5-HT1Ä SEROTONIN RECEPTOR AGONIST

❖ Principal action of flibanserin (Addyi) in stimulating libido
❖ An effect of trazodone and nefazodone
❖ Offsets EPS caused by D2 antagonists

AGONIST OF 5-HT1B AND 5-HT1D RECEPTORS

❖ Principal vasoconstrictive effect of sumatriptan (Imitrex) in treating acute migraine

5-HT2Ă AGONIST

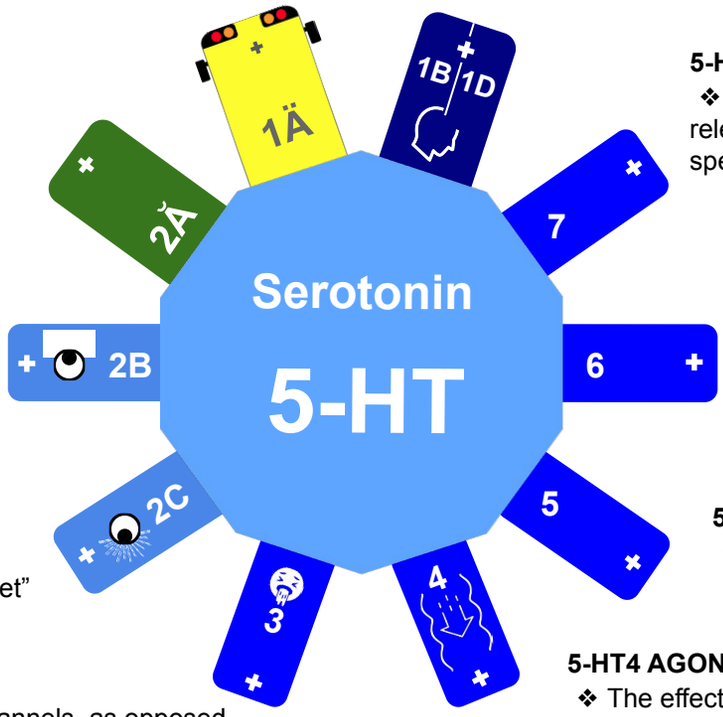
❖ The psychomimetic and antidepressant effect of psilocybin
❖ 5-HT2Ă receptors are implicated in serotonin toxicity

5-HT7 AGONIST

❖ Psychiatric relevance but nothing specific to memorize

5-HT2B AGONIST

❖ Appetite suppressant effect, e.g., fenfluramine, which damages heart valves—"I would pray 2B thin, but it might hurt my heart". The FDA will not approve any new drug that activates 5-HT2B receptors.



5-HT6 AGONIST

❖ Psychiatric relevance but nothing specific to memorize

5-HT2C AGONIST

❖ Appetite suppressant effect of lorcaserin (removed from market)— "I'd like '2C' my feet"

5-HT5 AGONIST

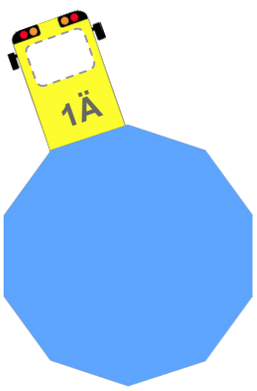
❖ Little is known

5-HT3 AGONIST

❖ Produces nausea
❖ 5-HT3 receptors are ligand-gated ion channels, as opposed to all other 5-HT receptors which are G protein-coupled.

5-HT4 AGONIST

❖ The effect of prucalopride (Motegrity) and tegaserod (Zelnorm) in increasing intestinal motility.



5-HT1Ä PARTIAL AGONIST

❖ Principal anxiolytic effect of buspirone (Buspar), which is a full agonist at some 5-HT1Ä receptors
❖ An effect of several antidepressants: vortioxetine, vilazodone, and gepirone
❖ An effect of most SGAs: aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, lurasidone, quetiapine, and ziprasidone
❖ Offsets EPS caused by D2 antagonists (similar effect to blocking 5-HT2A)
❖ May enhance the antidepressant effect of SRIs
❖ May counter SRI-induced sexual dysfunction
❖ Similar effect to blocking 5-HT2A—opposes D2 antagonism by causing more dopamine release in side-effect pathways
❖ Seemingly all good things

5-HT2Ă SEROTONIN RECEPTOR ANTAGONIST

❖ Antipsychotic effect
❖ Offsets EPS caused by D2 antagonists
❖ Offsets prolactin elevation caused by D2 antagonists
❖ Possible reduction of negative symptoms in schizophrenia
❖ Possible mood stabilizing and anxiolytic effect
❖ Seemingly all good things
❖ The sole antipsychotic effect of pimavanserin (Nuplazid), an inverse agonist ("super-antagonist")

5-HT1Ä ANTAGONIST

❖ A purported effect of the β-blocker pindolol, which was researched as an add-on therapy to make SRI antidepressants work faster.

