Behavioral Health Treatment Guidelines

Developed by: **Kootenai Health Psychopharmacology Study Group**

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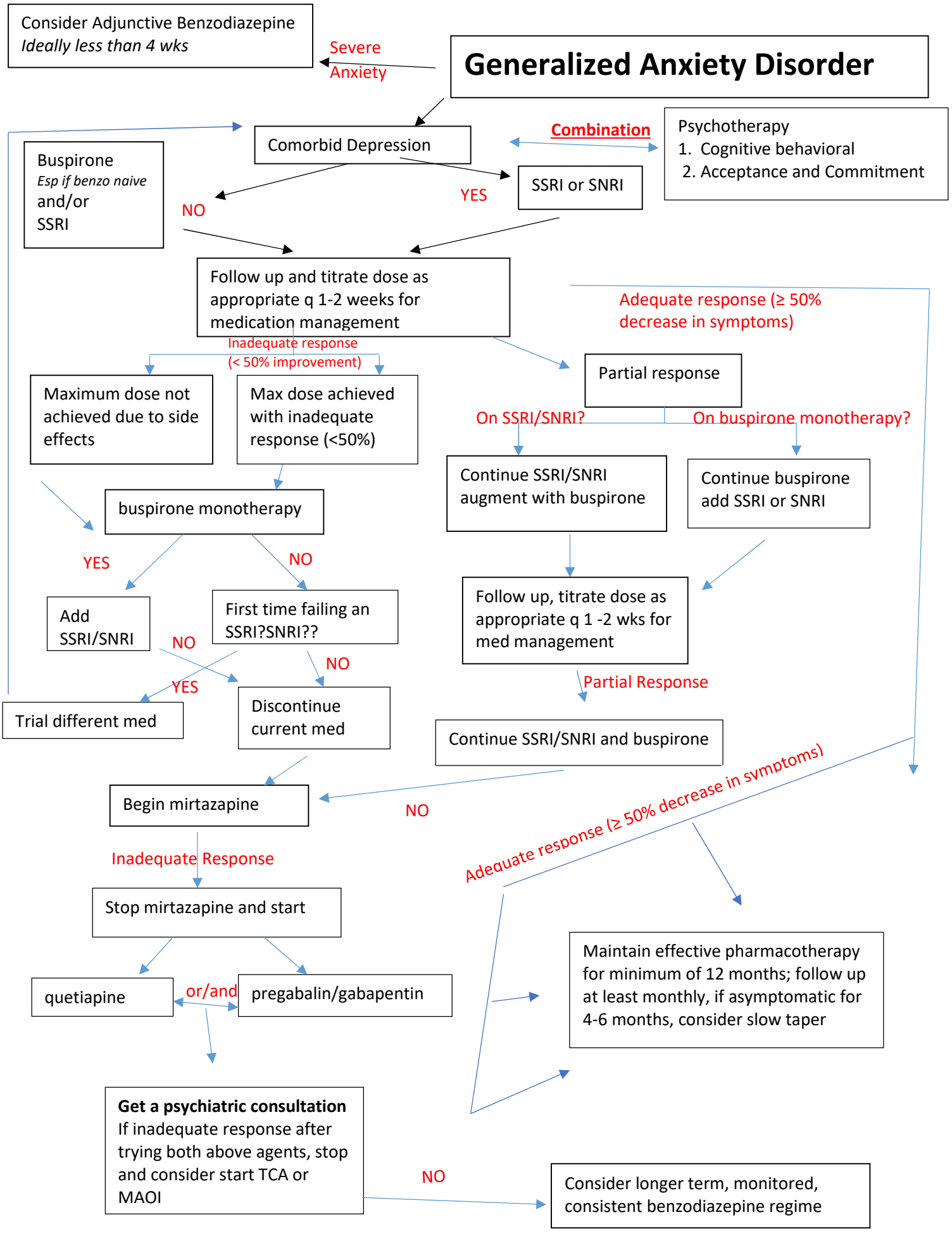
These are guidelines to help with the evaluation, diagnosis and treatment of common behavioral health issues. There are situations which these guidelines do not cover, or where the suggested path may not be appropriate for the unique clinical scenario. If questions arise, a thorough evaluation and appropriate consultation is encouraged.

Anxiety Disorders Treatment Guidelines: Focus on GAD, Panic Disorder, PTSD and OCD

Developed by: Russ Symbal, RPh, BCPP; Leanne Rousseau, MD; Stephanie Sargent, MD; Lauren Fletcher, PharmD; Nathan Bertsch, PharmD; William H. Miller, MD


Generalized Anxiety Disorder
Severe Anxiety
Consider Adjunctive Benzodiazepine
Ideally less than 4 wks
Comorbid Depression
Combination
Psychotherapy
1. Cognitive behavioral
2. Acceptance and Commitment
Buspirone
Esp if benzo naive
and/or
SSRI
YES
SSRI or SNRI
NO
Follow up and titrate dose as appropriate q 1-2 weeks for medication management
Adequate response (≥ 50% decrease in symptoms)
Inadequate response
(< 50% improvement)
Partial response
Maximum dose not achieved due to side effects
Max dose achieved with inadequate response (<50%)
On SSRI/SNRI?
On buspirone monotherapy?
Continue SSRI/SNRI augment with buspirone
Continue buspirone add SSRI or SNRI
buspirone monotherapy
YES
NO
Add SSRI/SNRI
First time failing an SSRI?SNRI??
Follow up, titrate dose as appropriate q 1 -2 wks for med management
NO
NO
YES
Partial Response
Trial different med
Discontinue current med
Continue SSRI/SNRI and buspirone
Begin mirtazapine
NO
Adequate response (≥ 50% decrease in symptoms)
Inadequate Response
Stop mirtazapine and start
Maintain effective pharmacotherapy for minimum of 12 months; follow up at least monthly, if asymptomatic for 4-6 months, consider slow taper
quetiapine
or/and
pregabalin/gabapentin
Get a psychiatric consultation
If inadequate response after trying both above agents, stop and consider start TCA or MAOI
NO
Consider longer term, monitored, consistent benzodiazepine regime

Anxiety Disorders Treatment Guidelines: Focus on GAD, Panic Disorder, PTSD and OCD

Overview

Psychotherapy

- Cognitive Behavioral Therapy (CBT), Eye Movement Desensitization and Reprocessing (EMDR), Trauma Focused Therapy, Supportive Psychotherapy are effective for anxiety disorders.
- Different therapies can work for different disorders and **remain the mainstay of effective treatment.**
- Relaxation techniques are often helpful and can include deep breathing, meditation, and biofeedback.
- Exercise helps elevate mood and improves overall health.

Medication

- In general, first line pharmacotherapy is SSRI. Start low and go slow with all anxiety disorders to prevent worsening symptoms, but don't be afraid to eventually push the dose
- Remove any stimulants being used
- buspirone can cause less physical dependence than a benzodiazepine but must get to therapeutic dose. buspirone works better for benzodiazepine-naive patients.
- In non-substance abusing patients, reserve using benzodiazepines for severe GAD and Panic disorder and for **short term** treatment only.
- Give medications enough time (6-8 weeks for adequate trial). Do not change medications too soon unless pt is experiencing a significant side effect. If no improvement after several medication changes, refer for psychiatric consultation.
- To reduce relapse, treat for 1 year after pt is symptom free before stopping treatment

GAD-7

- GAD-7 is based on the diagnostic criteria for Generalized Anxiety Disorder described in DSM-IV
- It is also sensitive for severity of social phobia, post-traumatic stress disorder and panic disorder
- A score above 10 indicated further evaluation is required.
- **A diagnosis of an anxiety disorder should not be made on the basis of the GAD-7 score alone.**

Clinical Pearls

- ~38% of patients seen in a medical clinic present with anxiety symptoms.
- Of the 10 most common complaints presenting to primary care, only 10% have a known cause at one year follow-up. Many complaints are anxiety-related like insomnia, abdominal pain, dizziness, headache.
- Medical rule outs must be considered include: cardiac, pulmonary, GI, endocrine, substance abuse, neurological issues.
- Consider co-morbidities commonly associated with anxiety disorders
    - Co-morbidity with depression
        - Administer the PHQ-9 to anxious patients to check for co-morbid depression
        - Significant increase in suicide risk with depression comorbidity
    - Co-morbidity with substance abuse
        - Consider substance dependency screening tool such as CAGE-AID
- Anxiety disorders are disabling. People can lose jobs, relationships, and social connections.
- People are at a greater risk for developing heart attacks and other cardiovascular problems.
- Very helpful to have another person attend the visit to validate symptoms and hear recommendations

Generalized Anxiety Disorder (GAD)

GAD: Diagnosis

3% lifetime risk, 55% female

- Excessive worry, more days than not for 6 months
- Difficulty controlling worry
- 3 of the following:
    - Restlessness or feeling on edge
    - Irritability
    - Easily fatigued
    - Muscle tension
    - Difficulty concentrating
    - Sleep disturbances
- Take a careful medical and psychiatric history to look for cause of anxiety symptoms

GAD: First Line Treatment

- Avoid coffee, alcohol and sympathomimetics
- CBT – more positive result than with benzodiazepine
- Pharmacologic – start low and go slow, at least ½ normal starting dose
    - buspirone (Buspar) – good first choice, much more effective if benzodiazepine-naïve
    - SSRI – **escitalopram, paroxetine**, sertraline, citalopram, fluoxetine
        - **fluvoxamine** (Luvox) - especially with concurrent OCD-type symptoms
    - SSRI – citalopram, escitalopram, paroxetine, sertraline
    - SNRI – venlafaxine, desvenlafaxine and duloxetine
        - may make some patients worse d/t activating effects of norepinephrine
    - Sleep disturbances can be addressed with short term non-benzodiazepine hypnotic agents
    - If severe presentation, add:
        - Benzodiazepines – regular dose, short term (2-6 weeks); **see appendix 1**
            - clonazepam, diazepam: longer acting (12hrs), BID (preferred)
            - lorazepam, alprazolam: short-acting (4 hrs), at least TID

GAD: Second Line Treatment

- CBT
- Switch to a different medication class
    - SSRI to SNRI or vice versa
    - Consider mirtazapine
- If substance abuse is a concern, consider augmentation with buspirone, gabapentin, pregabalin, baclofen, or hydroxyzine
- Consider augmenting with propranolol for significant autonomic symptoms
- Augment with benzodiazepines
    - Longer acting, regular dose, short term (2-6 weeks)
    - When stopping, use a **slow taper** of several weeks
    - Avoid if history of substance abuse
    - Long term use is rarely needed
        - Monitor closely for signs of induced physiologic dependence

GAD: Third Line Treatment

- CBT
- Switch to tricyclic antidepressant (TCA) – imipramine, doxepin
    - Start low, go slow
    - Monitor for side effects (i.e. anticholinergic effects, drowsiness, orthostasis)
- Add low dose quetiapine, olanzapine, risperidone
    - Short term, discuss risks & benefits
- Consider psych consultation
- Consider MAOI

Panic Disorder- *Must rule out medication, substance, cardiac, thyroid, and/or epilepsy issues*

Panic Disorder: Diagnosis - *0.5 – 3.5% lifetime risk*

- Recurrent panic attacks
  - Shortness of breath, smothering sensation
  - Dizziness, palpitations, tachycardia
  - Trembling, sweating, choking
  - Nausea, paresthesias, chest pain
  - Depersonalization, derealization
  - Flushing, fear of dying, fear of "going crazy"
- Followed by one or more of following for at least 1 month:
  - Persistent concern of having additional panic attacks (anticipatory anxiety)
  - Worry about implication of attack
  - Phobic avoidance with significant change of behavior (with or without agoraphobia)
- R/O medical issues with thyroid studies, tox screen, other medications and EKG
- Higher rate of suicide and vascular events

Panic Disorder: First Line Treatment

- Psychotherapy
  - CBT, biofeedback, exposure therapy
  - Very effective, higher levels of functioning and longer rates of success than medication treatment
  - Important in combination with medication
- Pharmacologic
  - **Start low and go slow (take 6 weeks to get to normal therapeutic dosage)**
  - **Continue treatment for at least a year after remission**
  - SSRI – citalopram, escitalopram, paroxetine, sertraline, fluoxetine
    - Higher doses are commonly needed
  - SNRI – venlafaxine, duloxetine, desvenlafaxine
    - Monitor for increased anxiety
  - Consider addition to mitigate anticipatory anxiety:
    - gabapentin, baclofen, or hydroxyzine
    - Benzodiazepines – regular dose, **short term** (6 weeks)
      - clonazepam, diazepam: longer acting (12 hrs), BID (preferred)
      - lorazepam, alprazolam: short-acting (4 hrs), at least TID
      - Significant risk of symptoms returning with taper (20-30%)

Panic Disorder: Second Line Treatment

- CBT
- Augment with benzodiazepines – regular dose, short term (6 weeks)
  - clonazepam, diazepam: longer acting (12 hrs), BID (preferred)
  - lorazepam, alprazolam: short-acting (4 hrs), at least TID
- Switch different class of medication
  - SSRI to SNRI or vice versa
- Switch to TCA
  - imipramine, desipramine, doxepin
    - Start low, go slow, Monitor for side effects

Panic Disorder: Third Line Treatment

- CBT
- Psychiatric consultation
- Add low dose second generation antipsychotic (SGA)
  - quetiapine, olanzapine, risperidone
  - Short term, discuss R&B
- MAOI
  - Dietary restrictions and drug interactions

Post Traumatic Stress Disorder (PTSD)

PTSD: Diagnosis

1-14% lifetime incidence

- Person exposed to a traumatic event
  - Event experienced actual or perceived event of threaten death or serious injury to self or others
  - Response involved intense fear, helplessness, or horror
- Person re-experiences event via:
  - Recurrent re-experiencing of the event (thoughts, dreams
  - Avoidance of stimuli associated with the trauma
  - Numbing of general responsiveness
  - Persistent feelings of increased arousal
    - Irritability, outburst of anger, difficulty falling asleep
    - Hypervigilance, exaggerated startle response
    - Dissociation, de-realization, detachment and absence of emotional reaction
- Symptoms greater than one month
- Common comorbid conditions: substance abuse, major depression, generalized anxiety disorder

PTSD: First Line Treatment

- **Psychotherapy** – first line and throughout treatment
  - CBT, EMDR, Trauma Focused Therapy, Group Therapy
- Pharmacotherapy in conjunction with psychotherapy
  - Pharmacology to treat presenting symptoms:
    - Depression/anxiety: SSRI (sertraline, paroxetine, fluoxetine)
    - Depression: SNRI (venlafaxine)
    - Depression and need sedation: mirtazapine
    - Night terrors: prazosin (adrenergic agonist)
    - Misperception/psychosis/severe anxiety: SGA (quetiapine, olanzapine, risperidone)
    - Anxiety: gabapentin, baclofen, hydroxyzine
    - Avoid benzodiazepines

PTSD: Second Line Treatment

- Reinforce psychotherapy
- Switch to different medication class/combination
- Use other augmentation strategies for symptoms, as in first line treatment
- Consider TCA
  - amitriptyline, imipramine, doxepin
- Resistant night terrors: alpha agonists (guanfacine, clonidine)
- Avoid benzodiazepines
  - May consider gabapentin
    - Start 100 mg q hs. Split dosing may be helpful
    - Titrate slowly , watch for sedation, renal function, edema
    - For anxiety/agitation not much improvement over 1800 mg/day

PTSD: Third Line Treatment

- Consider psychiatric consult
- Reinforce psychotherapy
- Switch to different medication class (TCA)/combination
- Add low dose SGA, especially if presenting with flashbacks and dissociation
  - quetiapine, olanzapine, risperidone
- If cycling, consider mood stabilizer
  - lithium, valproate, lamotrigine

Obsessive Compulsive Disorder (OCD)

OCD: Diagnosis

2-3% lifetime incidence

- Either obsessions (thoughts) or compulsions (behaviors)
- Person recognizes obsessions or compulsions are unreasonable
- Obsessions or compulsions cause marked distress, are time consuming, interfere with person's normal routine, occupational functioning, usual social life and/or relationships
- Strong relationship with depression (63%) and other anxiety disorders (45%)
- Associated with medical issues – rheumatic fever, hypothyroidism, tic disorders

OCD: First Line Treatment

- Psychotherapy, usually in conjunction with an SSRI
    - CBT, exposure therapy
- Pharmacology
    - SSRI
        - fluoxetine, paroxetine, sertraline, citalopram
        - fluvoxamine may be considered
        - OCD often needs higher doses of SSRI's and longer treatment
    - SNRI
        - venlafaxine, desvenlafaxine, duloxetine
        - May make some patients worse
    - Benzodiazepines are not effective

OCD: Second Line Treatment

- Ensure adequate dosage and length of trial (at least 8 weeks)
- Switch to fluvoxamine or different SSRI
- Continue to reinforce psychotherapy

OCD: Third Line Treatment

- Psychiatric consultation
- TCA after 2 or 3 failed trials with SSRI **and** CBT
    - imipramine, clomipramine
    - Monitor side effects and drug interactions
- Continue to reinforce psychotherapy
- Trial of mirtazapine
- Carefully combine SSRI (fluvoxamine) with clomipramine
    - Watch for serotonin syndrome and amplification of other side effects
- Consider augmenting with SGA
    - quetiapine, olanzapine, risperidone
- Consider augmenting with mood stabilizer
    - lithium, lamotrigine
- Consider augmenting with antianxiety agent
    - buspirone, gabapentin, clonidine
- Consider MAOI
- ECT, neurosurgery

Anxiolytic Pharmacology

Benzodiazepines

Targets GABA receptors, enhancing GABA activity in the brain, depressing the nervous system

- Low-potency, long-acting benzodiazepines (chlordiazepoxide, clonazepam, diazepam)
  - Safer and effective
- High-potency, short-acting benzodiazepines (alprazolam, lorazepam)
  - Effective
  - Higher risk of inter-dose rebound symptoms
  - Higher risk of dependence
- Goal is **short term use** for stability (4 -8 weeks)
  - Avoid long term, daily, chronic PRN use of benzodiazepines
    - Careful monitoring of increased frequency of use
    - Careful counseling to avoid regular use
  - Long term use is rarely necessary, but can be helpful for some patients
    - monitor for dependence
    - Attempt periodic tapers
- Start at low doses
  - Sedation is a common side effect, but tolerance to sedation develops over time
  - Side effects include ataxia, depression, dizziness, confusion, **disinhibition**
  - Rarely produces anterograde amnesia
  - **Overdose usually with other CNS depressants: alcohol, opiates, barbiturates**
- Discontinuation symptoms divided into three areas (lots of overlap):
  - ½ life and duration of action do not always coincide (see appendix 1)
  - Recurrence of disorder
    - Loss of therapeutic effect
    - Resume treatment
  - Rebound
    - Greater intensity of original symptoms
    - More common with high potency, short-acting benzodiazepines
    - Resume and taper very slowly, ~ 10%/1-2weeks over months
    - Consider switch to long-acting benzodiazepine then taper
  - Withdrawal
    - Original symptoms plus new symptoms such as:
      - tachycardia, increased blood pressure
      - irritability, tremulousness, sweating, diarrhea, seizures, delirium
    - Peak in 1 -5 days, disappear over 3 weeks
    - More common with high potency, short acting benzodiazepines
    - Resume and taper very slowly
    - Consider switch to long-acting benzodiazepine then taper
- Monitor closely in elderly
  - Increase risk of falls
  - Slower metabolism – longer ½ life, higher levels
    - Elevated blood levels especially with longer half-life benzodiazepines

Other Anti-Anxiety Agents

gabapentin (Neurontin) – inhibits glutamate

- Start 100 mg QHS; split dosing may be helpful
- For insomnia, start with 100 mg QHS, increase by 100 mg each night to a max dose of 300 mg QHS
- Titrate slowly, monitor for sedation, renal function, edema
- May use higher doses for neuropathy/pain
- For anxiety/agitation not much improvement over 1800 mg/day
- Excreted in the urine
- Available as tablet, liquid, capsule

pregabalin (Lyrica) – Ca channel blocker

- Dosages between 150 and 600 mg in divided doses
- Effective for GAD
- Especially with bipolar and substance abuse issues
- Excreted in the urine

hydroxyzine – Histamine antagonist

- Sedation, activation, confusion
- Mild anxiety and sedation
- 25 -50 mg up to 4 times daily

Selective Serotonin Reuptake Inhibitors (SSRIs)

- ***They are not the same!*** *Differences noted below, see appendix for detailed side effect profiles*
- *As a group can be more effective in premenopausal women*

- **fluoxetine** (Prozac): also blocks 5-HT_{2c} resulting in enhanced release of NE and DA
  - Some activating effects; useful for some patients, not others
    - Administer in the morning
  - Long $T_{1/2}$ (3 days, 14 days metabolite) – no withdrawal, no need to taper
  - Potent CYP2D6 inhibitor (↑aripiprazole, metoprolol, risperidone, etc.)
- **sertraline** (Zoloft): also a weak dopamine reuptake inhibitor
  - Result ↑energy, motivation, concentration (esp. atypical depression)
  - Few drug-drug interactions, safe in breastfeeding
- **paroxetine** (Paxil): mild anticholinergic effects
  - ↑sedation & calming effects
  - Short $T_{1/2}$ = withdrawal symptoms and cholinergic rebound
  - Potent CYP2D6 inhibitor (↑aripiprazole, metoprolol, risperidone, etc.)
- **citalopram** (Celexa): mild antihistamine properties from the "R" enantiomer
  - Dose limitation due to QTc prolongation
  - Weak CYP2D6 inhibition (may increase beta blockers and other psych meds)
  - May have favorable benefit in treatment of depression in elderly (particularly those with agitation or paranoia secondary to neuropsychiatric symptoms of dementia)
- **escitalopram** (Lexapro): the cleanest SSRI available ("S" citalopram)
  - Best tolerated
  - More effective in lower dose range than citalopram
  - Less QTc prolongation and drug interactions than citalopram
- **fluvoxamine** (Luvox): OCD and anxiety; no indication for depression
  - Sigma receptor agonist = ↑antianxiety effects
  - **Short $T_{1/2}$ requires BID dosing**
  - CYP1A2 inhibitor (clozapine, olanzapine)

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

- ***Better efficacy in post-menopausal females (SSRIs in pre-menopausal females)***
- *Greater efficacy as dosage increases*
- *They also increase DA in the prefrontal cortex (only) thereby have a 3rd mechanism of action (Blocking NE transporters in PFC actually increase DA there but not in other areas)*

- **venlafaxine:** ↑5-HT at low doses, NE at high doses (≥ 225 mg)
  - XR formulation better tolerated – sweating, HBP at doses > 225 mg
  - Withdrawal reactions are common
- **desvenlafaxine (Pristiq):** metabolite of venlafaxine, greater NE effects
- **duloxetine:** 5-HT/NE roughly 1:1 at 40-60 mg/day
  - Effectiveness in depression, pain alone, and depression with pain (SNRIs superior to SSRIs for pain)
  - Split dose if tolerability issues, lower incidence of HTN
  - More side effects (HA, nausea), so need to start at low dose 20- 30 mg

Norepinephrine Dopamine Reuptake Inhibitors

bupropion: relatively low NET and DAT occupancy

- Low DAT allows for efficacy without risk of abuse (occurs when >50% = euphoria, etc.)
- Has slower DAT occupancy makes it useful for ADHD, nicotine addiction
- Increase of DA useful to ↑ energy, ↑ happiness, ↑ pleasure, ↓ sexual dysfunction
- Activating and stimulating, administer in morning – **useful as augmentation medication**
    - Caution combined use with SNRI
- Beware of seizure potential
- XL better tolerated
- Strong CYP2D6 inhibitor; watch for drug-drug interactions

Atypical Antidepressants

mirtazapine: *blocks pre-synaptic α2 auto-receptor (regulates neurotransmitter synaptic release) resulting in increase 5-HT and NE*

- Blocks H_1, $5\text{-}HT_{2a\ \downarrow anxiety}$, $5\text{-}HT_{2c\ \uparrow dopamine}$, $5\text{-}HT_{3\ \downarrow gut}$ resulting in sedation, weight gain, antianxiety, less N/V, less sexual dysfunction
- Combine with SNRI to increases 5-HT and NE via different mechanisms of release
    - = "California Rocket Fuel" – Stephen Stahl
- More sedation at low doses (7.5 mg), increase dose = ↑NE, DA and activation
- Can block the effects of clonidine and guanfacine (alpha-2 agonists)

trazodone: *blocks 5-HT reuptake; antagonist at $5\text{-}HT_{2a\ \downarrow anxiety}$, $5\text{-}HT_{2c\ \uparrow dopamine}$, $5\text{-}HT_{7,}$ various α receptors; blocks $histamine_1$*

- Low doses block 5-HT2a, α1, and histamine1 interfering with monoamine arousal mechanisms resulting in hypnotic effects and augmentation of antidepressants
- Higher doses result in serotonin reuptake inhibition and 5-HT 1D, 2C, 7 and α2 antagonism as well as 5-HT1A agonist actions resulting in its antidepressant effects
- Lacks sexual dysfunction, reduces anxiety and insomnia
    - Good adjunct for sleep with other antidepressants
- Risk for priapism!

Antipsychotics

- ***5-HT1a agonist*** *leads to increased dopamine in the striatum*
    - *reduction of EPS, antidepressant effect, "pines" (clozapine, quetiapine, asenapine) and partial dopamine agonists*
- ***5-HT2c antagonism*** *leads to increased dopamine in the PFC*
    - *antidepressant effect, "pines" (olanzapine, quetiapine)*
- ***5-HT7 antagonism*** *leads to increased 5-HT release downstream*
    - *antidepressant effect, partial dopamine agonists*

- **olanzapine** (Zyprexa): 5-HT2c antagonist, α2 antagonist, 5-HT7 antagonist
    - improves mood, sedating
- **quetiapine** (Seroquel): NET inhibitor, 5-HT7 antagonist, α2 antagonist, 5-HT1a partial agonist
    - Improves mood; sedating, no EPS or prolactin release
    - -50 mg = sedative, 300 mg = antidepressant, 800 mg = antipsychotic
- **aripiprazole (**Abilify): 5-HT1a agonist, 5-HT7 antagonist
    - Improves mood, More metabolic neutral, more akathisia, less sedating
- **risperidone** (Risperdal)
    - MOA: D2 and 5HT2A antagonism
    - Atypical, but becomes more "typical" at higher doses
    - More risk of EPS
    - Can raise prolactin levels even at low doses
    - **Highest rates of sexual dysfunction (60-70%)**
    - Moderate risk for weight gain and dyslipidemia

TCAs: *SNRI, also antihistaminic, anticholinergic, cardiotoxic*

- Secondary amines (amoxapine, desipramine, nortriptyline) increase NE > 5-HT
- Tertiary amines (amitriptyline, clomipramine, doxepin, imipramine) increase 5-HT > NE
- Third-line agents due to toxicity – potentially lethal in overdose
    - Caution use in those with impulsivity or suicidality
- **clomipramine** (Anafranil) – specifically for OCD
    - Most effective
    - Most side effects (orthostasis, constipation, dry mouth)
    - Higher serotonin effect

Augmentation Agents

- **buspirone (**Buspar) – partial agonist serotonin 5-HT1a
    - May reverse some sexual side effects
    - Good first choice for mild/moderate GAD
    - Best in benzodiazepine-naive patients
    - Takes 6 weeks to maximum benefit
    - Slow increase to 20 – 30 mg in divided doses
    - Sedation free
    - Does not produce dependence
- **prazosin** (Minipress**)** – alpha adrenergic receptor antagonist
    - Helps with nightmares, especially with PTSD
    - Side effects: dizziness, drowsiness, fatigue, headache
- **lithium** – role in decreasing suicidality;
    - Adjunct for OCD, target level 0.5
- **propranolol –** beta blocker in CNS,
    - Blocks physical manifestations of anxiety; heart rate and blood pressure

Appendix 1

Benzodiazepine Equivalency Table					
Generic	**Brand Example**	**Peak Onset (Hours)[1-6]**	**Approximate Half-Life (may include active metabolites)[1-9]**	**Approximate Equivalent Dose*[1-4,7-9]**	**Dosage form**
Alprazolam	Xanax®	0.5-1.5	6-27 hours	0.25-1 mg	Tablet
Chlordiazepoxide	Librium®	1-4	3-120 hours	10-25 mg	Capsule
Clonazepam	Klonopin®	1-4	18-50 hours	0.25-1 mg	Tablet
Clorazepate	Tranxene®	1-2	40-120 hours	7.5-15 mg	Tablet
Diazepam	Valium®	0.5-1	40-120 hours	5-10 mg	Tablet
Flurazepam	Dalmane®	0.5-1	47-113 hours	15-30 mg	Capsule
Lorazepam	Ativan®	2-4	10-20 hours	1-2 mg	Tablet
Oxazepam	Serax®	2-3	5-20 hours	15-30 mg	Capsule
Temazepam	Restoril®	0.75-1.5	3.5-20 hours	10-30 mg	Capsule
Triazolam	Halcion®	0.75-2	1.5-5.5 hours	0.25-0.5 mg	Tablet

*All values (derived from 5 mg and 10 mg of diazepam, respectively) are estimates that vary across resources and should only be used as an estimation for conversion. Individualized selection of an approximate equivalent dose value in benzodiazepine tapering requires clinical judgment.

*The half-life of a drug does NOT always correlate with duration of action. It takes a drug about 5 half-lives until it reaches steady state. A single dose of diazepam does NOT last 40-120 hours, for example. This is just the elimination half-life of the drug. Each drug has different pharmacokinetic parameters that determine its' duration (volume of distribution, metabolism, absorption, blood-brain-barrier penetration, protein binding, etc).

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Major Depression Treatment Guidelines

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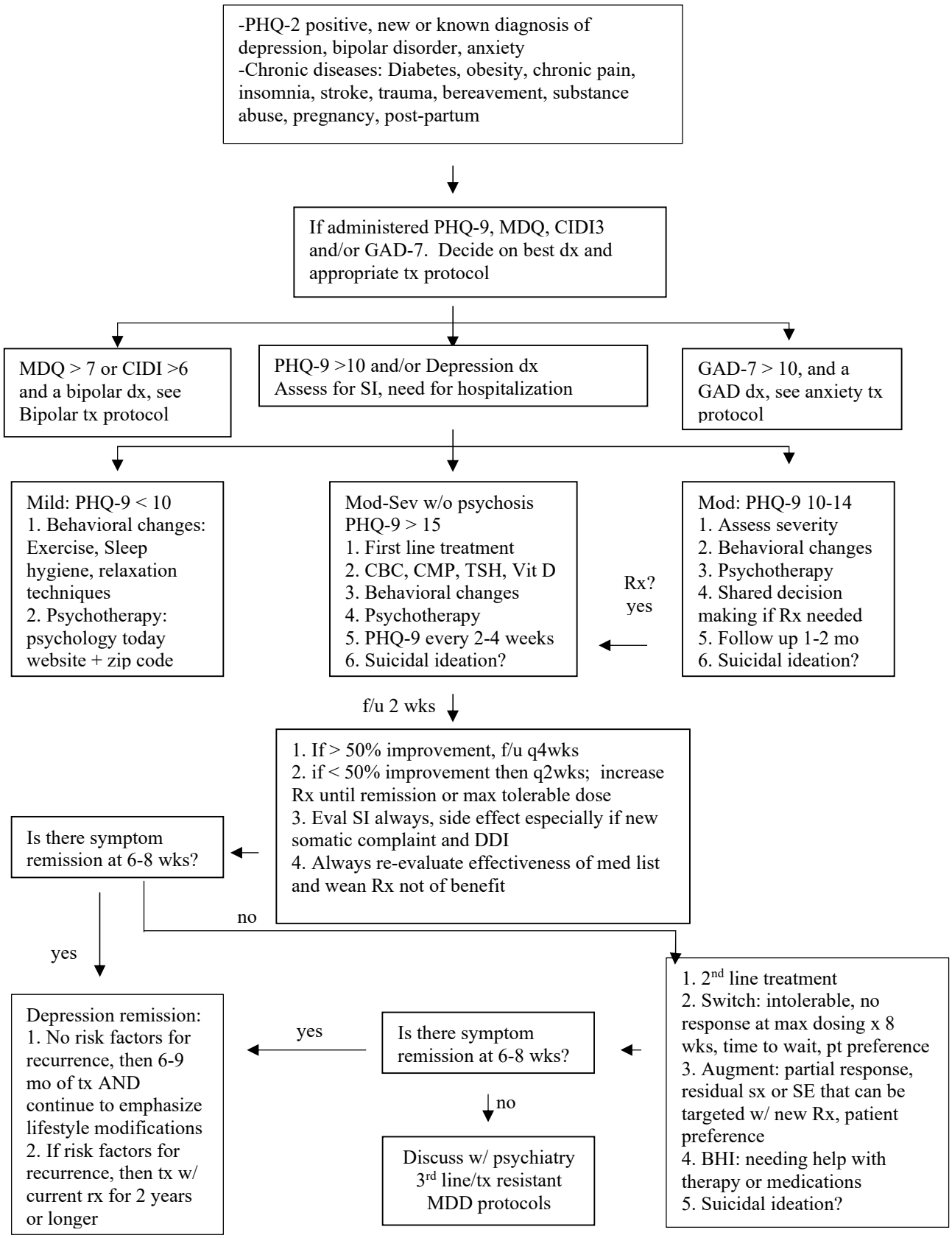
DEPRESSION TREATMENT FLOW CHART



Major Depression Treatment Guidelines

Diagnostic Criteria

5 of following for major depression diagnosis, 2 of the following for dysthymia diagnosis:

1. Depressed mood most of everyday
2. Diminished interest or pleasure in almost all activities
3. Significant wt. loss or gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue/loss of energy
7. Feelings of worthlessness/inappropriate guilt
8. Diminished ability to think/concentrate or indecisiveness
9. Recurrent thoughts of death/suicide

- These symptoms must cause significant stress/impairment in social, occupational, or other areas of function to meet criteria for depression.
- R/O: Cyclic mood disorder, Substance abuse, Medical issues, Bereavement

Rating Scales (PHQ-9, Becks' Depression Scale, Hamilton Depression Scale)

- Low score - Not a substitute for thorough clinical interview or clinical judgment
- High score - Needs follow up discussion prior to treatment
- Helps quantify patient symptoms
- Monitor response to treatment

Depression Pathophysiology

Monoamine Hypothesis: Depressive symptoms are related to deficiencies in serotonin, norepinephrine, and dopamine

- Neurotransmitters increase quickly but the antidepressant response is delayed
- Thought to decrease post-synaptic receptor sensitivity over time resulting in diminished side effects
- 5-HT increase from antidepressants causes pre-synaptic autoreceptors desensitize resulting in an increased outflow of 5-HT into the synapse. The delay is due to the time it takes receptors to desensitize.

