 5. Among these diverse strategies, lithium and thyroid augmentation have extensive track records from the TCA era (see, e.g., the review by Thase and Rush[3]). However, these strategies have not yet been studied definitively in SSRI nonresponders.

Thyroid augmentation is a safe and well-tolerated strategy that should always be considered early in treatment algorithms for patients with evidence of borderline or subclinical thyroid deficiency.[3] Augmentation with L-triiodothyronine (T_3) is typically preferred over thyroxine (T_4) on both theoretical and clinical grounds.[3,28] In the only controlled trial directly contrasting T_3 and Li^+ augmentation of TCA nonresponders,[29] both strategies were more effective than placebo, though a uniform definition of treatment resistance was not required for patients to enter this trial.

For TCA nonresponders, a trial of lithium augmentation is often chosen ahead of an MAOI trial.[3] The use of lithium salts also conveys the possibility of response to Li^+ as a primary antidepressant.[3,8] Lithium augmentation, typically in doses of 600 to 1200 mg/day, has an extensive track record and reliably yields 30% to 50% response rates.[3] However, Li^+ augmentation may be somewhat less useful with SSRIs than observed with TCAs because of lower efficacy,[30] relapse after initial response,[31] or increased side effects.[32] For example, in the comparative study of Fava et al.,[30] low-dose lithium augmentation (i.e., 300–600 mg/day) of fluoxetine was significantly less effective than simply increasing the fluoxetine dose. Also, the proposed mechanism of lithium augmentation, enhanced serotonergic neurotransmission, may be less relevant for treatment of patients who have already failed to benefit from the potent SSRIs. For these reasons, we suggest that augmentation is better used for TCA nonresponders with Stage II–resistant depression.[3]

Another theoretically targeted augmentation strategy involves the antihypertensive agent pindolol.[33,34] Although developed as a β-blocker, pindolol also is a potent inhibitor of the presynaptic 5-HT_{1A} autoreceptor. Thus, it is hypothesized that pindolol augmentation prevents the autoreceptor-mediated down-regulation of serotonergic neurotransmission triggered by potent reuptake inhibition. It is not yet certain, however, that this promising strategy is as effective as alternate strategies, and several controlled clinical trials are underway to confirm this notion. If the effectiveness of pindolol augmentation is confirmed by double-blind trials, it would "move up" in our algorithm to join the strategies for Stage I–resistant depression because of its feasibility for SSRI nonresponders.

Currently, many clinicians opt for a combination or cotherapy strategy by adding a secondary amine TCA, such as desipramine or nortriptyline, to an ineffective SSRI.[3] Combined treatment with one of these TCAs and an SSRI offers a potent "one-two punch" on noradrenergic and serotonergic neurotransmission. This strategy, which may be orchestrated as a transitional step between SSRI and TCA monotherapy trials, also capitalizes on pharmacokinetic interactions that slow TCA metabolism, resulting in disproportionately increased TCA blood levels. Thus, relatively lower doses of the TCA are typically required.

In a preliminary open-label study, Weilburg et al.[35] observed a 65% response rate in fluoxetine-resistant patients augmented with a TCA. In the Zajecka et al.[36] open-label study of an antidepressant-resistant group of patients (typically at Stage III–treatment resistance), SSRI-TCA cotherapy yielded a 35% response rate. In the comparative double-blind trial of Fava et al.,[30] low-dose desipramine (25–50 mg/day) added to fluoxetine resulted in only a 25% (3/12) response rate, which is substantially lower than the simpler strategy of increasing the fluoxetine dose. Unfortunately, blood desipramine levels were not reported. No other data are available. In this context, we are hard pressed to find an advantage for TCA + SSRI cotherapy when compared to vigorous trials with alternate monotherapies that affect both norepinephrine and serotonin, such as venlafaxine, clomipramine, or imipramine. If comparably effective, venlafaxine monotherapy would convey a definite advantage over cotherapy, both the TCA+SSRI combination and the tertiary amine TCAs, with respect to cardiovascular side effects and safety in overdose. For these reasons, we list the SSRI + TCA strategy with other possible treatments for Stage III resistance, recognizing that the "jury is still out" and that there is room for differences of opinion.

