Less Stress When You Don’t Guess:

Testing Options for Anxiety & Insomnia

Bradley Bush, ND
Disclaimer

- Dr. Bradley Bush works for NeuroScience, Inc. that offers neuro–endo–immune testing and a small nutritional product line.
Anxiety

18% of the population

60% more likely

Insomnia

- Some 70 million people in the United States have a sleep problem.

(National Heart, Lung and Blood Institute
Menopause and Anxiety

Recently, research has shown that certain hormones can have fast acting effects in the CNS.

During menopause, when fluctuations in these hormones occurs, there can be a resulting increase in mood related issues.
Leaning objectives

At the conclusion of the lecture attendees will be able to:

- treating anxiety and insomnia using functional tests and natural medicines.
- educate patients about anxiety / insomnia’s:
  - frequency rates in peri/menopausal pollutions
  - relationship to stress.
- be able to Integrate functional laboratory markers and natural treatments.
Topics

- Anxiety and Insomnia in peri–post menopausal women
- Biological considerations
- Functional testing for anxiety and insomnia
- Natural treatments
Insomnia risks

- Postmenopausal women with greater insomnia scores, especially non-obese women, had a significantly increased risk of thyroid cancer.

- 142,933 postmenopausal women (50–79 yo) and enrolled in the Women's Health Initiative.

- The significant association between insomnia score and thyroid cancer was confined to nonobese women (hazard ratio = 1.71, 95% confidence interval: 1.12, 2.62) and was not seen in obese women (hazard ratio = 0.94 95% confidence interval: 0.48, 1.84) (P for interaction = 0.07).

Insomnia/Anxiety/Depression Relationship

- 237 peri- and post-menopausal women (3 yrs)
- Menopausal Health–Related Quality of Life (MHR–QOL) and Hospital Anxiety and Depression Scale (HADS) questionnaires

Conclusions
- Insomnia is highly prevalent.
- Difficulty in initiating sleep (DIS) is strongly associated with anxiety.
- Non-restorative sleep (NRS) is strongly associated with depression.

Depression, Menopause Statistics

- 685 women ages 45–59
- Mean age was 50.6 years
- Prevalence of depression symptoms among perimenopausal and postmenopausal women was 41.8%
  - Of all women in study, 23.2% premenopausal, 56.9% postmenopausal
- Depressive symptoms 1.8x higher in perimenopausal–postmenopausal period than in premenopausal period
- High level of prevalence of depression symptoms in peri/postmenopausal women

2002 Gallup poll of menopausal women

- hot flashes (70%)
- night sweats (68%)
- mood disturbances (50%)
- Sleep disturbances (49%).

Effectiveness of controlling

- Estrogen 77% (reduction of 2.5–3 incidents daily)
- SSRIs 50–66% (study durations 4wks – 9 months)
- Clonidine 44–55% (many poor studies, works better as a co–treatment (w/ estradiol)
- Red clover isoflavones 17–48%
- Soy isoflavones 24–61%

### Table 6. Summary of Trials

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. of Trials in Review</th>
<th>Trial Quality</th>
<th>No. of Comparisons in Meta-analysis</th>
<th>Mean Difference in No. of Daily Hot Flashes vs Placebo (95% CI)*</th>
<th>Severity or Composite Score (% Difference)†</th>
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<tbody>
<tr>
<td>SSRIs or SNRIs</td>
<td>6</td>
<td>Fair-good</td>
<td>7</td>
<td>-1.13 (-1.70 to -0.57)</td>
<td>Improved in 4 of 6 trials (10-36)</td>
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<tr>
<td>Veralipride</td>
<td>3</td>
<td>Poor</td>
<td>0</td>
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<td>Improved in 2 of 2 trials (40)</td>
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<tr>
<td>Moclobemide</td>
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<td>Poor</td>
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<td>†</td>
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<tr>
<td>Clonidine</td>
<td>10</td>
<td>Poor-fair</td>
<td>4 at 4 wk</td>
<td>-0.95 (-1.44 to -0.47)</td>
<td>Improved in 4 of 7 trials (13-26)</td>
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<td></td>
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<td>2 at 8 wk</td>
<td>-1.63 (-2.76 to -0.05)</td>
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<td>Methyldopa</td>
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<td>Gabapentin</td>
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<tr>
<td>Belogal Retard</td>
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<tr>
<td>Red clover isoflavone extracts</td>
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<td>Poor-good</td>
<td>8</td>
<td>-0.44 (-1.47 to 0.58)</td>
<td>No difference</td>
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<tr>
<td>Soy isoflavone extracts</td>
<td>11</td>
<td>Poor-fair</td>
<td>5 at 4-6 wk</td>
<td>-1.15 (-2.33 to 0.03)</td>
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<td>4 at 12-16 wk</td>
<td>-0.97 (-1.82 to -0.12)</td>
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<td>2 at 6 mo</td>
<td>-1.22 (-2.02 to -0.42)</td>
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Abbreviations: CI, confidence interval; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

