

Benzodiazepines (BZDs), Herbal and Alternative Treatments for Anxiety & Depression



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1

BZD Learning Objectives

- List at least three uses for benzodiazepines
- Discuss at least two risk factors associated with benzodiazepine prescriptions

2

Clinical Uses of BZDs

- Treat a variety of anxiety disorders
- Hypnotics
- Muscle relaxants
- To produce anterograde amnesia
- Alcohol & other CNS depressant withdrawal
- Anti-convulsant therapy

3

BZD Pharmacokinetics

Generic Name	Trade Name	Rapidity	½ Life	Dose (mg)
alprazolam	Xanax	Intermediate	Short	0.75-4
chlordiazepoxide	Librium	Intermediate	Long	15-100
clonazepam	Klonopin	Intermediate	Long	0.5-4
diazepam	Valium	Rapid	Long	4-40
triazolam	Halcion	Intermediate	Very short	0.125-0.5
temazepam	Restoril	Short	Short	7.5-30

4

Issues with BZDs

- Addictive potential
- Confusion between “anti-anxiety” effects and the “warm-fuzzy)
- Large dose ranges
- Comparison of BZDs with medications like Buspar, etc.
- They work, they work well and they work quickly

5

Herbal Medication and Alternative Therapies Used in the Treatment of Depression and Anxiety



6

Alternative Tx. Learning Objectives

- List several amino acid treatments for depression
- List at least three of the most common herbal treatments used to reduce the symptoms of anxiety and depression
- List the benefits of vagal nerve stimulation (VNS) for depression
- Describe the relationship between ketamine and neurogenesis/neuroplasticity

7

Background Information on herbals: Natural does not necessarily mean “safe”

- Side-effects and adverse reactions
 - Herbal medications are “drugs” although they are considered supplements by the FDA
 - These compounds do, for the most part, act on the CNS
- Production of allergic reactions
- Interactions with other herbs and with more traditional medications



8

Background Information on herbals:
Natural does not necessarily mean “safe”

- Dosing is somewhat more difficult
 - % of active ingredients may differ across manufacturers
 - Herbs are not “pure”
 - Variety of administration formulas
 - Capsules (regular vs. SR vs. XR)
 - The dried herb itself
 - Liquid extract
 - Tincture
 - Transdermal application

9

Background Information on herbals:
Natural does not necessarily mean “safe”

- Because herbals are “supplements”:
 - Labeling is not regulated
 - Herbal cannot be patented
 - Thus, rigorous testing may or may not be available
 - Data may be missing regarding:
 - long-term safety
 - dose-response curves
 - Drug interactions



10

Some “safe” ways to go re: herbal products

- Commission E: part of the German Regulatory Authority
- The Herbal PDR
- Nature’s Way & other companies
- Vitacost.com
- Naturopaths & pharmacists
- Peer-reviewed journals
- Cross-referencing of sources



11

11

Non-Pharmaceutical
Approaches to
Treating Depression:
St. John’s Wort



12

Saint John's Wort

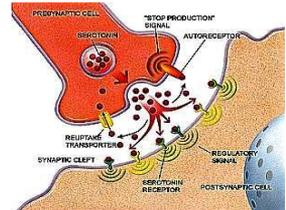


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13

Herbal Treatment of Depression: Saint John's Wort

- Clinical effects: mild anti-depressant
 - Mechanism of action: MAOI or SSRI
 - Inhibits reuptake of 5-HT, NE, DA
 - May cause down regulation of 5-HT2 autoreceptors



14

Herbal Treatment of Depression: Saint John's Wort

- Clinical effects/uses:
 - Anxiety
 - Depression
 - Insomnia
 - Menopausal mood changes/premenstrual syndrome
 - OCD
 - Social anxiety disorder



15

15

Herbal Treatment of Depression: Saint John's Wort

- Other Clinical effects/uses:
 - Inflammation of the skin
 - Blunt injuries, wounds, burns (has anti-bacterial properties)
 - Migraine headaches
- Drug interactions:
 - Anti-depressants (especially serotonergic)
 - Protease inhibitors
 - Contraceptives



