Assessing the Adequacy of Past Antidepressant Trials: A Clinician's Guide to the Antidepressant Treatment Response Questionnaire

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Many depressed patients do not remit on antidepressant medication despite an adequate dosage and a sufficient duration of treatment.[1] This has spawned endeavors to define *treatment-resistant depression* as a depressive episode that has shown insufficient response to 1 or more adequate trials of an antidepressant.[1] What constitutes *insufficient, inadequate,* or *partial response* is still a matter of debate. Recently, an operational classification of degree of treatment resistance was proposed,[2] with categorical distinctions defined by the percent symptom reduction from baseline as follows: nonresponse, < 25% reduction; partial response, 25%–49% reduction; and response without remission, ≥ 50% reduction but without achievement of remission.[1]

To determine the adequacy and outcome of treatment in a way that can be communicated among clinicians and researchers, it is crucial to employ a reliable and valid instrument. While historical rating of treatment is not as accurate as a prospective trial, there are many instances in which a decision is needed before the next trial is carried out. Several tools have been proposed, such as the Antidepressant Treatment History Form (ATHF),[3] the Harvard Antidepressant Treatment History (HATH),[4] and the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ).[1,5] The ATHF and HATH have the advantage of integrating clinical judgment in the assessment of treatment resistance, but these questionnaires are quite burdensome.[5] The ATRQ (Appendix 1) and accompanying questions are meant to provide clinicians with a user-friendly tool for assessment of prior treatment.

It is often the case that a patient remembers whether a past treatment was somewhat helpful, although it is frequently difficult for him or her to remember exactly which antidepressant was taken, how long it was taken, and at what dose. However, it is important that the clinician explore past trials thoroughly using a systematic approach in order to characterize the adequacy of the trial and the degree of improvement. The clinician version of the ATRQ[1,5] examines the adequacy of duration and dose of prior and current antidepressant treatments in a step-by-step procedure. It cannot be emphasized enough that, when assessing the duration and dose of clinical trials of antidepressants, clinicians must always inquire about *adherence* to each treatment trial. In addition, the ATRQ assesses the degree of improvement (in the most efficacious trial or in all trials during the current episode, depending on the version of the instrument) on a scale from 0% (not improved at all) to 100% (completely improved) (Table 1).

Table 1. Efficacy/Duration/Dose ("EDD") Questions to Ask to Determine Treatment Resistance for Each Antidepressant Used

Efficacy	1. Did the medication help at all? *If no, then this is a clear nonresponse.* *If yes, ask the following:* 2. Did it help a lot, say, made you feel more than 50% better? *If yes, this is a response.* 3. Did it help a little, say, made you feel somewhere between 25% and 50% better? *If yes, this is a partial response; if no, this is a nonresponse.*
Duration	1. For how long did you take the medication? *If the patient isn't sure, prompt as follows:* 2. Would you say you were on it for at least a month? 3. What about longer than that, say, at least 2 months? 4. Longer than that? *(This should give a good estimate of the adequacy of the treatment period.)*
Dose	1. Do you remember what dose you took? *If the patient isn't sure, prompt as follows:* 2. Were you on a single pill per day? 3. Was your dose increased at any time? *(This should give an idea of whether the patient stayed on a starting dose or received a higher dose.)*

The previous treatment may have been monotherapy, an augmentation trial, a trial of 2 antidepressants (combination therapy), or a switch to another antidepressant. Our group has adopted conventions to define resistance to each of these approaches. At the outset it is noted that the doses and durations required for adequate treatment are based on expert consensus[1] rather than systematic research. We define an adequate monotherapy trial as a trial lasting at least 6 weeks at a minimum effective dose. In the context of this initial trial, the adequate duration for augmentation or combination treatment is at least 3 weeks. However, a combination trial from the onset (ie, starting with 2 drugs together) must be 6 weeks. Six weeks is also required for a switch to a different antidepressant. Each of these trials is considered a new trial. An increase in dose for at least 4 weeks represents optimization and is not considered a new or separate trial. However, if remission is later followed by relapse, a dose increase represents a new trial for the new episode.

