Recognition and Treatment of Anxiety in the Medically Ill

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Disclosure

- Dr. Welton has no relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.
Objectives

By the end of this session attendees will be able to:

- Recognize anxiety as both a set of symptoms and a series of specific disorders
- Outline the underlying neurobiology of anxiety
- Rate the quality of evidence regarding the treatment of anxiety in medical conditions
- Propose treatment recommendations based on their understanding of the underlying neurobiology
Problem with “Anxiety”

Coke =

Anxiety Disorders
Anxiety

- **Anxiety is a set of specific disorders**
  - Generalized Anxiety Disorder, Phobias, Panic Disorder
- **Anxiety is a general symptom**
  - Can be the result of other psychiatric conditions
    - Major Depression, Schizophrenia
  - Can be caused or mimicked by other medical conditions
    - COPD, Pheochromocytoma
  - Can be caused by drugs or medications
    - Stimulants, steroids
    - Alcohol withdrawal
Anxiety is a Complex Response

Responses to perceived threats will be highly personalized
Anxiety Symptoms

- **Cognitive**
  - Worry
  - Doubts
  - Ruminations

- **Emotional**
  - Fear
  - Apprehension

**Physical**

- Dizziness, decreased sex drive, irritability
- Increased muscle tension
- Rapid breathing & breathlessness
- Heart palpitations
- Chest pain
- Increased blood pressure
- Nausea or diarrhea
- Numbness
- Chills / hot flashes
Where Does Anxiety “Live”

- What parts of the brain and body are responsible for anxiety
- What hormones and neurotransmitters are involved
Neuroanatomy of Fear and Anxiety

Modified from Goddard and Charney 1997
Brain Regions Involved in Anxiety

- Fear / Danger Response Systems (Amygdala, Locus Ceruleus)
  - Overly active and reactive
  - Activates physical response to fearful stimuli
    - Sympathetic Nervous System
    - Hypothalamic-Pituitary-Adrenal Axis
- Orbitofrontal and Medial Pre-Frontal Cortex and Cingulate Cortex
  - Experience, evaluation and control of emotions
Brain Regions Involved in Anxiety

- Hippocampus
  - Emotional content of memory
  - Context
- Prefrontal Cortex
  - Planning
  - Decision making
  - Predicting the consequences of future action
General Summary

- Over-activation of fear/danger response system
  - Amygdala, Locus Ceruleus, Sympathetic Nervous System

- Under-activation of control systems
  - Prefrontal Cortex
  - Cingulate Cortex

- Helpful if facing acute danger, not helpful on a day in and day out basis
Neurohormonal Component

- Activated by locus ceruleus and amygdala
- Activates/coordinates general body stress response
- Modulates inflammatory system which seems related to mood state
Hypothalamic-Pituitary-Adrenal Axis

- Hypothalamus – Corticotropin Releasing Hormone (CRH)
- Pituitary – Adrenocorticotropic Hormone (ACTH)
- Adrenal – glucocorticoids
Hypothalamic-Pituitary-Adrenal Axis

Anxiety Disorders
Corticotropin Releasing Hormone

- 41 amino acid peptide released by hypothalamus and central nucleus of amygdala
- CRH R-1 activation is anxiogenic
- CRH stimulates locus ceruleus
- Associated with:
  - Increased fearfulness
  - Decreased sleep, eating, sex

Landgraf 2005
Cortisol

- Released by adrenal gland
- Normally provides negative feedback to HPA system
- Modulates inflammatory system
- Chronic elevations are neurotoxic to neurons in the hippocampus and other regions of the brain
- May suppress neurotrophic factors (BDNF)
Neurotransmitters and Anxiety

- Glutamate
- Gamma-aminobutyric Acid (GABA)
- Norepinephrine
- Serotonin
- Neuropeptide Y
- Substance P
Glutamate

- Primary excitatory neurotransmitter
- Stress increases glutamate activity in hippocampus and prefrontal cortex
  - Chronic elevation may be neurotoxic

- Glutamate (especially NMDA activation) essential for long-term potentiation of neurons (learning)
  - Fear-based learning
  - Fear extinction

Cortese 2005
Gamma-aminobutyric Acid (GABA)

- Primary inhibitory neurotransmitter
- Linked to barbiturate, alcohol and benzodiazepine receptors
- Increases influx of Cl\(^{-}\) leading to hyperpolarization

