THE PHARMACOLOGIC MANAGEMENT IN THE TREATMENT OF DEPRESSION

Steven Smith, NP
Family Practice
Community Medical Arts Center
Tallassee, Alabama

What is Depression?

Definition of Major Depressive Disorder (aka Unipolar Affective Disorder or Melancholia in the old movies) per DSM-IV:

MDD must include the symptoms of either:
• Depressed mood for most of the day, nearly every day
• Loss of interest or pleasure in all or almost all activities most of the day, nearly every day

*AND*

SIG E CAPS:
Sleep - too little or too much
Interest – anhedonia (loss of pleasure or joy)
Guilt
Energy
Concentration
Appetite – 5% weight gain or loss
Psychomotor – retardation or agitation
Suicidal ideation

Definition of MDD (continued):
5+ of the following daily over 2 week period representing a change from previous,
• Sadness, hopelessness, discouragement
• Decreased appetite with significant weight loss
• Sleep disturbance
• Psychomotor changes, agitated or slowing down
• Decreased energy or fatigue
• Poor concentration or decision making
• Sense of worthlessness or guilt
• Recurrent thoughts of death or suicidal ideation

DEPRESSION STATISTICS:
• Affect >78 million in US
• 15% lifetime risk of having MDD, female up to 26% lifetime risk
• 4th most common reason to visit HC provider
• Up to 30% of primary care patients have depressive symptoms
• Female > Male (2:1)
• Onset commonly in mid 20’s
• 5% of the elderly suffer depression over the course of a given year
• >65 yo’s account for 16% of successful suicides
SHAMELESS PLUG:

NEW DAY SENIOR CARE
AT TALLASSEE COMMUNITY HOSPITAL
• 10 Bed geriatric psych unit
• LOS 10-12 days
• Drs. Freeman and Harwood of Montgomery
• Excellent, my personal recommendation
• 334-283-3859

(I do not work for Tallassee Hospital nor was I paid for this shameless plug)

DEPRESSION RISK FACTORS:
• Female 2:1
• <40 and >65 years old
• Hx of many of the psychiatric disorders
• Prior episodes of mood/behavioral disorders
• Prevalence of chronic disease, chronic pain
• Recent MI or stroke
• Peptic ulcer disease
• Strong FH of Dep., bipolar, subs. abuse, suicide
• Domestic abuse or violence

DEPRESSION RISK FACTORS: (continued)
• Substance abuse and dependence, alcoholism
• Losses and stressful life events
• Single, divorced, unhappily married
• Decreased social support (loneliness)
• History of child sexual abuse
• Alternative sexual orientation (LGBT)
• Any of the Personality Disorders
• Anxiety Disorders and Panic Disorder

DEPRESSION DIFFERENTIAL DIAGNOSES:
• Mental disorders:
  Grief/bereavement – 6 mo limit, then MDD
  Bipolar Disorders - Any lifetime episode of mania is Bipolar Disorder not MDD)
  Dysthymia – Chronic mild depression or mild sadness, loss of interest, withdrawal, >2 years
  PMS, Postpartum depression
  Anxiety Disorders, SAD (seasonal)

DEPRESSION DIFFERENTIAL DIAGNOSES: (cont)
• Medical disorders – Alcoholism, Stimulant withdrawal, Parkinson, Epilepsy, Cerebrovascular disease, Dementias, Tumors, (anterior brain lesions more than posterior), Thyroid disorders, Diabetes, Adrenal disease (Cushing), Liver/renal failure, Malignancies, FMS/ Chronic Fatigue Syndrome, Lupus, RA, Pernicious anemia (B-12), Pellagra (niacin), Chronic pain, infertility, hypogonadism in men, menopause in women

DEPRESSION DIFFERENTIAL DIAGNOSES: (cont)
• Medications:
  CV – Antihypertensives (β blockers are worse than CCB’s), reserpine, central α-agonist,
  Anticholesterolemic agents, Antiarrhythmics
  Neuro – Antiparkinsons, anticonvulsants, analgesics, benzodiazepines
  Other – Glucocorticoids, Interferon (Hep C), many others
**FAMILY HISTORY:**
Depression, Bipolar, Suicide, Substance abuse, Criminality (50% in identical, 25% frat. twins)

**SOCIAL HISTORY:**
Occupation, Edu. Level, Relationships (marriage, sexual pref., children, household, church involvement, support systems), Faith, Cigs/Alcohol/Drugs, legal trouble

**REVIEW OF SYSTEMS:**
You’re getting clobbered with somatic complaints until you know that this is going to be a level 4 visit, so this is where I ask the most important question of the visit. What’s the most **important question** of the visit?

