A Computer Algorithm for Calculating the Adequacy of Antidepressant Treatment in Unipolar and Bipolar Depression

Maria A. Oquendo, M.D.; Enrique Baca-Garcia, M.D.; Alexei Kartachov, M.D.; Vadim Khait, Ph.D.; Carl E. Campbell, M.S.; Monique Richards, B.A.; Harold A. Sackeim, Ph.D.; Joan Prudic, M.D.; and J. John Mann, M.D.

Background: Major depression is often treated with medications in doses that are too low or too short in duration. We published an early version of the Antidepressant Treatment History Form (ATHF) that rates the adequacy of antidepressant treatment. The updated ATHF presented here includes newer medications and a computer algorithm to automate the evaluation of the adequacy of pharmacotherapy or electroconvulsive therapy for depression.

Method: The computer algorithm was written in MS-DOS Q-BASIC and in Visual Basic 5.0. Treatment data from 47 depressed (Structured Clinical Interview for DSM-III-R) patients were scored by the computer algorithm and assigned a number from 0 to 5 for the adequacy of antidepressant treatment. A psychiatrist blinded to the computer ratings manually rated the treatment using the ATHF.

Results: The computer algorithm, based on an updated version of the ATHF, estimates the adequacy of treatment of unipolar and bipolar depression. Computer algorithm results agreed with those generated by a clinician completing the form manually (κ = 0.88 to 1.00).

Conclusion: The computer algorithm can be used to analyze large databases and may help reduce the morbidity and mortality associated with major depression by improving the assessment of adequacy of pharmacologic treatments for research and quality assurance purposes. The availability of the updated ATHF on the Internet for downloading allows for modifications according to the user's purposes.

(J Clin Psychiatry 2003;64:825–833)

Received July 26, 2002; accepted Dec. 30, 2002. *From the Silvio O. Conte Centers for the Neuroscience of Mental Disorders (CCNMD) for the Study of the Neurobiology of Suicidal Behavior and the Stanley Foundation Center for Applied Neuroscience of Bipolar Disorders, New York (Drs. Oquendo and Mann); Department of Neuroscience, New York State Psychiatric Institute, New York (Drs. Oquendo, Khait, Sackeim, Prudic, and Mann); the Department of Psychiatry, Columbia University, New York (Drs. Oquendo, Sackeim, Prudic, and Mann and Mr. Campbell); Albert Einstein College of Medicine, New York (Dr. Kartachov); State University of New York, Downstate Medical Campus, New York, N.Y. (Ms. Richards); and Universidad Autonoma de Madrid, Spain (Dr. Baca-Garcia).*

This work was supported by NIMH grants MH35636, MH46745, MH40695, and MH48514 and the Stanley Medical Research Institute, Bethesda, Md. Clinical ratings were completed by members of the Clinical Evaluation Core of the CCNMD.

Dr. Mann is a consultant for GlaxoSmithKline and Pfizer; serves on the speakers or advisory boards for GlaxoSmithKline; and has received grant/research support from Pfizer. Dr. Baca-Garcia has received grant/research support from the National Alliance for Research on Schizophrenia and Depression (NARSAD) and Fondo de Investigacion Sanitaria (FIS), Madrid, Spain.

Corresponding author and reprints: Maria A. Oquendo, M.D., Columbia University/NYSPI, 1051 Riverside Dr., Unit #42, New York, NY 10032 (e-mail: moquendo@neuron.cpmc.columbia.edu).

Major depression results in extensive morbidity and mortality estimated at $43.7 billion annually in terms of health care dollars spent, loss of productivity, and days of work lost[1] and carries the risk and consequences of suicidal behavior.[2] However, major depression is inadequately treated in the community,[3–6] general psychiatric settings,[7,8] and academic psychiatry university settings.[9]

Recently, algorithms for the treatment of unipolar and bipolar depression have been generated.[10] However, a computer-assisted search did not uncover published algorithms to evaluate the strength of prescribed antidepressant treatments. We report the development of a computer algorithm based on an updated version of the Antidepressant Treatment History Form (ATHF),[11] a rating scale based on community standards for antidepressant treatment and suggestions by Keller et al.[12] for the evaluation of medication or electroconvulsive therapy (ECT) in the treatment of mood disorders.

METHOD

The Rating Form

The ATHF rates the adequacy of antidepressant treatment based on diagnosis (unipolar or bipolar depression, with or without psychotic features). The ATHF was originally written in 1990 (J.P., H.A.S.)[11] and last updated in 1999 (M.A.O., A.K.)[7] to include medications that became available in the intervening time period. Developed to classify research subjects presenting with major depression as treatment refractory, the ATHF uses stringent dose ranges to define treatment adequacy. The scale, including details regarding cutoff doses and how administration of multiple medications is rated, appears in Appendix 1, Appendix Tables A–J.

