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Update on the assessment of resistance to antidepressant treatment: Rationale for the Antidepressant Treatment History Form: Short Form-2 (ATHF-SF2)

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ABSTRACT

All definitions of treatment-resistant depression (TRD) require that patients have experienced insufficient benefit from one or more adequate antidepressant trials. Thus, identifying "failed, adequate trials" is key to the assessment of TRD. The Antidepressant Treatment History Form (ATHF) was one of the first and most widely used instruments that provided objective criteria in making these assessments. The original ATHF was updated in 2018 to the ATHF-SF, changing to a checklist format for scoring, and including specific pharmacotherapy, brain stimulation, and psychotherapy interventions as potentially adequate antidepressant treatments. The ATHF-SF2, presented here, is based on the consensus of the ATHF workgroup about the novel interventions introduced since the last revision and which should/should not be considered effective treatments for major depressive episodes. This document describes the rationale for these choices and, for each intervention, the minimal criteria for determining the adequacy of treatment administration. The Supplementary Material that accompanies this article provide the Scoring Checklist, Data Collection Forms (current episode and composite of previous episodes), and Instruction Manual for the ATHF-SF2.

1. Introduction

Treatment-resistant depression (TRD) is common, costly, disabling, and deadly (Brenner et al., 2021; Johnston et al., 2019; Lundberg et al., 2023; McIntyre et al., 2023a; Mrazek et al., 2014; Taipale et al., 2020; Weissman et al., 2021; Zhdanava et al., 2021). Multiple definitions of TRD have been proposed (Berlim and Turecki, 2007a; Demyttenaere and Van Duppen, 2019; Gaynes et al., 2018; Ruhe et al., 2012), with the most common approach requiring, at minimum, failure to benefit sufficiently from at least two distinct trials of accepted antidepressant treatments delivered at adequate dose and duration (Conway et al., 2017; European Medicines Agency, 2013; Thase and Rush, 1995). Although differing in important details, fundamentally all approaches to the assessment of treatment resistance require evaluation of the extent of clinical benefit

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achieved and the adequacy of treatment administration for distinct antidepressant interventions.

The assessment of antidepressant treatment resistance informs clinical practice, treatment guidelines, regulatory labeling and staging of medications and devices, and reimbursement and other public policies. Increasingly, Food and Drug Administration (FDA) and European Medicines Agency (EMA) labeling and public and third-party reimbursement policies stipulate a minimum number of "failed adequate trials" before use of specific interventions. For example, the FDA guidance on Transcranial Magnetic Stimulation (TMS) in the treatment of MDD considers it safe and effective "in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode" (US Food and Drug Administration, 2011). The labelling of esketamine restricts its use to patients with TRD, defined as "Patients with MDD who, despite trying at least two antidepressant treatments given at adequate doses for an adequate duration in the current episode, have not responded to treatment" (US Food and Drug Administration, 2020). In contrast, the labeling for vagus nerve stimulation in TRD restricts its use to patients who "have not had an adequate response to four or more adequate antidepressant treatments" (US Food and Drug Administration, 2005). Reliable and valid assessment of antidepressant treatment resistance is also fundamental to clinical research on the phenomenology, neurobiology, and therapeutics of TRD (Fabbri et al., 2019, 2021; Xiong et al., 2023) and other forms of difficult-to-treat depression (DTD) (Rush et al., 2022).

2. History of the ATHF, ATHF-SF, and ATHF-SF2

The Antidepressant Treatment History Form (ATHF) was one of the earliest and most widely used instruments to systematically assess antidepressant treatment trials and characterize treatment resistance (Sackeim, 2001). This instrument identified the specific pharmacological and neuromodulatory interventions considered effective in the acute treatment of major depressive episodes (MDE) and provided explicit criteria for evaluating the adequacy of individual treatment trials. Of similar instruments (e.g., MGH Antidepressant Treatment Response Questionnaire [ATRQ]) (Chandler et al., 2010; Desseilles et al., 2011), the ATHF was unique in providing separate criteria for unipolar and bipolar MDE, as well as psychotic and non-psychotic MDE (Hazari et al., 2013) (see Table 1). The ATHF has been used for sample characterization and prediction of outcome in studies of electroconvulsive therapy (ECT) (Dombrovski et al., 2005; Heijnen et al., 2010; Prudic et al., 2013; Prudic et al., 1996; Prudic et al., 1990; Rasmussen et al., 2007; Rasmussen et al., 2009; Sackeim et al., 2009; Sackeim et al., 2001a; Sackeim et al., 1990; Sackeim et al., 2000; Sackeim et al., 2008; van den Broek et al., 2004), TMS (George et al., 2010; Lisanby et al., 2009; O'Reardon et al., 2007; Wathra et al., 2023), VNS (Aaronson et al., 2017; Rush et al., 2005; Sackeim et al., 2001b), and multiple pharmacological interventions (Blumberger et al., 2011; Buchalter et al., 2019; Hsu et al., 2016; Joel et al., 2014; Joo et al., 2005; Kocsis et al., 2008). It has been used to characterize the adequacy of care in particular patient subgroups (Baca-Garcia et al., 2009), such as psychotic depression (Andreescu et al., 2007; Mulsant et al., 1997), or particular provider subgroups (Dew et al., 2005). The ATHF has also been used to document the adequacy of care surrounding sentinenal events, such as suicide (Oquendo et al., 1999, 2002).

