ETHICS AROUND PRESCRIBING: MENTAL HEALTH DRUGS AND BIOLOGICS (AKA DISEASES OF THE DRUGS: NERVOUS SYSTEM, PART 2 & IMMUNE SYSTEM, PART 3)

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MENTAL HEALTH MEDS

BY SALES
- Abilify, aripiprazole #1
- Cymbalta, duloxetine
- Lyrica, pregabalin
- Seroquel XR, quetiapine
- Invega Sustenna, paliperidone
- Pristiq, desvenlafaxine
- Latuda, lurasidone HCl

BY VOLUME
- Cymbalta, duloxetine
- Lyrica, pregabalin
- Abilify, aripiprazole #15
- Pristiq, desvenlafaxine
- Seroquel XR, quetiapine
- Viibryd, vilazodone

TOP 10 DRUG CLASSES IN GLOBAL SALES, 2017

1. Oncologics, $81.1 billion
2. Pain, $76.1 billion
3. Diabetes, $72.2 billion
4. Auto-immune, $47.5 billion
5. Cardiovascular, $40.6 billion
6. Respiratory, $38.5 billion
7. Antibiotics/vaccines, $38.3 billion
8. Mental health, $36.1 billion
9. HIV antivirals, $26.7 billion
10. Other antivirals, $23.8 billion

HOW THINGS GO WRONG...

- Direct effects of the drug (mechanism of action)
- Indirect effects of drug (downstream effect, most notably in this presentation glucose disruption)
- Nutrient depletions by the drug (that can also be direct and indirect)
- Iatrogenic effects of the drug (compensatory mechanisms of the body—pharmacokinetics—and/or all of the above listed “problems”

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COMMON DRUGS THAT CAN CAUSE PERCEIVED MENTAL HEALTH ISSUES

- Anti-hypertensive agents
  - ACE inhibitors (mood changes, decreased libido)
  - Beta blockers (nightmares, hallucinations)
  - Calcium channel blockers (depression, distorted sense of reality/identity, anxiety, restlessness)
- Cholesterol reducers
  - Statins (nightmares, fatigue, insomnia)
  - Fibrates (depression, insomnia, anxiety)
  - Ezetimibe (depression)

- Anti-diabetic drugs
  - Sulfonylureas (anxiety, depression, paresthesias, confusion, nervousness, nightmares, seizures, hostility, irritability)
  - Metformin (anxiety, depression, confusion, nervousness, seizures, behavioral change similar to drunkenness, difficulty concentrating)
  - Thiazolidinediones (hypothesthesia, insomnia)
  - DPP4 inhibitors (nightmares, depression, anxiety, nervousness)
  - GLP-1 agonists (anxiety, depression, nightmares, seizures, slurred speech, hostility, irritability)
  - SGLT-2 antagonists (anxiety, depression, confusion, nightmares, seizures, slurred speech)

MORE ABOUT ANTI-DEPRESSANTS AS A CLASS OF PHARMACEUTICAL AGENTS

- ALL CLASSES of anti-depressants can cause WORSENING of depression to the point of suicidal/homicidal idea- tion and action!
- ALL CLASSES of anti-depressants can CAUSE anxiety.
- Anti-depressant use is a primary cause of bipolar II disorder in this country. (See next slide. This is no longer “Fleetwood’s opinion.”)
- Decrease/eliminate these last and very slowly, as they present an especially difficult time for many people to stabilize, after having their neurotransmitters and mid/hind-brain chemically altered for a time.
- Make yourself available and keep other variables constant!
- If also on anti-psychotics, anti-convulsants, and/or benzodiazepines, remove in reverse order prescribed. Think Hering’s Law.

BIPOLAR DISEASE: DSM-IV AND DSM-V

- In DSM-IV, the change of major depression into hypomania under antidepressant treatments (ADs) was in principle an exclusion criterion. In DSM-5, that change is explicitly a criterion for bipolar II disorder. In addition, DSM-5 provides new formal criteria for substance/medication-induced bipolar and related disorder.

- Are we “unmasking” bipolar II disease, or creating it?
COMMON DRUGS THAT CAN CAUSE PERCEIVED MENTAL HEALTH ISSUES

- Directly
  - Anti-psychotic agents
    - Classical anti-psychotics (sexual dysfunction, extrapyramidal effects (Parkinsonian symptoms, tardive dyskinesia))
    - Atypical anti-psychotics (restlessness, Parkinson’s symptoms, extrapyramidal reactions, mental impairment, trouble sleeping, hyperactivity, sexual dysfunction, anxiety, inability to focus thoughts)
    - Anti-convulsants (mental impairment, easily angered or annoyed, confused, anxious, mood changes, suicidal), including the GABA analogues (anger issues, mood changes, hyperactivity, suicidal ideation, problems focusing, problems sleeping, anxiety)

“Mood Stabilizers”

MOOD STABILIZER CAVEAT…

- Anti-convulsant use increases the risk of suicidal ideation. (Mere Warning…)
- Antipsychotics also increase the risk of suicidal ideation and have adverse effects that may be irreversible. (BLACK BOX WARNING)

ANTI-CONVULSANTS, AKA “MOOD STABILIZERS”

- Carbamazepine (Tegretol/Equeetro)
- Valproate (Depakote)
- Lamotrigine (Lamictal)
  - These are the ONLY anti-convulsants with FDA approval for use in mental health issues
  - Where’s gaba-dam-pentin? NOT ON THIS LIST!!

GABAPENTIN (NEURONTIN)

Indications for use

- Management of postherpetic neuralgia in adults
- Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy
- THERE IS NOTHING ELSE!
### Common Drugs That Can Cause Perceived Mental Health Issues

**Directly**

- **Anxiolytics**
  - Benzodiazepines (depression, problem behavior, extrapyramidal reactions, inability to focus thoughts, memory loss, hallucinations, suicidal ideation, aggressive behavior, drug abuse, nervousness, easily angered or annoyed, loss of reality/identity, false sense of well-being, sexual dysfunction)
  - 5HT1A selective agonists [buspirone] (confusion, excitement, hostile feelings/behavior, nervousness)
- **Non BZD GABA potentiators/sleep aids** (depression, abnormal dreams, memory loss, hallucinations, restlessness, aggressive behavior, inability to focus thoughts, trouble sleeping, nervousness, easily annoyed/angered, anxiety, loss of reality/identity)

- **Pain Medications**
  - Opioids (depression, hallucinations, trouble sleeping, extreme sense of well-being)
  - Centrally acting analgesics (extreme sense of well-being, trouble sleeping, nervousness, over-excitement, anxiety, hallucinations, depression, restlessness, drug abuse, apathy)
  - COX inhibitors (nervousness, anxiety, mood changes)
  - H2 blockers (restlessness, hallucinations, depression, feeling unwell, trouble sleeping)
  - Steroids (nervousness, hallucinations, depression, aggressive behavior, delirium, mood changes, paranoia, false/extreme sense of well-being, personality changes, overexcitement)
  - Muscle relaxants (restlessness, psychosis, trouble sleeping, nervousness)

- **Asthma Medications**
  - Short-acting beta-agonists (nervousness, depression, hyperactivity, trouble sleeping, anxiety)
  - Long-acting beta-agonists (trouble sleeping, nervousness, restlessness, hyperactivity, anxiety, feeling unwell)
  - Leukotriene blockers (anger, suicidal ideation, restlessness, aggression, depression, abnormal dreams, disturbed attention, trouble sleeping, nervousness, anxiety)

- **Antibiotics**
  - Beta-lactams (restlessness, trouble sleeping, problem behavior, anxiety)
  - Macrolides (restlessness, aggressive behavior, hyperactivity, nervousness, feeling unwell, anxiety)
  - Fluoroquinolones (mental disorder resulting from poisonous agents, loss of sense of reality/identity, nightmares, depression, trouble sleeping, nervousness, feeling unwell, paranoia, anxiety)
  - SMX-TMP (depression, apathy, anxiety, trouble sleeping, nervousness)

**Reminder:**

Deviations away from *normal blood glucose* can precipitate depression and/or anxiety!
COMMON DRUGS THAT CAN CAUSE PERCEIVED MENTAL HEALTH ISSUES, Indirectly--through blood glucose dysregulation

- Thiazide diuretics
- Loop diuretics
- Calcium channel blockers
- Fibrates
- Niacin
- Statins

- Atypical antipsychotics
- GABA analogues
- Centrally acting analgesics
- Steroids
- Short-acting and long-acting beta-agonists
- Muscarinic blockers
- Fluoroquinolones

NUTRIENT DEFICIENCIES THAT CAN PRESENT WITH SYMPTOMS OF DEPRESSION, ANXIETY, IRRITABILITY, FOGGY THINKING, SLEEP DISORDERS...

