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The VA augmentation and switching treatments for improving depression outcomes (VAST-D) study: Rationale and design considerations

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ABSTRACT

Because two-thirds of patients with Major Depressive Disorder do not achieve remission with their first antidepressant, we designed a trial of three "next-step" strategies: switching to another antidepressant (bupropion-SR) or augmenting the current antidepressant with either another antidepressant (bupropion-SR) or with an atypical antipsychotic (aripiprazole). The study will compare 12-week remission rates and, among those who have at least a partial response, relapse rates for up to 6 months of additional treatment. We review seven key efficacy/effectiveness design decisions in this mixed "efficacy-effectiveness" trial.

1. . Introduction

Major Depressive Disorder (MDD) is a painful, chronic, highly debilitating and sometimes fatal disorder that accounts for 4.4% of the entire global burden of disease and over half of all disability attributable to mental illness (Horton, 2012). Although many effective treatments are available, less than one-third of patients with MDD achieve remission in the first trial of antidepressant therapy (Trivedi et al., 2006b). Thus, the identification of the most effective and safe "next-step" strategy for the remaining two-thirds is a public health priority of global importance.

The current "best practice" of pharmacotherapy when the initial antidepressant medication fails is either to switch to another antidepressant or to augment with a second treatment. Because

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there are no studies to inform prescribers whether, or under what circumstances, to switch or augment, or which agent is most effective and safe for either purpose, decisions are at present based on trial and error efforts that can involve months of delay of significant relief from disabling and potentially life threatening depressive symptoms (Rush et al., 2003). Although treatment guidelines may help, most of these guidelines rely on expert opinion rather than empirically based research (American Psychiatric Association, 2006; Yager et al., 2014).

Considerable emphasis has been placed, in recent years, on comparative effectiveness trials or pragmatic trials that compare FDA approved treatments against each other – treatments whose superiority to placebo has already been established (Rush, 2007; Lieberman et al., 2005; Wang et al., 2009). The largest and most comprehensive study of this type that evaluated treatments for MDD, thus far, was the National Institute on Mental Health-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D), which was itself designed to determine best "next-step" treatments for depressed patients who did not respond satisfactorily to their initial treatment. STAR*D confirmed the need for "next-step" treatments for the majority of patients and provided many useful guidelines for clinical care (Rush, 2007). However, the study did not meet its overriding objective of identifying optimally effective "next-step" treatments (Rush et al., 2009). In addition, atypical antipsychotics were first approved by the FDA for augmentation of depression treatments in 2007, after STAR*D was complete, and have been frequently used for this purpose even prior to FDA approval (Leslie et al., 2009; Mohamed et al., 2009). Thus two of the important questions that were left unanswered are: (1) for which patients, under what circumstances, is switching to vs. augmenting with other antidepressants the most effective "next-step" strategy? and (2) how does augmentation with atypical antipsychotics compare to either switching or augmenting with antidepressants?

The VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) study, a Veterans Affairs (VA) Cooperative Study (VA CSP#576) is the first to systematically compare benefits and risks of three commonly used switch and augmentation strategies for patients with MDD who have not remitted after an initial adequate antidepressant trial. A planning committee of experts in the fields of depression and psychiatry research and methodology (Appendix B) was assembled in order to address the various decisions/issues involved in designing a study of this magnitude. This paper describes a series of study design decisions made in attempting to answer the two primary study questions: (1) is switching or augmenting more effective "next-step" strategy in real-world practice?; and (2) does augmentation with atypical antipsychotics improve outcomes compared to augmenting with another antidepressant? First we present the final study design and then review key considerations that led to it, articulating methodological design principles that guided critical decisions and solutions.

2. Summary of study design

VAST-D is a multi-site, prospective, randomized, "next-step" clinical trial of outpatients with nonpsychotic MDD. VAST-D's planned enrollment is 1518 total Veterans (approximately 50 participants at each of 30–35 participating VA Medical Centers) including both genders and all ethnic/racial and socioeconomic backgrounds. All participants were intended to meet DSM-IV-TR criteria for nonpsychotic MDD. The diagnostic criteria for eligibility are established by clinical interview by qualified site investigators supplemented with the 9-item Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001). Only participants with a suboptimal outcome to a well-documented, adequately delivered (as determined by past dose and duration) trial with an antidepressant (SSRI, SNRI, or mirtazapine) are eligible for the study. Failure of treatment to result in an adequate outcome is ascertained by a QIDS-$C_{16} \geq 16$ (Rush et al., 2003) (considered severe depression) after at least 6 weeks of treatment or QIDS-$C_{16} \geq 11$ (considered moderately severe depression) after at least 8 weeks of treatment. Otherwise, the inclusion criteria are broad and the exclusion criteria are few; generally, participants with most comorbid general medical or psychiatric disorders are included to provide a broadly representative sample (Fig. 1).

