Drug Augmentation for Treatment-resistant Depression

Table 1 offers drug augmentation options when there is an inadequate antidepressant response from at least two sufficient trials of selective serotonin-reuptake inhibitors (SSRI) or selective norepinephrine-reuptake inhibitors (SNRI) at therapeutic doses and after excluding alternative diagnoses and nonadherence.

- When augmenting an SSRI or SNRI antidepressant for Treatment-resistant Depression (TRD), consider:
- The value of peer and social support which is integral in the treatment of depression.
- Many aspects of identity and individual circumstances (e.g., social determinants of health) have not been evaluated in research as possible confounding factors that may impact effectiveness or safety.
- Medications known to be safe with the patient's current medications and comorbidities; obtain a second opinion (e.g., Oregon Psychiatric Access Line at OHSU) for unfamiliar drug combinations if the risk-benefit ratio is unclear.

Table 1. Drug Augmentation *with Evidence* for Use

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Medication (alphabetical)	Effectiveness	Harms	Comments
Antidepressants, non-SSRI, SNRI: ► **Bupropion sustained release (SR) or extended release (XL)** ► **Mirtazapine** *References:* ▪ *Cheon, et al.* ▪ *Kessler, et al.* ▪ *McGrath, et al.* ▪ *Mohamed, et al.* ▪ *Trivedi, et al.*	► High-quality randomized controlled trials have shown bupropion improves depressive symptoms and fatigue when used as augmentation for TRD. ► Bupropion augmentation may reduce depression and severity of symptoms relative to buspirone. ► Bupropion augmentation may be as effective for TRD as augmentation with aripiprazole. ▪ Augmentation with mirtazapine may result in improved depression scores in some studies; however, studies evaluating treatment remission have not found additional efficacy in patients in patients with TRD. ▪ Little evidence of a demonstrable difference between specific	► Relatively safer option for TRD versus an antipsychotic, with low risk of serious adverse effects and long-term side effects. ► Risk of seizure is dose-related; avoid in patients with history of seizure or with concomitant drugs that lower seizure threshold. Caution use in patients with eating disorders, particularly purging, that may induce seizure. ▪ Augmentation with mirtazapine to an antidepressant may result in more adverse effects and place the patient at risk for stopping treatment. ▪ Adverse effects include significant weight gain, drowsiness, and dry mouth. ▪ Avoid concomitant use with benzodiazepine and alcohol due to	► *Bupropion augmentation* shows *consistent benefit* in TRD and may be a relatively safer long-term augmentation strategy for some patients versus augmentation with an antipsychotic drug. ▪ *Caution routine use of mirtazapine* to augment SSRI/SNRI therapy due to lack of clear evidence of benefit combined with the increased burden of adverse effects.

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Medication (alphabetical)	Effectiveness	Harms	Comments
▪ *VA/DoD*	augmentation with mirtazapine or switching therapy to mirtazapine for achieving remission.	significant somnolence. ▪ Use with caution in patients with bipolar depression, seizure disorder, renal or hepatic impairment.	
Antipsychotics, Second-Generation (SGA) ► **Aripiprazole** ► **Brexpiprazole** ► **Olanzapine** ► **Quetiapine extended release (ER)** ► **Risperidone** ► **Ziprasidone** *References:* ▪ *Edwards, et al.* ▪ *Liebowitz, et al.* ▪ *Maglione, et al.* ▪ *Thase, et al.*	► Augmentation of SSRIs with an SGA is likely beneficial in patients with TRD. ► Aripiprazole, brexpiprazole and quetiapine ER have FDA approval as augmentation with SSRIs and SNRIs in TRD. ► Olanzapine has FDA approval as adjunct therapy with fluoxetine. ► Aripiprazole, brexpiprazole, quetiapine ER, and risperidone have demonstrated consistent efficacy at improving depression when used as augmentation to SSRIs/SNRIs for major depressive disorder; olanzapine and ziprasidone may also be effective.	► It is unknown whether augmentation with an SGA to SSRIs is superior to augmentation with lithium. ► Monitor weight, lipid and glucose levels ► Monitor adverse effects (e.g., extrapyramidal side effects; prolactin-related side effects with risperidone) ► Risperidone may be less sedating than other SGAs. ► Olanzapine may result in more weight gain than other SGAs; ziprasidone may be associated with less weight gain than other SGAs. ► SGAs are associated with increased risk of death in elderly patients with dementia and agitation.	► Overall evidence for SGA augmentation shows *consistent benefit* in TRD ► Treatment with SGAs requires *diligent monitoring* to prevent adverse effects.
Esketamine nasal spray *References:* ▪ *Daly, et al.* ▪ *Popova, et al.* ▪ *Ochs-Ross, et al.*	► Approved by FDA for augmentation in TRD based on depression reduction in one trial and prevention of relapse in patients who were in stable remission in another trial. ► Esketamine augmentation has not shown to improve depression in patients 65 years of age or older.	► Available through a Risk Evaluation and Mitigation Strategy (REMS) program. ► Common adverse effects: dissociation (41%), dizziness (29%), nausea (28%), and sedation (23%).	► *Demonstrated efficacy in younger adults* ► Administered under the direct supervision of a healthcare provider. ► *Requires significant time commitment*, up to half days twice weekly.
Lithium *References:*	► Augmentation of SSRIs with lithium is likely beneficial in patients with TRD. ► Consistent benefits with lithium augmentation have been observed across studies.	► It is unknown whether augmentation with lithium to SSRIs is more effective than augmentation with an SGA. ► Monitor renal and thyroid function at baseline and every 6 months during	► Overall evidence for lithium augmentation is *limited but results show consistent benefit*. Treatment with lithium requires *diligent monitoring* to prevent adverse effects.