The ATHF assigns a score from 0 to 5, scaled for each type of treatment (specific medication or ECT), and takes into account dose, duration of treatment, and patient compliance with the treatment. A 0 indicates that no psychopharmacologic treatment was prescribed, and a rating of 1 or 2 indicates inadequate treatment. Treatment receives a rating of 1 if the medication dose is less than 50% of an adequate dose; a rating of 3 or greater indicates not only adequacy, but also increasing strength of antidepressant prescription (see Appendix 1, Appendix Tables A–J for exact cutoff doses). The increasing ratings above adequate rating reflect the fact that in clinical practice psychopharmacologists often increase the dose above that considered minimally effective in an attempt to maximize response. A method for rating aggressive treatment may be especially helpful in evaluating treatment-refractory patients.

For a treatment to be considered adequate, it must be taken for at least 4 weeks except in the case of ECT (see Appendix 1, Appendix Tables A–J). The ATHF only rates as adequate treatments those approved by the U.S. Food and Drug Administration for major depression or for which there is substantial evidence of antidepressant efficacy in the literature. Lithium and carbamazepine are rated differently for unipolar and bipolar depression. Only lithium is considered an augmenting agent.

Computer Algorithm

The computer algorithm was written in MS-DOS Q-BASIC (Microsoft, Redmond, Wash.) and in Visual Basic 5.0 (Microsoft, Redmond, Wash.) (V.K., A.K., E.B.G.) and implements the rules of the ATHF. It requires the availability of the following data: (1) subject identification number; (2) type of major depression (unipolar or bipolar); (3) assessment of psychosis (present/absent); (4) date of onset of current episode; (5) patient compliance with treatment; (6) name of medication (generic or commercial) or ECT (bilateral or unilateral); (7) dose or, preferably, blood level; (8) date of onset of treatment; and (9) date of treatment discontinuation. In the case of missing data, when treatment is with a standard antidepressant, the ATHF assigns a rating of 1 by default. When data are missing regarding patient characteristics, the program defaults to unipolar depression, nonpsychotic episode. If patient compliance ratings are missing, the program assumes 100% compliance. The program does not account for treatment response in calculating adequacy of response.

Table 1. Number of Pharmacologic Agents Used in Antidepressant Treatments

Medication Category	Number of Medications		Maximum Number of Medications
	Mean	SD	
Antidepressant	1.16	.77	3
Antipsychotic	0.18	.39	1
Benzodiazepines	0.20	0.46	2
Lithium	0.08	0.28	1
Mood stabilizers	0.47	0.54	2
Other	0.14	0.35	1

Subjects

Subjects were recruited at a university teaching hospital as part of a larger study and gave informed consent as approved by the Institutional Review Board. Subjects were 47 patients with either major depressive disorder (i.e., unipolar subtype) (N = 38) or bipolar (N = 9) major depressive episode diagnosed using the Structured Clinical Interview for DSM-III-R (SCID).[13] Only 3 patients had psychotic features as part of the major depressive episode. Patients were interviewed and characterized in terms of their diagnosis (bipolar or unipolar), episode characteristics (psychotic or nonpsychotic), and date of onset of the depressive episode. Data regarding the drug name, dose or blood drug levels, duration of treatment, and compliance were also recorded for all medications reportedly taken by the patient in the 3 months prior to study entry. In some cases, information from medical records and treating physicians was also recorded.

Evaluation of Treatment Adequacy

Data from the ATHF were scored by the computer algorithm and assigned a number from 0 to 5 for the adequacy of antidepressant treatment. An experienced psychiatrist (M.A.O.) blinded to the computer ratings manually rated the adequacy of treatment of depressed patients using the ATHF.

Statistical Analysis

All data are expressed as means and standard deviations. The ratings conducted by the clinician were compared with those generated by the computer algorithm using a weighted kappa.

RESULTS

Table 1 summarizes the pharmacologic agents used for the treatment of major depressive episode. The scores for

Table 2. Depressed Subjects (N = 47) Receiving Treatments of Each Adequacy Rating[a]

Adequacy	N	%
1	20	42.6
2	5	10.6
3	8	17.0
4	14	29.8
5	0	0

[a]A rating of 1 or 2 indicates inadequate treatment. A rating of 3 or greater indicates not only adequacy, but also increasing strength of antidepressant prescription.

the adequacy of the antidepressant treatments received by the study group are indicated in Table 2.

The kappa score was 1.00 for the unipolar subjects and 0.88 for the bipolar subjects (0.98 for the combined group), reflecting a single disagreement between the assessment by the clinician and the computer assessment. This disagreement led to the discovery of an error in the computer algorithm, which was subsequently corrected. Thus, the adjusted kappa after the correction of the computer algorithm was 1 for both groups. The computer algorithm proved to be equivalent to manual generation of adequacy scores by an experienced clinician. The adequacy of treatment data (Table 2) showed a bimodal distribution.