Participants are randomized to switching or augmenting arms of the study. Treatment arms include randomization (1:1:1 ratio): to (1) switch to bupropion sustained release (bupropion-SR) alone ($n=506$), (2) augment antidepressant therapy with bupropion-SR ($n=506$), or augment antidepressant with aripiprazole ($n=506$). Using strategies of "measurement-based care" (Trivedi, 2009), treatment is guided by patient-rated symptom measures (using the PHQ-9) and global side effects measures (the Frequency, Intensity, and Burden of Side Effects Rating or FIBSER) obtained at each treatment visit. Medication dosing recommendations are provided to study physicians based on VA/Department of Defense (DoD), Texas Medication Algorithm Project (TMAP), STAR*D and American Psychiatric Association (APA) approved guidelines for standard practice (Crismon et al., 1999; American Psychiatric Association, 2006; Trivedi et al., 2006a; The Management of MDD Working Group, 2009) and are designed to ensure adequate delivery of medications while maximizing safety and tolerability. Study medications are actively titrated up from 150 to 400 mg daily (divided dose) for bupropion-SR or from 2 to 15 mg once daily for aripiprazole as long as depressive symptoms have not yet remitted and side effects are tolerable.

Acute treatment phase visits are frequent, occurring at baseline and at weeks 1, 2, 4, 6, 8, 10, and 12 to ensure delivery of appropriate and tolerable pharmacotherapy. Participants who tolerate the acute treatment and achieve at least partial response as measured by the QIDS-C_{16} (≤ 10) at 12 weeks are eligible to enter the 6-month phase 2 continuation treatment, during which relapse is the central outcome, the assigned treatment is continued, and visits are reduced to monthly intervals. Throughout both phases of the study, neither the participant nor the treating clinician is blinded to treatment; however, an independent evaluator, who is blinded to treatment assignment, administers the primary outcome measure, the QIDS-C_{16}. Fig. 1 illustrates the flow of participants from screening through the end of continuation treatment.

The primary outcome for the VAST-D study is *remission* of depressive symptoms, defined by a QIDS-C_{16} score of ≤ 5, for 2 consecutive visits during the 12 weeks of the acute treatment phase. Key secondary outcomes are (a) response at the end of acute and continuation treatment (defined as $\geq$50% improvement from baseline on the QIDS-C_{16}, and, as a separate response measure, a score of 1 or 2 (much improved or very much improved) on the Clinical Global Impressions (CGI) Improvement Scale), (b) percent change on the QIDS-C_{16} from baseline to end of acute and continuation treatment, and (c) relapse (defined as having a QIDS-$C_{16} \geq 11$ after remission or during the continuation treatment). At each visit, the primary outcome variable (QIDS-C_{16}) is assessed along with global depression ratings, side effect ratings and adherence measures. The PHQ-9 is administered at each visit to help guide dosing (Table 1).

Additional comprehensive health assessments are administered at baseline, at the end of the acute treatment phase (week 12), midway through continuation (week 24), and at study completion (week 36 or at study exit). These additional assessments include measures of depression associated systems (anxiety and

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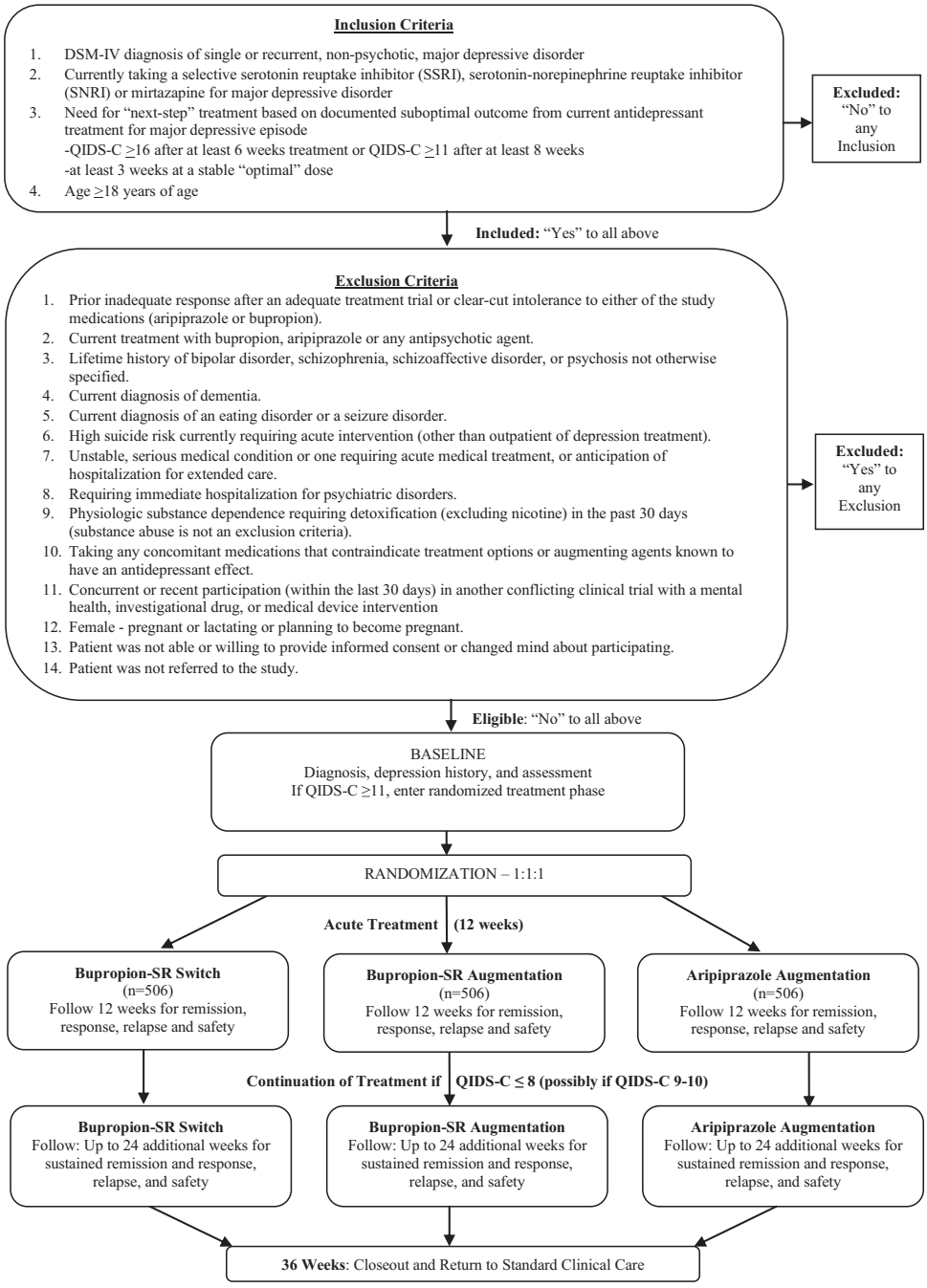