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Medication (alphabetical)	Effectiveness	Harms	Comments
▪ *Edwards, et al.* ▪ *Schweitzer, et al.*	► Serious adverse reactions were rarely reported in trials.	treatment ► Monitor ECG in patients at risk for cardiovascular disease. ► Monitor lithium levels 1 week after initiation and each dose change until stable, and every 3 months thereafter ► Use extreme caution in elderly.	
Stimulants ► **Modafinil** *References:* • Goss, et al.	► Augmentation with modafinil may improve overall depression scores and remission rates in patients with TRD. ► Modafinil may also improve fatigue symptoms after the first week of treatment.	► Modafinil augmentation therapy is generally safe and well tolerated with no significant adverse effects found in studies. ► Modafinil may have an advantage over stimulants like methylphenidate and amphetamine in terms of long-term adverse effects.	► Augmentation with modafinil *may be effective* at improving depression in patients with TRD and fatigue symptoms. ► Modafinil may be a safer option relative to other augmentation therapies.

Table 2. Drug Augmentation with *Insufficient* Evidence

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Medication	Effectiveness	Harms	Comments
Anticonvulsants ► **Lamotrigine** *References:* ▪ Goh, et al.	► Augmentation with lamotrigine may improve depression in patients with treatment-resistant unipolar depression. ► Further studies are warranted to clarify the optimal dosage when used to augment antidepressants.	► Lamotrigine augmentation was well-tolerated in studies in terms of all-cause discontinuation rate and adverse events.	► May be safe and effective but recommend *against* routine use due to low quality evidence.
Benzodiazepines ► **Alprazolam** ► **Clonazepam** *References:* ▪ *Ogawa, et al.*	► Studies primarily limited to clonazepam and alprazolam. ► May be a short-term augmentation strategy in patients with anxiety as prominent feature. ► May improve depressive symptoms in adults with major depression ► A strategy for patients suffering from acute suicidality or acute psychotic features.	► Prescribers must consider dependence and limit to short-term use whenever possible. ► Cannot be discontinued immediately due to the risk of potential withdrawal reactions ► High risk for cognitive impairment, falls, and hip fractures in older patients.	► Recommend *against* routine use due to insufficient evidence of benefit and risk for harms.
Buspirone *References:* ▪ *Trivedi, et al.* ▪ *VA/DoD*	► An option in patients with anxiety as prominent feature. ► Augmentation with buspirone to an SSRI may help achieve remission in patients with TRD but may not reduce depression as much as augmentation with bupropion.	► Avoid use in patients with significant renal or hepatic impairment. ► Augmentation with buspirone to an SSRI is associated with more adverse effects and discontinuation of therapy then augmentation with bupropion.	► Recommend *against* routine use due unless alternatives augmentation options have been tried.

Table 2. Drug Augmentation with Insufficient Evidence

Medication	Effectiveness	Harms	Comments
Pindolol *References:* ▪ *Liu, et al.* ▪ *Martiny, et al.* ▪ *Whale, et al.*	► Pindolol augmentation with an SSRI may reduce depression in the first 4 weeks, but effectiveness is less clear beyond 4 weeks. ► Pindolol may accelerate anti-depressive response in some patients over the short-term. ► Study results showing benefit are inconsistent. ► May also improve anxiety when pindolol is given with an SSRI.	► Monitor heart rate and blood pressure	► Recommend *against* routine use due to insufficient evidence.
Thyroid hormones *References:* ▪ *Lorentzen, et al.* ▪ *VA/DoD*	► Thyroid augmentation with T3 or other thyroid hormones in patients with TRD is not more effective than augmentation with placebo regardless of thyroid abnormalities.	► Caution use in patients with cardiovascular disease/arrhythmias, diabetes, renal impairment, or untreated adrenal insufficiency.	► Recommend *against* routine use due to insufficient evidence.