Lydiard 2003

http://thebrain.mcgill.ca/flash/a/a_04/a_04_m/a_04_m_peu/a_04_m_peu.html

Anxiety Disorders
Norepinephrine

- Locus ceruleus produces much of the brain’s NE
- Neurotransmitter of the Sympathetic Nervous System
  - Tachycardia, hypertension, tremor, muscle tension
- Increasing NE activity induces panic attacks in vulnerable populations
  - e.g. Yohimbine
Serotonin (5HT)

- Projections to the locus ceruleus and amygdala
- 5HT-1A agonists are anxiolytic
- Other 5HT receptors are anxiogenic
- Serotonergic agents are effective in treating numerous anxiety disorders (GAD, PTSD, OCD, Social Anxiety)

Ninan 1999
Neuropeptides

- Neuropeptide Y
  - CNS infusion decreases anxiety
  - Buffers the effect of CRH

- Substance P
  - Involved in emotion and pain
  - Blocking Substance P decreases anxiety behavior
New Summary

- Over-activation of fear response system
- Under-activation of control systems
- These are mediated and/modulated by neurotransmitters
- Because of the considerable overlap among anxiety symptoms…

Treatments for anxiety are largely focused on these underlying factors rather than discrete treatments for individual problems. 
Under-activation of control systems

- Focus of Psychotherapy
- Top-Down approach – strengthens control over limbic activity

Studies showing partial normalization of brain activity in patients with:
- Panic Disorders, Social Phobia, Specific Phobias (arachnophobia), Post-traumatic Stress Disorder
Therapy Options
Types of Therapy

- **Cognitive Therapy**
  - Identifies the patient’s beliefs about themselves, others and the world around them
  - Challenges to see if they are accurate
  - Decrease anxiety by having a more realistic view of reality
  - *If I have cancer my life is over*

- **Behavior Therapy**
  - Encourages health promoting behavior (e.g. relaxation, exercise, enjoyable activities)
  - *If I felt better I would be more active…No, be more active and you will feel better*
Types of Therapy

- **Supportive Therapy**
  - Improve decision making
  - Access means of support
  - Very practical and focused
  - *How can you help yourself get through these next few days while you are waiting for your test results*

- **Psychodynamic Therapy**
  - Explores life long patterns of behavior, emotions and relationships
  - Less likely to be helpful in dealing with acute medical problems
Treatment Options

- Using neurotransmitters to modulate an overactive fear response system.
  - Focus of pharmacological interventions

- Primary pharmacological options
  - Antidepressants
    - Tricyclics, SSRIs, SNRIs
  - Buspirone
  - Benzodiazepines
  - Others
    - Antihistamines, antipsychotic medications
Antidepressants

- **Tricyclic Antidepressants**
  - Amitriptyline, nortriptyline, desipramine, imipramine
  - Increase serotonergic and noradrenergic activity
  - Antihistamine, antiadrenergic, anticholinergic activity may be problematic in the medically ill

- **Serotonin Reuptake Inhibitors**
  - Fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine
  - Increase serotonin concentrations in synapses
Other Antidepressants

- Serotonin-Norepinephrine Reuptake Inhibitors
  - Venlafaxine, desvenlafaxine, duloxetine

- Vilazodone
  - Blocks reuptake of serotonin, partial 5-HT1A agonist

- Mirtazapine
  - Increases release of serotonin and norepinephrine
  - Blocks selected serotonin receptors

- Bupropion
  - Perhaps dopaminergic
  - No documented indications for anxiety disorders
Antidepressants and the FDA

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<th>GAD</th>
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XX = FDA Approval
## Antidepressants and the FDA

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**XX = FDA Approval**
Antidepressants

- Effect of antidepressants on anxiety
  - Alter neurotransmitter concentrations within hours
    - Does not appear to be directly related to antianxiety effect
  - Enhances neural plasticity and neurogenesis through activation of receptors including 5-HT1A
  - Decrease activity of locus ceruleus and limbic system over an extended period of time

Ninan 2002
Santarelli 2003
Duman 2005
West 2008
Antidepressants and Neural Plasticity

- Antidepressants increase synaptic serotonin (5-HT) and norepinephrine (NE)
- 5-HT and NE activate Cyclic-AMP related protein kinases
- Increases C-AMP response element binding protein (CREB) and others
- These alter gene transcription including increasing Brain Derived Neurotropic Factor (BDNF)
- BDNF and others promote neuron health and growth

Duman 2005
Effect of Antidepressants

Matthew in Neuropsych 2008
Buspirone

- Partial agonist of serotonin 1-A receptor
  - No immediate effect
  - No addictive potential
  - No significant sedation
- Effective in generalized anxiety
- Probably works through neural plasticity as well
- Seems to take a long time (> 4 weeks) at full dose (at least 45 mg per day in divided doses)
Benzodiazepines