*Based on meta-analysis of eligible trials.
†Composite score equals frequency × severity.
‡Between-group differences not reported.
Serotonin & Women’s Health

- Selective serotonin reuptake inhibitors (SSRIs) are frequently used to address:
  - Depression
  - Headaches
  - Sleep disturbances
  - Libido issues
  - Menopausal symptoms

- However, relationship between estrogen and serotonin is ignored
What goes up, can also come down

- 76, 57, and 51 women included in the analysis for VMS frequency, severity, and bother.

- 34.2%, 38.6%, and 37.3%, respectively, had relapse

- 1/3\textsuperscript{rd} of women relapsed quickly after discontinuing escitalopram (10mg) (those taking 20mg were titrated to 10mg before discontinuing.

50 y.o. Female

Hot flashes, anxiety, fatigue, depression, difficulty initiating sleep, wakes up tired, VMSs (reduced with bHRT)

- Low
  - Estrogens
  - Progesterone
  - Testosterone

- On bHRT
  - Started with progesterone 50mg cream b.i.d.
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Menopausal Transitions and Neurotransmitters

Hormones affect the menopause, levels of this can lead to anxiety, insomnia.
Functional Tests

- Urinary neurotransmitter testing
  - Serotonin, NE, EPI, PEA, Glutamate
- Interfering factors
  - Dilute urine samples
  - Serotonin (Inflammation): Reduced levels can accompany chronic inflammation. Immune activation causes shunting of tryptophan down the kynurenine pathway, leading to reduced serotonin synthesis
  - Glutamate (Inflammation and immune activation)
  - Norepinephrine (Inflammation and immune modulation) Down-regulates innate cell stimulation
Functional Testing

• Food sensitivity tests
  • IgG, electro-dermal, etc.
  • Use to increase pt compliance to elimination

• Genetic
  • MTHFR (methylation and monoamine synthesis)
  • COMPT (methylation, estrogen processing, NE/Dopamine balance, Dopamine levels)
Hormone effects on Neurotransmitters

• Estradiol
  • Decreases MOA activity
  • Increases NT levels

• Progesterone
  • Increases MOA activity
  • Decreases NT levels
# NeuroEndocrine Connection

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<td>L-Tryptophan</td>
<td>Increases Availability</td>
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<tr>
<td>5 HT2a Receptors</td>
<td>Increases Number</td>
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<tr>
<td>MAO Activity</td>
<td>Inhibits</td>
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<tr>
<td>BDNF (brain derived neurotrophic factor)</td>
<td>Increases</td>
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<td>NT Receptors on Estradiol Responsive Neurons</td>
<td>Activates</td>
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<td>Glutamate: NMDA</td>
<td>Inhibits</td>
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Estrogen

• Incidence of major depression was found to be greater (2:1) in women than in men in the U.S.
• Research indicates that risk of mood disorders intensifies with hormonal changes
• Studies show efficacy of estrogen therapy for depression during perimenopause

Estrogen–Serotonin

- Estradiol increases serotonin levels by increasing tryptophan hydroxylase (rate limiting enzyme in serotonin synthesis).
- Estradiol inhibits monoamine oxidase (MAO) enzyme responsible for degradation of monoamines like serotonin.
- Estradiol stimulates an increase in serotonin receptor sites (5HT2a); involved mood, cognition, temperature regulation and the inhibition of pain.
- Estrogen and serotonin influence the thermoregulatory set point in the
Estrogen–Serotonin