“Are you depressed?”
You will probably get one of 3 responses:
1. They may laugh. (They’re fine.)
2. They will look up, pause for a few seconds, and they will say, “I’m doing OK.” (They are in the fight but they’re OK)
3. Their head will go down. A tear may fall. They fall silent. They may nod. (They’re ready for help.)
PHYSICAL EXAM:
• Do a good exam but do a complete neurological exam
• Don’t forget to rule out your Differential Diagnoses
• Document what you observe in their appearance and demeanor like affect, mood, cleanliness, grooming, hair, make-up, eye contact, sense of relatedness, distractibility, agitation vs. retardation, impulse control, motor behaviors

Should we screen all patients for Depression?

NO
No. The United States Preventive Services Task Force (USPSTF) said don’t screen adults, it did not change outcomes.
Screen 12 to 18 year olds for MDD only if you are in a system to ensure accurate diagnosis, psychotherapy and follow-up. (knocks out AL)
Don’t screen 7 to 11 year olds, insufficient evidence of benefit.

DIAGNOSTIC TOOLS FOR DEPRESSION:
• Beck’s Depression Inventory for Prim. Care
• HAM-D
• MADRS
• CGI-I
• Patient Health Questionnaire-9 (PHQ-9)
• Geriatric Depression Scale (GDS)
• Child Depression Inventory (CDI)
• Zung and many others

DIAGNOSTIC TOOLS FOR DEPRESSION: (cont)
PHQ-9 is my favorite.
• Short but accurate, one page
• Self administered, good for Primary Care
• Spanish, Chinese, other languages
• Easy to score
• Use at baseline and then at follow-up visits to assess level of improvement for dose adjustment and/additional meds/therapies
• Google or www.depression-primarycare.org

DIAGNOSTIC TESTS:
• CBC
• Chem Profile for glucose, liver & kidney function/failure, (r/o hypercalcemia, hyponatremia)
• TSH
• Testosterone in men if other symptoms of hypogonadism

PATHOPHYSIOLOGY:
• Before we treat pharmacologically, we must understand the pathophysiology.
PATHOPHYSIOLOGY:
THE LIMBIC SYSTEM OF THE CENTRAL NERVOUS SYSTEM INCLUDES:
• Hypothalamus – ANS/homeostasis, sex, pain, anger
• Hippocampus - memory
• Amygdala - aggression
• Cingulate gyrus – attention to emotional event
• Basal ganglia - repetition, reward, focusing
• Prefrontal cortex – planning, taking action, pleasure

PATHOPHYSIOLOGY:
THE LIMBIC SYSTEM IS THE CONTROLLER OF OUR EMOTIONAL LIFE
• Motivation, Attention, Emotion, Memory
• 4 “F’s”: Fear, Fight, Food, Fornicate
• Biologic rhythms, Love, Hate
• Gender role, Territoriality, Bonding
• Loyalty to Alabama or Auburn football
• Your AFFECT, your emotional and behavioral state

PATHOPHYSIOLOGY:
THE LIMBIC SYSTEM IS FULL OF NEURONS AND SYNAPSES.
THE SYNAPSES CONTAIN NEUROTRANSMITTERS.