DISCUSSION

Major depression is often inadequately treated psychopharmacologically, even in situations in which patients seek care from a psychiatrist.[9] Patients treated with tricyclics or monoamine oxidase inhibitors have been reported to receive inadequate somatic therapies (51% of inpatients, 81% of outpatients) even in academic centers.[9] Although one study showed that adequate doses of selective serotonin reuptake inhibitors (SSRIs) are given by both psychiatrists (83%) and other physicians (79%) more often than tricyclics (53% for psychiatrists and 68% for other physicians) or atypical antidepressants,[14] lower doses than the ones used in the ATHF were considered adequate. A survey of prescribing practices, which also defined adequate treatment at lower doses than our criteria, found that 87% of SSRI prescribing practices fell in the adequate range, compared with 29% for tricyclics.[15] In contrast, we found that patients received equally inadequate treatment regardless of the agent used (18% received adequate treatment).[7]

Some subgroups of patients may be at risk for receiving poor somatic treatment. Patients with psychotic depression did not receive an antipsychotic 47% of the time and only 4% received at least 1 adequate medication trial before being referred for ECT.[16] Clinicians either failed to recognize psychotic symptoms or prescribed subtherapeutic doses of antipsychotic medication. A prospective study from the Netherlands[17] found that elderly, depressed inpatients received inadequate antidepressant treatment in 55% of cases, more often when receiving tricyclic medications (82%) than other antidepressants including SSRIs (36%). Although this report[17] did not make explicit what was considered an adequate treatment, Heeren et al.[17] documented that low doses were often prescribed because of side effects (21%) or patient's refusal to increase the dose (7%). Only in 21% of cases was dosing low because of reluctance on the part of the physician. Of interest, in 45% of cases in which a low dose was prescribed, the physician reported that a "good response" had been attained although the physician also reported a less than full recovery.[17] Depressed elderly patients hospitalized for medical problems also received inadequate antidepressant treatment.[18] Close to 60% of those patients received no antidepressants at all, despite chart documentation of major depression. Antidepressants were prescribed in adequate doses in only 29% of cases.[18]

Similarly, in a study of outpatient mental health community clinics,[19] white patients received a recommendation for antidepressant medications more often than Hispanic and black patients (84%, 56%, and 30%, respectively). This was true even though there were no differences in depressive subtype, suicidality, severity of depression, or length of current episode when minority and white groups were compared.[19]

Like the ATHF, the algorithm presented here considers the issue of compliance in addressing adequacy of treatment. Noncompliance with medication treatment has been reported to range from 15% to 44%.[20] Perhaps newer, better-tolerated antidepressants such as the SSRIs lead to fewer problems with compliance. One study showed that patients were more likely to refill their antidepressant prescriptions if they were prescribed an SSRI rather than a tricyclic medication.[13] However, other factors influence compliance as well.[21] Research that attends to compliance in a rigorous way may lead to further understanding of patient characteristics such as diagnosis, age, body weight, and ethnicity that may influence compliance with certain antidepressants.

Retrospective use of our algorithm for the ATHF may aid in the analysis of existing databases to evaluate outcome variables that depend on treatment adequacy, such as length of hospital stay, reduction in symptoms, or reduction of suicidal behaviors. The computer algorithm can also be used to categorize patients as treatment resistant.[11] Prospectively, the algorithm may serve as a way of verifying adequacy of treatment as it evolves, thereby alerting the pharmacist and/or physician if the prescribed treatment appears inadequate. The clinician can then verify the need for lower doses in cases such as slower metabolism in an individual or briefer duration of treatment if there are intolerable side effects leading to trial discontinuation. On a larger scale, this type of algorithm may assist drug utilization review methods currently in

use by health maintenance organizations or federal programs such as Medicaid.[22]

Practically, this computerized version of the ATHF has clinical and research uses and can be downloaded from the Internet (http://excalibur.cpmc.columbia.edu/intensity/Intensity.zip). The simplicity of the program allows for modification for the user's purposes, making it an important research and clinical tool. Evaluating adequacy of treatment in a methodical fashion, this algorithm may further knowledge about how clinicians select and use currently available treatments with efficacy for major depression.

