

The Sequenced Treatment Alternatives to Relieve Depression Studies: How Applicable are the Results for Older Adults?

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Reports emerging from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study¹⁻⁶ promise an enormous advance in the treatment of depression both in primary care and mental health settings.⁷ The results would seem to apply, with minor reservations, to older adults with depressive disorders. A brief review of the study subjects, measures, methods, and outcomes follows to describe the strengths and limitations.

STUDY SUBJECTS

At the outset, the STAR*D investigators sought to provide a more generalizable sample of real-world patients seeking care and making choices at clinical centers rather than recruited through advertisement or public service announcements. The lead investigators assembled 14 regional centers representing 18 primary care and 23 mental healthcare sites, including both public and private outpatient venues. As a result, 37.9% of the sample of 2,876 people were primary care patients cared for by primary care physicians (PCPs) who would treat their depression. Participating patients ranged from 18–75 years of age, with 741 (28%) ≥51 years of age. Only 5.6% were retired. Most had comorbid general medical conditions. The most common comorbid psychiatric conditions were anxiety disorders. More than 75% met criteria for recurrent depression and approximately 18% reported a history of at least one suicide attempt. Patients with depression complicated by psychosis, dementia, or bipolar disorder were not included. Seventy-five percent of the sample were Caucasians, 17.6% were African Americans, and 13% were Hispanic. Twenty-five percent was college educated, but >33% had no health insurance.¹ In sum-

mary, the racial and ethnic character of the sample was similar to that seen among older Americans and a substantial segment of the patients received depression care from PCPs. However, patients >75 years of age were not included, and most patients were not experiencing their first episode of depression.

MEASURES

Depression severity measures included the 17-item version of the Hamilton Rating Scale for Depression (HAM-D₁₇) and the 16-item self-report version of Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR). The HAM-D is the most widely used measure of symptom severity in antidepressant trials. The QIDS-SR was developed for ease of patient self-report with responses based more on symptom severity than frequency of occurrence. The primary outcome of interest was remission defined as a score of ≤7 on the HAM-D. The secondary outcome of interest was remission defined by a score of ≤5 on the QIDS-SR.⁸ Both outcomes represent a virtual absence of depressive symptoms and thereby minimal risk of relapse. Both measures were administered over the telephone.

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Disclosure: Dr. Kennedy has received research support or honoraria from AstraZeneca, Eli Lilly, Forest, Janssen, and Pfizer.

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However, the QIDS-SR was administered every other week, with results included in a Web-based treatment monitoring system that allowed clinical research coordinators to help guide physicians in antidepressant dosing when symptoms remained elevated and side effects were negligible.⁹

METHODS

STAR*D used an innovative process of allocating patients who did not experience remission with the first antidepressant trial to subsequent trials. Because each alternative choice within a new trial was considered equally desirable, subjects were sorted through a process of equipoise stratified randomization. In practice, this meant that all subjects who did not achieve a QIDS-SR–defined remission with citalopram were encouraged to accept any one of seven potential second-trial options including switching to another single drug (monotherapy), drug augmentation, and/or cognitive behavioral psychotherapy. However, as in actual practice settings, patients could opt not to accept one or more options, in which case they were randomized to the remaining “acceptability strata.” Table 1¹⁻⁶ displays the various alternatives within each of four levels of trials. For all participants, citalopram was started at 20 mg/day, raised to 40 mg/day by week 4, and to a maximum 60 mg/day by the end of week 6. The protocol recommended treatment visits at 2, 4, 6, 9, and 12 weeks. After an optimal trial based on guideline-defined dose and duration, all who did not achieve remission were encouraged to enter the subsequent randomized trial. Patients could discontinue citalopram and move to the next trial before 12 weeks if intolerable side effects required a medication change, an optimal dose increase was not possible because of side effects or participant choice, or significant symptoms (QIDS score ≥ 9) were present after 9 weeks or 12 weeks (QIDS > 5) despite maximally tolerated doses.

Table 2 displays the pharmacologic profile of the medications employed in the trials. Regarding ease of administration, bupropion and bupirone were taken twice daily, while all others were taken once daily. Dietary precautions were necessitated for tranylcypromine. Medications chosen for first- or second-trial monotherapy included citalopram, sertraline, venlafaxine, and bupropion. This group is characterized by relatively low risk of dangerous side effects and drug interactions, and greater familiarity among PCPs. Citalopram and sertraline exhibit primarily serotonin reuptake inhibition, whereas venlafaxine shows serotonergic and noradrenergic reuptake inhibition. Bupropion is both noradrenergic and serotonergic but is neither a selective

serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI). As a result, the choices for the first and second monotherapy trials offered different mechanisms of action with little difference in safety or ease