PATHOPHYSIOLOGY:
NEUROTRANSMITTERS
• Acetylcholine (Alzheimer’s)
• **MONOAMINES** (MDD, Anxiety d/o, Schiz.)
• Amino acids (seizures, endorphins)
• Neuropeptides (pain)
• >30+ others

PATHOPHYSIOLOGY:
MONOAMINES
• Serotonin (SHT)
• Norepinephrine (NE)
• Dopamine (DA)
• Epinephrine
• Histamine
• Melatonin

THE MONOAmine HYPOTHESIS OF DEPRESSION:
Depression is caused by a functional insufficiency of one or more monoamine neurotransmitters (serotonin, norepinephrine, dopamine) in the brain based on two observations:
1. Depression can be induced with drugs that deplete monoamines in the brain. (reserpine)
2. Depression is treated with drugs that intensify monoamine-mediated neurotransmission (SSRI’s)
**NEUROTRANSMITTERS:**

**SEROTONIN** or **5HT** (5-hydroxytryptamine)

Serotonergic Receptors:
- 5HT1a – Depression, buspirone, Viibryd (new)
- 5HT1b-f
- 5HT2a-c – Depression, most SSRI’s Tx
- 5HT3 – SSRI’s may have some agonist affect
- 5HT4 – tegaserod (Zelnorm) for IBS-D
- 5HT5-7 and others

This is why SSRI’s are **SELECTIVE** Serotonin Reuptake Inhibitors

**NEUROTRANSMITTERS:**

Serotonin involved in:
- Mood regulation, anxiety, pain perception, appetite, sleep, sexual behavior, obsessive-compulsive behavior

**NEUROTRANSMITTERS:**

**NOREPINEPHRINE**

Receptors for NE:
- Alpha 1 (clonidine, prazosin) a-blocker
- Alpha 2

Norepinephrine is involved in mood regulation, arousal/alertness vs. lethargy, memory

**NEUROTRANSMITTERS:**

**DOPAMINE**

Receptors for Dopamine:
- D1-5
- D2 receptor – schizophrenia meds

Dopamine acts as the brain’s natural reward system but sets up for addiction. (That’s why cigarettes are sooooooooo good!). Pleasure, motivation, attention, speed of cognition.

**PATHOPHYSIOLOGY OF DEPRESSION:**

With Depression there are changes in the **receptor-neurotransmitter relationship** in the limbic system where serotonin and norepinephrine are the primary neurotransmitters involved (with dopamine less so).

**PATHOPHYSIOLOGY OF DEPRESSION:** (cont)

As the action potential is passed on, the neurotransmitter is either:
- Reabsorbed into the neuron where it is either destroyed by an enzyme or actively removed by a reuptake pump and stored until needed or,
- Destroyed by monoamine oxidase (MAO) in the mitochondria of the neuron cell.
PATHOPHYSIOLOGY OF DEPRESSION: (cont)

Depression symptoms are related to decreased levels of SEROTONIN (irritability, hostility, and suicidal ideation) and/or NOREPINEPHRINE (dullness and lethargy) in the Limbic System neurons and synapses.

ETIOLOGY OF DEPRESSION: (continued)

• Impaired synthesis of neurotransmitters
• Increased metabolism of neurotransmitters
• Environmental factors and learned behaviors may affect neurotransmitters and/or have an independent influence on depression

THE CHICKEN OR THE EGG QUESTION:

How does Depression start? Which came first?
• Use up or don’t make enough of your monoamine neurotransmitters leading to depression
OR
• Do environmental factors and learned behaviors affect neurotransmitter depletion leading to depression.

TREATMENT OF DEPRESSION:

Goals of Depression Treatment
• Remission – Absence of depressive symptoms with a return to full recovery
• Recovery – No longer meets depression criteria for eight weeks
• Response – Response to therapy is not the goal. Remission is the goal

TREATMENT OF DEPRESSION:

What are the first couple of things that you always want to do before initiating treatment for Depression?
• Rule out serious Suicidal Ideation. (refer)
TREATMENT OF DEPRESSION:
What are the first couple of things that you always want to do before initiating treatment for Depression?
• Rule out serious Suicidal Ideation. (refer)
• Rule out Bipolar Disorder.

Why?

TREATMENT OF DEPRESSION:
Rule out Bipolar Disorder.
Why?
If you start an antidepressant medication and the patient has had even just one episode of mania in the past (knowingly or unknowingly) you may throw them into a manic episode. It is up to the provider to assess for mania.