Almost 20 years after its publication, the ATHF was significantly revised in 2018 and replaced by the Antidepressant Treatment History Form-Short Form (ATHF-SF) (Sackeim et al., 2019). In the original ATHF, each trial was rated on a 1–5 scale for "antidepressant potency", with the threshold for adequate dose and duration corresponding to scores of 3 or greater, with higher medication dosage or use of an augmenting agent leading to higher scores. This grading of trial potency required tracking medication dose changes over time, and often for multiple concurrent medications. This level of granular information about treatment history was often unavailable in many settings or required substantial resources to access previous providers, patient and family member informants, and medical and pharmacy records. The ATHF-SF significantly streamlined trial evaluation by only documenting whether an intervention was administered at all, and, if so, whether the trial met threshold criteria for resistance, i.e., insufficient benefit in the context of a minimally adequate trial. Explicit criteria were provided for evaluating clinical outcome, adherence, dose and duration when making the binary judgment of "failed-adequate". The ATHF-SF also updated the interventions considered as effective antidepressant treatments, including the use of atypical antipsychotic monotherapy in bipolar MDE (Geddes and Miklowitz, 2013; Goodwin et al., 2016; Thase and Sachs, 2000; Yildiz et al., 2023) or combination treatment with an antidepressant and an atypical antipsychotic medication for unipolar MDE (Gobbi et al., 2018; Nelson and Papakostas, 2009; Nunez et al., 2022; Papakostas et al., 2007; Simons et al., 2017; Wang et al., 2015). Two

Table 1
Essential features of assessment instruments and models of treatment-resistant depression.

	Explicit Operational Criteria	Inclusion of Non-pharmacological interventions	Separate Criteria for Depression Subgroups	Criteria for Combination and/or Augmentation Trials	Additional information used for TRD score
Antidepressant Treatment History Form (ATHF) (Sackeim, 2001; Sackeim et al., 1990)	Yes	ECT only	Bipolar vs. Unipolar MDE; Psychotic vs. Nonpsychotic MDE	Yes	No
Thase and Rush Staging Model (Thase and Rush, 1995; Thase and Rush, 1997	No	ECT only	No	No	No
European Staging Model (European Medicines Agency, 2013; Souery et al., 1999)	No	None	No	Yes	Duration of treatment
Massachusetts General Hospital Staging Model (MGH-s)((Fava, 2003) and the Antidepressant Treatment Response Questionnaire [ATRQ]) (Desseilles et al., 2011)	Yes	ECT only	No	Yes	No
Maudsley Staging Model (van Belkum et al., 2018; Fekadu et al., 2009)	Yes	ECT only	No	Yes	Duration of episode; Baseline symptom severity
Conway et al. Staging Model (Conway et al., 2017)	No	Unspecified brain stimulation and psychotherapies	No	No	No
Antidepressant Treatment History Form: Short Form (ATHF-SF) (Sackeim et al., 2019); Antidepressant Treatment History Form: Short Form-2 (ATHF-SF2)	Yes	Multiple brain stimulation and psychotherapy interventions	Bipolar vs. Unipolar MDE; Psychotic vs. Nonpsychotic MDE	Yes	No

neuromodulation interventions, TMS and VNS, had been approved by the FDA with specific labeling for use in TRD (US Food and Drug Administration, 2005, 2011). In addition, the ATHF-SF expanded the domains of effective antidepressant interventions beyond psychopharmacology and neuromodulation and provided criteria for evaluating the adequacy of psychotherapy trials, for the first-time offering characterization of this form of treatment resistance.

The publication introducing the ATHF-SF appeared in this journal. To make this instrument widely available without cost, a set of documents were included as Supplementary Material to the ATHF-SF publication, downloadable with the paper (Sackeim et al., 2019). These documents included the ATHF-SF Instruction Manual, ATHF-SF Data Collection Form: Current Episode, ATHF-SF Data Collection Form: Composite of Prior Episodes, and the ATHF-SF Scoring Checklist. The Scoring Checklist inventories all potentially adequate antidepressant treatments with specific thresholds for determining the adequacy of dose and duration of each treatment. While there have been informal updates to the ATHF-SF criteria since its publication (Conway et al., 2020), the versions downloadable via links in the original 2019 paper are unmodified and labeled as Version 2018.1.

There have been notable advances in the treatment of MDE since the publication of the ATHF-SF (Thase, 2023). These include esketamine in the treatment of TRD (McIntyre et al., 2021; Reif et al., 2023), the use of combination dextromethorphan and bupropion in MDD (Iosifescu et al., 2022; Tabuteau et al., 2022), brexanolone (Edinoff et al., 2021; Meltzer-Brody et al., 2018) and zuranolone (Deligiannidis et al., 2021, 2023) for post-partum depression, gepirone (extended release) as the first selective 5-HT_{1A} partial agonist approved for treatment of MDD (US Food and Drug Administration, 2023), the intermittent Theta Burst Stimulation (ITBS) protocol for Transcranial Magnetic Stimulation (TMS) in TRD (Blumberger et al., 2018) and the Stanford Neuromodulation Therapy (SNT) protocol for accelerated TMS in TRD (Cole et al., 2022). Atypical antipsychotic medications are also newly approved as monotherapy in bipolar MDE (Kadakia et al., 2021; Yildiz et al., 2023) or as augmentation agents in unipolar MDE (Nunez et al., 2022). There has also been progress in the development of evidence-based psychotherapies for major depressive episodes (MDEs), particularly Acceptance and Commitment Therapy (Bai et al., 2020; Gloster et al., 2020; Zettle, 2015). This publication updates the ATHF-SF to a new version, the ATHF-SF2, and summarizes the considerations of the ATHF-SF2 workgroup in modifying (or not) the instrument. These considerations included broad issues, such as whether the duration of pharmacological trials should be increased from a minimum of 4 weeks at the minimally effective dose to a longer duration, as well as the specific issues as to which new interventions should be included as effective antidepressant treatments and considered when assessing treatment resistance.

