The Definition and Meaning of Treatment-Resistant Depression

Harold A. Sackeim, Ph.D.

Most patients treated for an episode of unipolar or bipolar major depression are treatment resistant in the sense that the majority do not achieve full remission with the first somatic or psychosocial treatment they receive. Little attention has been given to formalizing criteria for evaluating the nature and extent of treatment resistance, even though determining the adequacy and outcome of prior treatment trials is key in clinical decision making about subsequent treatment. Furthermore, determining the adequacy of prior treatment is essential since substantial evidence indicates that large numbers of depressed patients are undertreated, resulting in prolonged episodes and the appearance of "pseudo-resistance." Adequacy of antidepressant treatment trials should be defined in terms of thresholds for the dosage and duration of medication, adherence, and clinical outcome. The Antidepressant Treatment History Form is presented as one method to formalize the evaluation of treatment adequacy and treatment resistance. *(J Clin Psychiatry 2001;62[suppl 16]:10–17)*

Treatment-resistant depression is a major public health problem. It is estimated that 20% to 40% of patients in a major depressive episode (unipolar or bipolar) do not show substantial clinical improvement to their first treatment with antidepressant medication, when improvement is defined as at least a 50% reduction in symptom scores. Moreover, about half of those who show substantial symptom reduction have significant residual symptoms that continue to have an impact on function.[1–3] Thus, broadly speaking, only between 20% and 40% of patients receiving their first treatment for a major depressive episode are expected to achieve a relatively asymptomatic state. Even when symptom remission is achieved, there is often a lag until there is full recovery of social and occupational functioning,[4,5] and long-term treatment may be necessary to result in remission and restored function.[6] Treatment-resistant depression results in disproportionate burdens, escalating medical and mental health care costs, clinician time, and personal suffering.[3,7]

From the Department of Biological Psychiatry, New York State Psychiatric Institute and the Departments of Psychiatry and Radiology, College of Physicians and Surgeons, Columbia University, New York, N.Y.

Supported in part by grants MH35636 and MH61609 from the National Institute of Mental Health, Bethesda, Md.

Presented at the planning teleconference "Recognizing Treatment-Resistant Depression," held November 6, 2000, and supported by an unrestricted educational grant from Eli Lilly and Company.

Reprint requests to: Harold A. Sackeim, Ph.D., Department of Biological Psychiatry, Unit 126, New York State Psychiatric Institute, 1051 Riverside Dr., New York, NY 10032 (e-mail: has1@columbia.edu).

While it is evident that treatment-resistant depression is common and a fundamental issue in the treatment of major depressive episodes, there are no agreed upon definitions of what constitutes treatment-resistant depression.[8] The field of psychiatry has expended considerable effort in deriving criteria for the diagnosis of specific disorders and developing semistructured interviews to enhance the reliability and validity of diagnosis. In contrast, relatively little attention has been given to deriving criteria for the adequacy of treatment trials and the evaluation of treatment resistance. This is ironic since there is considerable overlap among psychiatric disorders in potentially effective forms of treatment, and determining whether or not patients have not benefited from a given type or class of treatment should be critical in decision making about subsequent steps in treatment. Thus, clinicians must regularly determine whether patients should be treated with a selective serotonin reuptake inhibitor (SSRI), a tricyclic antidepressant (TCA), a monoamine oxidase inhibitor (MAOI), any of a class of new antidepressant agents (e.g., bupropion, nefazodone, venlafaxine), anticonvulsant medications, or augmentation trials (e.g., with lithium, thyroid supplement, stimulant). These decisions should be based, in part, on the patient's responsiveness to previous trials of specific medications or medication classes. Yet, the methods to determine the adequacy and outcome of prior treatment are underdeveloped.

DEFINING TREATMENT-RESISTANT DEPRESSION

In principle, antidepressant trials should be characterized in terms of the maximal dosage (or blood level) achieved, the duration at maximal and submaximal dosage,

compliance with the treatment, and clinical outcome. These are the 4 features that determine the adequacy of antidepressant treatment and the judgment that the patient has not responded to an adequate treatment trial.

Over the past 20 years, there is substantial evidence that many, if not most, patients with major depression do not receive adequate treatment trials.[9–11] For reasons not fully understood, patients in both community and academic settings are typically undertreated[7] and are administered doses of medication that are below accepted thresholds for adequacy. Thus, many patients who appear to be "treatment-resistant" are in fact "pseudoresistant" since they have not received adequate treatment. One way of gauging this is to evaluate referrals to electroconvulsive therapy (ECT) for which treatment-resistant depression is the primary indication for use.[12] Using strict criteria for treatment-resistant depression, recent studies suggest that only approximately 50% of major depressive episode patients meet minimal criteria for having received a single adequate medication trial during the index episode.[13,14]

Dosage Evaluation

Numerous randomized clinical trials (RCTs) have established the minimal dosage necessary for antidepressant agents to exert therapeutic effects. In a few cases with tricyclic agents, there is evidence for a relationship between plasma levels and therapeutic outcome, with the possibility of a therapeutic plasma level window.[15,16]

The Antidepressant Treatment History Form (ATHF) is probably the most commonly used instrument to evaluate formally the adequacy of prior antidepressant treatment.[13,14,17–19] The ATHF scoring instructions and rating scales are presented in Appendices 1 and 2, and score sheets for using the ATHF may be obtained from the author. In general, the ATHF levels for considering a trial adequate (ratings of 3 or above) correspond to the minimal dosage at which RCTs have shown the agent to be effective in major depression, or more generally, to two thirds of the maximal *Physicians' Desk Reference* (PDR) recommended dose.