- Thiamine (B-1): mental confusion, disordered thinking, irritability
- Niacin (B-3): irritability, insomnia, mental confusion, hallucinations, severe depression
- Pantothentic acid (B-5): insomnia, paresthesias, depression
- Pyridoxine (B-6): depression, irritability, convulsions
- Cobalamin (B-12): depression, confusion, memory loss, psychosis
- Folic acid: psychosis, depression, confusion, disorientation, dementia
- Calcium: insomnia, ADHD, post-menopausal depression, anxiety
- Cystine (amino acid): depression, psychosis
- Tryptophan (amino acid): depression, insomnia, suicidal thoughts
- Tyrosine (amino acid): depression
- Phenylalanine (amino acid): depression
- Methionine (amino acid): depression
- Taurine (amino acid): depression, insomnia
- Omega 3 fatty acids: useful in treating bipolar, depression, anxiety, “melancholia”
- Vitamin D3: seasonal affective disorder

EVIDENCE OF THE NEUROTRANSMITTER MYTH

1. To date, there is an astonishing LACK OF PROOF that there is any significant difference in neurotransmitters (serotonin, norepinephrine, GABA, dopamine) in the depressed population vs the non-depressed population. There IS evidence to support a significant difference in particular neurotransmitters in Obsessive Compulsive Disorder (lower serotonin) and Parkinson’s Disease (lower dopamine).

2. Mechanism of action for SARIs, SSRIs, SNRIs, atypical and tricyclic antidepressants is “PRESUMED to be…”.

3. Anti-depressants, ALL classes, are indicated for use in MAJOR DEPRESSIVE DISORDER only— not mild or moderate depression, not “stress”.

4. ALL classes of anti-depressants, regardless of class, have the unfortunate potential of WORSENING depression, to the point of suicidal and/or homicidal ideation AND COMPLETION.

5. ALL classes of anti-depressants, regardless of class, can CAUSE anxiety.

AND YET…
STANDARDS OF CARE
(WRITTEN BY MEDICAL DOCTORS FOR MEDICAL DOCTORS)

• First line of therapy for depression—SSRI; give along with “mood stabilizer” (i.e. anti-convulsant or anti-psychotic agent) if family history of bipolar disorder or depression is refractive.
• First line of therapy for anxiety—SSRI.
• If the first SSRI prescribed for anxiety fails, second line of therapy is another (different) SSRI.

INDICATIONS FOR USE

• Antidepressants, ALL classes, are indicated for use in MAJOR DEPRESSIVE DISORDER only—not mild or moderate depression, not “stress”

Prototypes of the sub-classes:
• Amitriptyline: For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states.
• Bupropion: Bupropion hydrochloride extended-release tablets (SR) are indicated for the treatment of major depressive disorder. Zyban is indicated as an aid to smoking cessation treatment.
• Trazodone: Trazodone Hydrochloride Tablets USP are indicated for the treatment of major depressive disorder (MDD) in adults.
• Fluoxetine: Fluoxetine is indicated for the treatment of major depressive disorder, OCD, bulimia nervosa, and panic disorder. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem®, Fluoxetine hydrochloride).
• Venlafaxine: Venlafaxine tablets, USPare indicated for the treatment of major depressive disorder.

DSM-V CRITERIA FOR MAJOR DEPRESSIVE DISORDER

Five of the below, simultaneously, for 2 weeks
• Persistent sad, anxious or "empty" mood
• Feelings of hopelessness, pessimism
• Feelings of guilt, worthlessness, helplessness
• Loss of interest or pleasure in hobbies and activities, including sex
• Decreased energy, fatigue, feeling "slowed down"
• Difficulty concentrating, remembering, making decisions
• Insomnia, early-morning awakening, or oversleeping
• Low appetite and weight loss or overeating and weight gain
• Thoughts of death or suicide, suicide attempts
• Restlessness, irritability
• Persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders and pain for which no other cause can be diagnosed.

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**STRESS VS DEPRESSION**


**COMMON EFFECTS OF STRESS**

- Headache
- Muscle tension or pain
- Chest pain
- Fatigue
- Change in sex drive
- Stomach upset
- Sleep problems
- Drug/alcohol abuse
- Anxiety
- Restlessness
- Lack of motivation or focus
- Irritability or anger
- Sadness or depression
- Overeating or undereating
- Angry outbursts
- Tobacco use
- Social withdrawal

**MDD/STRESS OVERLAY**

Five of the below, simultaneously, for 2 weeks
- Persistent sad, anxious or "empty" mood: Anxiety, Sadness or depression
- Feelings of hopelessness, pessimism
- Feelings of guilt, worthlessness, helplessness
- Loss of interest or pleasure in hobbies and activities, including sex: Change in sex drive, Social withdrawal
- Decreased energy, fatigue, feeling "slowed down": Fatigue
- Difficulty concentrating, remembering, making decisions: Lack of motivation or focus
- Insomnia, early-morning awakening, or oversleeping: Sleep problems
- Low appetite and weight loss or overeating and weight gain: Overeating or undereating
- Thoughts of death or suicide, suicide attempts
- Restlessness, irritability: Restlessness, Irritability or anger, Angry outbursts
- Persistent physical symptoms, unresponsive to treatment: Headache, Muscle tension/pain, Chest pain, Stomach upset
- Thoughts of death or suicide, suicide attempts
- Restlessness, irritability: Restlessness, Irritability or anger, Angry outbursts
- Persistent physical symptoms, unresponsive to treatment: Headache, Muscle tension/pain, Chest pain, Stomach upset

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**BIG DIFFERENCES?**

- Drug and alcohol abuse, tobacco use listed with stress
- Feelings of hopelessness, helplessness, worthlessness...
  which could lead to... suicidal/homicidal ideation listed with MDD.

- A major limitation of the PHQ-9 is the lack of an item addressing suicidal ideation.
- (PHQ-2 asks about interest or pleasure in doing things over past 2 weeks & feeling “down, depressed or hopeless”. PHQ-9 continues with sleep issues, energy levels, appetite, feeling “bad about yourself...you’re a failure or have let yourself or your family down”, focus issues, speed, and finally, “thoughts that you would be better off dead or of hurting yourself in some way”)

**DSM-V CRITERIA FOR MAJOR DEPRESSIVE DISORDER**

Five of the below, simultaneously, for 2 weeks
- Persistent sad, anxious or "empty" mood
- Feelings of hopelessness, pessimism
- Feelings of guilt, worthlessness, helplessness
- Loss of interest or pleasure in hobbies and activities, including sex
- Decreased energy, fatigue, feeling "slowed down"
- Difficulty concentrating, remembering, making decisions
- Insomnia, early-morning awakening, or oversleeping
- Low appetite and weight loss or overeating and weight gain
- Thoughts of death or suicide, suicide attempts
- Restlessness, irritability
- Persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders and pain for which no other cause can be diagnosed.

