Combining and Augmenting Antidepressants

Less than one-third of patients achieve remission with the first antidepressant tried.[41] The chart below provides practical considerations for combining or augmenting antidepressants. (For information on alternative strategies [e.g., switching], see **footnote a**.) Combining or augmenting antidepressants may help patients who have a partial response (>25% improvement) to a single antidepressant.[1] Combining or augmenting instead of switching avoids the risk of antidepressant withdrawal symptoms and loss of benefit from the first antidepressant.[14] Choose an agent based on target symptoms, side effects, and cost.[1,2] Look for early improvement after two to four weeks.[1] The optimal duration of combination treatment is unclear, but most patients stay on combination therapy for months.[43] Consult product labeling regarding switching to/from or combining medications with MAOIs. Keep in mind, many of the combinations below can increase the risk of serotonin syndrome.

Combining Antidepressants

Combining two antidepressants is a common strategy, but is not supported by high-level evidence.[1,12] The rationale is that targeting different receptors will have a synergistic effect.[12] Combinations of an SSRI or venlafaxine with **bupropion** or **mirtazapine** have the best evidence of efficacy.[1,2,5,10] Less evidence for tricyclics as add-ons.[1]

Combination	Comments
Bupropion added to SSRI or SNRI	• Bupropion plus an SSRI is the most common antidepressant combination.[10,43] • Consider adding bupropion for patients with fatigue, low energy, or SSRI/SNRI sexual side effects.[5,10] • Bupropion is associated with seizures and increased blood pressure.[2] • Bupropion may cause agitation or insomnia and is less effective for depression than SSRIs for patients with high levels of anxiety.[2,10] • Bupropion can inhibit metabolism of some SSRIs or SNRIs through CYP2D6 inhibition.[2] • Most studies of the combination have used the bupropion SR formulation.[17,32,41] • Total bupropion dose is 150 to 400 mg/day.[1,17,41] A total daily dose of 300 mg may be needed to ameliorate SSRI-associated sexual dysfunction.[32]
Mirtazapine added to SSRI or SNRI	• A second-line option, per Canadian guidelines.[1] • The addition of mirtazapine to an SSRI or SNRI in patients with depression despite at least six weeks' treatment with an SSRI or SNRI alone showed no benefit over the addition of placebo.[46] Adverse effects were more common in mirtazapine-treated patients [Evidence level A-1].[46] • In an open-label study (n=112), the addition of mirtazapine in patients who did not respond to venlafaxine was not as effective as switching to imipramine.[47]

Continued…

Combination	Comments
Mirtazapine added to SSRI or SNRI, continued	• Mirtazapine may ameliorate SSRI/SNRI sexual side effects, but studies are limited.[11] Mirtazapine may also offset the activating effects of SSRIs or SNRIs.[10] • Sedating: consider for patients with insomnia (give at bedtime).[1,2,10] • Consider to improve appetite or reduce nausea.[2,6] Weight gain may be especially problematic if used with paroxetine.[34] • Serotonin syndrome reported with mirtazapine/venlafaxine combo.[28] • Hypomania reported with SSRI (sertraline) combo.[33] • Bleeding reported when mirtazapine used with SSRI (escitalopram) plus SNRI (venlafaxine).[36]
Trazodone added to SSRI or SNRI	• A third-line add-on, per Canadian guidelines.[1] • Sedating: consider for patients with insomnia.[1,2] • Warn men about the risk of priapism.[2] • Consider max daily trazodone dose of 100 mg with antidepressants that can inhibit its metabolism via CYP2D6 and/or CYP3A4.[2,12,14] • Risk of serotonin syndrome, particularly with additional CYP2D6 inhibitors or serotonergic drugs.[29,30]
Tricyclic added to SSRI or SNRI	• Use low tricyclic dose (e.g., 25 to 75 mg daily) with antidepressants that can inhibit their metabolism (i.e., most antidepressants to some extent).[12] Monitor tricyclic blood levels to prevent cardiac toxicity.[5,12] • Theoretical risk of serotonin syndrome when combined with an SSRI or SNRI.[13] • Sedating: consider for patients with insomnia (give tricyclic as single dose at bedtime).[2] • Consider for patients with comorbidity that may benefit (e.g., neuropathic pain, migraine, tension headaches).[2] • May not be a good combination in the elderly due to tricyclic anticholinergic effects.[13]
SSRI plus SNRI	• Rationale: provide additional serotonergic activity, plus adrenergic activity (i.e., hit additional receptors). • Case reports only, mostly with venlafaxine. • Any benefit may be due to an increase in the total SSRI effect; venlafaxine is more like an SSRI at low doses.[2] • Risk of serotonin syndrome and increased blood pressure; may be due to SSRI-induced CYP2D6 inhibition of venlafaxine metabolism (e.g., by fluoxetine).[12,35] Paroxetine/duloxetine combo poses same drug interaction concern.[37] • Bleeding reported with SSRI (escitalopram)/SNRI (venlafaxine)/mirtazapine combination.[36]
SSRI plus SSRI	• Rationale: agents differ slightly in potency and neurotransmitter effects (i.e., hit additional receptors).[12] Example, sertraline has some dopaminergic activity, and paroxetine and fluoxetine have some noradrenergic activity.[12] • Case reports only. • Success combining fluvoxamine (*Luvox*) or fluoxetine with citalopram might result from increased levels of the more potent S-citalopram due to a drug interaction, rather than a combined antidepressant effect.[12,35] • Risk of drug interactions.[12] Risk of increased serotonergic side effects or serotonin syndrome.[12,13]