MANIC EPISODE SYMPTOMS:
• Greatly increased energy
• Severe trouble sleeping
• Racing thoughts
• Reckless behavior
• Unusually grand ideas
• Excessive happiness or irritability
• Talking more or faster than usual
Just one lifetime episode excludes monotherapy with an SSRI/SNRI without a mood stabilizer.

TREATMENTS OF DEPRESSION:
• “Better living through PHARMACEUTICALS”
• CBT – Cognitive Behavioral Therapy
• ECT – ElectroConvulsive Therapy
• rTMS – Focused, pulsed, magnetic fields (FDA approved but not proven)
• Deep Brain Stimulation (surgical, extreme)
• If uninsured: $4 worth of cheap beer/wine
• Jesus: most effective, longest lasting (eternity), cheapest (He paid the price)

The MOOD Continuum Theory:
I see MDD as on a continuum with one end being the people who are depressed with anxiety, OCD symptoms, mind racing, hand wringing, “my nerves are bad”.
On the other end of the continuum are the people who are depressed who “turn their face to the wall”, “just want to go to bed”, “just want to eat and sleep”, sleep excessively.

The MOOD Continuum Theory (cont)
Depression with Anxiety (the majority)

VS

Depression with Lethargy (the minority)
The MOOD Continuum Theory (cont)

If Depression with Lethargy:
Go straight to bupropion (Wellbutrin)

DOSAGE: Goal is to get 150 to 300 mg/day. Since it is improves alertness and motivation it is best given in the morning (XL).

bupropion (Wellbutrin)

The MOOD Continuum Theory (cont)

bupropion (Wellbutrin)

THE BAD  ***SEIZURE PRECAUTION***
Overall: Will lower seizure threshold. Will induce seizure if previous seizures, may induce seizure even if no previous seizures. Never use with threshold lowers like Ultram, TCA’s
Noradrenergic SFX: Tremor, Tachycardia
Dopaminergic SFX: Psychomotor over activation, aggravation of psychosis.

The other end of the continuum of MDD, the Anxiety-dominant Depression, are best serve by treating according to the STAR*D Study recommendations.

“Anxiety in the heart of a man causes depression, but a good word makes it glad.” Proverbs 12:25

PHARMACOLOGY:

THE STAR*D STUDY has become the Gold Standard of Primary Care Provider treatment of Major Depression Disorder
(STAR*D = Sequenced Treatment Alternatives to Relieve Depression)
STAR*D reported that nearly 10% of primary care office visits are depression related.

The STAR*D STUDY:
• Only 47% of patients respond to the initial one medication treatment for MDD and only 33% achieved remission.
• This large study set up 4 Levels of treatment and measured the remission rates for each level
• These 4 Levels have become a good common-sense approach to treating MDD
The STAR*D STUDY:
LEVEL 1: Citalopram (Celexa) 20 mg (LOL 10mg)

Which is the best SSRI?

Meta-analysis of RCT’s found response vs. drop out rates marginally best with escitalopram (Lexapro) and sertraline (Zoloft). Overall, for benefits, acceptability, and cost, sertraline (Zoloft) had a slight edge. For the most part, the SSRI’s are all nearly equally effective.

What are the Selective Serotonin Reuptake Inhibitors (SSRI’s)?
- Fluoxetine (Prozac): generic available
- Sertraline (Zoloft): generic available
- Paroxetine (Paxil, Paxil CR): generic available
- Citalopram (Celexa): generic available
- Escitalopram (Lexapro):
- Vilazodone (Viibryd): Newest on the market

How do SSRI’s work?
The SSRI’s selectively slow the neuronal reuptake pump of SHT2 in the pre-synaptic terminal thereby increasing the amount of the serotonin in the synapse so as to increase neurotransmission.