It appears that the most common source of lack of response in major depression, other than treatment-resistant depression, is administration of inadequate dosage.[9,10]

Duration of Treatment

There is little consensus on how long patients should be treated at an optimally tolerated dose before considering a trial to be ineffective. Quitkin and colleagues[20,21] argued that antidepressant response is often slow, and trials may need to be 8 weeks or longer to manifest maximal benefit. This work has been criticized for use of a slow titration schedule to reach maximal dosage and, thus, subsequent prolongation of time to response. Nonetheless, the optimal duration at maximal dosage may vary with patient subgroups. For instance, there is some evidence, although quite uncertain, that elderly patients may require longer exposure to medications at maximal dosage to achieve the same level of response/remission observed in younger patients.[22]

The ATHF is neutral in this regard. It only requires that the threshold dosage (or blood level) for adequate treatment be administered for 4 weeks to classify the patient as not responding or remitting to the trial. Four weeks may well be a conservative threshold, since recent work indicates that with prolonged treatment, patients with chronic depression, often the most resistant to standard pharmacologic treatment, show progressive improvement.[6]

Adherence With Treatment

Patients are unlikely to improve if they do not adhere to treatment. It is a mistake to describe a patient as resistant to a treatment if the treatment regimen was not followed. In the case of pharmacologic treatment, the degree of adherence is often difficult to determine, unlike somatic treatments, such as ECT, for which there are absolute indices of treatment administration. Across medicine, nonadherence is highly prevalent and a major contribution to nonresponse. Its evaluation in the context of treatment-resistant depression is especially important, since it may rule in or out classes of treatment strategies.

Treatment Outcome

In evaluating any antidepressant treatment trial, it is important to distinguish whether the patient (1) did not show substantial clinical improvement (nonresponse); (2) sustained a response without a remission (significant residual symptoms), (3) obtained remission (no or few residual symptoms), or (4) responded or remitted, but relapsed on the current regimen.[8] By ATHF criteria, trials are considered treatment failures if conditions 1 or 4 apply.

More generally, response in the absence of remission (i.e., elimination of virtually all depressive symptomatology) portends early relapse. The evidence is consistent that the greater the level of depressive symptomatology following pharmacologic treatment or ECT, the higher the probability of rapid relapse.[23,24] Thus, the goal in treating the acute episode is to achieve remission.

The ATHF does not distinguish between response and remission. Using a conservative approach, trials are rated as reflecting treatment-resistant depression if an adequate dose and duration have been achieved, with good compliance, but with failure to achieve response, let alone remission.

Summary

Clinicians must be able to recognize whether patients are treatment resistant despite some inconsistencies in the literature regarding the definition of *treatment-resistant depression*. Souery et al.[25] proposed an operational definition as the failure to respond to 2 adequate trials of different classes of antidepressants. Treatment resistance for major depression may also more broadly be defined as the administration of an adequate dose of an antidepressant

medication (or at minimal plasma levels) for sufficient duration, with good treatment adherence, and yet resulting in nonresponse or lack of remission. The term *treatment-resistant depression* also applies when relapse/recurrence occurs while patients continue to adhere to the same medication regimen that produced response or remission.

DEPRESSION SUBTYPES

There is evidence that pharmacologic treatments differ in their effectiveness among depression subtypes. Thus, in evaluating treatment-resistant depression, a critical consideration is the type of major depressive episode presented by the patient.

Psychotic Depression

There is considerable evidence that treatment with an antidepressant agent alone or antipsychotic agent alone is less effective in treating psychotic or delusional depression than the combination of the antidepressant and an antipsychotic agent.[26,27] Thus, monotherapy of patients with psychotic depression using an antidepressant or antipsychotic should be considered inadequate. For adequate treatment of psychotic depression, the ATHF requires administration of an antidepressant at the usual threshold dosage and duration and coadministration of a typical or atypical antipsychotic medication at a dosage equivalent to 400 mg/day chlorpromazine equivalents (CPZe). The threshold dosage of the antipsychotic is rarely achieved in clinical practice. It was chosen based on the empirical evidence. Spiker et al.[26] randomly assigned psychotically depressed patients to amitriptyline alone, perphenazine alone, or the combination, titrating dosage to therapeutic response. The combination treatment was clearly superior, and average perphenazine dosage with the combination was over 600 mg/day CPZe. In a retrospective study, Nelson et al.[28] found that combined antidepressant/antipsychotic treatment with antipsychotic dosage less than 400 mg/day CPZe was substantially less effective than treatment at the same antidepressant dosage with the antipsychotic medication at or above 400 mg/day CPZe.