Studies done on ovariectomized rats given estrogen treatment have shown estrogens ability to regulate serotonin

- Acute estradiol administration increased serotonin and its metabolite 5-HIAA in various brain regions
  - Dorsal raphe
  - Striatum
  - Medial preoptic nuclei
  - Ventromedial and cortical amygdaloid nuclei
- Increase of serotonin turnover in these regions

Chronic administration of estradiol or estradiol and progesterone were found to increase the accumulation rate and levels of serotonin in dorsal raphe of ovariectomized rats

- Estradiol found to promote serotonin synthesis and release
- Acute or chronic estrogen therapy were shown to increase 5-HT$_{2A}$ receptor binding in the frontal cortex, striatum, anterior cingulate, primary olfactory cortex, and nucleus accumbens

Estrogen increases Serotonin Recycling

- Estrogen administration was found to increase serotonin transporter (SERT) binding
  - Leads to connection with enhanced mood
- SSRIs prevent uptake by SERT and reuptake sites have been observed to be deficient in patients with depression
- Proposed genetic component for SERT inefficiency

Estrogen and Neuropeptides

Estrogens can modulate β-endorphin activity and receptor expression.

β-endorphin exerts behavioral, analgesic, thermoregulatory, and neuroendocrine properties.

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So how does this change our approach?

- Serotonin (urine)
  - L 82 (150–200)
- What medications or supplements can be offered?
  - SSRI/ SNRI
  - L–tryptophan
  - 5–HTP
Clinical Pearl

- Decreased estrogen is associated with decreased serotonin and increased serotonin receptor function in the hypothalamus. Serotonin release triggered by internal or external stimuli may activate these up-regulated hypothalamic serotonin receptors to trigger a hot flash.
- 5-HTP can temporarily increase hot flashes in patients with very low urinary serotonin values (<60).
  - Start with L-tryptophan 500–1000mg h.s.
    - 1000mg b.i.d. if anxiety present
  - Transition to 5-HTP 15–50mg per dosing
Neuroactive steroids such as allopregnanolone induce anxiolytic, anticonvulsant, and sedative effects.

These effects are due to the binding of allopregnanolone to GABAa receptors as an agonist.
Progesterone

- GABAergic effects of its active metabolite (allopregnenolone)
  - Supports GABA

- Increases MAO activity
  - Can help reduce norepinephrine activity
Neuroactive Steroids

Potent neuroactive steroid modulators of the GABA_A receptor function include:

- allopregnanolone (ALLO)
- allotetrahydrodeoxycorticosterone (THDOC) (metabolized from progesterone)
  
  • THDOC and ALLO act as positive allosteric agonists of the GABA_A receptor

- Dehydroepiandrosterone (DHEA) in the sulfated form can display antagonistic properties at the GABA_A receptor... beware

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Does this change our approach?
Glutamate and GABA

- Under normal physiological conditions, glutamate and GABA activity is in balance.
- Glutamate increase with:
  - Stress
  - Inflammation
  - Immune activity
Causes for Increased

- Vitamin B6 deficiency (rate limiting factor for glutamate decarboxylase enzyme to facilitate the conversion to GABA)
- Gluten sensitivity creates gliadin antibodies which specifically inhibit the glutamate decarboxylase enzyme.
- Immune activity (infection or leaky gut)
Glutamate

- Glutamate from microglial cells
  - Binds directly to receptors on T cells
  - This potentially influences cytokine expression in a concentration-dependent manner
    - Enhancing production at lower concentrations
    - Decreasing production at very high concentrations.

- Glutamate from dendritic cells
  - The most abundant antigen-presenting cells in the body
  - When dendritic cells mature and come into contact with T cells, glutamate is released.
  - 80–90% of dendritic cells are in the GI tract.


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Slight elevation = NT imbalances

Moderate elevations = leaky gut, food allergies

Very high (>90) = all the above and/or active/chronic infection/exposure
So how does this change our approach?