THE GOOD:
SSRI’s effect and treat so many co-morbid conditions such as Anxiety Disorder, Panic Disorder, Binge-purge eating disorders, Obsessive Compulsive Disorder, Bi-Polar Disorder (with a mood stabilizer)

THE BAD:
Side FX’s are nausea, headache, insomnia, weak/dizzy/fatigue, diarrhea, excessive sweating, hyponatremia (esp. in LOL’s), cycle into Mania and many more

THE BIGGIE: Affecting compliance are the Sexual Side Effects like decreased libido, delayed ejaculation/orgasm, ED (Viagra and others help)

THE BAD BIGGIE: Abnormal bleeding

THE REALLY BAD BIGGIE: SEROTONIN SYNDROME
### SSRI’s SIDE EFFECTS

#### THE BAD BIGGIE: Abnormal Bleeding

The Serotonin released by platelets plays an important role in hemostasis. Concomitant use of ASA, NSAID’s, warfarin, and other anticoagulants may increase bleeding. Caution with upper GI bleeding or ulcers especially.

### SSRI’s SIDE EFFECTS

#### REALLY BAD BIGGIE: SEROTONIN SYNDROME

(or Neuroleptic Malignant Syndrome):
- Agitated, hallucinations, mental status change
- Coordination problems or muscle twitching
- Tachycardic, high or low fever
- Sweating or vomiting
- Nausea, vomiting or diarrhea
- Muscle stiffness, hyperreflexive, rigidity

---

#### SEROTONIN SYNDROME (cont)

- Potentially life threatening, need ER/ICU
- May occur with SSRI alone at higher doses but mostly occurs as a drug interaction with other serotonergic medications
- Cyproheptadine (Periactin) - The antidote, a 5HT antagonist

What are other serotonin affecting medications?

---

### SSRI Drug-Drug Interactions (DDI’s):

- Other psychotrophic drugs and antipsychotics
  - Atypical antipsychotics – Don’t think just dopamine but they also affect serotonin not as a re-uptake inhibitor but at the receptor as a 5HT2a antagonist and a 5HT1a agonist. They are often used together for MDD, Bipolar, Schizophrenia. You just have to be careful to watch for Serotonin Syndrome
  - The old stuff: Old antipsychotics, TCA’s, tramadol

---

### SSRI Drug-Drug Interactions (DDI’s):

- Other psychotrophic drugs and antipsychotics
  - MonoAmine Oxidase Inhibitors (MAO-I’s) – The neuron mitochondrial production of MAO oxidizes or destroys Serotonin. An MAO-I inhibits the destruction of Serotonin there by increasing Serotonin in the synapse. The SSRI inhibits the reuptake of Serotonin so NEVER, NEVER, NEVER, EVER, EVER, use an MAO-I and a SSRI TOGETHER. Needs a 14 day washout changing one to another or, again, may get Serotonin Syndrome. Many food interactions.

- Medications that are Serotonin Agonist that may lead to Serotonin Syndrome (agonist is a substance that acts like another substance to stimulate an action)
  - The Triptans for Migraine are agonist for the 5HT1d serotonin in the vascular
  - Buspironne (Buspar) is a 5HT1a receptor agonist
  - Tramadol (Ultram) inhibits SHT2c receptor function and it is a Norepinephrine Reuptake Inhibitor as well and is a opioid mu receptor agonist
SSRI Drug-Drug Interactions (DDI’s):

- Other Medications that may lead to Serotonin Syndrome
  - Nearly all of the other antidepressants – SSRI’s including St. John’s Wort, SNRI’s, Tricyclics, Tetracyclics, MAO-I’s, and Serotonin Agonists
  - L-tryptophan and SHTP (Shydroxytryptophan) – Tryptophan is an essential amino acid from the food we eat. Serotonin/SHT/S-hydroxytryptamine is biologically derived from tryptophan. L-tryptophan (OTC) is taken for sleep (or eat turkey)

SSRI’s REMEMBER

THE BAD:
THE BIGGIE: Sexual Side Effects affecting compliance
THE BAD BIGGIE: Abnormal Bleeding
THE REALLY BAD BIGGIE: Serotonin Syndrome

What is the BIGGEST, BADDEST OF THE BIG BAD BIGGIES you must seriously consider when starting an SSRI or any antidepressant for that matter?

What is the BIGGEST, BADDEST OF THE BIG BAD BIGGIES you must seriously consider when starting an SSRI or any antidepressant for that matter?

SUICIDE

Increased suicide rates in children up to age 24 following the initiation of antidepressants.