Chronic Stress Model: Stress causes HPA axis secretion of glucocorticoids and cortisol which deplete BDNF, leading to a decrease in neurogenesis in the hippocampus

- Antidepressants increase neuronal cell proliferation in the hippocampus
- Ketamine increases of signal transduction cascades and an increase in the density of dendritic spines through BDNF modulation

Treatment Guidelines

Psychotherapy alone should be considered:

- As an initial option for depression if not severely impaired
- As an option for Dysthymia, which often does not respond to medication

Adjunct supports and treatment options

- Psychotherapy should always be an adjunct to medication treatment
- Exercise has been shown to be effective alone and in conjunction with other modalities of treatment
- Adequate sleep very important
  - Educate about appropriate sleep hygiene
  - Possible sleep study, if indicated
- Encourage appropriate nutrition and social interaction

Suicide Risk Assessment (1/2 to 2/3 all suicides diagnosed with depression)

- Document initially and every visit, important even with improvement
- Risk Factors
  - **Severe Anxiety***
  - **Drugs/EtOH***
  - **Psychosis***
  - Previous attempt
  - Family Hx
  - Hopelessness
  - Age

  *most predictive
- Protective Factors
  - Support
  - Religious
  - Future oriented
  - Compliance

Hospitalization

- Acutely suicidal,
- Lack of support,
- Debilitated (poor ADL's),
- Serious concurrent disease,
- Stuporous, agitated, psychotic state

When to treat depression with medication

- Consistent vegetative signs
  - Psychomotor retardation, anhedonia, isolation
- Psychosis
- Severe Anxiety
- P and/or family hx of response to meds
- Consistent decreased functioning work, home, or school
- Not responsive to psychotherapy

Deciding what drug to use

- All drugs about 50-70% effective; differ in side effect profiles (see Appendix)
  - Evaluate interactions between ADEs and comorbid conditions/concomitant medications
  - Assess symptoms and how side effects may be helpful/hurtful
- Past response
- Family member's response
- Elderly /medically ill 50% dosing
- Very anxious slower dosing
- Cytochrome p 450 enzyme system considerations
- See pharmacology section below

Follow-Up and Duration of Treatment

- Frequent contact initially (1-2 wks); Continue to evaluate side effects (see Appendix)
- Repeat PHQ 9 at least monthly
- Give at least 2 wks before increasing dose
- Give at least 6 wks before switching (89%)
- After 6-12 mos of stability, consider slow taper over a month (20-50% decrease in relapse)
- If high risk factors: severe depression: psychosis, SI, gravely disabled, comorbid psych/medical conditions consider longer treatment (up to 2 yrs)
- After ~2 attempts to taper followed by relapse, consider long term treatment
  - Always assess/monitor/document for suicide risk every visit, especially after new Rx
  - Continue to monitor/discuss side effects at every visit

First Line Treatment - Mild to moderate depression

- *Psychotherapy*
  - With mild depression may not need medication,
  - **Strongly recommended with medication**
- *Pharmacology*
  - SSRI, SNRI, mirtazapine, bupropion
    - escitalopram, sertraline good first choice
  - Treat for desired side effects
    - Want activation: bupropion, SNRI (venlafaxine, duloxetine)
    - Want sedation: mirtazapine, or add trazodone
    - Decrease anxiety, ruminations: paroxetine, SSRI
  - Sometimes need to start low and go slow
- *Severe with psychotic features*
  - Antidepressant + Antipsychotic
    - aripiprazole, quetiapine, olanzapine, risperidone
  - May hold off psychotherapy till able to process thoughts
    - Consider psychiatric consult and/or hospitalization

Second Line Treatment

- *Non-response*
  - Maximize dose
  - Switch to different antidepressant in same group (20+%)
  - Switch to antidepressant with different mechanism (20+%)
    - SSRI, SNRI, mirtazapine, bupropion, vortioxetine, TCA
  - **Don't forget Psychotherapy!**
- *Partial response*
  - Maximize dose
  - Augment with antidepressant with different mechanism
    - SSRI, SNRI, mirtazapine, bupropion (avoid SSRI and SNRI combination)
  - **Don't forget Psychotherapy!**

Third Line Treatment –

Treatment Resistant Depression

- **Consider psychiatric consult**
- Optimize dose and duration of treatment
- Re-evaluate medication side effects (see appendix)
- Re-evaluate medical issues
- Re-evaluate substance abuse
- Re-evaluate bipolar diagnosis
- Re-evaluate personality disorder diagnosis
- Re-evaluate medication interactions
- **Pharmacogenetic testing**
  - May be considered for patients with treatment resistant depression, unusual side effects to antidepressants at normal dosing, or those with lack of efficacy to higher doses of drugs.
  - Recommend discussion with psychiatry or pharmacy before proceeding.
- Non-response
  - Re-evaluate switch to different mechanism antidepressant
    - SSRI, SNRI, mirtazapine, bupropion
    - Consider TCA and/or MAOI
- Partial response
  - Re-evaluate augmentation with antidepressant with different mechanism (>20+%)
    - SSRI, SNRI, mirtazapine, bupropion
    - buspirone – may reverse some sexual SE
  - Re-evaluate augmentation with antipsychotic, even if not psychotic (<30%)
    - aripiprazole, quetiapine, olanzapine, risperidone
  - Augment with LiCO2 (40%) (target level 0.5)
  - Consider stimulant in elderly (modafinil, methylphenidate)
- Consider ECT, TMS, ketamine options
- **Don't forget Psychotherapy**

Depression Pharmacology

Selective Serotonin Reuptake Inhibitors (SSRIs)

- ***They are not the same!*** *Differences noted below, see appendix for detailed side effect profiles*
- *As a group can be more effective in premenopausal women*

- **fluoxetine:** also blocks 5-HT_{2c} resulting in enhanced release of NE and DA
  - Accounts for fluoxetine's activating effects; useful for some patients, not others
    - Administer in the morning
  - Long $T_{1/2}$ (3 days, 14 days metabolite) – no withdrawal, no need to taper
  - Potent CYP2D6 inhibitor (↑aripiprazole, metoprolol, risperidone, etc.)
- **sertraline:** also a weak dopamine reuptake inhibitor
  - Result ↑energy, motivation, concentration (esp. atypical depression)
  - **Augment with bupropion get even more DA increase******
  - Few DDIs, safe in breastfeeding
- **paroxetine:** mild anticholinergic effects
  - ↑sedation & calming effects
  - Short $T_{1/2}$ = withdrawal symptoms and cholinergic rebound
  - Potent CYP2D6 inhibitor (↑aripiprazole, metoprolol, risperidone, etc.)
- **citalopram: mild antihistamine properties from the "R" enantiomer**
  - Dose limitation due to QTc prolongation
  - Weak CYP2D6 inhibition (may increase beta blockers and other psych meds)
  - May have favorable benefit in treatment of depression in elderly (particularly those with agitation or paranoia secondary to neuropsychiatric symptoms of dementia)
- **escitalopram: the cleanest SSRI available ("S" citalopram)**
  - Best tolerated
  - More effective in lower dose range than citalopram
  - Less QTc prolongation and drug interactions than citalopram
- **fluvoxamine:** OCD and anxiety; no indication for depression
  - Sigma receptor agonist = ↑antianxiety effects
  - **Short $T_{1/2}$ requires BID dosing**
  - CYP1A2 inhibitor (clozapine, olanzapine)

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

- ***Better efficacy in post-menopausal females (SSRIs in pre-menopausal females)***
- *Greater efficacy as dosage increases*
- *They also increase DA in the prefrontal cortex (only) thereby have a 3rd mechanism of action (Blocking NE transporters in PFC actually increase DA there but not in other areas)*

- **venlafaxine:** ↑5-HT at low doses, NE at high doses (≥ 225 mg)
  - XR formulation better tolerated – sweating, HBP at doses > 225 mg
  - Withdrawal reactions are common
- **desvenlafaxine (Pristiq):** metabolite of venlafaxine, greater NE effects
- **duloxetine:** 5-HT/NE roughly 1:1 at 40-60 mg/day
  - Effectiveness in depression, pain alone, and depression with pain (SNRIs superior to SSRIs for pain)
  - Split dose if tolerability issues, lower incidence of HTN
  - More side effects (HA, nausea), so need to start at low dose 20- 30 mg
- **levomilnacipran (Fetzima):** NE>5-HT activity useful for both depression and fibromyalgia

Norepinephrine Dopamine Reuptake Inhibitors

- **bupropion:** relatively low NET and DAT occupancy
  - Low DAT allows for efficacy without risk of abuse (occurs when >50% = euphoria, etc.)
  - Has slower DAT occupancy makes it useful for ADHD, nicotine addiction
  - Increase of DA useful to ↑ energy, ↑ happiness, ↑ pleasure, ↓ sexual dysfunction
  - Activating and stimulating, administer in morning – **useful as augmentation medication**
    - Caution combined use with SNRI
  - Beware of seizure potential
  - XL better tolerated
  - Strong CYP2D6 inhibitor; watch for drug-drug interactions

Atypical Antidepressants

mirtazapine: *blocks pre-synaptic α_2 auto-receptor (regulates neurotransmitter synaptic release) resulting in increase 5-HT and NE*

- Blocks H_1, 5-HT_{2a} ↓anxiety, 5-HT_{2c} ↑dopamine, 5-HT_3 ↓gut resulting in sedation, weight gain, antianxiety, less N/V, less sexual dysfunction
- Combine with SNRI to increases 5-HT and NE via different mechanisms of release
  - = "California Rocket Fuel" – Stephen Stahl
- More sedation at low doses (7.5 mg), increase dose = ↑NE, DA and activation
- Can block the effects of clonidine and guanfacine (alpha-2 agonists)

vortioxetine *SSRI, agonist at 5-HT_{1a} antidepressant, ↑sex, blocks 5-HT_3 ↓gut and 5-HT_7 ↑cognition*

- Evidence show well tolerated, somewhat higher efficacy compared to other antidepressants
- Claimed to work faster (2 weeks)
- Useful for geriatric depression (↑cognition), "less sexual & GI SEs" numbers don't agree
- Long $T_{1/2}$ – 66 hours - no withdrawal reactions

trazodone *blocks 5-HT reuptake; antagonist at 5-HT_{2a} ↓anxiety, 5-HT_{2c} ↑dopamine, 5-HT_7, various α receptors; blocks $histamine_1$*

- Low doses block 5-HT2a, α1, and histamine1 interfering with monoamine arousal mechanisms resulting in hypnotic effects and augmentation of antidepressants
- Higher doses result in serotonin reuptake inhibition and 5-HT 1D, 2C, 7 and α2 antagonism as well as 5-HT1A agonist actions resulting in its antidepressant effects
- Lacks sexual dysfunction, reduces anxiety and insomnia
  - Good adjunct for sleep with other antidepressants
- Risk for priapism!

vilazodone *blocks 5-HT reuptake; partial agonist at 5-HT_{1A}*

- More immediate and robust elevation of brain serotonin levels
- Essentially an SSRI with buspirone or an atypical antipsychotic added
- Less sexual dysfunction or weight gain
- Titrate upwards due to GI side effects

Antipsychotics

- ***5-HT1a agonist*** *leads to increased dopamine in the striatum*
    - *reduction of EPS, antidepressant effect, "pines" (clozapine, quetiapine, asenapine) and partial dopamine agonists*
- ***5-HT2c antagonism*** *leads to increased dopamine in the PFC*
    - *antidepressant effect, "pines" (olanzapine, quetiapine)*
- ***5-HT7 antagonism*** *leads to increased 5-HT release downstream*
    - *antidepressant effect, partial dopamine agonists*

- olanzapine – 5-HT2c antagonist, α2 antagonist, 5-HT7 antagonist
    - improves mood, sedating
- quetiapine (and norquetiapine) – NET inhibitor, 5-HT7 antagonist, α2 antagonist, 5-HT1a partial agonist
    - Improves mood; sedating, no EPS or prolactin release
    - -50 mg = sedative, 300 mg = antidepressant, 800 mg = antipsychotic
- aripiprazole, brexpiprazole: 5-HT1a agonist, 5-HT7 antagonist
    - Improves mood, More metabolic neutral, more akathisia, less sedating
- lurasidone – 5-HT2a antagonist, 5-HT1a partial agonist, 5-HT7 antagonist improves mood
    - Improves mood; metabolic neutral

TCAs: ***SNRI, also antihistaminic, anticholinergic, cardiotoxic***

- Secondary amines (amoxapine, desipramine, nortriptyline) increase NE > 5-HT
- Tertiary amines (amitriptyline, clomipramine, doxepin, imipramine) increase 5-HT > NE
- Third-line agents due to toxicity – potentially lethal in overdose
    - Caution use in those with impulsivity or suicidality

Augmentation Agents

- **buspirone** – may reverse some sexual ADEs
- **lithium** – role in decreasing suicidality; target level 0.5
- **stimulants (modafinil, methylphenidate)** – consider in elderly; monitor BP
- **L-methylfolate (LMF)** – involved in monoamine synthesis. 2/3 have gene that slows synthesis of LMF from folic acid. 15mg/day as adjunctive treatment shows 30% improvement

Other Agents/Modalities

MAOIs: blocks the enzyme (MAO-A) that metabolizes NE & 5-HT; MAO-B metabolizes DA

- Results in increased neurotransmitters in the synaptic cleft to decrease depression
- phenelzine, isocarboxazid, and tranylcypromine are non-selective MAOIs
- tranylcypromine also has amphetamine-like effects
- selegiline is MAO-B at low doses, non-selective at higher doses
- **Do not use in combination with other antidepressants**
    - Requires washout, seek consultation
- Dietary restrictions (tyramine -> HTN) and DDIs (serotonin syndrome)

ketamine: NMDA receptor antagonist **leads to downstream glutamate release** and increase of signal transduction cascades and **an increase in the density of dendritic spines**

- IV administration (esketamine nasal administration)
- Rapid-acting, but short duration; dissociative effects, HTN

Electro-Convulsive Treatment (ECT)

Done under general anesthesia, in which small electric currents are passed through the brain, intentionally triggering a brief seizure. ECT seems to cause changes in brain chemistry that can quickly reverse symptoms of certain mental health conditions.
Electroconvulsive therapy (ECT) can provide rapid, significant improvements in severe symptoms of several mental health conditions
ECT is used to treat:

- Severe depression, particularly when accompanied by detachment from reality (psychosis), a desire to commit suicide or refusal to eat.
- Treatment-resistant depression, a severe depression that doesn't improve with medications or other treatments.
- Severe mania, a state of intense euphoria, agitation or hyperactivity that occurs as part of bipolar disorder
- Catatonia, associated with schizophrenia and certain other psychiatric disorders. In some cases, catatonia is caused by a medical illness.

ECT may be a good treatment option when medications aren't tolerated or other forms of therapy haven't worked.

- During pregnancy, when medications can't be taken because they might harm the developing fetus
- In older adults who can't tolerate drug side effects
- In people who prefer ECT treatments over taking medications
- When ECT has been successful in the past

Although ECT is generally safe, risks and side effects may include:

- Confusion. Immediately after treatment, you may experience confusion, generally more noticeable in older adults.
- Memory loss. Some people have trouble remembering events that occurred right before treatment or in the weeks or months before treatment or, rarely, from previous years. For most people, these memory problems usually improve within a couple of months after treatment ends.
- Physical side effects. On the days of an ECT treatment, some people experience nausea, headache, jaw pain or muscle ache. These generally can be treated with medications.

Medical complications as with medical procedures involving general anesthesia

Trans-Magnetic Stimulation (TMS)

- Noninvasive form of brain stimulation in which a changing magnetic field is used to cause electric current at a specific area of the brain through electromagnetic induction.
- Does not require general anesthesia
- Repetitive TMS can be considered when standard treatments for depression, such as medications and talk therapy (psychotherapy) don't work.
- Adverse effects of TMS are rare, and include fainting and seizure. Other potential issues include discomfort, pain, hypomania, cognitive change, hearing loss, and inadvertent current induction in implanted devices such as pacemakers or defibrillators.
- In 2008, the US Food and Drug Administration authorized the use of TMS as a treatment for depression that has not improved with other measures.
- Research on the efficacy of TMS in non-treatment-resistant depression is limited

Pearls on Initial Prescribing

- **Always evaluate, monitor and be aware of side effects of *all medications* prescribed to patient**
- **If possible give antidepressant enough time at an adequate dose before stopping**
- **Be aware of polypharmacy**
    - Taper off meds if not helpful after adequate dose and trial
    - The higher the dose and the longer the patient has been on any antidepressant, the slower and longer the taper should usually be.
- SSRIs for anxious (go slow), OCDish, slightly activating, no help with sleep but helps ruminators, needs slow taper, sexual side effects; GI ADEs lower dose, go slow
    - **escitalopram, sertraline** good first choices
    - **paroxetine** known for antianxiety effect (go slow)
    - All SSRIs good for OCD; **fluvoxamine** and **clomipramine** (TCA) specifically for strong OCD
- **mirtazapine** if sleep problems the major concern; serotonin, norepinephrine and antihistamine stimulator, wt. gain, lower doses better sleep
- **bupropion** is norepinephrine, some dopamine focused, most activating, ↑ seizure risk, less risk of inducing cycling, watch for hypertension in higher doses, less sexual ADEs; ↑anxiety, ↓ smoking
- SNRI: serotonin and norepinephrine (less than TCA)
    - **venlafaxine** faster onset, needs slower taper, serotonin in lower doses norepinephrine in higher doses, watch for hypertension in higher doses
    - **duloxetine** similar to venlafaxine
        - Very effective for depression
        - Start duloxetine dosing at 20-40mg if hx of intolerance to antidepressants .
        - Approved for chronic pain
        - May need higher doses for chronic pain
        - May have more SE
        - High incidence of nausea, dyspepsia, and dizziness that leads to discontinuation in clinical practice.
- SSRI & SNRI affect clotting with hx GI, CNS bleed especially with NSAIDS
- All antidepressants can rarely cause priapism, **trazodone** known as higher risk
- **trazodone** - serotonin agonist, is good adjunct for sleep with other antidepressants (Priapism!)
- If severe anxiety; consider short term benzodiazepine,
    - Avoid long term use, taper when stable
    - If concerns about SA then consider **gabapentin, baclofen, hydroxyzine**, low dose neuroleptic
- Duloxetine, bupropion > fluoxetine, sertraline:
    - Watch out for insomnia or sleep disturbances (muscle jerks, jumpy legs).
    - Watch for tremors or abnormal muscle jerks with more activating antidepressants
    - Please assess this before starting patient on a medicine for essential tremors.
- Patients with IBS-D and anxiety/depression respond well to SSRIs/TCAs. Slow titration is critical. TCAs may actually be more effective, even at lower dosing (amitriptyline 10-25mg works for many)

Table 7. Prevalence of Adverse Events among Newer Antidepressants: Unadjusted Frequency (%) of Common Adverse Events as Reported in Product Monographs.

	Nausea	Constipation	Diarrhea	Dry Mouth	Headaches	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased Appetite	Weight Gain	Male Sexual Dysfunction
Citalopram	21		8	19				3	3	2		5	11		8	4			9
Escitalopram	15	4	8	7	3	6	4	2	2		8	5	3		2		2	2	10
Fluoxetine	21			10			13	14	12		16		8	9	10	11			2
Fluvoxamine	37	18	6	26	22	15	26	2	2	16	14		11	5	11	15			1
Paroxetine	26	14	11	18	18	13	23	5	5	2	13		11	15	8		1		16
Sertraline[a]	26	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1		16
Desvenlafaxine[b]	22	9		11		13	4	<1	3		9	7	10		2				6
Duloxetine	20	11	8	15		8	7		3		11	8	6		3				10
Levomilnacipran	17	9		10	17	8			2		6		9						11
Milnacipran	12	7		9	10				4		7	3	4		3				
Venlafaxine IR	37	15	8	22	25	19	23	13	6	2	18		12	12	5	11			18
Venlafaxine XR	31	8	8	12	26	20	17	10	2	3	17		14	8	5	8			16
Agomelatine[c]	C	C	C		C	C	C		C		C	C	C						
Bupropion SR[d]	11	7	4	13	28	7	3	5	5	2	8		2	2	3				
Bupropion XL	13	9		26	34	6			5	2	16				3				
Mirtazapine		13		25		7	54							8	7		17	12	
Moclobemide	5	4	2	9	8	5	4	4	3	5	7	3	2	1	5				
Vilazodone[e]	24		29	7	14	8	5				6	3					3	2	5
Vortioxetine[f]	23	4	5	6		5	3				3	3	2						<1

When data from multiple doses were reported separately, the data from the minimum therapeutic dose were used (indicated by footnotes). Data sources and references are available in Supplemental Table S3. Clear cells represent 0% to 9%; shaded cells, 10% to 29%; and black cells, 30% and higher.

[a]Data from all indications.

[b]Data from 50-mg dose.

[c]C, common effects, ≥1% and <10%.

[d]Data from 100- to 150-mg dose.

[e]Data from 40-mg dose.

[f]Data from 10-mg dose.

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Bipolar Disorder Treatment Guidelines

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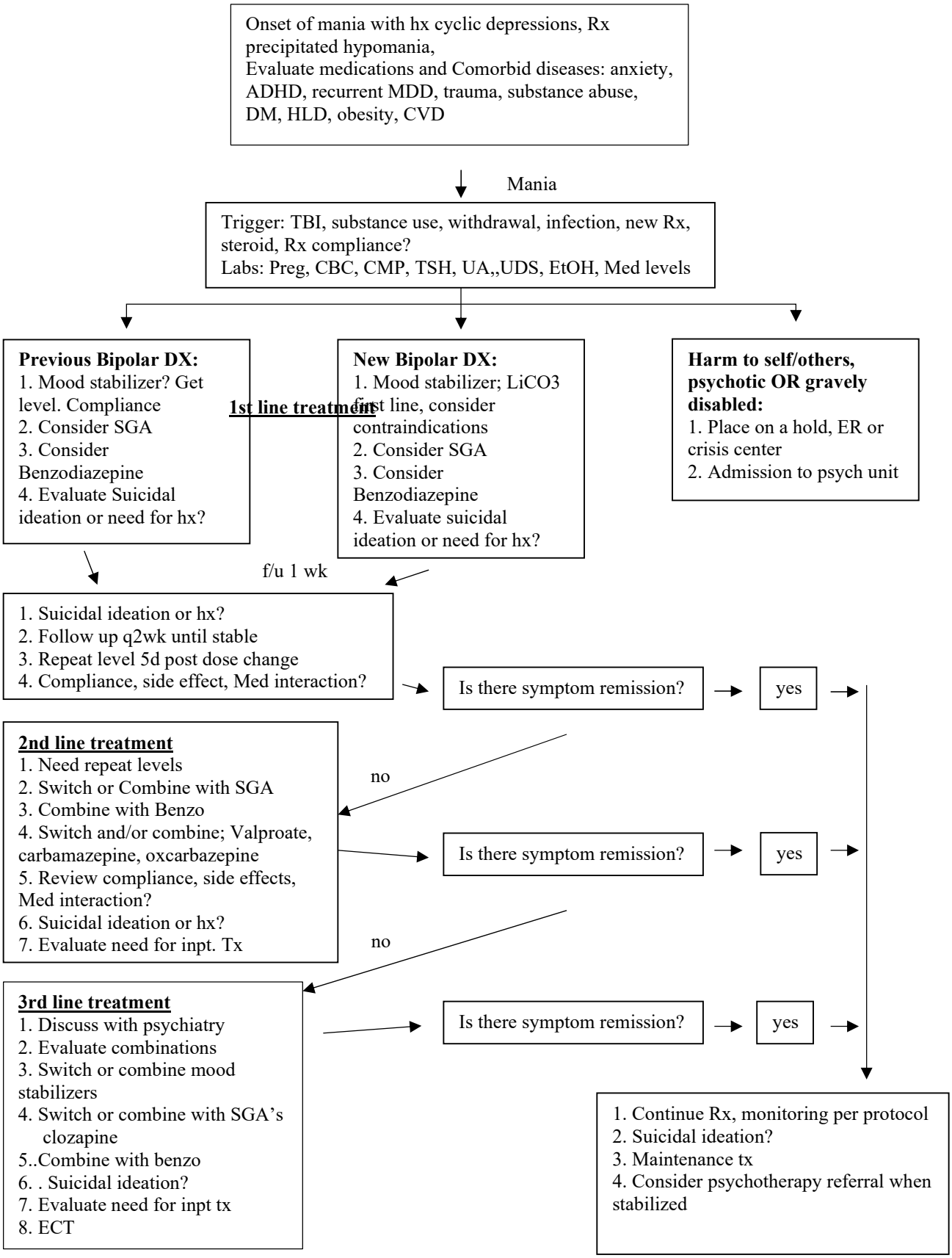
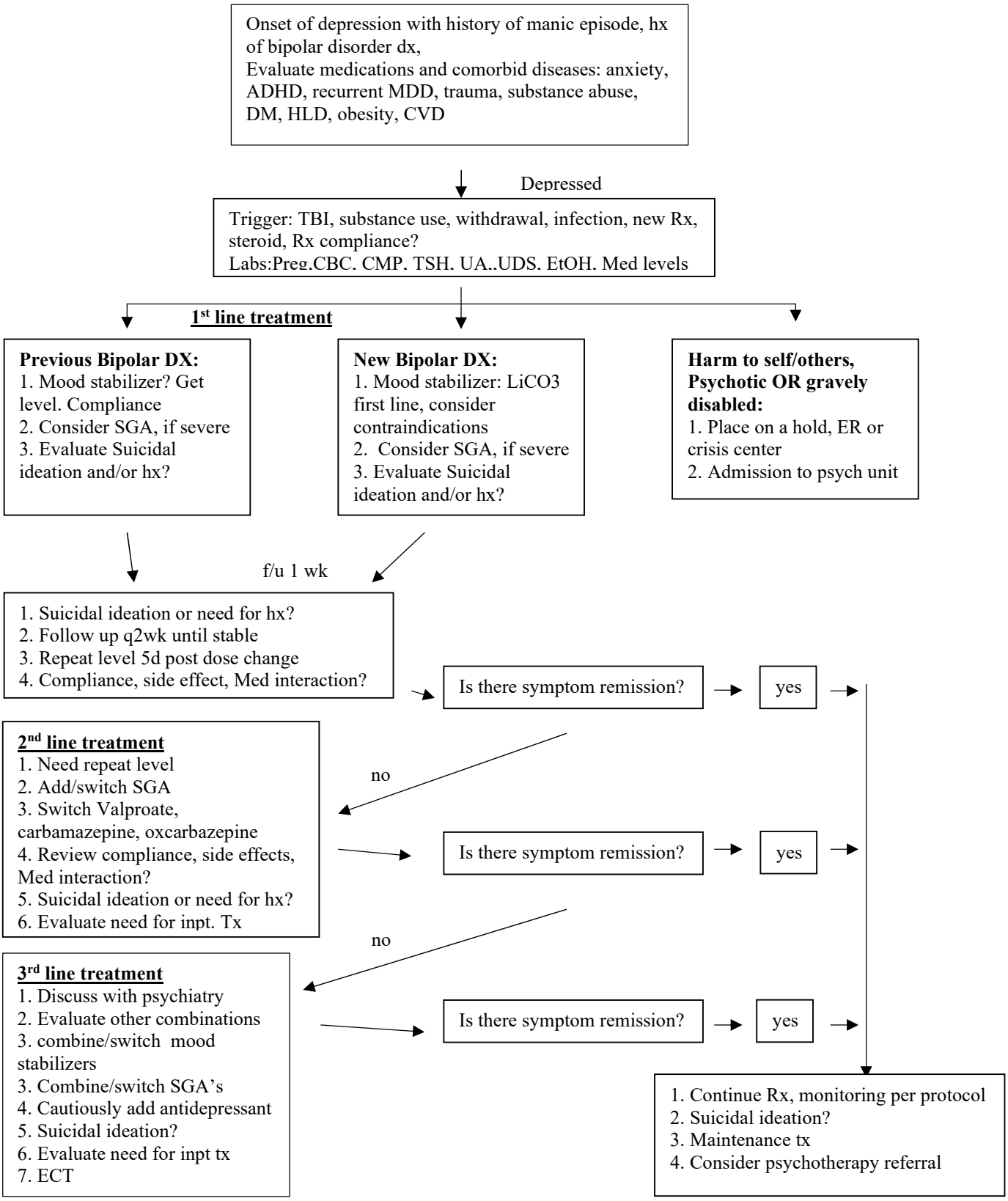
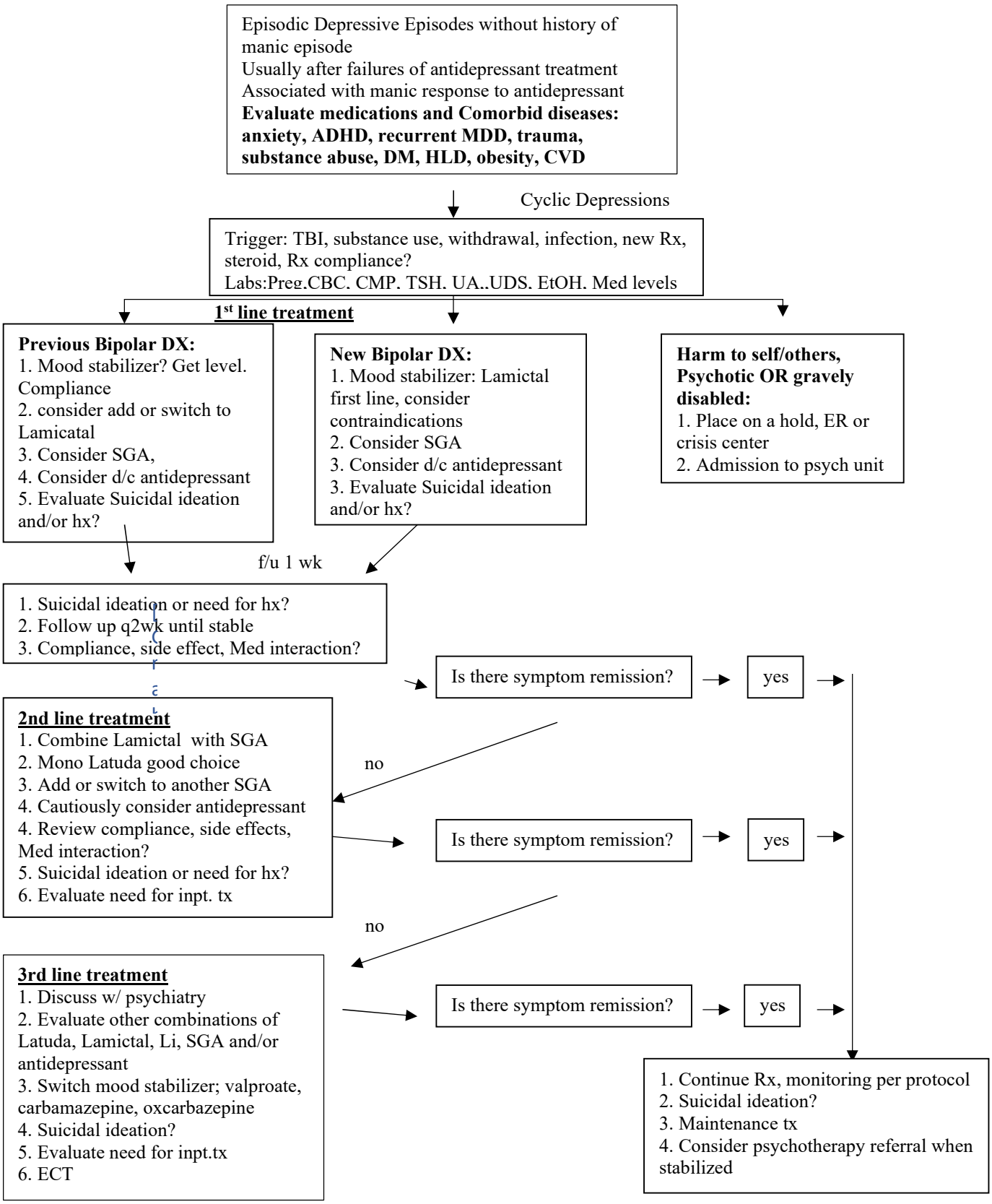
BIPOLAR MANIA TREATMENT FLOW CHART



BIPOLAR DEPRESSION TREATMENT FLOW CHART



BIPOLAR II TREATMENT FLOW CHART



Bipolar Disorder Treatment Guidelines

Up to 69% of patients who seek treatment during the first year of onset are misdiagnosed.

Since symptomatic bipolar patients spend more time in a depressed state (about 1/3 of life) than in a manic, hypomanic, or mixed state they are often misdiagnosed with unipolar depression and treated with antidepressant monotherapy.