- Activate a GABA-Benzodiazepine receptor complex increasing GABA activity
  - Anxiolytic
  - Sedation
  - Psychomotor retardation
- May interact with nitrous oxide in the cell
- Less certain about them affecting neural plasticity
- Associated with tolerance, withdrawal and abuse potential
- Associated with cognitive problems and falls
Other Off Label Options

- **Antihistamines**
  - Diphenhydramine, hydroxyzine
  - Work primarily through sedation

- **Antipsychotics**
  - None are FDA approved for the treatment of anxiety
  - Many rely on sedation
  - Some may have significant enough serotonergic effect to make them worth considering
  - But significant metabolic side effects
Other Off Label Options

- Beta-blockers
  - Propranolol crosses the blood brain barrier
  - Reducing the physical signs of anxiety (heart rate, tremor, muscle tension) reduces emotional aspects of anxiety
  - Obvious limitations based on medical impact
Treating Anxiety in Medical Illnesses

- Prepare to be underwhelmed
Anxiety in Medical Conditions

**Stroke**

- 20-25% of stroke survivors have significant anxiety
- Cochrane Database Review in 2011
  - No placebo controlled trials
  - 2 meaningful treatment trials with 175 people
  - Buspirone and paroxetine seemed to be effective
  - Psychotherapy augmentation of paroxetine did not show significant benefit

Campbell 2011
Anxiety in Medical Conditions

- **Inflammatory Bowel Disease**
  - Cochrane Database Review
  - 1 study with 174 patients
  - Provided Cognitive-Behavior Therapy to control stress
    - No change in remission rates at one year
    - Increased Quality of Life in young, recently diagnosed patients with more severe symptoms
    - (Only 49% of patients assigned to CBT went to at least half their sessions)

Mikocka-Walus 2015
Anxiety in Medical Conditions

- **Chronic Obstructive Pulmonary Disease**
  - Air hunger, hyperventilation
  - 13 - 51% have significant anxiety
  - Fear was indirectly linked to perceived mastery (control)
  - Cochrane database reviewed 370 studies;
  - 2 SSRI studies trended positive but no conclusions because of small size and poor design

- **Palliative Care**
  - Panic attacks and generalized anxiety common in advanced illness
  - Legitimate concerns of pain and death
  - Agitation may be related to medications (e.g. antipsychotics)
  - No reliable evidence regarding treatment

References:
- Usmani 2011
- Breland 2015
- Candy 2012
Anxiety in Medical Conditions

- **Breast Cancer Survivors**
  - 146 patients disease free for 2 years
  - 14% had significant anxiety
  - Decreased Quality of Life
  - Education not enough
  - Required cognitive restructuring

  Akechi 2015

- **Parkinson Disease**
  - Anxiety and/or depression in 50% of patients
  - 14 patients in a trial of Cognitive Behavior Therapy
  - Worked reasonably well for depression
  - Effect on anxiety did not reach statistical significance

  Calleo 2015
Anxiety and Cardiovascular Disease

- 81 Patients after first myocardial infarction
  - Randomized to receive 10 Supportive Therapy sessions
    - Decreased perceived stress
    - Improved subjective mental and physical health
    - At 1 year lower non-fatal re-infarction
    - At 2.5 years lower fatal re-infarction

Seldenrijk 2014
Rakowska 2015
HIV and Anxiety

- 25-40% of individuals with HIV have Anxiety Disorders
- Up to 70% may have significant anxiety
- Fearful about their future and prognosis
- HIV related medical illnesses cause/worsen anxiety – hypoxia, cardiomyopathy, CNS infections, sepsis
- Medication related symptoms
- No specific recommendations – Be very careful about drug interactions

Cohen - APA Presentation 2012
We Are Not Happy

- Very limited evidence for how to best treat anxiety in medical illness
- Base treatment decisions on:
  - Clinical Experience
  - Potential Causes
  - Common Underlying Neurobiology
An Unofficial Algorithm

Normal Worry?

Yes

No
Normal Anxiety

• Normal Anxiety
  • Worry about their future limitations
  • Worry about loved ones
  • Worry about pain and/or death

• Abnormal Anxiety
  • They are miserable or are making others miserable
  • Irrational Fears
  • They are not functioning because of the anxiety
  • They are too anxious to take care of themselves
An Unofficial Algorithm

Normal Worry?