We recognize that the conventions used to define adequate dose and duration are not established and that other conventions, for example, a duration of 12 weeks, might be preferred. The ATRQ can be adapted to accommodate various definitions of dose and duration. Likewise, the threshold of resistance in terms of percent response may vary, depending on the questions being asked within a given clinical trial.

Clinical Vignettes

The following 3 vignettes are provided as examples of how the ATRQ might be used to assess patients.

1. *After an initial improvement of 30% on treatment with sertraline 100 mg/d for 2 months, a patient is prescribed augmentation with lithium for 4 weeks, resulting in a 60% improvement (from the original pretreatment clinical state).*
   This would be scored as an initial failed trial (sertraline), followed by a response to the lithium augmentation trial. This patient would not be considered treatment-resistant because of the response to the augmentation strategy.

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2. *A patient tried an antidepressant a few years ago at an adequate dose for several months, and it worked very well (80% improvement). He felt so much better that he stopped taking it. After several months, he experienced a recurrence of depression. He resumed the same medication, this time with only 20% improvement.*

This would be considered as a successful trial of the antidepressant for an initial episode of major depressive disorder (MDD), followed by a failed trial of the same antidepressant for a subsequent episode of MDD. This patient would thus be considered resistant to antidepressant treatment during the current episode.

3. *Six months after an initial response to citalopram 20 mg/d, a patient experiences a recurrence of symptoms, which is followed by a dose increase to 40 mg/d for 3 weeks. At the time of interview, the patient reports an improvement of 40%.*

Tachyphylaxis ("poop-out") represents a special challenge in assessing resistance. There is evidence that increasing the dose leads to response in approximately two-thirds of patients relapsing during antidepressant treatment.[6] Since the duration of treatment with the increased dose was too short to be counted as an adequate trial, the patient is not considered to be currently failing a trial. For the purpose of establishing eligibility for a clinical trial in treatment-resistant depression, the current medication dose (40 mg/d) should be continued for 1 additional week, and the patient should then be reassessed. If the patient has not responded after 4 weeks or more of an increased dose, the patient is considered resistant to a single trial of a higher dose.

It is crucial to obtain a precise antidepressant history for both research and clinical practice. We propose that the ATRQ and the accompanying questions (with the mnemonic "EDD") can be used for this purpose in order to facilitate treatment decisions in clinical practice and systematize screening and patient selection for clinical trials in treatment-resistant depression.

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Appendix 1. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire[a]

Please indicate the correct answer to the following questions:

(1) Have you received any treatment with medications since the beginning of **THIS CURRENT** episode or period of depression? Please circle the correct answer. **YES** **NO**

(2) If **YES**, please review the list below and put a check next to any medication(s) that you have taken for at least 6 or 10 weeks during THIS episode or period of depression.

(3) Of those medication(s) that you have checked from the list, please put a second check next to those that you have taken at a dosage equal to or greater than the minimum dosage listed for that medication.

(4) Of those medication(s) that you have checked from the list, please put a third check next to those that you have taken with another drug (eg, buspirone [Buspar], lithium, psychostimulants such as methylphenidate [Ritalin], atypical antipsychotics such as olanzapine [Zyprexa]) added to augment or boost the antidepressant effect.

(5) Of the medications that you have checked, please write below the name of the one that you feel helped you the most with your depression:

_____

(6) If a rating of 100 is "completely improved" and 0 is "not improved at all," how close to 100 did you get on this medication? Please put a check next to the answer that best applies to you.