REFERENCES

1. Greenberg PE, Stiglin LE, Finkelstein SN, et al. The economic burden of depression in 1990. J Clin Psychiatry 1993;54:405–418
2. Mann JJ, Oquendo M, Underwood MD, et al. The neurobiology of suicide risk: a review for the clinician. J Clin Psychiatry 1999;60(suppl 2):7–11
3. Isacsson G, Boëthius G, Bergman U. Low level of antidepressant prescription for people who later commit suicide: 15 years of experience from a population-based drug database in Sweden. Acta Psychiatr Scand 1992;85:444–448
4. Isometsä E, Henriksson M, Heikkinen M, et al. Suicide and the use of antidepressants: drug treatment of depression is inadequate [letter]. BMJ 1994;308:915
5. Rihmer Z, Rutz W, Pihlgren H. Depression and suicide on Gotland: an intensive study of all suicides before and after a depression-training programme for general practitioners. J Affect Disord 1995;35:147–152
6. Rutz W, Von Knorring L, Wálinder J. Frequency of suicide on Gotland after systematic postgraduate education of general practitioners. Acta Psychiatr Scand 1989;80:151–154
7. Oquendo MA, Malone KM, Ellis SP, et al. Inadequacy of antidepressant treatment of patients with major depression who are at risk for suicidal behavior. Am J Psychiatry 1999;156:190–194
8. Oquendo MA, Kamali M, Ellis SP, et al. Adequacy of antidepressant treatment after discharge and the occurrence of suicidal acts in major depression: a prospective study. Am J Psychiatry 2002;159:1746–1751
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. Expert Consensus Guideline Series: Treatment of Bipolar Disorder. J Clin Psychiatry 1996;57(suppl 12A):1–89
11. 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
12. Keller MB, Klerman GL, Lavori PW, et al. Treatment received by depressed patients. JAMA 1982;248:1848–1855
13. Spitzer RL, Williams JBW, Gibbon M, et al. Structured Clinical Interview for DSM-III-R (SCID). New York, NY: Biometric Research, New York State Psychiatric Institute; 1987
14. Shasha M, Miller SI, Lyons JS, et al. Serotonin reuptake inhibitors and the adequacy of antidepressant treatment. Int J Psychiatry Med 1997;27:83–92
15. Isometsä E, Seppälä I, Henriksson M, et al. Inadequate dosaging in general practice of tricyclic vs other antidepressants for depression. Acta Psychiatr Scand 1998;98:451–454
16. 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
17. Heeren TJ, Derksen P, van Heycop Ten Ham BF, et al. Treatment outcome and predictors of response in elderly depressed in-patients. Br J Psychiatry 1997;170:436-440
18. Koenig HG, George LK, Meador KG. Use of antidepressants by non-psychiatrists in the treatment of medically ill hospitalized depressed elderly patients. Am J Psychiatry 1997;154:1369–1375
19. Sirey JA, Meyers BS, Bruce ML, et al. Predictors of antidepressant prescription and early use among depressed outpatients. Am J Psychiatry 1999;156:690–696
20. Hall D, Wiles DH, McCreadie RG. Compliance with antidepressant medication. Br J Psychiatry 1990;157:453–454
21. Fawcett J. Compliance: definitions and key issues. J Clin Psychiatry 1995;56(suppl 1):4–8
22. Lipton HL, Bird JA. Drug utilization review in ambulatory settings: state of the science and directions for outcomes research. Med Care 1993;31: 1069–1082

Appendix appears on pages 829–833.

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

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 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 photocopy of a patient's medical record, pharmacy computer output, etc. 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 members, and prescribing psychiatrists, the treatment history form itself serves as the raw data, with a separate form completed for each individual interviewed, for each episode of depression. Repeat interviews (e.g., following remission of the acute episode) require completion of a new form.

Treatment History Form

The treatment history forms consist of a face sheet and a continuation form. 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.

Identifying information about the characteristics of a particular episode should be ascertained and recorded as accurately and in as much detail as possible. The RDC or DSM diagnosis, the designation of unipolar/bipolar and psychotic/nonpsychotic, and the duration of episode will be critical to later determinations of the potency of drug trials and the relative resistance to 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 drug or drug 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."

Episodes designated as nonpsychotic can be rated without considering the antipsychotic equivalency scales. Please note that lithium 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 should be considered in the following manner. First, rate antidepressant therapies. Then consider the concurrent antipsychotic treatment ratings for the drug trial. A chlorpromazine (CPZ) equivalency list is provided.

General Principles

Nonpsychotic depression trials for medication groups 100–300 and medications 402 and 602 (medications with demonstrated antidepressant activity) with a duration less than 4 weeks or missing duration receive a score of "1." For selective heterocyclic antidepressants (HTCs), information regarding blood levels takes precedence over oral dosage. *Nonpsychotic depression* trials for medication groups 400–1200 (excluding 402, 602, and 900) receive score "1" independent of dose or duration.

