Initial Treatment in Primary Care for Depression Based on Comorbidities

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Executive Summary

When pharmacotherapy is indicated for the treatment of depression, antidepressants are the treatment of choice. However, there are several subclasses of antidepressants that have slightly different mechanisms of action and adverse effect profile.
Generally, first line pharmacotherapy options include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), mirtazapine or bupropion.[13]
When determining which antidepressant to start, various disease states can influence preferred treatment options for patients with depression as well as side effects, drug interactions and cost.
An evaluation of treatment options in the presence of comorbid conditions is necessary to ensure safe and effective medications are utilized.

Acronym	Acronym Spelled Out or Defined
TCAs	Tricyclic Antidepressants
SNRIs	Serotonin and norepinephrine reuptake inhibitors
SSRIs	selective serotonin reuptake inhibitors
MAOIs	Monoamine Oxidase Inhibitors
CrCl	Creatinine Clearance (calculated)
CV	Cardiovascular
ESRD	End Stage Renal Disease
CKD	Chronic Kidney Disease

Diagnosis	Drug of Choice	Additional Notes
Cardiac Disease[4,5,15-17,28,36,40,45]	SSRIs, could consider SNRIs or bupropion	▪ Caution with TCAs ▪ The presence of depression increases the risk of cardiovascular disease and the rate of mortality post-myocardial infarction ▪ If SNRIs or bupropion are used, monitoring for cardiac symptoms such as hypertension and tachycardia should occur ▪ Doses of citalopram should not exceed 40 mg/day (20 mg/day in patients over 60 years of age or those with hepatic impairment) due to increased risk of dose-dependent QTc prolongation
Diabetes[14,25,33]	SSRIs	▪ Caution with: TCAs ▪ Some evidence suggests TCAs may be associated with worsening glycemic control
Epilepsy[2,20,22,34]	SSRIs or SNRIs, some anticonvulsants (see 5.e.)	▪ Avoid: TCAs, bupropion ▪ TCAs and bupropion may lower seizure threshold ▪ SSRIs and SNRIs are the least likely to increase the risk of developing seizures ▪ Some anticonvulsants (e.g. carbamazepine, valproate, lamotrigine) may also provide some benefit in the treatment of mood disorders such as depression
Glaucoma[24]	Agent lacking anticholinergic activity	▪ Caution with: agents with potent anticholinergic activity (e.g. TCAs, paroxetine, venlafaxine) as this may precipitate acute narrow-angle glaucoma in susceptible individuals
Hepatic dysfunction[21,27,30,39]	SSRIs	▪ Avoid in hepatic impairment: duloxetine, nefazodone, isocarboxazid, phenelzine, tranylcypromine ▪ SSRIs are the safest options for patients with chronic liver disease based on side effect profile and high therapeutic index although lower doses may be required ▪ If an antidepressant is initiated, response to treatment, need for dosage adjustments and emergency of side effects should be monitored
HIV and Hepatitis C[11]		▪ More studies need to be done to evaluate the efficacy of different classes of antidepressants ▪ Desvenlafaxine may be used due to minimal hepatic metabolism if patient has adequate payer source