Clues

- Family history: first degree relative with a bipolar spectrum disorder
- Manic symptoms:
  - Underreported
  - Get additional history from someone close to the patient
  - Can present in different ways
    - Impulsivity, spending sprees, hyper-sexuality, increased substance use
    - Grandiosity, hyper-religiosity, special powers
    - Irritability, decreased sleep, relationship issues
- Depressive symptoms
  - Often first symptom
  - Low energy, tired with poor sleep
  - Hopelessness
  - Antidepressants
    - Medication treatment failures
    - Rapid recovery with antidepressants followed by abrupt loss of effect
    - Antidepressant-associated insomnia, agitation, and anxiety
- Other factors associated with diagnostic change to bipolar disorder from major depressive disorder
  - Rapid onset of depressive symptoms
  - Substance abuse
  - Greater than 4 depressive episodes a year
- Other symptoms
  - Over/undereating, mood lability, psychotic symptoms, and suicidal thoughts
- Adolescent onset of bipolar disorder
  - 59% of patients with bipolar disorder reported experiencing their first bipolar symptoms during childhood or adolescence (only 16% after age 30)
  - Symptoms are predominantly irritable mood, mania mixed with depression, and more chronic in nature
  - Typically have persistent irritability, anhedonia, psychomotor retardation;
  - High rate of suicide, poor response to treatment
- Typical adult presentation of euphoric mania and more biphasic and episodic course
  - Prevalence: 2.6% of the U.S. adult population
- Comorbidities
  - Anxiety – 56% co-occurrence
  - Substance use disorders – 60.7% lifetime prevalence
  - ADHD – 20%
  - Medical – diabetes, cardiovascular, obesity, dyslipidemia more frequent
  - Reduced life expectancy of approximately 10 years compared to general population

Pathophysiology

- Monoamines DA, NE, and 5-HT are "out of tune"
- GABA deficiency and glutamate excess can cause changes in DA and NE that lead to bipolar symptoms
- Alterations in hypothalamic-pituitary-adrenal (HPA) axis function
- Immune-mediated dysfunction: bipolar disorder is a pro-inflammatory illness, similar to depression
- Circadian dysfunction: disruptions in our sleep-wake cycle can trigger both manic and depressive episodes

Differential Diagnosis

- **Bipolar Disorder from Unipolar Depression**
    - Longstanding episodes of cycling
    - Psychosis
    - Hypersomnia and increased appetite
    - Increased incidence of substance abuse and anxiety with bipolar disorder
    - Activation by antidepressants
- **Substance Abuse (narcotics, EtOH, benzodiazepines) and Bipolar Disorder**
    - Most often neglected
    - Intoxication and withdrawal associated with:
        - Cycling anxiety and agitation
        - Psychosis
        - Depression, sometimes for days after drug use
    - "Mood swings" statements very poor indication of bipolar disorder
    - Bipolar disorder is frequently associated with substance use
    - Must have symptoms remote from substance use, even for several months for initial diagnosis
- **Borderline Personality Disorder**
    - A long-standing, consistent pattern of dysfunctional interpersonal behavior problems, impulsivity
    - "Mood swing" statements very poor indication of bipolar disorder
    - Not commonly associated with bipolar disorder
    - Treatment with mood stabilizers can be effective

Outpatient Treatment Considerations

Presentation

There are many different presentations other than the classic Cyclothymia, Bipolar I, and Bipolar II diagnosis. Treatment should be tailored to the symptom presentation. Symptom complexes to consider include:

- **Classic Bipolar I:** Full-blown manic episodes or mixed episodes of mania plus depression, often followed by a depressive episode
    - When mania recurs at least 4 times a year it is called rapid cycling
- **Classic Bipolar II:** At least one hypomanic episode that follows a depressive episode
- **Cyclothymia:** Mood swings that are not as severe as full mania and full depression, but still wax and wane above and below the boundaries of normal mood
- **Schizoaffective Disorder**: Does not fit neatly into the psychotic disorder nor mood disorder category. Symptoms include psychosis, mania, and a mood disorder and require treatment with mood stabilizers and antipsychotics.

- **Other Symptom Presentations of the Bipolar Spectrum**
  - An unstable form of unipolar depression that responds sometimes rapidly but un-sustained to antidepressants ("poop-out"). These patients have an unstable mood but not a bipolar disorder and often benefit from a mood stabilizer in addition to full-dose antidepressant treatment.
  - Patients typically have protracted or recurrent hypomania without depression
  - Cyclothymic patients are often just considered "moody" and do not get treatment until they develop a full depressive episode. It is important to recognize these patients as part of the bipolar spectrum as treatment with an antidepressant may trigger increased mood cycling or even a full manic episode.
  - Patients with hyperthymic temperament, often described as sunny, optimistic, high-output, successful individuals, with a stable temperament for years then develop a sudden collapse into severe depression. Treatment with antidepressants in these patients may lead to rapid cycling, hypomanic, or mixed states. Mood stabilizers may be a better option.
  - Patients initially diagnosed with a depressive disorder:
    - When treated with an antidepressant develop mania or hypomania
    - With associated significant substance abuse issues.
- **Take Aways**
  - Different symptom presentation for individual people
  - **Mood/symptom monitoring is important – Appendix 2**
  - Individual treatment plans
    - **Focus on presenting symptoms**
    - How sick: How fast do they need to be stabilized?
    - History of previous response
    - Comorbidities
      - Medical co-morbidities
      - Substance use
      - Other Medications

Presenting with: Acute Depression with Bipolar Diagnosis

- **First line treatment** with history of manic episode
- Make sure on mood stabilizer
  - lithium is good first consideration
- With no history of manic episode
  - See Bipolar 2 guidelines
- Combination therapy mood stabilizer plus
  - With more severe depression consider adding antidepressant
    - **If suicidal, consider psychiatric consult or admission**
  - With psychosis add second generation antipsychotic, (SGA- aripiprazole, risperidone, olanzapine, quetiapine, lurasidone, ziprasidone)
    - quetiapine is good first consideration
    - **If psychotic, consider psychiatric consult or admission**
- **Second line treatment**
  - Depending on continued symptoms, combination therapy, mood stabilizer plus
    - Combine with another mood stabilizer, ie. Li and lamotrigine or
    - Combine with SGA
    - Combine with other antidepressants; SSRI, bupropion, venlafaxine, MAOI
    - Maximize dosing
    - Consider discussing with psychiatrist
    -

- **Third line treatment**
  - Consultation with psychiatrist
  - Other combinations of mood stabilizers, antidepressants, SGA
  - ECT

Presenting with: Acute Mania with Bipolar Disorder Diagnosis

- **First Line treatment**
  - Make sure on patient mood stabilizer (lithium, valproate, carbamazepine, oxcarbazepine)
    - lithium is a good first consideration
    - With mixed features, lithium may not be as effective
  - Add short term benzodiazepine (except with history of substance abuse)
  - Add SGA (aripiprazole, risperidone, olanzapine, quetiapine, ziprasidone)
    - **If psychotic, consider psychiatric consult or admission**
- **Second Line Treatment**
  - Switch or combine mood stabilizers
  - Switch or add SGA
  - Add short term benzodiazepine (except with history of SA)
  - Maximize dosing
- **Third line treatment**
  - Consult psychiatrist
  - Other combinations
    - Add lithium with other mood stabilizers
    - switch SGA, may consider clozapine
    - maximize dosing
  - ECT
  -

Presenting with: Bipolar II Disorder

Episodic depressive episodes without history of manic episode

- *Usually after failures of antidepressant treatment*
- *Associated with manic response to antidepressant*

- **First line treatment**
  - Monotherapy if not severe
    - Start lamotrigine and increase per-protocol (adequately dose up to 300 mg)
    - Avoid antidepressant alone
  - Mono/Combination therapy with more severe symptoms
    - Add SGA (aripiprazole, risperidone, olanzapine, quetiapine, ziprasidone)
      - If psychotic, consider psychiatric consult or admission
- **Second line treatment**
  - Lamotrigine levels
  - Combination therapy lamotrigine plus:
    - If continued depression, add antidepressant
  - Monotherapy – lurasidone (Latuda)
    - Add if not psychotic and lamotrigine fails to decrease cycles
- **Third line treatment**
  - Consultation with psychiatrist
  - Combine lamotrigine and lurasidone
  - Combine lithium and lamotrigine
  - Combine/switch with other mood stabilizers
  - Combine with SGA and/or antidepressant with lithium and lamotrigine
  - Combine with other antidepressants; bupropion, venlafaxine, MAOI
  - ECT

Maintenance Phase

- Recommended that drugs used to achieve remission from most recent episode be continued into maintenance phase
- After at least 3 -6 months of mood stability, doses can be slowly adjusted to the lowest effective dose
- Monotherapy is preferred once stabilized for 3 - 6 months
    - If possible, try to decrease/discontinue SGA, and/or benzodiazepine and continue mood stabilizer
- Depending on severity of presentation and effectiveness of response can consider a very slow taper after 1 year or more, especially if patient's first episode
    - Need patient agreement
    - Rapid reinstitution of medication if symptoms recur

Medications Used to Treat Bipolar Disorder

***see tertiary resources for specific dosing information and recommendations**

Mood stabilizers - *With a bipolar diagnosis, most need to be on a mood stabilizer –See Appendix1*

Lithium

- Indication: Classic Bipolar I manic episode
    - Effective for manic episodes and maintenance
    - Non-rapid cycling (<4 episodes a year)
    - Felt to decrease suicide risk
- MoA: unknown, may affect second messenger systems
- Adverse Effects – **Appendix 3**
    - Diarrhea, weight gain, alopecia, acne, tremor, sedation, dry mouth/thirst
        - Weight gain of 4-6kg in the first 2 years of treatment
    - No liver issues, can be nephrotoxic
        - Loss of CrCl ~2mL/min/year
    - Can cause hypothyroidism in 8-19% of patients
    - Pregnancy issues in first trimester
- Drug-Drug Interactions
    - ACEs, ARBs, NSAIDs, thiazide diuretics, and dehydration can increase lithium levels
- Drug Levels
    - Require blood monitoring
    - Target serum concentration of 0.6-1 for maintenance and 0.8-1.2 for acute treatment
    - Reaches steady-state concentration after 5 days
    - Onset in 6 to 10 days, full effect could take 3 weeks

valproic acid (Depakote)

- Indication: Classic Bipolar I manic episode
    - Has shown efficacy in treating acute mania, but less data for maintenance
    - Mixed and rapid cycling (>4/yr)
    - Can help with impulsive aggression
- MoA: unknown, could be related to inhibition of voltage-gated sodium channels
- Adverse Effects - **Appendix 3**
    - Alopecia (Selenium can be helpful), weight gain (6-8kg), dizziness, sedation, thrombocytopenia
    - Black box warnings for hepatotoxicity, pancreatitis, and teratogenicity
        - Can cause neural tube defects and developmental delays if used in pregnancy
        - Folate supplementation of 4mg per day can reduce teratogenicity risk

- Drug Levels
  - Require blood monitoring
  - Target serum concentration 50-125
    - Saturable protein binding means a doubling of dose could lead to a more than double increase in serum concentration
  - Long-acting have 20% lower blood level
  - Benefit is usually seen in 3 to 5 days
- Clarify any drug interactions and pregnancy issues

carbamazepine (Tegretol)

- Indication: Classic Bipolar I manic episode
  - Best at treating acute mania, may be less effective at treating depression
  - Mixed and rapid cycling (>4/yr)
- MoA: unknown, could be related to inhibition of voltage-gated sodium channels
- Adverse Effects: **Appendix 3**
  - Sedation, dizziness, hyponatremia, blood dyscrasias, liver toxicity
  - neural tube defects
    - Folate 4mg can decrease teratogenicity risk
  - Stevens-Johnson Syndrome (SJS)
    - Patients of Asian descent are at a greater risk of SJS and should be tested for HLAB1502; if positive they have 10x risk
  - Weight neutral
- **Drug-Drug Interactions**
  - **Significant potential drug interactions with many medications due to cytochrome P450 induction**
- Drug Levels
  - Require blood monitoring
  - Therapeutic serum concentration 4-12 for epilepsy, but this may not correlate to bipolar treatment
- Clarify any drug interactions and pregnancy

oxcarbazepine/eslicarbazepine (Trileptal/Aptiom)

- Has been used off label
- Structurally related to carbamazepine
- Less drug interactions than carbamazepine, but more hyponatremia

lamotrigine (Lamictal)

- Indication: Bipolar II Depression
  - Not FDA approved for bipolar depression, but commonly used
  - Not effective for mania
- MoA: unknown, binds to voltage-gated sodium channels and reduces glutamate release
- Adverse Effects - **Appendix 3**
  - Generally well tolerated
  - Rash issues/Steven Johnson Syndrome (SJS), follow dosage guidelines,
    - If rash - Derm referral
    - Must be titrated every 2 weeks to prevent SJS
    - Patients of Asian descent are at a greater risk of SJS. They should be tested for HLAB1502, and if positive they have 10x risk
- Follow recommended dose titration
  - Takes ***at least*** 6 weeks to reach effective maintenance dose
- Drug-Drug Interactions
  - When used with valproic acid, cut lamotrigine dose in half
  - When used with carbamazepine, a slightly different titration is used
    - All doses are double, but week 6 is 300mg/day (200mg/day in normal titration)
- Safer in pregnancy

Second Generation Antipsychotics
Remember regular AIMS testing

quetiapine (Seroquel)

- Indication: effective for acute and maintenance mania and depression
- MoA: D2 receptor antagonism with fast dissociation
    - Greatest affinity for H1 receptor followed by 5HT and DA
    - Anticholinergic properties lead to sedation, but also decreased incidence of EPS
        - DA inhibits ACh in the nigrostriatal pathway which is involved in movement
    - 5HT2A antagonism and 5HT1A partial agonism could explain efficacy in depression and mania
    - 5HT2C antagonism could explain benefits in depression and weight gain
- Adverse Effects: weight gain
- Dosing Ranges:
    - 50-300 sedation effect (antihistamine)
    - 300-600 mood stabilizing effect
    - 600-800 antipsychotic effect

olanzapine (Zyprexa)

- Useful in treatment of acute and maintenance depression and mania
- MOA:
    - D2 and 5HT2 antagonism
    - Highly anticholinergic
- SE: weight gain, sedation, sexual
    - Weight gain may be due in part to 5HT2C and histamine antagonism

aripiprazole (Abilify)

- Indication: Useful in treating acute mania
- MOA: D2 partial agonist
        - Little affinity for muscarinic and histaminergic receptors - Little sedation or weight gain
- Adverse Effects:
    Lowers prolactin levels - Sexual dysfunction rates lower (16-27%)
    - Can lower QT interval (1-4)
    - Higher risk of akathisia

lurasidone (Latuda)

- Indication: Useful in treating depression
- MOA: D2 and 5HT2A antagonism
    - Little affinity for muscarinic or histaminergic receptors
- Adverse Effects:
    - Little weight gain or sedation
    - Does not prolong the QT interval
- Must be taken with 350 calories for proper absorption

cariprazine (Vraylar)

- MOA: D2 receptor partial agonism
    - "Colder than aripiprazole"
    - More antagonism than agonism when compared to aripiprazole
- At lower doses, binds D3 more than D2
    - May be procognitive
- Long half-life
    - Half-life cariprazine 2-4 days
    - Half-life active metabolite 1-3 week

risperidone (Risperdal)

- Indication: effective at treating acute mania
- MOA: D2 and 5HT2A antagonism
    - Atypical, but becomes more "typical" at higher doses
        - More risk of EPS
- Can raise prolactin levels even at low doses
    - **Highest rates of sexual dysfunction (60-70%)**
- Moderate risk for weight gain and dyslipidemia

ziprasidone (Geodon)

- Indication: used to treat mania or depression with mixed features
- MOA: D2 and 5HT2A antagonism
- Dosed BID with 500 calories
- Little risk of weight gain or sedation
- QT prolongation (1.3-20.3)

Benzodiazepines

- Helpful with rapid control of acute mania
- Anxiety and sleep issues
- Avoid with CD history
- Try to taper off when stable for 2-4 weeks
- Careful with elderly

Antidepressants

- Use of antidepressants is controversial
- Can increase the risk of mania or mixed episodes
    - Bupropion may have the lowest risk, and TCAs may have the highest
    - If antidepressant is providing some benefit, consider continued use with close monitoring
- **Should always be used with a mood stabilizer**

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The Prevalent Clinical Spectrum of Bipolar Disorders: Beyond DSM-IV, Journal of Clinical Psychopharmacology: April 1996 – Volume 15, Issue 2- p45-145

The Evolving Bipolar Spectrum: Prototypes I, II, III, and IV, Psychiatric Clinic of North America: Volume 22, Issue 3, Sept. 1999, p 517-534

Yatham, LN et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018, Guidelines for Management of Patients with Bipolar Disorder: Bipolar Disorders. Wileyonlinelibrary/Journal/bdl; 2018; 20: 97-120

Appendix 1

Bipolar Disorder
Carol Ott, PharmD, BCPP

Figure 7. Acute and Maintenance Polarity Coverage of Select Agents used in Bipolar Disorder*

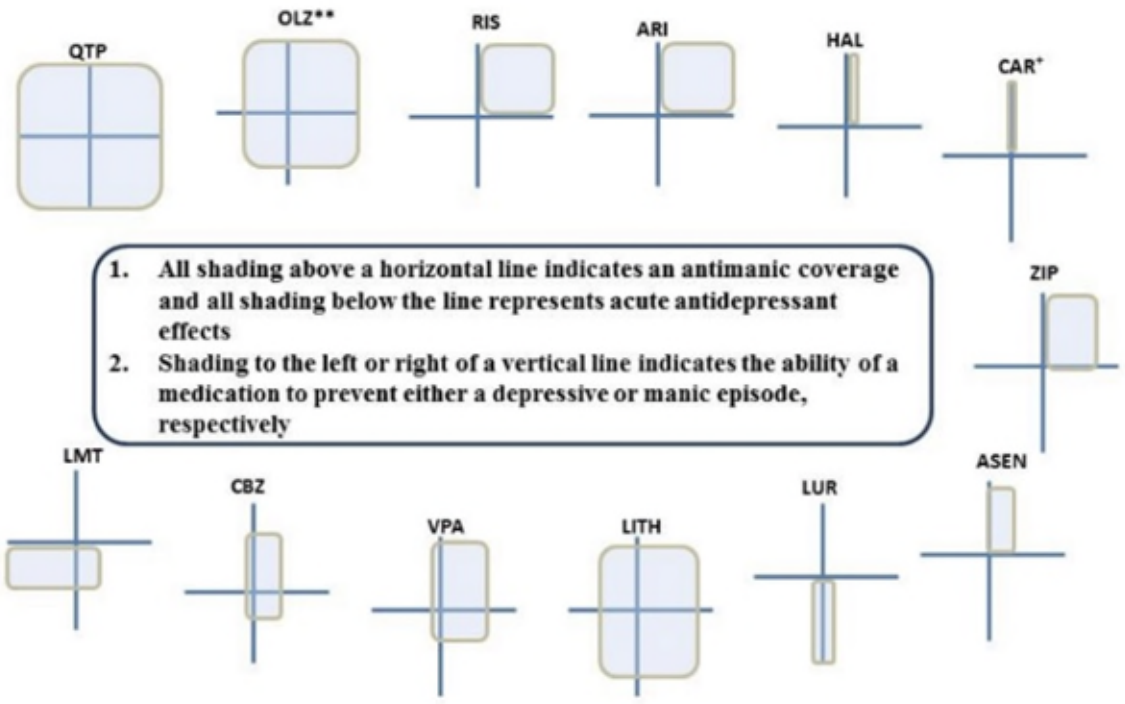


*Figure based on available studies, meta-analyses, and expert opinion and intended to provide a general understanding of a medication's predilection to cover a particular polarity; either acutely or as prevention. Figure does not allow for the ability to make direct comparisons between agents related to efficacy nor does it take into account tolerability; **For depression, OLZ refers to olanzapine + fluoxetine combination, + cariprazine FDA approved September 2015 for manic or mixed episodes associated with bipolar disorder; phase II studies indicate potential benefit in bipolar depression. ARI=aripiprazole, ASEN=asenapine, CAR=cariprazine, CBZ=carbamazepine, HAL=haloperidol, LITH=lithium, LMT=lamotrigine, LUR=lurasidone, OLZ=olanzapine; QTP=quetiapine, RIS=risperidone, VPA=valproate, ZIP=ziprasidone

Appendix 2

Mood/Sleep Chart

From __/__/__ to __/__/__

Day		Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
MOOD LEVELS	+5 (Manic)							
	+4							
	+3							
	+2							
	+1							
	0 (Normal)							
	-1							
	-2							
	-3							
	-4							
	-5 (Depressed)							
Sleep (total hours)								
Energy level (0-5)								
Notes								

Appendix 3

Mood Stabilizer Safety and Tolerability Concerns

Lithium	Valproate	Carbamazepine	Lamotrigine
Gastrointestinal	Gastrointestinal	Gastrointestinal	Gastrointestinal
Weight gain	Weight gain	Rash	Rash
Neurotoxicity	Tremor	Neurotoxicity	Headache
Renal toxicity	Hepatotoxicity	Hepatotoxicity	Dizziness
Thyroid toxicity	Thrombocytopenia	Thyroid changes	Pruritis
Hair Loss	Hair Loss	Blood dyscrasias	Dream abnormality
Cardiac toxicity	Pancreatitis	Cardiac toxicity	
Acne, Psoriasis	PCOS	Hyponatremia	
Teratogen	Teratogen	Teratogen	Teratogen
	Suicidality (?)	Suicidality (?)	Suicidality (?)

☐ = *boxed warning in prescribing information; (?) = recent alert*

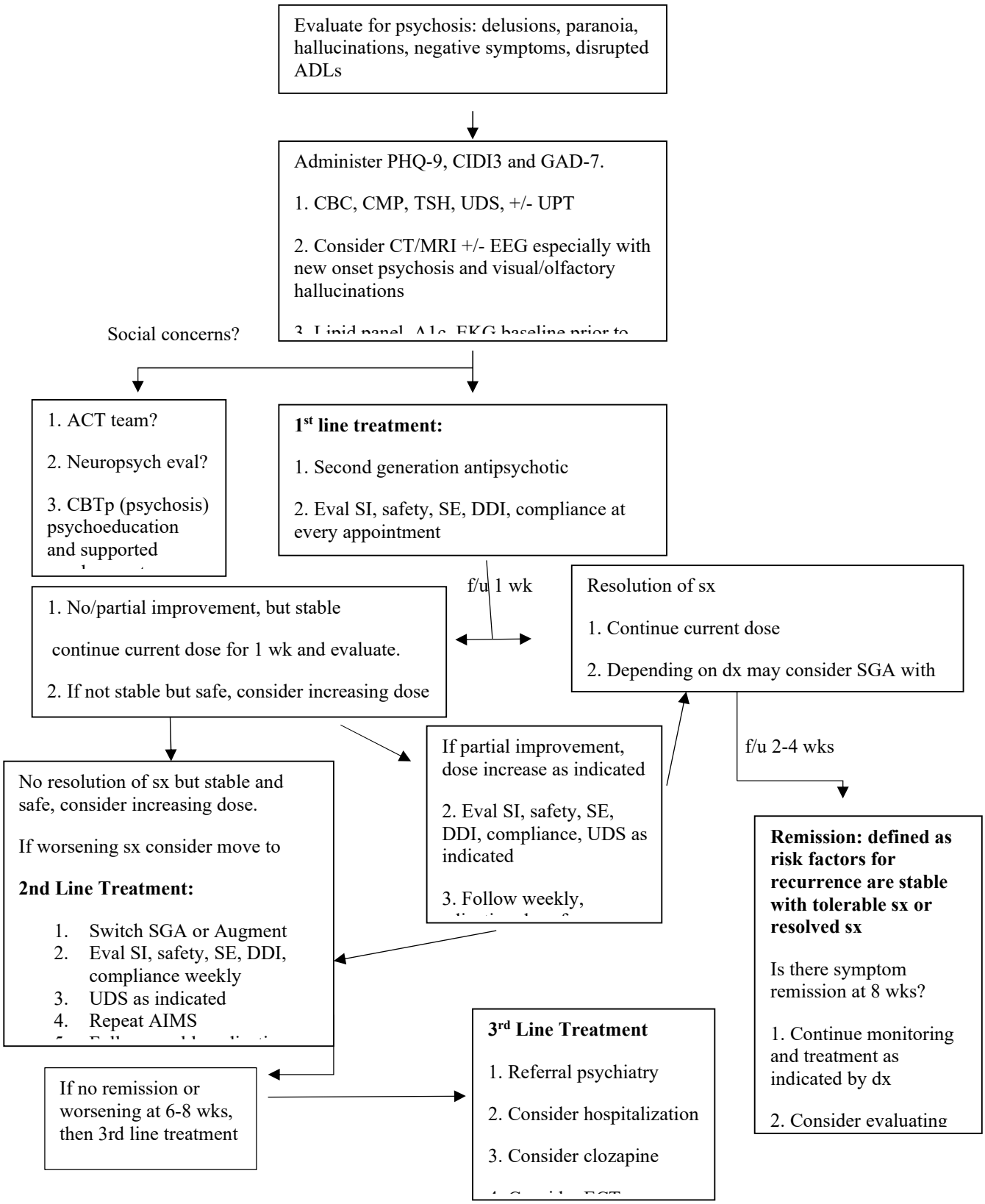
All Mood Stabilizers Have at Least One Boxed Warning

In: Ketter TA (ed). Advances in the Treatment of Bipolar Disorder. 2005.
Physician's Desk Reference. 2008.

Psychosis/Schizophrenia Treatment Guidelines

Developed by: Russ Symbal, RPh, BCPP; Leanne Rousseau, MD; Stephanie Sargent, MD; Lauren Fletcher, PharmD; Nathen Bertsch, PharmD; William H. Miller, MD

PSYCHOSIS EVALUATION & TREATMENT GUIDELINE



Psychosis/Schizophrenia Treatment Guidelines

Psychosis

- A mental and behavioral symptom causing gross distortion or disorganization of a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others to the degree of interfering with that person's capacity to cope with the ordinary demands of everyday life.
- Includes disorder of:
    - Thought processing
    - Thought content

Symptoms of psychosis

Core symptoms

- Delusions – fixed false belief that is unable to be changed despite conflicting evidence,
    - Can be persecutory, referential, somatic, religious, grandiose
- Hallucinations – involuntary sensory experience without external stimulus
    - Auditory most typical, perceived as distinct from patient's thoughts, can be familiar or unfamiliar, voices that talk to each other about patient more typical
    - If smells or taste, consider EEG to rule out other causes
    - Visual atypical are more common with physiologic medical cause, substance use, delirium, trauma, (DID)
    - Hypnagogic (occur while falling asleep) or hypnopompic (occur while waking up) considered within range of normal experience
- Disorganized speech or thinking – frequent derailment or loose associations due to jumping from topic to topic without ability to follow or incoherence "word salad" which resembles receptive aphasia
    - Speaking in tongues or possessive trance as part of religious culture belief not representative of psychosis unless other symptoms present

Other symptoms

- Grossly disorganized – difficulty with ADLs due to problem with any goal-directed activity
- Catatonic behavior – markedly decreased reactivity to environment, or can have mutism with complete lack of verbal and motor responses
- Negative symptoms
    - flat affect, blunted mood
    - absence of speech
    - lack of emotion, initiative, enthusiasm
    - inattention
    - anhedonia
- Cognitive symptoms
    - poor executive function, inability to learn from mistakes
    - anosognosia – patient unable to believe diagnosis of schizophrenia

Differential Diagnosis

Symptoms of psychosis applies to many diagnosis

- **Substances and Medications**
- **Medical Causes**
  - Syphilis
  - Neurodegenerative (Parkinson's, Huntington's, Lewy Body Dementia, Alzheimer's, Frontotemporal Lobar Degeneration, Creutzfeldt Jakob Disease)
  - Lupus
  - Delirium
  - Stroke
  - Seizures
  - Brain tumor
  - Anti-NMDA receptor encephalitis
  - Advanced HIV or other encephalitis
  - Traumatic Brain Injury
  - Myxedema
- **Psychiatric disorders where psychosis can be an associated feature**
  - Mania
  - Depression
  - Anxiety disorders
  - Post-traumatic stress disorder
  - Cognitive disorders
  - Alzheimer's dementia
- **Schizophrenic Spectrum Disorders <u>where psychosis is a primary feature</u> (Appendix 1)**
  - ***Schizoaffective Disorder*** – 1 core symptom + 1 other symptom with major mood episode (depressive or manic) concurrent with schizophrenia
    - Mood symptoms present for majority of the illness
    - Delusions or hallucinations for > 2 weeks in the absence of a major mood episode
  - ***Schizophrenia*** – 1 core symptom for 1 month (or less if tx) + 1 other symptom
    - Level of function with work, relationships, or ADLs below level prior to onset or failure to achieve expected level of functioning if sx develop as pediatric
    - Persist for at least 6 months
    - If prior hx of autism spectrum disorder or communication disorder, schizophrenia dx if prominent delusions or hallucinations, w/ other required symptoms of schizophrenia for 1 mo
  - ***Schizophreniform Disorder*** – 1 core symptom + 1 other symptom
    - Lasts 1 to 6 months
  - ***Brief Psychotic Disorder*** – 1 or more core symptom, can have other symptoms
    - Duration < 1 month, return to level of functioning prior to episode
  - ***Delusional Disorder*** – 1 or more delusions, no dx of schizophrenia, hallucinations related to delusion can be present
    - Duration of 1 month or longer
    - If manic or depressive episodes, must be brief relative to duration of delusion
    - Functioning is not markedly impaired, and behavior is not obviously bizarre or odd

Schizophrenia

Positive Symptoms -- Psychosis (loss of contact with reality)

- Delusions (false belief)
- Hallucinations (perceptions that don't exist)
- Disorganized thinking & speech (doesn't make sense)
- Catatonic behavior
- Disorganized behavior
- Severe agitation

Negative Symptoms

- Blunted affect
- Cognitive blunting
- Avolition (lack of interest, apathy)
- Anhedonia (inability to experience pleasure)
- Isolation

Alogia (inability to speak)

Anosognosia (inability to believe diagnosis of schizophrenia)

Impact of schizophrenia

- Interferes with ability to think clearly, manage emotions, make decisions, relate to others
- Usually begins in late teens to early 30's, affects 1% of U.S. population
    - **Early consistent treatment has better response = improved outcomes!**
- Results in:
    - Higher healthcare cost (3-11x increase, cost $9,550 – $35,000/yr)
    - Higher unemployment rate (>70%)
    - Economic burden (>$700 million annual government disability costs)
    - Lower levels of community functioning
- Causes: multifactorial
    - Genetics – excessive pruning of synapses
    - Environment – perinatal insults; autoimmune diseases; inflammation/infection
    - Brain chemistry – Excessive dopamine and glutamate
    - Substance abuse –Marijuana and methamphetamine use increase risk
        - Strong association with earlier age of cannabis use
        - Marijuana use increases risk of ongoing psychotic incidents

Pathophysiology

Dopamine Pathways

- Schizophrenia involves increased dopamine synthesis, DA release, D2 receptor density excess presynaptic DA and/or increased sensitivity of D2 receptors results in positive psychotic symptoms
- Mesolimbic pathway –positive symptoms of psychosis and motivation, pleasure and reward, D2 blockage improves these symptoms, early model for schizophrenia
- Mesocortical pathway - associated with negative/cognitive symptoms from deficit and excess of D2, D2 blockage can worsen negative symptoms, dec motivation, cognition, processing emotion/information
- Nigrostriatal pathway –coordination and initiation of movement, D2 blockage results in movement issues, also associated with the reward system, inc Dopamine reduces adaptation to rewards
- Tuberoinfundibular pathway – to hypothalamus/pituitary, block D2 gives rise to galactorrhea, amenorrhea
- So blocking some D2 pathways is helpful, blocking others is harmful:
    - Want to decrease DA in some sites and increase DA in other sites and leave it alone in other sites

Glutamate

- Excitatory neurotransmitter
- Multiple glutamate pathways in the brain
- NMDA receptors involved in maintaining balance excitatory/inhibitory functioning
- Glutamate stimulates NMDA (ionotropic) receptors
- May precede or give rise to dopamine transmission problems
- Drugs affecting glutamate, glycine may help at various stages of schizophrenia

GABA

- Pre & post-synaptic inhibitory neurotransmitter
- Balances with glutamate excitatory neurotransmitter
- GABA may play a role in cognitive symptoms

Serotonin

- Hyperactivity/imbalance of 5-HT_{2A} in the cortex can result in psychosis
- Serotonin has more than a dozen receptor types, some of which regulate other neurotransmitters in downstream brain circuits (e.g. dopamine, glutamate, norepinephrine)

How Medications Treat Psychosis

- Psychosis is due to too much dopamine attaching to brain receptors causing over-activation
- Negative symptoms = ↓ dopamine & glutamate in other areas of the brain
- Antipsychotics block dopamine D_2 receptors (keeps the brain cells “locked”) to prevent over-activation of brain cells
- Medicines treat symptoms but do not “cure” the illness
    - Treatment goal: improve overall functioning and outcomes
- Early non-adherence to treatment results in increased hospitalizations

Medication Options

- Typical antipsychotics (1st generation antipsychotic; FGA): Block D_2
- Atypical antipsychotics (2nd generation antipsychotic; SGA): Block D_2 and $5HT_{2A}$
- Both SGA/FGA can have mechanism of action at H_1, ACh, $Alpha_1$

First Generation (Typical) Antipsychotics (FGA)

▪Thorazine®	chlorpromazine	▪Inapsine®	droperidol
▪Trilafon®	perphenazine	▪Navane®	thiothixine
▪Prolixin®	fluphenazine	▪Loxatane®	loxapine
▪Haldol®	haloperidol		

- *Tightly bind to dopamine receptors in CNS. Effective for positive symptoms; nausea; usually inexpensive. No longer used as "first-line" treatment due to side-effects. Often referred to as "neuroleptics"*

Second Generation (Atypical) Antipsychotics (SGA)

• Abilify®	aripiprazole	• Clozaril®	clozapine
• Fanapt®	iloperidone	• Geodon®	ziprasidone
• Invega®	paliperidone	• Latuda®	lurasidone
• Rexulti®	brexpiprazole	• Risperdal®	risperidone
• Saphris®	asenapine	• Seroquel®	quetiapine
• Vraylar®	cariprazine	• Zyprexa®	olanzapine

- *Considered "first-line"*
- *Used for schizophrenia, bipolar disorder, delirium, agitation, depression, anxiety disorders, insomnia, autism, etc.*
- *Equal positive symptom effect, low extrapyramidal and prolactin effects*
- ***Second-generation antipsychotics (SGAs, atypicals) have less risk of EPS versus FGAs through a variety of mechanisms (not all SGAs possess all of them):***
    - *5-HT2a and DA receptor antagonism (most SGAs)*
    - *DA receptor antagonism with rapid dissociation/weak D2 binding (clozapine, quetiapine)*
    - *DA receptor partial agonist (aripiprazole, brexpiprazole, cariprazine)*
    - *5-HT1a partial agonism (clozapine, quetiapine, aripiprazole, brexpiprazole, cariprazine, ziprasidone)*
- ***Explanation:***
    - *Serotonin regulates a number of brain neurotransmitters. SGAs modulate the serotonin receptors to various degrees resulting in different effects:*
    - *5-HT2a antagonism leads to increased dopamine in striatum resulting in reduction of EPS and improvement in negative symptoms*
    - *5-HT1a agonist leads to increased dopamine in the striatum resulting in and antidepressant effect as well as reduction of EPS.*
    - *5-HT2c antagonism leads to increased dopamine in the PFC resulting in an antidepressant effect*
    - *5-HT7 antagonism leads to increased 5-HT release downstream resulting in an antidepressant effect and increased cognition*

- ***Additional effects:***
    - *H1 antagonism (antihistamine) leads to sedation*
    - *ACh antagonism (anticholinergic)*
    - *α-1 antagonism leads to hypotension*
    - *Metabolic issues increase when H1 & 5-HT2c antagonism occur concurrently*

Choice of Medication

- Unfortunately, we still are not very good at targeting medication to impact specific psychotic/schizophrenic disorder symptoms.
- Still best determined by side effects we want vs side effects we don't want

Common Second Generation Antipsychotics **Remember regular AIMS testing**

quetiapine (Seroquel)

- MoA: Weak D2 receptor antagonist; NRI; $5HT_{2A}$, $5HT_{2C}$, H1, ACh, and α_1 antagonist; $5HT_{1A}$ partial agonist
- Effects: antipsychotic, antidepressant, antianxiety, sedative
- Adverse Effects: anticholinergic, sedation, weight gain, orthostatic hypotension
- Dosing Ranges: 600-800 mg antipsychotic effect

olanzapine (Zyprexa)

- MoA: D2, $5HT_{2A}$, $5HT_{2C}$, H1, ACh, and α_2 antagonist
- Effects: antipsychotic, antidepressant, antianxiety, sedative
- Adverse Effects: anticholinergic, sedation, weight gain
- Smoking decreases levels

aripiprazole (Abilify)

- MoA: D2 partial agonist, 5-HT_{1A} agonist, 5-HT_7 antagonist
- Little affinity for muscarinic and histaminergic receptors - less sedation or weight gain
- Effects: antipsychotic, antidepressant
- Adverse effects: akathisia
- **Long Acting Injectable available**
    - Abilify Maintena: IM every 4 weeks
    - Aristada: IM every 4-8 weeks

lurasidone (Latuda)

- MoA: D2, $5HT_{2A}$, $5HT_7$, α_2 antagonist; 5-HT_{1A} agonist
- Little affinity for muscarinic or histaminergic receptors – little sedation or weight gain
- Effects: antipsychotic, antidepressant
- Does not prolong the QT interval
- Must be taken with 350 calories for proper absorption!

cariprazine (Vraylar)

- MoA: D2 and D3 partial agonist, 5-HT_{1A} agonist, α_2 antagonist
- D3 partial agonist property may improve cognition, mood, and negative symptoms
- Effects: antipsychotic, antidepressant
- Long half-life
    - Half-life cariprazine 2-4 days, Half-life active metabolite 1-3 week

risperidone (Risperdal)

- MoA: D2 and $5HT_{2A}$ antagonism
- Atypical, but becomes more "typical" at higher doses
- Effects: antipsychotic, behavioral symptoms in elderly (not anticholinergic)
- Adverse effects: EPS, hyperprolactinemia, sexual dysfunction, weight gain, orthostasis
- **Long Acting Injectable**
    - Consta: IM q2wk, 3-week oral overlap
    - Perseris: SC q4wk, no oral overlap required

ziprasidone (Geodon)

- MoA: D2 and $5HT_{2A}$ antagonism
- Dosed BID with at least 500 calories
- Effects: antipsychotic
- Adverse effects: Somewhat activating, QTc prolongation

paliperidone (Invega)

- MoA: D2 and $5HT_{2A}$ antagonism
- Active metabolite of risperidone
- Effects: antipsychotic
- Adverse effects: EPS, hyperprolactinemia, weight gain
- Long Acting Injectable
    - Sustenna: IM q 4 wks
    - Trinza: IM q 12 wks
    - Hafyera: IM q 6 mos

clozapine (Clozaril)

- MoA: Weak D2 receptor antagonist; $5HT_{2A}$, $5HT_{2C}$, H1, ACh, and α_1 antagonist; $5HT_{1A}$ partial agonist
- Medication of choice for Treatment Resistant Schizophrenia (TRS)
    - No significant improvement in positive symptoms after treatment with 2 or greater SGA with adequate dose, duration and adherence
    - 30% non-response with 2 or greater antipsychotic trials
- Adverse effects: weight gain, hypotension, sialorrhea, sedation, hyperglycemia, dyslipidemia
- Smoking decreases levels
- **Must monitor absolute neutrophil count per Risk Evaluation and Mitigation Strategy (REMS), a drug safety program mandated by U.S. Food and Drug Administration**
    - https://www.newclozapinerems.com/home
- Studies show 30% would respond by 6 weeks, a further 20% by 3 months and an additional 10–20% by 6 months. Therefore, it seems reasonable to try clozapine monotherapy for 6 months.

