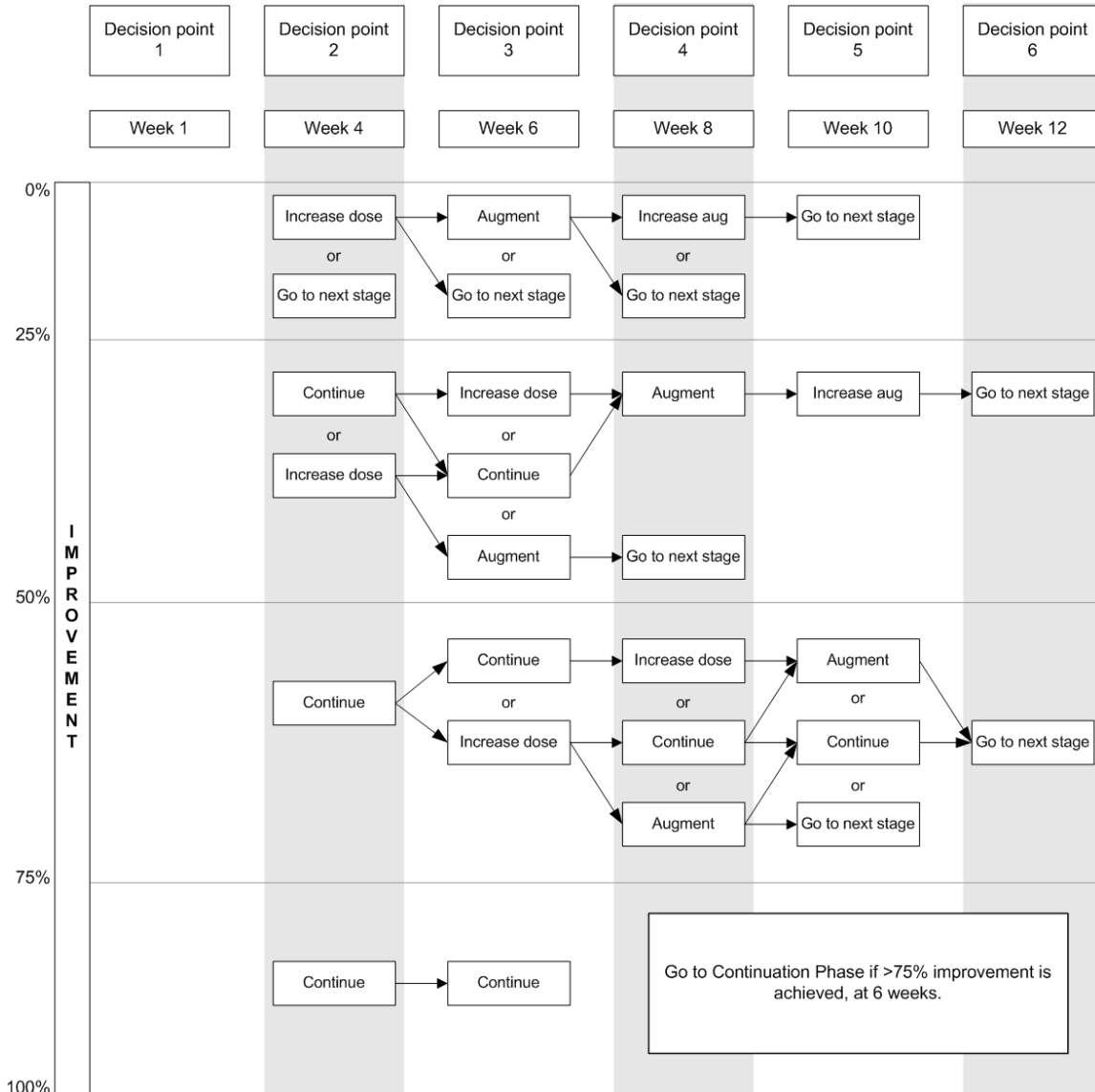


**EXHIBIT 3**  
**Critical Decision Points (CDPs) for Major Depressive Disorder:  
 Tactics for the Treatment of Major Depression (Nonpsychotic)**



**TREATMENT OF DEPRESSION WITH ANTIDEPRESSANTS**

- 50 percent of patients either do not receive adequate levels of antidepressants or are not treated for an adequate period of time.
- 10 to 20 percent of patients are intolerant to an initial trial of antidepressant medication.
- 25 to 30 percent of patients who complete an adequate trial do not show an acceptable response.

- The strategies for achieving remission include maximizing the dose as tolerated, switching to a different class if indicated, augmenting a partial response, or combining antidepressants when needed.