If the duration of a *nonpsychotic depression* trial equals or exceeds 4 weeks and the medication belongs to group 100–300 or is 402, 602, or 900, the trial receives a score between 2 and 5, depending on the dose of antidepressant (see Tables C–G), and diagnosis. For combination trials (e.g., HTC and SSRI), each medication is rated separately. An exception is made for lithium augmentation. The ratings for these trials are increased by 1 point if lithium was administered for at least 2 weeks and the score for the antidepressant met the threshold for an adequate trial (antidepressant adequacy > 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), while for other agents with uncertain efficacy the maximum score could be "2" (alprazolam, specific anticonvulsants, lithium).

Group 1300 receives score "0" independent of dose, duration, and diagnosis.

Psychotic depression trials first should be rated in accordance with the rules for nonpsychotic depression trials. Then all medications that belong to group 500 should be calculated in terms of the CPZ equivalence. If the group 500 medications are prescribed in doses equivalent to ≥ 400 mg of CPZ and the duration of the trial is ≥ 3 wk, then the adequacy should be rated separately (if used alone) or in combination with 100–300, 402, and 602 if used with antidepressants.

See Calculation of Adequacy of Treatment When Antipsychotic Trials Overlap and Table B for instructions.

Psychotic depression trials with combined antidepressant-antipsychotic therapy should be scored as separate trials for each antidepressant (100–300, 402, and 602).

900 ECT is rated separately and is not augmented by 209 (Li) or 500 (neuroleptics).

Only a simultaneous combined treatment trial can be considered augmented; any combined treatment given in sequential order must be rated separately.

For bipolar patients, carbamazepine and lithium treatment alone can receive a maximum rating of 3.

Evidence of noncompliance diminishes the rating of trial strength. Abandoning a trial because of side effects in the context of significant clinical improvement diminishes the rating of trial strength.

continued

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

Calculation of Adequacy of Treatment
When Antipsychotic Trials Overlap

If there is more than one antipsychotic medication, the following rules should apply:

If the AP1 CPZ > 400 and > 3 wk

And

If the AP2 CPZ > 400 or > 3 wk then it is considered as an adequate trial and rated as 2

Or

It can be rated as 2–5 if there is a combination of AP1, AP2 + AD1 + . . . rated as 1–5

If the AP1 CPZ < 400 or < 3 wk

And

If the AP2 CPZ < 400 or < 3 wk

Then

If the trials are consecutive, the duration of the trials should be added and the lowest dose should be used:

Example:
AP1 CPZ = 600 and D = 2 wk

And

AP2 CPZ = 400 and D = 1 wk

Then

AP1 + AP2 = CPZ 400 and D 3 wk, Adequacy = 2

If the trials are overlapping and the D of overlapping wk ≥ 3, then CPZ equivalents should be added.

If D overlapping < 3 wk, then duration of the 2 trials should be added.

Compliance

If information about compliance (C) is missing or not available, it is assumed that C = 100%.

The compliance should be calculated by the following equation:

$$C = \frac{\text{Total Medication Given} \times \text{Daily Dose Prescribed}}{\text{Total Medication Prescribed}}$$

Total Medication Given: Total amount of medication that the patient took during the treatment (e.g., sum of total number of milligrams taken over the course of treatment).

Daily Dose Prescribed: Dose after induction phase of treatment (e.g., 30 mg per day).

Total Medication Prescribed: Total amount of medication prescribed during the treatment (e.g., 30 mg per day for 28 days = 840 mg).

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 starting 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 HTC/MAOI combinations and HTC/SSRI 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 ECTs 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 number 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 number and outcome of ECT trial.
5. High Confidence Rating: Trial dose, duration, compliance, and outcome or number 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 1–5 rating scale as used for the global confidence rating should be applied to these specific ratings.

Equivalent Doses of Antipsychotic Drugs*

Generic name (trade names)	Equivalent Doses		
Phenothiazines			
Chlorpromazine (Thorazine)	100 mg	200 mg	400 mg
Thioridazine (Mellaril)	100 mg	200 mg	400 mg
Mesoridazine (Serentil)	50 mg	100 mg	200 mg
Trifluoperazine (Stelazine)	4 mg	8 mg	16 mg
Fluphenazine (Prolixin, Permitil)	1.5 mg	3 mg	6 mg
Fluphenazine decanoate	0.25 cc/mo	0.5 cc/mo	1 cc/mo
Perphenazine (Trilafon)	10 mg	20 mg	40 mg
Prochlorperazine (Compazine)	15 mg	30 mg	60 mg
Thioxanthenes			
Thiothixene (Navane)	5 mg	10 mg	20 mg
Chloprothixene (Taractan)	50 mg	100 mg	200 mg
Butyrophenone			
Haloperidol (Haldol)	2 mg	4 mg	8 mg
Haloperidol decanoate		0.25 cc/mo	0.5 cc/mo
Dibenzoxazepine			
Loxapine (Loxitane)	15 mg	30 mg	60 mg
Amoxapine (Asendin)	125 mg	250 mg	500 mg
Dibenzazepine			
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
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

*Please note the rating for amoxapine.