Long Acting Injectables (LAIs) (Appendix 4)

- A major challenge with the treatment of schizophrenia is poor compliance with antipsychotic therapy
- LAIs are known to be at least as effective as oral antipsychotics for treating schizophrenia, and yet are underutilized. Further, LAIs address many of the problems associated with adherence to oral therapy.
- LAIs have been shown to decrease repeated hospitalizations, to decrease cost of care, and to increase adherence to treatment
- Recent evidence suggests that LAIs, in some cases, are effective for treating first-episode psychosis and for early initiation of treatment for schizophrenia.
- **It is important to maintain patient/care provider contact with frequent brief appointments even with long term injectables.**

Major areas of side effects (Appendix 2 and 3)

- Increased sedation(H1& M1): clozapine, olanzapine, quetiapine
- Weight gain (5-HT_{2C} & H1): clozapine, olanzapine, quetiapine, risperidone, paliperidone
- Orthostatic (α_1): clozapine, olanzapine, quetiapine, paliperidone
- Prolactin(D_2 antagonist): risperidone, paliperidone
- QTc: ziprasidone
- Akathisia: aripiprazole(some D_2 agonist properties)
- EPS: risperidone, paliperidone
- Neuroleptic malignant syndrome

Treatment of Extrapyramidal Symptoms (EPS)

- Anticholinergics – diphenhydramine, benztropine
- Beta-blockers, benzodiazepines
- Monitoring, lower dose, switch medications

Tardive Dyskinesia

- Tardive dyskinesia (TD) is a disabling, disfiguring movement disorder, involving involuntary choreoathetoid movements of the orofacial region caused primarily by the prolonged use of neuroleptic drugs. 1 It is typically persistent with no definitive treatment.
- In adults, the annual rate of development with second-generation antipsychotics is 2.98% versus 7.7% with first-generation antipsychotics.
- **Pathophysiology:** Likely related to chronic blockade of dopamine in the CNS. This may lead to super-sensitivity or upregulation of dopamine receptors or an imbalance in effect between D1 and D2 receptors.
- **Risk Factors:** Advanced age, female, duration of neuroleptic use, mental retardation
- **Screening/Prevention: AIMS testing (Appendix 5)**
    - **Should be done at 3 and 6 months. Some patients who develop TD show symptoms in the first 3 months (sooner in elderly, 1 month)**
    - **<u>Chronically should be done and documented q 3-6 months</u>**

Treatment of TD

- If abnormal movements are present, try to decrease neuroleptic dose or switch to atypical if using a typical neuroleptic
- Discontinuing neuroleptic may decrease symptoms, although not in all patients. (abrupt withdrawal of the drug is rarely recommended and may worsen the condition)
- Based on limited research, lowering the dose or switching to another neuroleptic does not decrease TD symptoms. (This is often done in practice however, and it is possible the TD can resolve if the offending drug is removed early)
- Vitamin E may prevent worsening of TD, but no data exist to support vitamin E as an effective treatment.
- **VMAT2 inhibitors:** There are no head to head comparisons of these drugs, caution with evidence interpretation. Expensive.
    - deutetrabenazine (Austedo) is approved for the treatment of TD in adults, at a starting dose of 6 mg bid increased weekly to a maximum dose of 24 mg bid. The NNT = 5 for comparison with placebo as defined as much or very much improved. Mean AIMS reduction of -3 with 38mg/day versus -1.6 with placebo.
    - valbenazine (Ingrezza) can be used at a starting dose of 40mg. Caution with CYP 2D6 inhibitors. This drug reduced the mean AIMS from baseline by -3.2 at a dose of 80mg versus placebo (-0.1).
    - tetrabenazine (Xenazine) can be dosed at 12.5mg daily for 1 week and increased by 12.5mg increments up to 75-150mg. Doses > 37.5mg should be divided TID. Caution with CYP2D6 inhibitors. Showed marked reduction or disappearance of dyskinesia in 70% of patients compared with no change for placebo at a dose of 150mg/day.
- Preliminary research suggests that benzodiazepines may improve symptoms, although the evidence is not strong enough to support routine use.
- Gabapentin, calcium channel blockers, choline, physostigmine, baclofen, progabide, sodium valproate, ceruletide, gamma-linolenic acid, estrogen, and lithium have not been shown to be effective.
- Refractory symptoms should see a movement disorder specialist and be considered for deep brain stimulation

Neuroleptic Malignant Syndrome (Hypodopaminergic)

- Incidence
    - Typicals – 0.2% - 0.6%
    - Atypicals – lower incidence than typicals
    - Recurrences when challenged - 30% (no difference between typical and atypicals)
- Characteristic symptoms
    - Fever 101 – 104, rigidity, altered sensorium,
    - Autonomic instability - BP, HR, diaphoresis, incontinence, dehydration
- Labs
    - CPK 2,000- 15,000 associated with myolysis
    - WBC 15 – 30 with left shift
    - Mildly elevated liver enzymes

- Patient Profile
    - Male. <35 y/o
    - Affective disorder > schizophrenia> with organic brain lesions
    - High potency neuroleptics, depot preparations, concurrent lithium
    - 90% within 10 days of starting or increase in dose
- Course
    - Develops within 24 to 72 hours
    - Usually subsides 5 –10 days after D/C of neuroleptics
    - 20 – 30% develop secondary complications
        - Respiratory complications: Dec respiratory drive, dysphasia and aspiration, rigid chest wall, pulmonary embolus
        - Renal failure from volume depletion, Acute tubular necrosis from myoglobinemia
        - Shock, rhythm disorders
        - DIC
- Differential Diagnosis
    - CNS infection – lumber puncture
    - Phenothiazine heat stroke – no rigidity or diaphoresis
    - Malignant hyperthermia – anesthetic exposure
    - MAO hypertensive crisis – Used MAO
    - Anticholinergic Crisis – dry, dilated pupils, no rigidity or diaphoresis
    - Serotonin syndrome – presence of myoclonus, hyperreflexia, shivering, GI symptoms, on serotonin (multiple) agents
    - Catatonia spectrum– often progresses to NMS, may be on the same spectrum

Augmentation Strategies

- Meta-analysis data does not always indicate significant impact of augmentation
    - These studies do not take into account individual patient's symptom/presentation
    - These studies often do not predict individual patient's response
    - Cautiously monitor for side effects and drug interactions
    - If not helpful, d/c in order to minimize medication exposure
- **Second Antipsychotic:**
    - Can provide improvement in some cases
        - Per CMS guidance for the use of multiple antipsychotics, require documentation of a history of a minimum of three failed multiple trials of monotherapy
    - Try to capture broader range of neurotransmitter impact
- **Mood stabilizers:**
    - Considered if mood liability part of presentation, monitor as target symptom
    - lithium has been shown to help with aggressive symptoms
    - Anticonvulsants; lamotrigine has demonstrated some beneficial effects
- **Antidepressants:**
    - Consider if depression part of presentation (7-65% incidence with schizophrenia)
    - SSRI, SNRI are good choice
    - Monitor for improvement

Pearls

- Although consistent antipsychotic treatment represents a critical part of treatment, A person centered approach to treating schizophrenia is essential for all aspects of care, including establishing and maintaining a therapeutic alliance, strengthening shared decision making and adherence, and achieving long-lasting recovery.
- Atypical antipsychotics treat negative and cognitive symptoms, often used as first line treatment
- Anosognosia – leads to poor treatment adherence and clinical course, difficult to treat, increased risk of relapse, involuntary treatment
- Smoking induces CYP1A2 which lowers doses of clozapine, olanzapine (Zyprexa) and smoking cessation can cause rapid increase in levels
- AIMS testing should be done regularly every 3 -12 months depending on dosage and history
- **Prevent relapse – reduce damage**
    - Careful not to delay clozapine trial if indicated
    - Partial adherence common, 74% discontinuation rate at 18 months (CATIE trial)
    - Meds give remission rate 60 – 75% first break; 75% non-responders remit with clozapine; ineffective for 10%
    - Subsequent recoveries are less complete
    - Relapse → "Revolving-door syndrome"
    - Mental illness "burns out" neurons. Meds put out the fire, salvaging the neurons from imminent death.
    - 3.7 x higher risk of premature death (cardiovascular, cancer, accidents)
    - Suicide more likely earlier in illness (5-6%)
    - A long-term illness, progressive gray matter loss in frontal and temporal lobes of the brain; 2-fold higher risk of dementia

Appendix 1

Schizophrenia Spectrum and Other Psychotic Disorders

	Features	Symptoms	Prevalence	Risk/prognostic factors	Development	Course	Functional Consequences
Schizophrenia	Cognitive, Behavioral and Emotional dysfunction with decrease in function	delusions, hallucinations, disorganized speech, disorganized behavior, dec emotional expression and motivation	0.5% to 1%	seasonal, urban , minorities, pregnancy complications; positive genetics, but most people diagnosed have no history	late teens to mid 30's; positive symptoms diminish over lifetime; negative symptoms persist	>6 mos symptoms persistent for at least 1mo.	Suicide 5%, SA-20%; significant social/occupational dysfunction; work/school, interpersonal relations, self care
Schizoaffective Disorder	Same as Schizophrenia with associated mood symptoms for the majority of the duration of the illness	psychotic symptoms for at least 2 weeks without mood symptoms; mood symptom for majority of the duration of the illness active and residual	0.30%	associated with a relative with schizophrenia	as with schizophrenia, some time later diagnosis because mood symptoms recognized later	>6 mos symptoms persistent for at least 1mo.	Suicide 5%, SA-20%; significant social/occupational dysfunction; work/school, interpersonal relations, self care; increased with depressive symptoms
Schizophreniform Disorder	Cognitive, Behavioral and Emotional dysfunction with decrease in function with total duration of at least one month and less than 6 mos.	delusions, hallucinations, disorganized speech, disorganized behavior, dec emotional expression and motivation	0.50%	associated with a relative with schizophrenia	late teens to mid 30's; 1/3 resolve in 6 mos., 2/3 go on to develop schizophrenia or schizoaffective disorder	total duration of at least one month and less than 6 mos.	significant social/occupational dysfunction; work/school, interpersonal relations, self care; if recover within 6 mos. have a very good prognosis
Brief Reactive Psychosis	Sudden onset of positive symptoms of psychosis; for at least 1 day but less than 1 month	delusions, hallucinations, disorganized speech or grossly abnormal behavior	9% of first onset psychotic disorders; 2f>m	preexisting personality with distrust and suspiciousness	From adolescence through life peak in early 30's	can be very brief and has a excellent out in terms of social functioning;	can have high rate of suicide during acute phase; high rates of relapse
Delusional Disorder	erotomanic, grandiose, jealous, persecutory, somatic type delusions	one or more delusions for more than one month; no history schizophrenia, and no significant psychosocial impairment apart form direct impact of delusions	0.2% ; most frequent is persecutory	Associated with family history of psychotic disorders	more prevalent in older individuals	other than direct impact of delusions; fairly good global function is noted, some will develop schizophrenia	circumscribed functional impairment can be substantial with impaired occupational and social functioning, secondary to delusional beliefs: often they keep beliefs hidden and look normal

Appendix 2

Selected adverse effects of antipsychotic medications for schizophrenia

	Weight gain/diabetes mellitus	Hyper-cholesterolemia	EPS/TD	Prolactin elevation	Sedation	Anticholinergic side effects	Orthostatic hypotension	QTc prolongation
First generation agents								
Chlorpromazine	+++	+++	+	++	+++	+++	+++	+
Fluphenazine	+	+	+++	+++	+	–/+	–	ND
Haloperidol	+	+	+++	+++	++	–/+	–	+
Loxapine	++	ND	++	++	++	+	+	+
Perphenazine	++	ND	++	++	++	+	–	ND
Pimozide	+	ND	+++	++	+	+	+	++
Thioridazine*	++	ND	+	+++	+++	++++	++++	+++
Thiothixene	++	ND	+++	++	+	+	+	+
Trifluoperazine	++	ND	+++	++	+	+	+	ND
Second generation agents								
Aripiprazole	+	–	+	–	+	–	–	–/+
Asenapine	++	–	++	++	++	–	+	+
Brexpiprazole	+	+	+	–/+	+	–/+	–/+	–/+
Cariprazine	+	–/+	+	–/+	+	–/+	–/+	–/+
Clozapine¶	++++	++++	–/+	–/+	+++	+++	+++	+
Iloperidone	++	++	–/+	–/+	+	+	+++	++
Lurasidone	–/+	–	++	–/+	++	–	+	–/+
Olanzapine	++++	++++	+	+	++	++	+	+
Paliperidone	+++	+	+++	+++	+	–	++	+
Quetiapine	+++	+++	–/+	–/+	++	++	++	+
Risperidone	+++	+	+++	+++	+	+	+	+
Ziprasidone	–/+	–/+	–	+	+	–	+	++

Adverse effects may be dose dependent.

EPS: extrapyramidal symptoms; TD: tardive dyskinesia; ND: no data.

* Thioridazine is also associated with dose-dependent retinitis pigmentosa. Refer to text.

¶ Clozapine also causes granulocytopenia or agranulocytosis in approximately 1 percent of patients requiring regular blood cell count monitoring. Clozapine has been associated with excess risk of myocarditis and venous thromboembolic events including fatal pulmonary embolism. These issues are addressed in the UpToDate topic review of guidelines for prescribing clozapine section on adverse effects.

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Appendix 3

Schizophrenia Spectrum and Other Psychotic Disorders

Lisa W. Goldstone, MS, PharmD, BCPS, BCPP

Figure 12. SGAs and Relative Risk for Selected Adverse Effects

Medication	EPS*			QTc prolongation	Hyperprolactinemia	Sedation	Orthostatic Hypotension	Weight Gain	Glucose Intolerance	Lipid Abnormalities
	Dystonias	Pseudoparkinsonism	Akathisia							
Aripiprazole	Low	Low-Moderate	Moderate-High	Very Low	Very Low	Low	Low	Very Low	Very Low-Low	Very Low
Asenapine	Low	Low-Moderate	Moderate	Low-Moderate	Low-Moderate	Low	Low	Very Low-Low	Low	Low-Moderate
Brexpiprazole	Very Low	Low	Low	Low	Low	Low	Low	Very Low-Low	Low	Low
Cariprazine	Moderate	Moderate	Moderate	Low	–	Low	Low	Low	Low	Low
Clozapine	Very Low	Very Low	Very Low	Dose-dependent	Low	High	High	High	High	High
Iloperidone	Very Low	Low	Very Low	Moderate	Low	Low	Moderate	Low	Low-Moderate	Moderate
Lurasidone	Moderate	Moderate	Low-Moderate	Low	Low	Low	Moderate	Very Low-Low	Very Low-Low	Very Low
Olanzapine	Low	Moderate	Moderate	Low	Low-Moderate	Moderate	Low	High	High	High
Paliperidone	Moderate-High	Low-Moderate	Low-Moderate	Low-Moderate	High	Low	Moderate	Moderate	Moderate	Low
Quetiapine	Low	Low	Very Low	Moderate-High	Low	Moderate-High	Moderate-High	Moderate-High	Moderate-High	Moderate-High
Risperidone	Moderate	Moderate	Low	Low-Moderate	Moderate-High	Low	Moderate	Moderate	Moderate	Low-Moderate
Ziprasidone	Low	Moderate-High	Low	High	Low	Low	Low	Very Low	Very Low-Low	Very Low

EPS=extrapyramidal symptoms

Appendix 4

Dose and admin of LAI antipsychotic for schizophrenia

	Aripiprazole extended release	Flupentixol decanoate*	Fluphenazine decanoate	Haloperidol decanoate	Olanzapine pamoate	Paliperidone palmitate	Pipotiazine palmitate*	Risperidone microspheres	Zuclopenthixol decanoate*
Generation	Second	First	First	First	Second	Second	First	Second	First
Injection interval	4 weeks	2 to 4 weeks	2 to 4 weeks	4 weeks	2 to 4 weeks	4 weeks	3 to 4 weeks	2 weeks	2 to 4 weeks
Available dosage strengths	300 mg 400 mg	20 mg/mL 100 mg/mL (variable dose)	25 mg/mL (variable dose)	50 mg/mL 100 mg/mL (variable dose)	210 mg 300 mg 405 mg	39 mg 78 mg 117 mg 156 mg 234 mg	25 mg/mL 50 mg/mL	12.5 mg 25 mg 37.5 mg 50 mg	200 mg/mL (variable dose)
Dose range (adult)˙	200 to 400 mg	10 to 50 mg	12.5 to 100 mg	20 to 450 mg	150 to 405 mg	39 to 234 mg	75 to 200 mg	12.5 to 50 mg	100 to 400 mg
Maximum recommended dose	400 mg every 4 weeks	100 mg every 2 weeks	100 mg every 2 weeks	450 mg every 4 weeks	300 mg every 2 weeks or 405 mg every 4 weeks	234 mg every 4 weeks	250 mg every 3 weeks	50 mg every 2 weeks	600 mg every 2 weeks
Conversion from oral tablets	Initiate LAI at 400 mg. Overlap oral aripiprazole 10 or 20 mg daily (or other oral antipsychotic) for 14 days concurrent with first LAI injection.	Initiate LAI at 4 times daily oral dose every two weeks or 8 times daily oral dose every 4 weeks. For first week, overlap with oral treatment.	1 mg of oral daily ≈ 1.25 mg LAI every 3 weeks.	Initiate LAI at 10 to 20 times daily oral dose, up to 100 mg. If initial conversion requires >100 mg, follow by balance in 3 to 7 days. Then administer at 4 week intervals.	If stable on oral 10 mg daily, then 210 mg LAI every 2 weeks or 405 mg LAI every 4 weeks for first 8 weeks, then 150 mg IM LAI every 2 weeks or 300 mg every 4 weeks. If stable on oral 15 mg daily, then 300 mg LAI every 2 weeks for first 8 weeks, then 210 mg LAI every 2 weeks or 405 mg LAI every 4 weeks. If stable on oral 20 mg daily then 300 mg LAI every 2 weeks.	Conversion from oral extended release: if stable on oral 12 mg daily, then 234 mg LAI; if 6 mg oral daily, then 117 mg LAI; if 3 mg oral daily, then 39 to 78 mg LAI.	Discontinue oral treatment. Initiate at 50 to 100 mg LAI every 3 weeks. Individualize dose and interval in 25 mg increments based on response no more frequently than every 2 to 3 weeks.	Initiate LAI at 25 mg every 2 weeks. For first 3 weeks overlap with full-dose oral treatment.	If stable on oral dose up to 20 mg daily then 100 mg LAI every 2 weeks. If stable on 25 to 40 mg oral daily, then 200 mg LAI every 2 weeks. If stable on 50 to 75 mg oral daily then 300 mg LAI every 2 weeks. If stable on more than 75 mg daily then 400 mg LAI every 2 weeks.
Injection site	Gluteal only	Gluteal or lateral thigh	Deltoid or gluteal	Deltoid or gluteal	Gluteal only	Deltoid only (load) Deltoid or gluteal (maintenance)	Gluteal	Deltoid or gluteal	Gluteal or lateral thigh
Injection technique	Standard	Z-Track	Z-Track	Z-Track	Standard	Standard	Z-Track	Standard	Z-Track
Solubilization and vehicle	Low solubility particles in aqueous suspension	Ester in medium chain triglycerides or coconut oil	Ester in sesame seed oil	Ester in sesame seed oil	Nanoparticles in aqueous suspension	Nanoparticles in aqueous suspension	Ester in sesame seed oil	Microsphere matrix in aqueous suspension	Ester in low viscosity vegetable oil

Long-acting preparations are administered by deep INTRAMUSCULAR administration only and NEVER given intravenously. Subcutaneous administration is not recommended due to variable absorption and increased risk of local site reaction. Details shown are specific to the preparations and forms available in US, unless otherwise noted. Dosing, administration and other details listed in licensed product information may differ for other forms and by country. Consult official product information for detail.

Appendix 5

Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration
National Institute of Mental Health

KEY: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 = Severe

NAME: _____

DATE: _____

Prescribing practitioner: _____

MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies.		RATER Date
Facial and oral movements	1. **Muscles of facial expression** eg, movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 1 2 3 4
	2. **Lips and perioral area** eg, puckering, pouting, smacking	0 1 2 3 4
	3. **Jaw** eg, biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4
	4. **Tongue** Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	0 1 2 3 4
Extremity movements	5. **Upper (arms, wrists, hands, fingers)** Include choreic movements (ie, rapid, objectively purposeless, irregular, spontaneous) athetoid movements (ie, slow, irregular, complex, serpentine). DO NOT INCLUDE TREMOR (ie, repetitive, regular, rhythmic).	0 1 2 3 4
	6. **Lower (legs, knees, ankles, toes)** eg, lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4
Trunk movements	7. **Neck, shoulders, hips** eg, rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4
Global judgments	8. **Severity** of abnormal movements overall	0 1 2 3 4
	9. **Incapacitation due to abnormal movements**	0 1 2 3 4
	10. **Patient's awareness of abnormal movements** Rate only patient's report - No awareness 0 - Aware, no distress 1 - Aware, mild distress 2 - Aware, moderate distress 3 - Aware, severe distress 4	0 1 2 3 4
Dental status	11. **Current problems with teeth and/or dentures?**	No Yes
	12. **Are dentures usually worn?**	No Yes
	13. **Edentia?**	No Yes
	14. **Do movements disappear in sleep?**	No Yes

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Adult Attention Deficit Disorder Treatment Guidelines

Developed by: Russ Symbal, RPh, BCPP; Leanne Rousseau, MD; Stephanie Sargent, MD;
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Adult ADHD Suspected Diagnosis Evaluation Flow Chart

Step 1:

Questionnaires for patients and also a person who knows patient well

Adult ADHD self-report scale (ASRS)

Step 2:

Medical/psychiatric history: Exclude medical and psychiatric causes of symptoms that could mimic or aggravate ADHD symptoms

Review nutrition and lifestyle habits Sleep, exercise, screen time, substance use, sexual activity, accidents

Step 3:

Review developmental history with collateral information from others; include family, educational, work, relationship history

Discuss with patient:

Observed and perceived strengths and review questionnaire responses

Consider impact of other psychiatric disorders, psychosocial factors, and/or learning disorders

Step 4:

Educate on ADHD diagnosis and discuss patient and family expectations

Review treatment options including:

Non-pharmacological treatments

- Pharmacological options
  - Stimulant

Adult ADHD Evaluation and Follow-up Appointment Flow Chart

INITIAL CONSULTATION

- Obtain and Review prior psych records
- Run Idaho and Washington PMP
- Discuss diagnostic tools and administer if indicated
- UDS
- Opiate Risk tool (Appendix #2)

WHEN you have enough data to diagnose **AND** intend to prescribe stimulant medications

- Discuss treatment guidelines and sign treatment contract (Appendix #3)

History of Substance Use <u>OR</u> High-risk ORT screening?

YES

- Consider Psychiatrist consultation

Trial Non-stimulant medications:
-atomoxetine
-bupropion
-clonidine
**See prescribing supplement (Appendix #4)*

NO

Refer to (Appendix #2)

Controlled Substance Risk assessment to determine:
-frequency of appointments
-frequency of UDS

<u>IF</u> hx Substance use disorder, s/p treatment and sober > 2 years

- Use long-acting formulations and limit abuse potential
- Make personalized treatment plan and explain need for stricter monitoring
- Mandate medication safety plan

(Lock box at home, initial 1 week scripts, random UDS, pill counts at every visit)

- Educate patient and family on signs/symptoms of relapse

<u>Follow up visits:</u>

- PMP
- UDS if indicated
- Progress tracker + discussion of therapeutic effect
- Refills as indicated by Risk Assessment from initial consult
- Schedule FU with appropriate provider at appropriate interval
- Document monitoring efforts

Adult Attention Deficit Disorder Treatment Guidelines

The purpose of this guide is not to overly constrict practice but to provide a structure, evidence and expert-based guidelines, and a standard basis to fall back upon to allow primary care providers to maintain sound clinical judgment that leads to appropriate safe care. There are situations which this guideline does not cover, or where the suggested path may not be appropriate for the unique clinical scenario. These situations may be appropriate for that individual and should be noted and documented in the record nonetheless.

Attention deficit disorder has a prevalence of about 2.8%. It can have major impact across multiple settings that interferes with one's life. Impairments in adults with ADHD manifest in various domains of life; work, academic settings and relationships. This disorder may occur in patients (>85%) where comorbid psychiatric diagnoses are being treated or strongly considered. These include anxiety, depression, learning disabilities, OCD, personality disorders, bipolar disorder and autism spectrum disorders. This disorder can present in patients who may display various degrees of dependence, addiction with prescribed medication and/or illicit substance use. ADHD symptoms themselves **do not** mean someone has ADHD diagnosis. A through medical, psychiatric, psychosocial history and functional review accompanied by physical examination are required to make a diagnosis. Ancillary testing may include laboratory tests, sleep studies, ECG, EEG, brain imaging and or psychological testing.

DSM-5™ diagnostic criteria for ADHD

- *Older adolescents and adults (over age 17 years) must have five or more symptoms from either (or both) the inattention group of criteria and the hyperactivity and impulsivity criteria*

Symptoms of inattention

- Often fails to give close attention to detail or makes mistakes
- Often has difficulty sustaining attention in tasks or activities
- Often does not seem to listen when spoken to directly
- Often does not follow through on instructions and fails to finish schoolwork or workplace duties
- Often has difficulty organizing tasks and activities
- Often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort
- Often loses things necessary for tasks or activities
- Is easily distracted by extraneous stimuli
- Is often forgetful in daily activities

Symptoms of hyperactivity and impulsivity

- Often fidgets with or taps hands and feet, or squirms in seat
- Often leaves seat in situations when remaining seated is expected
- Often runs and climbs in inappropriate situations (in adolescents or adults, may be limited to feeling restless)
- Often unable to play or engage in leisure activities quietly
- Is often 'on the go', acting as if 'driven by a motor'
- Often talks excessively
- Often blurts out answers before a question has been completed
- Often has difficulty waiting their turn
- Often interrupts or intrudes on others

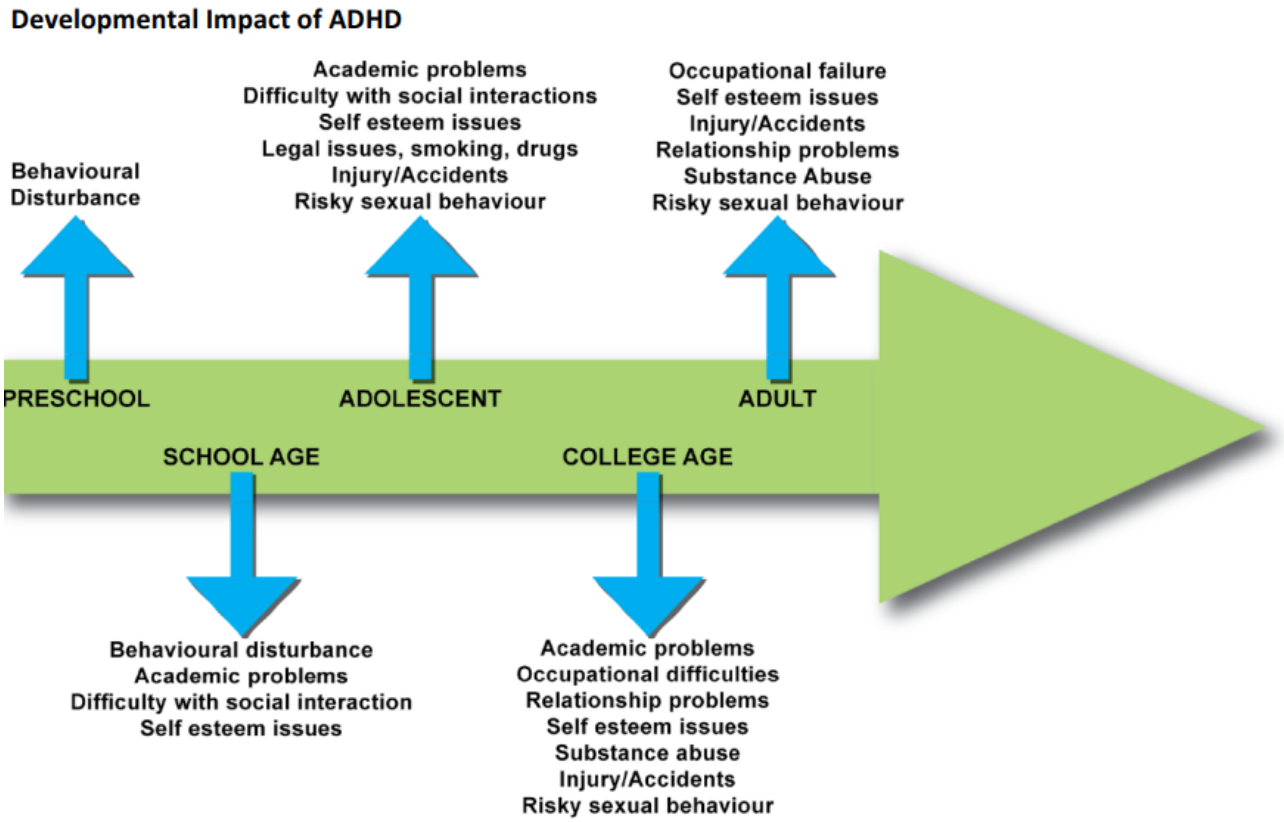
Additional Symptoms

- Several inattentive or hyperactive-impulsive symptoms present prior to age 12 years.
- Several inattentive or hyperactive-impulsive symptoms present in two or more settings (e.g. at home, school or work; with friends or relatives; in other activities)
- Clear evidence that the symptoms interfere with, or reduce the quality of social, academic or occupational functioning
- Symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder, and are not better explained by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal)

Things to Look for in Diagnosing an Adult with ADHD

- **Trouble Getting Organized**
  - For people with ADHD, the responsibilities of adulthood (e.g. bills, jobs, and children) can make problems with organization more obvious and more problematic than in childhood
- **Reckless Driving and Traffic Accidents**
  - ADHD makes it hard to keep your attention on a task, so spending time behind the wheel of a car can be hard
  - ADHD symptoms can make some people more likely to speed, have traffic accidents, and lose their driver's licenses
- **Marital Trouble**
  - Many people without ADHD have marital problems, so a troubled marriage shouldn't necessarily be seen as a red flag for adult ADHD. But there are some marriage problems that are likely to affect the relationships of those with ADHD.
  - Often, the partners of people with undiagnosed ADHD take poor listening skills and an inability to honor commitments as a sign that their partner doesn't care.
  - If you're the person with ADHD, you may not understand why your partner is upset, and you may feel you're being nagged or blamed for something that's not your fault.
  - Difficulty with parenting responsibly.
- **Extremely Distractible**
  - ADHD is a problem with attention, so adult ADHD can make it hard to succeed in today's fast-paced, hustle-bustle world
  - Many people find that distractibility can lead to a history of career under-performance, especially in noisy or busy offices
  - If you have adult ADHD, you might find that phone calls or email derail your attention, making it hard for you to finish tasks
- **Poor Listening Skills**
  - Do you zone out during long business meetings?
  - Did your husband forget to pick up your child at baseball practice, even though you called to remind him on his way home?
  - Problems with attention result in poor listening skills in many adults with ADHD, leading to a lot of missed appointments and misunderstandings
- **Restlessness, Trouble Relaxing**
  - While many children with ADHD are "hyperactive," this ADHD symptom often appears differently in adults
  - Rather than bouncing off the walls, adults with ADHD are more likely to be restless or find they can't relax. If you have adult ADHD, others might describe you as edgy or tense.