Fig. 1. Schematic of VAST-D study design.

suicidal ideation), safety, and quality of life. Information on participants' health care utilization and costs are obtained from administrative data sources and patient self-report throughout the trial.

The assumptions for the power analyses were based on data from published large-scale antidepressant trials, primarily STAR*D for effects of bupropion (Rush et al., 2006a; Trivedi et al., 2006a), and randomized controlled trials of aripiprazole used to augment antidepressants in the treatment of refractory depression, including the pivotal trials that were submitted to the FDA for approval of this indication (Berman et al., 2007; Marcus et al., 2008). The study was designed to have 90% power to detect a 10% difference in remission (35% versus 25% remission, odds ratio = 1.62) in the 12-week acute treatment phase between one of two augmentation treatments and switching to bupropion-SR monotherapy in the acute treatment phase, and 84% power for the second augmentation comparison, testing the two co-primary hypotheses of augmentation vs. switching at the 0.05 and 0.025 level, respectively, using the Hochberg method for multiple comparisons (Hochberg, 1988). For the secondary hypothesis comparing the two augmentation strategies, there will be 80% power to detect a 9 percent increase in remission from 30% to 39% (odds ratio = 1.49), and 50% power to detect a smaller difference of 6.5% (32.5% vs. 39%; odds ratio = 1.33). With these estimates, assumptions, and adjusting for a possible 15% withdrawal rate, we determined a sample size of 1518 patients (506 per treatment group).

3. Design considerations

Randomized clinical trials have been described along a

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Table 1
Study measures.

Domain	Measure	Method	Baseline	Treatment visits†	Outcome visits††
Characteristics	Demographics	C	x		
	Cumulative illness rating scale (CIRS) (Linn et al., 1968; Miller et al., 1992)	C	x		
	Mini international neuropsychiatric interview (MINI) (Sheehan et al., 1998)	C	x		
	Adverse childhood experiences (ACE) (Bernstein et al., 2003)	SR	x		
	Grief screen	SR	x		
Depressive symptoms	Quick inventory of depressive symptomatology-clinician-report (QIDS-C_{16}) (Rush et al., 2003)	IE	x	x	x
	Clinical global impression-severity (CGI-S) and improvement (CGI-I) (Guy, 1976)	IE	x	x	x
	Patient health questionnaire (PHQ-9) (Kroenke et al., 2001)	SR	x	x	x
Associated symptoms	Beck anxiety inventory (BAI) (Beck et al., 1988)	SR	x		x
	Columbia suicide severity rating scale (CSSRS) (Posner et al., 2007)	C	x	*	x
	Mania/hypomania symptom questionnaire	SR	x		x
	Positive health questionnaire	SR	x		x
	PTSD checklist (PCL-5) (Weathers et al., 2013)	SR	x		x
Side effects/safety	Vital signs (BP, P, weight, waist circumference)	C	x	x	x
	Side effect checklist	C	x	x	x
	Frequency, intensity, and burden of side effects rating (FIBSER) (Wisniewski et al., 2006)	SR	x	x	x
	Serious adverse event/adverse event form	C	*	*	*
	Chemistry panel	C	x		x
	Barnes Akathisia Scale (BAS) (Barnes, 1989)	SR	x		x
	Arizona sexual experience scale (ASES) (McGahuey and Gelenberg, 1997)	SR	x		x
Quality of Life	Quality of life enjoyment and satisfaction questionnaire (Q-LES-Q) (Endicott et al., 1993)	SR	x		x
	Euro QoL health questionnaire (EQ-5D) (Sapin et al., 2004)	SR	x		x
	Work and social adjustment scale (WSAS) (Mundt et al., 2002)	SR	x		x
	The work productivity and activity impairment scale (WPAI) (Reilly et al., 1993)	SR	x		x
Health related costs	Income and employment	C/SR	x		x
	Use of VA resources	MR	*	*	*
	Use of non-VA resources	C/SR/MR	*	*	*
Medications	Study medication tracking form	C	x	x	x
	Adherence questionnaire	C	x	x	x
	Concomitant medications	C	x	x	x

C=clinical assessment, IE=independent evaluation (blinded to treatment assignment), SR=self-report, MR=medical records, x=assessment completed at each visit, *=completed as needed, †=treatment visits are scheduled at weeks 1, 2, 4, 6, 8, 10 and 12 in the acute phase, and at weeks 16, 20, 24, 28, 32 and 36 in the continuation phase, ††=outcomes are assessed at weeks 12 and 36 or at study exit; longer battery of assessments are scheduled at week 12, 24 and 36 or at study exit.