For these reasons, the ATHF adopts a threshold of 400 mg/day CPZe (for traditional and atypical antipsychotics) in determining the adequacy of combined antidepressant/antipsychotic treatment of psychotic depression. Due principally to low administration of antipsychotic medication and intolerance, we reported that approximately 4% of patients with psychotic depression who received treatment with ECT had received a single adequate combination trial of an antidepressant and antipsychotic medication during the index episode.[18]

Bipolar and Unipolar Depression

There is some evidence that a broader range of medications may be effective in bipolar relative to unipolar depression.[29] A substantial body of evidence suggests that lithium carbonate may be an effective agent in bipolar depression, with uncertain effects in unipolar depression. RCTs support the antidepressant efficacy of lamotrigine, and other studies suggest that carbamazepine may exert antidepressant effects in bipolar disorder.[30–33] For these reasons, the ATHF considers these medications, when given at adequate dose (or plasma level) and duration, adequate in the treatment of bipolar but not unipolar depression.

Atypical Depression

There is substantial evidence that patients with atypical depression, defined by reversed vegetative signs, i.e., oversleeping, overeating (especially craving sweets or carbohydrates), leaden paralysis, rejection sensitivity, and reactive mood, are more responsive to MAOIs than TCAs.[34,35] However, the extent to which SSRIs and other newer agents (e.g., bupropion, nefazodone, venlafaxine) mirror the efficacy of MAOIs in this condition is uncertain. For this reason, and given the low use of MAOIs, the ATHF makes no distinction between typical and atypical depression in evaluating the adequacy of antidepressant trials.

MEANING OF TREATMENT-RESISTANT DEPRESSION

In medicine, failure to respond to an effective treatment for a disorder generally indicates a lower probability of response to other effective treatments.[36] In other words, treatment resistance portends treatment resistance. The same appears to be true in major depressive episode. Several studies have shown that the degree of treatment-resistant depression predicts an inferior response to ECT.[13,14,24] It also appears that there is a strong inverse relationship between the number of adequate antidepressant trials that did not result in response and likelihood to respond to vagus nerve stimulation (H.A.S., unpublished observations). Ironically, there are virtually no data on the extent to which lack of response or remission to pharmacologic trials predicts the outcome of subsequent pharmacologic trials. Generalizing from the experience with other somatic treatments and the general observations across medical disciplines, it would be expected that patients who do not respond adequately to an effective pharmacologic treatment for major depressive episode have a lower probability of responding to a second or third treatment for this condition. However, this perspective has yet to receive extensive empirical testing.

Duration of the current episode is one of the most consistent predictors of subsequent lack of response or remission to various forms of antidepressant treatment, including ECT.[37] It is not known whether some patients are "predestined" to be resistant to treatment and have prolonged episodes or whether ineffective treatment, in prolonging the episode, contributes to an active process that

makes patients more difficult to treat. Findings suggesting that the number of lifetime days depressed is associated with the degree of hippocampal atrophy implicate an active degenerative process.[38] For these reasons, it is possible that failure to use adequate dosages for adequate durations may have an iatrogenic effect, prolonging the episode and resulting in increased resistance to treatment.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), amoxapine (Asendin and others), bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), chlorprothixene (Taractan), citalopram (Celexa), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clonidine (Catapres and others), clozapine (Clozaril and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), diphenhydramine (Benadryl and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), liothyronine (Cytomel, Triostat), lorazepam (Ativan and others), loxapine (Loxitane and others), L-thyroxine (Levothyroid, Synthroid), mesoridazine (Serentil), methylphenidate (Ritalin and others), mirtazapine (Remeron), molindone (Moban), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil), pemoline (Cylert), perphenazine (Trilafon and others), phenelzine (Nardil), pimozide (Orap), prochlorperazine (Compazine), protriptyline (Vivactil), quetiapine (Seroquel), risperidone (Risperdal), selegiline (Eldepryl), sertraline (Zoloft), thiothixene (Navane), topiramate (Topamax), tranylcypromine (Parnate), trazodone (Desyrel and others), trifluoperazine (Stelazine), trimipramine (Surmontil), valproic acid (Depakene and others), venlafaxine (Effexor), zolpidem (Ambien).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES

1. Nierenberg AA, McColl RD. Management options for refractory depression. Am J Med 1996;101:45S–52S
2. Nierenberg AA, Muloy R. Declaration of treatment failures. In: Rush AJ, ed. Modern Problems in Psychopharmacology, vol 25. Basel, Switzerland: Karger; 1997:17–33
3. Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom F, Kupfer D, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995:1081–1098
4. Lonnqvist J, Sihvo S, Syvalahti E, et al. Moclobemide and fluoxetine in the prevention of relapses following acute treatment of depression. Acta Psychiatr Scand 1995;91:189–194
5. Lonnqvist J, Sintonen H, Syvalahti E, et al. Antidepressant efficacy and quality of life in depression: a double-blind study with moclobemide and fluoxetine. Acta Psychiatr Scand 1994;89:363–369
6. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression [see comments]. N Engl J Med 2000;342:1462–1470
7. Hirschfeld RM, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. JAMA 1997;277:333–340
8. Rosenbaum JF, Fava M, Nierenberg AA, et al. Treatment-resistant mood disorders. In: Gabbard GO, ed. Treatment of Psychiatric Disorders. 3rd ed. Washington, DC: American Psychiatric Press. In press
9. Keller MB, Lavori PW, Klerman GL, et al. Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. Arch Gen Psychiatry 1986;43:458–466
10. Keller MB, Klerman GL, Lavori PW, et al. Treatment received by depressed patients. JAMA 1982;248:1848–1855
11. Dawson R, Lavori PW, Coryell WH, et al. Course of treatment received by depressed patients. J Psychiatr Res 1999;33:233–242
12. American Psychiatric Association. The Practice of ECT: Recommendations for Treatment, Training and Privileging. 2nd ed. Washington, DC: American Psychiatric Press; 2001
13. Prudic J, Sackeim HA, Devanand DP. Medication resistance and clinical response to electroconvulsive therapy. Psychiatry Res 1990;31:287–296
14. Prudic J, Haskett RF, Mulsant B, et al. Resistance to antidepressant medications and short-term clinical response to ECT. Am J Psychiatry 1996;153: 985–992
15. Asberg M. Plasma nortriptyline levels: relationship to clinical effects. Clin Pharmacol Ther 1974;16:215–229
16. Asberg M, Sjoqvist F. On the role of plasma level monitoring of tricyclic antidepressants in clinical practice. Community Psychopharmacol 1978;2: 381–391
17. Sackeim HA, Prudic J, Devanand DP, et al. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. J Clin Psychopharmacol 1990;10:96–104
18. Mulsant BH, Haskett RF, Prudic J, et al. Low use of neuroleptic drugs in the treatment of psychotic major depression. Am J Psychiatry 1997;154: 559–561
19. Oquendo MA, Malone KM, Ellis SP, et al. Antidepressant treatment is inadequate in patients with major depression who are at risk for suicidal behavior. Am J Psychiatry 1999;156:190–194
20. Quitkin FM, Rabkin JG, Ross D, et al. Duration of antidepressant drug treatment: what is an adequate trial? Arch Gen Psychiatry 1984;41: 238–245
21. Quitkin FM, McGrath PJ, Stewart JW, et al. Can the effects of antidepressants be observed in the first two weeks of treatment? Neuropsychopharmacology 1996;15:390–394
22. Georgotas A, Cooper T, Kim M, et al. The treatment of affective disorders in the elderly. Psychopharmacol Bull 1983;19:226–237
23. Prien R, Kupfer D. Continuation drug therapy for major depressive episodes: how long should it be maintained? Am J Psychiatry 1986;143:18–23
24. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. Arch Gen Psychiatry 2000;57: 425–434
25. Souery D, Amsterdam J, de Montigny C, et al. Treatment resistant depression: methodological overview and operational criteria. Eur Neuropsychopharmacol 1999;9:83–91
26. Spiker DG, Weiss JC, Dealy RS, et al. The pharmacological treatment of delusional depression. Am J Psychiatry 1985;142:430–436
27. Parker G, Roy K, Hadzi-Pavlovic D, et al. Psychotic (delusional) depression: a meta-analysis of physical treatments. J Affect Disord 1992;24:17–24
28. Nelson JC, Price LH, Jatlow PI. Neuroleptic dose and desipramine concentrations during combined treatment of unipolar delusional depression. Am J Psychiatry 1986;143:1151–1154
29. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990
30. Sachs GS, Printz DJ, Kahn DA, et al. The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. Postgrad Med 2000;Spec No. 6:1–104
31. Bowden CL, Calabrese JR, McElroy SL, et al. The efficacy of lamotrigine in rapid cycling and non-rapid cycling patients with bipolar disorder. Biol Psychiatry 1999;45:953–958
32. Bowden CL, Mitchell P, Suppes T. Lamotrigine in the treatment of bipolar depression. Eur Neuropsychopharmacol 1999;9(suppl 4):S113–S117
33. Calabrese JR, Bowden CL, McElroy SL, et al. Spectrum of activity of lamotrigine in treatment-refractory bipolar disorder. Am J Psychiatry 1999; 156:1019–1023
34. Liebowitz MR, Quitkin FM, Stewart JW, et al. Antidepressant specificity in atypical depression. Arch Gen Psychiatry 1988;45:129–137
35. Stewart JW, McGrath PJ, Quitkin FM, et al. Relevance of DSM-III depressive subtype and chronicity of antidepressant efficacy in atypical depression: differential response to phenelzine, imipramine, and placebo. Arch Gen Psychiatry 1989;46:1080–1087
36. Goodman LS, Gilman AG, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 7th ed. New York, NY: Macmillan; 1985
37. Nobler MS, Sackeim HA. Electroconvulsive therapy: clinical and biological aspects. In: Goodnick PJ, ed. Predictors of Response in Mood Disorders. Washington, DC: American Psychiatric Press; 1996:177–198
38. Sheline YI, Sanghavi M, Mintun MA, et al. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 1999;19:5034–5043

Appendix 1. Antidepressant Treatment History Form (ATHF) Instruction Guide[a]

Introduction

The ATHF was developed to organize information from various sources about the treatment history of patients with major depression and to rate the antidepressant potency of medication trials and/or other somatic treatments (e.g., electroconvulsive therapy [ECT]) that a patient may have received in the current or previous episodes.

Raw Data

Raw data consist of such items as a copy of a patient medical record or a pharmacy computer output. These should be obtained with patient consent and incorporated into the research record. In general, a record will be more accurate than a verbal report from memory. For interviews of the patient, family member, and prescribing psychiatrists, the treatment history form itself serves as the raw data, with a separate form completed for each individual interviewee for each episode of depression. Repeat interviews (e.g., following remission of the acute episode) require completion of a new form. The more complete the information about the treatment received during an episode, the more accurate the characterization of treatment history and treatment resistance. For this reason, it is important to not simply interview patients about prior treatments, but to also obtain information from past treatment providers, pharmacies, and medical records.