- **Trouble Starting a Task**
  - Just as children with ADHD often put off doing homework, adults with ADHD often drag their feet when starting tasks that require a lot of attention
  - This procrastination often adds to existing problems, including marital disagreements, workplace issues, and problems with friends
- **Lateness**
  - There are many reasons for this. First, adults with ADHD are often distracted on the way to an event, maybe realizing the car needs to be washed and then noticing they're low on gas, and before they know it an hour has gone by
  - People with adult ADHD also tend to underestimate how much time it takes to finish a task, whether it's a major assignment at work or a simple home repair
- **Angry Outbursts**
  - ADHD often leads to problems with controlling emotions
  - Many people with adult ADHD are quick to explode over minor problems
  - Often, they feel as if they have no control over their emotions
  - Many times, their anger fades as quickly as it flared, long before the people who dealt with the outburst have gotten over the incident
- **Prioritizing Issues**
  - Often, people with adult ADHD mis-prioritize, failing to meet big obligations, like a deadline at work, while spending countless hours on something insignificant.
- **Trouble in Workplace:**
  - Low job stability, behavioral and/or poor performance at work, fired from workplace



Attention Deficit Disorder is a complex problem that often is squeezed into an already complex initial visit. This can lead to incomplete assessment of risks, partial discussions of patient expectations and clinic protocols, and abbreviated education for patient on informed decision making and realistic goal setting. For this reason, it is recommended that a dedicated appointment be scheduled for intake and assessment that allows adequate time to address this topic.

When scheduling the initial intake encounter, patients should be forewarned the following:

- New patients may not be provided stimulants at first visit.
- Stimulants should not be prescribed until records from previous treating physicians and other resources have been reviewed.
- Pre-emptive records release should be encouraged when patients are scheduling their intake appointment to help facilitate a timelier transition of care.
- **Strongly encourage them to bring a family member or friend to the appointment to get further information**.

- Review of records if available at time of intake or if not yet obtained, getting permission to release records for review when become available.
- **Other suggestions to help with solidify diagnosis:**
    - **It is very helpful to have a family member or friend to help validate symptoms.**
    - A set of resources are available to assist in history taking on new patients, or patients presenting with a new complaint, which should include:
        - Adult ADHD Self-Report scale (ASRS-v1.1) (See Appendix #1)
            - » Minimum requirement for diagnosis
            - » Recommended screening tool for majority of patients at initial visit
        - Opiate Risk Tool (ORT, see Appendix #2)
            - » Should be performed on all patients at initial visit
        - PHQ-9
        - Baseline urine drug screen should be performed on all patients at initial visit
        - **The Idaho Prescription Monitoring Program and the Washington Prescription Monitoring Program database should be checked at the initial visit on all patients to ensure that prescriptions from other facilities are not being filled.**
            - » All physicians and NPs do have the ability to sign up for these databases and ancillary staff can be given delegate access to promote efficient access.
                - Idaho PMP: https://idaho.pmpaware.net/login
                - Washington PMP: https://secureaccess.wa.gov/
- **Psychosocial Treatment Considerations:**
    - The clinical focus towards functional impairment and outcome, with improvement of overall life quality as the main goa of treatment.
    - Psychoeducation is important to educate, demystify and empower patients and families
    - Comprehensive, collaborative and multimodal treatment approach tailored to the individual is optimal
    - This includes cognitive behavioral therapy, behavioral interventions, mindfulness and social skill training

- **Medication Treatment Considerations:** (Appendix #4)
  - First line treatment agents
    - Stimulants - If stimulant therapy is deemed necessary and/or reasonable at the intake appointment and after review of records
      - » Methylphenidates and Amphetamines
      - » Efficacy and tolerability vary by individual
      - » Long acting are preferable
        - Easier dosing, Diminished diversion risk, Better tolerability
      - » These patients may have a variety of risk factors of abuse or susceptibility to adverse effects from these medications.
        - If a patient has a substance abuse history caution must be observed
        - There is recognition of the harm that prescription of stimulants can have on patients.
        - Failure to identify patients at risk for abuse puts patients at risk, as does failure to identify patients who are misusing their medications.
        - Misuse of prescription stimulants is recognized as major risk for patient wellbeing.
      - » It will be important to stress to the patient that it will be continued/started on a trial basis—
        - **Goals of stimulant therapy focus on improvement of functional status.**
        - If stimulants are prescribed a controlled substance agreement signed (Appendix #3)
  - Second line treatment agents (Appendix #4)
    - atomoxetine, guanfacine XR
      - » With any history of substance abuse trials of non-stimulant options should be considered first
      - » Use of stimulant medication in someone with a recent/current history of substance abuse is strongly not recommended.
      - » Non-stimulants can be used in combination with first line agents for potential augmentation
  - Third line treatment agents
    - bupropion, clonidine, modafinil
    - Used when stimulants are contraindicated or for augmentation
  - **If the patient has a remote history of substance abuse >2 years clean and has completed a substance abuse treatment program, after failing non stimulant options, consideration of stimulants can be considered with the following guidelines:**
    - Use long-lasting medications as they help reduce the potential for abuse.
    - Providers should make patients sign a written therapeutic contract with clearly defined consequences if abuse or violations of the agreement should occur. The contract should be kept on file and periodically reviewed with the patient.
    - At the patient's home, stimulants should be kept in a safe place and medications should be taken under the supervision of a responsible adult.
    - Provider should write prescriptions for only one week at a time.
    - Providers and family members should learn to recognize drug-seeking behaviors. Self-medication should not be tolerated.
    - Patient must bring in medication for pill counts at each visit
    - Patient may be subjected to random drug screens

- **Although there is no evidence that the use of stimulants for treating ADHD can lead to substance abuse. ADHD is clearly associated with increased risk of substance abuse. In certain rare situations treatment of ADHD can actually decrease risk of substance abuse**.
- **Consider psychiatric/pharmacy consult if:**
    - **Opiate Score is in the high moderate to high range**
    - **Patient is on other psychotropic medication or has other psychiatric diagnoses or symptoms such as mania, psychosis, suicidality**

If prescribed stimulants:

1. Patients must be seen at an appropriate interval based on risk. Risk level is determined by the Opiate Risk Tool (ORT, see Appendix #2) at the initial visit. Clinical judgment should be used to assess whether the ORT accurately assesses a patient's true risk.

a. Low risk patients should be seen at least every 6 months, once stabilized.
b. Moderate risk patients should be seen at least every 3 months, once stabilized.
c. High risk patients should initially be seen at least every 1 month, once stabilized.
d. An appropriate follow-up plan for high-risk patients should be developed and clearly documented in and on the prescription, as well as outlined to the patient so appropriate expectations are established up front.
e. Risk levels can be modified at depending on patient's history and level of compliance.

2. **Urine Drug screens should be done on all patients in the program. Recommendations for urine drug screens are as follows:**
    a. Low risk: Minimum of 12 months
    b. Moderate & High risk: Every 1 - 3 months
    c. Aberrant behavior or suspicious activity may prompt more frequent Urine Drug Screening. All patients should be subject to random urine drug screens as per provider request.
    d. Aberrant urine drug screens are frequently due to cross reactivity with other substances. Aberrant findings should prompt confirmatory testing rather than immediate discharge.
    e. Confirmed aberrant findings should prompt individualized assessment of risk and mitigation of offending behavior in a shared conversation with the patient
    f. Urine Drug screening should be conducted with standards as per clinic UDS protocol to minimize tampering or alterations to UDS screening. Please refer to protocol.
    g. Some drug screen will not identify methylphenidates
        i. If positive, may mean using other stimulants
        ii. If negative, does not necessarily mean they are not taking the medication
3. **The Idaho & Washington Prescription Monitoring Program database should be checked at every appointment, to ensure that prescriptions from other facilities are not being filled.**
    a. Idaho PMP: https://idaho.pmpaware.net/login
    b. Washington PMP: https://secureaccess.wa.gov/
    c. (These reports can be generated by staff prior to prescriber's engagement with the patient.)
4. **Adult ADHD Self-Report scale (ASRS-v1.1) as a progress tracker should be filled out every visit. (See Appendix #1)** If no progress is made with medication prescribed, evaluation of medication options and or diagnosis should be examined. **If no improvement is noted stimulants should not continue to be prescribed.**
5. Document for stimulant prescribed, amount of prescribed and number of refills
    a. Be wary of patient needing ever increasing doses of stimulants and early refill
6. Schedule patient with PCP or Provider prescribing controlled substances when able to ensure continuity. Utilize recall system to ensure appointment with appropriate provider.
    - Review stimulant treatment plan, goals and objective yearly and document in the chart.
    - **MAKE SURE NEXT APPOINTMENT IS SCHEDULED TO MATCH REFILLS GIVEN. THIS ELIMINATES OTHER INDIVIDUALS HAVING TO DETERMINE IF REFILL REQUESTS ARE VALID.**

A common difficulty in stimulant management is managing refills over the telephone. Here are some guidelines that can minimize inappropriate refills.

1. **Refills will take up to 5 business days to process**. "Urgent" refills or partial refills "To get by" should be against policy. This allows the PCP adequate time to make decisions on refills, so that on-call physicians are not being required to make judgment calls on patients they are unfamiliar with.
2. **Only low risk patients should be allowed to get a telephone refill.** Moderate and high-risk patients, should have visits at least every 3 months for reevaluation. These patients should receive hard copy prescriptions for opiates or controlled medications at the time of their clinic visit. Multiple paper prescriptions up to 3 months can be provided to give adequate supply through their next scheduled visit.
3. **All telephone refills should be approved by primary care provider**.
4. **Telephone refills for stimulants that are early shall not be given.** If a patient is having escalating symptoms requiring greater than planned usage of prescribed medication, or if a patient 'ran out early' this may represent a change in clinical situation that requires an in person clinic appointment and re-negotiation of a change in plan. It can also represent diversion or misuse, the risk for which will have to be assessed again in person at a clinic appointment preferably by the patient's PCP if available.
5. **Refills will only be authorized by the patient's PCP** with the exception of PCP being out of the office for a prolonged duration that would exceed the 5-day minimum refill request expectation such as with vacation, CME, or other leave of absence.

Initial Visit

1. Review of records, if not yet obtained, get release of records.
2. Review Diagnostic Criteria:
    a. If possible, validate symptoms with another family member or friend at appointment
    or
    b. Encourage family member or friend to attend follow up appointment to validate symptoms.
3. Patient should fill out:
    a. Adult ADHD Self-Report scale (ASRS-v1.1) (See Appendix #1)
    b. Opiate Risk Tool (See Appendix #2)
    c. Urine drug screen
    d. Report from the Idaho Prescription Monitoring Program.
    e. Controlled substance agreement signed
4. If Opiate Score is in the high moderate to high range (>4) consider psychiatric consult
5. If a patient has a substance abuse history caution must be observed.
    a. With any history of substance abuse trials of non-stimulant options should be considered first (atomoxetine, bupropion and clonidine)
    b. Use of stimulant medication in someone with a recent/current history of substance abuse is strongly not recommended.
    c. If the patient has a remote history of substance abuse >2 years clean and has completed a substance abuse treatment program, after failing non stimulant options, consideration of stimulants can be considered with the following guidelines:
        i. Use long-lasting medications as they help reduce the potential for abuse.
        ii. Sign a written therapeutic contract
        iii. Stimulants should be kept in a safe place and be taken under the supervision of a responsible adult.
    d. Physicians should write prescriptions for only one week at a time.
    e. Self-medication should not be tolerated.

Follow-Up Visits

1. Review stimulant treatment plan, goals and objective yearly and document in the chart
2. Risk level will be assessed with the Opiate Risk Tool at the initial visit. (Appendix#2)
    a. Clinical judgment should be used to assess a patient's true risk.
    b. Low risk patients (<3) should be seen at least every 6 months.
    c. Moderate risk patients (3-7) should be seen at least every 3 months.
    d. High risk patients (>7) should initially be seen at least every 1-2 months.
    e. An appropriate follow-up plan for high-risk patients should be developed and documented in the chart up front
3. Urine Drug screens, if Opiate Risk Tool score:
    a. Low risk: (Score: 0-3) Minimum of12 months
    b. Moderate (Score: 4-7)- High risk (Score >7): Every 1 - 3 months (can be changed at provider's discretion)
    c. In addition, all patients should be subject to random urine drug screens at provider's discretion.
    d. Aberrant findings should prompt confirmatory testing.
    e. Confirmed aberrant findings should prompt individualized assessment of risk and mitigation
    f. Urine Drug screening should be conducted with standards as per clinic UDS protocol.
4. The Idaho Prescription Monitoring Program database should be checked at every 6 months at least.
5. Adult ADHD Self-Report scale (ASRS-v1.1) as a progress tracker should be filled out every visit. (Appendix #1)
6. Make clear documentation in chart; type of stimulant prescribed, amount of prescribed and number of refills.
7. **MAKE SURE NEXT APPOINTMENT IS SCHEDULED TO MATCH REFILLS GIVEN.**

Remember: Goal of stimulant therapy focuses on improvement in functional status

Appendix #1:
Instructions for Adult ADHD Self-Report Scale Symptom Checklist (ASRS v1.1)

Symptoms

1. Ask the patient to complete both Part A and Part B of the Symptom Checklist by marking an "X" in the box that most closely represents the frequency of occurrence of each of the symptom
2. Score Part A. If four or more marks appear in the darkly shaded boxes within Part A then the patient h symptoms highly consistent with ADHD in adults and further investigation is warranted.
3. The frequency scores on Part B provide additional cues and can serve as further probes into the patient's symptoms. Pay particular attention to marks appearing in the dark shaded boxes. The frequency-based response is more sensitive with certain questions. No total score or diagnostic likelihood is utilized for the twelve questions. It has been found that the six questions in Part A ar most predictive of the disorder and are best for use as a screening instrument.

Impairments

- Review the entire Symptom Checklist with your patients and evaluate the level of impairment associa with the symptom.
- Consider work/school, social and family settings.
- Symptom frequency is often associated with symptom severity, therefore the Symptom Checklist m also aid in the assessment of impairments. If your patients have frequent symptoms, you may want to them to describe how these problems have affected the ability to work, take care of things at hom get along with other people such as their spouse/significant other.

History

- Assess the presence of these symptoms or similar symptoms in childhood. Adults who have ADHD ne not have been formally diagnosed in childhood. In evaluating a patient's history, look for evidence o early-appearing and long-standing problems with attention or self-control. Some significar symptoms should have been present in childhood, but full symptomology is not necessary.

Appendix 1

ADULT ADHD SELF-REPORT SCALE (ASRS-V1.1) SYMPTOM CHECKLIST

Patient Name _____ **Today's Date** _____

Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.

PART A	Never	Rarely	Sometimes	Often	Very Often
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?					
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?					
3. How often do you have problems remembering appointments or obligations?					
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?					
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?					
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?					
PART B					
7. How often do you make careless mistakes when you have to work on a boring or difficult project?					
8. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?					
9. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?					
10. How often do you misplace or have difficulty finding things at home or at work?					
11. How often are you distracted by activity or noise around you?					
12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?					
13. How often do you feel restless or fidgety?					
14. How often do you have difficulty unwinding and relaxing when you have time to yourself?					
15. How often do you find yourself talking too much when you are in social situations?					
16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?					
17. How often do you have difficulty waiting your turn in situations when turn taking is required?					
18. How often do you interrupt others when they are busy?					

Appendix #2: Opioid Risk Tool

Opioid Risk Tool (ORT)

Patient Form

Name _____ **Date** _____

Mark each box that applies		Female	Male
1. Family history of substance abuse	▪ Alcohol ▪ Illegal drugs ▪ Prescription drugs	[ ] [ ] [ ]	[ ] [ ] [ ]
2. Personal history of substance abuse	▪ Alcohol ▪ Illegal drugs ▪ Prescription drugs	[ ] [ ] [ ]	[ ] [ ] [ ]
3. Age (mark box if 16-45 years)		[ ]	[ ]
4. History of preadolescent sexual abuse		[ ]	[ ]
5. Psychological disease	▪ Attention-deficit/ hyperactivity disorder, obsessive-compulsive disorder, bipolar disorder, schizophrenia ▪ Depression	[ ] [ ]	[ ] [ ]

Opioid Risk Tool Clinician Form

(includes point values to determine scoring total)

Mark each box that applies.

	Female	Male
1. Family History of Substance Abuse:		
Alcohol	☐ 1	☐ 3
Illegal Drugs	☐ 2	☐ 3
Prescription Drugs	☐ 4	☐ 4
2. Personal History of Substance Abuse:		
Alcohol	☐ 3	☐ 3
Illegal Drugs	☐ 4	☐ 4
Prescription Drugs	☐ 5	☐ 5
3. Age (mark box if between 16-45)	☐ 1	☐ 1
4. History of Preadolescent Sexual Abuse	☐ 3	☐ 0
5. Psychological Disease:		
Attention Deficit Disorder, Obsessive Compulsive Disorder, Bipolar, Schizophrenia	☐ 2	☐ 2
Depression	☐ 1	☐ 1
Scoring Totals:	_____	_____

Total Score Risk Category:

Low Risk: 1

Moderate Risk: 4

High Risk: 8

Appendix #3

Controlled Substance Risk Assignment & Monitoring Protocol

<Last Updated 6/9/17>

Date of assessment: _____ Patient: _____ DOB: _____

Risk Assignment (circle): LOW……MODERATE……..HIGH

CHECK-LIST:

LOW RISK:

[ ] UDS frequency: _____ (Minimum of once annual UDS)

[ ] Appointment frequency: _____ (Minimum of every 6 months)

[ ] PMP report frequency: _____ (Minimum of bi-annually)

MODERATE/HIGH RISK:

[ ] UDS frequency: _____ (Minimum of Q3mo UDS)

[ ] Appointment frequency: _____ (Minimum of every 3 months)

[ ] PMP report frequency: _____ (Minimum of every 3 months)

Patient acknowledgement of provider assessment and plan:

My provider has reviewed my assigned risk level for prescribing stimulant medication for Attention Deficit Disorder. All questions I have in regard to my risk assignment have been answered. I understand the expectations outlined in my above personalized plan, including urine drug screening frequency, appointment frequency, concurrent use of other potentially addicting medication and prescription monitoring program reporting.

Patient Signature: _____ Date: _____

Provider Signature: _____ Date: _____

Appendix 4

Stimulants

Drug Name	Duration of action	Dose	Stimulant Class	Starting dose	FDA max	Comments
methylphenidate (Ritalin, Concerta) FDA: ADHD ages 6 + Do not take with food	IR: 2-4 hrs SR: 4-6 hr LA: 8 hr, 2 pulses Concerta SR: 12 hr	Peds: up to 2mg/kg/day Adults 20-30mg/day IR, SR, LA Tablets, oral suspension, patch	Methyl +Dextro	Depends on formulation chosen	Peds: 60mg/day Adults: 40-60mg/day	SE: insomnia, anorexia, tremor, agitation, palpitations *can have dips with ER formulations *caution use with SSRI, TCA, seizure meds *Do NOT use with MAOI
D-methylphenidate (Focalin) *considered to be twice as potent and D, L methylphenidate	4-6 hrs	IR: 2.5-10mg twice daily ER: Peds: 10-30mg daily Adults 10-40mg daily		IR: 2.5mg twice daily ER: start with 5mg daily and titrate up to effect	IR: 10mg twice daily ER: Peds: 30mg daily Adults: 40mg daily	Same as above
Dextroamphetamine (Dexedrine, Pro Centra, Zenzedi) PDA: 3–6-year-old and up	IR: 3-6hr SR: 8 hrs Tablets, capsules, oral solution	5-40mg/day Frequency depends on formulation IR: 2.5mg-40mg ER:	Dextro	IR: 2.5mg twice daily SR: 5mg once daily	40mg daily Peds max depend on age	*avoid tablets in aspirin allergic patient Do not take with fruit juice or sodium bicarb
Amphetamine salt combo (Adderall, Adderall XL) FDA ADHD age 3 and up	IR: 3-6hr ER: 8hr IR, ER, oral suspension, ODT	5-40mg daily Frequency dictated by formulation	Dextro + methyl	IR: 5mg once or twice daily ER: 10mg daily	40mg daily Peds max depends on age	Same as D-amphetamine above and All stimulants Thought to be more balanced between dopamine and norepinephrine effect than D-amphetamine
lisdexamfetamine (Vyvanse) FDA ADHD age 6+	Capsule: once daily 10-12hr duration of action	30-70mg daily	Dopamine and nor-epi reuptake inhibitor and releaser stimulant	30mg/day in AM Increase 10-20mg/week to target behaviors	70mg/day	Pro-drug, not active until absorbed and converted to active drug SE: insomnia, HA, anorexia Same as all stimulants

Non-Stimulants

Drug Name	Duration of action	Dose	Class	Starting dose	FDA max	Comments
Atomoxetine (Strattera) FDA ADHD 6yr +	½ life =5hrs	Peds: 0.5-1.2 mg/kg Adults 40-100mg/d	Nor-epi reuptake inhibitor	Peds: 0.5mg/kg/ Adults: 40mg/day	Peds: weight based Adults: 100mg	SE: sedation, fatigue, tachycardia, increased BP Not habit forming Caution use with bipolar disorder Caution with co-administration with par fluoxetine
bupropion (Wellbutrin) OFF label for ADHD In adults	IR: TID SR: BID XL: daily	IR: 225-450 mg divi TID SR: 200-450mg divided BID XL:150-450mg daily	Dopamine reuptake inhibitor and releaser	150mg XL daily	450mg daily	Dry mouth, constipation, nausea, anorexia, sweating insomnia, hypomania, SI Rare stevens-Johnson Do not use if Hx Seizures
Clonidine (Catapres) FDA approved for ADHD in adults and kids 6+	ER for ADHD Half-life: 12-16 hours	ER: 0.1-0.4mg/day i divided doses	Norepi receptor agonist	0.1mg qHS	0.4mg/day divided	Dry mouth, dizziness, cons sedation If stopped- rebound hypertension for 4-7 days Taper on, taper off Concern with kids and GI illness for acute disconti
Guanfacine (Intuniv, Tenex) FDA for ADHD kids 6+	Differ by formulation	IR: 1-2 mg/day ER: 1-4mg day	Norepi receptor agonist 2A receptors in pre-frontal cortex (think more impulse control))	IR: 1mg qHS	IR: 2mg/day ER: 4mg/day	Sedation, dizziness, dry constipation, fatigue, hypotension *do not give with high meals *significant drug interactions

From Stahl's Essential Psychopharmacology Prescriber's guide, sixth edition

With stimulants or non-stimulants:

- Screen for seizure disorder hx, structural or atherosclerotic heart disease, hyperthyroidism, co-occurring mental health diagnosis (anxiety, bipolar, depression, psychosis)
- Weight
- Yearly labs (CBC, CMP)
- Medication reconciliation

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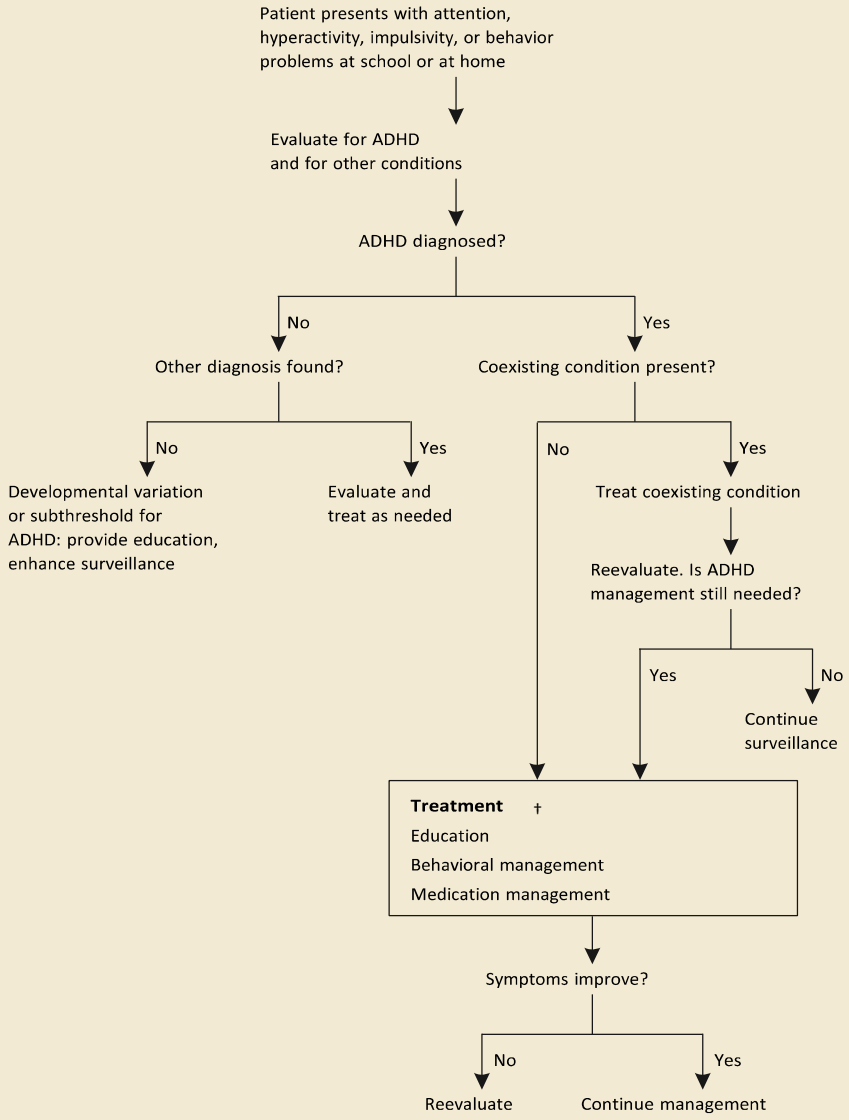
Childhood ADHD

Developed by: Russ Symbal, RPh, BCPP; Leanne Rousseau, MD; Lauren Fletcher, PharmD; Nathen Bertsch, PharmD; Marlee Novak, MD; Benjamin Linker, PharmD; William H. Miller, MD;

Evaluation and Treatment of ADHD in Children and Adolescents*



*—*In general, the overall sequence of evaluation and treatment is similar in children and adults.*

†—*The treatment for preschoolers begins with behavioral management; treatment for older children, adolescents, and adults begins with medication therapy.*

Childhood ADHD

Clinical Presentation

- One of the most common chronic conditions of childhood
- Difficulty controlling behavior
- Affects cognitive, academic, behavioral, emotional, and social functioning
- Affects 4 to 12% of school age children
- 3x more common in boys than girls

DSM-5 Criteria

- Symptoms of Hyperactivity / Impulsivity
  - Occurs often
  - Present in **more than one setting**
    - Home, school, work, social situations
  - Persist for at least 6 months
  - Present before the age of 12 years
    - This is often not recognized until older age
  - **Impaired functioning**
    - Academic
    - Social
      - Difficulty forming friendships
      - Peer rejection
    - Occupational activities
  - Excessive for the developmental level of the child
- < 17 years requires 6+ symptoms of inattention or 6+ symptoms of hyperactivity/ impulsivity
- 17 + years requires 5+ symptoms of inattention or 5+ symptoms of hyperactivity/ impulsivity

Symptom Groups

- **Inattentive (formerly known as ADD)**
  - Symptoms
    - Difficulty paying attention, not listening; daydreaming
    - Easily distracted by irrelevant stimuli
    - Inattention to details / careless mistakes
    - Difficulty following instructions
    - Difficulty completing multi-step tasks
    - Disorganization
    - Loses important things (school books, sports equipment)
    - Forgetful of important things (homework, chores, morning routines)
    - Avoids doing things that require ongoing mental effort
  - Often goes undiagnosed because they are not disrupting the classroom or other activities
  - Most common form among girls
  - Reduced speed of cognitive process and responding
  - Typically not apparent until age 8 to 9

- **Hyperactive / Impulsive**
  - Symptoms
    - Fidgety/squirmy
    - Cannot stay seated
    - Runs and climbs in inappropriate situation
    - Difficulty playing quietly
    - Constantly in motion "as if driven by a motor"
    - Talks excessively
    - Calls out answers before question is completed; interrupts
    - Difficulty taking turns
    - Poor patience while waiting for things/acts/speaks without thinking
  - Hyperactive symptoms peak in severity at age 7 to 8 years and then decline
    - May be barely noticeable by adolescence
  - Impulsivity symptoms usually persist throughout life
    - Substance use
    - Risky sexual behavior
    - Impaired driving
  - Safety issues need monitoring
    - Traffic, firearms, swimming pools, tools (i.e. lawnmowers), poisonous chemicals, cleaning supplies, medicines
- **Combined Type (Inattentive and Hyperactive/Impulsive)**
  - Most common presentation
  - Meets criteria for both symptoms of inattention and symptoms of hyperactivity/impulsivity

Diagnosis in Preschool Children

- ADHD without subtyping can be applied to children as young as 4
- Difficult to meet criteria of impairment in two settings if not attending preschool or child care program
- Caregiver and teacher ratings can be discordant
  - Differing expectations
  - Differing structure

Diagnosis in Adolescents

- May spend less time at home
- At least 2 teachers, counselors, tutors, coach, etc.
- Strict adherence to the presence of symptoms before age 12
  - May fail to identify if more subtle symptoms or above average cognitive abilities
- Frequent digital media use
  - May disrupt development of sustained attention
  - Impulse control
  - Inability to delay gratification
  - Displaces other activities that build attention span and executive function
- Consider intentional misreporting symptoms
  - To obtain medication
  - For school accommodations
  - For accommodations for standardized testing

Etiology

- Lower level of activity in the parts of the brain that control attention and activity
- Functional Brain Imaging
  - Reduced global activation
  - Reduced local activation of basal ganglia and anterior frontal lobes
  - These areas are affected with administration of methylphenidate
- Genetic Factors
  - Increased risk in first-degree relatives (2 to 8x)
  - Often a parent is diagnosed at the same time as the child
- Significant head injuries
- Prematurity
- Prenatal exposures
  - Alcohol
  - Nicotine

Evaluation

Questions to Ask

- How is your child doing in school?
  - Teachers are often first to notice inattention, hyperactivity, or impulsivity
- Any issues with learning that you or your child have seen?
- Is your child happy in school?
- Any difficulties with completing class work or homework?
- Any concerning behavior in school, at home, or when playing with friends?