Drug-Placebo difference in number of cases of SUICIDALITY per 1000 patients initially treated with an antidepressant:

<table>
<thead>
<tr>
<th>Age</th>
<th>Increases compared to placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>14 additional cases</td>
</tr>
<tr>
<td>18-24</td>
<td>5 additional cases</td>
</tr>
<tr>
<td></td>
<td>Decreases compared to placebo</td>
</tr>
<tr>
<td>25-64</td>
<td>1 fewer case</td>
</tr>
<tr>
<td>65+</td>
<td>6 fewer cases</td>
</tr>
</tbody>
</table>

THE FDA BLACK BOX WARNING:

“Antidepressants increase the risk compared to placebo of suicidal thinking and behavioral (suicidality) in children, adolescents, and young adults in short-term studies of MDD and other psychiatric disorders. Anyone considering the use of any antidepressant in a child, adolescent or young adult must balance this risk with the clinical need.”

Discuss with family to be vigilant and be very cautious. I refer the children.
My spiel when I initiate an antidepressant:
- “This medicine will help but . . .”
- Joke: What do you hear when you play a country music song backward?
- This opens the door for Cognitive Behavioral Therapy. “A PILL will not make your husband love you, your children behave, your truck get fixed, you boss sing your praises”

My spiel when I initiate an antidepressant:
- This is not like Xanax. You cannot take this medicine just when you feel bad. The pill you take today is the one helping you in 2 weeks and you don’t know how you will be feeling in 2 weeks. (sort of a half truth for compliance’s sake)
- “God loves you, Jesus died for you, you are loved!” then, tears will open them to CBT (Cognitive Behavioral Therapy)

What is COGNITIVE BEHAVIORAL THERAPY?
**ABC**
A: **Activating Events of life, “Stuff happens”**

What is COGNITIVE BEHAVIORAL THERAPY?
**ABC**
A: **Activating Events of life, “Stuff happens”**

B: **Behavioral Response, how you react to the Activating Events**

What is COGNITIVE BEHAVIORAL THERAPY?
**ABC**
A: **Activating Events of life, “Stuff happens”**

B: **Behavioral Response, how you react to the Activating Events**

C: **Consequences of your Response**

The STAR*D STUDY:
- **LEVEL 1:** Any SSRI
  - At 2 to 4 weeks go up on the dose if needed.
  - Reevaluate at 3 months. If in remission, then stay at that dose and reevaluate/retest at one year.
  - At this point I give them a warning:
The STAR*D STUDY:
• LEVEL 1: Any SSRI
  – At 2 to 4 weeks go up on the dose if needed.
  – Reevaluate at 3 months. If in remission, then stay at that dose and reevaluate/retest at one year.
  – At this point I give them a warning:
  “Sometime before your one year visit it will be time to refill your med and you will say to yourself, ‘I can’t even remember why I taking this, I feel fine.’ and you’ll be tempted to stop. DON’T STOP!” Why?

Don’t stop your depression medicine without asking your health care provider because:
• You may suffer withdrawals:
  – Moody, irritable, agitated, dizzy, anxious, “electric shock through the head”, emotional, seizures
  – If you start and stop antidepressants often enough they will eventually not work anymore

At ONE YEAR on the SSRI, assess for:
• “SSRI POOP-OUT” What is it?
  – “I’m Blah, I’m just there”, unmotivated, not happy/not sad, some will say the med is not working/some will say its working too well, “I don’t do anything but then again I don’t care if I do anything”
  – Unsupported by “the scientific community” other than to say it’s “tachyphylaxis”. I disagree.

Don’t stop your depression medicine without asking your health care provider because:
• You may suffer withdrawals:
  – Moody, irritable, agitated, dizzy, anxious, “electric shock through the head”, emotional, seizures
  – If you start and stop antidepressants often enough they will eventually not work anymore
  – If you want off of them you need to come in so we can discuss it and TAPER you off to avoid withdrawals