**MORE EVIDENCE: ANTIDEPRESSANT TRIALS**

- 2-3 trials; typically 4-6 weeks long
- Fluoxetine had biggest sample sizes and one 16-week trial on bulimia

**MECHANISM OF ACTION... "UNKNOWN"...?!?**

Prototypes of the sub-classes:
- Amitriptyline (tricyclic): Amitriptyline HCl is an antidepressant with sedative effects. Its mechanism of action in man is not known.
- Bupropion (atypical): While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.
- Trazodone (SARI): The mechanism of Trazodone’s antidepressant action is not fully understood, but is thought to be related to its potentiation of serotonergic activity in the CNS.
- Fluoxetine (SSRI): The antidepressant, antiobsessive-compulsive, and antibulimic actions of Fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. The mechanism of action of fluoxetine in premenstrual dysphoric disorder (PMDD) is unknown, but is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin.
- Venlafaxine (SNRI): The mechanism of the antidepressant action of Venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that Venlafaxine and its active metabolite, O-desmethylVenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake.
**PHYSIOLOGY QUESTION…**

- If a drug causes the body to delay the reuptake of a given neurotransmitter in the brain (i.e. serotonin), leaving more in the synapse for a longer period of time, wouldn't the body then either downregulate the amount of serotonin being produced and/or upregulate the numbers of receptors on the other side, resulting in an over-all effect of less neurotransmitter?

**The Law of Dual Effect strikes again!**

**CONCLUSION…**

- Either the whole “Neurotransmitter” piece is a myth
- OR, it’s the best example of the Law of Dual Effect EVER

**NUTRIENT DEPLETIONS**

Prototypes of the sub-classes:
- **Amitriptyline** (tricyclic): CoQ10, Vitamin B2 (Riboflavin), Sodium
- **Bupropion** (atypical → NDRI): Melatonin
- **Trazodone** (atypical → SARI): none known
- **Fluoxetine** (SSRI): Sodium, Melatonin, Folic acid
- **Venlafaxine** (SNRI): none known

**AMITRIPTYLINE**

Suicidality and Antidepressant Drugs:
- Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Amitriptyline hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Amitriptyline hydrochloride is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients and PRECAUTIONS: Pediatric Use.)
**BUPROPION**

**Suicidality and Antidepressant Drugs**

**Use in Treating Psychiatric Disorders:** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of bupropion hydrochloride extended-release tablets (SR) or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Bupropion hydrochloride extended-release tablets (SR) are not approved for use in pediatric patients. (See **WARNINGS: Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders** and **PRECAUTIONS: Information for Patients** and **PRECAUTIONS: Pediatric Use**)

**Use in Smoking Cessation Treatment:** WELLBUTRIN®, bupropion hydrochloride extended-release tablets (SR) and WELLBUTRIN XL® are not approved for smoking cessation treatment, but bupropion under the name ZYBAN® is approved for this use. Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking bupropion for smoking cessation. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depressed mood, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking bupropion who continued to smoke.

**All patients being treated with bupropion for smoking cessation treatment should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking ZYBAN® in the postmarketing experience. When symptoms were reported, most were during treatment with ZYBAN®, but some were following discontinuation of treatment with ZYBAN®. These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of ZYBAN®.

**BUPROPION, MORE WARNINGS**

- Advise patients and caregivers that the patient using bupropion for smoking cessation should stop taking bupropion and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of ZYBAN® was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

- The risks of using bupropion for smoking cessation should be weighed against the benefits of its use. ZYBAN® has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (See **WARNINGS: Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment** and **PRECAUTIONS: Information for Patients**)

**TRAZODONE**

**WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS**

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Trazodone hydrochloride tablets or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Trazodone hydrochloride tablets are not approved for use in pediatric patients (see Warnings and Precautions (5.1) and Patient Counseling Information (17.1)).
Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Fluoxetine or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Fluoxetine is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

FLUOXETINE

SHOW ME THE RESEARCH!

I won't go into the conflicts of interest, the placebo effect, researcher bias, and blatant fraud that takes place within this “scientific” community...

VENLAFAXINE

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Venlafaxine hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Venlafaxine hydrochloride is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

VENLAFAXINE

BUPROPION

• The efficacy of the immediate-release formulation of bupropion as a treatment for depression was established in two 4-week, placebo-controlled trials in adult inpatients with depression and in one 6-week, placebo-controlled trial in adult outpatients with depression.
• Although there are not as yet independent trials demonstrating the antidepressant effectiveness of the sustained-release formulation of bupropion, studies have demonstrated the bioequivalence of the immediate-release and sustained-release forms of bupropion under steady-state conditions.
• On the market since 1989 as amfebutamone (substituted amphetamine); renamed in 2000.
**TRAZODONE**

- The efficacy and safety of Trazodone hydrochloride was established from both inpatient and outpatient trials of the Trazodone immediate release formulation in the treatment of *major depressive disorder*. On market since 1981.

**FLUOXETINE**

- The efficacy of Fluoxetine for the treatment of patients with *major depressive disorder* (≥ 18 years of age) has been studied in 5- and 6-week placebo-controlled trials.
- **Two 6-week** controlled studies (N=671, randomized) comparing Fluoxetine 20 mg and placebo have shown Fluoxetine 20 mg daily to be effective in the treatment of elderly patients (≥ 60 years of age) with *major depressive disorder*.
- The efficacy of Fluoxetine 20 mg/day for the treatment of *major depressive disorder* in pediatric outpatients (N=315 randomized; 170 children ages 8 to < 13, 145 adolescents ages 13 to ≤ 18) has been studied in **two 8- to 9-week** placebo-controlled clinical trials.
- On the market since 1987.

**FLUOXETINE**

- The effectiveness of Fluoxetine for the treatment of *obsessive-compulsive disorder (OCD)* was demonstrated in **two 13-week**, multicenter, parallel group studies (Studies 1 and 2) of adult outpatients.
- In **one 13-week** clinical trial in pediatric patients (N=103 randomized; 75 children ages 7 to < 13, 28 adolescents ages 13 to < 18) with OCD, patients received Fluoxetine 10 mg/day for 2 weeks, followed by 20 mg/day for 2 weeks.

**FLUOXETINE**

- The effectiveness of Fluoxetine in the treatment of *panic disorder* was demonstrated in **two double-blind**, randomized, placebo-controlled, multicenter studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-IV), with or without agoraphobia. Study 1 (N=180 randomized) was a 12-week flexible-dose study. Study 2 (N=214 randomized) was a 12-week flexible-dose study.
- The effectiveness of Fluoxetine for the treatment of *bulimia* was demonstrated in **two 8-week and one 16-week**, multicenter, parallel group studies of adult outpatients meeting DSM-III-R criteria for bulimia.
**FLUOXETINE**

- The effectiveness of Sarafem for the treatment of PMDD was established in 3 placebo–controlled trials (1 intermittent and 2 continuous dosing). Patients on oral contraceptives were excluded from these trials; therefore, the efficacy of fluoxetine in combination with oral contraceptives for the treatment of PMDD is unknown. In an intermittent dosing double-blind, parallel group study of 3 months duration, patients (N=280 randomized) were treated with fluoxetine 10 mg/day, fluoxetine 20 mg/day, or placebo. Fluoxetine or placebo was started 14 days prior to the anticipated onset of menstruation and was continued through the first full day of menses. The average Daily Record of Severity of Problems (DRSP) total score decreased 38% on fluoxetine 20mg/day, 35% on fluoxetine 10 mg/day, and 30% on placebo. In the first continuous dosing double-blind, parallel group study of 6 months duration involving N=320 patients, fixed doses of fluoxetine 20 and 60 mg/day given daily throughout the menstrual cycle were shown to be significantly more effective than placebo as measured by a Visual Analogue Scale (VAS) total score (including mood and physical symptoms). The average total VAS score decreased 7% on placebo treatment, 36% on 20 mg, and 39% on 60 mg fluoxetine.

**FLUOXETINE**

- In a second continuous dosing double-blind, cross-over study, patients (N=19) were treated with fluoxetine 20 to 60 mg/day (mean dose = 27 mg/day) and placebo daily throughout the menstrual cycle for a period of 3 months each. Fluoxetine was significantly more effective than placebo as measured by within cycle follicular to luteal phase changes in the VAS total score (mood, physical, and social impairment symptoms). The average VAS total score (follicular to luteal phase increase) was 3.8 times higher during placebo treatment than what was observed during fluoxetine treatment.