Diagnosis	Drug of Choice	Additional Notes
Hypertension[38,42]	SSRIs	▪ Caution with: bupropion, SNRIs ▪ Trazodone and TCAs may interact with alpha blockers by antagonizing the same receptor the alpha-1 receptor
Insomnia[13]	mirtazapine (doses < 60 mg/day), paroxetine	▪ Could consider: trazodone, prazosin (if insomnia associated with nightmares) ▪ Caution with: bupropion, SNRIs ▪ Low dose TCAs may also be used to improve sleep architecture, though consider risks
Obesity[1,8,46]	bupropion	▪ Caution with: mirtazapine, TCAs, MAOIs ▪ Bupropion is generally weight neutral and has been associated with modest weight reduction ▪ SSRIs and SNRIs have the potential to cause weight gain ▪ Caution should be warranted when using antidepressants in individuals diagnosed with an eating disorder due to increased risk for electrolyte abnormalities and seizures
Osteoporosis[7]		▪ Caution with: SSRIs, TCAs ▪ SSRIs and TCAs may increase risk of falls and fractures ▪ Impact of other antidepressants on fracture risk is unclear due to lack of evidence
Renal dysfunction[9,19,21,30]	SSRIs	▪ Avoid if CrCl < 30 mL/min: duloxetine ▪ Avoid in severe renal impairment: isocarboxazid, phenelzine ▪ Moderate to advanced CKD and ESRD have generally been excluded in antidepressant trials because of adverse events concerns ▪ SSRIs likely a prudent choice due to established safety in CV disease although lower doses may be required ▪ If an antidepressant is initiated, response to treatment, need for dosage adjustments and emergence of side effects should be monitored
Pain Syndromes[6,10,12,26,29]	SNRIs, low dose TCAs	▪ Overall, antidepressant treatment has been associated with a reduction in pain symptoms ▪ Neuropathy: TCAs and duloxetine have been shown to be effective in alleviating neuropathic pain ▪ Fibromyalgia: Duloxetine and milnacipran are both indicated for treatment, amitriptyline also has been associated with reducing fibromyalgia-related pain ▪ Migraine/Tension-type Headaches: TCAs show greater efficacy than SSRIs, but SNRIs also have some evidence for efficacy
Parkinson's Disease[18,37]	SNRIs or bupropion	▪ SSRIs may be used, but pose a potential risk of worsening Parkinson's disease symptoms (increases in "off" time and exacerbation of tremor) ▪ Bupropion provides some beneficial effect, but may cause symptoms of psychosis in some patients due to its dopaminergic activity ▪ MAOIs (tranylcypromine, phenelzine, isocarboxazid) may interact with L-dopa products
Sexual Dysfunction[13,23,41,44]	bupropion, mirtazapine	▪ Caution with: SSRIs, SNRIs, TCAs ▪ Bupropion and mirtazapine have been associated with less risk for sexual dysfunction than other antidepressants and may be added to existing SSRI therapy ▪ Studies have found rates of sexual dysfunction in untreated depression can range from 25 to 75%
Stroke[3,31,32,35,43]	SSRIs	▪ The presence of depression one month following stroke has been associated with an increased mortality ▪ SSRIs (fluoxetine, sertraline, and citalopram) and nortriptyline have shown benefit in the treatment of depression post-stroke

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Switching Between Antidepressants and Antipsychotics

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Executive Summary

In recent years, there has been an increase in the number of adults taking an antidepressant or antipsychotic in the United States.[2] Although there are some patients that have been able to take the same antidepressant or antipsychotic for long durations, there are a few reasons that may lead to switching agents, such as partial-/non-response, adverse effects, cost and drug-drug interactions.

When considering a medication switch, a primary concern is precipitating withdrawal symptoms (i.e. if switching to a medication with a different mechanism of action and increasing the risk of relapse or destabilization).

While there are no specific guidelines for switching between antidepressants or antipsychotics, there are several strategies available with pros and cons to each approach. There are three key factors that should always be taken into consideration when determining the most appropriate strategy when switching medications within these classes. They are:

1. Patient preference/agreeability
2. Indication for use
3. Risk vs. benefit

Withdrawal symptoms are possible when switching between agents with different half-lives or mechanisms of action. Consider the cross-taper approach when these factors are present.

Antidepressants[4-6]

See **Table 1.1** for major approaches in switching agents

Key Takeaways:

- Individualize based on tolerability/symptom reemergence
- Direct switch: existing antidepressant is stopped one day and the new antidepressant is started the following day
  - Preferably used when switching to an agent within the same class
- Cross-taper: existing antidepressant gradually reduced while the new antidepressant is initiated and dose titrated to therapeutic level
  - Usually done over 1 to 2 weeks
- In general, cross-taper is preferred when possible
- Equivalent dose conversions for antidepressants have not been clearly defined

Table 1.1 – Pros and Cons of Switching Strategies (Antidepressants)

Approach	Pros	Cons
Direct switch	No washout period	▪ Limited to use in specific drug classes ▪ May precipitate discontinuation syndrome if have slightly different mechanisms of action
Cross-taper	▪ Reduces symptom recurrence ▪ Minimizes withdrawal symptoms ▪ No washout period required ▪ Beneficial for patients at higher risk of relapse	▪ Risk of drug interactions ▪ Dependent on frequency of dose adjustments