The authors of this article constituted the ATHF-SF2 workgroup and, except for one issue, reached consensus on the modifications introduced in this update. The work of the group was partly supported by LivaNova, Inc, who has used the ATHF-SF in studies of VNS in TRD (see Disclosures) (Conway et al., 2020). As before, the supplemental files attached to this paper provide the ATHF-SF2 Instruction Manual, Data Collection Form: Current Episode, Data Collection Form: Composite of Prior Episodes, and the ATHF-SF2 Scoring Checklist which contains the scoring criteria for all antidepressant interventions. There are no restrictions on the use or dissemination of these documents. The versions attached to this paper are labeled Version 2024.1.

3. Core issues in evaluating antidepressant treatment resistance

The ATHF-SF2 workgroup reconsidered a variety of issues intrinsic to evaluating the adequacy of antidepressant treatments. These included identifying the domains of treatment that should be considered (e.g., pharmacology, brain stimulation, psychotherapy), the patient subgroups that required separate criteria (e.g., bipolar vs. unipolar MDE, nonpsychotic vs. psychotic MDE), how trial-by-trial ratings are made (e.g., dichotomous evaluation of adequacy vs. multi-level rating of trial potency), how antidepressant treatments should be grouped into classes, whether separate criteria should be offered for augmented or combination psychopharmacology trials (e.g., antidepressant plus lithium), and conventions for evaluating trial dosage, duration, clinical benefit and adherence. The rationales for the positions taken on these organizing principles in the ATHF-SF were previously detailed (Sackeim et al., 2019).

The ATHF-SF2 workgroup considered whether modifications were needed in any of the core issues and conventions. For example, no changes were made in the domains evaluated: pharmacotherapy, brain stimulation, and psychotherapy. The inclusion of psychotherapy in the ATHF-SF as a domain of potentially effective antidepressant treatment has been supported by a large body of evidence (Cuijpers et al., 2008, 2020), and documentation of resistance to an adequate psychotherapy trial has become an element in some reimbursement policies for TRD interventions (Cigna, 2023). The ATHF-SF2 workgroup continued to exclude complementary, dietary, or naturopathic supplements from consideration as effective antidepressant treatments (e.g., S-adenosyl-l-methionine [SAM-e], St. John's Wort, omega-3 fatty acids, folate, B-vitamins) based on insufficient or inconsistent evidence of efficacy, especially as monotherapies, and concerns about consistency of dosing and bioavailability.

The workgroup did not recommended change regarding any of the organizing principles of the ATHF-SF. There continues to be compelling need to evaluate antidepressant trials differently for patients with bipolar and unipolar MDE (Baldessarini et al., 2020; Bauer et al., 2017). This is routinely expressed in the regulatory approval process and labeling of antidepressant interventions (US Food and Drug Administration, 2017). Similarly, the subtype of psychotic depression requires distinct criteria when evaluating pharmacological treatment adequacy, given the superior acute and long-term efficacy of combined treatment with antidepressant and antipsychotic medications over monotherapies (Blumberger et al., 2011; Farahani and Correll, 2012; Flint et al., 2019; Meyers et al., 2009; Wijkstra et al., 2010). The checklist format adopted in the ATHSF-SF documents for every intervention whether it was administered or not and, if administered, whether the trial was "failed-adequate" or not. This approach was thought to simplify and speed completion of the instrument, enhancing its utility relative to the more detailed and labor-intensive ratings of trial potency used in the original ATHF.

3.1. Duration of antidepressant pharmacology trials

The minimally adequate duration for pharmacological trials was the issue that work group debated at length and for which there were significant differences in recommendations. The ATHF and ATHF-SF stipulated 4 weeks as the minimum duration for pharmacological trials to be considered adequate, given sufficient dose over this period. The use of a uniform threshold for adequacy of trial duration across pharmacological treatments was justified given the absence of meaningful differences among antidepressant medications in the time course of symptomatic improvement (Cheng et al., 2020; Gelenberg and Chesen, 2000; Machado-Vieira et al., 2010), with the recent exception of rapid-acting NMDA-antagonists (Daly et al., 2018; Ionescu et al., 2019; Sanacora et al., 2017). However, the workgroup debated whether the minimum duration should be maintained at four weeks or increased, noting that there is variability among the various approaches to assessing TRD in the minimum duration of medication trials required for adequacy.

Four weeks has been the most commonly used cutoff, but TRD studies have also required six or eight weeks for trials to be considered adequate (Berlim and Turecki, 2007a, 2007b). The ATHF (Sackeim, 2001) and Antidepressant Treatment Record (ATR) (Carpenter et al., 2012; Dunner et al., 2014) use a four-week minimum cutoff, while the original ATRQ (Chandler et al., 2010; Desseilles et al., 2011) required six weeks. Given uncertainty about the optimal duration cutoff, the original

ATRQ also documented whether the minimal dosage was given for at least ten weeks. The current version of the ATQR split this difference and requires 8 weeks at the minimum therapeutic dose for evaluating resistance (Massachusetts General Hospital Clinical Trials Network and Institute, 2023). Reflecting this variability, some third-party health policies, when documenting treatment resistance for pre-authorization of TMS, stipulate "use of an antidepressant medication at adequate therapeutic doses for at least four weeks with no significant reduction in depressive symptoms (p. 2)" (Cigna, 2023), while others stipulate that antidepressants be administered for at least 8 weeks (Aetna, 2024).