5-HT2B ANTAGONIST

❖ Appetite-stimulating effect of cyproheptadine (Periactin)

5-HT1B/D ANTAGONIST

❖ Possible pro-cognitive and antidepressant effects, e.g., vortioxetine (Trintellix), which does not appear to cause headaches beyond expected an antidepressant

5-HT2C ANTAGONIST

❖ Contributes to weight gain of SGAs
❖ Antidepressant effects

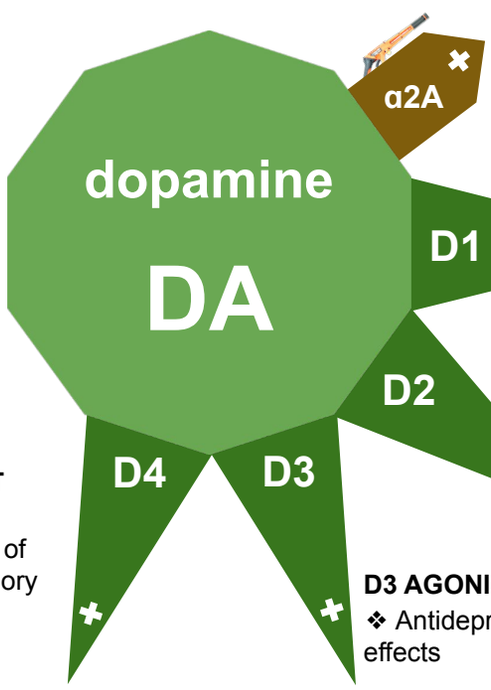
5-HT3 ANTAGONIST

❖ The antiemetic effect of ondansetron (Zofran) and ginger
❖ Antidepressant and pro-cognitive effects
❖ An effect mirtazapine (Remeron)
❖ An effect of vortioxetine (Trintellix)

5-HT4 ANTAGONIST

❖ Constipation

You can download the entire STAR*D slideshow at cafermed.com/november—scroll to bottom of the page



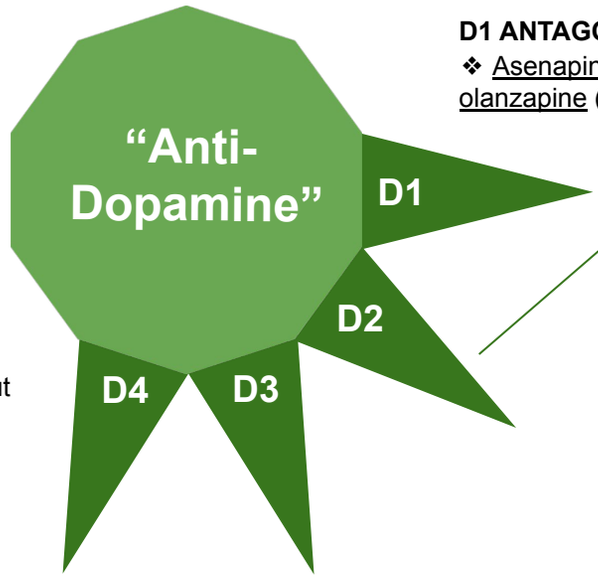
α2A ADRENERGIC RECEPTOR AGONIST
❖ Dopamine activates α2A receptors, although binding affinity is less than with norepinephrine.
❖ See norepinephrine ballicule.

