Major Depression and Anxiety in Adolescents and Adults

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NO DISCLOSURES

OBJECTIVES

* Recognize Major Depressive D/O and Anxiety and to differentiate it from misery.
* Understand basic pharmacological strategies for treating Depression and Anxiety
* Understand secondary strategies for treating Depression and Anxiety
* Recognize when to refer to a mental health professional

TREATMENT TYPES

Psychotherapy
Medications
Complementary medications
– SAM-e, St. John's wort (little evidence)
Light therapy
ECT, TMS
DBT, VNS

STEP 1

Clarify Diagnosis.

Be sure you are dealing with a clinical depression rather than human misery.

STEP 2

If considering medication, think about:

- Therapeutic Alliance
- Side effects
- Comorbid conditions
- Family history of response to antidepressants
- Cost

In terms of efficacy:

SSRI's= SNRI's= = bupropion= TCA's= MAOI's

STEP 3

- Start SSRI or SNRI or SARI or bupropion or mirtazapine. SSRI's are usually the first choice
- SSRI's are usually the first choice
- It takes 4-8 weeks to see full effect of medication
- If there is NO improvement after a month, switch medication
- If there is partial improvement, increase the dose of the medication

SSRI's

Prozac / fluoxetine has the longest half life so if your pt is going to be unreliable about taking medication, it is a good choice. There is not much evidence that it is activating but that is still what is said.

Paxil/ paroxetine has the shortest half life so pts will feel discontinuation symptoms quickly. It has more drug interactions than other SSRI's and after six months is more likely to contribute to weight gain.

SSRI's

Celexa/ citalopram:

- Few drug interactions and well tolerated by geriatric patients. May need to increase dose but not over 40 mg when there is a possibility of QTc prolongation. Has some antihistaminic effects.

Lexapro-escitalopram:

- Similar to citalopram but does not have R enantiomer which causes antihistaminic effects so is the best tolerated SSRI

SSRI's

Zoloft/ sertraline:

Also has very few drug interactions and is easy to titrate slowly from a starting dose of 25 mg a day for very sensitive people. (Normal starting dose is 50 mg). Can titrate to 200 mg a day. It takes about 2 weeks to see effect of an increased dose.

A poor response to one SSRI does not correlate to a poor response with a second SSRI so it is reasonable to switch SSRI's before switching families of medication

SSRI PHARMACOLOGY

SSRIs initially block SERT and acutely increase concentration of serotonin in the synaptic cleft

- This is unlikely to be the cause of efficacy given the delayed onset of improvement

With recurrent administration there is reduction in the sensitivity of somatodendritic and termina 5-HT_{1A} autoreceptors, which is temporally correlated with antidepressant response

PHARMACOKINETICS

BLE 13–2. A comparison of several selective serotonin reuptake inhibitors

	Fluoxetine	Paroxetine	Sertraline	Citalopram	Fluvoxamine	Escitalopra
lume of distribution (L/kg)	3–40	17	20	12–16	>5	12–16
rcentage protein bound	94	95	99	80	77	56
ak plasma level (hours)	6–8	2–8	6–8	1–6	2–8	5
rent half-life (hours)	24–72	20	24–26	33	15	27–32
jor metabolite half-life	4–16 days	NA	66 hours	NA	NA	NA
ndard dose range (mg)	20–80	10–50	50–200	10–40	50–300	10–20
sorption altered by fast or fed tus	No	No	Yes	No	No	No
ered half-life in geriatric ient	No	Yes	Yes	Yes	No	Yes
duced clearance in renal ients[a]	±	+	±	±	±	±

e. NA = not applicable.[a] + = yes; ± = somewhat/mixed.

relatively long half-life of fluoxetine confers greater protection from the discontinuation syndrome that is associated
upt discontinuation or noncompliance related to interruption of treatment than more rapidly cleared SSRIs. Conversel
re prolonged vigilance for drug–drug interactions following discontinuation is required for fluoxetine; for example, a 5
k washout from fluoxetine is recommended before initiating an MAOI (Ciraulo and Shader 1990; Lane and Baldwin 19

STEP 4

If the patient has a poor response to 2 SSRI's:

Switch families of medication

Or

Augment with another medication

SNRI

Similar to TCAs, these drugs block both serotonin and norepinephrine reuptake

- Minimal affinity for muscarinic or histaminerg postsynaptic receptors, which explains why they are fairly well tolerated

Approved for various disorders including MDD, GAD, social anxiety disorder, panic disorder, diabetic neuropathy, and fibromyalgia

SNRI's

- **Effexor / venlafaxine:**

Works as an SSRI until the dose is increased to 150 mg a day and then it is both a serotonin and norepinephrine reuptake inhibitor. Can raise blood pressure if HTN is already present. Needs to be discontinued at a VERY slow rate.