Use of a longer treatment duration to determine adequacy is supported by data on the time course of antidepressant effects. In Level 1 of STAR*D (treatment with citalopram), the average time to achieve remission was nearly 7 weeks, and 40% of eventual remitters required 8 or more weeks. Approximately, one-third of eventual responders attained this status after 6 weeks (Gaynes et al., 2008; Trivedi et al., 2006). In addressing the conventions for an adequate antidepressant pharmacological trial, Gaynes et al. (2008) recommended "at least 8 weeks with at least moderately vigorous dosing" (p. 61). In a large sample of patients receiving open treatment for 12 weeks with fluoxetine, Quitkin et al. (2003) concluded that "nonresponse to fluoxetine should not be declared until 8 weeks of treatment have elapsed (p. 734)." In a large European multisite study (Uher et al., 2011), latent class analysis based on individual trajectories of symptom severity differentiated patients with early (1–3 weeks) and delayed (4–6 weeks) onset of improvement during open 12-week trials of nortriptyline or escitalopram. Early and delayed improvement were equally common. Approximately half of final remitters had delayed onset of improvement, and their final status could not be predicted at early time points. Uher et al. (2011) concluded, "Six to eight weeks of treatment constitutes an adequate trial of an antidepressant (p. 1479)."

These prospective, open label studies recommended that a minimum of six-to-eight weeks elapse before abandoning a new pharmacological regimen in favor of alternative antidepressant treatment. In contrast, the ATHF, ATHF-SF and the ATR require only 4 weeks at sufficient dose to determine trial adequacy. This apparent discrepancy hinges on the distinction between recommendations for optimizing ongoing clinical practice as opposed to optimizing retrospective evaluation of trial adequacy. Ensuring a six-to-eight week trial duration before considering a change in treatment may maximize the number of patients who meaningfully benefit from treatment by reducing rates of premature termination. However, longer duration cutoffs also entail prolonging the treatment of those who do not benefit. For the purpose of retrospective evaluation of pharmacological trials, the key issue is where to set the duration cutoff so that it is both broadly applicable and informative about treatment resistance. The choice of the four-week cutoff has the advantage of recognizing that the total duration of exposure to a medication is often longer due to upward titration of dose at treatment outset. Thus, 4 weeks at adequate dose often translates to six or more weeks of treatment exposure. Most critically, however, there is ample evidence that early lack of symptomatic improvement with antidepressant medications has strong negative predictive value for final response and remission status (Athreya et al., 2021; de Vries et al., 2019; Leuchter et al., 2009; Nierenberg et al., 1995; Papakostas et al., 2006; Sackeim et al., 2006; Szegedi et al., 2003). For example, in a meta-analysis of 41 clinical trials involving more than 6000 patients, Szegedi et al. (2009) reported that, after two weeks of antidepressant medication treatment, lack of improvement (<20% reduction in symptom severity) had powerful negative predictive values (82–100% accurate) regarding final response and remission status. Nonetheless, this pattern is not consistently observed and other investigations report that 20–30% of patient without early improvement eventually remit with extended treatment (de Vries et al., 2019; Gorwood et al., 2013; Wagner et al., 2017).

There is no "correct" answer to this problem. Increasing the minimum duration from four to six or eight weeks would purify TRD samples by reducing the false positive rate but would also increase the false negative rate and reduce the incidence of TRD. Complicating this problem is the fact that terminating a treatment after 4 weeks at minimally adequate dose may have different implications for ascribing treatment-resistance when patients have shown no improvement or worsening as opposed to partial benefit. Nonetheless, the position taken on this issue has substantial public health consequences since health care reimbursement policies now often mandate the minimum duration of "failed" trials (Aetna, 2024; Cigna, 2023) and since it is also known that a large percentage of depressed patients discontinue newly started pharmacological antidepressant treatment within 30 days, often in the context of lack of benefit (Olfson et al., 2006).

While the workgroup remained divided in opinions on this issue, there was agreement to retain the four-week convention in the ATHF-SF2, and to revisit this question at the next major revision. This decision was based in part on the desire to maintain consistency with earlier versions of the instrument in the characterization of clinical research samples, as well as cognizance that a longer duration threshold will likely be reflected in public policies that limit treatment access. However, the workgroup recognized that the minimum duration of adequate pharmacological trials is the ATHF-SF2 convention most likely to be modified to address particular research needs. For example, increasing the duration cutoff could be of value in contexts in which identifying individuals with unequivocal TRD is paramount.

4. Changes introduced in the ATHF-SF2

A new class of pharmacological treatment was added, N-methyl-D-aspartate (NMDA) antagonist, reflecting the inclusion of racemic ketamine, esketamine, and combination dextromethorphan and bupropion as effective antidepressant interventions (Carter et al., 2020). This is the routine pharmacological classification for these medications (Moore et al., 2022; Ogden and Traynelis, 2011), although they also have complex neurochemical effects including modulation of other transmitter systems (Williams et al., 2018).

A total of 6 medications are newly treated as effective antidepressants, including the three NMDA antagonists, racemic ketamine, esketamine, and combination dextromethorphan and bupropion, and gepirone, a 5-HT1A agonist. Also newly included were an atypical antipsychotic, lumateperone, as monotherapy in bipolar depression, and the atypical antipsychotic, cariprazine, as an augmentation agent in MDD.

For some specific interventions, the ATHF-SF only documented that they were administered and did not evaluate adequacy, given insufficient information to support the efficacy of the intervention or to guide selection of dose and duration. For example, this grouping in the ATHF-SF included the pharmacological interventions, pramipexole and reboxetine, and the neuromodulation interventions, transcranial electrical stimulation (other than ECT), deep brain stimulation (DBS), and light therapy. In the ATHF-SF2, brexanolone and zuranolone have been added to this grouping. The rationale for the inclusion (or not) of each new interventions as effective antidepressants is provided below.