- Yes: Talk To Someone
- No: Medication Induced?

Medication Induced?

- Yes: Talk To Someone
- No: Normal Worry?
Medication Induced

- Aminophylline and theophylline
- Anticholinergics
- Antipsychotic medications
- Calcium Channel Blockers
- Hormones – estrogen and thyroid medications
- Levodopa
- Salicylates
- Stimulants and sympathomimetics (caffeine, cocaine, phenylephrine, phenylpropanolamine, etc.)
- Steroids

Reconsider medication; minimize dose
An Unofficial Algorithm

1. Normal Worry?
   - Yes: Talk To Someone
   - No:
     2. Medication Induced?
        - Yes: Adjust Medications
        - No:
          3. Medical Illness?
             - Yes: Adjust Medications
             - No:

Notes:
- Anxiety Disorders
Medical Illness

- **Cardiovascular Conditions**
  - Congestive heart failure
  - Coronary insufficiency
  - Dysrhythmia
  - Cardiac valve disease (especially MVP)
  - Angina
  - Myocardial infarction

- **Respiratory Disease**
  - Chronic Obstructive Pulmonary Disease
  - Asthma
  - Pneumonia
  - Pneumothorax
  - Pulmonary embolus
  - Pulmonary edema
Medical Illness

- **Endocrine**
  - Hyperthyroid
  - Hypothyroid
  - Hyperparathyroid
  - Hypoparathyroid
  - Hypocalcemia
  - Carcinoid syndrome
  - Pheochromocytoma

- **Immunological and Metabolic**
  - Systematic lupus erythematosus
  - Rheumatoid arthritis
  - Anemia
  - Hyperkalemia
  - Hyponatremia
  - Insulinoma
  - Wilson’s disease
Additional Medical Illnesses

- **Gastrointestinal**
  - Crohn’s disease
  - Ulcerative colitis

- **Neurological**
  - Huntington’s Disease
  - Multiple sclerosis
  - Vertigo
  - Transient Ischemic Attacks and Stroke

- **Substance**
  - Withdrawal from alcohol or benzodiazepines
For Medical Conditions

- Optimize treatment of the underlying condition before medicating the anxiety
- If the treatment is optimized consider therapy for accepting what can not be changed
An Unofficial Algorithm

1. Normal Worry?
   - Yes: Talk To Someone
   - No: Medication Induced?
      - Yes: Adjust Medications
      - No: Medical Illness?
         - Yes: Treat Illness
         - No: Episodic, Infrequent?
An Unofficial Algorithm

Episodic, Infrequent?

No

Yes
Episodic Anxiety

- Phobias, occasional panic attacks
- Goal = Make symptoms bearable
- If less than a couple of times per week consider as needed medications or lifestyle modification
  - Antihistamines
  - Propranolol
  - Benzodiazepines
    - Be cautious if there is a history of substance abuse
Episodic Anxiety

- If infrequent but causing significant impairment than consider ongoing treatment (therapy or antidepressant)

- Psychotherapy (especially Cognitive-Behavior Therapy) is effective for:
  - Phobias
  - Social Phobia
  - Panic Disorder
An Unofficial Algorithm

Episodic, Infrequent?

- Yes
- No

Persistent or Recurrent?

- Yes
- Yes

prn Medications
Persistent Anxiety

• Generalized Anxiety, Post-Traumatic Stress Disorder, Panic Disorder (frequent attacks)
• Goal = Alter brain functioning
• Referral for psychotherapy
• Antidepressants
  • All are likely equally effective (except bupropion)
  • Consider drug-drug interactions and side effects
  • SSRIs and SNRIs over TCAs
Benzodiazepines

- Effective for Generalized Anxiety Disorder
- Effective for Panic Attacks
  - Most true panic attacks subside with 30 minutes
- Problems
  - Significant risk of abuse and dependence
  - Teach unhelpful coping strategies (numbing, avoidance, just take a pill)
  - Cognitive slowing
An Unofficial Algorithm

Episodic, Infrequent?

prn Medications

Yes

No

Persistent or Recurrent?

Chronic Medications

Yes

Still a Problem?

Consult Psychiatry
Anxiety In the Medically Ill
Algorithm
Randon S. Welton

Normal Worry?
Yes
Talk to Someone
No
Medication Induced?
Yes
Adjust Medication
No
Medical Illness?
Yes
Treat Illness
No
Episodic, Infrequent?
Yes
prn Medications
No
Persistent or Recurrent?
Yes
Chronic Medications
No
Consult Psychiatry
Still a Problem?
Questions?