Appendix Table A. Medication Names and Codes[a,b]

Group Class	Drugs in Class	Drugs in Class	Drugs in Class
0 = none			
100 = Norepinephrine agonists	101 desipramine (Norpramin) 102 maprotiline (Ludiomil)	103 bupropion (Wellbutrin, Zyban) 104 nortriptyline (Pamelor)	105 protriptyline (Vivactil)
200 = Serotonin agonists	201 trazodone (Desyrel) 202 fluoxetine (Prozac) 203 fluvoxamine (Luvox)	204 paroxetine (Paxil) 206 sertraline (Zoloft) 207 nefazodone (Serzone)	208 buspirone (BuSpar) 209 lithium (Eskalith, Lithobid) 210 citalopram (Celexa)
300 = Combined norepinephrine and serotonin agonists	301 amitriptyline (Elavil, Endep) 302 imipramine (Tofranil) 303 amoxapine (Asendin) 304 venlafaxine (Effexor)	305 clomipramine (Anafranil) 306 doxepin (Sinequan, Zonalon) 307 tranylcypromine (Parnate) 308 phenelzine (Nardil)	309 isocarboxazid (Marplan) 310 mirtazapine (Remeron)
400 = Mood stabilizers	401 valproic acid (Divalproex Na, Valproate, Depakene, Depakote)	402 carbamazepine (Tegretol) 403 gabapentin (Neurontin)	404 lamotrigine (Lamictal) 405 topiramate (Topamax)
500 = Neuroleptics	501 haloperidol (Haldol) 502 perphenazine (Trilafon) 503 clozapine (Clozaril) 504 risperidone (Risperdal) 505 chlorpromazine (Thorazine)	506 pimozide (Orap) 507 fluphenazine (Prolixin, Permitil) 508 trifluoperazine (Stelazine) 509 thiothixene (Navane) 510 loxapine (Loxapac, Loxitane)	511 thioridazine (Mellaril) 512 olanzapine (Zyprexa) 513 quetiapine (Seroquel) 514 ziprasidone (Geodon) 515 molindone (Moban)
600 = Tranquilizers	601 lorazepam (Ativan) 602 alprazolam (Xanax) 603 clonazepam (Klonopin)	604 temazepam (Restoril) 605 hydroxyzine (Atarax, Vistaril) 606 flurazepam (Dalmane)	607 oxazepam (Serax)
700 = Stimulants	701 dextroamphetamine (Dexedrine)	702 methylphenidate (Ritalin)	703 pemoline (Cylert)
800 = Antihistamines/ anticholinergics	801 diphenhydramine (Benadryl, Dephedril)	802 benztropine (Cogentin) 803 trihexyphenidyl (Artane)	804 promethazine (Phenergan)
900 = ECT	900 unknown	901 unilateral ECT	902 bilateral ECT
1100 = Hypnotics	1101 chloral hydrate 1102 amobarbital Na (Amytal Na) 1103 butibel 1104 butabarbital Na (Butisol Na)	1105 methobarbital (Mebaral) 1106 methohexital Na (Brevital) 1107 pentobarbital Na (Nembutal, Pentobarb) 1108 phenobarbital (Phenob, Luminal)	1109 primidone (Mysoline) 1110 zolpidem (Ambien) 1111 secobarbital Na (Seconal Na, Tuinal)
1200 = MWADA	1201 clonidine (Catapres) 1202 L-tryptophan	1203 thyroid hormones (Cytomel, Synthroid) 1204 estrogens 1205 fenfluramine (Pondimin)	1206 phototherapy 1207 Ca channel blockers
1300 = MWNADA	1301 acetylsalicylic acid (aspirin) 1302 acetaminophen (Tylenol) 1303 indomethacin (Indocin) 1304 antibiotics 1305 cardiac glycosides	1306 stool softeners, laxatives 1307 vitamins 1308 H_2 blockers 1309 glucose-lowering (Sulfonurea class) 1310 insulin	1311 antiacid medication 1312 β-blockers 1313 pseudoephedrine

[a]All medications are encoded with 3- or 4-digit codes in accordance with their antidepressant activity.
[b]The first number in 3-digit codes or first 2 numbers in 4-digit codes encode the medication type; the second 2 digits encode the medication name.
Abbreviations: ECT = electroconvulsive therapy, MWADA = medication with antidepressant activity, MWNADA = medication with no antidepressant activity.