At the suggestion of European colleagues, two older tricyclic antidepressant medications were added to the TCA/tetracyclic classification, dosulepin and lofepramine.

In the ATHF-SF, carbamazepine and lamotrigine, were the two anticonvulsant medications that could constitute adequate trials in bipolar patients. This is unchanged in the ATHF-SF2. However, the ATHF-SF also tracked whether or not other anticonvulsants were administered in bipolar MDEs. These included clonazepam, gabapentin, and valproic acid. In the ATHF-SF2, clonazepam was removed from this list, but is considered for all patients in the benzodiazepine grouping. Tiagabine and oxcarbazepine have been added to the list of anticonvulsants whose use is documented in bipolar patients but are not considered potentially adequate interventions.

In the ATHF-SF five forms of evidence-based psychotherapy were considered potentially adequate treatments of MDE. In the ATHF-SF2,

Acceptance and Commitment Therapy (ACT) has been added to this grouping.

4.1. NMDA antagonists: esketamine, racemic ketamine, and combination dextromethorphan and bupropion

Esketamine was approved by the US FDA in 2019 for treatment-resistant depression (US Food and Drug Administration, 2020), and there is a substantial body of evidence indicating that racemic ketamine and esketamine have rapid and potent antidepressant effects (Carlson et al., 2013; Carter et al., 2020; Fava et al., 2018; Hasselmann, 2014; Ibrahim et al., 2012; McIntyre et al., 2021; Nugent et al., 2014; Papakostas et al., 2020; Sanacora et al., 2017; Zarate and Niciu, 2015), including rapid reduction in suicidality (Canuso et al., 2021; Wilkinson et al., 2018). Comparative studies suggest that intravenous racemic ketamine and intranasal esketamine are both effective in TRD (Bahji et al., 2022; Correia-Melo et al., 2020; McIntyre et al., 2021; Singh et al., 2023). Recent meta-analyses have supported the efficacy of both preparations, but have also indicated that racemic ketamine has more potent antidepressant effects than esketamine (Bahji et al., 2021; Nikolin et al., 2023).

To be considered adequate, esketamine should be administered at a schedule of at least 2 treatments per week over 4–6 weeks (i.e., 8 treatments in a 6-week period). Each esketamine treatment should involve administration as a dose of at least 56 mg. Higher, but not lower, doses are considered adequate. In the ATHF-SF2 Checklist, a non-adequate trial of esketamine would be documented as "Administered" on the line for esketamine if there is any reduction in the frequency or dosage of esketamine below the adequacy criteria. There has been less research using repeated dosing protocols of IV racemic ketamine administered over a period of several weeks. In a recent comparator trial of ketamine vs. ECT (Anand et al., 2023), IV racemic ketamine (0.5 mg/kg) was given twice per week for 3 weeks. This intervention was compared to ultrabrief right unilateral (RUL) ECT (3 times per week for 3 weeks, 9 treatments) and the antidepressant effects were indistinguishable (although the remission rates were low in both groups). Singh et al. (2016) reported a placebo-controlled RCT using 0.5 mg/kg racemic ketamine randomizing TRD patients to 2 or 3 times per week for 2 weeks; nonresponder could receive an additional 2 weeks of treatment. There was no difference in outcomes with 2 vs 3 times per week schedules, with both protocols markedly superior to placebo. Extending the trial to 4 weeks resulted in additional benefit in the two active groups. Thus, the ATHF-SF2 workgroup determined that for a racemic ketamine trial to be considered adequate, at minimum an IV dose of 0.5 mg/kg should be administered, with twice per week administration over 4–6 weeks (i.e., 8 treatments in a 6-week period). This mirrors the protocol for esketamine, only differing in route of administration and IV (0.5 mg/kg) vs nasal (86 mg) dosage.

Note that racemic ketamine is not approved by the FDA for the treatment of MDE, and there is little financial incentive for industry to seek such approval. FDA approval is not a requirement for ATHF-SF2 evaluation of treatment adequacy. Some medications are not considered as potentially effective antidepressants that have FDA approval (e.g., brexanolone, reboxetine), and the ATHF-SF2 considers some medications as potentially adequate that do not have FDA approval for the acute treatment of MDE (monotherapy with clozapine in UP or BP depression; lithium in BP depression).

The oral, fixed-dose combination of dextromethorphan hydrobromide (an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist) and the antidepressant bupropion hydrochloride (an aminoketone and CYP2D6 inhibitor) was approved by the FDA for treatment of MDD in August 2022 (Keam, 2022). While bupropion is itself an effective antidepressant, its CYP2D6 inhibition increases the bioavailability of dextromethorphan (Stahl, 2019).

The dextromethorphan-bupropion combination showed rapid onset of antidepressant effects, with separation from placebo at one week (Iosifescu et al., 2022) and separation from the active comparator, bupropion alone, at two weeks (Tabuteau et al., 2022), and progressive improvement over the first 4 weeks of administration. The large Phase 2 and Phase 3 trials administered the fixed-dosage combination of 45 mg dextromethorphan and 105 mg bupropion once per day for the first 3 days and then twice per day (at least 8 h apart) thereafter. Accordingly, the threshold for adequacy in the ATHF-SF2 requires treatment with the 45 mg dextromethorphan—105 mg bupropion tablet twice per day for at least 4 weeks. It should be noted that this dose of bupropion is lower than the minimum adequate dose when bupropion is used as a monotherapy (i.e., 300 mg/d).