continuum from effectiveness to efficacy studies, recognizing that aspects of both are usually present in what have been called "hybrid trials" (Bauer et al., 2001). The goal of a pure efficacy trial is to determine what treatment works best under ideal "laboratory" circumstances, maximizing internal validity by controlling all extrinsic factors that can contribute variability to treatment effects. Essential features of the efficacy study are the high degree to which participant selection is narrowed and subjects are homogeneous, conducting interventions by highly trained clinicians following formalized protocols, masking of clinicians and participants from the treatment assignment, using methods such as measurement-based treatment to assure optimal dosing, and focusing on symptoms as the primary outcome. The advantage of studies that adhere to these efficacy features is that they are conducted under highly controlled conditions to precisely answer the question of whether a medication works better than placebo or another medication. The disadvantage of the efficacy approach is that results may not be generalizable to the heterogeneity of patients and treatment environments encountered in real-world clinical care (Depp and Lebowitz, 2007). In contrast, the goal of an effectiveness trial is to maximize external validity by addressing practical questions about the risks, benefits, and costs of an intervention as they would occur in routine clinical practice (Tunis et al., 2003). The selection of participants is broad with few exclusions, a wide array of outcomes is utilized, interventions are delivered in actual practice settings in a less controlled fashion, dosing is flexible and patients and clinicians may not be masked to treatment (although assessment biases are still minimized). In this way, generalizability of study results is maximized.

We describe the methodology used in this study as that of a "mixed efficacy-effectiveness" study, which includes selected components of both efficacy and effectiveness designs. On the one hand, key elements of efficacy trials including random assignment to treatment conditions; use of one objective inclusion criterion (among others) and a series of objective outcome measures; measurement-based treatment; masked raters for the primary outcome; and independence of outcome assessment from treatment delivery. On the other hand, the study also includes key elements of effectiveness trials such as: broad inclusion criteria with few exclusions other than a minimal symptom cutoff; a mixture of evidence-based treatment guidelines with clinical judgment guiding dosing and duration decisions; comparison of treatments with equal likelihood of being effective and safe; no placebo or untreated wait list groups; treatment provided in real-world functioning clinics by practicing clinicians; evaluation of cost effectiveness and other outcomes in addition to disease symptoms; provider/patients not blinded to treatment assignment; and relatively long-term follow-up.

In designing a mixed efficacy-effectiveness study complex enough to compare two different treatment strategies (augmentation vs. switching) involving three treatment groups in both short- and long-term contexts, seven critical decision points were encountered that can be viewed as central to the design of any "next-step" intervention and to balancing efficacy and effectiveness elements of study design. Most of these design decisions are in the service of maximizing the probability that findings will be applicable to typical patients with nonpsychotic major depression and readily transportable to both primary care and specialty psychiatric clinics and patients. The seven critical decision points central to the design of VAST-D, or any other "next-step"

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intervention, seek to balance efficacy and effectiveness elements of study design.

3.1. Is another multi-site "next-step" study justifiable?

STAR*D, the previous major study of pharmacotherapies for MDD, was itself an ambitious multi-million dollar clinical trial, which aimed to determine the most effective and well-tolerated "next steps" for patients with MDD who did not achieve remission to initial treatment with an SSRI. Arguably, its most suggestive finding was that combining the initial SSRI with bupropion-SR was more effective than augmenting with buspirone on some, but not all, measures and was better tolerated (Trivedi et al., 2006a; Bech et al., 2012). An additional important finding was that switching to bupropion-SR, sertraline or venlafaxine revealed no single superior alternative (Rush et al., 2006b).

Conclusive guidance for "next-step" treatment, however, did not emerge from STAR*D (Rush et al., 2007). Because its unique methodology allowed participants to opt out of certain randomizations, too few participants agreed to enter the randomization that included both switching and augmenting medication options. Furthermore, participants who accepted only switch strategies differed from those who accepted only augmentation strategies (Rush et al., 2006a). Thus, STAR*D had inadequate power to provide comparative information on the effectiveness, safety or costs of the basic choice of switching vs. augmenting with antidepressants.

In addition, STAR*D could not evaluate what is now one of the most widely used "next-step" strategies, augmenting with atypical antipsychotics, because when STAR*D was designed, atypical antipsychotics had not yet received FDA approval for use in MDD. In 2007, aripiprazole became the first atypical antipsychotic approved by the FDA for adjunctive treatment with an antidepressant for treatment of resistant MDD. By the time planning began for VAST-D in 2009, several studies had demonstrated the short-term efficacy of several atypical antipsychotics as compared to placebo in augmenting antidepressant therapy in the treatment of refractory MDD (Cabana et al., 2002; Clayton et al., 2004). At present, the FDA has approved three medications in this class for that purpose. Two of these medications, aripiprazole and quetiapine, have become among the most prescribed agents for patients with MDD nationally, including in the Veterans Health Administration (DeBattista and Hawkins, 2009; Mohamed et al., 2009). However, data on the long-term effectiveness, safety and total health care costs of this treatment for patients with major depressive disorder are sparse.

Thus, the need for a rigorous comparison of the benefits, risks and costs of switching vs. augmentation with antidepressants and of augmentation with an atypical antipsychotic offered a compelling and practical target for a major study. VAST-D is meant to provide that comparison.