- **Cymbalta/ duloxetine:**

May have less effect on blood pressure and be easier to discontinue. Helps with neuropathic pain but not all pain

NEWER ANTIDEPRESSANTS

* **Viibryd/ vilazadone** (SPARI= serotonin partial agonist reuptake inhibitor)
- Start at 10 mg for 7 days, can then increase to 20 mg. Max dose is 40 mg a day with or without food.
- Main side effects can be nausea and vomiting and insomnia
- If patients are taking a CYP3A4 inducer, vilazadone will be cleared more quickly and a higher dose will be required.

NEWER ANTIDEPRESSANTS

* **Trintellex/ vortioxetine:** (also a SPARI)
- Normal starting dose is 10 mg a day but can start at 5mg for patients who are very medication sensitive.
- Aim for 20 mg a day as tolerated
- Main side effects are nausea and vomiting and constipation
- If taking CYP2D6 inhibitors such as bupropion or paroxetine, a lower dose of vortioxetine will be needed
- If taking a CYP2D6 inducer like carbamazepine or phenytoin, a higher dose will be needed

NEWER ANTIDEPRESSANTS

* **Fetzima/ levomilnacipran :** (an SNRI)
- Start with 20 mg a day, with or without food for 2 days and then increase to 40 mg a day.
- Main side effects are nausea and vomiting, constipation, diaphoresis, increased hear rate/ palpitations and erectile dysfunction.
- Need a lower than average dose for patients also taking CYP3A4 inhibitors like anti-fungals

TCA

- Equally efficacious to SSRIs, SNRIs, others
- Clinically thought to be more helpful for melancholic type
- Some examples include nortriptyline, amitriptyline, desipramine, and imipramine
- Blood drug levels correlate with both efficacy and side effects

OTHER ANTIDEPRESSANTS

Bupropion (Wellbutrin)

- Combined noradrenergic-dopaminergic reuptake inhibitor; dopamine seemingly only at high doses
- SSRIs modestly better for MDD w/ anxiety; no prima indication for anxiety d/o
- Favorable side effect profile
- Avoid with eating disorders or alcohol abuse
- Often used for augmentation with SSRIs
- Indicated for MDD (Wellbutrin) and smoking cessatio (marketed as Zyban)

OTHER ANTIDEPRESSANTS

mirtazepine (Remeron)
- Antagonist at 5-HT2A, 5-HT2C, and α-2 receptors
- Reasonably safe in overdose
- Increased appetite and sleep via histamine

trazodone
- Antagonist at 5-HT2 and α-2 receptors; weakly inhibits serotonin reuptake
- Limited evidence to support use as a hypnotic
- Priapism is rare side effect, most often early on

AUGEMENTATION STRATEGIES FOR ANTIDEPRESSANTS

* Combine a non-SSRI antidepressant with an SSRI
* Add a low dose of a second generation antipsychotic suc
  as aripiprazole (Abilify) or risperidone (Risperdal)
* Add lithium at 300 mg a day. After a few days increase t
  300 mg bid. Should reach steady state in about 5 days.
  Level should be between 0.4 and 0.8 mg/dl
* Mixed evidence on T3. Can add 25-50 mcg/day of cytome

AUGEMENTATION STRATEGIES FOR ANTIDEPRESSANTS

Add L-methylfolate. Approved by FDA as a medical food. Sold as Deplin. Need 15 mg a day for 30 days

Omega 3 Fatty Acid 1.2 grams/ day for 8 weeks

ANTIDEPRESSANTS

FDA issued black box warnings on all antidepressants in 2004

- Initially applied to children and adolescent
- Issued over concerns about "suicidal thinking and behaviors"

Warning expanded to include young adults up to age 24 in 2007

ZERO!