After nearly a decade of resurgence,[9,10] the MAOIs have again drifted back to a state of relative disuse. This is specifically because the irreversible, nonselective MAOIs available in the United States are harder to use than all other classes of antidepressant medication. Moreover, the need for the patient to maintain a low-tyramine diet and to avoid sympathomimetics represents both an inconvenience and a potential hazard that warrant a careful consideration of the risks and benefits for each patient. Further, the safer reversible and selective MAOI, moclobemide,

which is available elsewhere in the world, is not likely to be available in the United States in the foreseeable future.[10]

Despite these drawbacks, the MAOIs are particularly effective antidepressants for treatment-resistant patients with atypical or reversed neurovegetative features,[9,10,37–39] including those with bipolar depression.[40] Indeed, for such patients, we recommend that an MAOI trial be performed earlier in the treatment sequence, e.g., instead of a TCA during Stage II treatment.[3,10]

In addition, the MAOIs, both alone and in combination with lithium, have consistently delivered 30% to 40% response rates in studies of more "typical" or melancholic treatment-resistant depressions.[10,37–39] Thus, we recommend a trial of at least one MAOI as the sine qua non for treatment before leaving the Stage III classification of resistant depression.

Stage IV Resistance

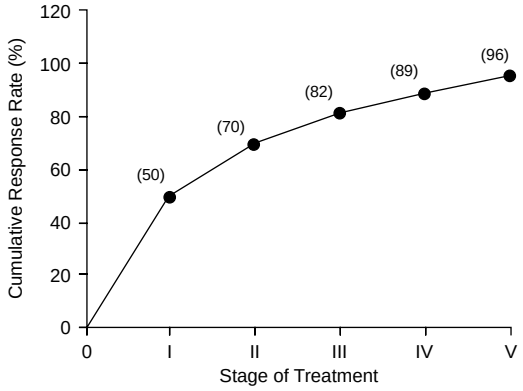
Electroconvulsive therapy (ECT) is the treatment of choice for Stage IV–resistant depression.[2,3,41,42] Moreover, ECT should be considered sooner in a treatment algorithm if the patient is hospitalized or suffers from psychotic depression, marked incapacity, or persistent suicidal ideations.[41,42] High-energy unilateral or bilateral modes of treatment administration are preferred; failure should not be declared until a minimum course of 12 treatments (including eight bilateral treatments) has been provided.[41,42] Yet, despite such unequivocal efficacy, ECT is also significantly less effective in treatment-resistant depression than it is in less complicated cases, with response rates of only 60% to 70% typically observed.[3,41] Furthermore, relapse is a common problem in treatment-resistant depression following successful ECT.[43] Preliminary results of an ongoing study of continuous pharmacotherapy following ECT suggest that this relapse risk may be as high as 40% despite prophylactic treatment with the combination of nortriptyline and lithium carbonate (Sackheim HA, Haskett RF, Prudic J, et al., unpublished data).

If one assumes acceptable treatment adherence, conscientious application of the sequential trials reviewed above, and an "average" chance of tolerability and response with each treatment strategy, what is theoretically possible? As illustrated in Figure 2, the cumulative probability of treatment response increases from 50% at the initial trial up to 96% following ECT for a Stage IV–resistant depression. Although confirmatory empirical data are lacking, it seems fairly certain that such a lofty response rate is not achieved in clinical practice settings where rates of chronicity typically range from 15% to 25%.[44,45]

Stage V Resistance

Patients who do not respond to ECT present a substantial challenge to their treating clinicians. To date, almost

Figure 2. The Hypothetical Chance of Cumulative Response to Following a Series of Sequential Strategies for Treatment-Resistant Depression*



*Data from reference 3.

40 years after the introduction of the first antidepressants, imipramine and iproniazid, few data have emerged about the subsequent treatment course of ECT nonresponders. As noted earlier, Nierenberg et al.[18] reported that only 2 of 15 ECT nonresponders benefited from venlafaxine therapy. Shapira et al.[46] reported a better response to clomipramine (five of seven) in a small series of ECT nonresponders, including two patients who had failed to respond to clomipramine prior to ECT. In another report including five patients with Stage V–resistant depression, Hale et al.[47] described response to the "New Castle Cocktail," i.e., a combination of clomipramine, lithium, and L-tryptophan. As the latter agent is currently available in the United States only as an investigational drug, clinicians are not able to call upon its potential as a serotonin precursor. Nevertheless, these findings illustrate that there is still hope that benefit can result from persevering with additional antidepressant trials after ECT failure.