3.2. Which specific strategies and agents need rigorous investigation?

The VAST-D planning committee (see Appendix B) determined that the most important agents to study should be those that were already widely used but had not yet been compared for their relative effectiveness or safety in a systematic way. Thus, we decided that studying the relative benefits and liabilities of switching to a frequently used antidepressant vs. augmenting with the same antidepressant and comparing augmenting with that antidepressant to augmenting with an atypical antipsychotic would be most useful. But the question remained of which antidepressant and which antipsychotic agent should be studied?

In considering this question, we initially faced the choice of randomizing participants to overall strategies (switch or augment), while letting physicians freely prescribe any agent of their choice, or specifying agents and doses as part of distinct randomization arms. Ultimately, we selected a more standardized approach that included randomization to specific switching or augmenting agents, a choice that tilts towards the efficacy end of the spectrum.

Bupropion-SR was chosen as the switching option because of its widespread use and demonstrated effectiveness (Trivedi et al., 2006a). It is effective for a broad spectrum of patients with MDD, including those with atypical, melancholic and anxious features (Thase et al., 2005; Papakostas et al., 2008), has low side effect burden, and has relatively low drug costs. Of special importance, bupropion-SR also has well-demonstrated efficacy and tolerability as an augmenting agent (Zisook et al., 2006). Evidence from STAR*D suggested that, as a switching agent, bupropion-SR was at least as effective as other commonly used SS/NRIs and, as an augmenting agent, is possibly more effective than other commonly used augmenting agents (Zisook et al., 2006). Finally, using bupropion-SR as both the switching agent and as one of the augmentation agents allows direct comparison of the effectiveness of switching and augmenting with the same agent in a secondary analysis.

Aripiprazole was selected as the atypical antipsychotic for this study because it was the first FDA-approved augmenting atypical antipsychotic for treatment of MDD, is now one of the most frequently used antidepressant augmentation agents, and has great potential for further expanding its use for patients with depression. Additionally, aripiprazole has a potentially favorable long-term side effect profile relative to other medications in its class (Potkin et al., 2003; Swainston Harrison and Perry, 2004) because it has a lower risk of metabolic side effects – at least during short-term treatment – than other antipsychotics (Newcomer, 2005). However, aripiprazole does have some other particularly troublesome adverse effects, such as akathisia (Marcus et al., 2008). The costs of aripiprazole are also considerably higher, at present, than antidepressants. Given the increasing use of aripiprazole and other second generation antipsychotics as augmenting agents for treatment of depression (Leslie et al., 2009; Mohamed et al., 2009) and the paucity of data on its long-term benefits and risks in patients with MDD, VAST-D was designed to provide both acute and continuation phase treatment data on the effectiveness, tolerability and safety of this specific and frequently prescribed medication for treatment resistant MDD. In addition, VAST-D will determine whether the incremental cost-effectiveness ratio of aripiprazole will be superior to that of other treatment strategies.

3.3. What target population merits the most attention?

The target population for the study was chosen to maximize generalizability to the broadest range of patients who are demonstrably in need of "next-step" treatments. To that end, it was critical to operationally define an adequate treatment trial in the current depression episode as a central criterion for entry into this "next-step" trial. This was paramount to ensuring that participants were not merely inadequately treated during their "first-step" treatment, e.g. due to insufficient dose or duration. Participants who would respond if simply provided more time on their first treatment or who simply had not received an adequate dose of their initial medication needed to be excluded.

At the same time, we did not want participants to linger in failed treatment any longer than necessary. The depression research literature provides some guidelines on the dose and duration of treatment that constitutes an adequate trial. Leaning on these guidelines, we decided to operationally require either: (a) comprehensive documentation that patients remain severely

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depressed with a score on the QIDS-$C_{16} \geq 16$ (Rush et al., 2003), despite at least 6-weeks of treatment including at least 3 weeks at a moderate to high dose (Crismon et al., 1999; American Psychiatric Association, 2006) of an approved effective antidepressant (SSRI, SNRI or mirtazapine); or (b) a moderate depression score on the QIDS-$C_{16} \geq 11$ after at least 8 weeks of treatment including at least the 3 most recent weeks on a stable "optimal" dose (i.e. the highest tolerated dose per APA guidelines or clinical judgment).

The rationale for requiring a QIDS-$C_{16} \geq 11$ after 8 weeks is that clinical consensus suggests that the vast majority of individuals who are going to remit or respond by the end of the "first-step" treatment phase, would be expected to be considerably less severely symptomatic by that time. If an individual was still moderately depressed after having had his/her dose maximized for 3 or more weeks, treatment guidelines suggest it would be time to try a different approach (Crismon et al., 1999; American Psychiatric Association, 2006; Trivedi et al., 2006a; Kennedy et al., 2009; The Management of MDD Working Group, 2009).

The rationale for including participants with more severe depressions (QIDS-$C_{16} > 16$) earlier (after only 6 weeks) is that most patients who are that depressed after 6 weeks of treatment at optimal doses could not be ethically expected to wait 2 more weeks before modifying the treatment approach. Indeed, the 2009 VA/DoD Management of Major Depressive Disorder Clinical Practice Guideline recommends taking action after 6 weeks if a patient has not achieved $>25\%$ symptomatic improvement, citing evidence that such patients are not likely to improve if left on their current treatment (Quitkin et al., 1996). Rather than expose these patients to undue pain, suffering, and risk of suicide, and/or lose them to possibly inadequate treatment, we decided to allow them to enroll in the study after 6 weeks.