Treatment History Form

The treatment history forms consist of a cover sheet and continuation sheets. One set should be used for each available source of information in a particular episode. A separate summary form is used for each episode to evaluate and collapse information from multiple sources. (Forms are available from H.A.S.)

Identifying information about the characteristics of a particular episode should be ascertained and recorded as accurately and in as much detail as possible. The DSM or Research Diagnostic Criteria (RDC) diagnosis, the designation of unipolar/bipolar and psychotic/nonpsychotic, and the duration of episode will be critical to later determination of the potency of treatment trials and the relative resistance to treatment. Criteria for assessing the adequacy of treatment vary with diagnosis (unipolar vs. bipolar or psychotic vs. nonpsychotic), and the determined duration of the episode establishes the time frame for evaluating the adequacy of treatment.

For ECT, the possibility of recording detailed information, even though it may not always be available, has been incorporated into the form. Evidence of inadequate seizure duration should be explicitly noted.

For each medication trial, each change of dose and each blood level should be recorded on its own line. The purpose is to provide a time line for each trial of the alterations in oral dose and the documentation of blood levels. The date that blood was drawn for levels should be recorded, if available. The reason for stopping the trial should be identified, with particular reference to relapse after acute response, limiting side effects, lack of efficacy, and noncompliance. The final outcome of the trial and compliance with the prescribed regimen should be rated using the scales at the top of the form. In addition, it should be indicated whether each trial was conducted on an inpatient or outpatient basis.

Rating Antidepressant Trials

Each medication or medication combination should be considered separately and rated on the "Summary Form." Information concerning ratings of specific agents is contained in the section "Criteria for Rating Medication Trials for Antidepressant Strength." A score of "3" is the threshold for considering a trial adequate and the patient resistant to that treatment.

Episodes designated as nonpsychotic can be rated without considering the antipsychotic equivalency scales. Note that lithium, lamotrigine, and carbamazepine have differing ratings for depressive episodes in unipolar versus bipolar patients. When blood levels are available for imipramine, desipramine, or nortriptyline, they take precedence in ratings relative to oral dose.

Episodes diagnosed as psychotic depression (by DSM or RDC) should be considered in the following manner: rate antidepressant therapies first, and then consider the concurrent antipsychotic treatment ratings for the drug trial (a chlorpromazine equivalency list is provided at the end of Appendix 2).

0 = Same as for nonpsychotic episodes
1 = Antidepressant alone *or* chlorpromazine equivalent (CPZe) < 400 mg/d for 3 wk
2 = Antidepressant at level 2 and CPZe < 200 mg/d for < 3 wk *or* CPZe 400 mg/d for minimum 3 wk
3 = Antidepressant at level 3 and CPZe ≥ 400 mg/d for minimum 3 wk
4 = Antidepressant at level 4 and CPZe ≥ 400 mg/d for minimum 3 wk
5 = Antidepressant at level 5 and CPZe ≥ 400 mg/d for minimum 3 wk

A separate Summary Form should be completed for each episode of major depression. Review all sources of information regarding each trial in making these determinations, giving greatest weight to medical documentation, blood levels, and multiple sources of confirmation. The start and stop dates for the period of the trial for which the patient is being rated (e.g., maintained oral dose or blood level for 4 weeks or greater) should be indicated, followed by the generic name(s) of the medication. Note explicitly combination trials and provide a separate rating for each agent in tricyclic antidepressant (TCA)/monoamine oxidase inhibitor, TCA/selective serotonin reuptake inhibitor (SSRI), or other combinations. In rating relative antidepressant resistance, note that noncompliance or instances of good therapeutic response followed by rapid relapse in the absence of continuation therapy at adequate levels or due to noncompliance prevent rating a trial at level "3" or higher. For each trial, provide a global confidence score for the antidepressant resistance rating. This score should reflect the rater's certainty regarding dose, duration, compliance, and clinical outcome of the medication trial. For ECT trials, the confidence rating should reflect certainty regarding the number of ECT treatments given and the outcome of the treatment. At this time, confidence in reports of dosage of ECT is not being rated, and compliance with treatment is usually 100% (patient was present at the treatment). The scale to be used for this judgment is provided below:

1. No Confidence Rating: Discrepant or clearly unreliable information regarding dose, duration, compliance, and outcome of a medication trial or number and outcome of ECT trial.
2. Low Confidence Rating: Information is marginal. Evidence of contradictions in information or significant doubt exists regarding dose, duration, compliance, and outcome of a medication trial or the number of treatments and outcome of ECT trial.
3. Moderate Confidence Rating: Adequate information is available but based largely on one source that appears reliable. Areas of doubt not critical in medication or ECT resistance rating.
4. Strong Confidence Rating: Adequate information is available from more than one reliable source without significant discrepancy regarding dose, duration, compliance, and outcome of a medication trial or the number of treatments and outcome of ECT trial.
5. High Confidence Rating: Trial dose, duration, compliance, and outcome or the number of treatments and outcome of ECT trial confirmed by multiple sources, with excellent documentation (blood levels, medication orders), strong evidence of compliance, and outcome certain.