Antipsychotics[1,3,5,7]

See **Table 2.1** for major approaches in switching agents

Key Takeaways:

- Individualize based on tolerability/symptom reemergence
- Abrupt switch: existing antipsychotic is stopped one day and the new antipsychotic is started the following day
  - Cross-titration: slowly tapering the existing antipsychotic while concomitantly increasing the dose of the new antipsychotic
    - For outpatient tapering schedules, ideal dose adjustments may occur every 1 to 3 weeks
  - Overlap and discontinuation: slowly increase dose of the new antipsychotic to a therapeutic dose, then slowly taper the existing antipsychotic
  - Depending on indication, cross-taper is preferred (e.g. schizophrenia)

Table 2.1 – Pros and Cons of Switching Strategies (Antipsychotics)

Approach	Pros	Cons
Abrupt switch	▪ Simplest approach	▪ May be best carried out in an inpatient setting ▪ Increased risk for precipitating discontinuation symptoms
Cross-titration	▪ Most common approach ▪ Lower risk of relapse	▪ Increased risk for adverse effects ▪ Potentially inadequate antipsychotic doses (temporarily)
Overlap and discontinuation	▪ Most conservative approach ▪ Most preferred for patients with high risk of relapse	▪ Overlap of two antipsychotics ▪ Increase likelihood of adverse effects ▪ Risk of planned taper does not occur

- Equivalent dose conversions for second-generation antipsychotics have not been defined
  - First-generation antipsychotics can be converted with chlorpromazine equivalents
- Consider mechanisms of action of existing and new antipsychotic as activity at different receptors may precipitate different withdrawal symptoms
  - Discontinuing agents with high histamine receptor affinity may lead to rebound insomnia
  - Discontinuing agents with potent anticholinergic activity may lead to cholinergic rebound

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Tapering Antidepressants and Antipsychotics

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Executive Summary

Antidepressants are one of the primary treatments for depression and are among the most frequently used therapeutic medications in the United States, according to the Centers for Disease Control and Prevention. Patients who wish to discontinue the use of antidepressants and/or antipsychotics will require some additional clinical considerations.

Prolonged use of antidepressants can cause withdrawal syndromes if discontinued abruptly, in addition to the possibility of relapse and exacerbation of depression. Thus, tapering (i.e. gradual dose reduction) is required to help decrease risks and severity of complications for patients.

When it comes to discontinuing antidepressants, there are no specific guidelines on tapering antidepressants that have been published; however, there are numerous publications that provide appropriate tapering schedules.[6]

General Key Takeaways

- Encourage patients to utilize non-pharmacologic techniques (e.g. exercise, sleep) for symptom reduction and to seek support (e.g. family, friends) throughout the tapering process.
- Tapering strategies will depend on medication, duration of use, current dose and any symptoms experienced during previous discontinuations.
- Individualize based on tolerability and symptom reemergence.

Antidepressants[2-4,6,10]

Important to consider medication's mechanism of action as activity at different receptors may precipitate different withdrawal symptoms (See Table 1.1)**.** Withdrawal symptoms typically emerge within hours to days after dose reduction.

Key Takeaways

- Tapering is required if medication was used for longer than 6 weeks.
  → With the exception of fluoxetine, due to its long half-life.
- Tapering strategies will depend on medication, duration of use, current dose and any symptoms experienced during previous discontinuations.
  - In general, gradually reduce the dose over a minimum of 4 weeks with dose reductions every 1 to 4 weeks.
    - The frequency of dose reductions may depend on the patient's readiness in stopping medication and a provider's comfortability with the patient following tapering directions, etc.
    - Medications with shorter half-lives (e.g. venlafaxine, paroxetine) may require a longer taper schedule.
    - If withdrawal symptoms emerge after dose decrease, may need to re-increase dose.

