

# DEPRESSION

## ANY QUESTION YOU EVER WANTED TO ASK ON DEPRESSION

by

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- Introduction – Philippians 4:13
  - Are you depressed?
  - Do you know someone depressed?
  - 1 in 20 people will experience MDD in the last month.
  - 1 in 10 people will experience MDD in the last year.
  - 1 in 5 people will experience MDD in their lifetime.
  - This is not to mention the thousands with dysthymia
  - 3 years after a MDD 50% relapse.
  - 15 years after a MDD 90% relapse.
  - Almost 1 million suicides worldwide per year.
  - MDD can damage the brain:
    - ↓ volume of hippocampus
    - ↓ volume of prefrontal cortex
    - ↓ volume of amygdala
    - ↑ cortisol
    - ↑ CRH
  - MDD (major depressive disorder) is often comorbid with other emotional issues:
    - 70% anxiety disorder
    - 25% substance use disorder
    - 30% impulse control disorder (anger)
  - Other facts
    - Women are more likely (2:1) to have MDD
    - Women are more likely (2:1) to attempt suicide
    - Men are more likely to succeed in suicide.
    - MDD is a leading cause of death in teenagers.
    - MDD is a leading cause of death in the elderly.
    - MDD increases morbidity and mortality – 80 intervene
- Scriptural Helps
  - Philippians 4:13
  - Proverbs 21:31
  - Isaiah 43:2-3
- Symptoms
  - Negative emotions (anhedonia, ↑sadness, ↑guilt, ↑anger, ↑worry, ↓concentration, ↓movement, ↓sleep, ↑or↓appetite, ↓energy (fatigue), ↓self-worth, ↑medical worries

- ↓cognition, ↓memory, ↓learning
  - Suicidal Ideations
- Etiology and Treatments
  - Chemical Factors
    - PET scans
  - Stress Factors
    - Relationship conflict
    - Job stress or loss
    - Financial stress
    - Personal loss
  - Choices – Make new ones – Forgive yourself for bad choices of the past - (I John 1:9)
    - Decrease stressors – it’s not worth dying over
    - Stay out of mental rumination – run from it
    - Seek help – medical, counselor, church, friend, residential, hospital
    - Learn to enjoy scripture Jeremiah 15:16
  - Schedule lighter times – for example, an excellent Christian movie by Mike Norris called “Maggie’s Passage” will be out soon. It is about a beautiful young lady that goes through a difficult journey and then finds triumph in Christ. Clips of the movie can be seen at [www.2ndfiddleentertainment.com](http://www.2ndfiddleentertainment.com) and click on “Maggie’s Passage.”
  - Plan a Vacation
- Medical treatments
  - Depression refers to a low or sad mood. It is a symptom, not a diagnosis. Many drugs have been tried either on-label or off-label for depression. These include SSRIs, SNRIs, atypical antidepressants, MAOIs, TCAs, tetracyclic antidepressants, alprazolam (Xanax), atypical neuroleptics (Seroquel, Geodon, Abilify), lithium, cytomel, Lamictal, Zonegran, stimulants, Provigil, SAMe (natural product), St. John’s wort (natural product), omega-3 fatty acids (natural product), Deplin (L-methylfolate), caffeine, and B<sub>6</sub> (pyridoxine). MDD (major depressive disorder) correlates with decreased hippocampal volume, decreased neurogenesis, and decreased BDNF (brain-derived neurotrophic factor).
  - Antidepressants—nuances of interest
  - The 5-HT<sub>1A</sub> effects of the SSRIs probably account for the antidepressant actions
  - The TCAs are absorbed in the small intestines, are lipophilic, are highly protein-bound, and are toxic at two to six times the therapeutic level
  - The SSRIs are not affected by food administration except for sertraline which is increased