- In another continuous dosing double-blind, parallel group study, patients with LLPDD (N=42) were treated daily with fluoxetine 20 mg/day, bupropion 300 mg/day, or placebo for 2 months. Neither fluoxetine nor bupropion was shown to be superior to placebo on the primary endpoint, i.e., response rate (defined as a rating of 1 (very much improved) or 2 (much improved)) on the CGI, possibly due to sample size.

**VENLAFAXINE**

- The efficacy of Venlafaxine hydrochloride as a treatment for major depressive disorder was established in 5 placebo-controlled, short-term trials. Four of these were 6-week trials in adult outpatients meeting DSM-III or DSM-III-R criteria for major depression. The fifth was a 4-week study of adult inpatients meeting DSM-III-R criteria for major depression with melancholia.

- On market since 1993.

**EVIDENCE SUGGESTS...**

- That antidepressants have been studied only short term and only for major depressive disorder.

- Therefore, these drugs should only be used in the short term (6 weeks or so) and only for major depressive disorder.

- So what happens in ‘real life’?
Research shows that certain nutrients work better than pharmaceutical agents for depression, certain herbs, various aromatherapies... And EXERCISE! Exercise beats out ALL the competition for the treatment of depression!

But staying with the conventional medical paradigm, this is STILL a disconnect from their “evidence”!

FEELING DEPRESSED?

Or maybe just a little bit anxious?

“MOOD STABILIZERS”: ANTI-Psychotics & Anti-Convulsants

- All antipsychotics—classical (haloperidol, thioridazine) and atypical (risperidone, aripiprazole...the ones flooding the market)—have a BLACK BOX WARNING around use in elders with dementia:

- **WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**
- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Risperidone is not approved for the treatment of patients with dementia-related psychosis.

- Aripiprazole (Abilify) atypical anti-psychotic

  - **WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTI-DEPRESSANT DRUGS**
  - Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.
  - Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older.
  - In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber.
**HALOPERIDOL (HALDOL) - CLASSICAL ANTI-Psychotic**

**WARNING: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking a typical antipsychotic drug, revealed a risk of death in drug-treated patients of 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristics of the patients is not clear. Haloperidol injection is not approved for the treatment of patients with dementia-related psychosis.

**ANTI-CONVULSANTS AS "MOOD STABILIZERS"**

- Antiepileptic drugs (AEDs), including Equetro, increase the risk of suicidal thoughts or behavior in patients using these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

**VALPROATE**

- **General Population:** Hepatic failure resulting in fatalities has occurred in patients receiving Valproate and its derivatives. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, fever, rash, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months.

- **Children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity,** especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When Valproate sodium injection is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

- **Patients with Mitochondrial Disease:** There is an increased risk of Valproate-induced acute liver failure and resultant deaths in patients with hereditary neutroimune syndromes caused by DNA mutations of the mitochondrial DNA (e.g., MELAS, MERRF, KSS). Valproate is contraindicated in patients known to have mitochondrial disorders caused by POI-G mutations and children under 2 years of age who are suspected of having a mitochondrial disorder.

- **Patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease:** Valproate should only be used after other anticonvulsants have failed. This group of patients should be closely monitored during treatment with Valproate for the development of a cutaneous rash, fever, malaise, vomiting, and/or anorexia. If these symptoms persist or worsen, Valproate should be discontinued. Treatment for the underlying medical condition should be initiated as clinically indicated.

**WARNING: LIFE THREATENING ADVERSE REACTIONS**

- **Hepatotoxicity**

- **Fetal Risk**

- **Pancreatitis**

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CARBAMAZEPINE

**WARNING: SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE**

- Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with Carbamazepine. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with Carbamazepine. Patients testing positive for the allele should not be treated with Carbamazepine unless the benefit clearly outweighs the risk.

APLASTIC ANEMIA AND AGNANULOCYTOSIS

- Aplastic anemia and agranulocytosis have been reported in association with the use of Carbamazepine. Data from a population-based case control study demonstrate that the risk of developing these reactions is 5 to 8 times greater than in the general population. However, the overall risk of these reactions in the untreated general population is low, approximately six patients per one million population per year for agranulocytosis and two patients per one million population per year for aplastic anemia.

- Although reports of transient or persistent decreased platelet or white blood cell counts are not uncommon in association with the use of Carbamazepine, data are not available to estimate accurately their incidence or outcome. However, the vast majority of the cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis.

- Because of the very low incidence of agranulocytosis and aplastic anemia, the vast majority of minor hematologic changes observed in monitoring of patients on Carbamazepine are unlikely to signal the occurrence of either abnormality. Nonetheless, complete pretreatment hematological testing should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

LAMOTRIGINE

**WARNING: SERIOUS SKIN RASHES**

- Lamotrigine can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.3% to 0.8% in pediatric patients (aged 2 to 17 years) and 0.08% to 0.3% in adults receiving Lamotrigine. One rash-related death was reported in a prospectively followed cohort of 1,983 pediatric patients (aged 2 to 16 years) with epilepsy taking Lamotrigine as adjunctive therapy. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate.

- Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash caused by Lamotrigine. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of Lamotrigine with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose of Lamotrigine, or (3) exceeding the recommended dose escalation for Lamotrigine. However, cases have occurred in the absence of these factors.

- Nearly all cases of life-threatening rashes caused by Lamotrigine have occurred within 2 to 8 weeks of treatment initiation. However, isolated cases have occurred after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as means to predict the potential risk heralded by the first appearance of a rash.

- Although benign rashes are also caused by Lamotrigine, it is not possible to predict reliably which rashes will prove to be serious or life-threatening. Accordingly, Lamotrigine should ordinarily be discontinued at the first sign of rash unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming disfiguring or permanently disabling or disfiguring.

DEPRESSION

- **Diagnosis is based on clinical presentation—no labs to confirm**

- **Physical symptoms account for about 65% of complaints**

- **According to WHO, depression presents the largest burden of non-fatal disease worldwide**

- **Primary care providers will manage about 80% of depressed patients**
CHAKRAS & EMOTIONS

• Strengthen weakened systems—EXERCISE!
• Nutrient depletions—replete!
• Find and treat the CAUSE, thereby treating the whole person; counseling
• Hear the story, listen to the language used; reframe the experience
• Physician, healthye yourself! Be a model of health/healing to your patients; get your own personal work done
• First, do no harm
• Gut health
• I see anxiety as spiritual issue; depression often a form of self-absorption

“RAGE IS ANGER TURNED OUTWARD; DEPRESSION IS ANGER TURNED INWARD.” – SIGMUND FREUD

“If you are depressed, you are living in the past. If you are anxious, you are living in the future. If you are at peace, you are living in the present.” – LAO TZU

“It is one of the beautiful compensations in this life that no one can sincerely try to help another without helping himself.” – RALPH WALDO EMERSON

“One of the best things you can do to improve the world is to improve yourself.” – JEN SINCERO

BILOGICS, SPECIFICALLY THE CYTOKINE INHIBITORS

What the drugs being used for autoimmunity are doing to those immune systems…
**IMMUNE SYSTEM SUPPRESSANTS**

**BY SALES**
- Humira, adalimumab #3, $5,936,288,498
- Enbrel, etanercept #6, $4,896,267,318
- Remicade, infliximab #7, $4,235,535,358
- Rituxan, rituximab #12, $3,320,475,967
- Avastin, bevacizumab #17, $2,742,284,655*
- Herceptin, trastuzumab #25, $1,971,724,243*
- Lucentis, ranibizumab #26, $1,917,919,037
- Sandimmune, ciclosporin #47, $1,083,660,282
- Synagis, palivizumab #80, $755,220,544
- Erbitux, cetuximab #90, $660,368,777*

**BY VOLUME**
- Humira, adalimumab #64, 1,882,887
- Enbrel, etanercept #74, 1,621,584
- Lotemax, loteprednol #91, 1,269,637

*for use in cancer treatment only

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**STEROIDS** (CORTICOSTEROIDS/GLUCOCORTICIDS)

- Loprednol
- Prednisone
- Prednisolone
- Methylprednisolone
- Dexamethasone
- Hydrocortisone
- Betamethasone
- Methylprednisolone
- Fluticasone
- Budesonide
- Triamcinolone
- Desonide
- Flucinolone
- Fluocinonide

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**COMMON SIDE EFFECTS, STEROIDS**

- Cushing’s Syndrome
- Low Amount of Calcium in the Blood
- Small Red Skin Lesions caused by Dilated Blood Vessels
- Irregular Periods
- Dry Skin
- Puffy Face from Water Retention
- High Blood Sugar
- Diabetes
- Infection
- Conditions of Excess Stomach Acid Secretion
- Chronic Trouble Sleeping
- Increased Hunger
- Nervous
- Bleeding of the Stomach or Intestines
- Thin Fragile Skin
- Osteoporosis

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**LESS COMMON SIDE EFFECTS, STEROIDS**

- Insufficiency of the Hypothalamus and Pituitary Gland; Depression; Blurred Vision
- Optic Disk Edema; A Rupture in the Wall of the Stomach or Intestine; Anemia
- Large Purple or Brown Skin Blotches; Mood Changes; Paranoia; Mental Disturbance
- False Sense of Well-Being; Decreased Neutrophils; Hemorrhage of Blood Under the Skin
- Absence of Menstrual Periods; Problem with Periods; Inflammation of Skin caused by an Allergy
- Skin Stretch Marks; Excessive Hairiness; Acne; Hives; Joint Pain; Muscle Weakness
- Sensation of Spinning or Whirling; Dizziness; Excessive Sweating; Rash; Visible Water Retention
- Small Reddish-Purplish Pin-Point Sized Spots on the Skin; Scaling of Skin; Swelling of the Abdomen; Confusion
- Presence of Sugar in the Urine; Numbness and Tingling; Not Feeling Well
- Overactive Thyroid Gland; Underactive Thyroid; Abnormal Fat Distribution; Over Excitement

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LESS COMMON SIDE EFFECTS, STEROIDS

- Pseudotumor Cerebri; Disease of the Nerves; Muscle Problems; Increased Pressure in the Eye
- Cataracts; Injury of the Optic Nerve; High Blood Pressure; Complete Stoppage of the Heart
- Slow Heartbeat; Fluid in the Lungs; Ulcers of Esophagus; Ulcer from Stomach Acid
- Abnormal Heart Rhythm; Chronic Heart Failure; Rupture of a Tendon
- Obstruction of a Blood Vessel by a Blood Clot; Blood Clot in Vein
- Obstruction of Blood Vessel caused by a Fat Globule; Vasculitis
- Acute Inflammation of the Pancreas; Lupus-Like Syndrome; Redness of Skin
- Delirium; Hallucination; Seizures; Trouble Breathing; Enlarged Liver
- Abnormal Liver Function Tests; Broken Bone; Impaired Wound Healing; Water Retention
- Life Threatening Allergic Reaction; Extreme Sense of Well Being; Loss of Memory; Faintness

NUTRIENT DEPLETIONS, STEROIDS

- Calcium
- Chromium
- Folic acid
- Magnesium
- Potassium
- Selenium
- Beta carotenes
- Vitamin B6
- Vitamin B12
- Vitamin C
- Vitamin D
- Vitamin K
- Zinc

MORE ABOUT STEROIDS

- Corticosteroid prednisone discovered in the 1940s and hailed as the “Miracle Cure”—too good to be true! Indeed.
- Anti-inflammatory agent, immunosuppressant.
- In the acute setting, can be life-saving; over the long-term, however, can wreak havoc.
- Consider licorice and adrenal adaptogens to help wean drug.
- Use when needed! Match the pathology with the necessary level of intervention.

DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDS)

- Methotrexate, Rheumatrex
- Sulfasalazine, Azulfidine
- Hydroxychloroquine, Plaquenil
- Azathiaprine, Imuran/Azasan
- Penicillamine, Cuprimine
- Tofacitinib, Xeljanz

NEW! JAK inhibitor:
DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDS)

- Methotrexate, Rheumatrex
- Sulfasalazine, Azulfidine
- Hydroxychloroquine, Plaquenil
- Azathiaprine, Imuran/Azasan
- Penicillamine, Cuprimine
- Tofacitinib, Xeljanz

INFLAMMATORY BOWEL DISEASE

5-amino salicylates:
- Sulfasalazine, Azulfidine
- Mesalazine (mesalamine), Asacol/Pentasa/Lialda
- (one of the active metabolites of sulfasalazine)
- MoA unknown. May be immunomodulatory or anti-inflammatory.
- Labeled uses: ulcerative colitis
- CI: patients with intestinal or urinary obstructions, porphyria, aspirin sensitivities, sulfa sensitivities
- SE: gastric distress, headache, nausea, oligospermia, vomiting, anorexia, fever
- Reduces absorption of folate; increases levels of MTX (which reduces levels of folate further).
- Nutrient depletion alert! Also, separate dosing from iron supplements, binding can take place.

SULFASALAZINE/MESALAMINE

SIDE EFFECTS & CONTRAINDICATIONS

- More common: anorexia, headache, nausea, vomiting, gastric distress, apparently reversible oligospermia
- Less common: skin rash, pruritus, urticaria, fever, Heinz body anemia, hemolytic anemia, and cyanosis
- For mesalamine: Very common (10% or more): Eructation (up to 16%), ulcerative colitis aggravated (up to 15%).
- Common (1% to 10%): Abdominal pain/cramps/discomfort, diarrhea, flatulence, nausea, gastroenteritis, gastrointestinal hemorrhage, rectal disorder, stool abnormalities (color or texture change), urinary frequency, dyspepsia, vomiting, bloating, rectal distension, pain on insertion of tip (enema formulation), hemorrhoids, rectal pain, colitis, constipation, abdominal distension
- Pregnancy category B

TOFACITANIB, APPROVED FOR USE IN RA, PsA, UC

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS
- Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled.
- Reported infections include:
  - Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR use.
  - Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
  - Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.
- The risks and benefits of treatment with XELJANZ/XELJANZ XR should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCIES
- Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.
HUMIRA, ADALIMUMAB BLACK BOX WARNING

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

- SERIOUS INFECTIONS
  - Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens.
  - Discontinue HUMIRA if patient develops a serious infection or sepsis during treatment.
  - Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.
  - Monitor patients for active TB during treatment, even if initial latent TB test is negative.
- MALIGNANCY: Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers, including HUMIRA.

HUMIRA WARNINGS AND PRECAUTIONS

- Invasive fungal infections: For patients who develop a systemic illness on HUMIRA, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic.
- Anaphylaxis or serious allergic reactions may occur.
- Hepatitis B virus reactivation: Monitor HBV carriers during and several months after therapy. Reactivation occurs, stop HUMIRA and begin antiviral therapy.
- Demyelinating disease; Exacerbation or new onset, may occur.
- Cytopenias, pancytopenia: Advise patients to seek immediate medical attention if symptoms develop, and consider stopping HUMIRA.
- Heart failure: Worsening or new onset, may occur.
- Lupus-like syndrome: Stop HUMIRA if syndrome develops.

REMCACE, INFLIXIMAB

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

- SERIOUS INFECTIONS: Patients treated with REMICADE are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. REMICADE should be discontinued if a patient develops a serious infection or sepsis.
- Reported infections include:
  - Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have been frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before REMICADE use and during the therapy. Treatment for latent infection should be initiated prior to REMICADE use.
  - Invasive fungal infections, including histoplasmosis, coccidioidomycosis, and aspergillosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness. Be aware of local and other infections due to opportunistic pathogens, including Legionella and Listeria.
  - The risks and benefits of treatment with REMICADE should be carefully considered prior to initiating therapy in patients with active or recent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and a few months after treatment with REMICADE, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.
- MALIGNANCY: Lymphoma and other malignancies, some fatal, have been reported in patients treated with TNF blockers including REMICADE. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with other TNF blockers before REMICADE, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.
REMICADE Warnings & Precautions

- **Serious infections; Invasive fungal infections; Malignancies (invasive cervical aneuploidy and lymphoma)** Due to the risk of HS TCL/hepa-splenocyt TCL lymphoma, carefully assess the risk/benefit especially if the patient has Crohn’s disease or ulcerative colitis, is male, and is receiving aza thioprine or mercaptopurine treatment.
- Hepatitis B virus reactivation – test for HBV infection before starting REMICADE. Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop REMICADE and begin antiviral therapy.
- Hepatotoxicity – severe hepatic reactions, some fatal or necessitating liver transplantation. Stop REMICADE in cases of jaundice and marked liver enzyme elevations.
- Heart failure – new onset or worsening symptoms may occur.
- Cytopenias – advise patients to seek immediate medical attention if signs and symptoms develop, and consider stopping REMICADE.
- Hypersensitivity – serious infusion reactions including anaphylaxis or serum sickness like reactions may occur.
- Cardiacaudal and Cerebrovascular Reactions – Cerebrovascular accidents, myocardial infarctions (some fatal), and arrhythmias have been reported during and within 24 hours of initiation of REMICADE infusion. Monitor patients during REMICADE infusion if serious reaction occurs, discontinue infusion.
- Demyelinating disease – exacerbation or new onset may occur.
- Lupus-like syndrome – stop REMICADE if syndrome develops.
- Live vaccines or therapeutic infectious agents – should not be given with REMICADE. Bring pediatric patients up to date with all vaccinations prior to initiating REMICADE. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants exposed in utero to infliximab.

REMICADE Most Common Adverse Events

- Most common adverse reactions (>10%) – infections (e.g. upper respiratory, sinusitis, and pharyngitis), infusion related reactions, headache, and abdominal pain.

ENBREL, ETANERCEPT (ANOTHER TNF BLOCKER)

**Warning: Serious Infections and Malignancies**

- **Serious Infections** Patients treated with Enbrel are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who develop these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Enbrel should be discontinued if a patient develops a serious infection or sepsis.
- Reported infections include:
  - Active tuberculosis, including reactivation of latent tuberculosis.
  - Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
  - Bacterial, viral and other infections due to opportunistic pathogens, including Legionella, and Listeria.

- The risks and benefits of treatment with Enbrel should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and a follow-up period with Enbrel. Including the possible development of tuberculosis in patients who were negative for latent tuberculosis infection prior to initiating Enbrel.

- **Malignancies** Lymphomas and other malignancies, some fatal, have been reported in children and adolescents treated with TNF blockers, including Enbrel.

ENBREL Warnings & Precautions

- Do not start Enbrel during an active infection. If an infection develops, monitor carefully and stop Enbrel if infection becomes serious.
- Consider empirical antifungal therapy for patients at risk for invasive fungal infections who develop a severe systemic illness on Enbrel (those who reside or travel in regions where mycoses are endemic).
- Demyelinating disease, exacerbation or new onset, may occur.
- Cases of lymphoma have been observed in patients receiving TNF-blocking agents.
- Congestive heart failure, worsening or new onset, may occur.
- Advise patients to seek immediate medical attention if symptoms of pancytopenia or aplastic anemia develop, and consider stopping Enbrel.
- Monitor patients previously infected with hepatitis B virus for reactivation during and several months after therapy. If reactivation occurs, consider stopping Enbrel and beginning anti-viral therapy.
- Anaphylaxis or serious allergic reactions may occur.
- Stop Enbrel if lupus-like syndrome or autoimmune hepatitis develops.
COMMON SIDE EFFECTS OF ENBREL

"ADVERSE REACTIONS >5%: INFECTIONS"

- Chickenpox; Acute Infection of the Nose, Throat or Sinus; Infection
- Throat Irritation; Inflammation of the Nose; Sinus Irritation and Congestion
- Head Pain; Feel Like Throwing Up; Fluid Retention in the Legs, Feet, Arms or Hands
- Stomach Cramps; Signs and Symptoms at Injection Site; Throwing Up
- Bacterial Infection of Blood or Tissues affecting the Whole Body
- High Blood Pressure; Abnormally Low Blood Pressure
- Pneumonia; Bronchitis; Abscess Within the Abdomen
- Inflammation of the Gallbladder; Bacterial Infection of the Kidney and Renal Pelvis
- Bacteria causing an Infection in the Joints; Abscess; Dizzy

LESS COMMON SIDE EFFECTS OF ENBREL

- Inflamed Spinal Cord; Multiple Sclerosis; Guillain-Barre Syndrome; Sudden Blindness and Pain Upon Moving the Eye
- Episodes of Hepatitis B Infection Symptoms; Drug Therapy that Worsens or Causes Psoriasis; Sarcoidosis
- Hepatosplenic T-cell Lymphoma; Worsening of Chronic Heart Failure; Overactive Macrophage Immune Cells
- Chronic Heart Failure; Vasculitis; Canker Sore; Legionnaire's Disease; Abscess of the Foot; Dry Mouth
- Inflammation of the Lining of the Stomach and Intestines; Indigestion; Inflammatory Bowel Disease; Anemia
- Liver Inflammation caused by Body's Own Immune Response; Acute Inflammation of the Pancreas; Retching
- Leg Ulcer; Decreased White Blood Cells; Dry Eye; Inflammation of the Eye; Decreased Blood Platelets
- Joint Pain; Bleeding of the Stomach or Intestines; Knots Beneath the Surface of the Skin; Loss of Appetite
- Toxic Epidermal Necrolysis; Stevens-Johnson Syndrome; Hives; Lupus-Like Syndrome; Seizures
- Infection due Candida; Inflammation of Bbod Vesick in the Skin; Pain; Rash; Malignant Lymphoma
- Infection caused by Coccioides Fungus; Type of Infection caused by Histoplasmosis Fungus; Low Energy
- Infection caused by Blastomyces Dermatitidis Fungus; Life-Threatening Allergic Reaction; Cough; Diarrhea
- Feeling Weak; An Infection - Aspergillus Infection; Infection caused by a Fungus; Active Tuberculosis
- Reactivated Tuberculosis; Malignant Tumor or Cancer; Infection caused by the Bacteria Listeria Monocytogenes
- Sore Throat; Decrease of All Cells in the Blood; Low Blood Counts due to Bone Marrow Failure; Leukemia

ORENCIA, ABATACEPT (TNF-A BLOCKER, MORE TARGETED)

- Indicated for use in: RA, JIA, PsA
- Warnings & Precautions:
  - Concomitant use with a TNF antagonist can increase the risk of infections and serious infections
  - Hypersensitivity, anaphylaxis, and anaphylactoid reactions
  - Patients with a history of recurrent infections or underlying conditions predisposing to infections may experience more infections
  - Discontinue if a serious infection develops
  - Screen for latent TB infection prior to initiating therapy. Patients testing positive should be treated prior to initiating ORENCIA
  - Live vaccines should not be given concurrently or within 3 months of discontinuation
  - Patients with juvenile idiopathic arthritis should be brought up to date with all immunizations prior to ORENCIA therapy
  - Based on its mechanism of action, ORENCIA may blunt the effectiveness of some immunizations
  - COPD patients may develop more frequent respiratory adverse events
- Adverse events (>10%): Headache, Upper respiratory tract infection, nasopharyngitis, and nausea

MONOCLONAL ANTIBODIES = RDNA TECHNOLOGY

- Abatacept is produced by recombinant DNA technology in a mammalian cell expression system
- Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system
- Infliximab, the active ingredient in REMICADE, is a chimeric IgG1 monoclonal antibody (composed of human constant and murine variable regions) specific for human tumor necrosis factor alpha (TNFα). Infliximab is produced by a recombinant cell line cultivated by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.
- HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). HUMIRA was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1 constant regions. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps.
TNF INHIBITORS, UP-AND-COMING COUSINS

Cytokine Inhibitors
- **Vedolizumab**, *Entyvio* for UC, CD
- **Certolizumab**, *Cimzia* for CD, RA, PsA, AS, Ps (BLACK BOX)
- **Natalizumab**, *Tysabri* for MS, CD (BLACK BOX)
  - Targeted against TNF-α (TNF blocker)
  - Increased risk of serious infections, malignancies, progressive multifocal leukoencephalopathy (PML)

Outside the risk of serious infections, these agents have very little in the way of adverse side effects—patients feel good on these!

FOR THE CONSUMER...
- **Very bad and sometimes deadly infections** have happened in patients who take infliximab injection. Most people who had these infections were taking other drugs to lower the immune system like methotrexate or steroid drugs. If you have any infection, are taking antibiotics now or in the recent past, or have had many infections, talk with your doctor.
- **TB (tuberculosis)** has been seen in patients started on this medicine. These patients were exposed to TB in the past, but never got the infection. You will be tested to see if you have been exposed to TB before starting infliximab injection.
- **Lymphoma and other cancers** have happened in people who take this medicine or drugs like it. This has been deadly in some cases. Talk with the doctor.
- **A rare type of cancer called hepatosplenic T-cell lymphoma (HSTCL)** has happened with infliximab injection and other drugs like it. These cases have been deadly. Almost all cases were in people who were using drugs like this one along with certain other drugs (azathioprine or 6-mercaptopurine). Most of the time, this happened during treatment for Crohn's disease or ulcerative colitis. Also, most cases were in male teenagers or young men. Talk with the doctor.

MORE FOR THE CONSUMER...
- Tell all of your health care providers that you take vedolizumab. This includes your doctors, nurses, pharmacists, and dentists.
- Have blood work checked as you have been told by the doctor. Talk with the doctor.
- You may have more chance of getting an infection. Wash hands often. Stay away from people with infections, colds, or flu.
- Very bad and sometimes deadly infections can happen with this medicine. Talk with the doctor.
- Make sure you are up to date with all your vaccines before treatment with vedolizumab.
- Talk with your doctor before getting any vaccines. Use with this medicine may either raise the chance of an infection or make the vaccine not work as well.
- Some patients have very bad side effects during the infusion. This could happen during the infusion or within many hours after care. Tell your doctor if you have any bad effects during the infusion:
  - Tell your doctor if you are pregnant or plan on getting pregnant. You will need to talk about the benefits and risks of using vedolizumab while you are pregnant.
  - Tell your doctor if you are breast-feeding. You will need to talk about any risks to your baby.

BUT, WAIT! THERE’S MORE...
- **A very bad brain problem called progressive multifocal leukoencephalopathy (PML)** has happened with natalizumab. It may cause disability or can be deadly. Tell your doctor right away if you have signs like confusion, memory problems, low mood (depression), change in the way you act, change in strength on 1 side is greater than the other, trouble speaking or thinking, change in balance, or change in eyesight.
- Watch for side effects while getting this medicine and for 6 months after your last dose.
- You may only get natalizumab through a special program. Talk with your doctor.

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Infections:

Retreatment in Patients with Granulomatosis with Polyangiitis (GPA)

Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following treatment with RITUXAN (rituximab) in some patients. Fatal infections have been reported in patients with prolonged hypogammaglobulinemia defined as hypogammaglobulinemia for >1 month after rituximab exposure. New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella-zoster virus, West Nile virus, and hepatitis B and C. Discontinue RITUXAN for serious infections and institute appropriate anti-infective therapy. Rituximab is not recommended for use in patients with severe, active infections.

Cardiovascular Adverse Reactions:

Cardiac adverse reactions including ventricular fibrillation, myocardial infarction, and cardiac arrest can occur in patients receiving RITUXAN. Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after infusions of RITUXAN in patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

Renal Toxicity:

Severe, including fatal renal toxicity can occur with RITUXAN administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitantly with cisplatin. Use of RITUXAN in patients with rising serum creatinine or creatinine should be considered closely for signs of renal failure and discontinue RITUXAN in patients with a rising serum creatinine or oliguria.

Bowel Obstruction and Perforation:

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving RITUXAN in combination with chemotherapy. In postmarketing reports, the median time to documented gastrointestinal perforation was 6.4 range 1–77 days in patients with NHL. Evaluate symptoms of obstruction such as abdominal pain or repeated vomiting occur.
STELARA, USTEKINUMAB

- Immune system target: human interleukin-12 and -23 antagonist
- Indications: Ps (from 12 yrs of age), Ps A, CD
- Warnings and Precautions only; no BLACK BOX at this time
- Ustekinumab is a human IgG1 monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. Using DNA recombinant technology, ustekinumab is produced in a well-characterized recombinant cell line and is purified using standard bio-processing technology. The manufacturing process contains steps for the clearance of viruses.

STELARA WARNINGS AND PRECAUTIONS

- Infections: Serious infections have occurred. Do not start STELARA® during any clinically important active infection. If a serious infection or clinically significant infection develops, consider discontinuing STELARA® until the infection resolves.
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances.
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with STELARA®. Initiate treatment of latent TB before administering STELARA®.
- Malignancies: STELARA® may increase risk of malignancy. The safety of STELARA® in patients with a history of a known malignancy has not been evaluated.
- Hypersensitivity Reactions: Anaphylaxis or other clinically significant hypersensitivity reactions may occur.
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): One case was reported. If suspected, treat promptly and discontinue STELARA®.
- Noninfectious Pneumonia: Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA®. If diagnosis is confirmed, discontinue STELARA® and institute appropriate treatment.

STELARA MOST COMMON ADVERSE EVENTS

- Psoriasis (≥3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue.
- Crohn’s Disease, induction (≥3%): vomiting.
- Crohn’s Disease, maintenance (≥3%): nasopharyngitis, injection site erythema, vulvovaginal candidiasis/mycotic infection, bronchitis, pruritus, urinary tract infection, and sinusitis.

LUCENTIS, RANIBIZUMAB

- Immune system target: vascular endothelial growth factor inhibitor.
- Indications:
  - Intravitreal injection
  - Neovascular (wet) age-related macular degeneration
  - Macular edema following retinal vein occlusion
  - Diabetic macular edema
  - Diabetic retinopathy
  - Myopic choroidal neovascularization.
LUCENTIS, RANIBIZUMAB

- No BLACK BOX
- Warnings & Precautions: endophthalmitis, retinal detachments, increases in intraocular pressure, thromboembolic events, fatal events in patients with DME and DR at baseline
- Most common adverse reactions: conjunctival hemorrhage, eye pain, vitreous floaters, and increased IOP

LUCENTIS® (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intravitreal use. Ranibizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab, which lacks an Fc region, has a molecular weight of approximately 48 kDa and is produced by an E. coli expression system in a nutrient medium containing the antibiotic tetacycline.

XGEVA, DENOSUMAB* (FOR CANCER TREATMENT)

- Immune system target: RANK ligand (RANKL) inhibitor
- Indications:
  - Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
  - Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or when surgical resection is likely to result in severe morbidity.
  - Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.
- NOT FOR OSTEOPOROSIS; only Prolia!

Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human RANKL. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

XGEVA, DENOSUMAB (ALSO BRANDED AS PROLIA)

- Same Active Ingredient: Patients receiving Xgeva should not take Prolia®.
- Hypersensitivity reactions including anaphylaxis may occur. Discontinue permanently if a clinically significant reaction occurs. Hyponatremia can cause severe symptomatic hyponatremia, and fatal cases have been reported. Correct hyponatremia prior to initiating Xgeva. Monitor calcium levels during therapy, especially in the first weeks of initiating therapy, and adequately supplement all patients with calcium and vitamin D.
- Osteonecrosis of the jaw (ONJ) has been reported in patients receiving Xgeva. Perform an oral examination prior to starting Xgeva. Monitor for symptoms. Avoid invasive dental procedures during treatment with Xgeva.
- Atypical femur fracture: Evaluate patients with thigh or groin pain to rule out a femoral fracture.
- Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons: Monitor patients for signs and symptoms of hypercalcemia, and manage as clinically appropriate.
- Multiple Vertebrae Fractures (MVF) Following Treatment Discontinuation: When Xgeva treatment is discontinued, evaluate the individual patient’s risk for vertebral fractures.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus and to use effective contraception.

XGEVA ADVERSE REACTIONS

- Bone Metastasis from Solid Tumors: Most common adverse reactions (>25%) were fatigue/asthenia, hypophosphatemia, and nausea.
- Multiple Myeloma: Most common adverse reactions (>10%) were diarrhea, nausea, anemia, back pain, thrombocytopenia, peripheral edema, hypocalcemia, upper respiratory tract infection, rash, and headache.
- Giant Cell Tumor of Bone: Most common adverse reactions (>10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity.
- Hypercalcemia of Malignancy: Most common adverse reactions (>20%) were nausea, dyspepsia, decreased appetite, headache, peripheral edema, vomiting, anemia, constipation, and diarrhea.
PROLIA, DENOSUMAB FOR OSTEOPOROSIS

- **RANK ligand inhibitor**

  - **Indications:**
    - Treatment of postmenopausal women with osteoporosis at high risk for fracture
    - Treatment to increase bone mass in men with osteoporosis at high risk for fracture
    - Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture
    - Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer
    - Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

  Prolia (denosumab) is a human IgG2 monoclonal antibody with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

DENOSUMAB AS PROLIA

- **Warnings & Precautions:**
  - **Same Active Ingredient:** Patients receiving Prolia should not receive XGEVA®
  - **Hypersensitivity including anaphylactic reactions may occur. Discontinue permanently if a clinically significant reaction occurs**
  - **Hypocalcemia:** Must be corrected before initiating Prolia. May worsen, especially in patients with renal impairment. Adequately supplement patients with calcium and vitamin D
  - **Osteonecrosis of the jaw:** Has been reported with Prolia. Monitor for symptoms (5.4) Atypical femoral fractures have been reported. Evaluate patients with thigh or groin pain to rule out a femoral fracture
  - **Multiple vertebral fractures have been reported following Prolia discontinuation. Consider transitioning to another antiresorptive agent if Prolia is discontinued**
  - **Serious infections including skin infections:** May occur, including those leading to hospitalization. Advise patients to seek prompt medical attention if they develop signs or symptoms of infection, including cellulitis
  - **Dermatologic reactions:** Dermatitis, rashes, and eczema have been reported. Consider discontinuing Prolia if severe symptoms develop
  - **Severe bone, joint, muscle pain may occur. Discontinue if severe symptoms develop**
  - **Suppression of bone turnover:** Significant suppression has been demonstrated. Monitor for consequences of bone over-suppression

- **Adverse reactions:**
  - **Postmenopausal osteoporosis:** Most common adverse reactions (>5% and more common than placebo) were: back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Pancreatitis has been reported in clinical trials.
  - **Male osteoporosis:** Most common adverse reactions (>5% and more common than placebo) were: back pain, arthralgia, and nasopharyngitis
  - **Glucocorticoid-induced osteoporosis:** Most common adverse reactions (>3% and more common than active-control group) were: back pain, hypertension, bronchitis, and headache
  - **Bone loss due to hormone ablation for cancer:** Most common adverse reactions (>10% and more common than placebo) were: arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials

- **Postmenopausal osteoporosis:** Most common adverse reactions (>5% and more common than placebo) were: back pain, muscle pain, and cystitis. Pancreatitis has been reported in clinical trials.

- **Male osteoporosis:** Most common adverse reactions (>5% and more common than placebo) were: back pain, arthralgia, and nasopharyngitis

- **Glucocorticoid-induced osteoporosis:** Most common adverse reactions (>3% and more common than active-control group) were: back pain, hypertension, bronchitis, and headache

- **Bone loss due to hormone ablation for cancer:** Most common adverse reactions (>10% and more common than placebo) were: arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials

- **Serious infections including skin infections:** May occur, including those leading to hospitalization. Advise patients to seek prompt medical attention if they develop signs or symptoms of infection, including cellulitis

- **Dermatologic reactions:** Dermatitis, rashes, and eczema have been reported. Consider discontinuing Prolia if severe symptoms develop

- **Severe bone, joint, muscle pain may occur. Discontinue if severe symptoms develop**

- **Suppression of bone turnover:** Significant suppression has been demonstrated. Monitor for consequences of bone over-suppression
MONOCLONAL ANTIBODIES, 2016

- Tocilizumab (Actemra): WARNING: SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
- Adalimumab (Humira): WARNING: SEVERE INFECTIONS and MALIGNANCY SEVERE INFECTIONS
- Ocrelizumab (Ocrevus): WARNINGS and PRECAUTIONS: INFUSION REACTIONS; INFECTIONS; MALIGNANCIES
- Nevikumab (Nipovo): WARNINGS and PRECAUTIONS: IMMUNE-MEDIATED PNEUMONITIS, COLITIS, HEPATITIS, ENDOCRINOPATHIES, NEPHRITIS/RENAL DYSFUNCTION, SKIN ADVERSE REACTIONS, ENCEPHALITIS; INFUSION REACTIONS, HEPATIC INJURY INCLUDING AUTOIMMUNE HEPATITIS and OTHER IMMUNE-MEDIATED DISORDERS

- Alemtuzumab (Lemtrada): WARNING: AUTOIMMUNITY, INFUSION REACTIONS, and MALIGNANCIES
- Brodalumab (Skyta): WARNING: SUICIDAL IDEATION AND BEHAVIOR
- Golimumab (Simponi, Simponi Aria): WARNING: SEVERE INFECTIONS and MALIGNANCY
- Eculizumab (Soliris): WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
- Bevacizumab (Fulvyta): WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- Vedolizumab (Entyvio): WARNINGS and PRECAUTIONS: IMMUNE-MEDIATED REACTIONS; INFECTIONS; MALIGNANCIES
- Ipilimumab (Yervoy): WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS
- Durvalumab (Imfinzi): WARNINGS and PRECAUTIONS: IMMUNE-MEDIATED PNEUMONITIS, HEPATITIS, COLITIS, ENDOCRINOPATHIES, Nephritis; INFECTIONS, INFUSION-RELATED REACTIONS, EMBRYO-FETAL TOXICITIES
- Pembrolizumab (Keytruda): WARNINGS and PRECAUTIONS: IMMUNE-MEDIATED PNEUMONITIS, HEPATITIS, COLITIS, ENDOCRINOPATHIES, Nephritis; INFECTIONS, INFUSION-RELATED REACTIONS, SKIN ADVERSE REACTIONS, ENCEPHALITIS; INFUSION REACTIONS, OTHER IMMUNE-MEDIATED ADVERSE REACTIONS, EMBRYO-FETAL TOXICITIES; COMPLICATIONS OF AUTOLOGOUS HSCT AFTER KEYTRUDA

WHY IS THIS CE UNDER “ETHICS” INSTEAD OF PHARMACY?

- Case study
- Refusal to prescribe
- What we decided to do—together—instead
- Final results
- How that was received by my “peers” the next day...
- “First, Do No Harm”
- Personal story—not “my” case/patient
- Why families won’t sue

NATUROPATHIC PRINCIPLES

- First, do no harm
- Identify & treat the cause
- Treat the whole person
- Doctor as teacher
- The healing power of nature
- Prevention
- Wellness
IS YOUR BRAIN SOOOO FULL NOW?
Thank you for being here with me today.

Christie Fleetwood, ND, RPh