After the global confidence rating is made for the rating of relative medication or ECT resistance, specific confidence ratings should be made with respect to dose, duration, compliance, and outcome of the trials. The same 1 to 5 rating scale used for the global confidence rating should be applied to these specific ratings.

cont.

Appendix 1. Antidepressant Treatment History Form (ATHF) Instruction Guide (cont.)

Use of Rating Criteria

The tables shown in Appendix 2 provide specific criteria to be used in rating the individual medication trials. These criteria are guides, but any departure from their use must be justified and documented. The general principles to be followed are as follows: (1) trials with a duration less than 4 weeks receive a score of "1," independent of dosage; (2) monotherapy with medications without established efficacy for unipolar depression receive a score of "1" independent of dosage or duration (e.g., antipsychotics, benzodiazepines, sedatives, stimulants, thyroid hormones, repetitive transcranial magnetic stimulation, herbal preparations), while for other agents with uncertain efficacy the maximum score could be "2" (alprazolam, specific anticonvulsants, lithium); (3) for selective heterocyclic antidepressants (HCAs), information regarding blood levels takes precedence over oral dosage; (4) evidence of noncompliance diminishes the rating of trial strength (e.g., clearly noncompliant patients should not receive a score of "3," the threshold for resistance); (5) abandoning a trial because of side effects in the context of significant clinical improvement also diminishes the rating of trial strength; (6) for combination trials (e.g., HCA and SSRI), each medication is rated separately. For all patients, an exception is made for lithium augmentation. The ratings for these trials are increased by one point if lithium was administered for at least 2 weeks and the score for the antidepressant met the threshold for an adequate trial (e.g., "3" or greater). In psychotic patients, an exception is also made for concurrent treatment with an antidepressant and antipsychotic (with or without lithium).

[a]The ATHF was developed by Harold A. Sackeim, Ph.D., and Joan Prudic, M.D.[17]

Appendix 2. Antidepressant Treatment History Form Rating Scales: Rating Medication Trials for Antidepressant Potency[a]

TCA/Tetracyclic

I. Amitriptyline (Elavil, Endep), imipramine (Tofranil), desipramine (Norpramin, Pertofrane), trimipramine (Surmontil), clomipramine (Anafranil), maprotiline (Ludiomil), doxepin (Sinequan, Adapin), nomifensine.
- By blood level: imipramine and desipramine only; levels take precedence
  - 4 = 4 wk or more and desipramine level ≥ 125 ng/mL
  - 4 = 4 wk or more and imipramine + desipramine level ≥ 225 ng/mL
- By dosage:
  - 1 = any drug < 4 wk *or* any drug < 100 mg/d
  - 2 = 4 wk or more and 100–199 mg/d
  - 3 = 4 wk or more and 200–299 mg/d
  - 4 = 4 wk or more and ≥ 300 mg/d

II. Nortriptyline (Pamelor, Aventyl)
- By blood level: levels take precedence
  - 1 = nortriptyline < 4 wk
  - 2 = 4 wk or more and level < 50 ng/mL
  - 3 = 4 wk or more and level 50–99 ng/mL
  - 4 = 4 wk or more and level > 100 ng/mL
- By dosage:
  - 1 = nortriptyline < 4 wk *or* 4 wk or more and nortriptyline < 50 mg/d
  - 2 = 4 wk or more and nortriptyline 50–75 mg/d
  - 3 = 4 wk or more and nortriptyline 76–100 mg/d
  - 4 = 4 wk or more and nortriptyline > 100

III. Protriptyline (Vivactil)
- 1 = drug < 4 wk *or* 4 wk or more and dosage ≤ 30 mg/d
- 2 = 4 wk or more and dosage 31–40 mg/d
- 3 = 4 wk or more and dosage 41–60 mg/d
- 4 = 4 wk or more and dosage > 60 mg/d

Notes:
- For TCA-MAOI combinations: score each agent alone, as a separate trial.
- For TCA-paroxetine/fluoxetine combination trials: after 1 week on 20 mg of paroxetine or fluoxetine, the dosage equivalent of the TCA should be doubled to determine resistance rating.

SSRIs

I. Fluoxetine (Prozac), citalopram (Celexa)
- 1 = drug < 4 wk *or* 4 wk or more and dosage 1–9 mg/d
- 2 = 4 wk or more and dosage 10–19 mg/d
- 3 = 4 wk or more and dosage 20–39 mg/d
- 4 = 4 wk or more and dosage ≥ 40 mg/d

II. Fluvoxamine (Luvox)
- 1 = drug < 4 wk *or* drug < 100 mg/d
- 2 = 4 wk or more and 100–199 mg/d
- 3 = 4 wk or more and 200–299 mg/d
- 4 = 4 wk or more and ≥ 300 mg/d

III. Paroxetine (Paxil)
- 1 = less than 4 wk *or* 4 wk or more and dosage 1–9 mg/d
- 2 = 4 wk or more and dosage 10–19 mg/d
- 3 = 4 wk or more and dosage 20–29 mg/d
- 4 = 4 wk or more and dosage ≥ 30 mg/d

IV. Sertraline (Zoloft)
- 1 = drug < 4 wk *or* 4 wk or more and dosage < 50 mg/d
- 2 = 4 wk or more and dosage 50–99 mg/d
- 3 = 4 wk or more and dosage 100–199 mg/d
- 4 = 4 wk or more and dosage ≥ 200 mg/d