DOPAMINE D1 RECEPTOR AGONIST
❖ Possible cognitive benefits, e.g., stimulants for ADHD

D2 AGONIST
❖ The effect of bromocriptine, ropinirole, pramipexole, rotigotine, and apomorphine in treating Parkinson's disease and restless legs syndrome
❖ The prolactin-lowering effect of cabergoline
❖ Reward motivated behavior
❖ Compulsive behavior
❖ Psychosis

D4 AGONIST
❖ Possible improvement of working memory
❖ Possible psychosis

D3 AGONIST
❖ Antidepressant effects

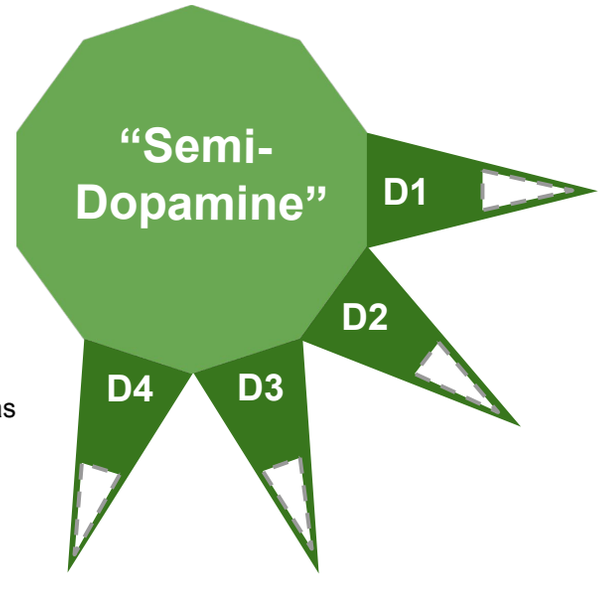


D1 ANTAGONIST
❖ Asenapine (Saphris), clozapine (Clozaril), and olanzapine (Zyprexa) block D1 (in addition to D2)

D2 ANTAGONIST
❖ Principal effect of most antipsychotics in reducing positive symptoms of schizophrenia
❖ Antimanic effects
❖ Antiemetic effects, e.g., metoclopramide
❖ EPS including tardive dyskinesia
❖ Hyperprolactinemia (from outside of the BBB)
❖ Second generation antipsychotics (SGAs) bind bind more loosely than first generation antipsychotics (FGAs)

D4 ANTAGONIST
❖ Most antipsychotics but significance is unclear
❖ Selective D4 blocker was found Ineffective for schizophrenia
❖ An effect of buspirone (Buspar)
❖ Does not cause extrapyramidal symptoms (EPS)

D3 ANTAGONIST
❖ Theoretically, a D3-selective antagonist would have antipsychotic effects without inducing EPS.
❖ Possible improvement of cognition and negative symptoms of schizophrenia



D1 PARTIAL AGONIST
❖ Decreased cocaine seeking and reward (when combined with a D3 antagonist)

D2 PARTIAL AGONIST
❖ Antipsychotic effect of aripiprazole (Abilify), brexpiprazole (Rexulti), and cariprazine (Vraylar)— "A, B, & C"
❖ Akathisia
❖ Unlikely to cause dystonia or tardive dyskinesia
❖ Does not elevate prolactin

D3 PARTIAL AGONIST
❖ Possible improvement of cognition and negative symptoms of schizophrenia
❖ Possible improvement of mood and motivation
❖ An effect of cariprazine (Vraylar), which is more selective for D3 vs D2

D4 PARTIAL AGONIST
❖ Flibanserin (as off-target effect)

α and β receptors are adrenergic receptors, referring to adrenaline (epinephrine, EPI) or noradrenaline (norepinephrine, NA). The principal difference between the two neurotransmitters is that EPI does not readily cross the blood-brain barrier. NE is more effective at α receptors, with EPI is more effective at β receptors.