Appendix Table B. Trial Adequacy Calculation for Psychotic Depression

Adequacy	Categories	Definition of Rating
0	Medications with no known psychotropic actions or no medication	No treatment
1	AD alone AP alone CPZ < 400 or D < 3 wk AD rated as 1 + AP CPZ < 400 or D < 3 wk	Minimal treatment
2	AD rated 2–5 + AP CPZ < 400 or D < 3 wk AP alone CPZ ≥ 400 and D ≥ 3 wk AD rated 1–2 + AP CPZ ≥ 400 and D ≥ 3 wk	Treatment of uncertain efficacy
3	AD rated 3 + AP CPZ ≥ 400 and D ≥ 3 wk	Adequate moderate treatment
4	AD rated 4 + AP CPZ ≥ 400 and D ≥ 3 wk	Adequate intensive treatment
5	AD rated 5 + AP CPZ ≥ 400 and D ≥ 3 wk	Aggressive treatment

Abbreviations: AD = antidepressant, AP = antipsychotic, CPZ = chlorpromazine equivalent, D = trial duration.

Appendix Table C. Heterocyclic Antidepressants (HTC)[a,b,c]

Drug Rating	HTC Dose	HTC Blood Level	Nortriptyline Dose	Nortriptyline Blood Level	Protriptyline Dose
1	Any drug < 4 wk or Any drug < 100 mg/d		NT < 4 wk or 4 wk or more and NT < 50 mg/d	NT < 4 wk	Drug < 4 wk or 4 wk or more and dosage < 30 mg/d
2	4 wk or more and 100–199 mg/d		4 wk or more and NT 50–75 mg/d	4 wk or more and level < 50 ng/mL	4 wk or more and dosage 31–40 mg/d
3	4 wk or more and 200–299 mg/d	4 wk or more and DMI level 125 ng/mL or greater	4 wk or more and NT 76–100 mg/d	4 wk or more and level < 50–99 ng/mL	4 wk or more and dosage 41–60 mg/d
4	4 wk or more and 300 mg/d or greater	4 wk or more and DMI + IMI level > 224 ng/mL	4 wk or more and NT > 100 mg/d	4 wk or more and level 100–150 ng/mL	4 wk or more and dosage > 60 mg/d

[a]For HTC-MAOI combinations, score each agent alone, as a separate trial.
[b]For HTC-paroxetine/fluoxetine combination trials: after 1 week on 20 mg of paroxetine or fluoxetine, the dosage equivalent of the HTC should be doubled to determine adequacy rating.
[c]Amitriptyline (Elavil, Endep), imipramine (Tofranil), desipramine (Norpramin, Pertofrane), trimipramine (Surmontil), clomipramine (Anafranil), maprotiline (Ludiomil), doxepin (Sinequan, Adapin), nomifensine, nortriptyline (Pamelor, Aventyl), protriptyline (Vivactil).
Abbreviations: DMI = desipramine, IMI = imipramine, MAOI = monoamine oxidase inhibitor, NT = nortriptyline.

Appendix Table D. Selective Serotonin Reuptake Inhibitors (SSRIs)[a]

Drug Rating	Fluoxetine, Citalopram	Fluvoxamine	Paroxetine	Sertraline
1	Drug < 4 wk or 4 wk or more and dosage 1–9 mg/d	Drug < 4 wk or drug < 100 mg/d	Less than 4 wk or 4 wk or more and dosage < 1–9 mg/d	Drug < 4 wk or 4 wk or more and dosage < 50 mg/d
2	4 wk or more and dosage 10–19 mg/d	4 wk or more and 100–199 mg/d	4 wk or more and dosage 10–19 mg/d	4 wk or more and dosage 50–99 mg/d
3	4 wk or more and dosage 20–39 mg/d	4 wk or more and 200–299 mg/d	4 wk or more and dosage 20–29 mg/d	4 wk or more and dosage 100–199 mg/d
4	4 wk or more and dosage ≥ 40 mg/d	4 wk or more and 300 mg/d or greater	4 wk or more and dosage 30 mg/d	4 wk or more and dosage ≥ 200 mg/d

[a]Fluoxetine (Prozac), citalopram (Celexa), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).

Appendix Table E. Novel Antidepressants[a]

Drug Rating	Bupropion	Mirtazapine	Nefazodone	Trazodone, Amoxapine	Venlafaxine
1	Drug < 4 wk or 4 wk or more and dosage < 150 mg/d	Less than 4 wk or 4 wk or more and dosage < 15 mg/d	Drug < 4 wk or 4 wk or more and dosage < 150 mg/d	Drug < 4 wk or 4 wk or more and dosage < 200 mg/d	Less than 4 wk or 4 wk or more and dosage < 75 mg/d
2	4 wk or more and dosage 150–299 mg/d	4 wk or more and dosage 15–29 mg/d	4 wk or more and dosage 150–299 mg/d	4 wk or more and dosage 200–399 mg/d	4 wk or more and dosage 75–224 mg/d
3	4 wk or more and dosage 300–449 mg/d	4 wk or more and dosage 30–44 mg/d	4 wk or more and dosage 300–599 mg/d	4 wk or more and dosage 400–599 mg/d	4 wk or more and dosage 225–374 mg/d
4	4 wk or more and dosage 450 mg/d	4 wk or more and dosage 45 mg/d or greater	4 wk or more and dosage 600 mg/d or greater	4 wk or more and dosage 600 mg/d	4 wk or more and dosage 375 mg/d

[a]Bupropion (Wellbutrin), mirtazapine (Remeron), nefazodone (Serzone), trazodone (Desyrel), amoxapine (Asendin), venlafaxine (Effexor and Effexor XR).