Augmenting Agents (Antidepressant Add-Ons)

For additional considerations in choosing an antidepressant, see our chart, *Choosing and Switching Antidepressants*.

Add-On	Comments
Agents with the Most Evidence	
Atypical Antipsychotics	• A first-line option, per Canadian guidelines.[1] • Aripiprazole more effective than bupropion as an add-on [Evidence level B-1].[41] • Aripiprazole, brexpiprazole (U.S.), and quetiapine have labeled indications for major depression. *Symbyax* (fluoxetine/olanzapine) is FDA-approved for treatment-resistant depression. Risperidone and ziprasidone have also been studied.[1] • Not all studies have shown benefit.[3,48] • Consider for patients with sexual dysfunction or insomnia.[15,16] • Lower doses than those used for schizophrenia may be effective.[2,15,16] • Monitoring for metabolic side effects (e.g., weight gain, hyperglycemia, dyslipidemia) is outlined in the product labeling, and in expert recommendations. Also see our chart, *Lab Monitoring for Common Medications*. • See our chart, *Comparison of Atypical Antipsychotics* (U.S.)(Canada) for dosing, CYP450 drug interactions, and comparative safety (metabolic side effects, QT prolongation, sedation). Antipsychotics also carry risks of movement disorders, hyperprolactinemia, and neuroleptic malignant syndrome.[2]
Lithium	• A second-line option, per Canadian guidelines.[1] Only a small number of patients have been studied.[43] • May reduce risk of suicide long-term, perhaps by decreasing aggression, impulsivity, and relapse.[2,26] • Consider targeting a serum level of 0.5 to 1.2 mEq/L.[13] • Response should be noticeable in one to two weeks.[13] • Most data from studies wherein lithium was added to a tricyclic, but seems to boost SSRIs and mirtazapine too.[1,4,31,43] • Drawbacks: lab monitoring, weight gain, and adverse thyroid and renal effects.[4,12]
Liothyronine (T3) (*Cytomel*)	• A second-line option, per Canadian guidelines.[1] • Most data from studies wherein T3 was added to a tricyclic.[43] • Efficacy similar to lithium as an SSRI add-on, but better tolerated than lithium (STAR*D trial).[7,8] • A dose of 25 mcg, increased if needed to 50 mcg after about a week, is a typical dose in euthyroid patients.[2] • Response should be noticeable in one to two weeks.[13] • Potential adverse effects include nervousness and insomnia.[12] • Ensure hypothyroid patients are optimally treated.[2]

Add-On	Comments
Add-Ons with Less Evidence	
Buspirone (*Buspar*)	• In STAR*D, remission and response rates were similar to add-on bupropion-SR, but bupropion-SR improved symptom scores more and was better tolerated.[17] • Consider for patients with anxiety[2] or SSRI sexual side effects [Evidence level B-1].[9] • Risk of serotonin syndrome when combined with a serotonergic antidepressant.[27]