We considered enrolling participants with milder MDD and lower QIDS-C_{16} scores to maximize generalizability as they, too, may require "next-step" treatments, but from the efficacy side, we were concerned that it would become difficult to demonstrate differential treatment effects if baseline depression scores were allowed to range too low (Fournier et al., 2010) and these patients were exclude. Perhaps even more germane, and from the safety side, the risks of adverse effects from augmentation with antipsychotics for up to 6 months may not be ethically justifiable for individuals whose depression is not at least moderately severe.

In addition to the clinical entry criteria, we needed to decide whether to enroll participants who have not achieved an adequate response of a broad range of antidepressants (e.g., any SSRI, SNRI, or other approved antidepressant) or limit the population to those who had failed on a specific antidepressant (or specific class of antidepressants), as one would in an efficacy study seeking a relatively homogeneous treatment group. We opted to allow participants to enter the study after a failed trial for their current depression episode of any SSRI, SNRI or mirtazapine – representing the current most commonly chosen initial antidepressants. We imposed no limit on the number of treatment failures or the degree of resistance. The advantages of this approach are that it enhances generalizability of findings and facilitates recruitment as it enlarges the pool of potential participants. This approach mimics real-world practice in which the physicians make their best guess first choice and if it doesn't work, they try something else. It helps us answer the important question of which treatment strategy is more effective for patients who have failed any SSRI, SNRI or mirtazapine-not just for those who have failed one specific antidepressant.

3.4. Should there be a "run-in"?

Closely related to the issue of whether there should be limits to "first-step" agents, is the broader question of whether there should be a "run-in" treatment phase, the most rigorous way of identifying non-responders in an efficacy study of "next-step" treatments. We considered whether to require a standardized uniform run-in treatment period, as had been used in STAR*D, to ensure that participants had indeed failed optimal treatment and were in need of a "next-step" treatment.

Some studies have used placebo run-in phases while others have used active treatment run-ins (Kane et al., 1988). The purpose of a placebo run-in is to eliminate placebo responders, thereby revealing more clearly any drug-placebo differences in the randomized phase. Some investigators have questioned the scientific value and ethics of placebo run-ins (Trivedi and Rush, 1994; Mann, 2007). For example, the meta-analysis of 101 studies by Trivedi and colleagues (1994), revealed that a placebo run-in does not lower the placebo response rate, increase the drug-placebo difference, or affect the drug response rate post-randomization in either inpatients or outpatients for any antidepressant drug group (Trivedi and Rush, 1994). Results of this meta-analyses showed that if there was a post-randomization placebo treatment cell, drug response rates were unchanged or were slightly lower than if there was no placebo treatment cell for outpatients. Thus, these results suggest that a placebo run-in provides no advantage in acute phase efficacy trials.

The second type, active-treatment run-in, has also been used in augmentation studies as a method to create a prospectively defined cohort with inadequate response to first-line treatment. However, a review of 35 articles involving 40 drug vs. placebo comparisons suggests that using historical data to define treatment resistance, without requiring patients to first undergo a prospective lead in phase, is a reasonable approach for identifying subjects to participate in clinical trials of alternative MDD augmentation strategies, including those who are partial responders (Iovieno and Papakostas, 2012).

A prime example in depression studies is STAR*D (Rush et al., 2006b), in which 3671 individuals received first-line treatment from a study physician in order to randomize 1439 who had not achieved remission with that first treatment. While a prospective run-in may increase the likelihood of adequate delivery of optimal first-line treatment and would provide the study with prospective data to assess refractoriness, this strategy is time consuming, expensive, complicates recruitment, increases dropout, and may not represent real-world practice despite treatment guidelines.

We determined that the unified, integrated electronic medical record of the VA Healthcare System would allow us to identify potential non-responders who had had adequate treatment offering a more efficient and potentially effective approach than a run-in period would. After a pre-screened patient is referred to VAST-D and consented, further screening assessment includes a diagnostic clinical interview ($\sim$30 min) by the study staff to assess DSM-IV-TR criteria for current and past MDD, as well as current and past treatment response. Next, information is supplemented by patient recall and data extracted from the medical record that corresponds to the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001). Discrepancies between the data obtained from the clinical interview and the record review are discussed with the local site investigator, and resolved, before the patient is randomized. Using this approach, data are readily available on past psychiatric diagnoses; filled antidepressant prescriptions including agents and dosage; and the duration of prescribed antidepressant treatment. The cost of an expensive and resource-dense run-in period can be avoided and past non-responders can be identified using data from real-world VA practice.

3.5. How long, exactly, should studied treatments be evaluated and how can the greater efficiency of a short-term study be balanced

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against the greater relevance of a long-term evaluation?

Of central importance to the goals of VAST-D is the balance of short- and long-term evaluation. While most "next-step", or treatment-resistant, studies have focused on short-term outcomes, generally lasting 6–12 weeks (which make them sufficient for efficacy assessment and far more economical to implement), long-term benefits, risks, and costs more typically addressed by effectiveness studies are of great importance in real-world practice. Over 1-year of follow-up in STAR*D, 55% of patients relapsed on "next-step" treatments, with significantly higher relapse rates for patients who did not achieve remission prior to entering the follow-up period (Thase, 2003; Rush et al., 2006a).