Table 3. Supplement Augmentation with *Insufficient* Evidence

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Supplement	Effectiveness	Harms	Comments
L-methylfolate *References:* ▪ *Papakostas, et al.* ▪ *Zajecka, et al.*	▶ Small studies show inconsistent results with L-methylfolate augmentation	▶ No serious safety concerns at moderate doses.	▶ Recommend *against* routine use due to insufficient evidence of efficacy.
Omega-3 fatty acids *References:* ▪ *Carney, et al.* ▪ *Gertsik, et al.* ▪ *Hallahan, et al.*	▶ Augmentation eicosapentaenoic acid (EPA) in some small studies has reduced depressive symptoms. ▶ Docosahexaenoic ▶ acid (DHA) has not demonstrated any benefit. ▶ Optimal dose of EPA is unclear; doses vary widely between studies. ▶ Larger randomized controlled trials are needed to confirm the antidepressant efficacy of EPA-predominant formulations when used as an augmentation for TRD.	▶ No serious safety concerns at moderate doses.	▶ Recommend *against* routine use due to insufficient evidence of efficacy.
S-adenosyl methionine (SAMe) *References:* ▪ *Sarris, et al.* ▪ *Targum, et al.*	▶ Augmentation with SAMe supplementation does not appear to improve depressive symptoms	▶ Very few placebo-controlled trials available to identify potential harms.	▶ Recommend *against* routine use due to insufficient evidence of efficacy.

Table 3. Supplement Augmentation with Insufficient Evidence

Supplement	Effectiveness	Harms	Comments
Vitamin D3 (cholecalciferol) *References:* ▪ *Alghamdi, et al.* ▪ *Gowda, et al.* ▪ *Khoraminya, et al.*	► Two small, short-term studies have shown daily or weekly augmentation of Vit D3 improve depressive symptoms ► Lack of demonstrated efficacy in larger, randomized controlled trials. ► Vitamin D does not appear to confer benefit in patients with depression and sufficient serum vitamin D levels at baseline.	► No serious safety concerns at moderate doses.	► Recommend *against* routine use due to insufficient evidence of efficacy.

Table 4. Dosing Guidance for Drug Augmentation in Adults with TRD

Antipsychotics, Second-Generation (SGA)	► Aripiprazole: start at 2-5 mg/day; may titrate by 5 mg at weekly intervals (max 15 mg/day); decrease dose 50% if taken with a CYP2D6 inhibitor (fluoxetine, paroxetine, etc.) ► Brexpiprazole: initially 0.5 or 1 mg/day; may titrate by 1 mg at weekly intervals (max 3 mg once daily); decrease dose 50% if taken with a CYP2D6 inhibitor (fluoxetine, paroxetine, etc.) ► Olanzapine: start at 5 mg each evening; may titrate up to 20 mg day. Available as a fixed-dose combination with fluoxetine. ► Quetiapine ER: start at 50 mg each evening; may titrate to 150 mg on evening of day 3 (max 300 mg/day) ► Risperidone: start at 0.25 to 0.5 mg/day; may titrate by 0.5 to 1 mg/day every 3 to 7 days (max 3 mg/day). ► Ziprasidone: start at 20 mg twice daily with meal; may titrate by 40 mg every week (max 80 mg twice daily).		
Bupropion	► Bupropion SR: 150 mg once daily; titrate to 150 mg twice daily as early as after 3 days. ► Bupropion XL: 150 mg once a day; titrate to 300 once daily as early as after 3 days.		
Esketamine nasal spray	**Weeks 1 to 4:** Administer twice weekly Day 1 starting dose: 56 mg Subsequent doses: 56 mg or 84 mg	**Weeks 5 to 8:** Administer once weekly 56 mg or 84 mg	**Week 9 and after:** Administer every 2 weeks or once weekly 56 mg or 84 mg
Lithium	► Start at 300 mg once or twice daily; if needed, may titrate by 300 mg/day every 1 to 5 days to a dose of 600 to 1,200 mg/day in divided doses. ► For most patients, a therapeutic response occurs with serum concentrations between 0.6 and 1.0 mEq/L but some respond to lower concentrations.		
Mirtazapine	► Start at 7.5 or 15 mg at bedtime; from 15 mg, may titrate by 15 mg every 1 to 2 weeks (max 45 mg/day).		
Modafinil	► Start at 100 mg/day for 3 to 7 days; may increase to 200 mg/day.		

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