#### EXHIBIT 4

### Strategies for Acute Phase Treatment of Major Depressive Episodes

Stage	Nonpsychotic depression	Psychotic depression
Stage 1	Monotherapy <sup>a</sup> SSRI, <sup>b</sup> Bupropion (BUP), Nefazodone (NEF), Venlafaxine (VLF), Mirtazapine (MRT) (A evidence <sup>c</sup> )	Antidepressant + Antipsychotic TCA + Antipsychotic (A-B evidence) <sup>d</sup> SSRI + Antipsychotic (B-C evidence) Amoxapine (B evidence) VLF + Antipsychotic (B-C evidence)
Stage 2	Monotherapy SSRI, BUP, NEF, VLF, Mirtazapine (MRT) <b>OR</b> a TCA <b>EFFICACY FAILURE:</b> Switch to another antidepressant. <b>SIDE EFFECT FAILURE:</b> Switch classes, or consider staying within the class if a contrasting SE profile is available or expected.	Antidepressant + Antipsychotic <b>EFFICACY FAILURE:</b> If nonTCA used in Stage 1, switch to TCA. If TCA used, try an antidepressant from a different class. <b>SIDE EFFECT FAILURE:</b> Switch to an agent from a different class.
Stage 3	Monotherapy SSRI, BUP, NEF, VLF, MRT, TCA or MAOI Choose a medication from a different class than used in Stage 1 or 2.	ECT If the patient refuses ECT or does not respond, go to the next stage or repeat an earlier stage with a different agent.
Stage 4	Augmentation Previously untried antidepressant + lithium, thyroid, <sup>e</sup> or buspirone Begin medications simultaneously.	Augmentation Previously untried treatment + lithium, thyroid, or buspirone Begin medications simultaneously.
Stage 5	Combination Therapy TCA + SSRI, SSRI + BUP, SSRI + NEF, BUP <sub>SR</sub> + NEF	Other Any antidepressant + antipsychotic not tried in Stage 1 or 2
Stage 6	ECT If patient refuses ECT or does not respond, go to next stage or repeat an earlier stage with a different agent.	Other Any antidepressant + antipsychotic not tried previously
Stage 7	Other Any antidepressant or combination not previously tried	Other Any antidepressant + antipsychotic not tried previously

<sup>a</sup>Acceptable antidepressants for Stage 1: Discuss treatment options with the patient and depending on prior treatment history, patient's clinical presentation, life style, and personal preferences, etc., assess the relative advantages of Stage 1 medications and make an initial treatment selection.

<sup>b</sup>FDA-approved SSRIs for depression include: fluoxetine (FLU), paroxetine (PRX), sertraline (SERT), and citalopram (CIT).

<sup>c</sup>Evidence level: A = controlled clinical trials; B = open trials and retrospective data analyses; C = clinical consensus and/or case reports.

<sup>d</sup>Acceptable TCAs for psychotic depression include: desipramine (DMI), nortriptyline (NT), amitriptyline (AMI), clomipramine (CMI), or imipramine (IMI).

<sup>e</sup>T<sub>3</sub> thyroid medication Cytomel (triiodothyronine) is suggested before T<sub>4</sub> Synthroid.

**EXHIBIT 5**  
**Critical Decision Points (CDPs) and Tactics for**  
**Acute Phase Treatment of Major Depression**

(within each strategy stage, approaches to conducting a therapeutic trial with an antidepressant)

Critical decision point	Clinical status	Plan <sup>a</sup>
Week 1 (CDP 1)	Symptomatic	Initiate medication; adjust dose to lower end of therapeutic dose range or serum level.
Week 4 (CDP 2)	Full Response	Continue current dose.
	Partial Response <sup>b</sup>	<ul style="list-style-type: none"> <li>• Continue current dose.</li> <li>• Consider increasing dose.</li> </ul>
	Minimal or No response	<ul style="list-style-type: none"> <li>• Increase dose.<sup>c</sup></li> <li>• Go to the next stage.</li> </ul>
Week 6 (CDP 3)	Full Response	Go to continuation phase if full response sustained for at least 4 weeks. Otherwise, continue current dose.
	Partial Response	<ul style="list-style-type: none"> <li>• Maximize dose.</li> <li>• Augment with lithium, thyroid, or buspirone.</li> </ul>
	No response or minimal response	<ul style="list-style-type: none"> <li>• Augment with lithium or alternative augmenting agent.</li> <li>• Go to the next stage.</li> </ul>
Week 8 (CDP 4)	Full Response	Go to continuation phase if full response is sustained for at least 4 weeks. Otherwise, continue current dose.
	Partial Response	<ul style="list-style-type: none"> <li>• Augment with lithium or alternative augmenting agent.</li> <li>• Go to the next stage.</li> </ul>
	No response or minimal response to lithium or alternative augmentation for 2–3 weeks	Discontinue and go to the next stage.
Week 10 (CDP 5)	Full Response	Go to continuation phase if full response is sustained for at least 4 weeks. Otherwise, continue current dose.
	Partial Response	<ul style="list-style-type: none"> <li>• Adjust dose (antidepressant and/or augmentation dose).</li> <li>• Go to the next stage.</li> </ul>
	No response or minimal response	Go to the next stage.
Week 12 (CDP 6)	Full Response	Go to continuation phase if full response is sustained for at least 4 weeks. Otherwise, continue current dose.
	Partial Response	Go to the next stage.

<sup>a</sup>For patients showing minimal or no response, total trial should not exceed 4–8 weeks. For patients with a partial response the trial may last up to 12 weeks to increase dose and implement augmentation strategy. Patients with only a partial response at any stage beyond 12 weeks should be considered for a medication change or a move to a subsequent treatment stage. In cases of treatment-resistant depression (TRD), longer trials may be necessary in later stages.

<sup>b</sup>With partial response, the clinician and patient assess both the absolute degree of improvement and the rate of improvement. No response is <25% improvement in overall symptoms, minimal response is 25–50% improvement in overall symptoms, partial response is 50–75% improvement in overall symptoms, full response is >75% improvement in overall symptoms.

<sup>c</sup>In patients with psychotic depression, dose increases may include the antidepressant, the antipsychotic, and/or the augmenting agent.