There is no randomized, controlled trial evidence to guide selecting among potential monotherapy, combination or augmentation agents with the purpose of preventing relapse/recurrence. We also do not know whether treatments that are more effective in the short-term will also be associated with more consistent, better longer-term symptom control, tolerability or safety. This may be particularly important for depressed patients treated with atypical antipsychotics because these medications are known to be associated with long-term adverse health problems such as weight gain, metabolic syndrome, and neurological side effects (e.g. tardive dyskinesia) (Wirshing et al., 1998; Allison et al., 1999; Kraus et al., 1999; Allison and Casey, 2001; Newcomer, 2007). If two possible "next-step" choices are similarly effective, but one is not well tolerated among remitters while the other is well tolerated and relatively safe, the second would clearly be the treatment of choice.

VAST-D goes beyond acute treatment effects by including an additional 24-week continuation treatment phase, which only includes participants whose symptoms remit and those who achieved a satisfactory response, to evaluate the sustainability of response/remission, long-term tolerability safety, and costs of the three treatment strategies. Having long-term follow-up for partial responders allows us to assess factors related to remission occurring beyond the first 12 weeks of treatment (Rush et al., 2006b). However, for safety and ethical reasons, we decided to exclude non-responders from long-term follow-up because remissions after 12 weeks in patients who have shown little initial response are infrequent (Rush, 2007) and those who do not respond or worsen in the acute treatment phase should be considered for transition to another intervention. In addition, study costs are conserved in this protracted phase by focusing only on those who show a reasonable response to acute treatment.

3.6. *What outcomes would be scientifically rigorous, clinically relevant, and practically and economically feasible?*

It is now well accepted that the goal of acute antidepressant treatment is remission, defined qualitatively as asymptomatic or nearly asymptomatic status. In VAST-D, we define remission as a sustained QIDS-C_{16} total score of ≤ 5 over at least 2 consecutive visits. Achieving and sustaining symptomatic remission is the first crucial step towards functional recovery. Failure to achieve remission is associated with continued suffering, impaired functioning and quality of life, medical morbidity, risk for suicide and rapid relapse and recurrence (Murphy et al., 1987; Judd et al., 1997; Miller et al., 1998; Judd et al., 2000).

The QIDS-C_{16} was selected as the primary outcome measure because it is psychometrically sound, clinically meaningful and can be accurately and relatively quickly administered by a trained research assistant to virtually all patients. STAR*D found comparable or better psychometric properties with both the QIDS-C_{16} and the QIDS-Self Report$_{16}$ (QIDS-SR_{16}) than with the Hamilton Depression Rating Scale (HRSD; (Hamilton, 1960)). The QIDS-SR_{16} was considered for VAST-D as it provides a cost-efficient, reliable outcome measure that does not require inter-rater reliability assessments and minimizes the cost of hiring and training raters. The FDA also now accepts self-reported depressive symptoms as primary outcomes for registration trials. However, the major disadvantage of relying on a self-report questionnaire for the primary outcome in this study is that neither participants nor prescribing physicians are blind to treatment (see # 7 below), which introduces a substantial source of potential bias. Having blinded raters at each site, who would not know what treatment is being delivered, was chosen to minimize rater biases and related threats to internal validity. Thus, we ultimately decided that the benefits of having ratings from a well-trained rater, blind to treatment, outweigh the advantages of a non-blind, non-trained patient rating for the primary outcome. In this instance we opted for a method that particularly strengthens the kind of internal validity typical of efficacy trials. In addition to the QIDS-C_{16},

VAST-D also collected the participant self-report responses to the PHQ-9, which will provide additional validation of clinician rated data. The primary objective of administering the PHQ-9, however, is to provide the investigator with symptom information to guide dosing decisions independent of the blinded outcome measures (i.e. measurement-based care). This deviates from routine care – a decision which tilts the design away from the effectiveness and toward the efficacy end of the spectrum and that may increase internal validity at some cost to generalizability.

Symptomatic relief is important, but alone it is too narrow an outcome for a severe, pervasive and disabling condition such as major depression. Therefore, we also included several secondary outcome measures including response, relapse, associated clinical features (suicidal ideation and behaviors, anxiety, hypomanic symptoms), safety (side effects, sexual function, motor function, metabolic indices), quality of life, functioning, positive health, medical health, satisfaction and costs, as these additional outcomes become more pertinent in the longer-term, more effectiveness phase of the study (Table 1). We also used these, and other dimensions (early life adversity, grief, mixed hypomania/mania features and anxious distress), to comprehensively characterize participants prior to study treatments so as to support posthoc moderator analyses. In each case, we opted for brief, pragmatic, self-rated questionnaires that balanced comprehensive and multidimensional assessment with minimal participant burden (Table 1). In most cases, well-studied and psychometrically sound measures were selected, with the exception of three dimensions, where we felt available tools did not quite meet our needs. For these we opted to introduce new self-rated measures for a complicated grief screen, mixed manic/hypomanic features and anxious distress.