- Reduce glutamate to:
  - Indirectly support GABA
  - Increase BDNF and reduce brain toxicity
- Identify cause of elevated glutamate
  - CBC (infection)
  - Food sensitivity/allergy test
  - Stool test (parasites)
  - Organic acid test (bacterial, yeast)
- Supplementation to reduce glutamate levels
  - L-theanine, 4-amino-3-phenylbutyric acid, NAC
Beta-Phenylethylamine (PEA)

- Excitatory monoamine neurotransmitter.
- Elevated levels associated with anxiety, insomnia, and “worrying”.
- Subnormal phenylethylamine levels have been linked to disorders such as attention deficit and depression.
- Observed to be low in patients with brain fog and other cognitive challenges.
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Clinical Significance

- The hormones and other physiological agents that mediate the effects of stress on the body have protective and adaptive effects in the short run and yet can accelerate *pathophysiology* when they are over-produced or mismanaged.
Allostatic Load

- defined as the physiological consequences of chronic exposure to fluctuating or heightened neural or neuroendocrine response that results from repeated or chronic stress

coined by McEwen and Stellar in 1993

McEwen 2000
Figure from McEwen 2000
Stress Mediators

• Primary mediators
  • Sympathetic NS = Cortisol, epinephrine, norepinephrine, DHEA

• Secondary outcomes
  • Systolic and diastolic blood pressure
  • Waist–hip ratio (also BMI)
  • Serum HDL and total cholesterol
  • HbA1c

• Tertiary outcomes
  • Physical disease
  • Mental disease

Addressing Hot Flashes in Estrogen Sensitive Women

- Consider:
  - Progestogens
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
    - Venlafaxine
    - Paroxetine
    - Fluoxetine
  - Gabapentin

Treat Endocrinol. 2006;5(2):83-7
Hot Flashes and Anxiety

Perception, processing, and evaluation of viscerosensory information are associated with the limbic network and the afferent projections of cortically processed information is reciprocally connected to the amygdala. Thus, the overlap in symptoms of hot flashes and panic attacks may likely be a result of similar neural correlates in the hypothalamic and locus coeruleus activation.
Temperature Regulation

- Imbalances in both hormone and neurotransmitter levels can lead to hot flashes and night sweats.

- Serotonin receptor 5HT$_2$A is responsible for temperature regulation throughout CNS.

Diagram:
- Decreased Estrogen Levels
  - Decrease in density of 5HT$_2$A
  - Decrease in serotonergic activity
Hot Flashes

- Development of **hot flashes** seems related to the **instability of serotonin and norepinephrine** activity in the hypothalamus
  - A narrowing of the hypothalamic thermoregulatory set point
    - Occurs in 70% of women

- Basis for the use of SSRIs and SNRIs

Jenkins JR, Sikons AL. CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 75 • SUPPLEMENT 4 MAY 2008
• Norepinephrine production and release in thermoregulatory nucleus is thought to be tonically inhibited by endorphins and estrogen
• Estrogen and testosterone can stimulate natural endorphin production and may exert a modulatory effect on NE release both directly and indirectly
Menarche

Regulation of GABA, serotonin, norepinephrine

Regulation of LH, FSH

Hypothalamus

Pituitary

Anterior Pituitary

LH, FSH

Maturation of ovarian follicles

Release of Estrogen from follicles provides negative feedback to hypothalamus and pituitary
Menopause

Release of Estrogen from follicles provides negative feedback to hypothalamus and pituitary

- Release of Estrogen from follicles provides negative feedback to hypothalamus and pituitary
- Increases in LH, FSH
- Maturation of ovarian follicles
- LH, FSH
- Increases in serotonin, GABA, norepinephrine
- Hot flash is initiated through alpha-2 adrenergic and/or 5-HT2 receptors, both of which are thermoregulatory and become sensitized during estrogen withdrawal

