Combining and Augmenting Antidepressants

Less than one-third of patients achieve remission with the first antidepressant tried.[41] 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] The chart below provides practical considerations for combining or augmenting antidepressants. (For information on alternative strategies [e.g., switching], see **footnote a**.) Choose an agent based on target symptoms, side effects, and cost.[1,2] Look for early improvement within one to four weeks, with full effects at about six weeks.[1,49] Expect only modest benefit.[1,2,8,41] 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.[43] The rationale is that targeting different receptors will have a synergistic effect.[52] Most data, albeit limited, has been with combinations of an SSRI with **bupropion** or **mirtazapine** plus an SSRI or SNRI.[4,17] There is less evidence for tricyclics (e.g., nortriptyline) as add-ons.[1,4]

Combination	Comments

Bupropion added to SSRI or SNRI	• Bupropion plus an SSRI is a commonly used antidepressant combination.[43] It is a second-line option, per Canadian guidelines.[1]
	• Most data involved adding the bupropion SR formulation to an SSRI.[17,32,41] No studies have used a placebo control.
	• Consider bupropion for patients with fatigue or low sexual desire.[1,53]
	• Drawbacks:
	  ○ Bupropion is associated with seizures and increased blood pressure.[2]
	  ○ The addition of bupropion may cause or worsen anxiety.[54]
	  ○ Bupropion can inhibit metabolism of some SSRIs or SNRIs through CYP2D6 inhibition.[2]

Mirtazapine added to SSRI or SNRI *Continued…*	• Mirtazapine plus an SSRI or SNRI is a commonly used antidepressant combination.[43] It is 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] • Mirtazapine may ameliorate SSRI-associated sexual side effects or nausea, but studies are limited.[11,23]

Combination	Comments

Mirtazapine added to SSRI or SNRI, continued	• Drawbacks:
	  o Side effects of the combination: sedation, weight gain (especially with paroxetine), headache.[34,46,52]
	  o Case report of hypomania with SSRI (sertraline) combo.[33]
	  o Case report of bleeding with triple combo (mirtazapine/SSRI [escitalopram]/SNRI [venlafaxine]).[36]
	• Unlikely to cause serotonin syndrome.[55] There is a case report of serotonin syndrome with venlafaxine.[28]

Trazodone added to SSRI or SNRI	• A third-line add-on, per Canadian guidelines.[1]
	• Commonly used as an SSRI add-on for its sedating properties.[13]
	• Drawbacks:
	  o Risk of priapism (educate patient).[2]
	  o Risk of drug interactions with antidepressants that can inhibit its metabolism via CYP2D6.
	  • Case reports suggest that CYP2D6 inhibitors (e.g., fluoxetine, paroxetine) may cause accumulation of the active metabolite of trazodone (metochlorophenylpiperazine), resulting in dysphoria, anxiety, and agitation.[6,10]
	• Unlikely to cause serotonin syndrome.[55] Low doses are commonly used safely with SSRIs for treatment of insomnia.[13] There are case reports of serotonin syndrome when trazodone is combined with venlafaxine +/-tramadol.[29,30]

Tricyclic added to SSRI or SNRI	• Consider the combination for patients with comorbidity that may benefit (e.g., tension headache, migraine prophylaxis, diabetic neuropathy, insomnia).[2,13]
	• Use a low tricyclic dose (e.g., 25 to 75 mg daily) if the SSRI or SNRI can inhibit tricyclic metabolism (i.e., most antidepressants to some extent), and monitor tricyclic blood levels to prevent cardiac toxicity.[12]
	• Drawbacks:
	  o Side effects of the combination: sedation (give tricyclic as single dose at bedtime), sexual dysfunction, constipation, weight gain, dry mouth, GI distress.[2,52]
	  o When adding a tricyclic (especially clomipramine or imipramine, the most serotonergic tricyclics) to an SSRI or SNRI, start low, increase the dose with caution, and watch for symptoms of serotonin syndrome for 24 to 48 hours after dosage increase.[55]
	  o Tricyclics pose risks in the elderly: sedation, falls, constipation, urinary retention, cognitive impairment, and confusion.[26]

SSRI plus SNRI *Continued…*	• Case reports only, with venlafaxine.[52] • Any benefit may be due to an increase in the total SSRI effect; venlafaxine is more like an SSRI at low doses.[52] • When adding an SSRI or SNRI, start low, increase the dose with caution, and watch for symptoms of serotonin syndrome for 24 to 48 hours after dosage increase.[55]