3.7. *Do study physicians and participants need to be blind to treatment?*

Due to the large number of possible SSRIs and SNRIs that would qualify as the initial antidepressant for the study, it was determined that the cost and logistics of blinding all possible antidepressants was impractical. We ultimately decided to mask only the evaluator for purposes of eliminating bias when assessing symptoms of depression, leaving the patients and clinicians unmasked to treatment. While un-masked patients and physicians might introduce bias in an open trial by prolonging a favored treatment longer than it should be, or by over- or under-estimating gains in assessments, an open measurement-based treatment study minimizes patient risks by linking treatment decisions to objective outcome measures We also believe that the likelihood of

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reporting biases by patients is low as the questions on the ratings scales are quite specific and objective and are administered by trained evaluators. Allowing both participants and prescribing physicians to know exactly what medications and doses are being prescribed assures that clinicians have complete information about the patients they are treating and thus, are positioned to assure their optimal response and safety. An additional reason to follow the single-blind design is that having the patients and prescribers know the treatment more closely replicates conditions in the real world of general clinical practice. Thus results will have greater external validity and be of more value in applying the results to clinical practice.

4. Summary and conclusions

In this paper, we have highlighted some of the key design decisions we faced as we finalized the VAST-D protocol. VAST-D is a multi-site, randomized, controlled treatment trial designed to compare three commonly used, "next-step" strategies for outpatients with nonpsychotic MDD who have not had acceptable outcomes to their prescribed antidepressants: switching to bupropion-SR or augmenting with either bupropion-SR or aripiprazole. VAST-D is designed to address questions left unanswered by STAR*D, specifically with respect to the comparison of augmentation and switching and with respect to the use of an antipsychotic as an augmenting agent. In addition to comparing the 3 treatments on the primary outcome, sustained remission, VAST-D also assesses response, relapse, depressive symptoms, suicidality, anxiety, co-morbid general medical and psychiatric conditions, functional status, side-effect burden (including sexual, metabolic and neurological side effects), quality of life, positive mental health, satisfaction and costs associated with MDD treatment in the short-term and the long-term. In this paper, we have highlighted some of the key design decisions combining elements of efficacy and effectiveness study designs in the VAST-D protocol.

5. Limitations

Although VAST-D is the largest and most comprehensive VA trial ever attempted for the treatment of major depression, it cannot answer every important question regarding the treatment of MDD after an initial antidepressant trial fails to achieve a satisfactory outcome, nor should it. While there are certainly other options that could also have been considered, none are routinely available in most practice settings, especially primary care settings. Alternative agents that were considered include other antipsychotics (e.g., quetiapine or olanzapine), antidepressants (e.g., tricyclics or monoamine oxidase inhibitors) or other medications (e.g., ketamine, analgesics, anti-inflammatory agents, thyroid or lithium), procedures (e.g., bright light, Transcranial Magnetic Stimulation (rTMS), Vagus Nerve Stimulation (VNS) or Deep Brain Stimulation (DBS)), or non-medical treatments (e.g., psychotherapy, exercise or meditation). We believe the selected strategies represent rational, evidence-based, theoretically grounded alternatives and are the most common approaches used in practice. In VAST-D, we note and document the use of some alternative approaches, but those that are FDA-approved for MDD (e.g., rTMS or VNS) are a basis for exclusion from the study. Although we are not evaluating psychotherapy and other psychosocial interventions (e.g. self-help or peer support per se), we do measure participation in these activities and will use them as covariates in analysis. Despite our use of uniform measurement-based practice guidelines and regular feedback to study clinicians regarding their adherence to these treatment guidelines, we anticipate some variability in the way medications are dosed from site to site and from physician to physician within sites. In the interest of generalizability of findings and applicability into clinical settings, we feel this variability is more desirable than the alternative of using strict treatment algorithms. It should also be noted that as a mixed efficacy-effectiveness study comparing effective, FDA approved treatments, differences between treatment arms are likely to be smaller that in placebo-controlled trials. Although our power analysis, based on assumptions supported by the consensus of experts on the planning committee, suggests that this study will be able to detetct significant differences of relevant magnitude, inter-site variability may increase the challenge of detecting significant differences between treatments. As such it will be important to point out that failure to find significant differences in a superioirty trial does not prove that there are no differences, i.e. failure to prove superiority is not itself proof of equivalence or non-inferiority. Rash policy decisions to limit drug availability on the basis of no-difference findings in a superiority trial would not be justified. Further, because this is a VA trial, the sample is composed of Veterans who are primarily male. Therefore, caution should be exercised when generalizing these results to all patients since MDD afflicts twice as many women than men, and factors affecting depression among Veterans may be different than those affecting depression among non-veterans.

Virtually every decision regarding design of the study was made to optimally balance internal and external validity. VAST-D combines efficacy and effectiveness elements so it is both rigorous and applicable to real-world practice. Participant selection is designed to assemble a broadly inclusive and representative sample from clinical sites. Considerations around the selection of outcome measures, the attention to both short-term and long-term effects, the use of flexible measurement-based care within clinic settings, the selection of the study drugs themselves, not blinding the participant or provider to treatment and the lack of placebo all contribute to the generalizability of study results and the applicability to real-life patients and setting. The results should provide important treatment guidelines that will inform clinicians and improve patient outcomes.

In addressing major methodological and treatment questions, such as these, several key study design issues invariably confront the investigator. The questions addressed in the particular case of "next-step" treatments for patients who have not achieved an optimal outcome to initial, standard antidepressant treatment, may be similar to those in other chronic mental illnesses. Decisions made in designing a "next-step" depression study are likely to be informative for others designing pivotal studies that seek to be maximally applicable to real-world practice as well as rigorously internally valid and thus designed to guide clinical practice and mental health system policies.

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ClinicalTrials.gov Identifier**:** NCT01421342

Appendix A

See Table A1

Table A1
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Appendix B

See Table B1

Table B1
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