16

16

Herbal Treatment of Depression: Saint John's Wort

- Side effects: St. John's Wort is fairly safe
 - Agitation, anxiety, irritability, restlessness
 - Dry mouth
 - Dizziness; headache
 - GI discomfort
 - Hypomania
 - Fatigue
 - Abnormal dreams



17

17

Herbal Treatment of Depression: Saint John's Wort

- Therapeutic dose:
 - 300 mg (3x/day)
 - Take 4-6 weeks (trial period)
- Cost: \$ 4.59/60 300mg tablets (10/2015)



18

18

Non-Pharmaceutical Approaches to Treating Depression: Ginkgo Biloba



19

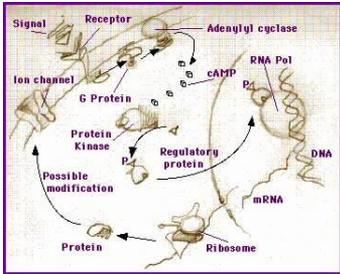
Herbal Treatment of Depression: Ginkgo Biloba (Ginkgo)

- Not listed in the "herbal PDR" for use as an anti-depressant
- Clinical effects: mild anti-depressant
 - Mechanism of action is not fully known
 - Increase in # of 5-HT receptors
 - Via increase in protein synthesis
 - Via antioxidant mechanism (decrease in free radical activity which damages cell membranes)

20

20

Ginkgo and Metabotropic Mechanism?

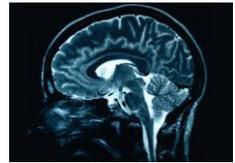


- Increase in receptors, via increase in protein synthesis, is a metabotropic effect
- Decrease in free radical activity may also be such an effect

21

Herbal Treatment of Depression: Ginkgo Biloba (Ginkgo)

- Increase in vascular flow (increases nutrients/O2 to the brain)
- Works well in persons over 50 years old (5-HT receptors decrease with age)



22

Ginkgo Biloba (cont.)

- Other indications (Commission E)
 - Symptomatic relief of organic brain syndrome/Alzheimer’s disease
 - Intermittent claudication
 - Vertigo (vascular origin)
 - Tinnitus (vascular origin)
- Drug interactions
 - Can take with traditional anti-depressants (unlike St. John’s Wort)
 - Anticoagulants/ASA (bleeding time)
 - May interfere with anti-convulsants



23

Ginkgo Biloba (cont.)

- Side effects: generally a safe herb to use
 - Increased bleeding time
 - Mild GI complaints
 - BP problems (maybe related to reported dizziness/headaches)
 - Allergic skin reactions
 - Adverse effects on oocytes



24

24

Non-Pharmaceutical Approaches to Treating Depression: Amino Acid Treatment



25

Depression: Amino Acid Treatment

- Amino acids used to treat depression include phenylalanine, tyrosine, tryptophan, and methionine
 - Phenylalanine & tyrosine are precursors to DA (converts to NE)
 - Tryptophan (and 5-hydroxytryptophan) are precursors to serotonin (5-HT)

26

Depression: Amino Acid Treatment

- Methionine gets converted to s-adenosyl-methionine (SAM)
 - The extract of this is SAME (“sammy”)
 - SAM increases levels of the monoamines
 - Improves monoamine binding naturally
 - SAM levels-lower in depressed persons
 - Side effects include nausea/vomiting
- Dose Maximum dose of 400 mg 4x/day to be reached gradually

27

Non-Pharmaceutical Approaches to Treating Depression: Nutritional supplements



28

27

Depression: Nutritional Supplements

- Eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA) : found in fish oils
 - Enhances levels of omega-3 fatty acids
 - Omega-3 levels have been shown to be reduced in people with depression
 - Amount to take unclear although 3 grams/day (3000mg) is of EPA/DHA not unusual
 - Side effects: high cholesterol and increased blood sugar

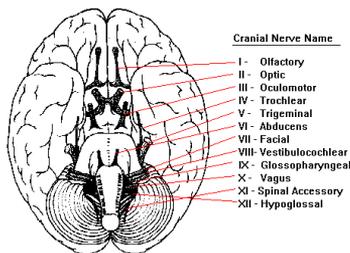
29

Depression: Nutritional Supplements

- Other supplements to consider: the “B” vitamins including folic acid, B6 & B12
- Iron supplements
- Take note:
 - Deficiencies in the levels of these supplements can worsen mood
 - Thus, such supplements
 - can decrease depressive symptoms
 - but will have little effect on depressed people with normal levels of the B vitamins & iron