Table 1.1 - Receptor-based Discontinuation Symptoms		
RECEPTOR ACTIVITY	SYMPTOMS	MEDICATION CLASSES
Serotonergic	Flu-like symptoms, insomnia, anxiety, paresthesia	SSRIs, SNRIs, TCAs, mirtazapine, vortioxetine, trazodone, vilazodone
Alpha- or beta- adrenergic	Tachycardia, hypertension, rebound anxiety or restlessness, sweating, tremors, headache	SNRIs, TCAs, bupropion, mirtazapine, trazodone
Cholinergic	Nausea, vomiting, sweating, headache, abdominal cramping, muscle spasms, urinary urgency	TCAs, some SSRIs/SNRIs (paroxetine, venlafaxine)
Histaminergic	Activation, insomnia, mild anticholinergic withdrawal (headache, sweating, nausea)	TCAs, mirtazapine, trazodone

Antipsychotics[1,5]

See Table 2.1 for various antipsychotics tapering strategies.

Key Takeaways

Several antidepressants are indicated for anxiety and anxiety-related disorders

- Same strategies described above may be followed if being used for anxiety
- May require longer taper schedule as anxiety disorders typically have higher target doses

Table 2.1 – Antipsychotics Tapering Strategies			
Generic Drug	Withdrawal Symptoms	Taper	Notes
Benzodiazepines	Rebound anxiety, headache, sleep disturbances, irritability, agitation, convulsions, tremors, nausea and vomiting	Required if taken for 2 weeks or longer: Strategies: 1. 25%/week for 2 weeks, then 12.5% every 4-7 days based on tolerability 2. Reduce dose by 10% every 1-6 weeks	Taper schedule over 4-8 weeks is typically appropriate
Gabapentin	Anxiety, agitation, insomnia, fatigue, irritability, headache, sweating, pain, dizziness, sensitivity to light	Gradually taper over at least 1 week or by 300mg daily every 4 days[9]	Withdrawal symptoms may last up to 10 days[8]
Pregabalin	Headache, anxiety, agitation, confusion, sweating, seizures, insomnia, mood changes	Gradually taper over a minimum of 1 week[6]	Acute withdrawal symptoms last 1 to 2days after stopping, but residual symptoms may last weeks
Buspirone	None	Not required	Drug will be diminished from body with 1-2 days
Hydroxyzine	None	None	None

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Add-on Therapy for Depression and Anxiety

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Executive Summary:

Nearly two-thirds of patients with depression will fail to achieve remission with initial pharmacotherapy. Moreover, 30% of patients will have a less than satisfactory response to four courses of antidepressant pharmacotherapy.

Currently, there are no evidence-based order for selecting augmenting agents, such as: second generation antipsychotic (SGA), lithium, second antidepressant from a different class (e.g. selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI) and thyroid hormone).

Potential reasons for initial non-response should be considered when determining course of treatment:

- Comorbid disorders (e.g. substance abuse)
- Inadequate dose
- Inadequate duration
- Incorrect diagnosis
- Non-adherence
- Adverse events
- Pharmacokinetic factors (e.g. poor metabolizer)
- Unaddressed psychosocial stressors

Add-on therapy should be considered after 4 to 8 weeks with either partial response or no response.

➔ See page 2 and 3 for depression and anxiety add-on therapeutic options.