Other Antidepressants

I. Bupropion (Wellbutrin)
- 1 = drug < 4 wk *or* 4 wk or more and dosage < 150 mg/d
- 2 = 4 wk or more and dosage 150–299 mg/d
- 3 = 4 wk or more and dosage 300–449 mg/d
- 4 = 4 wk or more and dosage ≥ 450 mg/d

II. Mirtazapine (Remeron)
- 1 = less than 4 wk *or* 4 wk or more and dosage < 15 mg/d
- 2 = 4 wk or more and dosage 15–29 mg/d
- 3 = 4 wk or more and dosage 30–44 mg/d
- 4 = 4 wk or more and dosage ≥ 45 mg/d

III. Nefazodone (Serzone)
- 1 = drug < 4 wk *or* 4 wk or more and dosage < 150 mg/d
- 2 = 4 wk or more and dosage 150–299 mg/d
- 3 = 4 wk or more and dosage 300–599 mg/d
- 4 = 4 wk or more and dosage ≥ 600 mg/d

IV. Trazodone (Desyrel), amoxapine (Asendin)
- 1 = drug < 4 wk *or* 4 wk or more and dosage < 200 mg/d
- 2 = 4 wk or more and dosage 200–399 mg/d
- 3 = 4 wk or more and dosage 400–599 mg/d
- 4 = 4 wk or more and dosage ≥ 600 mg/d

Note: Amoxapine will also receive an antipsychotic rating.

V. Venlafaxine (Effexor and Effexor XR)
- 1 = less than 4 wk *or* 4 wk or more and dosage < 75 mg/d
- 2 = 4 wk or more and dosage 75–224 mg/d
- 3 = 4 wk or more and dosage 225–374 mg/d
- 4 = 4 wk or more and dosage ≥ 375 mg/d

cont.

Appendix 2. ATHF Rating Scales: Rating Medication Trials for Antidepressant Potency (cont.)[a]

MAOIs

I. Phenelzine (Nardil)
- 1 = drug < 4 wk *or* 4 wk or more and dosage ≤ 30 mg/d
- 2 = 4 wk or more and dosage 31–60 mg/d
- 3 = 4 wk or more and dosage 61–90 mg/d
- 4 = 4 wk or more and dosage 91 mg/d or greater

II. Moclobemide
- 1 = less than 4 wk *or* 4 wk or more and dosage < 150 mg/d
- 2 = 4 wk or more and dosage 150–299 mg/d (100 mg–200 mg = 30 mg phenelzine)
- 3 = 4 wk or more and dosage 300–599 mg/d (300 mg = 60 mg phenelzine)
- 4 = 4 wk or more and dosage ≥ 600 mg/d (600 mg = 90 mg phenelzine)

III. Selegiline (Eldepryl)
- 1 = drug < 4 wk *or* 4 wk or more and dosage ≤ 20 mg/d
- 2 = 4 wk or more and dosage 21–40 mg/d
- 3 = 4 wk or more and dosage 41–59 mg/d
- 4 = 4 wk or more and dosage ≥ 60 mg/d

IV. Tranylcypromine (Parnate), isocarboxazid
- 1 = drug < 4 wk *or* 4 wk or more and dosage ≤ 20 mg/d
- 2 = 4 wk or more and dosage 21–40 mg/d
- 3 = 4 wk or more and dosage 41–60 mg/d
- 4 = 4 wk or more and dosage ≥ 61 mg/d

Notes:
- MAOI inhibition: 80% inhibition will rate 4.
- For TCA-MAOI combinations, score each agent considered alone.
- TCA/SSRI and any other combinations, e.g., SSRI/bupropion, should be treated as TCA/MAOI combinations; rate each medication separately.

Lithium

I. Lithium alone

For bipolar patients: levels take precedence over dosage
- 1 = drug < 4 wk *or* 4 wk or more and level ≤ 0.4 mEq/L *or* 4 wk or more and dosage < 600 mg/d for any duration
- 2 = 4 wk or more and level 0.41–0.6 mEq/L *or* 4 wk or more and dosage 600–899 mg/d
- 3 = 4 wk or more and level > 0.6 mEq/L *or* 4 wk or more and dosage ≥ 900 mg/d

Unipolar patients can receive a maximum rating of 2 for lithium alone.

II. Lithium as an augmenting agent
- 4 = antidepressant drugs (TCAs, SSRIs, others, MAOIs) rated level 3 and lithium for at least 2 wk

Carbamazepine rated level 3 and lithium for at least 2 wk
- 5 = antidepressant drugs (TCAs, SSRIs, other antidepressants, MAOIs) rated level 4 and lithium for at least 2 wk

ECT

I. Unilateral or unknown ECT
- 1 = 1–3 unilateral ECT
- 2 = 4–6 unilateral ECT
- 3 = 7–9 unilateral ECT
- 4 = 10–12 unilateral ECT
- 5 = 13 or more unilateral ECT

II. Bilateral ECT
- 1 = 1–3 bilateral ECT
- 2 = 4–6 bilateral ECT
- 4 = 7–9 bilateral ECT
- 5 = 10 or more bilateral ECT

Notes:
- A point is added to an ECT trial if the patient has had ≥ 7 adequate bilateral treatments. The highest rating is a 5.
- If ECT and antidepressant medication are given simultaneously, this does not constitute a combination/augmentation trial. Each should be rated separately.