Stimulants	• **General considerations**:
	  • There is limited data supporting stimulant and stimulant alternatives (e.g., modafinil) for depression.[38,39,44]
	  • Modafinil is a second-line option, and other stimulants are third-line, per Canadian guidelines.[1]
	  • U.S. guidelines suggest considering stimulants and modafinil for augmentation.[2]
	  • Some studies show no benefit when adding modafinil or other stimulants.[1,38,39,42] Other studies demonstrate benefit with methylphenidate and modafinil within a few days to two weeks of initiation, much sooner than when traditional antidepressant therapies are initiated without a stimulant.[38,39]
	  • Duration of therapy with stimulants is not well established.[38,39] Study durations with methylphenidate have ranged from eight to 16 weeks.[44]
	• **Methylphenidate**
	  • Studies suggest that geriatric patients may benefit from the addition of immediate-release methylphenidate to an SSRI (citalopram was studied) to modestly improve antidepressant response [Evidence level B-2].[44]
	  • Augmenting with methylphenidate may improve depression-related apathy or fatigue (regardless of impact on depression).[20]
	  • Consider starting with a dose of 2.5 mg twice daily, titrating about every two to three days based on response and side effects, and aiming for 5 mg to 10 mg twice daily.[40,44,45] Suggest scheduling the second dose of the day at or before 3 PM, to minimize nighttime wakefulness.[40]
	  • Consider tapering off methylphenidate, once the antidepressant has had time to take full effect, in about eight to 16 weeks.[40,44]
	  • Avoid methylphenidate in patients with a history of substance abuse,[40] anxiety, arrhythmias, recent MI, etc.[2,40] Recommend monitoring heart rate and blood pressure with methylphenidate, especially in patients with coronary artery disease, hypertension, or heart failure.[2]
	• **Modafinil**
	  • Consider adding modafinil 100 to 400 mg once daily for patients with residual fatigue, sleepiness, or antidepressant-associated sedation, especially those with severe depression.[2,10,19]
	  • Modafinil side effects include nausea, jitteriness, and life-threatening dermatologic reactions.[2,19]
	  • Be aware that modafinil can reduce efficacy of oral contraceptives via CYP3A4 induction.[2]

Add-On	Comments
Anticonvulsants	• Lamotrigine has the most evidence, but data are limited.[18] • Valproic acid and carbamazepine have also been used.[2] • Consider for patients who also need them for a comorbid condition (e.g., migraine prevention).
Folate	• A small study suggests NNT = 6 for *response* to L-methylfolate 15 mg (similar to lithium or atypical antipsychotics), but *remission* not different from placebo.[5] • Good tolerability.[5] • Current evidence does not support efficacy of folic acid as an add-on for most patients [Evidence level B-1].[22,23] • Consider folic acid supplementation for patients with low folate [Evidence level B-3][24,25] and women of reproductive age.[2] Discourage supplementation with >400 mcg due to evidence of cancer risk.[21]
Light therapy	• See our FAQ, *Seasonal Affective Disorder*.
SAM-e (S-adenosyl-L-methionine)	• Well-tolerated.[5] • U.S. guidelines say it can be considered in patients who prefer a "natural" treatment.[2] • A dose of 400 to 800 mg twice daily is effective as an SSRI add-on.[5] • More effective than placebo (NNT = 6 for response; NNT = 7 for remission) [Evidence level B-1].[5]

a. Switching is a common strategy if there is no response (<25% improvement) four to eight weeks after dose optimization, or the patient cannot tolerate an adequate dose.[1,2] Our chart, *Choosing and Switching Antidepressants*, provides practical considerations for selecting among, and switching antidepressants. Also consider adding psychotherapy (cognitive behavioral therapy [CBT], interpersonal psychotherapy, etc). Psychotherapy is safe and has good evidence of efficacy; adding CBT is as effective as adding bupropion.[2]

Abbreviations: MAOI - monoamine oxidase inhibitor; SSRI - selective serotonin reuptake inhibitor; SNRI - serotonin norepinephrine reuptake inhibitor

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*****	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*****	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56. http://www.aafp.org/afp/2004/0201/p548.pdf.]

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