Supplementary Table 2:
Description of Levels 1-4 Treatments

Level 1:

STAR*D investigators report that Citalopram (Celexa) was chosen as the first-line SSRI treatment because (1) absence of discontinuation symptoms; (2) demonstrated safety in elderly and medically fragile patients; (3) easy once-a-day dosing with few dose adjustments; and (4) favorable drug–drug interaction profile. [1] Citalopram was started at 20 mg/day and then raised to 40 mg/day by day 28 and up to 60 mg/day by day 43 and onward. Dose adjustments were based on how long a patient had received a particular dose, symptom changes, and side effect burden.

Level 2 switch treatments:

Citalopram was discontinued without a tapering at the initiation of each level 2 switch treatment. STAR*D investigators chose pharmacologically distinct switch medications. The level 2 treatments were:

- Sertraline (Zoloft), an SSRI with the same pharmacological profile as citalopram. Sertraline was started at a daily dose of 50 mg and increased to 100 mg at day 8, to 150 mg at day 28, and to 200 mg at day 63 and onward.
- Sustained-release bupropion (Wellbutrin SR), an “out-of-class” agent whose neurochemical action mechanisms are unknown; other than that, it does not inhibit serotonin reuptake and is believed to produce antidepressant effects by blocking the reuptake of dopamine and norepinephrine. The daily dose of sustained-release bupropion was 150 mg for week 1, 200 mg from day 8 to 27, 300 mg from day 28 to 41, and 400 mg from day 42 onward.
- Extended-release venlafaxine (Effexor), a “dual-action” agent that inhibits the reuptake of both serotonin and norepinephrine. The starting daily dose of extended-release venlafaxine was 37.5 mg for week 1 and increased to 75 mg from day 8 to 14, to 150 mg from day 15 to 27, to 225 mg from day 28 to 41, to 300 mg from day 42 to 62, and to 375 mg from day 63 onward.
- Cognitive therapy was provided by a trained psychotherapist and scheduled twice weekly for the first four weeks, then once weekly for the remaining 8 weeks (16 sessions total).

Level 2 Citalopram augmentation treatments:

During the augmentation trial, the citalopram dose was kept constant but reduced if side effects developed. The level 2 augmentation treatments were:

- Buspirone (Buspar), a partial agonist at the postsynaptic 5-hydroxytryptamine 1A (5-HT1A) receptor that is believed to enhance the activity of SSRIs through the 5HT1A receptors. The starting dose was 15 mg per day week 1, increasing to 30 mg per day week 2, and then to 45 mg per day for weeks 3 through 5, and a final, maximum dose of 60 mg per day week 6 and onward.
- Sustained-release bupropion (Wellbutrin SR) whose neurochemical action mechanisms are unknown but is believed to produce antidepressant effects by blocking the reuptake of dopamine and norepinephrine. The initial dose was 200 mg per day during weeks 1 and 2, increasing to 300 mg per day by week 4 and to 400 mg per day week 6 and onward.
- Cognitive therapy was provided by a trained psychotherapist and scheduled twice weekly for the first four weeks, then once weekly for the remaining 8 weeks (16 sessions total).

Level 3 switch treatments:

At entry into the Level 3 switch trial, all level 2 medications were discontinued without tapering at the initial Level 3 treatment visit. The level 3 switch treatments were:

- Nortriptyline (Pamelor), a tricyclic antidepressant. Recommended doses were 25 mg/ day for 3 days, 50 mg/day for 4 days, and then 75 mg/day by day 8, 100 mg/day by day 28, and, if necessary, 150 mg/day by day 42 and onward
- Mirtazapine (Remeron), a tetracyclic antidepressant that blocks inhibitory a2-adrenoceptors on norepinephrine and serotonin neurons to enhance both norepinephrine and serotonin neurotransmission. Recommended mirtazapine doses were 15 mg/day for the first 7 days, 30 mg/day by day 8, 45 mg/day by day 28, and, if necessary, 60 mg/ day by day 42 and onward.

Level 3 augmentation treatments of level 2 medications:

The two medication augmentation options used in level 2, buspirone and sustained-release bupropion, were discontinued without tapering in the initial level 3 visit. The two medication augmentation treatments in level 3 were added to ongoing treatment with citalopram, sertraline, sustained-release bupropion, or extended-release venlafaxine. The level 3 augmentation treatments were:

- Lithium started at 450 mg/day, and at week 2 it was increased to the recommended dose of 900 mg/day. If participants could not tolerate the initial dose, it could be reduced to 225 mg/day for 1 week then increased to 450 mg/day. There was no monitoring of lithium levels.
- Triiodothyronine (T3), a thyroid hormone, started at 25 µg/day for 1 week and then increased to the recommended dose of 50 µg/ day. There was no pretreatment assessment, nor ongoing monitoring, of thyroid functioning.

Level 4 switch treatments:

The level 4 switch treatments were:

- Tranylcypromine (Parnate), a monoamine oxidase inhibitor. A 2-week washout period of Level 3 medications was required for patients assigned to the tranylcypromine group. The recommended dosing for tranylcypromine was 10 mg/day for the first 2 weeks, followed by weekly increases of 10 mg/day until a maximum of 60 mg/day.
- Co-administered venlafaxine (Effexor) and mirtazapine (Remeron) to inhibit the reuptake of both serotonin and norepinephrine and block inhibitory a 2-adrenoceptors on both norepinephrine and serotonin neurons to enhance both norepinephrine and serotonin neurotransmission. Level 3 medications were discontinued without tapering for patients assigned to this group. The dosage of extended-release venlafaxine was 37.5 mg/day for the first week, 75 mg/day for the second week, 150 mg/day for weeks 3–5, 225 mg/day for weeks 6–8, and 300 mg/day onward. Mirtazapine was started at 15 mg/day for the first 3 weeks, 30 mg/day for weeks 4 to 8, and then 45 mg/day onward.