α2A AGONIST

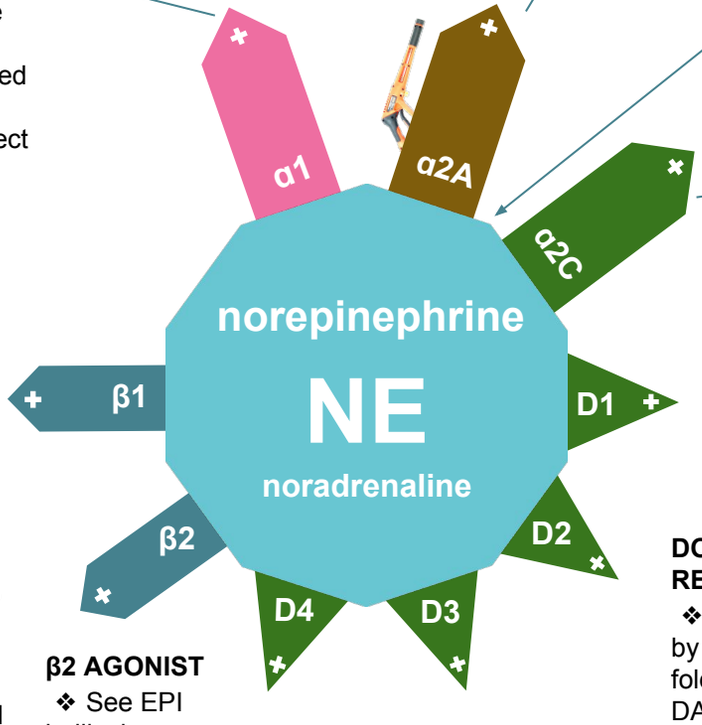
❖ The effect of guanfacine (α2A selective) which enhances prefrontal cortical function in ADHD—also clonidine, which activates α2 non-selectively in addition to imidazoline receptors. Guanfacine is "cleaner" (than clonidine), with less sedative effect.
❖ Vasodilation and decreased BP by negative feedback in CNS
❖ relief of opioid withdrawal symptoms
❖ analgesia
❖ dry mouth as side effect

α2B AGONIST

❖ Not shown because most α2B agonists are non-selective, stimulating all α2 receptor subtypes

α1 ADRENERGIC RECEPTOR AGONIST

❖ "Fight or flight" response including increased BP, pupillary dilation, and reduced digestive activity
❖ The vasoconstrictive effect of effect of midodrine and phenylephrine (neither of which cross the blood-brain barrier)



α2C AGONIST

❖ Sedative and analgesic effect of dexmedetomidine (Precedex, Igalmi) which is α2 nonselective

β1 AGONIST

❖ NE binds β receptors with lower affinity than EPI.
❖ See EPI ballicule for peripheral effects.
❖ In the context of NE reuptake inhibitors (NRIs), e.g., bupropion (Wellbutrin), anxiety can be transiently worsened, then eventually improved as β1 adrenergic receptors downregulate and desensitize.

β2 AGONIST

❖ See EPI ballicule

DOPAMINE D1-D4 RECEPTOR AGONIST

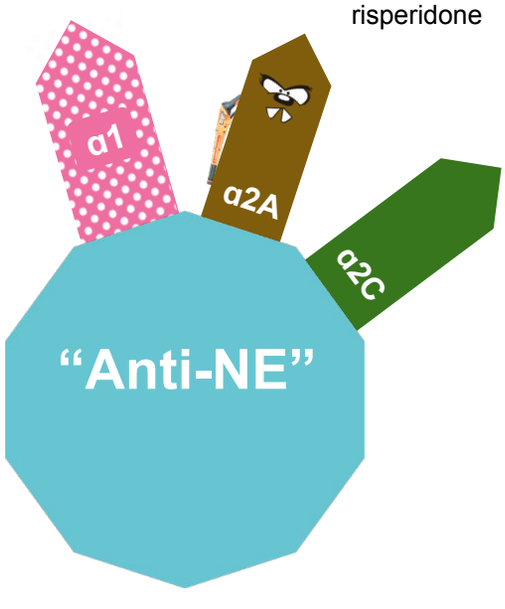
❖ DA receptors are activated by NE, although at 50 to 100-fold higher concentrations than DA

α1 ANTAGONIST

❖ The effect of prazosin (Minipress) in lowering blood pressure and improving PTSD-related nightmares
❖ Relaxation of bladder neck and prostate—useful for symptoms of urinary obstruction due to benign prostatic hypertrophy (BPH)
❖ Postural hypotension is common with the initial dose
❖ Antipsychotics *with* α1 blocking activity– "built-in prazosin"—cause orthostatic hypotension if titrated too quickly: clozapine, quetiapine, ziprasidone, iloperidone, risperidone, paliperidone, brexpiprazole, chlorpromazine, perphenazine
❖ Antipsychotics *without* α1blocking activity can be titrated more quickly without causing orthostatic hypotension: olanzapine, lumateperone, asenapine, aripiprazole, and cariprazine
❖ For treatment of BPH: terazosin, doxazosin, alfuzosin, tamsulosin, and silodosin

α2A ANTAGONIST

❖ Principal antidepressant effect of mirtazapine (Remeron) and gepirone (Exxua), with downstream release of serotonin of which causes an increased release of serotonin and norepinephrine.
❖ Mirtazapine blocks the antihypertensive effect of clonidine, potentially precipitating hypertensive crisis
❖ An effect of SGAs clozapine, paliperidone, and risperidone



α2C ANTAGONIST

❖ May contribute substantially to antipsychotic effects of clozapine, olanzapine, risperidone, paliperidone, and brexpiprazole. The peg is green for "little green men".