Anticonvulsants

I. Carbamazepine (Tegretol)

For bipolar patients:
- 1 = Carbamazepine < 4 wk *or* 4 wk or more and level < 6 mEq/L
- 2 = 4 wk or more and level 6–7.9 mEq/L
- 3 = 4 wk or more and level ≥ 8 mEq/L

Note: Unipolar patients can receive a maximum rating of 2 for carbamazepine alone.

II. Lamotrigine (Lamictal)

For bipolar patients:
- 1 = drug < 4 wk *or* 4 wk or more and dosage < 50 mg/d
- 2 = 4 wk or more and dosage 50–199 mg/d
- 3 = 4 wk or more and dosage ≥ 200 mg/d

Note: Unipolar patients can receive a maximum rating of 2 for lamotrigine alone.

III. Gabapentin (Neurontin)

For bipolar patients:
- 1 = drug < 4 wk *or* 4 wk or more and dosage ≤ 800 mg/d
- 2 = 4 wk or more and dosage ≥ 1600 mg/d

Note: Unipolar patients can receive a maximum score of 1 for gabapentin alone.

IV. Clonazepam (Klonopin), valproic acid (Depakene), and topiramate (Topamax) can be rated 1 if used alone; they are not considered augmenting agents

Benzodiazepines

I. Alprazolam (Xanax)
- 1 = alprazolam < 4 wk *or* 4 wk or more and dosage < 4 mg/d
- 2 = 4 wk or more and dosage ≥ 4 mg/d

II. Other benzodiazepines
- 1 = any dosage for any duration

Note: These drugs are not considered augmenting agents.

Miscellaneous

I. Stimulants, e.g., dextroamphetamine (Dexedrine), methylphenidate (Ritalin), pemoline (Cylert)
- 1 = any dosage for any duration

Note; These drugs are not considered augmenting agents.

II. Antipsychotics
- 1 = any dosage for any duration

Note: These drugs are not considered augmenting agents.

III. Antipsychotics
- 1 = when used in nonpsychotic patients and should be rated together into one continuous trial, no matter how many different neuroleptics were given

IV. Clonidine (Catapres), L-tryptophan, thyroid hormones (e.g., liothyronine [Cytomel, Triostat], L-thyroxine [Levothyroid, Synthroid]), estrogen, fenfluramine
- 0 = any dosage for any duration

Note: These drugs are not considered augmenting agents.

V. Sedatives (buspirone [BuSpar], zolpidem [Ambien], lorazepam [Ativan], clonazepam [Klonopin], and diphenhydramine [Benadryl])
- 1 = any dosage for any duration when used as a psychotropic

Note: If the patient uses different sedatives, with the exception of alprazolam, it should be rated as one continuous trial.

VI. Phototherapy in any form: 1

VII. Herbal agents and uncertain somatic therapies (e.g., St. John's Wort, repetitive transcranial magnetic stimulation, vagus nerve stimulation) all receive a score of 1.

cont.

Appendix 2. ATHF Rating Scales: Rating Medication Trials for Antidepressant Potency (cont.)[a]

Equivalent Doses of Antipsychotic Drugs[a]

Generic name (U.S. trade name)	Equivalent Doses		
Phenothiazines			
Chlorpromazine (Thorazine)	100 mg	200 mg	400 mg
Thioridazine	100 mg	200 mg	400 mg
Mesoridazine (Serentil)	50 mg	100 mg	200 mg
Trifluoperazine (Stelazine)	4 mg	8 mg	16 mg
Fluphenazine	1.5 mg	3 mg	6 mg
Fluphenazine decanoate	0.25 cm^3/mo	0.5 cm^3/mo	1 cm^3/mo
Perphenazine (Trilafon, Etrafon)	10 mg	20 mg	40 mg
Prochlorperazine (Compazine)	15 mg	30 mg	60 mg
Thioxanthenes			
Thiothixene (Navane)	5 mg	10 mg	20 mg
Chlorprothixene (Taractan)	50 mg	100 mg	200 mg
Butyrophenone			
Haloperidol (Haldol)	2 mg	4 mg	8 mg
Haloperidol decanoate	...	0.25 cm^3/mo	0.5 cm^3/mo
Dibenzoxazepine			
Loxapine (Loxitane)	15 mg	30 mg	60 mg
Amoxapine (Asendin)	125 mg	250 mg	500 mg
Dibenzepine			
Clozapine (Clozaril)	60 mg	120 mg	240 mg
Dihydroindolone			
Molindone (Moban)	10 mg	20 mg	40 mg
Diphenylbutylpiperidine			
Pimozide (Orap)	2 mg	4 mg	8 mg
Other atypical antipsychotics			
Risperidone (Risperdal)	1.5 mg	3 mg	6 mg
Sulpiride	300 mg	600 mg	1200 mg
Olanzapine (Zyprexa)	5 mg	10 mg	20 mg
Quetiapine (Seroquel)	100 mg	200 mg	400 mg

[a]Trade names shown parenthetically. Abbreviations: ATHF = Antidepressant Treatment History Form, ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, XR = extended release.