TABLE 1
STAR*D REMISSION, SIDE EFFECTS, AND INTOLERANCE RATES BY MEDICATION AND TRIAL SEQUENCE¹⁻⁶

<i>Alternative Medication</i>	<i>Mean Dose</i>	<i>Remission</i>	<i>Side Effects</i>	<i>Intolerant</i>
Trial 1				
None				
Citalopram	41.8 mg	32.9%	30.2%	8.6%
Trial 2				
Switch				
Bupropion SR	282.7 mg	25.5%	31.0%	27.2%
Sertraline	135.5 mg	26.6%	27.1%	21.0%
Venlafaxine XR	193.6 mg	25.0%	35.4%	21.2%
Augment				
Citalopram+bupropion	54.8 mg+ 267.5 mg	39.0%	23.4%	12.5%
Citalopram+bupirone	55.0 mg+ 50.9 mg	32.9%	27.2%	20.6%*
Trial 3				
Switch				
Nortriptyline		12.4%	41.1%	N/A
Mirtazapine		8.0%	45.3%	N/A
Augment medications from Trial 2 with lithium	859.8 mg	13.2%	34.4%	23.2%
Augment medications from Trial 2 with T ₃	45.2 µg	24.7%	29.0%	9.6%†
Trial 4				
Switch				
Tranylcypromine	36.9 mg	13.8%	16.7%	41.4%‡
Augment				
Venlafaxine+mirtazapine	210.3 mg+ 35.7 mg	15.7%	24.5%	21.6%

Remission defined by a score of ≤ 5 on the Quick Inventory of Depressive Symptomatology Self Report. Side-effects burden defined as moderate-to-marked impairment.

* $P < .05$ compared to citalopram+bupropion.

† $P < .05$ compared to agents augmented with lithium.

‡ $P < .05$ compared to venlafaxine+mirtazapine.

STAR*D=Sequenced Treatment Alternatives to Relieve Depression; SR=sustained release; XR=extended release; N/A=not available; T₃=triiodothyronine.

Kennedy GJ. *Primary Psychiatry*. Vol 13, No 11. 2006.

of administration. Medications chosen for third- or fourth-trial monotherapy included nortriptyline, mirtazapine, and tranylcypromine. Nortriptyline inhibits the reuptake of norepinephrine and is an effective serotonergic and γ -aminobutyric acid agonist. However, it also exhibits anticholinergic activity and is considered higher risk due to cardiovascular effects. As a monoamine oxidase inhibitor, tranylcypromine is associated with life-threatening diet and drug interactions. Mirtazapine has the disadvantage of associated weight but the advantage of sedation.

Medications chosen for augmentation (bupropion, buspirone, mirtazapine) possessed mechanisms of action com-

patible with but not duplicating SSRI or SNRI properties. Similarly, the use of lithium and triiodothyronine (T_3) for augmentation reflected choices based on different theoretical mechanisms not incompatible with any monotherapy or augmentation combinations from the first or second trials. Moreover, lithium and T_3 are the most widely studied medications used to augment the effects of antidepressants.⁶ The dosing and safety monitoring for T_3 is familiar to PCPs, whereas lithium is more familiar to psychiatrists. Cognitive-behavioral therapy was an alternative in both the switch and augmentation options in the second trial, but the data have yet to be published.

TABLE 2
PHARMACOLOGIC PROFILE OF MEDICATIONS USED IN STAR*D¹⁻⁶

<i>Generic Name</i>	<i>Trade Name</i>	<i>Dose</i>	<i>Amnesia, Arrhythmia Potential</i>	<i>Hypotensive Potential</i>	<i>Sedative Potential</i>	<i>Precautions</i>	<i>Advantages</i>
Citalopram	Celexa	AM	Low	Low	Low	Nausea, tremor; reduce dose for renal insufficiency	SSRI: Few drug interactions, oral solution available
Sertraline	Zoloft	AM	Low	Low	Low	Nausea, tremor, insomnia	SSRI: Few drug interactions
Venlafaxine	Effexor XR	AM	Low	Low	Low	Mild hypertensive, headache, nausea, vomiting, do not stop abruptly; reduce dose for renal insufficiency	SSRI and SNRI: few drug interactions
Bupropion	Wellbutrin SR	BID	Low	Low	Low	Agitation, insomnia, seizures,	Anxiolytic, dopaminergic, noradrenergic,
Nortriptyline	Pamelor Aventyl	HS	Moderate	Moderate	Moderate	May be fatal in overdose; glaucoma, prostatic disease, diabetes	Serotonergic, SNRI, GABAergic; therapeutic window 50–150 ng/mL
Mirtazapine	Remeron Sol-tabs	HS	Low	Low	Moderate	Prolonged $t_{1/2}$, dry mouth, weight gain; reduce dose for renal insufficiency	Sedative, serotonergic; noradrenergic but not SSRI or SNRI
Tranylcypromine	Parnate	AM	Low	Moderate	Low	Life-threatening diet and drug interactions	MAOI stimulant, short half-life
Buspirone	Buspar	BID	Low	Low	Low	For augmentation only, not a benzodiazepine substitute	Serotonergic but not SSRI; antianxiety agent with no dependence
L-triiodothyronine	Various T_3	AM	Moderate	Low	Low	Anorexia, arrhythmia, hypertension, only for augmentation	Rapid onset of action
Lithium carbonate	Eskalith CR	AM	Low	Low	Low	Renal clearance is sole route of elimination; toxicity may appear below therapeutic range. Tremor is a benign universal side effect. Nausea and vomiting are signals of toxicity. Risk of hypothyroidism. For augmentation only.	Treatment level 0.6–1.2 mEq/L