Hypothalamus

Pituitary

Anterior Pituitary

LH, FSH

Increases in LH, FSH
<table>
<thead>
<tr>
<th>VMS Markers</th>
<th>Result</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>0.9</td>
<td>Menopause: 1.0-2.0</td>
</tr>
<tr>
<td>Estrone</td>
<td>1.1</td>
<td>Menopause: 1.0-3.0</td>
</tr>
<tr>
<td>Estriol</td>
<td>9</td>
<td>Menopause: 20-50</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.061</td>
<td>Menopause: 0.200-0.500</td>
</tr>
<tr>
<td>Testosterone</td>
<td>12</td>
<td>15-35</td>
</tr>
<tr>
<td>DHT</td>
<td>5</td>
<td>5-12</td>
</tr>
<tr>
<td>DHEA</td>
<td>112</td>
<td>200-400</td>
</tr>
<tr>
<td>Cortisol</td>
<td>4.9</td>
<td>7-10</td>
</tr>
<tr>
<td></td>
<td>2.3</td>
<td>3-6</td>
</tr>
<tr>
<td></td>
<td>6.4</td>
<td>2-4</td>
</tr>
<tr>
<td></td>
<td>2.9</td>
<td>&lt;1.5</td>
</tr>
</tbody>
</table>
Hot Flashes

- **Endocrine**
  - Unstable adrenal gland
  - ↓ estrogen and/or progesterone
  - ↑ cortisol or altered rhythm
  - ↓ testosterone

- **Neurotransmitter (General Guide)**
  - ↓ Norepinephrine
  - ↓ Serotonin
  - ↑ Norepinephrine, ↓ serotonin
  - Challenged GABA / ↑ Glutamate
Clinical Peal

Neurotransmitter balancing in patient with VMS controlled by bHRT.

• Estrogen tx
  • 5-HTP and adrenal support can cause a return of VMS
    • Lower estrogen tx while slowly adding serotonin and NE support
    • Consider working on lowering glutamate and PEA first

• Progesterone
  • Oral micronized can slowly be replace/complement with additional GABA support
Sympathetic/ HPA axis

- Elevated cortisol
- Desensitized cortisol receptors
- Altered cortisol rhythms
Adrenals as a Source of Sex Hormones

• Pre-menopause
  – Primary source of:
    • Androstenedione
    • Testosterone
    • DHT

• Post-menopause
  – Primary source of:
    • Progesterone (via adrenal produced pregnenolone)
    • Estrogens (adrenal cortex and peripheral tissue conversion of androstenedione)
    • As well as androstenedione, testosterone, and DHT
Stages of Adrenal Fatigue

Cortisol & DHEA Levels

Early-Stage

Mid-Stage

End-Stage
Early-Stage Adrenal Fatigue

Biomarker Levels

- ↑ DHEA
- ↑ Cortisol
- ↑↑ Epinephrine
- ↑ Norepinephrine
- ↑↓ Optimal Serotonin
Mid-Stage Adrenal Fatigue

Biomarker Levels
- ↑↓ DHEA
- ↓ Cortisol
- ↑↓ Epinephrine
- ↑↓ Norepinephrine
- ↓ Serotonin
Common Mid-Stage

Anxiety
- Serotonin: L
- NE: H
- Glutamate: H
- PEA: H

Insomnia
- Serotonin: L
- Cortisol: H (pm-bed)
- Glutamate: H
- PEA: H
- NE: H (in many cases)
- EPI: H (in sympathetic overdrive)
Common Mid-Stage Curves

Salivary cortisol
- 4 point collection
  - L-shaped cortisol curve
  - Reversed cortisol rhythms
- Interfering factors
  - Hydrocortisone
  - Stress
  - Blood contamination
  - Poor glycemic control
Menopausal Transition and Catecholamines

Increase in norepinephrine release

Decrease in dopamine release

L-Dopa well tolerated for non-stimulating energy support.

End-Stage Adrenal Fatigue

Biomarker Levels
- ↓ DHEA
- ↓ Cortisol
- ↓ ↓ Epinephrine
- ↓ ↓ Norepinephrine
- ↓ Serotonin
BMI

• BMI is associated with anxiety
  – 89 patients
  – Strong correlation of anxiety with BMI and resistance vessel dysfunction