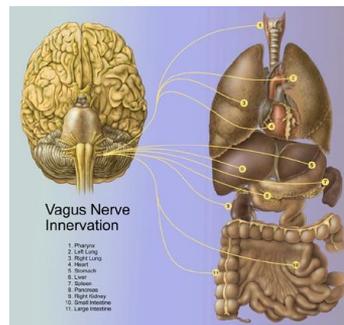
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Polyvagal Theory, Vagal Nerve Stimulation (VNS) and Trauma & Depression



31

The Vagus Nerve



Picture provided by Peter Jurek, MA, MS <http://www.peterjurek.com>

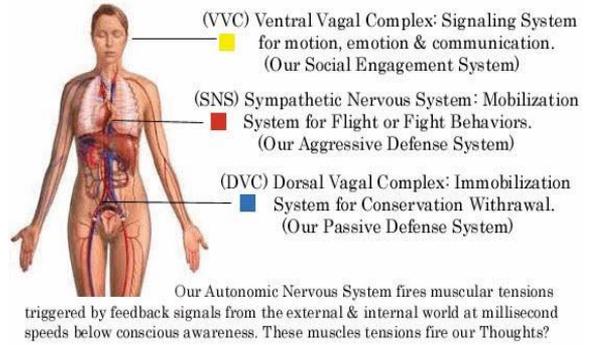
32

Polyvagal Theory

- Cortical Control of brainstem
- Brainstem regulation of the autonomic nervous system
- Autonomic nervous system
 - Sympathetic nervous system
 - Parasympathetic nervous
- Mammals versus reptiles and vagal evolution (and the freezing response)

33

Polyvagal Theory: Dr. Stephen Porges



34

Polyvagal Theory

- In what clinical conditions might you expect to see the freezing response?
 - Traumatic exposure
 - Depression
 - Anxiety diagnoses
 - Other?

35

Social Engagement System

- Changes in cardiopulmonary function
- Voice quality: prosody
 - Intonation and tone
 - Stress and rhythm
 - Vocalizations in our pets (my lovely Noelle!)
- Eye contact and movement
- Facial and head muscles



36

Polyvagal Theory in Practice: what can we do?

- Explain the roles the different systems play
- Educate that what their nervous systems/bodies are doing is based on survival, trying to keep the person safe (minimize disappointment, shame or anger about these biological responses)
- Discuss that interpersonal interactions can change nervous system function
- Minimize “older” circuit activity (next slide)

37

What is vagal nerve stimulation (VNS)?

- Note: this is an FDA approved technique (2005) for refractory depression; also approved (1997) as adjunctive therapy for partial-onset epilepsy
- A pulse generator is surgically implanted in the left chest area under the clavicle
- The leads from the generator are “wrapped” around the left vagus nerve branch; the right branch is avoided since it controls some aspects of cardiac function
- Intermittent pulses are delivered to the nerve

38

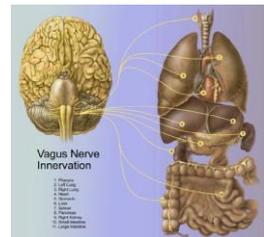
How does VNS work?

- Exact anti-depressant mechanism unknown
 - Stimulation does affect blood flow in various regions of the brain
 - As a result, neurotransmitter activity increases, including 5-HT and NE which would have an anti-depressant affect
- Side-effects: alteration of voice quality & loudness (during pulses only), hoarseness, throat pain, dyspnea (shortness of breath) & paresthesia
- Enhance social engagement system???

39

Other uses for VNS?