• “SSRI POOP-OUT” Treatment:
  – If patient says, “I want to laugh again, I want to cry again, I want to care again, I want to have emotions” then it may be time to come off the SSRI and resume life with all it’s emotional ups and downs. SSRI’s can leave some emotionally flat as a flitter.
  – If patient says, “I feel blah, this medicine ain’t working no more.” Correct their double negative and either:
    • Add Bupropion (Wellbutrin) to pick them up, or
    • Stop the SSRI and go to an SNRI for the NE effect
  Which leads us to Level 2
The STAR*D STUDY:
• LEVEL 1: Any SSRI
  – At 3 months, Level 1 remission rate is about 33% tested
  – If still depressed......
• Level 2: Augment or Switch

The STAR*D STUDY:
• LEVEL 2: Augment or Switch
  – AUGMENT: Keep the SSRI and add either
    • Bupropion (Wellbutrin), or
    • Buspirone (Buspar). Wellbutrin did a little better, or
    • CBT - in the study CBT did as well as augment med
  – SWITCH: Stop the SSRI and add either
    • A different SSRI, or
    • Bupropion (Wellbutrin), or
    • SNRI – Serotonin Norepinephrine Reuptake Inhibitor, or
    • CBT – Did about as well as a medication (not as fast)

The STAR*D STUDY:
• LEVEL 2: Augment or Switch
  – Level 1 got a 33% remission rate.
  – Level 2 got their overall cumulative rate of remission up to 57%.

We looked at Wellbutrin already.
Let’s look at Buspar.

Buspirone (Buspar)
• Since most SSRI’s are 5HT2 it makes a good add-on since it is a 5HT1a
• Vilazodone (Viibryd) is the newest SSRI and it has both a 5HT2 and a 5HT1a effect so don’t add Buspar. It’s a two for one special.

The STAR*D STUDY:
Buspirone (Buspar)
• Classified as an antianxiolytic
• 5HT1a receptor agonist and moderate D2 receptor agonist
• No effect on Benzo or GABA receptors
• Little sedation, not anticonvulsant, not muscle relaxer
• 5, 10, 15, 30mg, start 15mg/d, max 60mg
• Slower onset than benzos

SNRI’S: SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS
• Venlafaxine (Effexor XR) generic available
• Duloxetine (Cymbalta)
• Desvenlafaxine (Pristiq)
Also to consider SNRI properties:
• Milnacipran (Savella) For FMS, not MDD
• Tramadol (Ultram) for pain
• Sibutramine (Meridia) for weight loss
• TCA’s (many), TeCA’s (Remeron)
SNRI'S: SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS

The **GOOD**:  
• All of the good SSRI antidepressant and anti-anxiety properties, and  
• The Norepinephrine Reuptake Inhibitor properties of decreasing lethargy and increasing alertness, and  
• BONUS POINTS: Decreased neuropathic pain like FMS, DPN, PHN

SNRI'S:

THE BAD: Remember all the bad Side Effects and interactions of the SSRI's, you can have all of them with the SNRI's. Sorry.

SSRI SIDE EFFECTS

THE BAD: Side FX's are nausea, headache, insomnia, weak/dizzy/fatigue, diarrhea, excessive sweating, sexual side effects, hyponatremia (esp. in LOL's), cycle into Mania and many more  
THE BIGGIE: The Sexual Side Effects, (compliance)  
THE BAD BIGGIE: Abnormal bleeding (Platelets)  
THE REALLY BAD BIGGIE: SEROTONIN SYNDROME  
THE BIGGEST, BADDEST OF THE BIG BAD BIGGIE: SUICIDAL IDEATION worse in the youngguns

SNRI'S:

The **BAD**:  
• All the SSRI Side Effects plus tremor  

The **BIGGIES**: Norepinephrine Side Effects that will cause cessation of the SNRI's  
  – Nausea  
  – Excessive Sweating  
  – Hypertension/tachycardia – Think cardiology, what does NE (Levophed) do? Pressor (constrictor) and inotrope (increase contractions), These 3 you’ll know in a week, need to d/c SNRI

SNRI'S:

**WARN THE PATIENT**

Sudden cessation of an SNRI is AWFUL!  
Need to TAPER, TAPER, TAPER DOWN.