- Evaluation should be initiated in children > 4 years of age
  - Who have symptoms of: Inattention, Hyperactivity, Impulsivity
  - Who have associated complaints
    - Poor school / childcare performance
    - Difficulty making/keeping friends
    - Difficulty with team sports
- Medical History
  - R/O anemia, hyperthyroidism
- Prenatal exposures
  - Review tobacco, drugs, alcohol
- Cardiac status
- R/O:
  - Autistic Spectrum Disorders
  - Fetal Alcohol Syndrome
  - Fragile X
  - Klinefelter Syndrome
- Social History
- Diet
- Sleep
- Environmental exposures
  - Lead
  - Tobacco smoke

- Family stress
- Family History
  - ADHD
- Neurologic assessment
  - Vision
  - Hearing
  - Coordination
  - Observation for verbal / motor tics
- Behavioral observation in office setting
  - Isolated – interpret cautiously
  - May not be apparent in structured office setting
  - Nervousness / apprehension may be misinterpreted as ADHD symptoms
  - Observation of communication skills
- Particularly non-verbal and pragmatic communication
- Behavioral Rating Scales
  - Vanderbilt Assessment Scale (NICHQ_Vanderbilt_Assessment_Scales.pdf)
  - Conner's CBRS Scale What Is the Conners Scale for Assessing ADHD? (healthline.com)
  - Given to both parent and teacher
  - Should both be positive
  - Completion establishes presence of core symptoms in more than one setting
  - Identifies sx of ADHD but does not determine cause
- Ancillary evaluations to consider
  - Speech therapy evaluation
  - Occupation therapy evaluation
  - Mental health evaluation
  - Blood lead level
  - Genetic testing / Genetics consultation
    - Polysomnogram
    - EEG

Coexisting Conditions

- Common with ADHD
  - May require treatment in conjunction with ADHD
  - Goal for monotherapy, limited evidence to support polypharmacy
  - May affect treatment for ADHD
- Sleep Disorders
  - Focus on sleep hygiene and bedtime routine
  - Timing/dose of stimulant
- Oppositional Defiant Disorder
  - Up to 35% of children with ADHD
  - More common with primarily hyperactive/impulsive type or combined type
- Mood Disorder / Depression
  - Up to 18% of children with ADHD
  - More common with inattentive type or combined type
  - Often a family history
  - Higher risk of suicide – especially during teenage years

- Anxiety Disorder
    - Up to 25% of children with ADHD
    - Consider trial of atomoxetine to improve both ADHD/anxiety symptoms
- Learning Disabilities
    - ADHD, itself, is not a learning disability
- Substance Use Disorder
    - Treat addiction first if present

Treatment

- Once diagnosis is confirmed, outlook for most children receiving treatment is encouraging
- No specific cure, but many treatment options
- Important to set target outcomes for behavior and review with patient/family, i.e.:
    - Improved relationships with parents, siblings, teachers, and friends
    - Being invited to friend's houses or parties
    - Improved academic performance
    - More independence in self-care, i.e. getting ready for school in the morning
    - Fewer disruptive behaviors
    - Increased safety, i.e. when crossing streets, accidents / injuries
- Team Approach to Treatment
    - Physicians, Parents, Teachers, Caregivers, Therapists, Child
    - Continuity of care is important
- Behavioral Therapy (best to include parent training)
    - Multimodal treatment approach with both medication and behavior therapy
    - Set specific goals
        - Staying focused on homework for a set amount of time
        - Get missing assignments turned in
        - Good reports from school
        - Set small, reachable goals
        - Aim for slow progress rather than instant results
    - Daily schedule
        - Consistent wake, eat, bathe, leave for school, sleep, etc.
    - Decrease Distractions
        - TV, music, video games during mealtimes / homework
    - Organize
        - Less likely to lose things if specific and logical places to keep schoolwork, toys, clothes, etc.
        - Charts and checklists
        - Frequent but friendly reminders
    - Positive Reinforcement
        - System of clear rewards or consequences
        - A specified reward every time a desired behavior is shown
        - Kind words/Hugs/Small prizes
    - Limit Choices
        - Only 2 to 3 options at a time
    - Use Calm Discipline
        - Time-out (removing child from the situation or distraction)

- Classroom Management
  - System of clear rewards or consequences
  - Daily or weekly reports
  - Seating near the front
  - Wiggle chairs
  - Smaller groups for activities
  - Keeping assignments short or breaking them into sections
  - Close supervision with frequent, positive cues to stay on task
- Individual and family counseling
- For preschool children (ages 4 to 5) recommendation is caregiver training in behavior management as initial therapy.
- **Can reduce longer term outcomes** such as:
  - Expulsion from preschool or daycare
  - Significant injury to self, other children, caregivers
  - Strong family hx of ADHD
  - Symptoms interfere with other therapies

Pharmacology

- **Stimulants (see Appendix 1)**
  - First line for children > 6 years
  - 80% of children treated with the right medication and right dose see significant improvement of symptoms
  - Primary MOA: increase central dopamine and norepinephrine activity which impacts executive and attentional function
  - Methylphenidates
    - MOA: dopamine and norepinephrine transporter inhibition
    - Available in immediate release, intermediate-acting, extended-release formulations
  - Amphetamines
    - MOA: dopamine and norepinephrine transporter inhibition and stimulates direct release of dopamine and norepinephrine
    - Available in immediate release, extended release formulations
  - Become familiar with a couple of medications in each category
    - Insurance coverage may ultimately decide which medication
    - Have a backup plan, so not to delay treatment
- **Non-Stimulants**
  - atomoxetine (Strattera)
    - MOA: selective norepinephrine reuptake inhibitor
    - Consider if comorbid mood, anxiety disorders, or exacerbation of tics on stimulants
    - Response may take up to 4 weeks
    - Adverse effects: somnolence, GI upset, decreased appetite
    - Warning for hepatotoxicity, baseline LFTs and periodically thereafter
    - Black box warning: suicidal ideation in children and adolescents

- Alpha-2 receptor agonists
  - Can augment stimulants
  - Consider in patients with disruptive/explosive behaviors
  - Clonidine (Kapvay)
  - guanfacine (Intuniv)
    - Longer half-life
    - Less sedating and less risk for hypotension
  - Always extended release
  - Response typically 2-4 weeks
  - No drug holidays
- bupropion (Wellbutrin)
  - Off label - low quality of evidence
  - Weak dopamine and norepinephrine transporter inhibition
  - SR or XL formulations studied most
- Atypical antipsychotics
  - Not currently recommended

- Various diet studies show no significant difference in outcomes
- **Side effects, generally dose dependent**:

Table 33. Stimulant Adverse Effects and Management

Adverse Effect	Management
Anorexia (lack of appetite or desire for food)	High-calorie meal when stimulant effects are low; consider cyproheptadine at bedtime
GI upset	Give with or after food; consider lower dose
Growth delay, reduced growth velocity	Consider drug holiday
Insomnia	Give as early as possible; D/C afternoon or evening dose; consider melatonin at bedtime
Irritability	Trial dose reduction
Dysphoria	Reduce dose; consider alternative stimulant
"Zombie" state	Reduce dose; consider alternative stimulant
↑ BP, HR	Monitor
Tics	Reduce dose, consider alternative stimulant
Hallucinations	D/C stimulant

BP = blood pressure; HR = heart rate.

- Medication Strategies
    - Manage expectations
        - Goal: dose that achieves optimal effect in controlling symptoms with minimal adverse side effects
        - Adjust dosages and schedule
    - Start on weekend to monitor for side effects
    - Response seen in a few days
    - Low and slow, titrate at 1 -2 week intervals, frequent follow-up
    - BID dosing can be helpful
    - Avoid late afternoon/evening dosage
    - Mix extended release with immediate release
    - Continuous treatment preferred
        - May consider drug holiday on weekends, vacations
    - Reassure hesitant parents
        - Not a lifelong commitment
        - ADHD's association with anxiety/depression, self-medication
        - If we don't like it, we can stop it.
    - If no improvement despite treatment
        - Rule out coexisting conditions
        - Re-evaluate and consider concomitant learning disability or alternative diagnosis
        - Non-adherence to treatment plan
        - Try alternate medication
            - 70% respond in first trial, 90% in second trial
            - Stimulant plus guanfacine or atomoxetine
            - Possible regression at 1-2 months, consider dose increase
- Monitoring
    - Follow-up q1month > typically every 3 months when positive response achieved
        - Continue to document using core symptoms
        - Review target goals - i.e. not walking around classroom, following instructions, decreased outbursts, test performance
    - Parents/teachers to repeat Vanderbilt assessment 3-6 months following medication initiation
    - HR, BP, height and weight
    - Consider titrating down/off medication as child advances into adolescence/adulthood
- Contraindications to stimulants
    - Do not combine stimulants with MAOIs, require 14 day washout
    - Dependency
    - Cardiovascular events: consider EKG, cardiology referral prior to starting pending history

Federal mandates that apply to treatment of ADHD

- Individualized Educational Program interventions
- Individuals with Disabilities Education Act
    - ADHD is considered a disability
    - May qualify for special education or services
- Section 504 of Rehabilitation Act of 1973
    - Classroom accommodations who don't qualify for special education services

Appendix 1:

Table 1. Stimulant Medications

Methylphenidate (MPH) for ADHD					
Medication	**Starting Dose**	**How Supplied**	**Dosage Form**	**Duration of Medication Effects**	**Given how many times a day?**
Adhansia XR	25 mg	25, 35, 45, 55, 70, 85 mg	capsules	Up to 16 hours	Once
Aptensio XR	10 mg	10, 15, 20, 30, 40, 50, 60 mg	capsules	12 hours	Once
Azstarys XR	26.1/5.2 mg	26.1/5.2, 39.2/7.8, 52.3/10.4 mg	capsules	12 hours	Once
Concerta	18 mg	18, 27, 36, 54 mg	capsules	12 hours	Once
Contempla XR	8.6 mg	8.6, 17.3, 25.9 mg	disintegrating tablets	12 hours	Once
Daytrana	10 mg	10, 15, 20, 30 mg	patch	6–16 hours	Once
Focalin	2.5 mg	2.5, 5, 10 mg	tablets	4–5 hours	Two to three times
Focalin XR	5 mg	5, 10, 15, 20 mg	capsules	10–12 hours	Once
Jornay PM	20 mg	20, 40, 60, 80, 100 mg	delayed-release capsules	12 hours	Once
Metadate CD	20 mg	10, 20, 30, 40, 50, 60 mg	capsules	8 hours	Once
Quillivant	<10 mg	25 mg	suspension	12 hours	Once
Quillichew	<10 mg	20, 30, 40 mg	chewable tablets	8 hours	Once
Ritalin IR	5 mg	5, 10, 20 mg	tablets	3–4 hours	Two to four times
Ritalin LA	20 mg	10, 20, 30, 40 mg	capsules	8 hours	Once

Amphetamine (AMPH) for ADHD					
Medication	**Starting Dose**	**How Supplied**	**Dosage Form**	**Duration of Medication Effects**	**Given how many times a day?**
Adderall	2.5–5 mg	5–30 mg	tablets	6 hours	Once to twice
Adderall XR	2.5–5 mg	5, 10, 15, 20, 25, 30 mg	capsules	12 hours	Once
Adzenys XR	6.3–12.5 mg	3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg	disintegrating tablets	12 hours	Once
Dexedrine Spansule	5 mg	5, 10, 15 mg	spansules	6 hours	Once to twice
Dexedrine Tablets	2.5–5 mg	5, 10, 15, 20 mg	capsules	3–5 hours	Two to three
Dyanavel XR	2.5–5 mg	2.5 mg	suspension	13 hours	Once
Evekeo	2.5–5 mg	5, 10 mg	tablets	3–5 hours	Two to three
Mydayis	12.5 mg	25, 50 mg	capsules	Up to 16 hours	Once
Vyvanse	30 mg	20, 30, 40, 50, 60, 70 mg	capsules	12–14 hours	Once

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Behavioral and Psychiatric Symptoms in Dementia

Treatment Guidelines

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Overview of Behavioral and Psychiatric Symptoms in Dementia

Behavioral and Psychiatric Symptoms in Dementia (BPSD)

Agitation	Psychosis	Euphoria	Non-Aggressive Pacing
Aggressive	Delusions	Apathy	Restlessness
Physical Aggression	Hallucinations	Irritability	Wandering
Vocalizing/Shouting	Mood/Anxiety/Sleep	Disinhibition	Purposeless motor behavior
Verbal Insults	Depression	Withdrawal	Sleep disturbance
Personality Changes	Obsessive ruminations	Hypersexuality	Appetite/eating

Why are BPSD Important?

Distressing for patient	Caregiver burnout	Reduced quality of life
Distressing for family and caregivers	Caregiver depression	Increase in risk for institutionalization
Increased cost of care		

How Common are BPSD?

At least 80-90% experience at least 1 symptom during the course of dementia

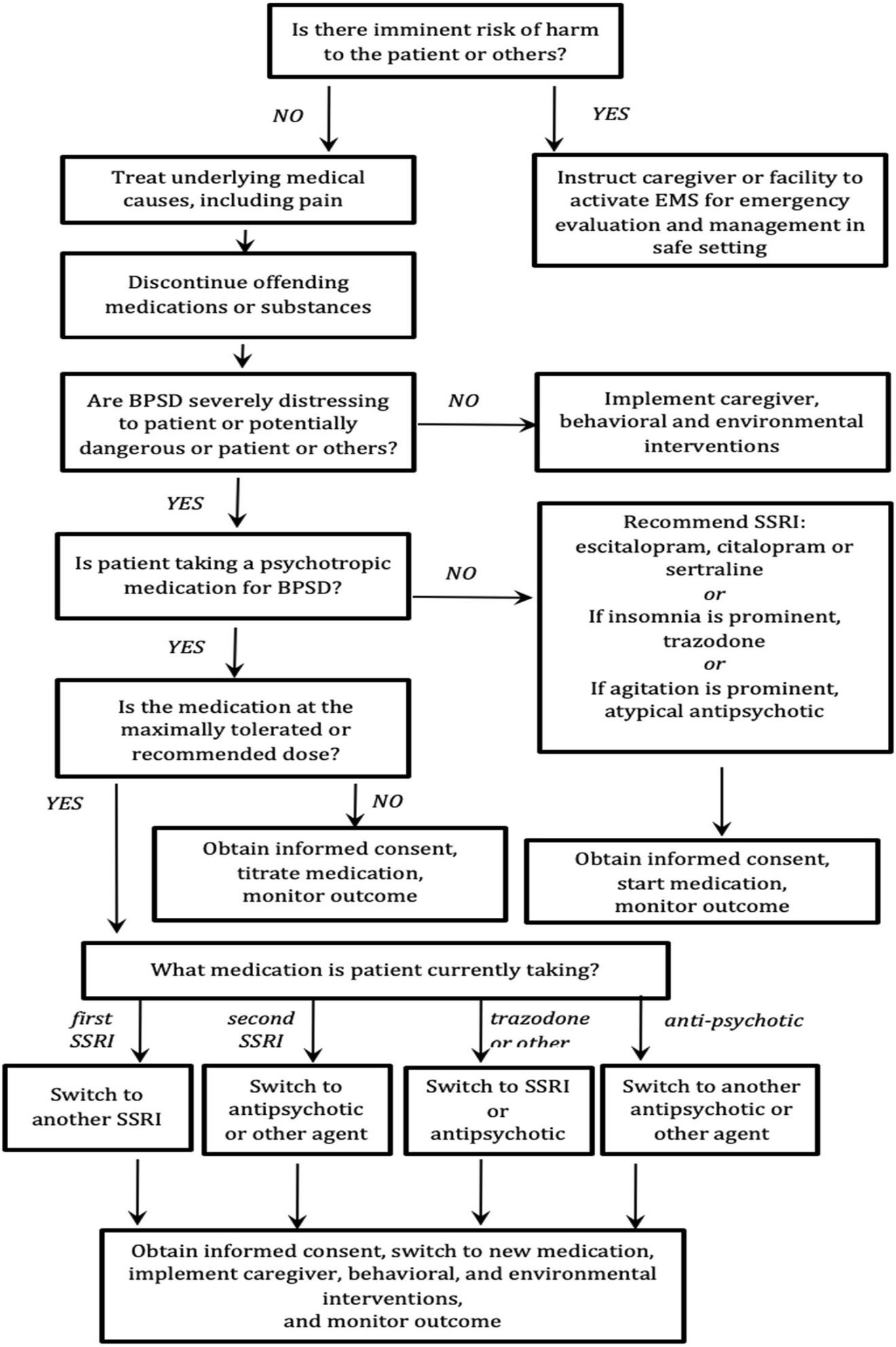
Agitation/Aggression	Psychosis	Depression
20% of patients with AD in clinical settings	25% of patients in clinical settings	20% of patients in clinical settings
40-60% of patients in Long Term Care		

Non-pharmacologic Treatment

Appropriate Stimulation	Assess physical needs:	Decrease complexity in physical environment
Activity and Structure	• Hunger	Simplify tasks
Establishing Routines	• Thirst	Redirection
Increase activity	• Toileting	Backing away, Leave the room!
Increase communication	• Pain	

Interventions for the family

Problem Solve with family	Caregiver education
Identify precipitating factors and modifiable causes	• UCLA Alzheimer and Dementia Care Program caregiver training videos: *https://www.uclahealth.org/dementia/caregiver-education*
Caregiver support	• Powerful Tools for Caregivers (offered by Alz Assoc., HONI)
Caregiver stress reduction and cognitive reframing techniques	• Caregiver Peer Support Groups online or in person (offered by Alz Assoc.)


Is there imminent risk of harm to the patient or others?
NO
YES
Treat underlying medical causes, including pain
Instruct caregiver or facility to activate EMS for emergency evaluation and management in safe setting
Discontinue offending medications or substances
Are BPSD severely distressing to patient or potentially dangerous or patient or others?
NO
Implement caregiver, behavioral and environmental interventions
YES
Is patient taking a psychotropic medication for BPSD?
NO
Recommend SSRI: escitalopram, citalopram or sertraline
or
If insomnia is prominent, trazodone
or
If agitation is prominent, atypical antipsychotic
YES
Is the medication at the maximally tolerated or recommended dose?
YES
NO
Obtain informed consent, titrate medication, monitor outcome
Obtain informed consent, start medication, monitor outcome
What medication is patient currently taking?
first SSRI
second SSRI
trazodone or other
anti-psychotic
Switch to another SSRI
Switch to antipsychotic or other agent
Switch to SSRI or antipsychotic
Switch to another antipsychotic or other agent
Obtain informed consent, switch to new medication, implement caregiver, behavioral, and environmental interventions, and monitor outcome

Principles of Pharmacologic Treatment of Aggression & Agitation in Behavioral and Psychiatric Symptoms

Non-Pharmacologic treatments are 1st line

- **Make sure all reversible causes of problem behaviors have been addressed such as pain, nicotine withdrawal, medication side effects, undiagnosed medical or neurological illnesses, including metabolic conditions and infections; and provocative environments that are either too stimulating or not stimulating enough, vison or hearing issues.**
- Many symptoms have remissions or fluctuate and may improve over several weeks
- Behaviors will wax and wane with or without medications, reassess every few weeks
- There are also real risks of non-treatment, including early institutionalization and harm to the patient or caregiver due to aggressive or violent behaviors.

Assess response with a quantitative measure (see Appendicx #1 & 2)

- Monitor timing of symptoms
- Monitor response to intervention

Develop a comprehensive treatment plan

- No FDA approved medications for treatment and many studies have shown most medications to provide little to no improvement versus placebo
- If pharmacologic interventions pursued:
    - Risks benefits assessed and reviewed with patient and family/surrogates
    - If analysis favors use, start low and titrate to lowest effective dose
    - If side effect occurs, review to assess if taper or discontinuation is appropriate
    - Start with least harmful and progress
    - **If treatment carries risk, discuss with patient/family**
    - If no documented improvement after 4 weeks of reasonable dosing, taper, D/C and/ or switch to another medication.
    - Don't leave them on medication without documented improvement.
    - Try to taper dose down after some stability to lowest effective dose
    - Consider tapering off slowly after 3 – 6 months of stability.
    -

Pharmacological Options

- Very few drugs help with problem behaviors or psychosis in dementia. Remember - the medications used to help control behaviors aren't fixing the underlying problem, they are just masking the manifestation of that problem. So, medication should never be a long-term solution and non-pharmacological strategies should always be maximized first to address underlying causes.

START LOW, GO SLOW

Cholinesterase Inhibitors

- Agents (available formulations)
    - donepezil (tablet, ODT)
        - Start at 5 mg, shoot for 10 mg
        - 23 mg associated with more intolerable side effects
    - galantamine (tablet, ER capsule, liquid)
    - rivastigmine (capsule, 24 hr TD patch)
- Utility
    - Small effect overall
    - No acute benefit
    - Possibly helpful for psychosis in DLB
    - Consider if not already added for AD

NMDA Receptor Blocker

- memantine (tablet, ER capsule, liquid)
    - Some benefit possibly over 3-6 months in AD, unclear role thus far
    - +/- memantine/Citalopram - 17 day trial in acute inpatients showed benefit

Antidepressants

- May not be very effective for the treatment of depression in individuals with dementia, but are still a useful option for agitation in this patient population.
- Side effects to watch out for: headache, stomach upset - less common are hyponatremia, increased risk of falls, bleeding, Parkinsonism, and akathisia.

Selective Serotonin Reuptake Inhibitors (SSRIs) – Consider treatment for mild agitation and aggression in dementia

- citalopram (tablet, liquid)
    - Start 10 daily
    - If needed up to 20 daily
    - Has mild antihistaminic properties due to H_1 binding
    - Treatment limited by QTc prolongation (citalopram max daily dose 20 mg)
- escitalopram (tablet, liquid)
    - Start 5 -10 mg daily
    - If needed - slow titration to 20 mg daily
    - Composed of the pure active S enantiomer, which removes antihistaminic properties found with citalopram
    - Perhaps better efficacy at lower doses (vs citalopram)
    - Still has a dose-dependent risk of QT prolongation
- sertraline (tablet, capsule, liquid)
    - Start 25 mg daily
    - If needed up to 100 mg daily
    - Careful, slower dose titration in panic disorder, anxiety
    - The most studied drug for depression in dementia
    - Often activating, can be useful in "atypical depression"
        - hypersomnia, low energy, mood reactivity
    - σ_1 binding may also contribute to utility in psychotic and delusional depression, anxiolytic effects
- fluoxetine (tablet, capsule, liquid)
    - Start 10 mg daily
    - If needed up to 20 mg daily
    - Activating due to $5HT_{2C}$ antagonism
        - May not be ideal choice in patients with agitation, insomnia, and anxiety
    - Long half-life of 2-3 days, 2 weeks for its active metabolite
- paroxetine (tablet, capsule, liquid)
    - Start 10 mg daily
    - If needed up to 20 mg daily
    - Calming, even sedating in early treatment – mild anticholinergic actions with M_1 receptor binding, debatable clinical significance
    - Sudden withdrawal can cause akathisia, restlessness, GI symptoms, dizziness - withdrawal due to shorter half-life compared to other SSRIs and muscarinic binding – can somewhat avoid with the controlled-release form

Serotonin/Norepinephrine Reuptake inhibitors (SNRIs) – Consider treatment for mild agitation and aggression in dementia
(*5HT & NE action + some DA action in prefrontal cortex)*

- duloxetine (capsule, stable up to 2hrs after opening capsule onto food)
  - Start 20 mg daily
    - Up titrate BID
  - Maximum 60 mg total daily
  - Good option for all types of pain including neuropathic pain, fibromyalgia, chronic musculoskeletal pain (ex: osteoarthritis, back problems)
  - Helped to propel the understanding that painful physical symptoms are frequently associated with a major depressive episode
  - Keep in mind, chronic depression occurs in dementia, thought to be associated with the increase in neurofibrillary tangles and plaque in the hippocampus of patients with Alzheimer's
  - Demonstrated efficacy in cognitive symptoms of depression that are prominent in geriatric depression (pro-noradrenergic and pro-dopaminergic effects of NET inhibition in the prefrontal cortex)
  - Lower incidence of hypertension vs venlafaxine
- venlafaxine (IR/ER tablet, ER capsule)
  - Start 37.5 mg daily
  - If needed up to 150 daily
  - Always choose the extended release formulation
  - Often requires careful dose titration
  - Known to cause sweating and hypertension
- desvenlafaxine (tablet)
  - Start 25 mg daily
  - Cleaner than venlafaxine (no CYP2D6 to worry about)

Norepinephrine/Dopamine Reuptake Inhibitors (NDRIs)
5HT + DA

- bupropion (try XL then SR tablet)
  - Lowers seizure threshold
  - Activating, stimulating
  - Useful in "reduced positive affect" – loss of happiness, joy, interest, pleasure, energy, enthusiasm, alertness, and self-confidence

Mirtazapine
Strong H_1 blocker, but minimal muscarinic (anticholinergic)

- Start 7.5 mg daily (tablet, ODT) - may even start at 3.75 mg for geriatric insomnia
- Rarely more than 15 mg needed
- Benefit of inducing sleep at low doses (most significant at beginning of therapy, possibly wears off after a couple weeks) and appetite stimulation
- Side effects: Orthostatic hypotension, changes in dreams, other anti-cholinergic effects
- Prominent α_2 properties, but also binds several 5HT receptors and H_1 histamine receptors (can cause weight gain) at low dose (7.5-15 mg/day) → NE binding at higher doses ($\geq$ 30 mg/day, less drowsiness at this dose, appetite/weight gain diminished at these doses d/t to NE)
- T ½ 20-40 hrs

5HT antagonist and reuptake inhibitor (SARI) – Consider treatment for mild aggression in dementia, good choice for insomnia

- trazodone (tablet)
  - Start 25 mg q hs
    - Use low doses (25-50 mg) to avoid orthostatic hypotension (usually becomes an issue at 150-300 mg/day) → could push 25-50 TID to QID for aggressive patients
  - Maximum dose 100 mg q hs
  - High doses ($\geq$ 200 mg) = 5HT/antidepressant actions
  - Low doses ($\leq$ 150 mg) = $5HT_{2A}$, H_1, α_1 (sedation, sleep, hypnotic)
  - Dose at night and start low to avoid orthostatic hypotension. Quick onset, short duration of action (no "hangover effect" with low, nighttime doses)
  - A preferred agent by experts for geriatric insomnia
  - May be useful in treating BPSD with a primary feature of aggression, can be calming for some patients
  - May be particularly useful for sun downing – not much evidence
  - Caution: fall risk, don't use if pt already orthostatic

Other medications

- Benzodiazepines
  - Avoid use if possible - use only for severe behavior or violence when an antipsychotic is not effective or contraindicated
  - NEVER initiate for insomnia in geriatric patients, same goes for z-drugs (ie, Ambien)
  - Beware falls, sedation, worsening cognition, disinhibition, worsening mental status
- Melatonin
  - Marketed doses are often way too high for geriatric patients, resulting in levels up to 20x that of normal, physiological levels.
  - Instruct patients to buy the children's form (usually sold in 1 mg chewable tablets) and start with 1 mg qhs, up to a max of 3 mg qhs
- Anticonvulsants – No clear evidence of benefit
  - Gabapentin (tablet, capsule, liquid)
    - Start 100 mg q hs. Split dosing may be helpful
    - For insomnia, start with 100 mg qhs, increase by 100 mg each night to a max dose of 300 mg qhs.
    - Titrate slowly , watch for sedation, renal function, edema
    - May use higher doses for neuropathy/pain
    - For anxiety/agitation not much improvement over 1800 mg/day
  - valproate (DR/ER tablet, IR/DR capsule, liquid)
    - A fairly recent 2018 Cochrane review concluded and supported earlier evidence that valproate is likely ineffective in treating agitation in people with dementia, but is likely associated with a high rate of adverse effects, and possibly serious adverse events. The study even discouraged further research into its utility in dementia patients, particularly in light of the increase risk of adverse effects in this often frail group of people and lack of efficacy (no evidence of improved behavior, specifically, agitated behavior - no effect on ability to perform daily activities).
- Alpha-blockers
  - prazosin (capsule) - Small 8-week trial showing benefit
    - Start 1 mg q hs
    - If needed up 6 mg daily
  - Orthostasis, peripheral edema monitoring

- Cannabinoids (Investigational only)
    - Dronabinol (capsule, liquid)
    - Medical Cannabis Oil
    - Delta-THC in a tablet
    - Nabilone capsule (9-Delta-THC)

- Presynaptic inhibition of glutamate release
    - Dextromethorphan/Quinidine (DM-Q) 5HT2A Inverse Agonist (Nuedexta – capsule)
        - For pseudobulbar affect, not dementia
        - Usually requires specialty pharmacy, expensive
    - Pimavanserin (Nuplazid® – capsule)
        - 34 mg daily
        - Approved for Parkinson disease psychosis – high 5HT2A, low 5HT2C, and sigma no DA, muscarinic, histaminergic, or adrenergic binding
        - Most common side effects: (1-10%) nausea, constipation, confusion, edema, gait changes
        - Expensive: may require neurology 'prior auth' for insurance

Antipsychotics

1st generation

- Best studied is haloperidol (tablet, liquid, IM/IV, LAI)
    - Start 0.5 mg daily
    - Useful for acute aggression, psychosis at doses 1 - 4 mg/day (don't need more than this without a primary psychiatric disorder, like schizophrenia, unless you want to increase your risk of EPS – you get sufficient DA binding at < 4 mg/day)
    - Typically reserve for acute problem behaviors in LTC/SNF or acute care setting
    - Don't use chronically/outpatient – more side effects, risk of death vs SGA
    - Helps with aggression
    - May help with psychosis
    - Not shown to help with non-aggressive agitation
    - Side effects include acute dystonias, extrapyramidal side effects, tardive dyskinesia

2nd generation

Side effects include weight gain, dyslipidemia, sedation, orthostatic hypotension and others

- risperidone (tablet, ODT, liquid, LAI)
    - Start 0.25 mg daily,
    - BID dosing
    - Maximum dose usually less that 1-2mg/day
    - Most favorable overall safety and efficacy in older demented patients
    - Side effects - orthostatic hypotension, galactorrhea,
    - Less sedation than quetiapine and olanzapine
    - Helps with aggression at 2 mg/day
    - Helps with psychosis at 1 mg/day
    - Not shown to help with non-aggressive agitation
- quetiapine (tablet IR/ER)
    - Start with 12.5 mg daily
    - Max 150 mg (greater efficacy may be achieved at 200 mg/day, but this exceeds the CMS max dose for chronic treatment of patients with dementia in LTCs)
    - Multiple times per day dosing (short half-life)
    - Preferred it patient has Parkinson's or Lewy body dementia – minimal EPS
    - Very sedative
    - Not the best choice for psychosis
    - Least EPS
    - Not shown to help with agitation

- aripiprazole (tablet, ODT, liquid, LAI)
    - Start 2 mg daily
    - Maximum up to 10 mg
    - Helps with aggression
    - Helps with psychosis at 10 mg/day
- Olanzapine (tablet, ODT, IM, LAI)
    - Start 2.5mg daily
    - No more efficacy with doses of > 7.5 mg per day.
    - Sedating, anticholinergic
    - Longer ½ life may lead accumulation and an increase in adverse effects, especially with renal impairment
- Other SGA's can be considered based on preference, patient presentation, clinical circumstances

Antipsychotics carry risk!		
Increased Mortality risk **Increased Cardiovascular risk** • QTC • Stroke • Postural hypotension	**Decreased cognition** **Increased Falls/fractures** **Edema** **Pneumonia**	**Anticholinergic effects** **Sedation** **EPS**

Other Dementias

Parkinson's/Lewy Body

• Pimavanserin (Nuplazid®)
  ○ 34 mg daily
  ○ Approved for Parkinson disease psychosis – high 5HT2A, low 5HT2C, and sigma no DA, muscarinic, histaminergic, or adrenergic binding
• Avoid antipsychotics if possible – quetiapine safest bet

Fronto-temporal/Pick's
• SSRIs may be helpful for the management of repetitive, ritualistic behavior   ○ Paroxetine – may worsen symptoms (anticholinergic) • Trazodone – often very effective for behavior, no change in cognition, but monitor for SE's • AChEI – very little benefit (pathophysiology isn't due to degeneration of cholinergic projections) • Stimulants – dextroamphetamine may help • Antipsychotics – don't use (due to dopamine deficit in temporal lobe)

Summary: When to Move to Antipsychotics

Agitation and irritability without risk to self or others
• Citalopram/Sertraline – Depression, irritability, anxiety and sleep disturbance. • Trazodone – Sleep disturbance, agitation • Benzodiazepines – Anxiety, agitation, but beware falls, sedation, worsening cognition, disinhibition • Cholinesterase Inhibitors – Consider if not already added for AD   o +/- memantine
• Antipsychotics may be required for acute situations for threatening to self or others with problematic aggression, dysphoric psychosis or delusions
• **Before prescribing an antipsychotic, make sure all reversible causes of problem behaviors have been addressed (similar to how you would approach delirium), such as pain, nicotine withdrawal, medication side effects, undiagnosed medical or neurological illnesses, and provocative environments that are either too stimulating or not stimulating enough.**
• **Black box warning** – increased mortality (from stroke, HF, sudden death, infections) Overall: for every 9-25 people helped by an antipsychotic, there is one additional death from treatment   o If possible always discuss with family or guardian and document conversation
Monitor and document throughout the day to assess response with a quantitative measure

• **Target symptom** → be specific (aggression? distressing hallucinations? Unspecified agitation is inappropriate, not specific)
• Appropriate treatment targets
  o Threat to self or others, aggression or violence
  o Severely distressing hallucinations or delusions (seeing spiders on food)
  o Behavior interfering with daily care that will result in patient harm
• Monitor timing of symptoms
• Monitor response to intervention

Dosing
• Always start at low doses (1/4 – ½ normal), often divided doses, increase slowly • Higher doses = usually more side effects without added benefit in this population • **<u>If no documented improvement after 4 weeks of reasonable dosing, taper, D/C and/ or switch to another medication.</u>**
• Minimal data Risperidone/Olanzapine/Aripiprazole – Aggression, agitation and psychosis, but only for severe symptoms and ideally for short term only
• In absence of delirium, avoid haloperidol as first line agent
• Avoid long acting injectable medications unless indicated for co-occurring chronic psychotic disorder
When to reduce or stop
• Behaviors will wax and wane with or without medications • If stable, try to taper dose down after some stability to lowest effective dose • Don't leave them on medication without documented improvement. • Consider tapering off slowly after 3 – 6 months of stability. • Many people do not worsen with discontinuation because we aren't doing anything to address or treat underlying cause (plaques and tangles, degeneration), some actually get better when antipsychotic is stopped

Appendix #1

BEHAVIOR MONITORING RECORD

NAME:

Mo./Yr.	**MEDICATION ORDER** (Chart **ONLY** episodes that occur on your shift **DO NOT CHART "0"**):	**JUSTIFYING DIAGNOSIS:**

TARGETED BEHAVIOR #1:

	Hr.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
#1	Noc																															
	Day																															
	PM																															

TARGETED BEHAVIOR #2:

#2	Noc																															
	Day																															
	PM																															

TARGETED BEHAVIOR #3:

#3	Noc																															
	Day																															
	PM																															

TARGETED BEHAVIOR #4:

#4	Noc																															
	Day																															
	PM																															

Care Plan Goals: _____ **Met/Unmet – Explain:** _____

Changes in behavior since last review: ☐ **YES** ☐ **NO**

If yes, explain: _____

ASSESSMENT OUTCOME: Med. change contraindicated:

- ☐ Previous attempts failed.
- ☐ Mental illness/Behavior: stable/maintenance – on current dose.
- ☐ Resident refuses reduction.