Combination	Comments
SSRI plus SNRI, continued	○ Case reports of serotonin syndrome, increased blood pressure, and anticholinergic-like effects; may be due to fluoxetine-induced CYP2D6 inhibition of venlafaxine metabolism.[12] Paroxetine/duloxetine combo poses same drug interaction concern.[1,37] • 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 or fluoxetine with citalopram might result from increased levels of the more potent S-citalopram due to a drug interaction, or just an increase in total SSRI exposure.[52] • Risk of increased serotonergic side effects (e.g., nausea, tremor) or serotonin syndrome.[52] ○ When adding an SSRI to an SSRI, start low, increase the dose with caution, and watch for symptoms of serotonin syndrome for 24 to 48 hours after dosage increase.[55]
Augmenting Agents (Antidepressant Add-Ons) For additional considerations in choosing an antidepressant, see our chart, *Choosing and Switching Antidepressants*.	
Agents with the Most Evidence	
Add-on	**Comments**
Atypical Antipsychotics	• A first-line option, per Canadian guidelines.[1] • Aripiprazole may be more effective than bupropion as an add-on, with more sedation, less anxiety, and similar effect on sexual function [Evidence level B-1].[41] • Agents with approved indications for depression include aripiprazole, brexpiprazole, cariprazine (US), olanzapine (US; treatment-resistant, with fluoxetine), quetiapine extended-release.[48,56] Risperidone also has efficacy.[4] • Lower doses than those used for schizophrenia may be effective.[2] • 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*. • Given their side effect profiles and cost, consider shared decision-making when choosing an agent. See our chart, *Comparison of Atypical Antipsychotics* (US)(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 *Continued…*	• A second-line option, per Canadian guidelines.[1] • Most data are from small, older studies wherein lithium was added to a tricyclic.[1] ○ Increasing the dose of the SSRI seems at least as effective as augmenting with lithium.[51] • Consider targeting a serum level of 0.5 to 0.8 mEq/L.[50]

Add-on	Comments
Lithium, continued	• Response should be noticeable within 10 to 14 days.[50] • May reduce suicide risk.[50] • Drawbacks: requires lab monitoring; tolerability is poor.[8] • Unlikely to cause serotonin syndrome.[55]
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] o 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-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.[2] • Unlikely to cause serotonin syndrome.[55] There is a case report of possible serotonin syndrome with fluoxetine.[27]

Stimulants
 	
Continued…
	• **General considerations**:
	  o There is limited, mixed data supporting stimulant and stimulant alternatives (e.g., modafinil) for depression.[1,38,39,42,44]
	  o Modafinil is a second-line option, and other stimulants are third-line, per Canadian guidelines.[1]
	  o US guidelines suggest considering stimulants and modafinil for augmentation.[2]
	  o Some studies demonstrate benefit with methylphenidate and modafinil within a few days to two weeks of initiation.[38.39]
	• **Methylphenidate**
	  o 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]
	  o Augmenting with methylphenidate may improve depression-related apathy or fatigue (regardless of impact on depression).[20]
	  o 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

Add-on	Comments
Stimulants, continued	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] o 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** o Consider adding modafinil 100 to 400 mg once daily for patients with residual fatigue, sleepiness, or antidepressant-associated sedation.[1,2,19] o Modafinil side effects include nausea, jitteriness, and life-threatening dermatologic reactions.[2,19] o Be aware that modafinil can reduce efficacy of oral contraceptives via CYP3A4 induction.[2]
Anticonvulsants	• Most studies used lamotrigine.[3,15,18] There is also data for carbamazepine, phenytoin, pregabalin, topiramate, valproate, and zonisamide.[15] Results are mixed, and conclusions cannot be drawn due to study limitations.[3,15.18] • Consider reserving anticonvulsants for patients who also need them for a comorbid condition (e.g., migraine prevention).
Folate	• One meta-analysis shows that taking L-methylfolate or folic acid as an adjunct to treatment with conventional antidepressants modestly improved response rate (risk ratio 1.36 [95% CI 1.16 to 1.59, p = 0.0001[) with a small improvement in remission rate (risk ratio 1.39 [95% CI 1 to 1.92, p = 0.05]) when compared with placebo and conventional antidepressants.[22] Good tolerability.[21] • 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	• Two meta-analyses of a total of 17 studies suggest that adding light therapy to antidepressants for up to 8 weeks is more effective than antidepressants alone for major depressive episodes, including non-seasonal depression.[5,9] • For information on selecting and using a light box, see these resources: o From the University of British Columbia: https://sad.psychiatry.ubc.ca/resources/public-resources/light-therapy-procedure-for-using-the-10000-lux-fluorescent-light-box/. o From the Mayo Clinic: https://www.mayoclinic.org/diseases-conditions/seasonal-affective-disorder/in-depth/seasonal-affective-disorder-treatment/art-20048298
SAM-e (S-adenosyl-L-methionine)	• US guidelines suggest it can be considered in patients who prefer a "natural" treatment.[2] • Canadian guidelines recommended it as a second-line adjunct in patients with mild to moderate depression[1]. • More effective than placebo (NNT = 6 for response; NNT = 7 for remission) [Evidence level B-1].[16] • A dose of 400 to 800 mg twice daily is effective as an SSRI add-on.[16] • Well-tolerated.[16]

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) or exercise.[31,57] Psychotherapy is safe and has good evidence of efficacy; adding CBT is as effective as adding bupropion.[2] It is also worthwhile to examine the impact of concomitant medications that have depressive symptoms as side effects.[31]

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

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

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 Feb 1;69(3):548-56.
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