4.2. GABA agonists: brexanolone and zuranolone

Brexanolone and zuranolone are neuroactive steroids and positive allosteric modulators of the $GABA_A$ receptor. In 2019, brexanolone was the first medication approved by the FDA specifically for post-partum depression (PPD). This medication is infused intravenously over a 60-h period in a supervised medical setting, in part because of sedation and syncope risks (Scarff, 2019). While placebo-controlled trials demonstrated that brexanolone produces a rapid and clinically meaningful antidepressant effect in PPD (Kanes et al., 2017; Meltzer-Brody et al., 2018), safety and efficacy in the broader population of patients with unipolar or bipolar MDE was not tested. In contrast, zuranolone is orally administered once per day, with a single, 14-day course the recommended treatment in PPD. This strategy received FDA approval for PPD in 2023 based on placebo-controlled trials with 30 mg/d or 50 mg/d of zuranolone (Deligiannidis et al., 2021, 2023). However, at the same time, the FDA rejected the application for approval of zuranolone for the treatment of MDD, based on insufficient evidence of effectiveness across three pivotal trials (Clayton et al., 2023a; Clayton et al., 2023b; Meshkat et al., 2023; ten Doesschate et al., 2022). The absence of studies that provided longer periods of exposure to zuranolone also may have contributed to the FDA's decision.

Neither brexanolone nor zuranolone are considered potentially adequate treatments of unipolar or bipolar MDE. While the evidence supports that they are effective in treatment of PPD, this indication is relatively narrow and may not generalize to MDE in general. In particular, there appears to be limited evidence that zuranolone is more effective than placebo with extended treatment. However, given the novelty of their pharmacological classification (i.e., GABA agonists), efficacy in PPD, and possible efficacy in MDE, treatment with brexanolone or zuranolone is documented in the ATHF-SF2 in the section on potential antidepressants that constitute trials that cannot (at this time) be considered "adequate".

4.3. 5-HT_{1A} agonist: gepirone

Gepirone hydrochloride (extended release, ER) was approved by the FDA for the treatment of MDD in September 2023 (US Food and Drug Administration, 2023). It is an azapirone and a pharmacologic analog of buspirone that selectively acts as a partial agonist on the pre- and post-synaptic $5HT_{1A}$ receptors (Kaur Gill et al., 2019; Kishi et al., 2014). Gepirone is more potent than buspirone for stimulation of 5-HT_{1A} receptors and has much lower affinity for D_2 receptors. However, like buspirone, gepirone is metabolized into 1-(2-pyrimidinyl)piperazine, an antagonist of the α_2-adrenergic receptor and gepirone also is an antagonist at the 5-HT_{2A} receptor (Chilmonczyk et al., 2002; Kaur Gill et al., 2019; Kishi et al., 2014; von Moltke et al., 1998).

Gepirone was first synthesized in 1986 and was only approved by the FDA for MDD in 2023 after rejections in 2002, 2004, and 2007 due to limited evidence of effectiveness. There was a negative vote by the FDA Psychopharmacologic Drugs Advisory Committee in 2015 when asked to reconsider these rejections. The regulatory dilemma was how to balance the fact that gepirone ER appeared to meet the minimum evidentiary standard of at least two successful, well controlled, randomized trials,

with the fact that previously there were multiple negative or failed trials with this agent (Alpert et al., 2004; Amsterdam et al., 2004; Bielski et al., 2008; Feiger et al., 2003; Robinson et al., 2003). The observations that gepirone ER did not appear to result in weight gain or sexual dysfunction may have been a consideration in the FDA's reversing the earlier disapprovals. Regardless, the approval of gepirone ER for the treatment of MDD was controversial and, while it is treated by the ATHF-SF2 as a potentially adequate antidepressant, this status will be reviewed at the next iteration of this instrument based on emerging evidence. As a 5-HT_{1A} partial agonist, gepirone is thought to have a novel mechanism relative to other antidepressants. However, in the ATHF-SF2, gepirone ER is not afforded its own pharmacological classification, but is listed with "Other Antidepressants" with diverse mechanisms. In part, this is due to the fact that gepirone also acts at the 5-HT_{2A} and α_2-adrenergic receptor, and because other medications with complex effects on serotonergic transmission, like vilazodone and vortioxetine, are included in this grouping.

4.4. Atypical antipsychotics in bipolar depression: lumateperone

In recent years, a variety of atypical antipsychotic medications have demonstrated efficacy in the treatment of bipolar MDE (Kadakia et al., 2021; Nierenberg et al., 2023; Yildiz et al., 2023), while members of this class have only shown efficacy in unipolar MDE when used as augmentation agents (Kishimoto et al., 2023; Nunez et al., 2022; Yan et al., 2022). The ATHF-SF identified asenapine, cariprazine, clozapine, lurasidone, olanzapine, and quetiapine as effective monotherapies in bipolar depression. Lumateperone is an atypical antipsychotic medication of the butyrophenone class that impacts on dopaminergic, serotonergic, and glutamatergic pathways (Munayco Maldonado and Schwartz, 2024). Based on RCT findings in mixed state and non-mixed state bipolar depression (Calabrese et al., 2021; McIntyre et al., 2023b), it was approved by the FDA in December 2021 for the treatment of bipolar I or bipolar II MDE as a monotherapy or as an adjunct to lithium or valproate (US Food and Drug Administration, 2021). Efficacy was demonstrated with a single daily dose of 42 mg. Lumateperone was associated with minimal emergent extrapyramidal symptoms or weight change (Abuelazm et al., 2023).