Need for M.D. Review: ☐ **YES** ☐ **NO**

- ☐ Frequency of behaviors decreased/increased.
- ☐ PRN use indicates need for M.D. review.
- ☐ Other (explain): _____

SIDE EFFECTS R/T MED. - ALTERNATIVE INTERVENTIONS

- ☐ None
- ☐ TD
- ☐ Tremors
- ☐ Increased confusion
- ☐ Dizziness
- ☐ Lethargy
- ☐ Other: _____

- ☐ Comfort (pain, position)
- ☐ Activities
- ☐ Redirection (what) _____
- ☐ 1:1 Interactions;
- ☐ Snack
- ☐ Toileting
- ☐ Touch/Back rub
- ☐ Reassurance/emotional

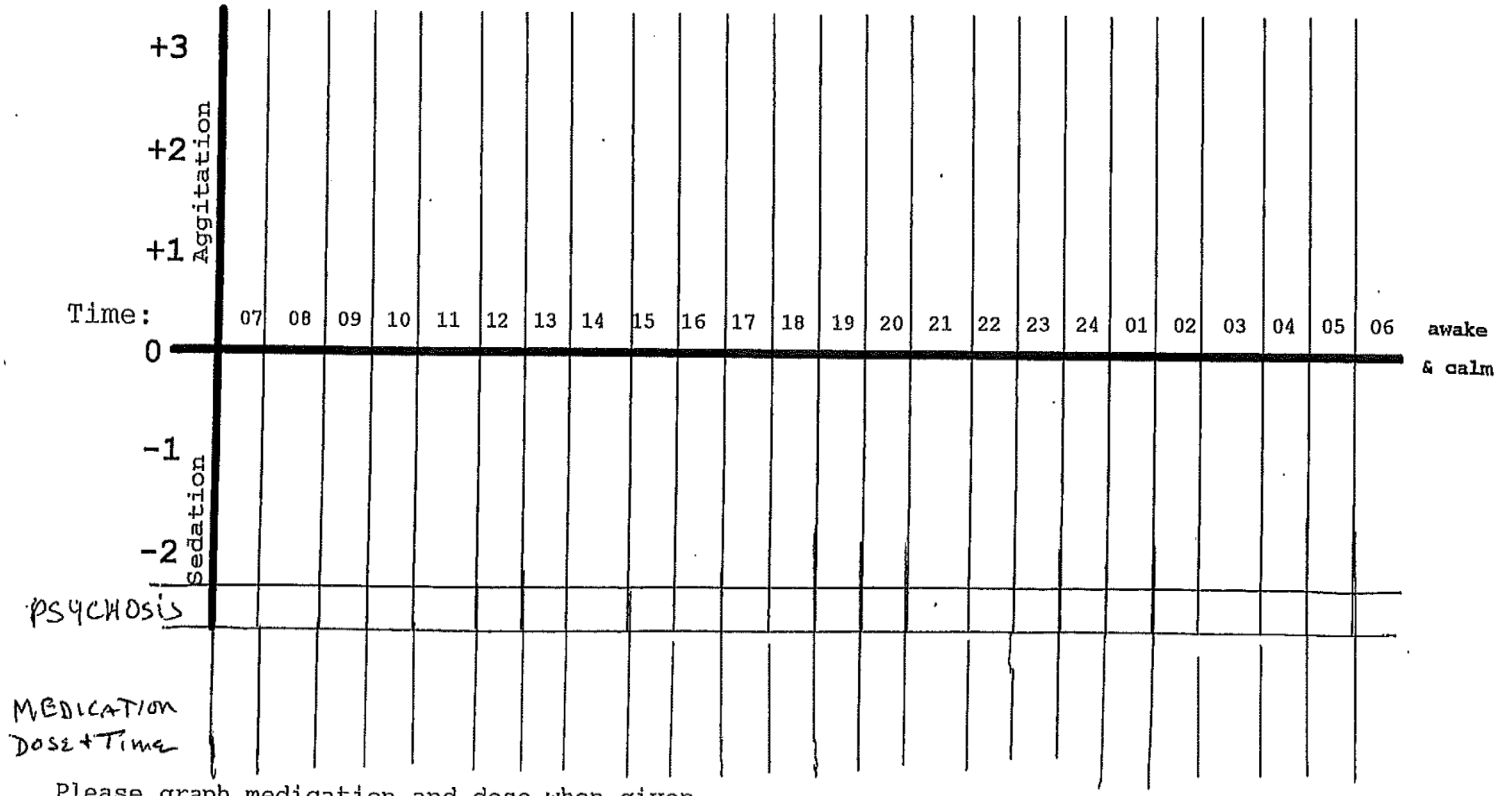
See nurses' notes for intensity/duration.

Nurse Signature: Date:

Patient : _____ DATE: _____

Aggitation
1 - restless, pulling at lines, able to redirect
2 - unable to redirect
3 - combative

Sedation
1 - sleeping, easily arousable
2 - difficult to arouse



Please graph medication and dose when given.

Appendix #2

References:

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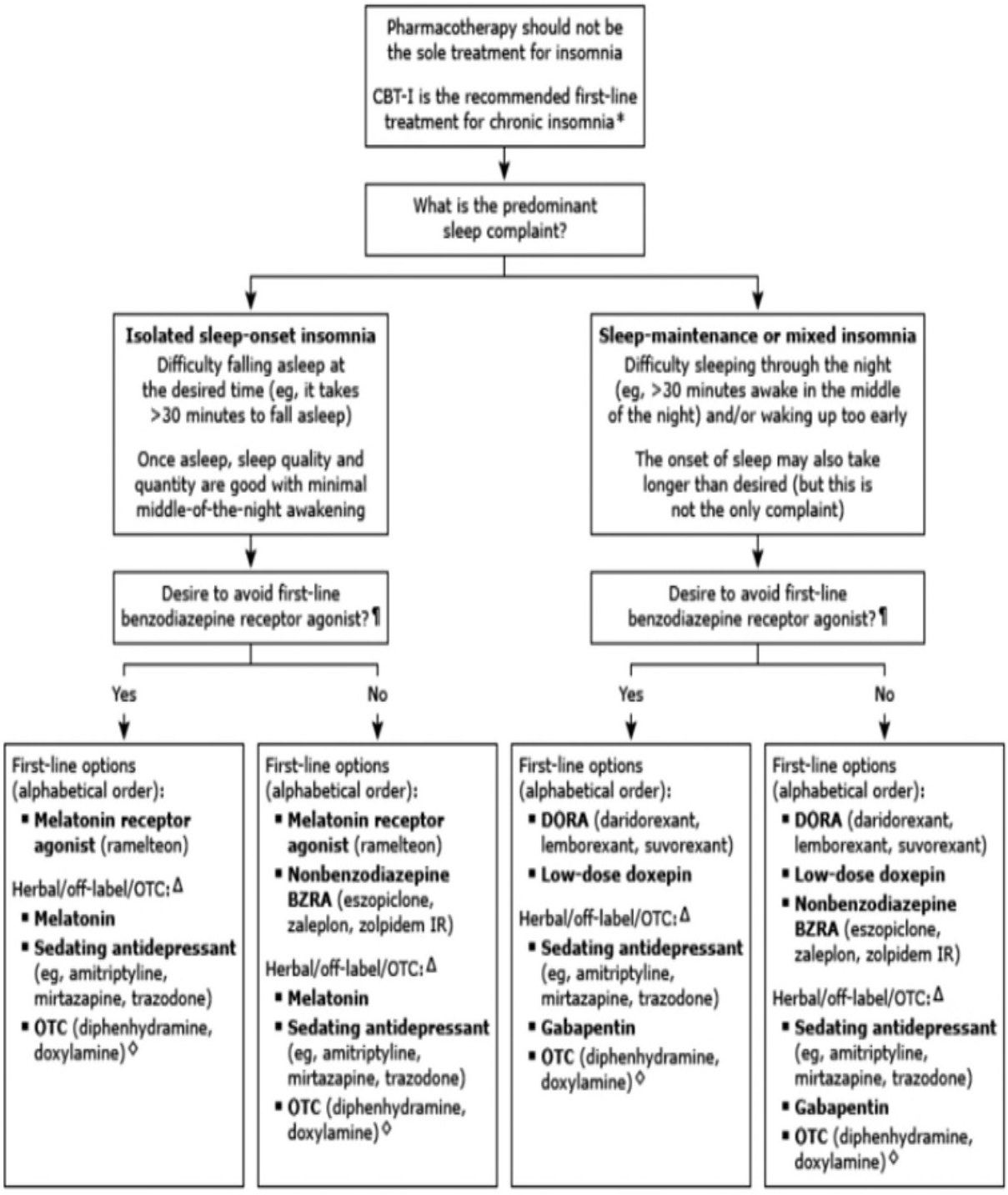
4. Responding to Behaviors Due to Dementia using Achieving Best Life Experience (ABLE) Care Planning Guide; Sunnybrook Health Sciences Center, Veterans Center, 2010
5. Management of Behavioral and Psychological Symptoms of Dementia; Current Psychiatry Reports (2019) 21: 66
6. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission; Gill Livingston, Jonathan Huntley, Andrew Sommerlad; Lancet 2020; 396: 413–46
7. Valproate preparations for agitation in dementia; Sarah F Baillon 1, Usha Narayana, Jay S Luxenberg, Andrew V Clifton; Meta-Analysis >Cochrane Database Syst Rev, 2018 Oct 5;10(10):CD003945. doi:10.1002/14651858.CD003945.pub4.

INSOMNIA DISORDERS

Develop by: Russ Symball, RPh, BCPP; Leanne Rousseau, MD; Marlee Novak, MD; Lauren Fletcher, PharmD; Nathen Bertsch, PharmD, William H. Miller,MD

Overview of pharmacotherapy for insomnia in adults



INSOMNIA DISORDERS

Chad Hagan, M.D. – 'Famous' sleep specialist: *If a patient can breathe peacefully, with a calm relaxed state of mind, and has a rest-activity cycle that is properly time-aligned with their circadian rhythm, then that individual sleeps without insomnia. Almost all insomnia to walk in to your office is due to an error in one or more of these three.*

Normal Sleep Architecture

- Non-rapid eye movement (NREM) sleep – approximately 75% of total sleep time
  - Stage N1 – transition state between wakefulness and sleep. Various physiologic changes subjectively experienced as drowsiness. Initiation of sleep occurs over 15-30 minutes.
  - Stage N2 – alpha wave sleep that makes up approximately half of total sleep time.
  - Stage N3 – delta wave sleep. Considered the most restorative sleep during which there appears to be protein synthesis, wound healing, and restoration of immune function.
- Rapid eye movement (REM) sleep – approximately 25% of total sleep time
  - May play a role in memory consolidation and sensorimotor system development
  - Associated with dreaming
  - Takes place approximately every 90 minutes and occurs 4-5 times per night.
- Neurobiology of Sleep
  - The daily cycle of sleep and wakefulness is mediated by two opposing drives: the *homeostatic sleep drive* and the *circadian wake drive.*
    - The homeostatic sleep drive accumulates throughout periods of wakefulness. It is dependent on the accumulation of adenosine, which increases as a person tires with fatigue throughout the day and eventually leads to the release of GABA in the sleep circuit, facilitating onset of sleep.
    - The circadian wake drive, mediated by light acting on the suprachiasmic nucleus, stimulates the release of orexin as part of the wake circuit which results in release of the wake-promoting neurotransmitters (histamine, acetylcholine, dopamine, norepinephrine, and serotonin).
    - Arousal is regulated by release of acetylcholine, histamine, norepinephrine, and serotonin in the cortical pathways originating in the hypothalamus (reticular activating system).

Insomnia *- Subjective difficulty with sleep (onset, maintenance, quality), despite adequate opportunity for slee plus some form of daytime impairment; Inability to switch off arousal related circuits*

- **1 sleep symptom + 1 daytime symptom for > 3 months**
  - Sleep symptoms
    - Difficulty initiating sleep
    - Difficulty maintaining sleep
    - Waking earlier than desired
    - Resist going to bed on appropriate schedule
    - Difficulty sleeping without parent/caregiver intervention
  - Daytime symptoms
    - Fatigue/malaise
    - Attention, concentration, memory impairment
    - Impaired social, family, vocational or academic performance
    - Mood disturbance/irritability
    - Daytime sleepiness**
    - Behavioral problems
    - Reduced motivation/energy/initiative
    - Proneness for accidents/errors
    - Concerns about/dissatisfaction with sleep

- Prevalence
  - Insomnia symptoms: 33-50% adults
  - Prescriptions: 5.3 million (1999) > 20.8 million (2010)
- Consequences:
  - Psychiatric disorders – depression, anxiety, substance abuse
  - Cognitive impairments – errors at work, car accidents
  - Increased health service utilization (cost)
- Evaluation
  - Schedule a visit specifically for insomnia
  - Medical/psychiatric history – comorbid conditions
  - Other Sleep Disorders to consider
    - Obstructive Sleep Apnea
    - Parasomnias
    - Restless Leg Syndrome
  - Sleep assessment tools
    - Insomnia severity scale and fatigue severity scale (Appendix 1)
    - Obstructive apnea assessment (Appendix 2)
    - Sleep log (Appendix 3)
  - **Take a thorough sleep apnea history - STOP BANG and Epworth scales** (Appendix 2)
    - Don't order sleep test as first line evaluation for insomnia in absence of any risk factors or symptoms of breathing or movement disorder
    - DO SEEK PSG for patients with possible sleep fragmented disorder (movement or breathing) that may be causing insomnia 'symptom'
    - Many WOMEN have unrecognized sleep apnea or mild forms of sleep disordered breathing and their sleep maintenance insomnia would improve with correction of their nasal obstruction or with CPAP
      - Bias to obtain sleep study in males and give hypnotics in females or lean males/females
    - Sleep disordered breathing is a common cause of sleep maintenance insomnia, but rarely a cause of sleep onset insomnia
  - Two-week sleep log (Appendix 3)
    - Bedtime
    - Sleep latency (SL: time to fall asleep following bedtime)
    - Number of awakenings and duration of each awakening
    - Nap times (frequency, times, durations)
    - Medications, ETOH, caffeine
- Comorbidities (Appendix 4)
  - Medical – numerous
    - Stroke, dementia, Parkinson's disease, chronic pain
    - Incontinence, nocturia, BPH
    - Pregnancy, menopause
    - Obstructive Sleep Apnea, restless leg syndrome (RLS)
    - Substance use
    - Asthma, COPD, emphysema
    - Heart failure, hypertension, angina
    - Circadian sleep-wake rhythm disorders
  - Psychiatric – 50% pts with insomnia have a psychiatric disorder; majority of pts with psychiatric disorder have insomnia
    - Depression – 80% have insomnia
    - Bipolar
    - Anxiety
    - Bereavement, stress

- Other concurrent medications - **Evaluate effects, interactions, side effects, dose and timing of doses of all medications** (Appendix 4)
    - Antidepressants, antipsychotics – akathisia , RLS, periodic limb movement disorder
    - Stimulants – methylphenidate, amphetamines, caffeine
    - Decongestants – pseudoephedrine, phenylephrine
    - Opioids
    - Beta blockers, diuretics, statins
    - theophylline, albuterol, steroids
    - Remember to evaluate OTC meds for sleep

Initial Management

- Start with behavioral/psychological intervention (ie. CBT). (Standard)
    - Maladaptive behaviors - staying in bed awake for a long time 'trying' to fall asleep >> heightened frustration and anxiety about not sleeping >> hyper-arousal and negative expectations
        - Goal: change poor sleep habits and challenge negative thoughts, attitudes, and beliefs about sleep

Aspects of CBT-I Behavioral Interventions

- Sleep Hygiene
    - Avoid before bed:
        - Caffeine and nicotine (ideally 6 hours prior)
        - Alcohol
        - Heavy meal
        - Exercise (close to bed-time)
    - Minimize:
        - Noise
        - Light
        - Excessive heat

  Stimulus Control
    - Goal: dissolve negative associations and form clear positive association between bed and sleep
    - How:
        - Go to bed when sleepy
        - Regular schedule
        - Avoid naps
        - Bed only for sleep and sex
        - Get out of bed if no sleep after ~20 minutes (perceived); do a relaxing activity, then back to bed when drowsy
- Relaxation Therapy
    - Goal: decrease level of arousal
    - How:
        - Progressive muscle relaxation – alternate tension/relaxation
        - Guided imagery
        - Abdominal breathing
- Sleep Restriction
    - Goal: limit time in bed to total sleep time (TST) to improve sleep continuity
    - How:
        - Mean TST from sleep log > set bed and wake-time to approximate
        - Goal to achieve >85% sleep efficiency (TST/TIB x 100%)
        - Modify per week –
            - If efficiency > 85%, increase time in bed by 15-20minutes
            - If efficiency < 85%, decrease time in bed by 15-20 minutes

- Contraindications for CBT-I:
    - Current substance abuse disorder
    - Psychologically or medically unstable
    - Those for who sleep deprivation is unsafe:
        - Seizure disorders
        - Bipolar disorder – if stable MODIFIED CBT-I
        - Panic Disorder
    - Excessive Daytime Sleepiness (Epworth > 10)
    - Untreated, or inadequately treated sleep apnea
        - Adequate CPAP treatment > or = 4 hours a night on at least 75% of nights
    - Individuals currently undergoing exposure therapy (CBT,PE) for PTSD
- One Session CBT-I (bare minimum – at least something!)
    - Wake up at the same time every day and get out of bed within a few minutes of alarm
    - Go to bed only when sleepy, but not before time prescribed (this is sleep restriction- limit opportunity for sleep for more efficient sleep and less, wakefulness)
    - If you can't sleep, stop trying. GET UP
    - Use the bed only for sleeping or sex. Do not read, eat, watch TV, use your phone, etc. in bed.
    - Avoid daytime napping unless needed for safety
    - Wind down 1 hour before bed

- **There is insufficient evidence that sleep hygiene alone is effective in the treatment of chronic insomnia. It should be used in combination with other therapies including CBT-I.**

CBT-I + Hypnotic Combo Literature

- 1st: there is a subgroup of patients likely to do their best with brief sedative early in combination with CBT-I then eliminate the RX early, but many will do best without hypnotic involved

- 2nd: continuing hypnotics long term undermines the very concept of CBT-I that behavior, cognitions, and habits can rebuild and sustain healthy normal sleep. Thus, part of the reason the extended zolpidem PRN group does worse is that they're continuing to reinforce the false belief that they need sleeping pills to sleep.

Pharmacology: Two Categories - Appendix 6

- **Enhancers of sleep drive** → increase GABA in the sleep circuit of the brain
    - Sleep Latency
    - Z-drugs
    - Benzodiazepines
- **Reduction of arousal**: Orexin blockers, histamine blockers, serotonin antagonists, alpha-antagonists (reduce NE)
    - Sleep Maintaince
    - DORA – dual orexin receptor antagonists
        - Decrease wake-promoting neurotransmitters but are reversible - as endogenous orexin increases they lose effect (morning awakening)
- **Only modestly helpful: often risks > benefits**
    - Acute/situational insomnia
    - Self-prescribed over the counter sleep aids and alcohol most common treatments for insomnia
- Caution
    - Daytime residual effects, especially elderly
    - Increased risk for sleep apnea
    - Increased risk for falls, fractures
    - Constipation

Medications – Appendix 7

- Over the counter medication options (Appendix 5)
- The choice of medication for insomnia should be individualized based on a variety of factors including a patient's age and comorbidities, type of insomnia complaint (sleep onset or awakening during sleep), side effect profile, cost, and shared decision making. (Appendix 6, 7 and 8)
- The goal for use of medications for sleep is to have them as an option for the nights when patients need them. Dependence and tolerance pose a risk to no longer having these options available. Counseling patients on the potential for dependence on these medications is imperative. **To preserve the utility of these meds, short term use is best.**

melatonin

- MoA: supplements endogenous pineal hormone melatonin produced in response to decreased light; affects circadian rhythm
- Utility: sleep latency
    - ER formulations may be beneficial for sleep maintenance
- Dosing:
    - Variable bioavailability
    - Consider starting dose of 1 mg 60-90 minutes prior to bedtime; 0.5 to 5 mg can be helpful if tolerated
        - Repeated consistent dosing over weeks is usually more helpful than increasing doses
    - May see benefit with administration earlier in the evening, perhaps even a few hours before bedtime
- SE: generally well-tolerated; vivid dreams/nightmares
- Consider in: older adults (production decreases with age), neurodegenerative disorders, respiratory disease

ramelteon (Rozerem)

- MoA: melatonin receptor agonist
    - Potent, selective agonist of melatonin receptors MT_1 and MT_2 (with little affinity for MT_3) within the suprachiasmic nucleus of the hypothalamus, an area responsible for determination of circadian rhythms and synchronization of the sleep-wake cycle
    - Agonism of MT_1 is thought to preferentially induce sleepiness, while MT_2 receptor activation preferentially influences regulation of circadian rhythms
    - ramelteon is eightfold more selective for MT_1 than MT_2 and exhibits nearly sixfold higher affinity for MT_1 than melatonin, presumably allowing for enhanced effects on sleep induction
- Utility: sleep latency
- Dosing: 8 mg at bedtime
    - Doses of 4-64 mg may have similar efficacy/side effects
- Relevant Pharmacokinetics Properties:
    - Low bioavailability
        - Despite recommended flat dose of 8 mg, some patients may require dose titration to achieve sufficient absorption
        - May consider increasing dose if lack of effect
    - Slower absorption/onset when taken with high-fat foods; avoid eating prior to bedtime
- SE: generally well-tolerated; dizziness, fatigue
- Lack of comparison studies to melatonin
- Decreased risk of hospital-associated delirium

Z-drugs

- *Benzodiazepine receptor agonists, targets certain subunits of GABA receptors; sedative > anxiolytic effect*
- *May cause less tolerance/dependence relative to benzodiazepines*
- ***Black Box Warning: Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur. Some of these events may result in serious injuries, including death.***

zolpidem (Ambien)

- MoA: enhance GABA via selective agonist at benzodiazepine-1 receptor to decrease neuronal excitability
- Utility: sleep latency and maintenance
- Dosing:
    - zolpidem (Ambien) IR
        - Women/lower body weight: 5 mg; Men: 5-10 mg at bedtime
    - zolpidem ER (Ambien CR) 6.25-12.5 mg at bedtime
        - 6.25 mg for lower body weight
        - May explore ER formulation if no benefit experienced with IR
    - Intermezzo (sublingual formulation) 1.75-3.5 mg – low dose specifically for middle-of-the-night awakenings when at least 4 hours still available for sleep
- Relevant Pharmacokinetics Properties:
    - Short half-life (~2.5 hours)
    - Delayed absorption with food – best to take on an empty stomach
    - Take at least 8 hours prior to planned wake-up time
- SE: complex sleep behavior, dose-dependent anterograde amnesia, dizziness, ataxia

eszopiclone (Lunesta)

- MoA: non-benzodiazepine hypnotic that binds to GABA-receptor complex domain
- Utility: sleep latency and maintenance
    - Studies demonstrated no tolerance development up to 6 months
- Dosing: 1-3 mg
    - Max 2 mg in older adults
    - 1 mg for those taking concomitant CYP 3A4 inhibitor
- Relevant Pharmacokinetics Properties:
    - Ideal duration of action (~6-7 hours)
    - Delayed absorption with food – best to take on an empty stomach
- SE: complex sleep behaviors, metallic taste, dose-dependent anterograde amnesia

zaleplon (Sonata)

- MoA: interacts with GABA-BZ receptor complex at omega-1 receptor
- Utility: sleep latency
- Dosing: 5-10 mg at bedtime; max 20 mg
    - Max 5 mg in older adults/lower body weight
- Relevant Pharmacokinetics Properties:
    - Very short half-life (~1 hour)
        - May be helpful for middle of the night awakenings when at least 4 hours still available for sleep
        - Less hangover effect/daytime sleepiness
        - Effect may diminish and result in increased wakefulness later in the night (not effective for sleep maintenance)
    - Slower absorption/onset when taken with high-fat foods; avoid eating prior to bedtime
- SE: complex sleep behaviors, ataxia, dizziness, dose-dependent anterograde amnesia

Benzodiazepines

- MoA: positive allosteric modulators of GABA-A receptor → more efficient GABA binding → enhanced inhibitory effect of GABA
    - Hypnotic effects secondary to alpha 1 subtype
    - Mostly change sleep architecture by increasing stage N2 sleep. Some studies have shown reduced time in deep wave (N3) and REM sleep.
- All benzodiazepines are effective for insomnia, though only 5 FDA-approved agents: **temazepam (most commonly)**, estazolam, triazolam, flurazepam, quazepam
- Utility: sleep latency and maintenance
    - Exception: short-acting agents effective only for sleep latency
        - triazolam, alprazolam, oxazepam
- Dosing:
    - Temazepam (Restoril) 7.5-30 mg at bedtime
    - estazolam (Prosom) 0.5-2 mg at bedtime
    - triazolam (Halcion) 0.125-0.25 mg at bedtime
- Relevant Pharmacokinetics Properties:
    - Long duration and active metabolites → potential hangover effect/daytime sleepiness
        - chlordiazepoxide, diazepam, flurazepam, and quazepam
- SE: dependence, potential for abuse, retrograde amnesia; elderly – falls, dementia risk
- Short term use recommended due to both tolerance development (generally after ~1 month) and risk of dependence/habituation

Antidepressants

doxepin (Silenor)

- MoA: histamine H1 antagonist
- Utility: sleep maintenance
    - Low doses approved for sleep maintenance, but may have some benefit for sleep latency
- Dosing: < 10 mg within 30 minutes of bedtime
    - FDA approved 6 mg for adults and 3 mg for older adults, though often expensive
    - Lower doses may be achieved with liquid formulation
    - Generic 10 mg capsules available, often utilized d/t cost
- Relevant Pharmacokinetics Properties:
    - Avoid administration within 3 hours of a meal
- SE: low dose well-tolerated, seemingly no anticholinergic effects observed at low dose
- Consider with: depression, anxiety, chronic pain, respiratory disease, older adults

trazodone (Desyrel)

- MoA: Histamine H1 antagonist, serotonin 5HT2A antagonist, alpha 1 antagonist
- Utility: primarily sleep latency
    - May also be beneficial for sleep maintenance
    - Off label indication despite prevalence of use; low quality evidence available
- Dosing:
    - Initial: 25-50 mg at bedtime
    - Increase slowly as tolerated, typical dose 50-150 mg
- SE: priapism, orthostatic hypotension, dizziness
- Consider with: depression, anxiety

mirtazapine (Remeron)

- MoA: potent histamine H1 antagonist
- Utility: both sleep latency and maintenance
    - May improve deep wave (N3) sleep
- Dosing: 7.5-15 mg at bedtime
    - Higher doses lose effect for sleep, but help more with depression
- SE: increased appetite, weight gain, anticholinergic effects
- Consider with: depression, anxiety

hydroxyzine (Vistaril)

- MoA: selective histamine H1 receptor inverse agonist, lower affinity for muscarinic acetylcholine receptors and less anticholinergic side effects than diphenhydramine/doxylamine; possess weak antiserotonergic effects and alpha 1 antagonism
- Utility: sleep latency
- Dosing: 50-100 mg at bedtime
- SE: anticholinergic effects
- Consider with: anxiety, respiratory disease

First-Generation Antihistamines

- MoA: Histamine H1 antagonist, antimuscarinic effects
- Dosing:
    - diphenhydramine (Benadryl) 25-50 mg at bedtime
    - doxylamine (Unisom) 25 mg 30 minutes before bedtime
- Utility: both sleep latency and maintenance
    - Short-term use (2-3 days)
    - May reduce sleep quality
- SE: anticholinergic properties (cognitive impairment, urinary retention, constipation), rebound insomnia, daytime sleepiness
    - Risks may outweigh benefits (especially in elderly); generally not recommended
- Consider in pregnancy

gabapentin/pregabalin

- MoA: structurally related to the neurotransmitter GABA (does not bind GABA); likely modulates the release of excitatory neurotransmitters like glutamate; enhances deep wave (N3) sleep
- Utility: sleep maintenance
- Dosing:
    - gabapentin (Neurontin): start at 100 mg at bedtime, increase by 100 mg each night as tolerated up to 300-600 mg at bedtime
    - pregabalin (Lyrica): start at 50 mg at bedtime, titrating by 50 mg weekly up to 150-300 mg based on effect/tolerability
- SE: edema, daytime sleepiness
- Consider with: anxiety, alcohol use disorder, chronic pain, respiratory disease, RLS, menopause

Antipsychotics

- MoA: histamine H1 antagonism, alpha 1 antagonism
- Utility: sleep latency and maintenance
- Dosing:
    - quetiapine (Seroquel) 50-200 mg at bedtime
    - olanzapine (Zyprexa) 2.5-10 mg at bedtime
- SE: anticholinergic effects, weight gain
- Consider with: psychotic disorder, bipolar disorder/mania, Parkinson's disease (quetiapine), Lewy body dementia (quetiapine)

Dual Orexin Receptor Antagonists (DORAs)

- Novel MoA: orexin receptor antagonists – suppress orexin which is a wake-promoting neuropeptide
- Utility: both sleep latency and maintenance
    - Studies with efficacy up to 1 year
- Dosing:
    - lemborexant (Dayvigo)
        - Initial: 5 mg before bedtime, having at least 7 hours available for sleep
        - Max: 10 mg
        - Concomitant *MILD* CYP 3A4 inhibitor: max 5 mg
    - suvorexant (Belsomra)
        - Initial: 10 mg within 30 minutes of bedtime, having at least 7 hours available for sleep
        - Max: 20 mg
    - daridorexant (Quviviq)
        - 25-50 mg before bedtime, having at least 7 hours available for sleep
- Relevant Pharmacokinetics Properties:
    - Approximate half-life
        - lemborexant: 17-29 hours
        - suvorexant: 12 hours
        - daridorexant: 8 hours
    - For all agents, concomitant use with strong CYP 3A4 inhibitors is not recommended
        - lemborexant: also avoid moderate CYP 3A4 inhibitors, dose reduce with mild
        - suvorexant/daridorexant: utilize lower dose with moderate CYP 3A4 inhibitors
    - Delayed absorption with food; avoid eating prior to bedtime
- SE: next-day impairment/drowsiness, abnormal dreams
- Consider: Neurodegenerative disorders

Monitoring

- Frequent follow-up and patient feedback – dedicated visits*
    - Repeat above scales
    - Repeat and review sleep log – work through sleep efficiency
- Effective therapy requires time and trust

Summary/Pearls (Appendix 8 & 9)

- Important to gather a complete history and sleep log to identify the type of insomnia (onset, maintenance, contributors) and target intervention
- Consider comorbidities, medications – need for PSG?
- CBT-I recommended 1st line, achieves SUSTAINED improvement - You can do behavioral interventions
- *Consider* initial pharmacotherapy while starting CBT, then discontinue after ~6 weeks and continue CBT
- Consider Comorbidities when selecting medications
- Utilize smartphone apps if able, potential local therapists
- Frequent follow-up important
- Attempt medication tapers to avoid long term medication exposure

Appendix 1

Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) = _____ your total score

Total score categories:
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)

Appendix 2

Sleep Apnea Screener - STOP BANG questionnaire and Epworth Sleepiness Scale

STOP BANG

(Answer yes or no for each question)

S (snore)
Do you snore?
T (tired)

Do you feel fatigued during the day?
Do you wake up feeling like you haven't slept?
O (obstruction)
Have you been told you stop breathing at night?
Do you gasp for air or choke while sleeping?
P (pressure)
Do you have high blood pressure or are on medication to control high blood pressure?

SCORE: If you checked YES to two or more questions on the STOP portion you are at risk for OSA.

B (BMI)
Is your body mass index greater than 28?
A (age)
Are you 50 years old or older?
N (neck)
Are you a male with neck circumference greater than 17 inches, or a female with neck circumference greater than 16 inches?
G (gender)
Are you male?

SCORE: The more questions you checked YES to on the BANG portion, the greater your risk of having moderate to severe OSA.

Epworth

(Rate 0 – 3 for each scenario)

How likely are you to doze off or fall asleep in the situations described below, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you haven't done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = Would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Sitting and reading
Watching TV
Sitting inactive in a public place (e.g. a theater or a meeting)
Sitting in a car as a passenger for a continuous hour
Lying down to rest in the afternoon when circumstances permit
Sitting and talking to someone
Sitting quietly after a lunch without alcohol
Sitting in a car stopped in traffic for a few minutes

SCORE: Add up your score for each scenario. 0–10 Normal range | 10–12 Borderline | 12–24 Sleepy

Appendix 3

TWO WEEK SLEEP DIARY

SleepEducation.org | AASM American Academy of SLEEP MEDICINE

INSTRUCTIONS:
(1) Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation. **(2)** Put the letter "C" in the box when you have coffee, cola or tea. Put "M" when you take any medicine. Put "A" when you drink alcohol. Put "E" when you exercise. **(3)** Put a vertical line (|) to show when you go to bed. Shade in the box that shows when you think you fell asleep. **(4)** Shade in all the boxes that show when you are asleep at night or when you take a nap during the day. **(5)** Leave boxes unshaded to show when you wake up at night and when you are awake during the day.

SAMPLE ENTRY BELOW: On a Monday when I worked, I jogged on my lunch break at 1 PM, had a glass of wine with dinner at 6 PM, fell asleep watching TV from 7 to 8 PM, went to bed at 10:30 PM, fell asleep around Midnight, woke up and couldn't get back to sleep at about 4 AM, went back to sleep from 5 to 7 AM, and had coffee and medicine at 7 AM.

Date	Day of the week	Type of Day (Work, School, Day Off, Vacation)	Noon	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	Midnight	1 AM	2 AM	3 AM	4 AM	5 AM	6 AM	7 AM	8 AM	9 AM	10 AM	11 AM
sample	Mon.	Work		E					A				|									C M				

week 1

Appendix 4

Table 8. Possible Contributors to Sleep Disorders

Medical Illnesses	Psychiatric Disorders	Drugs	
Anemia	Anxiety disorders	Alcohol	Levodopa
Angina	Depression	Amphetamines	Nicotine
Arthritis or chronic pain	Manic episodes	Antipsychotics	SNRIs
Asthma	Mood disorders	β-Blockers	SSRIs
COPD	Psychotic disorders	Bupropion	Theophylline
GERD or peptic ulcer disease	Substance use disorder(s)	Caffeine	Thyroid supplementation
Head injury		Cocaine	TCAs
Hepatic or renal failure		Decongestants	
Hypoglycemia		Diuretics	
Malignancy			
Parkinson disease			
Seizure disorders			
Sleep apnea			

COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease.

Appendix 5

Over-the-Counter Medications, Supplements, and Foods to Help with Sleep	
Chamomile Tea	Chamomile has a soothing/calming effect. Drinking other warm, soothing beverages and teas may work similarly. Do not drink too much, or you may wake up to go to the bathroom.
Foods Rich in Tryptophan and Melatonin	These two are present in the nervous system and have a soothing or calming effect on the mind. It can take time to raise levels after eating. Eat at least one hour before bedtime, or earlier, to avoid possible heartburn and prevent weight gain. • **Foods high in tryptophan:** eggs (the whites), cod, soy, dairy products, poultry, bananas, sesame and sunflower seeds, whole grain cereals. **Foods high in melatonin**: cherries, meats, bananas, rice, whole grains/cereals, plums, oranges, apples, tomatoes, cucumbers, cabbage, almonds, walnuts, sunflower seeds, mustard seed, fennel.
5HTP (5-Hydroxy Tryptophan)	This is an important ingredient of serotonin, a chemical in the brain that helps regulate mood. There is not a lot of research about how effective this is, but many people feel it is helpful, and it has few side effects. Talk with your healthcare professional about taking this (and about possible side effects) if you also take other antidepressant or anti-anxiety medications.
Lavender or Sweet Almond Essential Oils	Place a few drops of essential oil on a cloth under your pillow or on your temples (if you do not have a skin allergy to essential oils). Inhaling the aroma can make you sleepy.
Magnesium	This common electrolyte/salt can have a calming effect on the mind and body. It can be taken as a supplement (a standard dose is 250 mg daily), absorbed in an Epsom salt bath soaks, or eaten in magnesium-rich foods. These include almonds, spinach, cashews, peanuts, black beans, soybeans (soy milk, edamame, and tofu), yogurt, potatoes, and avocados. If it loosens your stools too much, cut back on the dose.
Melatonin (Regular or Extended Release)	A common starting dose is 0.25 mg to 3 mg. • The regular/immediate release form works over 1-3 hours, and helps people **get to sleep**. • The extended release form slowly allows the melatonin to be digested over time, helping people **stay asleep**. Take either form 60-90 minutes before going to bed, and 7-8 hours before you plan to wake up.
Valerian Root	Take 400-900 mg 30 minutes—2 hours before bedtime. Valerian works best if used every night for 4-6 weeks. It does not work as well on an "as needed" basis. Slowly taper off since withdrawal symptoms can occur (this is very rare).
Diphenhydramine (Examples: Benadryl, Tylenol PM)	It only works for 3-4 days and then becomes ineffective. Should not be used by older adults.[16] Increases risk of developing dementia later in life.[17]

Appendix 6

Table 9. Pharmacotherapy Selection According to Type of Insomnia

Medication	Sleep Latency	Sleep Maintenance	Both
Temazepam			x
Doxepin		x	
Eszopiclone			x
Lemborexant			x
Suvorexant			x
Ramelteon	x		
Trazodone	x		
Zaleplon	x		
Zolpidem IR	x		
Zolpidem CR			x

CR = controlled release

Appendix 7

Table 5—Summary of "critical" outcomes by indication.

Recommended for Treating Sleep Onset Insomnia	
Eszopiclone	**Sleep latency:** Mean reduction was 14 min greater, compared to placebo (95% CI: 3 to 24 min reduction); **Quality of sleep*:** Moderate-to-Large[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 2, "Harms" *This recommendation is based on trials of 2 mg and 3 mg doses of eszopiclone.*
Ramelteon	**Sleep latency:** Mean reduction was 9 min greater, compared to placebo (95% CI: 6 to 12 min reduction); **Quality of sleep*:** No improvement[b] in quality of sleep, compared to placebo; **Side effects:** See Recommendation 7, "Harms" *This recommendation is based on trials of 8 mg doses of ramelteon*
Temazepam	**Sleep latency:** Mean reduction was 37 min greater, compared to placebo (95% CI: 21 to 53 min reduction); **Quality of sleep*:** Small[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 6, "Harms" *This recommendation is based on trials of 15 mg doses of temazepam.*
Triazolam	**Sleep latency*:** Mean reduction was 9 min greater, compared to placebo (95% CI: 4 to 22 min reduction); **Quality of sleep*:** Moderate[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 5, "Harms" *This recommendation is based on trials of 0.25 mg doses of triazolam.*
Zaleplon	**Sleep latency:** Mean reduction was 10 min greater, compared to placebo (95% CI: 0 to 19 min reduction); **Quality of sleep*:** No improvement[b] in quality of sleep, compared to placebo; **Side effects:** See Recommendation 3, "Harms" *This recommendation is based on trials of 5 mg and 10 mg doses of zaleplon.*
Zolpidem	**Sleep latency:** Mean reduction was 5–12 min greater, compared to placebo (95% CI: 0 to 19 min reduction); **Quality of sleep*:** Moderate[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 4, "Harms" *This recommendation is based on trials of 10 mg doses of zolpidem.*
Recommended for Treating Sleep Maintenance Insomnia	
Doxepin	**Total sleep time:** Mean improvement was 26–32 min longer, compared to placebo (95% CI: 18 to 40 min improvement); **Wake after sleep onset:** Mean reduction was 22–23 min greater, compared to placebo (95% CI: 14 to 30 min reduction); **Quality of sleep*:** Small-to-moderate[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 8, "Harms" *This recommendation is based on trials of 3 mg and 6 mg doses of doxepin.*
Eszopiclone	**Total sleep time:** Mean improvement was 28–57 min longer, compared to placebo (95% CI: 18 to 76 min improvement); **Wake after sleep onset:** Mean reduction was 10–14 min greater, compared to placebo (95% CI: 2 to 18 min reduction); **Quality of sleep*:** Moderate-to-Large[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 2, "Harms" *This recommendation is based on trials of 2 mg and 3 mg doses of eszopiclone.*
Temazepam	**Total sleep time:** Mean improvement was 99 min longer, compared to placebo (95% CI: 63 to 135 min improvement); **Wake after sleep onset:** Not reported; **Quality of sleep*:** Small[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 6, "Harms" *This recommendation is based on trials of 15 mg doses of temazepam.*
Suvorexant	**Total sleep time:** Mean improvement was 10 min longer, compared to placebo (95% CI: 2 to 19 min improvement); **Wake after sleep onset:** Mean reduction was 16–28 min greater, compared to placebo (95% CI: 7 to 43 min reduction); **Quality of sleep*:** Not reported; **Side effects:** See Recommendation 1, "Harms" *This recommendation is based on trials of 10, 15/20, and 20 mg doses of suvorexant.*
Zolpidem	**Total sleep time:** Mean improvement was 29 min. longer, compared to placebo (95% CI: 11 to 47 min. improvement); **Wake after sleep onset:** Mean reduction was 25 min greater, compared to placebo (95% CI: 18 to 33 min reduction); **Quality of sleep*:** Moderate[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 4, "Harms" *This recommendation is based on trials of 10 mg doses of zolpidem.*
Not Recommended for Treating either Sleep Onset or Sleep Maintenance Insomnia	

Appendix 8

Treatment options by comorbidities: group consensus based on evidence and practice

Comorbidities	Treatment Options
None	zolpidem, zaleplon, eszopiclone, temazepam, suvorexant, ramelteon
Psychiatric disorders **Depression**	trazodone, doxepin, mirtazapine
Anxiety	hydroxyzine, gabapentin/pregabalin, trazodone, doxepin, mirtazapine, benzodiazepine, quetiapine, clonidine
Psychotic disorder	quetiapine, olanzapine, risperidone
Bipolar/mania	quetiapine, olanzapine, risperidone, divalproex, other mood stabilizers
Alcohol use disorder	gabapentin/pregabalin, topiramate, baclofen
Neurodegenerative disorders **Parkinson's disease, Alzheimer's disease**	melatonin, trazodone, quetiapine, citalopram, suvorexant
Chronic Pain	doxepin, amitriptyline, gabapentin/pregabalin
Respiratory Disease	melatonin, gabapentin, hydroxyzine, trazodone, doxepin
Sleep apnea	eszopiclone
Restless Leg Syndrome	gabapentin/pregabalin
Pregnancy	doxylamine, diphenhydramine
Menopause	citalopram, eszopiclone, gabapentin, perhaps venlafaxine/fluoxetine but caution of worsening sx

*reference UTD, U Wisconsin, guidelines (AAFP, AASM), Stahl's

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Major Psychopharmacologic Medication Side Effects and Complications

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Major Psychopharmacologic Medication Side Effects and Complications

Extrapyramidal symptoms (EPS) secondary to antipsychotic medication

- *Dopamine blocking agent prescribing has greatly expanded, being used to treat a variety of psychiatric disorders*
    - *The non-adherence of these medication leads to poorer outcomes and significant increase in health care costs*
    - *A significant factor in non-adherence is lack of tolerability secondary to constellation of symptoms associated with EPS*

Dystonia

- Muscle contractions that lead to involuntary muscle spasm, cramping, and abnormal posturing
    - It can affect the neck, arms, legs, tongue, eyes, jaw, lips and larynx
    - Stress, anxiety, lack of sleep, and cold temperatures can worsen symptoms
- Multiple neurologic causes; differential diagnosis includes:
    - Drug induced
    - Focal dystonia
    - Heredo-familial
    - Other neurological disorders
- If antipsychotic medication-induced, likely related to:
    - Dose
    - Higher potency dopamine blockade
    - Dopamine: acetylcholine RATIO
- **High risk factors**
    - Young male
    - Previous EPS
- **Complications**
    - Non-adherence with medications
    - Dislocation
    - Trauma
    - Asphyxiation
- **Treatment :**
    - Anticholinergics
        - benztropine (Cogentin)
        - procyclidine (Kemadrin)
        - trihexyphenidyl (Artane)
    - Antihistamine – (diphenhydramine)
        - After starting treatment, observe if stable
            - Taper after 14 days if asymptomatic
            - Consider lower dose
        - Prophylactic treatment is not recommended

Parkinsonism

- **Presentation**
  - Tremor, bradykinesia, rigidity
  - Impaired social and occupational functioning
  - Impaired cognitive function
- **Differential Diagnosis**
  - Drug induced acute parkinsonism
  - Tardive dyskinesia (*see Table 1*)
  - Other neurological disorders
    - Parkinson disease
    - Essential tremor
    - Progressive supranuclear palsy
    - Wilson's disease
  - Cardiac disease
  - Bradykinesia from psychiatric disease
- **Related to:**
  - Higher potency dopamine blockade
  - Dose
- **High risk factors**
  - Previous history
  - Younger and older
  - Female
- **Complications**
  - Non-adherence
  - Falls
- **Treatment**
  - Dose reduction
  - Change drug to less potent dopamine blocker
    - **risperidone, ziprasidone > olanzapine > clozapine, quetiapine**
  - Antiparkinsonian agents
    - amantadine – not as effective, but less side effects

TABLE 1. Parkinsonism vs Tardive Dyskinesia

	Parkinsonism	TD
Current exposure to dopamine receptor 2 (D2) antagonist (especially more potent agents)	Yes	Not necessarily (requires past exposure)
Tremor	Yes	No
Predominant movement type	Hypokinetic, regular	Hyperkinetic, irregular
Rigidity	Often	No
Onset	After dosage increase	After prolonged exposure
Effect of antipsychotic reduction/discontinuation	**Improves symptoms**	**May transiently worsen symptoms**
Effect of anticholinergics or amantadine	Improves tremor, rigidity	Worsens dyskinesia
Note: TD and parkinsonism can co-exist		

Akathisia

- **Presentation**
  - Often presents as anxiety, associated with movement disorder
  - Restlessness, intense sensation of unease
  - Compulsion to move, usually in lower limbs
  - Need to move, causes distress
  - Unable to sit or stand still
  - Time of onset and duration – considered phenomenologically the same
    - Acute - begins in early days of treatment
    - Chronic – lasts for more than 6 months
    - Tardive – delayed onset > 3 months, associated with Tardive Dyskinesia
    - Withdrawal – associated with reduction or stopping certain medications
- **Differential diagnosis:**
  - Drug induced
  - Restless leg syndrome
  - Tardive dyskinesia
  - Substance intoxication
  - Parkinson disease
  - Traumatic brain injury
  - Encephalitis
- **Etiology**
  - Blocking certain dopamine receptors in brain
  - If antipsychotic medication induced related to:
    - Dose
    - Higher potency dopamine blockade
    - Dopamine: acetylcholine RATIO
    - Often occurs in early days of treatment
- **High risk factors**
  - Young male
  - Previous EPS
  - 24% of patients with schizophrenia on medication have chronic akathisia
    - One study 39% patients taking clozapine
    - 45% on first generation (typical) antipsychotics
- **Complications**
  - Worsening psychotic symptoms
  - Increased suicidality
  - Non-adherence with medications
- **Treatment**
  - Dose reduction
  - Beta-blockers - propranolol – start with low dose
    - Monitor for hypotension, bradycardia, orthostasis
    - First choice option with precautions
  - Benzodiazepines - Short term therapy for acute akathisia with gradual taper
    - Risk of dependence and cognitive adverse effects
  - 5-HT2a antagonist - mirtazapine, trazadone
    - Low dose, response in 5 -7 days
    - Good choice if propranolol contraindicated or ineffective
    - Good choice for chronic akathisia treatment
  - Anticholinergics - Limited evidence
    - Risk of cognitive and anticholinergic adverse effects
    - Not recommended for routine use

Two major psychotropic medication complications are Serotonin Syndrome and Neuroleptic Malignant Syndrome

- *Both are associated with autonomic dysregulation, altered mental status, and neuromuscular excitation*
- *Several potentially life-threatening diseases share similar signs and symptoms, making the importance of an accurate and timely diagnosis imperative*
- *In addition, alcohol, benzodiazepine, barbiturate and antidepressant withdrawal can mimic these disorders*

Table 2: Differential Diagnosis

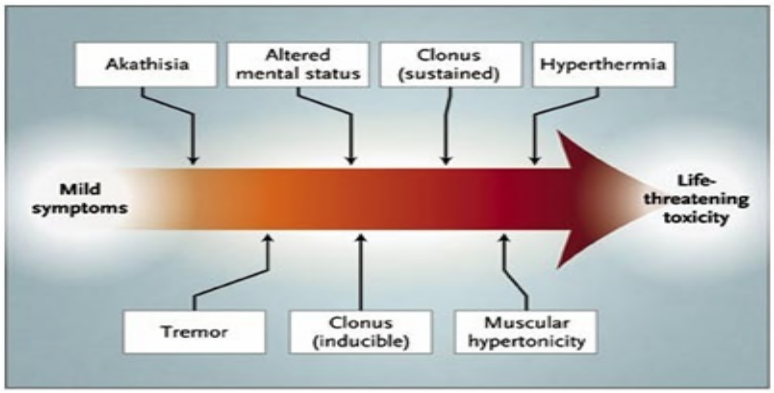
Disease	Medication Exposure	Shared Clinical Features	Distinguishing Clinical Features
Serotonin Syndrome	Serotonergic medications	Hypertension	Clonus, hyperreflexia Hyperactive bowel sounds
Neuroleptic Malignant Syndrome	Dopamine antagonists	Tachycardia	No clonus or hyperreflexia Bradykinesia
Anticholinergic Toxicity	Acetylcholine antagonist	Hyperthermia	No clonus or hyperreflexia Dry skin Absent bowel sounds
Malignant Hyperthermia	Halogenated anesthetics succinylcholine	Altered mental status	No clonus or hyperreflexia Extreme muscular rigidity

Key factor: - <u>What is the medication exposure</u>???

Serotonin Syndrome

- Diagnostic signs:
  - Mental status changes (change in CNS activity, hallucinations, agitation, lethargy, confusion)
  - Neuromuscular abnormalities (clonus, hyperreflexia)
  - Autonomic hyperactivity (abdominal pain, diarrhea, flu-like symptoms, sweating, flushing, hypertension)
  - **Hallmark signs are clonus and tremor**
- Occurs when central and peripheral serotonin receptors are overstimulated
  - Increased dose, overdose, addition of another serotonergic drug (esp. if different mechanism)
  - Increased **formation** (tryptophan)
  - Increased **release** (amphetamines, mirtazapine)
  - Impaired **reuptake** (SSRIs, tramadol, TCAs, cyclobenzaprine, SNRIs)
  - Inhibited **metabolism** (MAOIs like phenelzine, linezolid)
  - **Direct agonists** (buspirone, triptans, ergotamine)
  - Increased **receptor sensitivity** (lithium, metoclopramide)
- Associated with high doses, drug-drug interactions, multiple serotonergic agents (*see Table 3*)
  - **75% of patient cases have symptoms within 24 hours of precipitating medication change**

- Presents with a spectrum of increasing symptoms



Treatment

- **Prevention**
  - Physician awareness
  - Clear communication between providers regarding medications changes
  - Awareness of metabolism and drug interactions of all new and previous prescribed medications
- **Mild adverse reactions**
  - Anxiety, agitation, akathisia, tremors, tachycardia, sweating, GI upset
  - Discontinue offending drugs
  - Unless the disease is recognized and the causative drugs are discontinued, it can rapidly progress to muscle rigidity, severe hyperthermia, and death
- **Full blown Serotonin Syndrome**
  - Clonus, hypervigilance, hyperthermia, hypertension, hyperreflexia
  - Discontinuation of offending drugs and supportive care
- **Severe Serotonin Toxicity**
  - Rigidity, hyperthermia >40°C, seizures, coma, potentially fatal
  - Discontinue offending drugs
  - Supportive and intensive care – intubation/ventilation, dialysis, neuromuscular paralysis
  - Medications
    - cyproheptadine (5-hydroxy-tryptamine antagonist)
    - Benzodiazepines, anticonvulsants, propranolol

Key Points

- Think about which drugs are associated with serotonergic activity
- Know which drugs your patient is taking
  - Starts with a good medication reconciliation (including OTCs and illicit drugs)
- Check for interactions
  - Detailed literature summaries available in different resources
    - Helps you translate the warnings in the context of a clinical scenario
- Weigh the risks vs. benefits
  - Consider discussing with the patient if you are concerned
- Patient counseling is critical (document):
    - Serotonin syndrome is extremely rare, but it is good to know what signs to watch for. It usually occurs within 24 hours of starting a new drug that affects serotonin. Signs to watch for include shakiness, twitching muscles, agitation, confusion, racing heartbeat, diarrhea, and nausea. Do not wait if you are feeling bad and call right away if you feel you may be having serotonin syndrome.

- Some patients tolerate serotonergic agents much better than others and it is very difficult to predict. So it is best to counsel all patients at risk so they can be prepared, especially if a dosage adjustment was just made.

Table 3: Examples of Drugs Associated with Development of Serotonin Syndrome, Classified According to their Mechanism of Action

Synthesis and Release		
Increase Serotonin Synthesis	Dietary supplements: L-tryptophan	
Increase Serotonin Release	Psychostimulants: amphetamines, phentermine, MDMA Antidepressants: mirtazapine Opioids: meperidine, oxycodone, tramadol Cough suppressants: dextromethorphan	
Metabolism		
Inhibit Serotonin Uptake	Psychostimulants: amphetamines, MDMA, cocaine Antidepressants: trazodone SNRI: desvenlafaxine, duloxetine, venlafaxine SSRI: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline TCA: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine Opioids: meperidine, methadone, tramadol Cough suppressants: dextromethorphan	
Inhibit Serotonin Metabolism	Anxiolytics: buspirone MAOI: furazolidone, isocarboxazid, linezolid, methylene blue, phenelzine, selegiline, tranylcypromine	
	CYP2D6 **CYP2C19**	**CYP3A4**
Inhibit Cytochrome	Inhibitors: fluoxetine, sertraline	Inhibitors: ciprofloxacin, ritonavir
Inhibitors: fluconazole	Substrates: citalopram dextromethorphan, oxycodone, risperidone, tramadol	Substrates: methadone, oxycodone, venlafaxine
Receptor Activation		
Activate Serotonin Receptors	Hallucinogen: LSD Anxiolytics: buspirone Antidepressants: trazodone Opioids*: fentanyl, meperidine Mood stabilizers: lithium	

* opioids most likely activate serotonergic receptors through a combination of postsynaptic 5-HT receptor stimulation
as well as synergistic μ-opioid and 5-HT receptor presynaptic inhibition of GABA release.

Neuroleptic Malignant Syndrome (Hypodopaminergic)

- **Etiology**
  - Associated with dopamine-receptor antagonist or rapid withdrawal of dopaminergic medications
  - Associated with every neuroleptic agent (*see table 2*)
- **Incidence**
  - Typicals – 0.2% - 0.6%
  - Atypicals – lower incidence than typicals
  - Recurrences when challenged - 30% (no difference between typical and atypicals)
- **Characteristic symptoms**
  - Mental status changes
  - Fever 101 – 104°F
  - Neuromuscular abnormalities such as rigidity, bradykinesia
  - Autonomic instability - BP, HR, diaphoresis, incontinence, dehydration, GI disturbance
- **Labs**
  - CPK 2,000- 15,000 or higher; associated with rhabdomyolysis
  - WBC 15 – 30 with left shift
  - Mildly elevated liver enzymes
  - Myoglobin in the urine
  - Metabolic acidosis
- **Patient Profile**
  - Male, <35 y.o.
  - Affective disorder > schizophrenia> with organic brain lesions
  - High potency neuroleptics, depot preparations, concurrent lithium
  - 90% within 10 days of starting or increase in dose
- **Course**
  - Develops within 24 to 72 hours
  - Usually subsides 2-14 days after discontinuation of neuroleptics
  - 20 – 30% develop secondary complications
    - Respiratory complications: Dec respiratory drive, dysphasia and aspiration, rigid chest wall, pulmonary embolus
    - Renal failure from volume depletion, Acute tubular necrosis from myoglobinemia
    - Shock, rhythm disorders
    - DIC
  - With early diagnosis and supportive care , mortality 10%
- **Differential Diagnosis**
  - CNS infection – lumber puncture
  - Phenothiazine heat stroke – no rigidity or diaphoresis
  - Malignant hyperthermia – anesthetic exposure
  - MAO hypertensive crisis – Used an MAOi
  - Anticholinergic crisis – dry, dilated pupils, no rigidity or diaphoresis
  - Serotonin syndrome – presence of myoclonus, hyperreflexia, shivering, GI symptoms, on serotonergic (multiple) agents
  - Catatonia spectrum– often progresses to NMS, may be on the same spectrum

- **Treatment; neurologic emergency**
  - Discontinue offending agent
  - Supportive therapy
  - If needed:
    - Aggressive cooling, fluid, and electrolyte balance
    - Monitor for arrhythmias and ventilation status
  - Medications
    - bromocriptine (dopamine agonist)
    - dantroline (muscle relaxant)
    - Benzodiazepines
    - If due to dopamine withdrawal: restart dopaminergic agent
  - Re-initiation of neuroleptics
    - Wait at least 2 weeks
    - Use lower potency agents
    - Start low and go slow
    - Avoid lithium
    - Maintain good hydration

Table 4: Examples of Medications Associated with Neuroleptic Malignant Syndrome

Typical Neuroleptics
haloperidol
chlorpromazine
fluphenazine
thioridazine
trifluordazine
thiothixene
loxapine
bromperidol
promazine
clopenthixol

Atypical Neuroleptics
olanzapine
clozapine
risperidone
quetiapine
ziprasidone
aripiprazole
zotepine
amisulpride

Antiemetics
droperidol
domperidone
metoclopramide
promethazine
prochlorperazine

Others
tetrabenazine
reserpine
amoxapine
diatrizoate
lithium
phenelzine
dosulepin
trimipramine
desipramine

Dopaminergic Agents (withdrawal)
levodopa
amantadine
tolcapone
dopamine agonists

Tardive Dyskinesia

- Tardive dyskinesia (TD) is a disabling, disfiguring movement disorder, involving involuntary choreoathetoid movements of the orofacial region caused primarily by the prolonged use of neuroleptic drugs. It is typically persistent with no definitive treatment.
- In adults, the annual rate of development with second-generation antipsychotics is 2.98% versus 7.7% with first-generation antipsychotics.
- **Pathophysiology:** Likely related to chronic blockade of dopamine in the CNS. This may lead to super-sensitivity or upregulation of dopamine receptors or an imbalance in effect between D1 and D2 receptors.
- **Risk Factors:** Advanced age, female, duration of neuroleptic use, mental retardation

Differential Diagnosis | Back to Top

Diagnosis	Features
Dyskinesia due to other medications	Medication use other than neuroleptics
Hyperthyroidism	Choreiform movements of the limbs
Poorly fitting dentures	Mouth movements disappear when dentures are rer
Occurs in children following a streptococcal infection	
Hallervorden-Spatz disease	No use of neuroleptics; associated with intellectual d
Stroke	Sudden onset

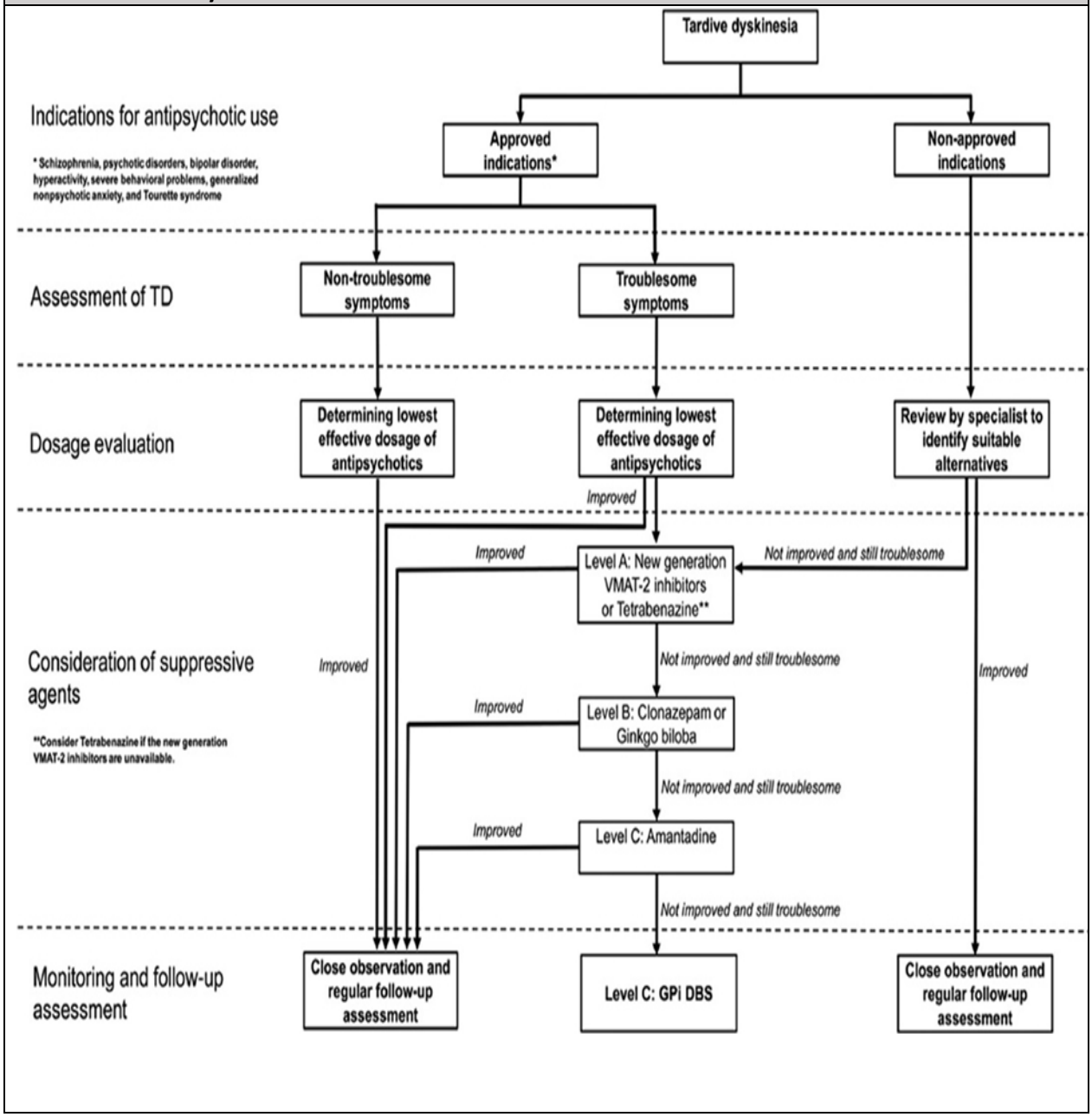
Treatment of TD

- If abnormal movements are present, try to decrease neuroleptic dose or switch to atypical if using a typical neuroleptic
- Discontinuing neuroleptic may decrease symptoms, although not in all patients. (abrupt withdrawal of the drug is rarely recommended and may worsen the condition)
- Based on limited research, lowering the dose or switching to another neuroleptic does not decrease TD symptoms. (This is often done in practice however, and it is possible the TD can resolve if the offending drug is removed early)
- Vitamin E and Vitamin B6 may prevent worsening of TD, no data exist to support as an effective treatment.
- **VMAT2 inhibitors:** There are no head to head comparisons of these drugs, caution with evidence interpretation. Expensive. (*see Table 4*)
    - **deutetrabenazine (Austedo)** is approved for the treatment of TD in adults, at a starting dose of 6 mg bid increased weekly to a maximum dose of 24 mg bid. The NNT = 5 for comparison with placebo as defined as much or very much improved. Mean AIMS reduction of -3 with 38mg/day versus -1.6 with placebo.
    - **valbenazine (Ingrezza)** can be used at a starting dose of 40mg. Caution with CYP 2D6 inhibitors. This drug reduced the mean AIMS from baseline by -3.2 at a dose of 80mg versus placebo (-0.1).
    - **tetrabenazine (Xenazine)** can be dosed at 12.5mg daily for 1 week and increased by 12.5mg increments up to 75-150mg. Doses > 37.5mg should be divided TID. Caution with CYP2D6 inhibitors. Showed marked reduction or disappearance of dyskinesia in 70% of patients compared with no change for placebo at a dose of 150mg/day.
- Preliminary research suggests that benzodiazepines may improve symptoms, although the evidence is not strong enough with the risks of sedation and dependency, to support routine use
- amantadine (N-methyl-D-aspartate receptor antagonist) - has shown some improvement
- gabapentin, calcium channel blockers, choline, physostigmine, baclofen, progabide, sodium valproate, ceruletide, gamma-linolenic acid, estrogen, and lithium have not been shown to be effective
- **Refractory symptoms** should see a movement disorder specialist and be considered for deep brain stimulation

Key Points

- With the increase use of atypical antipsychotics for numerous indications, TD will present not only in schizophrenia but also in patients with mood or complex anxiety disorders or developmental disabilities.
- **Screening/Prevention: AIMS testing**
    - **Should be done at 3 and 6 months. Some patients who develop TD show symptoms in the first 3 months (sooner in elderly, 1 month)**
    - **<u>Chronically should be done and documented q 3-6 months</u>**
- Recent self-report screeners have shown patients can be very sensitive in detecting TD *when asked the right questions*.
    - **Have you noticed unusual movements in your tongue or lips?**
    - **Have you noticed any unusual movements in your hands or fingers?**
    - **Is there any other part of your body where you have noticed abnormal tremors or movements?**
- Patients at high risk for developing TD include those who previously developed EPS, patients receiving anticholinergics, women, and those over the age of 55
- Three mistakes that can place both your patients and your practice at risk include:
    - **Forgetting to screen for TD in mood, anxiety, and other mental health conditions**
    - **Missing the diagnosis of TD in individuals prescribed anticholinergics**
    - **Increasing the dose of antipsychotic temporarily masks TD but worsens it over time!**

Table 5: Tardive Dyskinesia Treatment Flow Chart



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Follow-Up Intervals and Psychotropic Drug Monitoring

Patient Classification	Recommended follow-up interval
Newly diagnosed patient starting on an antidepressant, mood stabilizer, or antipsychotic with *significant concerns* and/or psychotic, manic, suicidal ideation/recent suicide attempt, or severely anxious	Within 1 week
Newly diagnosed depressed patient who you are not overly concerned about, starting a new antidepressant	Call in 1-2 weeks Clinic visit in 2-4 weeks
Depressed patient with concerns and increasing or switching antidepressants and/or adding mood stabilizer or antipsychotic	1-2 weeks
Any adolescent patient starting on a new antidepressant	Within 1 week and f/u every 1-2 weeks until stable
Stable patient on antipsychotics	3-6 months, at least yearly

- **Antidepressants**
  - Baseline: TSH and CBC. EKG if pt > 40 yo or starting tricyclic antidepressant (TCA).
  - Routine: Yearly CBC, CMP, and PHQ-9.
- **Antipsychotics**
  - Baseline: CMP, lipids, AIMS, and EKG.
  - Routine: CMP, lipids, and AIMS test q6-12 months. EKG yearly.
  - NOTE: AIMS test exists as a template in NextGen called "BH-AIMS"
- **Lithium**
  - Baseline (within last 3 months): TSH, CBC, and CMP. EKG if has CV risk factors or if > 40 years' old, pregnancy test
  - Initiation: BMP q3months during first 6 months. TSH once within first 6 months
  - Routine: BMP, CBC, EKG, TSH, and Lithium level every 6-12 months.
  - Drug Level Frequency: Lithium level in 5-7 days after initiation and after each dose change. Repeat x 1 in 2 weeks once therapeutic. Recheck at 3 months and then q6-12 months thereafter.
  - Therapeutic Levels (drawn at least 8-12 hours after last dose): **0.6-1.2 mEq/L**
- **Divalproex (Depakote)**
  - Baseline (within last 3 months): CBC and CMP, pregnancy test
  - Initiation: Repeat CMP within 1 month of initiation.
  - Routine: CBC and CMP every 6 months. Valproic acid level q6-12 months.
  - Drug Level Frequency: Check in 3-5 days after initiation and after each dose change. Repeat x 1 in 2 weeks once therapeutic.
  - Valproic Acid Levels (drawn 8-12 hours after last dose): **50-125 mcg/mL**
- **Carbamazepine/Oxcarbazepine (Tegretol and Trileptal)**
  - Baseline (within last 3 months): CBC and CMP
  - Routine: CMP q 6 months. Yearly CBC.
  - Drug Level Frequency: Level in 3-5 days after initiation and after each dose change. Repeat at 3, 6, and 9 weeks. Then q6months thereafter.
  - Goal Carbamazepine Level: **4-10 mcg/mL**
- **Stimulants** – Initial follow-up in 2 weeks and adjust dose and follow-up every month until stable. When stable, follow-up at least **every 6 months**. EKG yearly. Watch blood pressure and weights.