ANTIDEPRESSANTS

Aftermath in years immediately following black box warning:

- Reported 20% reduction in antidepressant prescriptions to children and adolescents
- Nearly 70% drop in number of depression diagnoses in this age group
- No increase in the rate of individuals using psychotherapy

LIGHT THERAPY

* Some evidence that it is helpful for seasonal affective disorder
* Bulb needs to be at least 10 thousand LUX
* Light needs to be a table lamp rather than overhead light fixture.
* Use at least 30 minutes a day

ECT

* ECT remains the gold standard for treatment of depression.
* Ultra- brief pulse width (0.3 msec) avoids memory problems
* Anesthetic is used. Usually methohexitol or propofol.
* A fall in EEG amplitude at the end of a seizure is the only predicto
  ECT outcome. ECT increases neuroplasticity through glutamate a
  MNDA receptors and produces neurogenesis in the hippocampu
* Start with right lateral ECT but if not effective, can switch to bila
* Most patients need 6 – 12 treatments and they should be tapere
  rather than stopped abruptly

TMS
Transcranial Magnetic Stimulation

* Uses electrical energy in insulated coil on the scalp to induce a pulsed magnetic field of 1.5 Tesla through the cranium for 2-3 cm. Affects the neural circuitry
* Approved by FDA in 2008
* Minimal side effects
* After 6 week trial, 51% of patients had response and 25% had remission.

John P. O'Reardon, M.D. 2015

VNS
Vagal Nerve Stimulation

* A pulse generator is implanted in left chest wall and connected to leads attached to left vagal nerve.
* Mild intermittent pulses are applied. When the pulse activates, the patient sounds hoarse if is speaking.
* After 12 months, there is a divergence in response between placebo and VNS
* This treatment is rarely reimbursed so is rare.

TREATING GENERALIZED ANXIETY AND PANIC

Depression circuits and anxiety circuits are in overlapping parts of the brain so many of the treatments are the same

Dr. Pollard has discussed non-medical strategies for treating anxiety

When using medical strategies, the same steps are necessary as when coming up with medical interventions for depression

STEP 1:
valuate for medical conditions that cause anxiet

* Hyperthyroidism
* COPD
* Asthma
* Pheochromocytoma
* Coronary heart disease
* Vitamin B deficiency
* Lyme Disease
* Attention Deficit Disorder
* Large overlap of GI symptoms/ IBS and anxiety

STEP 2

If considering medication, think about:

- Therapeutic Alliance
- Side effects
- Comorbid conditions
- Family history of response to antidepressants
- Cost

In terms of efficacy:

SSRI's= SNRI's= = bupropion= TCA's= MAOI's

STEP 3

* Start SSRI or SNRI .
* SSRI's are usually the first choice . Use a smaller dose than fo depression so anxiety is not precipitated
* It takes 12 weeks to see full effect of medication
* If the is NO improvement after a month, switch medication
* If there is partial improvement, increase the dose of the medication
* Anxiety often needs higher doses of medication than depression does.

STEP 4

If the patient has a poor response to 2 SSRI's:

Switch families of medication

Or

Augment with another medication

AUGMENTATION STRATEGIES

* Benzodiazepines work on GABA receptors. They are often useful while an SSRI is getting started. Clonazepam is usually first line since it has the longest half-life. Alprazolam/ Xanax is the worst benzo to use. It has the shortest half-life so it is easier to develop tolerance and it works on a neurotransmitter that none of the other benzo's do so nothing ever feels as good.

* Lorazepam is not metabolized by the liver so is the best benzo to use in patients who have liver damage.

AUGMENTATION STRATEGIES

* Add bupirone/ buspar. Try a minimum of 30 mg for thirty day to judge response. This is a serotonin 1A partial antagonist. (azapirone) Try a minimum of 30 mg for thirty days to judge response. It only works as an adjunct and only for GAD.
* alpha-delta Ca++ channel blockers (gabapentin and pregabalin)
* Beta blocker- work within 30 – 60 min.
* Antihistamines like hydroxyzine

SWITCHING STRATEGIES

* Try other SSRI's and SNRI's
* Try TCA's (tricyclic antidepressants)
* Although MAOI's are effective, you will likely refer for that

When to Refer to Psychiatry

* Comorbid conditions
* Psychotic symptoms
* Suicidal Ideation
* Treatment resistance

* The art of making a referral