4.5. Atypical antipsychotic augmentation in unipolar depression: cariprazine

There is substantial evidence in unipolar MDE that adding an atypical antipsychotic medication can improve clinical outcomes when monotherapy with an antidepressant medication is ineffective (Kishimoto et al., 2023; Yan et al., 2022). In unipolar MDE, the ATHF-SF had identified five atypical antipsychotic medications as effective augmentation agents (aripiprazole, brexpiprazole, olanzapine, quetiapine, and risperidone), with clozapine as the only effective antipsychotic monotherapy. On the basis of two positive RCTs (Riesenberg et al., 2023; Tarzian et al., 2023), cariprazine was approved by the FDA in 2022 as an adjunctive treatment to antidepressants in adults with MDD. The findings suggested that the starting dose 1.5 mg/day was as effective as higher doses. There is no evidence to support the use of doses higher than 3.0 mg/day for adjunctive therapy of MDD.

4.6. Anticonvulsants in bipolar depression

It is well established that some anticonvulsants are effective in the treatment of MDEs in bipolar disorder, while others are not (Goodwin and Jamison, 2007; Reinares et al., 2012). Unchanged from the ATHF-SF2, carbamazepine and lamotrigine are the anticonvulsants considered potentially adequate treatments for bipolar depression. However, other anticonvulsants are widely used in this condition with variable degrees of evidence (Baldessarini et al., 2020; Bowden, 2009). In the ATHF-SF, clonazepam, gabapentin, and valproic acid were listed as anticonvulsants whose administration was documented for patients with bipolar depression but were not considered as potentially adequate. In the ATHF-SF2, clonazepam was removed from this list. First, while clonazepam is useful in the treatment of acute mania, there is little evidence that it is effective in bipolar depression (Bobo et al., 2014; Lappas et al., 2023; Sachs, 1990; Winkler et al., 2003). Second, clonazepam is a benzodiazepine, and the administration of any benzodiazepine is separately documented for both unipolar and bipolar patients.

The ATHF-SF2 added oxcarbazepine and tiagabine as anticonvulsants whose administration is documented for bipolar patients (but not considered adequate), given suggestive evidence of efficacy in bipolar depression (Popova et al., 2007; Schaffer et al., 2002; Vasudev et al., 2011, 2012). Other anticonvulsants are not documented due to an absence of or negative evidence regarding efficacy in bipolar depression (Pigott et al., 2016).

4.7. Transcranial magnetic stimulation protocols: intermittent Theta Burst Stimulation (iTBS) and Stanford Neuromodulation Therapy (SNT)

TMS obtained regulatory clearance from the US FDA in 2008 for treatment-resistant MDD based on the findings of multisite, randomized, sham-controlled tria ls (George et al., 2010; O'Reardon et al., 2007). Subsequently, the effectiveness of TMS has been supported by large observational studies of real-world outcomes (Carpenter et al., 2012; Hutton et al., 2023; Sackeim et al., 2020), and use of this intervention in MDE has rapidly grown. In providing criteria for the adequacy of TMS trials, the ATHF-SF recognized two distinct protocols as effective interventions: $\geq$20 sessions in a 6-week period of either fast ($\geq$5 Hz) left frontal or slow ($\leq$1 Hz) right frontal TMS. Implicit in these criteria was the assumption that daily TMS sessions were scheduled at a rate of 4–5 sessions per week. The minimum threshold of 20 sessions in a 6-week period for establishing trial adequacy is supported by research on the time course of clinical improvement with TMS (Hutton et al., 2023; Sackeim et al., 2024), and the efficacy of both fast left frontal ($\geq$5 Hz) and slow ($\leq$1 Hz) right frontal TMS in MDE continues to be supported by meta-analyses (Chen et al., 2013; Mutz et al., 2019; Somani and Kar, 2019).

Since the publication of the ATHF-SF, two additional TMS protocols have been cleared by the FDA for treatment of MDE. In 2018, the FDA cleared the use of intermittent Theta Burst Stimulation (iTBS) for treatment-resistant MDD. TBS uses a pulse pattern that is thought to mimic hippocampal theta patterns and to have greater impact on neuroplastic processes than traditional slow or fast frequency stimulation in which pulse frequency is invariant throughout the treatment (Di Lazzaro et al., 2005; Huang et al., 2005). TBS consists of pulse triplets delivered at 50 Hz and repeated every 200 ms (5 Hz). TBS can be delivered continuously (cTBS), such that 600 pulses are administered over a 40 s period. This protocol is thought to be inhibitory and has been shown to result in a short-term reduction in motor evoked potential (MEP) amplitude following cTBS to the motor cortex. TBS can also be delivered intermittently (iTBS), administering the 600 pulses with a duty cycle of 2-s on and 8-s off for 190 s (or a treatment period of 3.17 min). This protocol results in a short-term (about 1 h) increase in MEP amplitude (Wischnewski and Schutter, 2015).

The approval of iTBS for treatment-resistant MDD was based on the findings of the Three-D study, a randomized noninferiority trial that compared traditional 10 Hz (fast frequency) TMS and iTBS, with both delivered to a left dorsolateral prefrontal cortex (DLPFC) target at 5 sessions/wk for 4–6 weeks (Blumberger et al., 2018). The 10 Hz TMS group received 3000 pulses per session delivered over 37.5 min, while the iTBS group received 600 pulses over slightly more than 3 min. Despite the marked differences in number of pulses and administration time, at the primary endpoint after 20 sessions iTBS was noninferior to 10 Hz TMS in all outcome measures with both groups manifesting strong antidepressant effects. Subsequent studies have shown that iTBS to the left DLPFC is more effective than sham, while generally not differing in

efficacy from fast frequency TMS (Blumberger et al., 2022; Bulteau et al., 2022; Chen et al., 2021; Chu et al., 2021; Ekman et al., 2023; Voigt et al., 2021). Accordingly, the ATHF-SF2 includes iTBS as an effective TMS protocol, requiring a minimum of 20 sessions of left frontal iTBS during a 6-week period.