A number of more exotic combination-treatment strategies are available for ECT nonresponders, including combinations of MAOIs, TCAs, lithium, and/or psychostimulants.[3] Other strategies to be considered in combination with antidepressants include the novel antipsychotics clozapine and risperidone or the "antikindling" anticonvulsant agents carbamazepine and divalproex sodium. In our experience, these strategies are more useful for patients with subtle features suggestive of either psychosis or bipolarity, respectively. Sleep deprivation and light therapy also may have beneficial effects for a subgroup of treatment-resistant patients.[3]

THE ROLE OF PSYCHOSOCIAL SUPPORT

There is little evidence that psychotherapy alone is an effective treatment of antidepressant-resistant depression, especially past Stage II.[45] Nevertheless, the ongoing treatment of patients with resistant depression requires a high

degree of psychotherapeutic support. Demoralization and frustration, if not exasperation, with the treatment process are commonplace. Often, the patient's protracted illness has led to an erosion of psychosocial supports and mounting interpersonal, vocational, and economic stresses that compound his or her problems.[45]

It is not uncommon for treating clinicians to also become frustrated or demoralized by the patient's lack of response. Competent, well-intentioned clinicians may deal with such frustration by distancing or withdrawing from such patients. Unfortunately, depressed people are particularly sensitive to such interpersonal cues, and the patient may conclude that "even my doctor thinks that I'm a hopeless case." Sometimes, the clinician may postulate that the patient has an unconscious, sadomasochistic wish to remain depressed. On other occasions, the clinician may surmise that the patient "uses" the depression to manipulate significant others. While such hypotheses warrant consideration in select cases, they are more likely to reflect a psychologically sophisticated form of "blaming the victim." Moreover, these attributions of the "cause" of the patient's treatment resistance are ultimately unhelpful unless they lead to a hypothesis-guided change in the treatment plan. Clinicians working with treatment-resistant patients need to be attuned to their own automatic negative thoughts about the patient and often benefit from peer support or professional supervision.

A summary of practical strategies for psychotherapeutic support of patients with resistant depression may be found in Thase and Howland.[45] General guidelines follow a model that may be called "Coping With a Chronic Illness." These guidelines include mobilization of the support of family and friends; planned assignments designed to increase pleasurable activities; specification of psychosocial problems and implementation of stepwise, problem-solving strategies; and maintaining a focus on accomplishing short-term goals. We have found the use of cognitive-behavioral strategies helps patients manage particular targeted symptoms, such as generalized anxiety, insomnia, and intrusive dysphoric ruminations.[45] When necessary, the pharmacotherapist may need to work with an experienced psychotherapist to "share the burden," although such collaborations require regular communication to avoid triangulation or splitting.[48]

Even when all promising pharmacologic-treatment options have been exhausted, supportive treatment has an important, life-sustaining function. Indeed, longitudinal data suggest that there is a modest, cumulative chance of spontaneous remission of chronic, refractory depressive states, ultimately totaling more than 30% over 5 years.[44] As in the case of internists caring for people with chronic and potentially fatal illnesses such as lymphocytic leukemia or chronic obstructive pulmonary disease, psychiatrists have a similar role in the long-term management of patients with treatment-resistant depression.

CONCLUSION

In the 1990s, an increasing amount of a psychiatrist's time is spent caring for depressed patients who do not respond to first-line treatment strategies. Fortunately, a wide array of options is available, and, with persistence and appropriate psychotherapeutic support, it is possible to successfully treat the vast majority of patients for so-called resistant depression. By following a logical, sequential approach to diagnosis, assessment, and treatment, these opportunities for success are maximized.

Drug names: bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), clomipramine (Anafranil), clozapine (Clozaril), despiramine (Norpamin and others), divalproex sodium (Depakote), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), pindolol (Visken), risperidone (Risperdal), sertraline (Zoloft), venlafaxine (Effexor).

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