The STAR*D STUDY:

- **LEVEL 1**: SSRI  33% Remission  
- **Level 2**: 57% Remission  
  Augment: Wellbutrin or Buspar or CBT **OR**  
  Switch: Another SSRI or Wellbutrin or SNRI or CBT  
  **THIS IS WHERE I DRAW THE LINE MOST OF THE TIME**  
- **Level 3**: 63% Remission  
  Augment: Lithium or T3 (Cytomel), **not T4 synthroid**  
  Switch: Mirtazapine (Remeron) or Nortriptyline
- **Level 4**: 67% Remission  
  Switch: MAO-I (Parnate) or mirtazapine plus SNRI
For the Primary Care Mid-level Provider this is probably a good place to stop and refer to Mental Health if still depressed. Why?

- The Law of Diminishing Returns – STAR*D says that you are only going to get 10% going from Level 2 to Level 4 (57% to 67% remission)
- I only use Remeron for patients who need to gain weight and it works well. Sleep & get fat.
- I’m not going to start a functioning adult on an antidepressant dose of a TCA b/c of sedation

For the Primary Care Mid-level Provider this is probably a good place to stop and refer to Mental Health. Why?

- I’m not starting anybody on Lithium or T3, it’s too much trouble.
- I’m not putting anybody on an MAO-I and I don’t recommend that you do either.

There is a newer option since STAR*D (2007) that I often go to for the next step past Level 2

Some of the “Atypical Antipsychotic” now have FDA approval for “Treatment Resistant MDD”

The “Atypical Antipsychotics” are usually used as an add on.

The main Atypical Antipsychotics:

- Aripiprazole (Abilify)
- Olanzapine (Zyprexa)(w/Prozac is Symbyax)
- Quetiapine (Seroquel) generic available
- Ziprasidone (Geodon)
- Others

The Atypical Antipsychotics:

- Shotgun affinity for many neuro receptors and neurotransmitter and even affects some reuptake
- Affects the Monoamines (5HT, NE,DA) and many others like ACh, H1, M1 that cause the anticholinergic and sedating effects.

The Atypical Antipsychotics:

- Increased mortality in the elderly (sundown)
- The now standard FDA suicide warnings
- Serotonin Syndrome
- Diabetes, Hypercholesterol, Weight gain
- Orthostatic Hypotension/Hypertension in kids
- Tardive Dyskinesia (much < old antipsychotics)
- CBC changes, Hyperprolactinemia
Summary of Pharmacological Treatment of Depression with:
Somnolence/lethargy: Wellbutrin
Anxiety: SSRI, SNRI, +Buspar
Insomnia: SSRI, +TCA, +Tetracyclic, or +Seroquel
Bipolar: SSRI, SNRI, and anticonvulsant, lithium, or atypical antipsychotic as mood stabilizer
Chronic Neuropathic Pain: SNRI, +anticonvulsant, add tramadol or TCA (but not both, seizure risk)

Precautions of Pharmacological Treatment of Depression:
• Serotonin Syndrome – You can use many of these drugs together just don’t stack your Serotonin reuptake up to high
  – SSRI/SNRI + Atypical Antipsychotic + TCA/TaCA + tramadol
  – NEVER, NEVER, EVER, EVER prescribe MAO-I’s
  – NEVER, NEVER, EVER, EVER add to an MAO-I’s

WHEN TO REFER:
• Treatment Failure at any point (they failed not you, don’t let them make you feel bad)
• Suicidal ideation
• Children up to age 24, Pregnant women
• Co-morbid psychiatric disorders that you are not comfortable with
• Personality Disorders or Self-Mutilation
• Patient becomes abusive, obnoxious, non-compliant, needy/clingy, weird, perverted
• You just get sick of them, DON’T FEEL BAD!

BUT,
If you help a patient crawl out of the PIT then you’ve got a friend and loyal patient for life.
THE END
SEE YOU IN 2 YEARS
CEU Certificates are on tables in lobby
QUESTIONS? Come up front

2 Corinthians 7:10   ABC’s of CBT
“Godly sorrow bring repentance that leads to salvation and leaves no regrets, but worldly sorrow leads to death.”
A: Activator – Sin causes Godly sorrow/depression.
B: Behavioral Response - Repentance is the change in your behavior.
C: Consequences – The restoration of the JOY of your salvation