- Various anxiety disorders
- Alzheimer’s disease
- Migraines
- Fibromyalgia



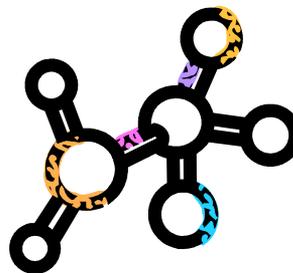
40

Treating Anxiety



41

The Biochemistry of Anxiety



42

The Biochemistry of Anxiety

- Important neurotransmitters
 - Gamma-aminobutyric acid (GABA: cortical and limbic areas)
 - Norepinephrine (sympathetic nervous system)
 - Serotonin
- Neurohormones: e.g. corticotropin releasing factor (CRF) inhibitors & the hypothalamic pituitary adrenal axis (HPA)

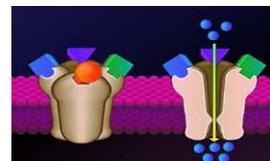


43

43

Anxiety

- Traditional treatment of anxiety
 - Medications/substances acting on the GABA complex
 - Alcohol
 - Barbiturates & non-barbiturate sedatives
 - Benzodiazepines



44

44

Non-Pharmaceutical Approaches to Treating Anxiety: Kava Kava



45

Kava Kava



46

46

Herbal Treatment of Anxiety: Kava Kava

- Clinical effects:
 - Muscle relaxant, anticonvulsive, anti-spasmodic
 - Hypnotic/sedative, analgesic, and anti-anxiety
 - Effects are mediated via GABA system
 - Compare these effects with benzodiazepines
- Other clinical effects:
 - Antithrombotic, asthmatic, nervous tension, stress and agitation

47

47

Herbal Treatment of Anxiety: Kava Kava

- Drug interactions:
 - Can potentiate effects of most CNS depressants
 - May potentiate St. John's Wort, valerian & traditional anti-depressants
 - Antagonizes effects of meds. designed to increase dopamine (e.g. L-Dopa)

48

48

Herbal Treatment of Anxiety: Kava Kava (cont.)

- Side Effects: dose dependent (occur primarily with higher dosages)
 - Yellowing of the skin, hair, nails
 - AM tiredness (early in tx. phase)
 - Minor movement inhibition/impaired motor reflexes; dyskinesia
 - Weight loss (only from high doses over an extended period)
 - Increased risk of suicide in persons with an endogenous depression

49

49

Herbal Treatment of Anxiety: Kava Kava (cont.)

- Side Effects (cont.):
 - Liver damage including:
 - Hepatitis
 - Liver failure
 - Cirrhosis
 - Some European countries have banned the sale of Kava Kava
 - Those at risk for or with known liver disease should not take Kava Kava



50

50

Herbal Treatment of Anxiety: Kava Kava (cont.)

- Therapeutic doses:
 - Anxiety: 50-70 mg kavalactones 3x/day
 - Insomnia: 150-210 mg kavalactones in a single dose before bed



51

Non-Pharmaceutical Approaches to Treating Anxiety: Valerian



52

Herbal Treatment of Anxiety: Valerian

- Clinical effects:
 - CNS depressant, hypnotic/sedative, anti-anxiety and muscle relaxant
 - Humans: reduces sleep induction time
 - Similar to Kava Kava and/or benzodiazepines
 - Increase GABA activity by binding to GABA receptors
 - Valerian also contains glutamine (which the brain converts into GABA)

53

53

Herbal Treatment of Anxiety: Valerian

- Other effects: anti-spasmodic & anti-ulcerogenic
 - Re: the latter reduces stress related hormone production
 - Perhaps through the HPA?
- Drug interactions:
 - Can potentiate the effects of the CNS depressants (like Kava Kava)
 - No hard evidence regarding potentiation of alcohol, however



54

54

Herbal Treatment of Anxiety: Valerian (cont.)

- Side effects:
 - Long term use: headaches, restless states, sleeplessness, disorders of cardiac function
 - Not recommended during pregnancy nor in nursing mothers
- Therapeutic doses
 - Restlessness: 220mg extract 3x/day (dosage for anxiety would be similar)
 - Sleep aid: 400mg to 900mg extract 30-45 minutes before bed
 - Cost: \$5.89 (60 servings)

55

55

Rauwolfia Serpentina



56

Herbal Treatment of Anxiety: Rauwolfia

- Clinical effects:
 - Anti-anxiety
 - Blocks NE storage & other monoamines within the nerve ending in both the CNS and PNS
 - Due to reserpine like alkaloids (medically, reserpine is used to lower blood pressure)
 - The bottom line is similar to Clonidine & Inderal (a reduction in NE activity)
- Other clinical effects: treat hypertension & snakebites, etc. (India)