In 2022 the FDA cleared the Stanford Neuromodulation Therapy (SNT) protocol, an accelerated form of TMS, for treatment-resistant MDD. SNT differs from traditional TMS in multiple dimensions. With SNT, the stimulation target within the left DLPFC is determined for each individual on the basis of structural and functional imaging that identifies the DLPFC site with maximal anticorrelation with the subgenual anterior cingulate cortex (Fox et al., 2012). SNT uses iTBS, with each iTBS session triple the duration of that used in daily treatment in the Three-D study (SNT: 50 Hz pulse triplets at 5 Hz frequency, 2-s on and 8-s off for 570 s; 1800 pulses per session). The SNT protocol involves 10 sessions per day, each separated by about 50 min, and repeated for 5 consecutive days (50 sessions and 90,000 pulses in total). SNT has been tested in a relatively small open-label trial (Cole et al., 2020) and a small sham-controlled RCT (Cole et al., 2022) with strikingly positive short-term results. In samples with high degrees of treatment resistance and symptom severity, SNT was markedly superior to sham and produced rapid clinical improvement in the majority of patients. Recently, rapid and marked antidepressant effects were also observed in a small trial of SNT in bipolar MDE (Raj et al., 2024).

Determining what constitutes a minimally adequate SNT trial is problematic. SNT has yet to be "unpacked" into necessary and/or sufficient components, and it is unclear whether using functional imagining to individualize targeting, tripling the duration of the iTBS session, providing 10 sessions per day for 5 consecutive days are each alone or together required to achieve the accelerated effect. Other attempts to accelerate TMS by providing only two sessions per day or by administering sequentially fast frequency stimulation to the left DLPFC and slow frequency stimulation to the right DLPFC (bilateral TMS) have not proven more effective or more rapid in antidepressant action than single daily sessions (Aaronson et al., 2022; Caulfield et al., 2022; Fitzgerald et al., 2018; van Rooij et al., 2024). Given the uncertainty about the critical components of the SNT protocol, the ATHF-SF2 adopted arbitrary thresholds, requiring at least 40 iTBS sessions within 7 days (each iTBS 1800 pulses with individualized, imaging-based DLPFC targeting) to consider the SNT trial adequate. As the field of accelerated TMS evolves it is likely that other protocols will be found safe and efficacious leading to revision of these criteria.

4.8. Psychotherapy protocols: Acceptance and Commitment Therapy (ACT)

The ATHF-SF identified 5 evidence-based psychotherapies as potentially adequate treatments for MDEs (Behavior Therapy, Cognitive-Behavior Therapy, Interpersonal therapy, Problem-Solving Therapy, and Short-term Psychodynamic Therapy). The ATHF-SF2 adds Acceptance and Commitment Therapy (ACT) (Hayes et al., 2011), an intervention that combines mindfulness and acceptance strategies. ACT has been examined in multiple RCTs across a variety of conditions, with positive evidence of effectiveness in MDE (Bai et al., 2020; Gloster et al., 2020; Zettle, 2015).

5. Conclusions

All definitions of TRD require that patients have insufficient benefit from one or more adequate antidepressant trials. Thus, identifying "failed-adequate trials" is key to the assessment of TRD. The ATHF-SF2 provides an update to the original ATHF (Sackeim, 2001) and the subsequent ATHF-SF (Sackeim et al., 2019), drafted in 2018. In producing this update, the ATHF-SF2 workgroup reached consensus on the novel interventions that have emerged since the last revision and that should or should not be considered effective treatments for MDE. The rationale for these choices were described, as well as, for each intervention, the minimal criteria for determining the adequacy of treatment administration. The documents available in the Supplementary Material provide the Scoring Checklist, Data Collection Forms (current episode and composite of previous episodes), and Instruction Manual for the ATHF-SF2.

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CRediT authorship contribution statement

Harold A. Sackeim: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Scott T. Aaronson:** Writing – review & editing, Validation, Investigation, Conceptualization. **Mark T. Bunker:** Writing – review & editing, Validation, Resources, Funding acquisition, Data curation, Conceptualization. **Charles R. Conway:** Writing – review & editing, Investigation, Funding acquisition, Data curation, Conceptualization. **Mark S. George:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **R. Hamish McAlister-Williams:** Writing – review & editing, Validation, Investigation, Formal analysis, Conceptualization. **Joan Prudic:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Michael E. Thase:** Writing – review & editing, Validation, Formal analysis, Data curation, Conceptualization. **Allan H. Young:** Writing – review & editing, Validation, Formal analysis, Conceptualization. **A. John Rush:** Writing – review & editing, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Dr Harold A. Sackeim serves as a scientific adviser and receives consulting fees from Cerebral Therapeutics Inc., Holmusk Technologies Inc, LivaNova PLC, MECTA Corporation, Neurolief Ltd, Neuronetics Inc, Parow Entheobiosciences LLC, and SigmaStim LLC. He receives honoraria and royalties from Elsevier Inc and Oxford University Press. He is the inventor on non-remunerative US patents for Focal Electrically-Administered Seizure Therapy (FEAST), titration in the current domain in ECT, and the adjustment of current in ECT devices, each held by Balance Point LLC. He is also the originator of magnetic seizure therapy (MST). His effort in chairing this revision of the ATHF and drafting the ATHF-SF2 documents was partially supported by LivaNova PLC.

Dr. Scott T. Aaronson reports no conflicts of interest directly relating to this work. He does report a number of other relationships with commercial entities. He serves as a consultant to Compass Pathways, Genomind, LivaNova PLC, Neuronetics Inc., and Sage Therapeutics. He has received research support from Compass Pathways.

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currently serves as a paid consultant to LivaNova PLC in designing studies involving vagus nerve stimulation.

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Appendix A. Supplementary data

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