Table 1.1 - Depression Add-on Therapy Options			
Generic Drug	**Usual Dosing as Adjunct**	**Pros/Tips**	**Cons**
Buspirone	30 to 60 mg/day	▪ May also help with anxiety symptoms ▪ Usually combined with SSRI	▪ Dizziness
Bupropion	150 to 400 mg/day	▪ Often combined with SSRI ▪ May also help to quit smoking	▪ Insomnia (take in the A.M.) ▪ Contraindicated (CI) – seizure disorder, anorexia nervosa ▪ CYP2D6 inhibitor (can increase levels of some SSRIs)
Mirtazapine	7.5 to 45 mg/day	▪ Useful in insomnia (especially lower doses)	▪ Weight gain, sedation
Tricyclic Antidepressants	Amitriptyline (75 to 150 mg) Nortriptyline (75 to 150 mg) Doxepin (25 to 300 mg)	▪ Third-line adjunct option ▪ Some can help with insomnia ▪ Chronic Migraine prevention ▪ Chronic Pain syndrome	▪ Lethal in overdose – caution use in suicidal patients ▪ Anticholinergic, cardiovascular and neurological side effects
Second Generation Antipsychotics (SGA)	Aripiprazole (2.5 to 15 mg) Brexipiprazole (0.5 to 3 mg) Quetiapine (25 to 400 mg) Olanzapine/Fluoxetine (6mg/25mg to 18mg/75mg) Risperidone (0.5 to 2 mg)	▪ FDA approved – Aripiprazole, Brexipiprazole, Olanzapine/Fluoxetine, Quetiapine ▪ Usually lower doses than used in schizophrenia and bipolar	▪ Side effects – weight gain, akathisia, tardive dyskinesia, EPS
Lithium	600 to 900 mg/day	▪ Extensively studied ▪ Quick response – 48 to 72 hours ▪ Can decrease long-term risk of suicide	▪ Requires lab monitoring ▪ Potential for significant side effects
Stimulants	MPH (10 to 60 mg/day) Modafanil (100 to 400 mg/day)	▪ Useful in targeting fatigue and apathy, for late-life treatment-resistant depression ▪ Combined with SSRI or SNRI	▪ Contraindicated-psychosis, anxiety, insomnia, substance abuse, cardiovascular disease
Triiodothyrine	25 to 50 mcg/day	▪ Response is generally quick ▪ Can be used regardless of thyroid status	▪ Requires BMD monitoring in post-menopausal women ▪ Do no use with CV disease ▪ Thyroid function tests at baseline and 3 months ▪ Potential to induce hyperthyroidism

EPS = *Extrapyramidal symptoms;* **SSRI** = *selective serotonin reuptake inhibitor;* **SNRI** = *serotonin norepinephrine reuptake inhibitor;* **SGA** = *second generation antipsychotic;* **MPH** = methylphenidate; **CV** = *cardiovascular*

Add-on Therapy for Anxiety

An estimated 50% of patients treated for Generalized Anxiety Disorder will not respond to first-line treatment. First line therapy are selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI).

No Response →	Switch to another SSRI or SNRI or consider a second generation antipsychotic (SGA), antihistamine, buspirone or pregabalin.
Partial response →	Titrate to maximum dose and reevaluate at 12 weeks, switch to another agent or augment with another agent.

While benzodiazepines have shown benefit in the short-term use, **long-term use is not recommended** due to the potential for dependence, misuse, and correlation to cognitive decline.

When atypical antipsychotics are used as adjunctive agents for treating anxiety, typically lower doses than those used in schizophrenia and bipolar are used for symptom improvement.

Table 2.1 - Anxiety Add-on Therapy Options

Generic Drug	Usual Dosing as Adjunct	(+) Pros/Tips	(-) Cons
Buspirone	15 to 60 mg/day in divided doses	Slow onset (2 to 4 weeks)	▪ Only modest efficacy ▪ Dosed multiple times daily
Mirtazapine	15 to 60 mg/day	Can also help with insomnia in lower doses	Weight gain, sedation
Hydroxyzine	25 to 50 mg 3 to 4 times daily as needed or at bedtime → max single dose of 100mg	Can also help with insomnia when dosed at bedtime	Anticholinergic side effects, sedating
Gabapentin	300 to 2400 mg in divided doses	Fast onset Renal dose adjustment	Sedation, tolerance and dependence possible
Pregabalin	50 to 600 mg in divided doses	Renal dose adjustment Needs to be tapered on discontinuation	▪ Controlled substance ▪ Risks associated with misuse and potential for addiction & dependence
Aripiprazole	2 to 15 mg/day	Risk of impulse control disorders	▪ SGAs (degree varies by medication) ➢ Metabolic side effects ➢ Risk of extrapyramidal symptoms
Olanzapine	5 to 20 mg/day	Increases appetite	
Quetiapine	50 to 300 mg/day		
Risperidone	0.25 to 3 mg/day	Increases prolactin levels	
Ziprasidone	40 to 160 mg/day in divided doses	▪ Administer with food ▪ QTc prolongation	

EPS = *Extrapyramidal symptoms;* **SSRI** = *selective serotonin reuptake inhibitor;* **SNRI** = *serotonin norepinephrine reuptake inhibitor;* **SGA** = *second generation antipsychotic;* **QTc** = *the duration of the QT interval adjusted for the patient's heart rate. Prolonged QTc's are associated with an increased risk of ventricular dysrhythmia and sudden death*

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