Appendix Table F. Monoamine Oxidase Inhibitors (MAOIs)[a,b,c]

Drug Rating	Phenelzine	Moclobemide	Selegiline	Isocarboxazid
1	Drug < 4 wk or 4 wk or more and dosage < 30 mg/d	Less than 4 wk or 4 wk or more and dosage < 150 mg/d	Drug < 4 wk or 4 wk or more and dosage < 20 mg/d	Drug < 4 wk or 4 wk or more and dosage < 20 mg/d
2	4 wk or more and dosage 31–60 mg/d	4 wk or more and dosage 150–299 mg/d (100–200 = 30 Nardil)	4 wk or more and dosage 21–40 mg/d	4 wk or more and dosage 21–40 mg/d
3	4 wk or more and dosage 61–90 mg/d	4 wk or more and dosage 300–599 mg/d (300 = 60 Nardil)	4 wk or more and dosage 41–59 mg/d	4 wk or more and dosage 41–60 mg/d
4	4 wk or more and dosage 91 mg/d or greater	4 wk or more and dosage 600 mg/d or greater (600 = 90 Nardil)	4 wk or more and dosage 60 mg/d or greater	4 wk or more and dosage 61 mg/d

[a]MAOI inhibition: 80% inhibition will rate 4.
[b]For HTC-MAOI combinations, score each agent considered alone.
[c]Phenelzine (Nardil), moclobemide, selegiline (Eldepryl), tranylcypromine (Parnate), isocarboxazid.
Abbreviation: HTC = heterocyclic antidepressant.

Appendix Table G. Lithium or Carbamazepine Alone[a,b]

Drug Rating	Lithium for Bipolar Patients: Levels Take Precedence Over Dosage	Carbamazepine
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	Carbamazepine < 4 wk or 4 wk or more and level < 6
2	4 wk or more and level: 0.41–0.6 mEq/L or 4 wk or more and dosage: 600–899 mg/d	4 wk or more and level 6–7.9
3	4 wk or more and level: > 0.6 mEq/L or 4 wk or more and dosage: > 900 mg/d	4 wk or more and level 8 or more

[a]Unipolar patients can receive a maximum rating of 2 for lithium alone.
[b]Unipolar patients can receive a maximum rating of 2 for carbamazepine alone.

Appendix Table H. Lithium as an Augmenting Agent

Drug Rating	Lithium as an Augmenting Agent
4	Antidepressant drugs rated level 3 and lithium for at least 2 wk; carbamazepine rated level 3 and lithium for at least 2 wk
5	Antidepressant drugs rated level 4 and lithium for at least 2 wk

Appendix Table I. Electroconvulsive Therapy (ECT)[a,b]

Drug Rating	Number of Treatments	
	Unilateral or Unknown ECT	Bilateral ECT
1	1–3	1–3
2	4–6	4–6
3	7–9	
4	10–12	7–9
5	13 or more	10 or more

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

Appendix Table J. Others

Drug Rating[a,b,c]	Alprazolam	Antipsychotics	Sedatives	Other Benzodiazepines[d]	Not Considered Augmenting Agents: Stimulants, eg, *d*-Amphetamine, Methylphenidate, Pemoline	Antipsychotics	Clonidine, L-tryptophan, Thyroid Hormones, Estrogen, Fenfluramine
1	< 4 wk or 4 wk or more and dosage < 4 mg/d	When used in nonpsychotic patients and should be rated together into 1 continuous trial, no matter how many different neuroleptics were given	Any dosage for any duration when used as a psychotropic	Any dosage for any duration	Any dosage for any duration	Any dosage for any duration	Any dosage for any duration
2	4 wk or more and dosage 4 mg/d or greater						

[a]HTC/SSRI and any other combinations, e.g., SSRI/bupropion, should be treated as HTC/MAOI combinations: rate each medication separately.
[b]If the patient uses different sedatives, with the exception of alprazolam, they should be rated as one continuous trial.
[c]Phototherapy in any form: 1.
[d]Clonazepam (Klonopin) and valproic acid (Depakene) can be rated 1 if used alone; they are not considered augmenting agents.
Abbreviations: HTC = heterocyclic antidepressant, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor.