PSYCHIATRIC MEDICATIONS: PRESCRIPTION AND "ALTERNATIVE"

INTRODUCTION

Every several months a new psychotropic medication is released into the mental health market. It is a high stakes business. Many hundreds of millions of dollars are invested in research, development and marketing. Big name psychiatric professionals are enlisted to author articles in professional journals and crisscross the country, giving educational talks about the advantages of the newest drugs. No expense is spared in promotion - from glossy pullouts in professional journals to direct-to-consumer advertising in weekly news magazines. The potential payout is enormous - billions of dollars in revenue in one of the fastest growing specialty markets in the industry.

The "alternative" medication market is just as big. Presently, it is a $20,000,000,000 a year industry. More than 70% of people worldwide utilize non-prescription herbal, hormonal, and natural remedies for their mental health problems.

This booklet will help the reader sort through the hype and learn the facts about the new (and old) psychotropic and alternative medications. Every effort has been made to present a balanced and fair view of the risks, benefits, and side effects of these treatments.

Disclaimer:
The author is not on any pharmaceutical advisory boards and does not receive research support from the industry. Every effort has been made to assure there are no errors in this publication, but this guide should not be used as a sole source of information for diagnostic or treatment purposes.

18th Edition

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NEURONS AND NEUROTRANSMITTERS

Neurons are the specialized cells of communication in the brain. There are 100-200 billion neurons in the brain. Each has 1,000 - 20,000+ connections with other neurons. There are 200 trillion connections, a trillion connections in each cubic centimeter, firing 10 million billion times per second. During gestation, the fetus adds 250,000 neurons per minute. The cells then migrate to the appropriate place in the brain. This migration to the prefrontal cortex is the equivalent of a person walking from New York to California. By the fifth month, most neurons have reached their destination. Then cells that fire together wire together. During their teens, adolescents remove (prune) 100,000 synaptic connections/sec., making their brains more efficient and faster.

The vast majority of neurons are involved with managing bodily functions (blood pressure, breathing rate, hormone levels, etc.) Only a fraction of the brain is involved with thinking, feeling, and experiencing. All of our thoughts, moods, and behaviors originate from biochemical and electrical interactions in our brains.

Neurons communicate by way of more than 50 different chemicals called neurotransmitters. An electrical impulse causes the presynaptic membrane to release a neurotransmitter that binds to a postsynaptic membrane. The most common neurotransmitters are:

1) amino acids (20) Glycine, glutamate, aspartate are the most common. Glutamate is the primary excitatory transmitter. GABA, the primary inhibitory transmitter, is made from glutamate and an enzyme. It is one of the most widely distributed transmitters in the brain involving 40% of all synapses.

2) monoamines

a) catecholamines - epinephrine, norepinephrine, dopamine

b) indoleamines - tryptophan, serotonin, melatonin. These cell bodies are primarily in the brain stem and branch over the brain.

3) acetylcholine - nerve and muscle junctions. Acetylcholine also originates in a subcortical structure above the brain stem.

4) heterogeneous group - histamine, nitric oxide, neuropeptides such as endorphins, substance P and K, etc. These are primarily neuro-modulators.

Drugs affect neurotransmitters by:

1) affecting synthesis
2) interfering with storage of neurotransmitters
3) affecting release

4) inhibiting degradation
5) blocking access to receptors
6) modifying the internal messenger systems of the cell

It is fair to say that we do not know the specifics of how psychiatric medications affect emotions and cognition. It is far more complicated than simply modifying levels of neurotransmitters. Glial cells, the other prominent class of cells in the brain, are also under active investigation for their role in mental and neurological illness.

GENDER ISSUES

(Seeman M 2006, Novosolov F 2012, Spinelli M 2012, Jarde 2016) www.womensmentalhealth.org, www.toxnet.nlm.nih.gov)

Genetics, age, height, weight, lean-fat ratio, diet, exercise, concurrent disease, smoking, alcohol, and additional drugs can cause a ten-fold variability in the medication dosage needed for an effective response. Men and women differ in most of these characteristics.

Antipsychotics: Women respond better to antipsychotics during their first episode of illness. They require half as much medication for maintenance than men. Because women have higher body fat content, long acting injections can be given less frequently.

Anti-epileptic drugs (AED's): Polycystic ovary syndrome (PCOS) is a metabolic condition that occurs in 7-15% of reproductive-aged women. These women have elevated androgens, chronic anovulation, insulin resistance, elevated LDL's with low HDL's, and a 3x risk of endometrial cancer. (They do not necessarily have polycystic ovaries.) Women with epilepsy and women with bipolar disorder have a high risk of anovulatory disorders and PCOS.

Drugs that induce cytochrome P450 (phenytoin, carbamazepine, phenobarbital, oxcarbazepine) speed up the metabolism of oral contraceptives and increase the rate of failure 5x. Drugs that inhibit cytochrome P450 (valproate) slow the metabolism of contraceptives and increase the levels of ovarian and adrenal androgens, increasing the risk of PCOS. Gabapentin and lamotrigine do not alter cytochrome P450.

Some AED's have a higher risk of osteoporosis and fractures, even in men and children (phenobarbital, carbamazepine, valproate). They also affect lipid metabolism.

Pregnancy: There is no such thing as a drug that is "no risk" to the fetus. All psychoactive drugs pass through the placenta. All drugs are secreted in breast milk. The more a drug is studied, the riskier it is found

to be. Even acetaminophen has been linked to impaired neurodevelopment.

Pregnant women are not included in drug studies, so our data regarding pregnancy and psychotropic medications are retrospective and often poorly verified. Findings are seldom replicated and must be interpreted in the context of a 2-4% baseline rate of birth defects in the general population. A final complication is the effect of the mother's psychiatric illness on the fetus, which is known to be quite substantial.

In general, anti-epileptic drugs are especially dangerous to the fetus. Valproate is suspected of causing developmental delays in children in addition to birth defects. Antidepressants have not consistently been shown to cause serious problems that are distinct from the toxic effects of depression on the pregnancy. Lithium is associated with a small risk (.05% - 1.0%) of Ebstein's anomaly (heart defect.) Benzodiazepines are not strongly linked to a risk of birth defects, nor are the second-generation antipsychotics.

When prescribing medication to reproductive age women, remember that 50% of pregnancies in the US are unplanned. However, it is also important to remember that mental illness in the mother increases the risk of symptomatic mental illness in the child. Depression during pregnancy is the strongest predictor of postpartum depression in mothers. 15% of women with untreated depression during pregnancy attempt suicide. Depression during pregnancy is associated with negative pregnancy outcomes, including long-term cognitive problems for the child. "No treatment" for the mother is also risky for children (Hasser et al. 2006.)

PHARMACOGENETIC TESTING

It is now possible to test for genetic variations in the P450 system, and there are expectations that genetic testing will be able to predict therapeutic response to medicines, as well as prevent side effects due to variations in metabolism. There is some evidence that response to antipsychotic and antidepressant medicine is a heritable trait (Arranz M, Kapur S 2008.) No convincing systematic epidemiologic studies have been done to determine the extent to which this is true, however, and the influence of environmental factors such as diet, nicotine and alcohol use, and medication adherence dwarf any genetic effects. These tests are expensive ($350-$1,000) and their value for general screening purposes remains controversial (*Carlat Psychiatry Report* March 2017.)

TREATMENT ADHERENCE TO MEDICATION

Most treatment studies anticipate 80% adherence to the treatment regimen. Good adherence increases the likelihood of a good outcome by a factor of 2.88. Most doctors estimate that clients comply with treatment 95% of the time. Electronic monitoring indicates clients are compliant 47% of the time, and this declines as time goes by. In all cases, adherence to treatment is extremely difficult to measure accurately (Pratt S et al. 2006, Byerly M et al. 2007) Estimates of non-compliance rates in chronic illness:

Arthritis - 55-71%

Bipolar Disorder - 20-57%

Diabetes - 19-80%

Hypertension - 50% drop out at 1 year

Seizure disorders - 54-82%

Schizophrenia - 24-88% (55%) Adherence seems to be worse in younger clients, and African Americans. Atypical antipsychotics do not have much better adherence, although clients like them better (Valenstein M et al. 2004.)

Non-adherence to health behavior recommendations (lose weight, go to therapy, exercise) is twice the rate of non-adherence to medication. Depression interferes with adherence to either kind of treatment (Elbogen E et al. 2005.) Research shows that interventions to improve adherence need to be complex with a focus on enhancing client convenience, providing information, reinforcement and enlisting social support. Written materials are less effective than telephone, individual or group formats. A recurrent finding is that the doctor-patient relationship is a crucial variable in determining whether a patient continues in treatment – the more collaborative the better (Lin E 2007.) Unfortunately, even the most effective interventions have only a modest effect.

Nonadherence is either inadvertent or intentional, and different interventions are appropriate for each case. Using environmental supports in a program known as “cognitive adaptation training” may be useful for inadvertent nonadherence. This training includes signs, medication containers with alarms, single-dose containers, notebooks for recording side effects, etc. Cognitive-behavior therapy can be adapted for intentional nonadherence (Velligan D, Weiden P 2006.)

UNDERSTANDING DRUG RESEARCH

Most of the information we have about the efficacy of psychopharmacology comes from studies sponsored by pharmaceutical companies and promoted by doctors who are "sponsored" by those companies. Since an industry sponsored study is virtually always favorable for the drug being studied, and since studies that are not favorable to the drug do not get published (Baker C et al. 2003), it is necessary to be informed about the following in order to evaluate the findings:

How big was the study? (Look for >100 subjects)
How were the drugs dosed? (Look for standard dosing)
How long was the study? (The longer the better)
How were the outcomes defined? (Improvement or remission)
How were the dropouts accounted for?
Who sponsored the study?
Who authored the paper?
Who published the paper?

It is important to understand the difference between studies of "drug efficacy" and "drug effectiveness." Efficacy is the potential effectiveness of a drug under ideal conditions. These are the studies that the FDA requires in approving a drug. They involve random, "blinded", controlled trials, usually with a small number of patients, who are highly selected. Care is very expensive with weekly follow-up and multiple tests. Comorbid conditions are excluded. Compliance is required. The control group receives placebo treatment, or treatment that is recognized as less effective (outmoded) treatment. Efficacy establishes that a specific kind of patient, under ideal circumstances will respond in a certain way.

Effectiveness is the actual improvement in patient outcome under the usual conditions of treatment. Care is routine. Follow-up may be over years. Clients are typical with comorbid conditions. Care is diverse with no "blinding." Compliance is variable. Effectiveness looks to see how generalizeable the treatment is to many different patents under a variety of circumstances (Lagomasino I, et al. 2005). Clearly, both kinds of studies - efficacy to determine that the drug is really an active agent, and effectiveness to make sure it works with real people in the real world - are needed.

The most balanced sources of data about drug efficacy and effectiveness are either non-industry sponsored studies (hard to find), or non-industry sponsored meta-analyses of many studies (also hard to

find). Good meta-analyses use "effect size" statistical methods to determine the effectiveness of a specific drug. An effect size of 0.2 is small and signifies that 15% of patients had a greater improvement than the control group. This size effect would probably not be noticeable to a clinician. An effect size of 0.5 is medium and equates to 33% having greater improvement. An effect size of 0.8 is regarded as large and indicates 47% of the treatment group had a greater response to the studied drug.

Another popular statistical result is “number needed to treat” (NNT) or “number needed to harm” (NNH) from side effects. The NNT reflects how many patients need to take the drug before you see any difference from placebo or a different treatment. An NNT of 10, for instance, would mean that ten patients would have to take the drug before you noticed any difference from placebo - clearly, the lower the better. The NNT for adolescents taking newer antidepressant medications is 3. Any NNT above 10 is considered to be clinically insignificant. The opposite is true for NNH. The higher the better (Citrome L 2007.)

THE PLACEBO EFFECT

The placebo effect is improvement in health, often measurable and observable, that is not attributable to treatment. Although there are some who dispute an actual placebo effect, there seems to be consensus that placebos have real results. Placebos have been shown to successfully treat depression, pain, arthritis, hypertension, asthma, warts, colitis, insomnia, and other conditions. Placebos also cause negative effects, including vomiting, dizziness, fatigue, numbness, hives, rashes, tremor, and death (voodoo.) Placebo effect probably accounts for most of the benefit due to acupuncture, aromatherapy, homeopathy, many “alternative treatments”, and approximately 33% of the response to antidepressant medications.

Why an inert substance or fake surgery would be effective is not known, but there are several theories:

Psychological theory: People get better because they believe they will get better. Beliefs may affect our biochemistry (naltrexone can block a placebo’s pain-killing effects) and our behavior (there is a certain amount of socially and culturally based role-playing in being sick.) There is evidence from fMRI studies that the reward/expectation centers of the brain are activated and the threat perception areas are repressed during the placebo response (Medina J 2006.)

Nature taking its course theory: We often heal spontaneously if we do nothing at all. This can even happen with cancer and chronic diseases.

Process of treatment theory: Some believe that the physical response is not caused by the placebo, but by the process of administering it – the touching, caring, attention, and communication with a caregiver.

Client's expectations have a lot to do with what they experience. Inspiring confidence, displaying diplomas, providing a diagnosis, doing some kind of testing, writing a prescription, and seeing a client more frequently can provide strong placebo benefits to the treatment (Brown 2006.)

Interestingly, the placebo response can happen even if the subject does not know he is getting any treatment at all. Rats can experience a "conditioned" placebo response, as can humans. In one experiment, human subjects received cyclosporine, an immune suppressant in a flavored drink. Their immune system showed a transient decline. This decline happened later when the subjects were given the flavored drink without the cyclosporine. The conditioned and "expectation" placebo responses act through different mechanisms. Naloxone can block a placebo pain response only if it is an expected response, not if it is a conditioned (unconscious) response (Niemi M 2009.)

A very reasonable response to the placebo question is to conclude that there is not one placebo response, but many different kinds of placebo responses working in different ways – conditioning, expectation, biological activation, etc. The best way for clinicians to use the power of the placebo response is to:

1) Reduce uncertainty about treatment effects
2) Induce hope and optimism
3) Help the patient look for improvement and recognize positive changes

(Linden 2017)

ANTIDEPRESSANTS

Depression is a serious disorder of mood that involves feelings of sadness and emptiness, along with an inability to experience pleasure, that continues for an extended period of time. Antidepressants are used to treat depression, panic disorder, obsessive-compulsive disorder, bulimia, premenstrual dysphoric disorder, and chronic pain. In fact, antidepressants are broad-spectrum pain-relieving drugs – physical and

emotional – with efficacy in a range of conditions, including fibromyalgia and migraines (Carlat D 2012.)

The controversy regarding antidepressants revolves around how effective they are for depression. Efficacy studies (the standard well-controlled pharmaceutical company study) on close analysis generally fail to find any large differences between active drug and placebo, and suggest that the more severe the depression, the more likely that the patient will show benefit from an active drug (Carlat D 2012.) Other authors dispute these conclusions (Gibbons R 2012.)

The largest independently funded effectiveness (clinical) trial for depression is the Sequenced Treatment Alternatives to Relieve Depression (STAR*D). The conclusions that can be drawn from STAR*D are the following (Rush A, et al. 2008, Carlat D 2012):

1) Expect 30% of depressed clients to achieve remission with their first drug.
2) Relapse rates will be high, even after achieving full remission. Only 40% of the subjects will achieve sustained recovery.
3) Anxious features were prevalent in almost half of the participants.
4) No significant differences were found between medication and cognitive behavior therapy in the second phase, except medication acted faster.
5) Attrition was high. 25% of participants dropped out soon after their first visit. Only 2.6% continued through the 12-month trial without dropping out or relapsing.
6) There is no difference in any of the treatments offered in terms of efficacy.
7) Treating depression is hard!

Research indicates that the use of rating scales may significantly improve client care and adherence, and the more frequently clients are seen, the better they do (*Psychiatric Services*, 2009.)

Choosing an Antidepressant

In general, all antidepressants have equal efficacy, so most clinicians choose an antidepressant based on a number of factors, including prior response of family members, side effects, and cost. Research to date does not identify any biologic or genetic predictors (e.g. previous response or family response in the past) of sufficient usefulness to guide the choice of medication (Simon G, Perlis R 2010.)

Since antidepressant efficacy is not a significant factor in choosing among medications, other factors may be helpful in making the choice

Symptom Profiles (Carlat Jul/Aug 2017):

- Anxiety: an SSRI
- Insomnia: mirtazapine
- Irritability: an SSRI
- Lethargy: bupropion
- Poor appetite: mirtazapine
- Poor concentration: bupropion

Prominent side effects (Gartlehner G, et al. 2008):

- Mirtazapine has the highest weight gain. Paroxetine in also high.
- Venlafaxine has the highest rate of nausea and vomiting.
- Paroxetine and venlafaxine have the highest discontinuation rates.
- Paroxetine has the highest rate of sexual side effects.
- Bupropion has the lowest rate of sexual dysfunction.
- Sertraline has the highest rate of diarrhea.

Other Risks (Carlat Jul/Aug 2017):

- Lethal overdose: the tricyclic antidepressants
- Drug interactions: MAOI's, paroxetine, fluvoxamine
- Prolonged QT interval: citalopram >40mg, tricyclics
- Discontinuation syndrome: venlafaxine, desvenlafaxine, duloxetine, paroxetine, fluvoxamine
- Suicide risk: Since the warning was first issued by the FDA that antidepressants may increase suicide risk in young people up to the age of 24, there have been a number of studies that challenge this finding. Untreated depression poses a far greater risk of suicide death than antidepressants, but everyone who is started on an antidepressant should be monitored closely for the appearance of suicidal ideation, agitation, and irritability, and be sure that this risk is discussed during the obtaining of informed consent (Winters N 2006.)
- Serotonin syndrome: SSRI's + SNRI's + buspirone, lithium, MAOI's
- Bleeding risk: seen with SSRI's or SNRI's + aspirin, NSAIDs anticoagulants

Antidepressants for specific groups (Connolly K, Shah D 2009)

- Uncomplicated major depression: bupropion

Depression with anxiety: sertraline
Depression with pain: venlafaxine, tricyclic
Depression, insomnia, low weight: mirtazapine, paroxetine
Depression and substance abuse: bupropion for smoking
Depression, osteoporosis, bleeding: bupropion, tricyclics
Depression, drug-drug interactions: citalopram, escitalopram, sertraline
Children: fluoxetine
Adolescents: fluoxetine, escitalopram (avoid paroxetine, venlafaxine, mirtazapine, nefazodone, tricyclics)
Older adults: citalopram, sertraline

At least 50% of clients who respond to antidepressants will respond in the first few days – certainly the first two weeks. The belief that antidepressants need at least two weeks to work is not accurate for many clients and is based on confusion between maximal clinical response versus initial clinical response, and concerns about placebo/drug separation (Taylor M, et al. 2006, Posternak M, Zimmerman M 2005.) Finally, there us no reason to believe that starting with a combination of two antidepressants is better than starting with a single antidepressant (Rush A et al. 2011.)

The Nonpharmacology of Pharmacology

Several analyses have determined that the response to antidepressants is largely determined by factors other than the antidepressant. By utilizing the power of the placebo effect as well as techniques to improve treatment adherence, all mental health clinicians, whether prescribers or not, can improve the efficacy of treatment. Some suggestions include (Mintz D 2012):

1) Promote a treatment alliance and shared decision making
2) Explore patient ambivalence toward medication (fears of dependence and loss of control, secondary gain from being depressed, etc.)
3) Focus on promoting health, not simply reducing depression

Stopping the Medication

Stopping an antidepressant suddenly increases the risk of depression relapse (Baldessarini R, et al. 2010.) All antidepressants, particularly SSRI's can cause withdrawal symptoms, including neurosensory (vertigo, parathesia, myalgia), neuromotor (tremor, myoclonus, ataxia),

gastrointestinal (nausea, vomiting, diarrhea), psychiatric (anxiety, depression, suicidality, irritability), and vasomotor (flushing, sweating.) Antidepressants should be tapered gradually (Shelton R 2006.)

A) Selective Serotonin Reuptake Inhibitors (SSRI)

citalopram (Celexa)
escitalopram (Lexapro)
fluoxetine (Prozac, Prozac Weekly, Sarafem)
fluvoxamine (Luvox, Luvox CR)
paroxetine (Brisdelle, Paxil, Paxil CR, Pexeva)
sertraline (Zoloft)

Advantages:

1) No anticholinergic, sedative, or orthostatic side effects
2) Safe in overdose
3) Easy to dose
4) Citalopram is the only SSRI with cardiac warnings (above 40 mg/day) and this is controversial (Bird S, et al. 2014)
5) Fluoxetine is available in a once weekly capsule
6) Sertraline has the best balance of side effects and efficacy for older adults (*J Am Geriatric Soc* May 2015)
7) Fluoxetine is the only SSRI to consistently perform better than placebo in young people (*Lancet* June 8, 2016)

Disadvantages:

1) Usually cause sexual dysfunction
2) May cause insomnia, agitation, anxiety
3) May cause nausea, vomiting, diarrhea
4) May interact with other drugs – serotonin syndrome when combined with MAOI, lithium, buspirone (excitement, rigidity, hyperthermia, coma, etc.)
5) Serotonin Discontinuation Syndrome – incoordination, aches, runny nose, n/v/d, sleep disturbance, tremor, irritability, etc. for up to 3 weeks.
6) Paroxetine is ineffective in children and adolescents, and carries a warning of birth defects
7) SSRI's may increase somatic anxiety
8) May increase the risk of osteoporosis, but only in older women (*NEJM Journal Watch: Psych* Nov 2013)

B) Atypical/Mixed Neurotransmitter Actions

bupropion (Wellbutrin IR, SR and XL, Forfivo XL, Aplenzin, Budeprion, Bupropan, Zyban) (serotonin, dopamine, and norepinephrine receptor effects at high doses)

Advantages:

1) Safe in overdose
2) No anticholinergic, sedation, orthostatic side effects
3) Safe for the heart
4) Less likely to cause weight gain and best choice to reduce the risk of sexual dysfunction
5) May be useful in ADHD and smoking cessation
6) May be a good choice for depression with fatigue and poor concentration

Disadvantages:

1) Causes seizures, agitation, insomnia, nausea at higher doses
2) Can give false positive urine screen for amphetamines

desvenlafaxine (Pristiq, Khedezla) (serotonin, dopamine, and norepinephrine)

Advantages:

1) As a metabolite of venlafaxine, the advantages are the same as above

Disadvantages:

1) The higher the dose, the less effective the medication
2) More nausea than venlafaxine
3) Expensive
4) No advantage over venlafaxine. The EU did not approve it.

duloxetine (Cymbalta) (serotonin and norepinephrine effects)

Advantages:

1) Dual indications for depression and for diabetic peripheral neuropathy, fibromyalgia, chronic musculoskeletal pain
2) Studies do not demonstrate any advantage over venlafaxine. Patients rend to discontinue it due to side effects more than they do venlafaxine. Hepatotoxicity with duloxetine is a problem.

Disadvantages:

1) Side effects seem to be similar to SSRI's
2) Hepatotoxicity (hepatitis, jaundice)
3) Nausea, sleep disturbance, appetite decrease, urinary hesitation

levomilnacipran (Fetzima) (SNRI)
Advantages:
1) In the same class as duloxetine, venlafaxine, and desvenlafaxine, but more selective for norepinephrine than serotonin at lower doses. That would make a difference if you believe in norepinephrine deficit depression (poor concentration, lack of energy, cognitive impairment) vs. serotonin deficit depression (anxiety, appetite disturbance, suicidality.)
Disadvantages:
1) No clear evidence of superiority over any other SNRI
2) Expensive
3) Nausea, vomiting, urinary hesitation
4) Dose needs to be titrated

mirtazapine (Remeron) (norepinephrine and serotonin effects)
Advantages:
1) Few anticholinergic or serotonergic side effects (nervousness, GI problems, sexual dysfunction)
2) Safe in overdose
3) No interaction with other drugs
4) It may have a faster onset of action than other antidepressants
Disadvantages:
1) Sedation (may be a plus with anxiety or insomnia)
2) Increased appetite and weight gain (may be a plus in cancer patients or elderly)

trazodone (Desyrel, Trialodine, Oleptro (extended release) (serotonin effects)
Advantages:
1) Sedation helps sleep
2) Safe in overdose
3) No anticholinergic side effects but does cause orthostasis.
4) Rarely used as an antidepressant. Mostly used for sleep
5) May cause false positive urine test for MDMA
Disadvantages:
1) Sedation
2) Low blood pressure
3) Priapism (painful, prolonged erections)
4) GI problems

venlafaxine (Effexor, Effexor XR) (serotonin, dopamine, and norepinephrine effects at high doses)
Advantages:
1) No anticholinergic, sedative, orthostatic effects
2) Safe in overdose
3) Safe for the heart
4) Age does not affect plasma levels
5) Available in an extended release preparation
6) May cause false positive urine for PCP
Disadvantages:
1) May increase blood pressure
2) May have some side effects similar to SSRI's
3) Risk of fatal overdose may be highest of new antidepressants

vilazodone (Viibryd) (SSRI and 5-HT1A receptor partial agonist)
Advantages:
1) Is a partial agonist like buspirone so it may have some additional efficacy for anxiety
2) It is possible it may have reduced sexual side effects, but this is unproven
Disadvantages:
1) Expensive
2) Efficacy has not been shown to be better than any other SSRI
3) Slow titration schedule, must be taken with food

vortioxetine (Trintellix) (SSRI, 5HT1A agonist, 5HT3A and 5HT7 antagonist)
Advantages:
1) Distinct biochemical profile
2) As effective as venlafaxine, but less effective than duloxetine in one study. It has slightly fewer sexual side effects than duloxetine, maybe fewer than escitalopram
3) Possibly more "pro-cognitive" due to 5-HT7 properties, but this has not been proven in humans
4) No significant weight gain
Disadvantages:
1) Dose related nausea
2) Expensive

C) Tricyclic Antidepressants (TCA's)

amitriptyline (Elavil)
amoxapine (Asendin)
clomipramine (Anafranil)
desipramine (Norpramin)
doxepin (Adapin, Sinequan, Silenor)
imipramine (Tofranil)
maprotiline (Ludiomil)
nortriptyline (Pamelor)
protriptyline (Vivactil)
trimipramine (Surmontil)

Advantages:

1) Inexpensive
2) Help with sleep because they are sedating
3) They may work better than newer antidepressants in some cases – in cancer to provide weight gain and pain relief, in Parkinson's because of no EPSE's, in treatment resistant depression
4) Clomipramine is used for obsessive-compulsive disorder

Disadvantages:

1) Easily fatal in overdose
2) Significant side effects - anticholinergic, sedation, orthostasis
3) Effect heart conduction
4) Hard to dose
5) No efficacy in children and adolescents

D) Monoamine Oxidase Inhibitors (MAOI's)

isocarboxazid (Marplan)
phenelzine (Nardil)
tranylcypromine (Parnate)
transdermal selegiline (EmSam)

Advantages:

1) May help some people who don't respond to other antidepressants
2) Transdermal selegiline at 6 mg. does not require dietary restrictions

Disadvantages:

1) Have to follow a special diet or they may cause a stroke
2) Can cause dizziness/orthostatic hypotension
3) May be fatal with other drugs

4) Fatal in overdose

The MAOI Diet (Carlatt D, 2006)

Tyramine is an amino acid that displaces norepinephrine from nerve endings, sending free norepinephrine into the blood stream causing vasoconstriction and an increase in blood pressure. Normally, monoamine oxidase in our GI tracts and liver metabolizes the tyramine. MAOI's prevent the breakdown of tyramine in the gut and also inhibit the breakdown of the excess norepinephrine. This can put a patient who is taking an MAOI at risk for a hypertensive crisis if they get an excessive amount of tyramine in their diet. Foods that have a lot of tyramine are those that have a lot of amino acids (protein) and those with a lot of bacteria (which converts tyrosine to tyramine.)

Foods to avoid on the MAOI diet:

- Aged cheese (cheddar, fontina, brie, blue, camembert munster, Swiss)
- Tap beer
- Fava beans
- Sauerkraut
- Aged meats (air-dried sausage, pastrami, salami, bologna, pepperoni)

Foods that are risky

- Tofu
- Soy sauce
- Miso soup

Foods that are safe

- Fresh cheese (mozzarella, American, cottage, ricotta, cream cheese)
- Alcohol, including red wine (except tap beer)
- Chocolate
- Coffee

Antidepressants and Pregnancy

Antidepressants probably do not cause birth defects, although there is debate about paroxetine, which carries an FDA warning. Antidepressants may cause premature birth, low birth weight and miscarriage, although the data to date is very contradictory and incomplete and does not yield enough information to know how significant these risks are (Nobleza D 2010.) A recent study showed that untreated depression and continuous SSRI exposure in depressed pregnant women both resulted in preterm birth rates exceeding 20% (Wisner K, et al. 2009.) More commonly, as many as 30% of newborns with third trimester exposure show transient withdrawal symptoms – lack of crying, increased muscle tone,

irritability, poor sleep. This must be balanced by the high risk of depressive relapse for mothers who are taken off their antidepressants during pregnancy. Health and emotional risks are high for mothers and children when the mother is depressed (Pies R 2006.) In general, sertraline may be the best choice during pregnancy (*BMJ* 2015.) Paroxetine is a bad choice. The American Psychiatric Association and the American College of ObGyn have issued guidelines that advise using antidepressants with women with moderate to severe symptoms, women with a history of severe or recurrent depression, women with significant comorbidities, or women who have not responded to psychotherapy in the past.

For information regarding breastfeeding, please see the following websites: www.motherisk.org and the LactMed database at the National Library of Medicine.

Lab Work (Carlat D 2007)

SSRI's: none in general, but watch out for bleeding, hyponatremia and osteoporosis in older adults

Venlafaxine XR: periodic blood pressure check, especially at high doses

Duloxetine: alanine transaminase (ALT) at some point after starting

Tricyclic antidepressants: ECG in patients with pre-existing cardiac disease

Phenelzine: liver function tests

Adherence with Antidepressant Treatment

It is estimated that10% of patients who are prescribed antidepressants never fill the prescription, 16% stop first week, 41% within 2 weeks, 59% in 3 weeks, 68% in 4 weeks. The following instructions to patients may increase adherence:

1) take the pills daily
2) the antidepressant won't work for 2-4 weeks
3) continue taking it even when you feel better
4) don't stop without talking to your doctor
5) feel free to call your doctor to talk about side effects or problems

ANTIPSYCHOTICS

Psychosis involves bizarre thinking and behavior that is out of touch with reality. Antipsychotics are used to treat disorganized thinking and hallucinations in people with schizophrenia, mania, traumatic head

injuries, delusional depression, and dementia. Sometimes they are used to sedate aggressive patients. (Generally, this is not acceptable practice because these drugs have significant side effects. There are better ways to sedate people.) Antipsychotic drugs can calm someone down within an hour. The antipsychotic thought clearing action of the drug may take place over the next few weeks to six months if you continue to give it. Monitoring blood levels is not generally required. Clinicians go by clinical response. Finally, a large Medicaid study (*JAMA Psych* Aug 17, 2016) failed to find that antipsychotics in the first trimester led to birth defects.

FIRST GENERATION (TYPICAL) ANTIPSYCHOTICS (FGA's)

FGA's have very similar actions and side effects. They are all efficacious in treating the positive symptoms of psychosis - hallucinations, delusions, and disordered thinking. They may have serious side effects including:

Extra-pyramidal side effects (EPSE's) - tremors, muscle spasms, slow movements, rigidity (like Parkinson's disease), restlessness.

Tardive dyskinesia - slow movements of the body, lip smacking, tongue movements. 5.3%/year, 60% after 10 years with typicals. 0.5%/year, ? after 10 years with atypicals.

Neuroleptic malignant syndrome (NMS) - potentially fatal high fever and rigidity

chlorpromazine (Thorazine)
haloperidol (Haldol)
fluphenazine (Prolixin)
mesoridazine (Serentil)
molindone (Moban)
perphenazine (Trilafon)
prochlorperazine (Compazine)
thiothixine (Navane)
trifluoperazine (Stelazine)

The primary reasons for using the first-generation antipsychotics are: 1) They're inexpensive 2) They've worked in the past for a particular client 3) Client preference

Side effect medication: These drugs are used to treat EPSE's. There is ongoing controversy as to whether these medications should be started automatically when a patient is at risk for EPSE's or wait until the symptoms develop. Sometimes they can be abused because they can cause an altered state of consciousness in high doses. They also can cause anticholinergic side effects that can further compromise cognitive functions in people with schizophrenia.

amantadine (Gocovri, Symmetrel)
benztropine (Cogentin)
trihexyphenidyl (Artane)

SECOND GENERATION (ATYPICAL) ANTIPSYCHOTICS

Antipsychotics developed after 1990 are called atypical antipsychotics because they act on different neuroreceptor sites than the first-generation antipsychotics. They differ from the FGA's by having a wider range of active sites in the brain. They have fewer movement side effects. They also seem to have mood stabilizing effects that the FGA's do not have. The main reason for using these medications is that they have different side effects than the FGA's and patients tolerate them better. Patients feel less anxious and depressed, although adherence to treatment is not necessarily better. SGA's have less risk of tardive dyskinesia. Unfortunately, some SGA's cause major weight gain, problems with glucose and lipid metabolism, increased prolactin, sexual dysfunction, sedation, and cardiovascular problems.

Weight Gain/ Metabolic Syndrome: Certain SGA's increase the risk for metabolic syndrome - increased weight, diabetes, and increased serum cholesterol. Monitoring recommendations are:

A) Metabolically "dirty" SGA's (olanzapine, clozapine, risperidone, quetiapine): determine BMI at baseline, once a month for 3 months, then every 3 months. Baseline fasting glucose, at 4 months, then yearly. Baseline lipids, at 3 months, then every 2 years
B) Metabolically "clean" SGA's (aripiprazole, lurasidone, pimavanserin, ziprasidone): baseline weight, at 6 months, then yearly. Baseline glucose and yearly. Fasting lipids every 2 years

Depression: Aripiprazole and quetiapine have been approved for use as an augmenter of antidepressants for treatment resistant depression. A review of available studies indicates that many SGA's may provide a

small boost as adjunctive antidepressants, but, of course, with side effects (Spielmans G. 2009.)

Efficacy: Three studies looking at the relative effectiveness of FGA's and SGA's have consistently failed to find any antipsychotic benefit for the SGA's. Even the side effect benefit disappears at low doses of first generation agents. The limitations of the SGA's have also been demonstrated in the TEOSS results in adolescents and children. In this study, neither risperidone or olanzapine showed any advantage over an FGA and showed significant more weight gain and metabolic problems (Sikich L, et al 2008.) The following differences are seen in comparison studies (Gelenberg 2009):

Clozapine, olanzapine and risperidone are slightly more efficacious than the other antipsychotics, in that order.

Clozapine, olanzapine, aripiprazole and quetiapine are better for depressive symptoms than FGA's.

Clozapine causes the most sedation, and clozapine and olanzapine are most likely to cause weight gain and glucose/lipid abnormalities.

Long-acting injectables: Prolixin Decanoate, Haldol Decanoate, Abilify Maintena, Aristada, Zyprexa Relprevv, Invega Sustenna, Invega Trinza, Risperdal Consta

Other issues: Higher mortality rate in geriatric patients with dementia-related psychosis, stroke/TIA risk in geriatric patients with dementia-related psychosis, neuroleptic malignant syndrome risk with all antipsychotics.

Side Effect Table (Puzantian T, Carlat D 2018)

	Wgt Gain	**EPS/Aka**	**QT+**	**Sedation**
Aripiprazole	Low	High	Low	Low
Asenapine	Moderate	Moderate	Low	Low/moderate
Brexpiprazole	Moderate	High	Low	Low
Cariprazine	Moderate	Moderate	Low	Low/moderate
Clozapine	High	Low	Low	High
Iloperidone	Moderate	Low	Moderate	Low
Lurasidone	Low	Moderate	Low	Low/moderate
Olanzapine	High	Low	Low	Moderate

Paliperidone	Moderate	High	Moderate	Low
Pimvanserin	Low	Low	Low	Low
Quetiapine	Moderate	Low	Moderate	Moderate
Risperidone	Moderate	High	Low	Low
Ziprasidone	Low	Low	High	Moderate

aripiprazole (Abilify, Abilify Maintena, Abilify MyCite, Aristrada)

Advantages:

1) Unique mechanism of action - partial agonist
2) Few side effects
3) Abilify Maintena is an injection that is given monthly, as is Aristada
4) Abilify MyCite has an embedded ingestible sensor to track adherence

Disadvantages:

1) Lacks sedation in use with acutely agitated patients
2) May not be as effective as other antipsychotics
3) Highest risk of akathisia among the SGA's.

asenapine (Saphris)

Advantages:

1) Allows sublingual dosing, black cherry flavor

Disadvantages:

1) Requires sublingual dosing
2) Weight gain
3) Sedation, dizziness
4) Oral numbness, potential for an allergic reaction

brexipiprazole (Rexulti)

Advantages:

1) Developed to replace aripiprazole when it went off patent, with all its advantages and disadvantages

Disadvantages:

1) Very expensive at this point

cariprazine (Vraylor)

Advantages:

1) Most recently approved SGA.
2) Manufacturer claims it has efficacy for negative symptoms, but this is not proven clinically yet.

Disadvantages:
1) More EPS and akasthisia than most SGA's.
2) Weight gain
3) Expensive

clozapine (Clozaril, FazaClo, Versacloz)
loxapine (Loxitane, Adasuve oral inhalation)
Advantages:
1) Clozapine has been a miracle drug for some patients and has the strongest effect size (0.49 - 0.68) of any drug compared to haloperidol in non-drug company sponsored reviews.
2) Clozapine does not cause tardive dyskinesia
3) Clozapine has a protective effect against suicide
4) FazaClo is orally disintegrating, Versacloz is an oral suspension
5) Loxapine is structurally related to clozapine. The inhaled version can treat agitation quickly without a shot.
Disadvantages:
1) Clozapine can cause agranulocytosis (1% incidence, 3% of that group die), and requires weekly blood test
2) Seizures possible at doses over 600 mg.
3) Clozapine is strongly anticholinergic and causes sedation
4) Clozapine causes significant weight gain
5) Inhaled loxapine has a risk of bronchospasm

iloperidone (Fanapt)
Advantages:
1) None to speak of
Disadvantages:
1) Twice a day dosing
2) Needs seven-day titration
3) QT prolongation, avoid in patients with cardiac history
4) Dizziness and orthostatic hypotension
5) Weight gain
6) May be less efficacious than other antipsychotics

lurasidone (Latuda)
Advantages:
1) No histamine effects, so less weight gain
2) Also approved for bipolar depression

Disadvantages:
1) Sedation, akathisia, EPS
2) Must take with food, at least 350 calories
3) Potential for drug interactions

olanzapine (Zyprexa, Relprevv, Symbyax with fluoxetine)

Advantages:
1) Rapid calming action for agitated patients
2) Had the lowest discontinuation rate in the CATIE study
3) Has a long-acting injection (Relprevv) and orally disintegrating form
Disadvantages:
1) Causes significant increased blood glucose, cholesterol/lipids, weight gain
2) Somnolence, dry mouth
3 Relprevv (long acting injection) has a potentially serious side effect – post injection delirium/sedation syndrome. It requires that the prescriber, healthcare facility, and pharmacy enroll in a Patient Care Program, and the patient must be observed for 3 hours post injection.

paliperidone (Invega, Invega Sustenna, Invega Trinza)

Advantages:
1) Preparation of metabolite of risperidone in an extended release form
2) Metabolized in the kidneys, so it has fewer potential drug interactions than risperidone
3) Available a long-acting injection, Sustenna, given every month or Trinza every 3 months
Disadvantages:
1) More expensive than risperidone for little benefit (fewer drug interactions)
2) Akathisia, EPS, tremor, somnolence, hyperprolactinemia, QT prolongation

pimavanserin (Nuplazid)

Advantages:
1) Approved for treatment of the hallucinations and delusions of later stage Parkinson's. It has no effect on dopamine receptors
2) No weight gain
Disadvantages:
1) Nausea, edema, confusion

quetiapine (Seroquel, Seroquel XR)
Advantages:
1) Does not seem to cause tardive dyskinesia
2) May have significant mood stabilizing effects
Disadvantages:
1) Twice a day dosing
2) No IM or long acting form
3) Moderate weight gain
4) Somnolence, dizziness

risperidone (Risperdal, Risperdal M-Tab, Risperdal Consta)
Advantages:
1) Few side effects at low doses
2) Long acting shot (Consta) given every two weeks, also comes as a liquid and rapidly dissolving pill (M-Tab)
3) Small effect size advantage (0.06 - 0.25) over haloperidol in non-industry sponsored meta-analyses.
Disadvantages:
1) Prolactin increase, EPS, anxiety
2) Acts like a typical antipsychotic at doses over 6 mg/day with movement side effects
3) Consta requires that a powder be refrigerated and mixed just before injection. It also requires a 3-week oral medication overlap when treatment is started.

ziprasidone (Geodon)
Advantages:
1) Available as IM injection
2) Little weight gain
Disadvantages:
1) Twice a day dosing, dizziness, somnolence
2) Can prolong the QTc interval
3) Requires dosage titration

ANTI-ANXIETY MEDICATIONS

These medications are used to treat anxiety, insomnia, panic attacks, stop seizures, relax muscle spasms, treat alcohol withdrawal, and sometimes treat the side effects from antipsychotics.

Benzodiazepines - The medications in this class are all very similar, differing only in how fast and how long they work. Some are marketed as muscle relaxants, some as sleeping pills, some as tranquilizers. The differences are primarily marketing. 87% of prescriptions for benzodiazepines are written by providers who are not psychiatrists (*Psychiatric Services* 2009.).

Whether or not benzodiazepines cause cognitive side effects (verbal learning, speed of thinking, etc.) is quite controversial. A recent meta-analysis concluded that they do cause cognitive dysfunction during treatment, and that while cognitive function improves after the benzodiazepine is discontinued, it does not return to the level of functioning in control groups that did not take benzodiazepines (Stewart S 2005.)

alprazolam (Xanax, Xanax XR, Niravam orally disintegrating)
Bars, Z-Bars, Zannies, Footballs, Blues, Blue Footballs
chlordiazepoxide (Librium)
clonazepam (Klonopin, Klonopin Wafers)
K-pins
diazepam (Valium)
mother's little helper, little yellow pill
lorazepam (Ativan)
oxazepam (Serax)

Advantages:
1) Very safe in overdose
2) Generally, they work quickly
3) Medication compliance is always good

Disadvantages:
1) All cause tolerance, dependence, and, in some cases, addiction
2) Sedating, with dangerous interactions with other sedatives
3) Can cause a similar impairment to being drunk - ataxia, slurred speech, poor judgement, etc.

Fast onset: midazolam, diazepam, chlorazepate, flurazepam
Intermediate onset: chlordiazepoxide, alprazolam, lorazepam, triazolam
Slow onset: oxazepam, temazepam, clonazepam, prazepam
Physical dependence onset parameters:

Diazepam – 15 mg. for 90 days
Alprazolam – 1.5 mg. for 45 days
Lorazapam – 6 mg. for 60 days

Withdrawal: anxiety, poor concentration, muscle pain, perceptual disturbances, seizures

Addiction: involves preoccupation with acquiring the drug, compulsive use, and relapse despite adverse consequences. Past addicts are the highest risk group. Drug preference studies show that addicts prefer alprazolam>diazepam>oxazepam. Most users do not abuse benzodiazepines.

There is a warning from the FDA about the dangers of combining benzodiazepines with opiates due to the risk of respiratory depression and death.

Successful tapering of benzodiazepines must be done very slowly. If done slowly enough, every client can complete a taper, although everyone will feel worse each time the drug is lowered. Clients expect they are going to feel terrible when the taper is complete, but virtually everyone feels better off the drug. They don't feel as sedated. They don't feel as clouded in their thought processes.

Antihistamines - Primarily these are sedatives. They don't relieve anxiety so much as put you to sleep. But they can be used to treat side effects from the antipsychotics.

diphenhydramine (Benadryl)
hydroxyzine (Atarax, Vistaril)

buspirone (Buspar)

Buspirone has a different mechanism of action than the benzodiazepines and requires more patience in the prescriber and client. The anti-anxiety effect gradually builds over a period of weeks, and is quite subtle, compared to the benzodiazepines.

gabapentin (Neurontin Gralise, Horizant)

Gabapentin is an anticonvulsant that is sometimes used as a non-addicting medication for anxiety. It is approved for neuropathic pain and restless leg syndrome. Side effects are primarily dizziness and weight gain.

SLEEPING MEDICATIONS

Treating insomnia is a major aspect of primary care medicine. Until the 1960's, barbiturates were the primary pharmacological agent used for sleep. They were easily abused and had significant withdrawal symptoms. They were also quite dangerous. From 1970 until the last few years, the benzodiazepines were the treatment of choice for the pharmacotherapy of insomnia. Today, zolpidem, a selective GABA receptor agonist, has become one of the most prescribed drugs in the world. These non-benzodiazepine GABA medications do not have any anxiolytic activity or muscle relaxant effects, and probably have less loss of efficacy over time than the traditional benzodiazepines. There are reports of abuse, but extremely large doses are required for a "high." They do carry an FDA warning for the side effect of "complex behavior" – sleep driving, eating, etc. while "asleep."

In 2007, a large NIH sponsored meta-analysis concluded that sleeping medication will reduce sleep latency by about 30 minutes: 12.8 minutes due to the medication and 17.2 minutes due to placebo effect. Total sleep time will be increased by only 11.4 minutes. Several research studies have shown that CBT is as effective as medications and has a more sustained benefit (*Carlat Report* April 2013.) A 2016 study reported that sleep medications provide an improvement in sleep, but not a cure for insomnia (*Sleep* Dec 16, 2016.)

Benzodiazepines marketed for sleep

Estazolam (ProSom, Eurodin, Nuctalon)
flurazepam (Dalmane): Long half-life leads to daytime grogginess
quazepam (Doral, Dormalin)
temazepam (Restoril): Short half-life makes this a first line benzodiazepine hypnotic
triazolam (Halcion): Banned in the UK and Brazil for frequency of severe psychiatric side effects and anterograde amnesia

Non-benzodiazepine GABA receptor agonists

eszopiclone (Lunesta)
No advantages over the others in this class, and with a longer half-life, it is more likely to cause daytime impairment. 40% of users experience a sustained unpleasant metallic taste.
zolpidem (Ambien, Ambien CR, Edluar sublingual, Zolpimist, Intermezzo low dose)

Safe, effective, popular. Now available as a generic and as an extended release.

zaleplon (Sonata)
Very short half-life – can be taken even in the middle of the night without daytime effects. Not good for sleep maintenance.

Novel mechanisms

ramelteon (Rozerem) (melatonin subtype)
No abuse potential, good choice for drug abusers and the elderly

suvorexant (Belsomra) (orexin antagonist) Since it appears that much insomnia is due to hyper-arousal, it is hoped that targeting this neuro-system may increase efficacy in treating insomnia. This medication shows daytime somnolence as its main side effect. Efficacy is not clear.

MOOD STABILIZERS

Mood stabilizers are used in the treatment of manic-depression (bipolar disorder) and schizoaffective disorder. Sometimes they are used in addition to antidepressants or antipsychotics in the hopes that they will make the primary medicine work better in patients who have very labile moods. In treating bipolar disorder, there are three actions to be considered for a drug: 1) Does it treat bipolar mania? 2) Does it treat bipolar depression? 3) Does it act prophylactically to prevent mania and/or depression?

The NIMH funded Systematic Treatment Enhancement Program for Bipolar Disorder (STEP BD) was a 5-year effectiveness study of 4,360 patients. The data indicate that after two years of excellent treatment 58% of clients achieve full recovery, but ~50% will experience a relapse, 72% to depression. Treating bipolar illness is hard (Perlis R, et al. 2006.).

lithium (Lithobid, Eskalith CR, lithium citrate oral solution) -
The time-honored treatment for manic-depression, lithium seems to have a suicide reducing effect that the other mood stabilizers do not. People don't like to take it because it makes them thirsty and have to urinate a lot (35%), causes memory problems (28%), tremor (27%), weight gain (19%), and gives them a metallic taste in their mouth. It can be toxic to the kidneys and the thyroid. It is dosed according to blood levels. If a person becomes dehydrated, or takes certain medicine, the lithium level rises. The result is vomiting and diarrhea, confusion, coarse tremor,

muscle twitching, slurred speech, and seizures. This requires emergency medical attention. Stopping lithium suddenly may cause a relapse and an increase in suicidality.

Antiepileptic Drugs

The FDA has issued a warning that patients who take antiepileptic drugs have twice the risk of suicidal behavior or ideation compared with patients given placebo. This is quite similar to the warning included for young people and antidepressants.

carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR, Teril oral solution) - An anticonvulsant medication that has been used as a second choice for manic-depression for patients who could not tolerate lithium, carbamazepine requires blood levels, is sedating, and can cause anemia and liver problems. It reduces the levels of benzodiazepines, haloperidol and olanzapine as much as 50%! Too much carbamazepine will cause sedation and lack of coordination. Don't use with oral contraceptives or clozapine. Only Equetro is FDA approved for bipolar disorder.

divalproex sodium (Depakote, Depakene oral liquid, Depakote sprinkles, Depakote ER) - An anticonvulsant medication that is used for mania in bipolar disorder and its variants, but the evidence that it works to prevent depression is not convincing. It generally has fewer noticeable side effects than lithium and patients like it better. It can cause GI problems, pancreatitis, liver problems, birth defects, decrease in platelets, and hair loss. There is some evidence that it may provide prophylaxis for new episodes Patients will require a higher dose with the extended release preparation. This medication does not work with bipolar children and adolescents.

lamotrigine (Lamictal, Lamictal CD chewable, Lamictal orally disintegrating, Lamictal XR) - Now approved for psychiatric treatment, lamotrigine is an anticonvulsant which shows moderate antidepressant action. It may be prophylactic for bipolar episodes, especially for depression. There is no good evidence for the treatment of mania. Dizziness, diplopia, vomiting, and rash are most common side effects and are generally mild. Don't use in patients under 16 and always

discontinue if patients get a rash. It needs to be increased slowly. Don't use with valproate in order to reduce chance of rash.

oxcarbazepine (Trileptal, Oxtellar XR) – Oxcarbazepine is an antiseizure medication similar to carbamazepine, but it does not induce its own metabolism or interact with the CYP450 system, meaning that it has minimal interactions with other drugs. It may contribute to hyponatremia. Causes dizziness, somnolence. There is some slight evidence that it may be anti-manic and prophylactic. Screen patients of Asian descent for HLA-B*1502 for increase in risk of Stevens-Johnson rash.

Second Generation Antipsychotics

The SGA's are all equally effective for mania (Perlis R, et al. 2006.) At this writing, only quetiapine, lurasidone, and olanzapine/fluoxetine are approved for bipolar depression, although aripiprazole is approved as an adjunct for major depression.

Treatment of mania:

1) All of the FGA's and SGA's treat mania.
2) Lithium treats classic mania, but has less effectiveness with mixed mania and rapid cycling. It may work better when started earlier in the illness with no interruptions. It does not work as well with comorbid substance abuse. It has anti-suicide properties.
3) Some antiepileptic drugs (AED's) treat mania and some do not. Divalproex and carbamazepine are effective. The others aren't.

Treatment of bipolar depression:

1) Most experts agree that bipolar depression should not be treated with antidepressants alone. It is not clear whether there is any benefit at all for using them, even with a mood stabilizer. STEP-BD provides evidence that antidepressants may be mood destabilizers in bipolar disorder (Schneck et al. 2008.)
2) FGA's do not treat bipolar depression. Some SGA's do.
3) Effective – lithium, lamotrigine, quetiapine, olanzapine, olanzapine + fluoxetine, lurasidone
4) Non-effective – FGA's, other SGA's, divalproex, carbamazepine, oxcarbazepine, gabapentin, topiramate, zonisamide

Bipolar maintenance:
The best evidence is for lithium, lamotrigine, olanzapine, aripiprazole

Lab Work (Carlat D 2007)
Lithium: level at 1 week, then yearly or as indicated; thyroid stimulating hormone at baseline, 2 weeks, 6 months, yearly; BUN/creatinine at baseline, 2 weeks, yearly; ECG for those with cardiac disease
Depakote: level at 1 week, then yearly or as indicated; liver function tests at baseline, 2 weeks, yearly; complete blood count 2 weeks, 6 months, yearly or if bruising is noticed
Tegretol: level at 1 week, one month, yearly; complete blood count at 1 week, 1 month, 3 months, yearly; sodium at 1 week, yearly; liver function tests at 2 weeks, yearly
Trileptal: baseline sodium, 1 month

DRUGS TO TREAT SUBSTANCE ABUSE

Smoking: Most nicotine dependent people report annual attempts to quit smoking, but it takes most people many tries before they are successful. Pharmacological aids include:

Nicotine replacement therapies: transdermal patches, patch + nicotine gum or nasal sprays can be effective short-term treatments for tobacco addiction.

bupropion (Wellbutrin SR, Zyban): same as the antidepressant, it is also a nicotine receptor agonist. It may help people not gain weight when they are quitting.

varenicline (Chantix): It partially activates the nicotine receptors in the brain and reduces the severity of craving and withdrawal. Satisfaction from smoking also is diminished while the subject is taking the pill. Concerns about psychiatric side effects have been alleviated, but insomnia and vivid dreams are common.

Alcohol Abuse: Alcoholism and drug abuse impose an enormous social and economic burden on society. There is a great hope that some pharmacological agent will provide a breakthrough in treatment. There is evidence that medication may help maintain abstinence in some substance abusers, but medical practitioners seem reluctant to prescribe them.

acamprosate (Campral): alleviates withdrawal symptoms that may contribute to relapse by working on several different receptor systems. It works best for those who are already abstinent.

disulfiram (Antabuse): blocks an enzyme that metabolizes alcohol, leading to nausea and vomiting when the subject drinks.

naltrexone (ReVia, Vivitrol long acting injection): thought to reduce the "high" from substance abuse by binding opiate receptors in the brain.

topiramate (Topamax): although not approved by the FDA for substance abuse, several small studies suggest it may be useful for alcohol dependence (Gelenberg A 2008.)

Opioid Abuse: Opioid abuse has become a public health crisis. The search continues for a vaccine to curb addictive craving, but at this time our only treatments either block the opioid effect on the brain, or substitute a safer opioid for a more dangerous one.

buprenorphine (Buprenex, Butrans, Sublocade extended release injection, Probuphine subdermal implant): buprenorphine is a substitute opioid – a partial agonist that does not stimulate the brain's opioid receptors as intensely as heroin or methadone. It is long-acting and fairly safe in overdose.

buprenorphine + naloxone (Bunavail, Suboxone, Zubsolv): When combined with naloxone, which blocks the opioid receptors in the brain completely when taken IV, it minimizes abuse potential. (Buprenorphine is taken sublingually.)

methadone (Dolophine, Methadose): opioid replacement, requires patients to come to a clinic daily.

naloxone (Evzio, Narcan): emergency opioid rescue medication, blocks opioid receptors, initiates withdrawal.

DRUGS TO TREAT ATTENTION DEFICIT DISORDER

Attention deficit hyperactivity disorder is the most common psychiatric disorder in childhood. Stimulant medication has become the mainstay treatment. Doctors generally start with a methylphenidate because methylphenidate preparations cause less insomnia and irritability than amphetamines. They also have less abuse potential. The various stimulants seem to be equally effective with about a 70% response rate. Some children do not respond to medication, and in most, medication

does not produce total remission of symptoms. Studies of efficacy beyond 2 years are rare. 70% of stimulant prescriptions are written by non-psychiatrists (*Psychiatric Services* 2009.)

Medications have a positive effect on academic performance and productivity as well as classroom behavior. The side effects are the same among the stimulant medications: decreased appetite, initial sleep difficulty, headaches, tics, and irritability. Growth suppression, if at all, appears dose related during the first year of treatment, and children's height and weight should be monitored. The question of medication effect on the development of substance abuse disorders remains unclear. Controlling for conduct disorder in these studies is difficult. There is no link between ADHD medications and risk of cardiovascular events (Gelenberg A 2012.)

amphetamines

Short acting: **Dexedrine, Desoxyn, Evekeo, ProCentra, Zensedi**

Intermediate: **Adderall**

Long acting: **Adderall XR, Adzenys XR-ODT, Dexedrine Spansules, Dyanavel XR, Mydayis, Vyvanse**

methylphenidates

Short acting: **Focalin, Methylin CT, Methylin Oral Solution, Ritalin**

Intermediate: **Metadate ER, Methylin ER, Ritalin SR**

Long acting: **Aptensio, Concerta, Cotempla XR-ODT, Daytrana transdermal patch, Focalin XR, Metadate CD, Quillichew ER, Quillivant XR, Ritalin LA**

Non-stimulants or Non-FDA Approved Medications

atomoxetine (Strattera) –norepinephrine reuptake inhibitor, side effects include potential liver problems, suicidal behavior. Recent studies suggest it is less effective than stimulants for most children, but has fewer side effects.

bupropion (Wellbutrin) – the antidepressant, not FDA approved for ADHD

Clonidine XR (Kapvay) – an alpha2-adrenergic agonist, may be helpful with insomnia

guanfacine (Tenex, Intuniv) – an alpha noradrenergic agonist available in long and short acting forms. Similar to the blood pressure medicine clonidine, which is also used for ADHD. Side effects include fatigue, headache, sleep problems.

imipramine, nortriptyline – tricyclic antidepressants, not FDA approved

modafinil (Provigil) – a stimulant approved only for treatment of narcolepsy or other sleep disorders in adults, requires higher doses for treatment of ADHD in children.

DRUGS TO TREAT ALZHEIMER'S DISEASE

The treatment of Alzheimer's disease remains controversial. Everyone desperately wants an effective treatment. The problem is that although these medications demonstrate a slowing of cognitive deterioration when given to a person early enough in the illness, the degree to which the patient is helped is generally not clinically observable, although improvement may be measurable on cognitive tests. By the time the client is significantly symptomatic (e.g. getting lost in familiar places), it is too late for the medication to be of much benefit. Are these minimal results enough reason to prescribe these medications? The National Health Care Service in the United Kingdom says no.

There are two kinds of agents used in treating Alzheimer's disease, cholinesterase inhibitors and glutamate agents. Much of the cognitive decline in Alzheimer's is due to degeneration of cholinergic neurons. There is no clear evidence of superior efficacy among the cholinesterase inhibitors, although there may be advantages in dosing and tolerability. The primary side effects are nausea, vomiting, anorexia, diarrhea, and abdominal pain. Donepezil causes fewer side effects than rivastigmine (Shah D, Threlfall A 2010.)

donepezil (Aricept, Aricept orally disintegrating): cholinesterase inhibitor, insomnia, GI effects

galantamine (Razadyne, Razadyne ER): cholinesterase inhibitor, GI effects, insomnia

memantine (Namenda, Namenda XR): non-competitive NMDA receptor antagonist, may be useful in combination with a cholinesterase inhibitor like donepezil.
memantine ER/donepezil (Namzaric): for patients who are already on these two medications
rivastigmine (Exelon, Excelon Patch): cholinesterase inhibitor, needs to be started at a low dose due to high rates of nausea and vomiting. Has additional indication for Parkinson's-related dementia.

Complementary and Alternative Medications (CAMS) for Psychiatric Disorders

(Edie C, Dewan N 2005, Tindle H, et al. 2005, Bausell R 2007, Sloan E 2007)

"Natural medications" have been used for centuries, and interest in the U.S. has increased markedly over the last decade. Health supplements are a $34 billion a year business (Nat'l Center for Complementary and Alternative Medicine, Jul 2009.). CAM modalities are described as either based on familiar mechanisms of action (complementary, e.g. herbs) or on a completely different conceptual framework (alternative, e.g. acupuncture.)

Studies suggest 35% of Americans and 70% of the population worldwide seek and obtain nontraditional treatments. In 1997, 42.1% of adults used an alternative therapy. There were 400 million visits to doctors, 629 million visits to alternative medicine providers. 18.6% of American adults are taking herbal medicines, mostly for fatigue, insomnia, anxiety, depression, and headaches. (Only 16% of Americans are satisfied with their energy level!) The highest rate of CAM use is among females, 40-64, with an annual income >$65,000. 41% will use more than one CAM therapy. Only 38% of these patients tell their regular MD's that they are taking CAMS.

Natural remedies are available at drugstores and natural food stores without prescription. Clients who use natural remedies don't tell their doctors because they think the doctors won't approve and don't know anything about them, anyway.

The actual benefits of these medications are not clear because of limited basic and clinical research. By and large, there are few large, placebo-controlled studies. Manufacturers and governments have been

reluctant to sponsor clinical research. Consequently, there is little guidance for optimal doses, contraindications, drug-drug interactions, or potential toxicity. Mostly prescribers must rely on anecdotal evidence in lay journals, magazines, television “infomercials,” and the Internet without peer review or scientific documentation.

Just because a medication is "natural," does not mean it is safe. Consumers get more information about a loaf of bread than they do about herbal supplements. Congress overwhelmingly opposes more government control over supplements, and almost vetoed the recent ephedra ban. Metabolife (leading manufacturer of ephedra) did not let the FDA know it had received 14,684 complaints, including 18 heart attacks, 26 strokes, 43 seizures, and 5 deaths. It wasn't until Steve Bechler, pitcher for the Baltimore Orioles, died that Congress dropped its objections to the ban.

59% of Americans believe that supplements must be approved by the government before they are sold to the public. 68% of Americans believe that warning labels are required to list side effects. 55% said that manufacturers couldn’t make safety claims without scientific support. None of this is true. The maker's only requirement is to send the FDA a copy of the language on the label. The 1994 Dietary Supplement Act (DSHEA) makes it necessary for the FDA to prove that supplements on the market are unsafe and denies the agency all but the most superficial information about safety. There are no regulations concerning purity, and no mandatory reporting of bad outcomes.

ConsumerLab.com has reported that 40% of herbal preparations failed to have as much active ingredient as the label claimed. In 1998, a product called Sleeping Buddha was found to contain estazolam, a benzodiazapine. 50 Ginseng preparations were analyzed for ginsenosides in the medical journal *Lancet* in 1994. The content varied from 2-9%. Six preparations had none! The California Department of Health Services looked at Asian Patent Medicines from California Herbal Stores, and reported in *The New England Journal of Medicine* (9/17/98) the presence, in 32% of 260 medicines, of 1) undeclared pharmaceuticals - ephedrine, methyltestosterone, chlorphenarimine, phenacetin 2) heavy metal contamination with lead, arsenic, and mercury. Because of a manufacturing error, one of the herbs was replaced with *Aristochia fangchi,* which is nephrotoxic and carcinogenic. An "internal cleansing" tablet had been contaminated with digitalis.

Due to the need created by lack of government oversight, private companies have formed a group to certify dietary supplements. The United States Pharmacopeia recently created the Dietary Supplement Verification Program to insure that a product 1) contains the ingredients stated on the label and in the declared amounts 2) has been screened for harmful contaminants such as pesticides and heavy metals 3) has been manufactured using safe, sanitary and well-controlled procedures 4) dissolves effectively to release nutrients into the body.

Finally, many alternative medications are quite expensive over the long run. Insurance companies don't cover them. And they may simply be money down the drain because they are unregulated, preparations made by different companies which vary in potency, quality, and purity, and hence, effectiveness.

The following are good sources of information about CAM treatments:

National Center for Complementary and Alternative Medicine
www.nlm.nih.gov/nccam/camonpubmed.html

Cochrane reviews www.cochrane.org/index0.htm

Complementary and Alternative Treatments in Mental Health Care Lake J and Spiegel D eds. 2006 American Psychiatric Publishing, Arlington VA.

Natural Medications for Psychiatric Disorders: Considering the Alternatives. Mishoulon D, Rosenbaum J eds. 2008 Lippincott & Wilkins, Philadelphia.

SAFETY SUMMARY

Toxicity

Contamination – Stick to higher quality brands
www.consumerlab.com
www.usp.org/USPVerified/dietarySupplements
www.nsf.org

Ginkgo: increased risk of bleeding, seeds may be lethal

Kava: severe hepatotoxicity – not available in Germany, Switzerland, Great Britain

St. John's Wort: GI effects, rash, possible mania

Antioxidants: a Cochrane review (April 2008) concluded that supplements in doses considerably larger than those in typical multivitamins increase the risk of death by 16% for vitamin A, 7% for beta-carotene, and 4% for vitamin E.

Drug-Herb Interactions

Try to avoid concomitant used of herbals and conventional medications.
Avoid herbal diuretics (green tea) and lithium.
Evening primrose oil may unmask temporal lobe epilepsy
Avoid MAOI's and herbals with sympathomimetic activity (ephedra, coffee, black tea, etc)
Avoid St. John's Wort and MAOI's.
Avoid ginseng and caffeine or other stimulants, warfarin.
Avoid kava and other sedatives.
Chinese herbal medications have not been well studied – avoid with conventional medications.

DIETARY SUPPLEMENTS FOR CHILDREN

(*Carlat Child Psychiatry Report* Nov 2013)

Whether or not special diets, dietary supplements, or other alternative treatments can benefit children with autism spectrum disorders or attention problems is highly controversial. Typically parents, with support from Internet communities believe these interventions help. But controlled studies do not support these opinions.

For a small subset of children with autism spectrum disorders, there is some suggestion that a gluten-free casein-free diet may improve their symptoms. The diet is very hard to stay with.

For children with ADHD, a number of different interventions have been tried. There is evidence that removing foods with significant artificial coloring and other additives may reduce hyperactivity in a portion of children with ADHD (Stevenson J, et al. 2013). Supplements, such as omega-3 fatty acids, zinc, iron, and megavitamins have little to no research support. Given that children with ADHD are often very picky eaters, the use of a multivitamin at regular RDA doses may be a good idea.

EVIDENCE AS ADJUNCTS TO ANTIDEPRESSANTS

(*Am J Psychiatry*, June 2016)

SAMe, methylfolate, omega-3, vitamin D were determined by a careful data analysis to show evidence of efficacy when used with an antidepressant when treating major depression. However, some of these trials were supported by manufacturers. Most side effects are mild, but folic acid and omega-3's have been associated with prostate cancer,

SAMe with switching to mania from depression, and high doses of vitamin D with hypercalcemia (*NEJM Journal Watch* June 2016.)

PLANTS and HERBS

(Bressler R 2006, PDR for Herbal Medicines, 3rd Edition. Thomson PDR; Montvale, NJ. 2004)

The seven best selling herbal medications in the US are ginko, St. John's wort, ginseng, kava, saw palmetto, garlic, and echinacea. (Since there is little empirical research, and different preparations vary considerably, there cannot be any universal dosage guidelines. The dosages printed here are simply ranges that have been found in various review articles. They are not intended to be prescriptive.)

Black Cohosh (*Climicifuga racemosa*)

Also called black snakeroot, bugbane, rattleroot, squawroot, macrotys, black cohosh is a member of the buttercup family. It is found in the New World from Maine to Wisconsin and has been used by Native Americans.

Indication: PMS

The root and the rhizome are used. It hasn't been well studied in terms of chemistry - lots of constituents - triterpene glycosides, aromatic acids, tannins, resin, fatty acids, starches, sugars. It is a remedy for heavy, intense aching pains related to female reproductive organs. It is used for PMS, menopause, dysmenorrhea, uterine spasm. It may have an antidepressant action. What little research there is indicates that while it may be helpful in menopause, there is no good evidence of efficacy in PMS.

Dosage: 20 mg twice a day

Side effects: Rare GI minor side effects. No long-term studies.

Ginkgo Biloba

(Sommer B, Schatzberg A 2002, Lake J 2006)

From China, the Maidenhair Tree is the oldest tree in the world. They were abundant 200 million years ago. It lives to 1000 years and grows to 122 feet. It is the only tree to survive Hiroshima.

Indications: treatment of dementia

The therapeutic agents come from the leaves, harvested at a certain time. Active ingredients are flavonoid glycosides, terpenes, and proanthocyanidins. The code name for the patented extract is EGb. The

most important component is EGb 761 with many different chemical constituents - at least 56. It is difficult to isolate a given molecule to test for biological activity. Flavonoids are low molecular weight substances that are common in the plant kingdom and occur as pigments in flowers. In general, they are active as free radical scavengers, anti-inflammatories, and cation chelators. Terpenoids also may work as an inhibitor of platelet activating factor. This results in a decrease in blood viscosity. These processes are all implicated in Alzheimer's disease.

The *Archives of Neurology* found only 4 of 50 studies in the English and non-English literature about Ginkgo which met the criteria for meta-analysis. 3 to 6 months of 120mg/day to 240mg/day produced a modest 3% difference in the Alzheimer's Disease Assessment Scale cognitive subtest. This would probably not be noticeable clinically.

Most recently, a 6-year trial involving 5 medical centers sponsored by the National Center for Complementary and Alternative Medicine and the National Institute on Aging involving 3,000 subjects in a randomized, placebo-controlled double-blind study was completed (Journal of the American Medical Assoc, 2008). Results indicate that ginkgo has no preventative effects for the development of Alzheimer's disease.
Dosage: 40-80 mg three times a day
Side effects: Ginkgo is a strong inhibitor of cytochrome P-450 2C9, so clearance of phenytoin, warfarin, and diazepam is impaired. Side effects include increased bleeding in vulnerable patients, GI upset, gas, and diarrhea.

Ginseng

Ginseng is one of the most popular herbal medications in the US. The main active component consists of the ginsenosides, which have a quite complex effect on various animal tissues.
Indications: improvement of physical and mental performance. There is little evidence for its efficacy. It may act via the hypothalamic-pituitary-adrenal axis to elevate corticotropin and corticosteroid levels.
Dosage: 1-2 g root
Side effects: Drug interactions are rare. There may be an interaction with phenelzine, and MAOI. There have been four reports of mania and psychosis associated with its use. Ginseng has lowered blood pressure in some people.

St. John's Wort (*Hypericum perforatum*)

(Meltzer-Brody, S 2001, Brenner R, et al. 2002, Werneke U, et al. 2004, Joshi K, Faubion M, 2005, Freeman M, et al. 2010)

Named after John the Baptist, SJW has been used for centuries to treat depression. It supposedly has its greatest potency on June 26 - the day that St. John was killed. Quite common, it was introduced in Australia as a medicinal plant, but became an out-of-control noxious weed. Now Australians are harvesting it as a cash crop.

Indication: depression

On one internet site, SJW is claimed to be effective for colds, syphilis, tuberculosis, dysentery, whooping cough, worms, fear, anxiety, irritability, mania, hypochondria, rheumatic pain, fatigue, hysteria, insomnia, neuralgia, tension, fibrosis, sciatica, healing wounds, varicose veins, mild burns, PMS, headache, alcoholism, SAD, and sinusitis.

There are more than 15 substances that may be responsible for the antidepressant effect of SJW. One active ingredient is hyperforin. It also contains phenylpropanes, flavonol glycosides, bioflavones, proanthocyanidins, xanthones, phloroglucinols, and naphthodianthrones. It may inhibit 5-HT, NE and DA uptake, binds GABA, weakly inhibits MAO.

For the treatment of mild to moderate depression, SJW has been shown to be more effective than placebo in 35-40 randomized controlled trials (Mischoulon D, Fava M 2008.) The studies generally have not been of high quality (small samples, short treatment periods, large placebo response, etc.)

No known studies of continuation or maintenance treatment have been published. In the best-designed study so far, a 2001 article compared 200 adults with major depression on 12 weeks of placebo or SJW. There was no difference. A recent meta-analysis published in 2004 failed to demonstrate significant efficacy for SJW. A review of studies indicates that the smaller the study, the more effective is SJW, suggesting that there is a significant publication bias effect. Conclusion - SJW may or may not work for mild depression. The evidence is not clear, but trials are ongoing.

Dosage: 500-1200 mg

Side effects: No deaths in 2400 years. Side effects are generally mild: dry mouth, dizziness, constipation, GI, confusion. Fewer than 2% of patients stop because of side effects. Overdose may result in photosensitivity. No interaction with alcohol. No cardiac effects.

SJW induces CYP-3A4, no effect on CYP-2D6. About half of all prescription drugs are processed through P450 3A4, so there are many interactions with other drugs. Watch for decreased levels of warfarin, cyclosporin, oral contraceptives, theophylline, fenprocoumon, digoxin, and indinavir. Watch out for HIV positive patients who are receiving protease inhibitors and transplant recipients.

Serotonin syndrome with concurrent SSRI use has been reported. (3 of the following symptoms: myoclonus, increased reflexes, shivering, sweating, diarrhea, agitation, mental status change - confusion or hypomania, ataxia. May also see muscle rigidity, restlessness, hyperthermia, tremor, tachycardia, hypertension, coma, dilated pupils, tachypnea, and nausea.) SJW has a mild MAOI activity.

Kava kava (*Piper methysticum*)

(Zal H 2000, Connor K, et al. 2001, Lake J 2007, Carlat D 2010)

The medication is derived from the root of this Pacific island plant. In Polynesian tribes, kava was traditionally prepared by virgins, who chewed kava roots, placed the mash in a fermenting pot, and prepared a hot, tea-like drink for the tribe members. It is a ceremonial and social drink, and has been drunk by Queen Elizabeth, Pope John Paul II, Lyndon and Lady Bird Johnson, and Hillary Clinton.

Indication: anxiety

200 years ago investigators noted the relaxing effect of kava liquid. It's the most potent anxiolytic available without prescription. It relieves muscle aches and chronic pain. It may have anti-craving properties. The active ingredients are the so-called kava-lactones: kavain, methysticin, yangonin, dihydrokavain, dihydro-methysticin, desmethoxy-yangonin. Possible mechanism - a glutamate suppressant, or a GABA enhancer.

It has been studied in 6 double-blind placebo controlled clinical studies in Europe and benefits are seen in 4 weeks that last for many months. See more benefit at 6 months. It doesn't work in panic disorder or acute anxiety states. 76% anxiety disorders improve versus 51% treated with placebo.

Dosage: 60 - 300mg

Side effects: The drug has been taken off the market in Canada and Europe due to hepatotoxicity and drug interactions. (This side effect is very rare, about 1:1,000,000 doses.) Side effects with moderate doses are rare, and may include GI, allergic skin reactions, headaches, and

dizziness. Kava inhibits virtually all CYP-450 enzymes, which would increase the levels of most medications.

Based on animal studies, kava is anxiolytic, tolerance and withdrawal are unlikely. High doses - 300-400 grams/week may result in ataxia, rash, hair loss, yellow skin, respiratory problems, and hepatitis. Prolonged use may cause yellowing of the skin, subnormal weight, hematuria, poor health, and pulmonary hypertension. These effects usually disappear after kava has been stopped. Don't use for longer than 3 months because of hepatotoxicity. Safety with pregnant women is unknown.

It is non-addictive and people rarely seem to develop a tolerance. It does not alter mental clarity, reaction time, alertness, or other cognitive abilities. It may or may not potentiate alcohol and sedatives.

There are a few cases of coma when used with alprazolam. There may be similar interactions with other sedatives such as barbiturates and phenothiazines. Kava may oppose the effect of dopamine agonists.

Rhodiola rosea

(Carlat Psychiatry Report July/August 2013)

This Russian folk medicine is superior to placebo for mild to moderate depression. It may also have efficacy for anxiety. It may suppress stress-activated protein kinases, including those which cause inflammation.

Valerian (*Valerian officialis*)

(James S, Mendelson W. 2003, Krystal A, Ressler I. 2001)

Heliotrope: the 19th Century Valium. Originally used as an antidote for the Black Plague, it was also used in WWII for shell shock. It is popular around the world, especially in Hispanics. Valerian is cultivated mostly in Western Europe. There are over 100 over–the-counter preparations. It has typically been ingested as tea, but it is available as capsules and tablets. It has a distinctive and unpleasant taste and aftertaste. Some clients immediately decline to try it.

The active parts of the plant are the rhizomes and roots. The chemical constituents are monoterpenes and sesquiterpenes, iridoids, alkaloids, and a number of amino acids. No one is quite sure which of these has the most important effect. They all may contribute. Valerian probably inhibits the breaking down of GABA.

Indication: sleep

Valerian has been used for anxiety and depression, but its traditional use has been for sleep. This is one of the best-studied botanical products, but very few large scientifically sound and convincing studies have been published. Clinical evidence is limited. Studies using formal sleep recordings show mixed results.

Approximately 10 controlled trials of various preparations have been done. Symptomatic individuals appear to require more time to respond. A study in Sweden for insomnia found it superior to placebo (drug 78%, placebo 11%). Two open label trails in Germany (n=11,168; n=1,689) found it helpful for sleep. In three placebo-controlled experiments, valerian was superior to placebo (N=128). 54% improved, versus 28% on placebo. Mostly it shortened the time needed to fall asleep. Subjects need to take it nightly, rather than as needed.

Dosage: 100-1800 mg depending on the manufacturer. The optimal dose is not known.

Side effects: There may be a dose/response relationship. Very few side effects have been reported. It is benign in overdose. It does not potentiate alcohol. There is no information about pregnancy.

NATURAL HORMONES

Melatonin (N-acetyl-5-methoxytryptamine)

(James S, Mendelson W 2003)

Melatonin is a phylogenetically primitive molecule found in unicellular organisms, plants and vertebrates. In vertebrates the main source of melatonin is the pineal gland in the center of the brain, long thought to be the seat of imagination and common sense.

Indication: sleep

Melatonin is involved in regulating the sleep/wake cycle in conjunction with ambient light. The major structures involved with sleep cycles include the eyes, the suprachiasmatic nuclei of the hypothalamus (SCN), and the pineal gland. (Blind people frequently develop cyclic bouts of insomnia. The free running circadian cycle is slightly longer than 24 hours.) These three structures are all involved in relating the sleep cycle to the cycle of the sun. Melatonin secretion is triggered by a signal from the SCN.

This rhythm is capable of continuing even in the absence of regular biological input. Two hours before habitual bedtime, melatonin automatically goes up and declines by morning. Exposure to darkness

during the day does not increase melatonin, but bright light at night can suppress it.

Newborns do not produce melatonin - they get it from mother's milk. By 12 weeks rhythmic melatonin production is increasing rapidly. It is highest in humans under five, and decreases throughout life. The lowest level is in the elderly. The biggest shift is during teenage years. Teenagers may have trouble getting sleepy after dark!

Studies in normal people indicate that taken orally, melatonin can increase fatigue and sleep efficiency. It does not affect sleep architecture. A very small number of studies showed a beneficial effect on sleep in various psychiatric disorders. It has not been particularly helpful to the blind. There is some evidence that it works with a variety of sleep disorders, jet lag, etc. There is no consistent relationship between melatonin levels and psychiatric illnesses.

The optimal dose is hard to predict from different preparations. It should be taken 30 minutes before bedtime. Since it is a hormone, levels need to be taken if this is part of a treatment program - there are lots of variables.

Dosage: 1-3 mg

Side effects: Side effects include disruption of normal circadian rhythms, lower body temperature, change in energy levels, changes in reproductive function (early/late puberty), can have vasoactive properties. Get very high levels of melatonin when taken with fluvoxamine.

Dehydroepiandrosterone (DHEA)

(Kaplan A 2004, Schmidt, P et al. 2005, Med Letter, May 9, 2005)

DHEA and its metabolite DHEA-S are the most plentiful adrenal corticosteroids in humans, but their physiologic role is uncertain. DHEA-S is made in the brain so it must have effects on the central nervous system. DHEA is a precursor to testosterone and estrogen. Concentrations are generally higher in men than women. Levels begin dropping in the 20's. By 40-50 years old, levels are at 50%. Low levels are associated with cardiovascular disease, decreased immune function, decreased bone density, negative lipid profiles, and increased fat to muscle ratio. Levels decrease with chronic stress and medical illness. It seems to increase in response to acute stress. Other glucocorticoids do not show this pattern.

DHEA is extracted from barbasco root or wild Mexican yam. Several countries have banned over-the-counter sales. The U.S. Attorney General is to give a report of its safety in next couple years because Congress is becoming more interested in regulating steroids.

Indications: to treat depression or to increase a sense of well-being

DHEA-S is low in clients with depression, poor life satisfaction, psychosocial stress, and functional limitations. It is high in happy, healthier, more exciting people. Findings are mixed in Alzheimer Disease.

Studies of giving DHEA to other patients are also mixed. Some studies show it enhances mood, energy, sleep, and sense of well-being, functional capabilities, and memory. It seems to work better in the elderly, depressed and infirm and works best after more than a month of treatment. In a double blind, placebo controlled crossover study with 23 men and 23 women, aged 40-65 with midlife onset depression, it improved mood and libido. A recent small study of 46 clients with depression at NIMH showed improvement after 6 weeks of treatment.

Dosage: 25-450 mg/day (<1500 mg/day)

Side effects: Testosterone levels increased 500% above baseline in women and 20% above baseline in men. Side effects included facial hair, weight gain, acne, temporary breast tenderness, baldness, and skin rash. May see insulin resistance at higher levels of testosterone. Side effects also include the possibility of hypomanic, aggressive, psychotic, disinhibited behavior. Be careful if there is a hormonally sensitive tumor. Need to take it 3 times a day. Over the counter preparations vary from 0% to 150% of the claimed content.

ESSENTIAL MICRONUTRIENTS

(Stampfer M. (ed.) *Vitamins and Minerals: A Harvard Medical School Special Health Report*. 2008. Harvard Health Publications, Boston, MA, Hyman M, et al. 2005, Medical Letter July 18, 2005)

There are at least 30 vitamins, minerals, and dietary components that our bodies need but cannot manufacture on their own. Vitamins are organic and break down in air, heat, or acid. They are often destroyed in the process of cooking and preparing food. Minerals are inorganic and are easily absorbed from food.

One area of interest has been the use of antioxidants as a way of minimizing damage from aging and environmental exposure. A review by the Cochrane Library looking at 67 randomized trials, there is no

evidence that antioxidants prolong life, and in some cases (when very high doses were used) might shorten it (April 16, 2008.)

VITAMINS

Vitamins are a heterogeneous group of organic molecules required by the body for a variety of essential metabolic functions. They are grouped as either fat soluble (D,E,A,K), or water soluble - thiamin, riboflavin, niacin, B6 (pyridoxine), B12 (cobalamin), folate, pantothenic acid, biotin, C (ascorbic acid). Deficiencies of single vitamins are rarely encountered, even in developing countries. Deficiencies with multiple vitamins along with protein-calorie malnutrition are seen more often. Many adults take vitamin supplements in the U.S., where syndromes of vitamin excess are more likely than vitamin deficiency. (The exceptions are **vitamin B12** in the elderly who may not be able to absorb the vitamin due to atrophic gastritis, and **vitamin D** in the elderly and those in northern climates.) Most health claims for the benefits of vitamin supplements remain unsubstantiated.

Biotin (B7)

Folic Acid (B9)

(Folate is the naturally occurring form, folic acid is the synthetic form, which is more bioavailable to the body when ingested.) Folate is a cofactor in hydroxylating phenylalamine and trytophan, which is a step in making dopamine, norepinephrine, and serotonin. Depressive symptoms have long been associated with folate deficiency states like malabsorption, anticonvulsant treated epilepsy, megaloblastic anemia, and dietary folate restriction. Higher rates of low red blood cell folate have been seen in depressed patients. There have been a few studies, but no good ones, in investigating whether high doses of folate might treat depression, alone or as an augmenter. One study of 299 older depressed males found no benefit when used alone (Ford A, et al. 2008.) It appears folate is most useful in depression when a folate deficiency is present (Mischoulon D, Fava M (2008.) The recommended minimal daily requirement is 0.4 mg/day. Pregnant women need folate supplements to prevent neural tube defects.

Niacin (B3)

Pantothenic acid (B5)

Riboflavin (B2)

Thiamin (B1)

Vitamin B6

Recommended daily dose is 25-50 mg. Some benefit in PMS has been reported. There is no evidence that B6 supplements aid depression in older adults (Ford A, et al. 2008.) Very high doses (600mg) have been used in treating akathisia. A sensory neuropathy, at times irreversible, has been reported in patients taking large doses (200 mg).

B12

B6, B9 (folic acid), and B12 are often low in people who have high homocysteine, which may be a risk factor for heart disease and Alzheimer's disease. Vitamin supplements can reduce homocysteine in weeks. There is no evidence that B12 is useful for depression in older adults (Ford A, et al. 2008.) Atrophic gastritis affects 10-30% of elderly, who are then unable to absorb B12, which is tightly bound to food protein. Supplements are recommended for older adults.

Vitamin C

Short term, randomized studies have found no benefit to high doses of vitamin C in preventing colds or other illnesses. There may be an increased risk of kidney stones.

Vitamin D

There has been a lot of publicity regarding vitamin D in the last few years. Vitamin D is predominantly produced by sunlight-exposed skin. Humans also receive some vitamin D from their diet. Vitamin D is an essential part of bone formation, but recent studies have also implicated a lack of vitamin D as a contributor to diabetes, multiple sclerosis, colon cancer, depression, inflammation, and even the flu. The problem with vitamin D, as with all vitamins, is that we don't know what the optimal levels are. We do know that lack of sun exposure during the winter in northern altitudes causes vitamin D levels to fall significantly in an individual. Taking vitamin D supplements during the winter is probably a good idea for people who do not get sunlight exposure during a significant part of the year.

Vitamin E

The hope that vitamin E may play a protective role as an antioxidant in cancer, coronary artery disease, Alzheimer's, and cataracts has faded. Large doses can increase bleeding risk in patients taking anticoagulants. In two recent studies involving 1100 patients, those taking 400IU or greater per day were more likely to die during the course of the study. Causes of death are presently under investigation. Vitamin E is used as a

possible prophylaxis for tardive dyskinesia. There is no good evidence it works for treatment of TD. Doses of 150-800 IU are typically recommended for treatments.

Vitamin A (and beta carotene – potent source of vitamin A)

Antioxidants in the lab, but like vitamin E, may have pro-oxidant effects in vivo. High intake of vitamin A is associated with increased risk of hip fracture in postmenopausal women and teratogenicity. Beta-carotene supplements increased the risk of lung cancer in smokers and asbestos exposed workers.

Vitamin K

Important for blood clotting

MAJOR MINERALS

These help maintain the correct water balance in the body; they are important for healthy bones; they help form skin, hair, and nails. We have about a pound of each. Some are absorbed easily, like water-soluble vitamins (potassium.) Others act more like fat-soluble vitamins (calcium.) Too much of one mineral may lead to an imbalance in another. This can happen with supplements.

Calcium: men should avoid calcium supplements because of links to prostate cancer

Chloride

Magnesium: heart and bone health

Phosphorus

Potassium: blood pressure, important for fluid/electrolyte balance

Sodium

Sulfur

TRACE MINERALS

A thimble could contain all of the trace minerals in the body, yet they are each essential for health. They carry oxygen, strengthen bones and teeth, help blood clot, and bolster immune response. Each of these can affect the balance of the others. The difference between "just enough" and "too much" of these is often very small. It is primarily a problem with supplements.

Chromium: some preliminary evidence that chromium supplements may treat depression

Copper

Flouride

Iodine
Iron
Manganese
Molybdenum
Selenium: may be protective of prostate cancer
Zinc

AMINO ACID DERIVATIVES

2-Phenylethylamine (PEA)

PEA is an endogenous amine that is produced and metabolized in brain tissue and distributed non-uniformly. It has amphetamine-like effects when systemically administered. PEA readily crosses the blood brain barrier. MAO rapidly breaks it down, so it requires high doses or the concomitant use of an MAOI. (Phenylalanine is metabolized to PEA. Clients take phenylalanine at doses from 500 - 1500 mg. It is also found in chocolate.)

Indication: depression

In depressed patients, there are lower levels of PEA. L-Phenylalanine (precursor of PEA) is a mild antidepressant, and a useful adjunct for MAOI's. PEA is a stronger antidepressant, but only with an MAOI. Some writers believe it increases psychological energy - social bonding, emotional warmth, and interpersonal harmony.

S-Adenosyl-L-Methionine (SAMe)

(Brown R, et al. 2002, Mischoulon D, Fava M 2008, Freeman M, et al. 2010)

SAMe is found throughout the human body, with particularly high concentrations in the liver, adrenal glands, and the pineal gland. It is also found throughout the brain. It's involved in the synthesis of a wide variety of neurotransmitters, including norepinephrine, serotonin, melatonin, and of neuronal membrane components. It takes part in the synthesis of endogenous anti-inflammatory substances and antioxidants.

Indication: depression

SAMe has been found to be low in the CSF of depressed patients. There have been 45 published randomized controlled trials of SAMe monotherapy against placebo or tricyclic antidepressants These trials have only involved a small number of patients. In these studies SAMe worked as well as TCA's. There have not been studies comparing SAMe

to newer antidepressants. A recent study found SAMe to be an effective adjunctive treatment to an SSRI (Papakostas G, et al. 2010.) The elderly have low levels of SAMe, so it may help as an adjunctive treatment for this group.

SAMe is the third most common antidepressant in Italy, after fluoxetine and amitriptyline. Cost studies have only looked at parental (shots, IV) doses. It may not even be effective when taken orally. Doses in Europe have been much higher, costing about $200/month. Probably the best use is as a treatment for mild depression when a patient doesn't want to take a conventional antidepressant.

Dosage: 800-1600mg

Side effects: The most serious side effect is the induction of mania. We don't know about actual concentrations in the preparations. Although no contraindications are known, there have been no studies of drug-drug interactions. There is a theoretical possibility that serum homocysteine levels could rise, which is a risk factor for cardiovascular disease. Overdose would require 140,000 mg.

OMEGA-3 FATTY ACIDS

(Martinez J, Marangell L 2004, Parker G, et al 2006, Freeman M, et al. 2010, Carlat D 2010)

The omega-3 and omega-6 fatty acids are naturally occurring lipids, which are termed “essential” polyunsaturated fatty acids, that is, vertebrates cannot make them and must get them in the food supply. Polyunsaturated means that they are more flexible. They are liquid at room temperature. (Saturated fatty acids are more rigid. They are solid at room temperature.) This is an important distinction for cell membrane function. The 3 predominant omega 3's are:

Docosahexanoic acid (DHA)
Eicosapentanoic acid (EPA)
Alpha-linolenic acid (ALA)

DHA and EPA are long-chain omega-3 fatty acids and are found primarily in the oil of cold-water oily fish - anchovies, mackerel, salmon, and tuna. ALA is shorter chain and comes from land-based plants, such as flaxseed, purslane, and others. The modern diet in Western nations is now largely depleted of omega-3 fatty acids. Omega-6 fatty acids (arachidonic AA and linoleic LA) are derived primarily from vegetable oil and are ubiquitous in the Western food supply.

Indication: depression, cardiac problems

Prevalence studies show major depression and suicidal ideation decrease in populations as fish consumption increases. We do not know if this can be remedied by taking fish oil capsules. There is evidence that deficiencies in omega-3 may contribute to the symptoms of schizophrenia, alcoholism, multiple sclerosis, dementia, and postpartum depression.

The omega-3's may improve abnormal intracellular signal transduction (the mood stabilizers seem to do this.) They modulate calcium channels, and may have a cardioprotective effect, and an anti-manic effect. They regulate inflammatory and immune function. They are balanced by omega-6, which tends to over-inflame. Such inflammation has been observed in bipolar disorder.

Omega-3's provide protection from heart disease. There is a 30% reduction in first MI, 30% reduction in sudden cardiac death with MI with treatment. They may have benefit in rheumatoid arthritis, Crohn's disease, and other inflammatory conditions.

There have been 15-20 randomized controlled trials that suggest efficacy for unipolar depression, particularly as an adjunct. Evidence in bipolar depression is mixed (Mischoulon D, Fava M 2008.) There are a few trials involving borderline personality disorder. All in all, the evidence of mental health benefit is very mixed, while the evidence of heart benefit is fairly clear. But since heart health = head health, omega-3 supplements are probably worthwhile in people with psychological stress.

Recent studies suggests that omega-3's may prevent the development of psychotic disorders in people at risk (*NEJM Journal Watch* Oct 2015, Gelenberg A 2010.)

Dosage: 1-6 grams/day. 1 gram of omega-3/ day is about equivalent to 3 salmon dinners/week. You can safely exceed 10 g per day. Some patients can't stand the taste of the liquid. Dose is individualized.

Side effects: Side effects are predominantly GI, fishy after taste, hypervitaminosis A if the liver is used, and impaired platelets - only moderate and transient, but monitor if the client is on anticoagulants. Other risks include that, in the flaxseed husks, there are cyanogenic nitrates and linamarin, which inhibit iodine intake by the thyroid gland and cause goiter. Anecdotal evidence suggests ALA>EPA>DHA for chances of inducing mania. Taking antioxidant vitamins (C, E) may prevent the oxidation of omega-3, which can create a chemically reactive compound.

NOOTROPICS (Neuroenhancers)

Up to 16% of young urban professional men and students may take substances to sharpen cognitive functions and help with school work. "Alpha Brain" is a mix of B6 and various herbs, particularly a cholinesterase inhibitor, similar to donepezil (Aricept.) We have no efficacy data. Another cholinesterase inhibitor used by these consumers is *Lycoris radiata*.

Cannabidiol in marijuana is neuroprotective and does not have the deleterious effects of THC, which is neurotoxic. Companies are working to develop this drug (*Carlat Psychiatry Report* July/Aug 2013).

ANTIOXIDANTS

Most supplements we classify as antioxidants (vitamin E) are not antioxidants *in vivo*; they bring forth the body's own antioxidant system when taken in appropriate doses. Some other antioxidants are:

N-acetyl cysteine (NAC): used to treat acetaminophen overdose in the ER. It is one of the few agents that can reduce glutamate. It may be useful as a treatment for trichotillomania, bipolar depression, and cocaine use. There are no significant drug-drug interactions.

Alpha-lipoic acid (ALA): may reduce insulin resistance and have some benefit in Parkinson's disease. It is not clear how effective it is with psychiatric disorders (*Carlat Psychiatry Report* July/Aug 2013).

OTHER

Chamomile *(Marticaria recutita)*

(Amsterdam J et al. 2009, Carlat D 2010)

One recent small study found chamomile capsules to reduce anxiety better than placebo in 57% of participants suffering from generalized anxiety disorder. There are no significant side effects.

Chaste Tree Fruit (*Vitex agnus-castus*)

Chaste tree is a shrub or small tree that grows along riverbanks in southern Europe. Hippocrates wrote about the fruit in 400BC. It contains essential and fixed oils, diterpenoids, iridoid glucosides and flavonoids.

It increases progesterone in humans by reducing prolactin A double blind randomized placebo controlled study for PMS found significant improvement in irritability, mood alteration, anger, headache and breast fullness. Dosage of 20-40 mg.

Common sage (*Salvia officinalis*)

An open study of 30 Alzheimer patients showed some success. Dosage is 60 drops.

English Lavender *(Lavandula angustifolia*)

(James S, Mendelson W. 2003)

This plant is used to treat nervousness and insomnia. Like hops, lavender is put into or beneath pillows. No good research data.

Hops (*Humulus lupulus*)

(James S, Mendelson W. 2003)

Hops is used for nervousness and insomnia. Hops-filled pillows were used to try to sedate mad King George III of England. No studies have been done looking at hops alone. Usually it is combined with Valerian.

Inositol

Inositol is a form of glucose. It is located primarily in cell membranes, where it is involved as a second messenger in response to serotonin, norepinephrine, and dopamine. The average adult consumes 1 gram of inositol in his daily diet. In European folk wisdom, inositol is regarded as a remedy for neurasthenia (neurosis of fatigue and anxiety) and mild depression.

In a placebo-controlled study, it reduced HAM-D scores in depression, reduced panic attacks, OCD, bulimia, and binge eating. It worked as well as fluvoxamine for depression, better for panic, and had fewer side effects. Inositol had no effect on schizophrenia, dementia, ADD, and autism. It may work on intracellular pathways. Studies were of ~15 people, 12 grams/day. A powder form is dissolved in fruit juice twice a day (Carlat D 2004.)

Lemon balm (*Melissa officinalis*)

(James S, Mendelson W. 2003)

An open study of 35 Alzheimer patients showed some improvement. This plant is traditionally considered as having memory and cognition enhancing properties. It has also been used as aromatherapy with some success. Dosage is 60 drops.

Passion flower (*P. incarnata*)

(James S, Mendelson W. 2003)

The name refers to the passion of Christ. The active ingredient is chrysin - a partial agonist of benzodiazepine receptors. No clinical trails have been done. Anecdotally it is helpful for anxiety, as a sedative/hypnotic and antispasmodic. Side effects include altered consciousness and hypersensitivity vasculitis. Dosage of 200-300 mg.

Other substances for sedation

Almonds, oats, poppy seeds, skullcap, Indian hemp.

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