- Fluoxetine (Prozac) has an active metabolite with a half-life of up to 15 days
- Venlafaxine (Effexor) has a very short half-life of 4 hours
- Bupropion (Wellbutrin) has been discouraged in eating disorders because of the increased risk of seizures
- Fluoxetine (Prozac) has been used in premenstrual dysphoria because serotonergic function is decreased during the luteal phase; intermittent dosing is often effective; an abatement of symptoms is seen in 60% of cases
- The TCA protriptylene (Vivactile) has been used off-label for sleep apnea
- The SSRIs have been used off-label for migraines, neuropathic pain, and various other kinds of pain
- African-Americans have an increased risk of being slow metabolizers of antidepressants; Asians have an increased risk of being slow metabolizers of nortriptyline (Pamalar)
- Renal impairment results in lower dose requirements of antidepressants; fluoxetine (Prozac) and sertraline (Zoloft) are exceptions to this rule
- Liver impairment also results in lower dose requirements of antidepressants
- Predictors of poor response to antidepressants are: agitation, anxiety, hyperphagia, hypersomnia, delusions, recurrences
- Imipramine (Tofranil) and desipramine (Norpramine) should have blood levels at 150 to 300 ng/ml; nortriptyline should be at 50 to 150 ng/ml
- Sertraline (Zoloft) has the most GI symptoms of the SSRIs
- Antidepressants are used for major depressive disorder, dysthymic disorder, panic disorder, generalized anxiety disorder, OCD, PTSD, bulimia, anorexia nervosa (except bupropion), body dysmorphic disorder, PMDD, binge eating [sertraline (Zoloft)], anorexia [fluoxetine (Prozac) is FDA approved], and dementia behavioral issues [trazadone (Desyrel)]
- Response rates for antidepressants are 60 to 70%
- Augmentation strategies for resistant depressions treated with antidepressants are lithium carbonate, thyroid hormone, an atypical neuroleptic, stimulants, buspirone, and combinations of antidepressants
- 50% of patients unresponsive to one antidepressant will respond to one of another class
- 14 days are often observed when switching from TCAs to MAOIs (Ensam might be less)
- The best predictors of relapse in depression are: previous episodes, dysthymic disorder, older age
- When discontinuation of TCAs is desired, some doctors decrease at 25 to 50 mg/day for 2 to 3 days; too rapid a decrease of TCAs

can result in cholinergic rebound with GI symptoms, autonomic hyperactivity (anxiety, anger, headache, diaphoresis) and insomnia; picture a man who stopped his TCA and has GI, autonomic, and insomnia cholinergic rebound; SSRIs [paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), and even sertraline (Zoloft)] may require a 1 week taper; SSRI withdrawal symptoms include GI, insomnia, and fatigue; SNRI withdrawal symptoms are similar to those of SSRI

- The most frequent side effect of TCAs is orthostatic hypotension
- Possible side effects of serotonin blockade
  - anxiety
  - GI = nausea, diarrhea
  - decreased sex drive
  - insomnia
- Possible side effects of norepinephrine blockade
  - anxiety
  - increased heart rate
  - decreased sex drive
  - increased sweating (diaphoresis)
- Symptoms of serotonin syndrome
  - anxiety
  - tremor
  - GI
  - CNS—confusion
  - fatigue
  - headaches
  - sweating
  - increased heart rate
  - rare = rhabdomyolysis, respiratory compromise, acidosis, intravascular coagulation, cardiac collapse, and death
  - picture a tired, anxious (tremor, diarrhea, headaches, sweating, rapid heart rate) man that just digested a TCA + SSRI
- Other nuances of interest with antidepressants
  - Possible anticholinergic side effects from TCAs, traditional neuroleptics, and anticholinergics [atropine, scopolamine, ipratropium (Atrovent), benztropine (Cogentin), trihexyphenidyl (Artane)] include:
    - constipation
    - dry mouth
    - eye—blurred vision, dilated pupils (mydriasis)
    - CV—rapid heart beat
    - GU—urinary retention
    - memory impairment
    - skin—reduced sweating, flushing