• Higher BMI the greater the VMS

# Pharmacological Interventions

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Key Clinical Features</th>
<th>Common Pharmacological Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>Characterized by excessive and uncontrollable worry about everyday things</td>
<td>Buspirone (20-30 mg/day), fluoxetine (20 mg/day), sertraline (25-200 mg/day), citalopram (20-40 mg/day), diazepam (4-40 mg/day), alprazolam (.25-4 mg/day)</td>
</tr>
<tr>
<td>Separation Anxiety Disorder</td>
<td>Excessive and uncontrollable anxiety in regards to being apart from a person or home of strong emotional attachment</td>
<td>Fluvoxamine (50-300 mg/day), sertraline (25-200 mg/day), fluoxetine (20 mg/day)</td>
</tr>
<tr>
<td>Specific Phobia</td>
<td>The persistent and irrational fear of an object or situation</td>
<td>Fluoxetine (20-30 mg/day), sertraline (25-200 mg/day), citalopram (20-40 mg/day), diazepam (4-40 mg/day), alprazolam (.25-4 mg/day)</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>The persistent and irrational fear of public situations and criticism, typically involving humiliation or embarrassment</td>
<td>Fluoxetine (20 mg/day), sertraline (25-200 mg/day), citalopram (20-40 mg/day), diazepam (4-40 mg/day), alprazolam (.25-4 mg/day)</td>
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## Pharmacological Interventions

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<td>Panic Disorder</td>
<td>Characterized by chronic and severe panic attacks, as well as the fear of future episodes</td>
<td>Fluoxetine (10-60 mg/day), sertraline (25-50 mg/day), diazepam (4-40 mg/day), clonazepam (.25-1 mg/day)</td>
</tr>
<tr>
<td>Obsessive-compulsive Disorder</td>
<td>Characterized by persistent thoughts that produce worry as well as repetitive behaviors that aim to reduce the anxious feelings</td>
<td>Fluvoxamine (50-300 mg/day), fluoxetine (20-60 mg/day), sertraline (25-200 mg/day), diazepam (4-40 mg/day), clonazepam (.25-1 mg/day), gabapentin (300-1800 mg/day), memantine (5-20 mg/day)</td>
</tr>
<tr>
<td>Post-traumatic Stress Disorder</td>
<td>Anxiety caused by a traumatic experience or chronic exposure to severe stressors.</td>
<td>Fluoxetine (20-60 mg/day), sertraline (25-50 mg/day), topiramate (50-400 mg/day), lamotrigine (100-400 mg/day), propranolol (160-480 mg/day)</td>
</tr>
</tbody>
</table>
GABA A receptor

benzodiazapine (BDZ) binding site

benzodiazapine
gamma sub-unit

post-synaptic membrane

cytoplasm

GABA A synaptic cleft

GABA

Cl-

Cl-

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Natural Alternatives

- 5-HTP
- L-Theanine
- L-Theanine
- 4-amino-3-phenylbutyric acid
- Glycine, Phosphatidylserine, Banaba leaf (Corosolic Acid), N-acetylcysteine (covered in other presentation)
5–HTP

• 5–HTP is a precursor to serotonin and supplementation leads to increased levels of serotonin which calm the mind and body.
• 25–150 mg/day
• Not always needed in lifelong anxiety cases, but almost always useful in all other cases of anxiety. My preferred precursor to serotonin. Avoid using it in the daytime, due to its competition with catecholamines for rate limiting enzymes.
L-tryptophan

- Similar to 5-HTP, L-tryptophan is a precursor to serotonin and serves to increase levels of serotonin in the body.
- 500–2000 mg/day
- Less effective than 5-HTP but better choice to support serotonin when patient’s levels are very low or have a history of GI complaints. It is also very useful to be used with 5-HTP therapy at the same time or during the day for low-level
L-theanine

- Antagonizes glutamate receptors and increases levels of GABA in the brain.
- 150–300 mg/day
- TID for anxiety. Can take PRN if feeling agitated.
4-amino-3-phenylbutyric

- Agonizes GABA(B) receptors and antagonizes β-phenethyamine. Does not bind to benzodiazepine receptor subtype.
- 100–800 mg/day
- Use this BID if anxiety is felt all day long or just at bed for insomnia. Dosing is effective for about 4–6
Take Homes

• Anxiety and insomnia frequently occur in the general population and at higher levels in women (especially peri–post–menopausal).
• The biochemistry behind hot flashes is similar to that that causes anxiety and insomnia.
• Functional tests can be used to focus treatment.
• Bradley Bush, ND
• bbushnd@gmail.com