_____ a) Less than 25% improved _____ b) Between 25% and 49% improved _____ c) Between 50% and 75% improved _____ d) More than 75% improved

List of Antidepressant Medications

Drug Class **Brand Name**	**Generic Name**	At Least **6 Weeks**	or	At Least **10 Weeks**	**Minimum** Dose	Equal to or Greater Than	**Maximum** Dose	Equal to or Greater Than	**Drug Was Added to Augment or Boost Effect**
Tricyclic Antidepressants									
Adapin	doxepin	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Anafranil	clomipramine	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Asendin	amoxapine	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Endep/Elavil	amitriptyline	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Ludiomil	maprotiline	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Norpramin	desipramine	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Pamelor	nortriptyline	_____		_____	75 mg/d	_____	125 mg/d	_____	_____
Sinequan	doxepin	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Surmontil	trimipramine	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Tofranil	imipramine	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Vivactil	protriptyline	_____		_____	30 mg/d	_____	60 mg/d	_____	_____
Azafen	pipofezine	_____		_____	150 mg/d	_____	300 mg/d	_____	_____
Agedal/Elronon	noxiptiline	_____		_____	100 mg/d	_____	200 mg/d	_____	_____
Monoamine Oxidase Inhibitors (MAOIs)									
Marplan	isocarboxazid	_____		_____	30 mg/d	_____	60 mg/d	_____	_____
Nardil	phenelzine	_____		_____	45 mg/d	_____	90 mg/d	_____	_____
Parnate	tranylcypromine	_____		_____	30 mg/d	_____	60 mg/d	_____	_____
Emsam	selegiline patch	_____		_____	6 mg/24 hrs	_____	12 mg/24 hrs	_____	_____
Aurorix	moclobemide	_____		_____	300 mg/d	_____	600 mg/d	_____	_____
Pirazidol	pirlindole	_____		_____	200 mg/d	_____	300 mg/d	_____	_____
Selective Serotonin Reuptake Inhibitors (SSRIs)									
Luvox	fluvoxamine	_____		_____	50 mg/d	_____	150 mg/d	_____	_____
Paxil	paroxetine	_____		_____	20/25 mg/d	_____	60/75 mg/d	_____	_____
Prozac	fluoxetine	_____		_____	20 mg/d	_____	60 mg/d	_____	_____
Zoloft	sertraline	_____		_____	50 mg/d	_____	150 mg/d	_____	_____
Celexa	citalopram	_____		_____	20 mg/d	_____	60 mg/d	_____	_____
Lexapro	escitalopram	_____		_____	10 mg/d	_____	30 mg/d	_____	_____
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)									
Effexor	venlafaxine	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Cymbalta	duloxetine	_____		_____	60 mg/d	_____	120 mg/d	_____	_____
Pristiq	desvenlafaxine	_____		_____	50 mg/d	_____	100 mg/d	_____	_____
Savella	milnacipran	_____		_____	100 mg/d	_____	200 mg/d	_____	_____
Other Antidepressants									
Viibryd	vilazodone	_____		_____	40 mg/d	_____	80 mg/d	_____	_____
Desyrel	trazodone	_____		_____	300 mg/d	_____	600 mg/d	_____	_____
Serzone	nefazodone	_____		_____	300 mg/d	_____	600 mg/d	_____	_____
Wellbutrin	bupropion	_____		_____	300 mg/d	_____	450 mg/d	_____	_____
Remeron	mirtazapine	_____		_____	15 mg/d	_____	45 mg/d	_____	_____
Valdoxan	agomelatine	_____		_____	25 mg/d	_____	50 mg/d	_____	_____
Stablon	tianeptine	_____		_____	37.5 mg/d	_____	75 mg/d	_____	_____
Edronax	reboxetine	_____		_____	4 mg/d	_____	8 mg/d	_____	_____
Bolvidon/Depnon, Norval/Tolvon	mianserin	_____		_____	30 mg/d	_____	90 mg/d	_____	_____
Insidon	opipramol	_____		_____	150 mg/d	_____	300 mg/d	_____	_____

Did you receive electro-convulsive treatment (ECT) **during the current episode** (please circle the correct answer): **YES** **NO**

Did you **ever** receive vagal nerve stimulation (VNS) or deep brain stimulation (DBS) (please circle the correct answer): **YES** **NO**

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