Bipolar Depression

Step 1 (if not ECT or IV ketamine)
- quetiapine
- lurasidone ~~$$$~~
- lamotrigine
- lithium > 0.8
- *lumateperone $$$*
- cariprazine *(less effective) $$$*

Taper antidepressants

Why not add Omega 3 's and/or light therapy?

Steps 2 - 4: combos of the above

Step 5 (augment with):
valproate

Why not add T3 or pramipexole?

Only if not bipolar I, mixed episode, rapid cycling or history of (hypo)manic switching, may use:
- bupropion
- fluoxetine + olanzapine combo
- other SSRIs *(less desirable)*

Then: ECT or IV ketamine (if ECT declined)

Regular Depression

Step 1 (assure not bipolar)
- **sertraline**
- **escitalopram**
- **bupropion**

If bipolar II is a possibility or strong family history of bipolar, treat as bipolar depression or choose bupropion and avoid SSRIs.

Step 2 (switch to)
- a different 1st-line:
  SERT, ESCIT, BUP
- **venlafaxine**
- **mirtazapine**
- TMS
- S-adenosylmethionine (SAMe)
- St John's wort

(or) augment with
- quetiapine (FDA-approved)
- aripiprazole (FDA-approved)
- risperidone (off-label)
- *brexpiprazole (FDA-approved)*
- *cariprazine (FDA-approved)*
- lithium
- **bupropion or mirtazapine**
- **T3 - triiodothyronine (Cytomel)**
- light therapy
- omega-3 fatty acids
- L-methylfolate
- N-acetylcysteine (NAC)
- *mediterranean diet*

Generalized Anxiety Disorder

Psychotherapy is recommended because effect size of pharmacotherapy for GAD is small.

Step 1
- SSRI (sertraline, escitalopram)
- or possibly duloxetine
- or possibly "main step 2 options"

Step 2 (if no response)
- other SSRI or duloxetine
- main step 2 options
  - buspirone
  - **hydroxyzine**
  - **pregabalin**
  - bupropion
- other options
  - lavender oil (CalmAid)
  - *lorazepam* (or other BZD)
  - venlafaxine
  - kava
  - rhodiola rosea

If partial response, augment with:
- **hydroxyzine**
- **pregabalin** *(or possibly gabapentin)*
- benzodiazepine

Step 3
- quetiapine
- risperidone
- valproate *Where's propranolol?*

Mania

--Taper antidepressants.
--Ensure sleep with benzo +/- antipsychotic +/- antihistamine (preferably not trazodone).
--Consider blue-blocking glasses.
--Preferred antipsychotic is **quetiapine**.
--*Alternate antipsychotics include olanzapine, risperidone, ziprasidone, asenapine.

Classic mania (60%)
Step 1: **lithium** *(+/- antipsychotic)*
Step 2: add **quetiapine** (or alt antipsychotic*)
Step 3: add **valproate** (unless childbearing)

Mixed mania (40%)
Step 1: **quetiapine** (or alternate antipsychotic*)
+/- valproate
Step 2: add **valproate** (unless childbearing)
Step 3: add **lithium**

Steps 4-6 for classic or mixed
Stop any ineffective medications and add:
1st tier:
- carbamazepine** (unless childbearing)
- olanzapine, risperidone, haloperidol

2nd tier: aripiprazole, asenapine, ziprasidone
3rd tier: clozapine or ECT
Also consider: *allopurinol or tamoxifen*

***Carbamazepine is a 3A4 in**D**ucer that will reduce blood levels of quetiapine by ~85%, aripiprazole by ~65%, haloperidol by ~40%, and risperidone +metabolite by ~35% within a few weeks of starting carbamazepine. in**D**uction - **D**own and **D**elayed*