- respiratory—bronchial dilation and decreased secretion
- CNS—drowsiness, hallucinations, coma
- anticholinergic delirium:
  - “Mad as a hatter”—confusion
  - “Hot as a hare”—hyperpyrexia
  - “Blind as a bat”—decreased vision
  - “Red as a beet”—peripheral vasodilation
  - “Dry as a bone”—dry mucous membranes
- Trazadone (Desyrel) can cause orthostatic hypotension
- Venlafaxine (Effexor) can increase blood pressure (perhaps 10-13% at a dose above 225 mg/day; the increase can be permanent)
- Fluoxetine (Prozac) can cause seizures especially at 100 mg per day
- Bupropion (Wellbutrin) can cause seizures especially at greater than 450 mg/day
- SSRIs can cause myoclonic twitches in 5-10%; a beta blocker is a treatment for this as is a benzodiazepine
- SSRIs can cause anxiety in some; this can be treated with a low dose of benzodiazepine (aloprasolam at ½ of a .25 mg b.i.d. has been used)
- SSRIs can cause weight gain in 30%
- Venlafaxine (Effexor) and duloxetine (Cymbalta) have the most frequent side effects of nausea
- SSRIs—sexual dysfunction in 30%; anorgasmia can be treated with:
  - amantadine (Symmetrel), a dopamine agonist
  - bethanechol (Urecholine), a AchM agonist
  - cyproheptadine (Periactin), an antihistamine with 5HT2 antagonism
  - nitric oxide drugs [vardenafil (Levitra), tadalafil (Cialis), sildenafil (Viagra)]
  - Decreased sex drive from SSRIs can be treated with bupropion (Wellbutrin)
  - Trazadone (Desyrel) has been associated with priapism
  - TCAs can aggravate a CV conduction problem and often should not be used in greater than a first-degree block or after an MI; TCAs can slow cardiac conduction
  - More than a week supply of TCA is potentially lethal in OD
  - 4% of children and adolescents on antidepressants have suicidal thinking compared to 2% on placebo
  - TCAs result in rashes in 5%
  - SSRIs can increase prolactin
  - MAOIs with sympathomimetics or high tyramine consumption can cause a hypertensive crisis with increased

blood pressure, headache, stiff neck, and vomiting; the treatment is phentolamine 5mg IV; medications to avoid with the MAOI patch, Ensam, include stimulants, other antidepressants, cyclobenzaprine (Flexeril), carbamazepine (Tegretol), oxycabazepine (Trileptal), BuSpar (buspirone), and meperidine (Demerol); other drugs to avoid with MAOIs are cold preparations, cocaine, antiparkinsonian medications, atropine, propoxyphene (Darvon), diphenhydramine (Benadry)

- TCAs absorption can be inhibited by cholestyramine (LoCholest)
- The TCA desipramine (Norpramine), plus methylphenidate (Ritalin) can be dangerous with ventricular tachycardia, tremor, nausea, and dry mouth
- Medications that lower TCAs are:
  - Phenobarbital
  - carbamazepine (Tegretol)
  - nicotine
- TCAs and the blood pressure medication guanfacine (Tenex) should often not be combined since guanfacine relies on neuronal receptors for its antihypertensive effect; clonidine, an alpha 2 agonist is also often contraindicated
- Trazadone (Desyrel) increases levels of digoxin, phenyton (Dilantin), and warfarin (Coumadin). Think “2 d’s and a c”.
- Bupropion (Wellbutrin) causes few drug-drug interactions overall; it can potentially be dangerous with other dopaminergic drugs
- Venlafaxine (Effexor) is not highly protein-bound, does not substantially inhibit the P450-CYP enzymes, and therefore tends to cause few drug-drug interactions
- Mirtazapine (Remeron) does not substantially inhibit the P450-CYP enzyme system but is highly protein-bound
- Pristiq (odesmethylvenlafaxine) is being studied for possible MDD, vasomotor symptoms of menopause, and neuropathic pain
- Agomelatine, a melatonergic agonist at the MT1 and MT2 receptors, is the first new antidepressant in years with a new mechanism of action. It is also an antagonist at 5HT2C receptor. It is weight neutral, does not decrease sex drive, does not cause insomnia, and decreases anxiety.

▪ Conclusion