57

57

Herbal Treatment of Anxiety: Rauwolfia

- Drug Interactions:
 - Alcohol: increase in impairment
 - Neuroleptics/Barbiturates: an ↑ in drug effect occurs with these meds.
 - Digitalis-glycosides: bradycardia
 - Levodopa (L-Dopa)
 - Decrease in the drugs' effects
 - Increase in EPS (movement side-effects)
 - Cough, flu remedies & appetite suppressants: may cause ↑↑ BP

58

58

Herbal Treatment of Anxiety: Rauwolfia

- Side effects: few for normal dose ranges
 - Depression (like reserpine); in fact, Rauwolfia contraindicated in depression
 - Tiredness, erectile dysfunction, nasal congestion and drowsiness
 - Should not be used with pregnant/nursing women nor in depressed individuals



59

Other Herbal Products for Reducing Anxiety (recommended by Commission E)

- Bugleweed
- Camphor Tree
- English Lavender
- Hops
- Lemon Balm
- Lily of the Valley
- Passion Flower (taken in combination with Valerian)



Passion Flower

60

Treating Anxiety by Reducing Lactic Acid



61

61

Anxiety and Lactic Acid

- Normal metabolic processes (involved with producing energy) are as follows:
 1. Glucose \Rightarrow Pyruvic acid + energy
 2. Pyruvic acid + O₂ \Rightarrow H₂O + CO₂
If no O₂ is available (which occurs during strenuous exercise) then:
 3. Pyruvic acid \Rightarrow H₂O + CO₂ + lactic acid
- In people who suffer from panic attacks:
 - High lactic acid/pyruvic acid ratio
 - Lactate (soluble lactic acid) sensitivity

62

62

Anxiety and Lactic Acid

- Methods of reducing anxiety by reducing lactic acid levels:
 - Reduce caffeine, alcohol and sugar intake
 - Increase intake of B-vitamins, niacin, pyridoxine, thiamin, calcium and magnesium



63

63

Clinical Use of Substances Of Abuse?

Ketamine Infusion Therapy

64

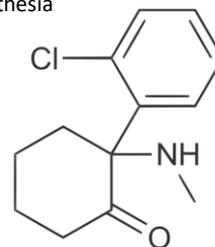
Substantial History of Using Substances of Abuse Clinically

- Freud and cocaine
- Benzodiazepines/barbiturates
- Methadone (and to lesser degree, Suboxone)
- Psychostimulants (ADHD)
- A whole host of analgesics
- THC: glaucoma, anti-emetic (chemo)
- More currently: Ecstasy & Ketamine

65

Ketamine: What is it?

- Ketamine is a dissociative anesthetic
- Uses include:
 - Starting or maintaining anesthesia
 - Analgesic
 - Sedation
 - Treatment of bronchospasm
 - **Antidepressant**
- Substance of abuse



66

Ketamine: How does it work?

- Has an effect on the glutamate system in the brain
 - Is an N-methyl-D-aspartate (NMDA) receptor antagonist
 - α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid agonist (AMPA)
 - Other glutamate receptors
 - Inhibitor of monoamine (DA, 5HT, NE) reuptake
 - Opioid receptors (weak)

67

Ketamine: Effect on BDNFs?

- What are brain-derived neurotrophic factors (BDNFs)?
 - A protein encoded by the BDNF gene. BDNF is a member of the neurotrophin family of growth factors, which are related to Nerve Growth Factor. Neurotrophic factors are found in the brain and the periphery.

68

Ketamine

- What are brain-derived neurotrophic factors (BDNFs)?
 - Psychological & immune system stressors may interact with genetic vulnerability
 - This decreases BDNF activity
 - Neuroplastic processes decrease
 - Result can be depression



69

Ketamine

- Ketamine enhances neuroplastic changes in
 - The hippocampus
 - The cortex
- The result is enhanced cellular connections and functioning which reduces depressive symptomology
- Effects of ketamine infusion can be seen within hours of treatment
- Effects may last up to 2 weeks

70

And that's all she wrote....good luck in your personal lives and your professional careers!!!



71