STAR*D=Sequenced Treatment Alternatives to Relieve Depression; SSRI=selective serotonin reuptake inhibitor; XR=extended release; SNRI=serotonin norepinephrine reuptake inhibitor; SR=sustained release; GABA= γ -aminobutyric acid; MAOI=monoamine oxidase inhibitor; T_3 =triiodothyronine; CR=controlled release.

Kennedy GJ. *Primary Psychiatry*. Vol 13, No 11. 2006.

RESULTS

Table 1 provides mean dose of medication at the end of each trial as well as percentages of marked-to-moderately burdensome side effects. Also included is the percentage of patients who were medication intolerant due to either side effects or lack of benefit and discontinued the trial prior to an adequate duration. Because the studies each report exhaustive detail on side-effect frequency, intensity, and burden, intolerance and moderate-to-marked burden were chosen as representing the most informative concise measures for the reader. The remission rates in the Table are based on the QIDS-SR rather than HAM-D, in as much as the QIDS-SR is more appropriate for primary care settings.

Within the initial citalopram trial, participants who were Caucasian, female, employed, or had higher levels of education or income had higher remission rates. Participants with longer index episodes of depression, more concurrent psychiatric disorders, more general medical disorders, and lower baseline function and quality of life experienced lower remission rates. Age was not a significant predictor of remission. Of those who achieved remission, 40.3% did so only at or after 8 weeks of citalopram. Of those who were not well but could tolerate nearly 60 mg of citalopram, an additional 33% experienced remission when bupropion sustained release (SR) or bupropion were added. Bupropion SR appeared to be the better of the two choices due to tolerability. Of patients not experiencing a remission with citalopram, 25% were made well simply by switching to sertraline, bupropion SR, or venlafaxine extended release (XR). However, 56% of this group were intolerant of the side effects of citalopram. As a result, the choice of the seemingly more desirable option of augmentation was precluded. Nonetheless, intolerance of the first SSRI did not automatically mean intolerance of the second.

For patients not well after two antidepressant trials of either monotherapy or augmentation, switching to nortriptyline, mirtazapine, or tranylcypromine, or adding venlafaxine to mirtazapine made approximately one in eight well. Without placebo controls, one cannot deny the possibility that one in eight was better than the spontaneous remission rate associated with the natural history of recurrent depression. In contrast, of patients who remained symptomatic but tolerated citalopram plus bupropion SR or venlafaxine XR; or monotherapy with sertraline, bupropion SR, or venlafaxine XR; nearly 25% were made well by the addition of T₃. T₃ was significantly better tolerated than lithium.

CONCLUSION

The STAR*D data provide substantial guidance for the sequenced treatment of depression among older adults despite

the modest number of seniors in the sample. When the first SSRI does not achieve remission, augmentation with a non-SSRI will reliably achieve remission in 33% of patients. Stopping the first medication and switching to another agent, including an SSRI, will achieve remission in 25%. Of those not well following the first and second trial of monotherapy or augmentation, subsequent augmentation with T₃ is preferable to monotherapy with nortriptyline, mirtazapine, or tranylcypromine, or augmentation with lithium or the combination of venlafaxine plus mirtazapine. Thus, drugs which heighten the risk (more serious for seniors) of cardiovascular side effects, drug interactions, and falls due to sedation do not seem worth the risk given the scant benefits. Because many in the STAR*D sample exhibited recurrent depression, the remission rates for seniors experiencing their first episode may be better than that reported in the initial citalopram trial. More rapid-dose escalation coupled with change in medication for patients experiencing little benefit by 6 weeks also might have reduced the delay in remission and the number of patients dropping out for lack of benefit. The authors of the initial citalopram study highlight the need for longer treatment duration, more vigorous medication dosing, and earlier assessment of response. Their recommendations are in concert with others who have argued that the treatment of depression in late life needs to be far more aggressive than current practice reflects.¹⁰ Missing from STAR*D are data on the choice of alternatives for patients with dementia complicated by depression not remitting with the initial SSRI trial. Nonetheless, the preferences outlined above would be equally applicable to depression in dementia based on the safety profile alone. In short, the data from STAR*D represent a major advance in the treatment of depression among adults of all ages. **PP**

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