Severe Melancholic Depression

Step 1 (assure not bipolar)
- ECT or IV ketamine if urgent indication
- **venlafaxine** or **mirtazapine**

Step 2
- **venlafaxine/mirtazapine**
- tricyclic antidepressant
  - nortriptyline or imipramine

(or) augment with
- Lithium or T3 - triiodothyronine

Treatment-Resistant Depression

Address comorbid conditions:
Chronic pain, OCD, ADHD, PTSD

If atypical features (reconsider bipolar):
- Reconsider **bipolar** diagnosis
- SSRI + aripiprazole
- Monoamine oxidase inhibitor
  - selegiline or phenelzine

Refer to Osser text for highly treatment-resistant

Psychotic Depression

Step 1 - Consider ECT

Step 2
Antipsychotic + SSRI/SNRI/TCA

Step 3
Add Lithium
Again, consider ECT

Step 4
Clozapine
Methylphenidate

Social Anxiety Disorder

Step 1:
- an SSRI
- may augment with buspirone

Step 2: (switch to)
- venlafaxine
- mirtazapine
- a different SSRI
- clonazepam
- phenelzine (MAOI) - *largest effect size*

Step 3: (including experimental options)
- gabapentin
- pregabalin
- tiagabine
- quetiapine
- risperidone *Where's propranolol?*

Schizophrenia

Step 1 - 2nd-gen antipsychotic (SGA)
- **aripiprazole**
- **risperidone**
- lurasidone
- ziprasidone
- **not** olanzapine *(metabolic)*
- **not** quetiapine *(too weak)*

Adequate trial is 4 to 6 weeks

Unsatisfactory response?
- **monitor drug plasma level**
- LAI if poor adherence

Step 2
A different antipsychotic
- consider risperidone *(again)*
- consider **olanzapine**
- consider 1st-gen antipsychotic

Step 3
Titrate **clozapine** and taper other antipsychotic(s)

Step 4 - add to clozapine:
risperidone or aripiprazole
Consider reducing clozapine to 1/3 dose & adding fluvoxamine to inhibit conversion to norclozapine.
Consider: lamotrigine, memantine, omega 3's, ECT

Step 5 - taper off clozapine and consider:
aripiprazole (or other antipsychotic)
high-dose olanzapine (monitor plasma levels)
1st gen antipsychotic + mirtazapine
2nd gen antipsychotic + celecoxib (Celebrex)
Consider importing amisulpride (1st line outside U.S.)
Consider medical ketogenic diet.

The least-evidenced option:
combo of antipsychotics not including clozapine

PTSD

If sleep is not disturbed: **SSRI**

If sleep is disturbed, start with:
- **prazosin** (if nightmares)
- **trazodone** (if not nightmares)

If symptoms remain, add **SSRI**

Benzodiazepines should be avoided.

If SSRI ineffective, change to:
SNRI or mirtazapine

Possible next steps include:
- nefazodone *(alt to trazodone)*
- clonidine *(alt to prazosin)*
- lamotrigine or topiramate
- 2nd-gen antipsychotics:
  quetiapine, risperidone, aripiprazole
- phenelzine (MAOI)
- levetiracetam

OCD

Step 1 - *SSRI* (assure not bipolar)
- sertraline
- fluoxetine *(CYP inhibitor)*
- fluvoxamine *(CYP inhibitor)*
- *Avoid SSRIs if bipolar*

SSRI at moderate dose for 8-12 weeks
Check antidepressant serum levels
Increase to FDA max, continue for 8-12 weeks
Check antidepressant serum levels

Increase SSRI beyond FDA max
- up to sertraline 400 mg, fluoxetine 120 mg, fluvoxamine 450 mg, escitalopram 60 mg.

Step 2
Augment antidepressant with:
- risperidone
- aripiprazole

Or switch to (less desirable)
- clomipramine

Step 3
- Add TMS

or augment with novel agents:
- memantine
- lamotrigine
- N-acetylcysteine (NAC)
- riluzole
- topiramate
- minocycline
- celecoxib
- ondansetron

Step 4 - neurosurgery
- deep brain stimulation *(electrode implant)* or
- capsulotomy (ablation with Gamma Knife)

Source: Psychopharmacology Algorithms by David Osser, 2021 *with modifications/comments by Jason Cafer, MD (italicized)* updated 11/11/23