Augment with one of the following: SSRI, SNRI, BUP, MRT, BUS, or T3. Choosing a different MOA than Stage 1 drug.

SSRI/SNRI + BUP, SSRI/SNRI + MRT, SSRI + TCA, . . . . . . . . . . . or . . . . . . . . . . .

If combo AD at Stage 3, use TCA ± Li or MAOI6. If TCA or MAOI at Stage 3, use combo AD, SSRI/SNRI + OLZ or RSP, SSRI + LTG, or ECT4.

Alternate 2 or 3 drug combo not used previously6. Consider ECT or VNS if not used.

ECT or VNS4.

Triple AD Rx5.

If combo AD at Stage 3, use TCA ± Li or MAOI, if TCA or MAOI at Stage 3, use combo AD, SSRI/SNRI + OLZ or RSP, SSRI + LTG, or ECT. Go to Maintenance phase when indicated.

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1EBPT is an option before starting pharmacotherapy or in combination with pharmacotherapy at any stage in the algorithm.

2TCAs ± Li or MAOIs should be considered over combination treatment, unless tolerability, prior response, or patient preference otherwise.

3Use MRT as an augmenting agent if an SSRI/SNRI + BUP is used in stage 3; use BUP as an augmenting agent if an SSRI/SNRI + MRT is used in stage 3.

4If VNS chosen, it augments pharmacotherapy.

5Use agents with different MOA; use agents with response in the past (even minimal); choose among SSRIs, SNRIs, BUP, MRT, TCAs, MAOIs, AAPs, LTG, Li.

6Use agents with a different MOA; use agents with response in the past; if not previously used, consider ECT or VNS here.

7Continuation phase treatment should include treatment 6–9 months a/f remission of symptoms with antidepressant(s) that achieved symptom remission.

Abbreviations: AD = antidepressant, AAP = atypical antipsychotic, BUP SR/XL = bupropion SR/XL; BUS = buspirone, EBPT = evidence-based psychotherapy, ECT = electroconvulsive therapy, Li = lithium, LTG = lamotrigine, MAOI = monoamine oxidase inhibitor, MOA = mechanism of action, MRT = mirtazapine, OLZ = olanzapine, RIS = risperidone, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, T3 = liothyronine, TCA = tricyclic antidepressant, VNS = vagal nerve stimulation.