Update on Stress and Anxiety Disorders
Jane Lueckens, RN, FNP-C, FMHNP-BC
Greater Los Angeles Veterans Healthcare System, West Los Angeles

What Ruins Your Day?

Stress and Anxiety
Normative Fears Through Childhood and Adolescence

![Diagram showing normative fears through childhood and adolescence.]

**FIGURE 1.** Normative Fears Throughout Childhood and Adolescence Figure Adapted from Beesdo-Baum and Knappe.

Adaptive versus Maladaptive Anxiety

- **Symptoms:** apprehension, fear, obsession, physical tension, increased heart rate, increased respiratory rate, chest tightness, stomach discomfort, restlessness
- **Adaptive:** reasonable response to real external threat proportional to threat
- **Maladaptive:** no obvious external threat or response is excessive plus impairment of function

DSM-V Changes

- Splits Anxiety Disorders, formerly one chapter, into three separate categories, based on research and differential in terms of physiology:
  - Obsessive-Compulsive Disorders
  - Trauma and Stressor-Related Disorders
  - Anxiety Disorders
DSM-V Changes

- Anxiety Disorders
  - Panic Disorder and Agoraphobia no longer linked
  - People with Social Anxiety over age 18 no longer have to recognize that the anxiety is unreasonable, six month duration extended to all ages
  - Separation Anxiety Disorder and Selective Mutism are now classified as anxiety disorders-formerly child adolescent
  - Wording of Separation Anxiety to represent adult onset no longer must be before 18, and duration must be 6 months

Simple Phobias

- Prevalence-12 month community prevalence 7-9%, 5% children, 16% adolescents, lower in elderly, 3-5%
- Suicide risk-60% more likely than those without dx, likely related to co-occurring personality disorders or other anxiety disorder
- Marked anxiety about a specific object or situation, almost always provokes intense fear or anxiety out of proportion to the actual danger posed. Last 6 months or more, causes significant distress or impairment in social, occupational areas of functioning, not better explained by another mental disorder
- Stimulus specifiers: Animal, Natural Environment, Blood-injection-injury, Situational, Other

Developmental Anxiety and Simple Phobias in the Medical Clinic

- Normal childhood fear of injury and separation anxiety translates to fear of needles, procedures, providers
- Some children and adults have injection or blood phobias
- At doorway observe for level of anxiety:
  - Mild: Able to focus on another activity, sitting alone, may be too engaged with activity to notice provider
  - Moderate: Alert, notices provider, if child sitting near parent - able to engage
  - Severe: Distress, avoidance as provider approaches, clinging to parent
Developmental Anxiety and Simple Phobias in the Medical Clinic

- Mild level of anxiety: make eye contact and approach patient, may begin exam with introduction and explanation
- Moderate level of anxiety: introduce self from a distance, ask for permission to approach, allow child to touch equipment
- Severe level of anxiety: speak to parent, parent permission to approach, perform exam with child on parent's lap if possible, if age appropriate allow child to touch or use equipment
- Comfort positioning for procedures
- Adults with high anxiety - Ask permission to approach, use simple terminology, ask permission to proceed, ask for feedback and participation in decision making. Potential for vagal stimulation and fainting with blood phobia.

Parent Education Resource

- Helping Your Child Cope with Medical Procedures

Simple Phobia and Desensitization

- Exposure Therapy, sometimes with CBT and relaxation training is effective
- Hx vasovagal blood phobia response - have patient look away during lab draws, and learn to tense muscles to help prevent hypotension
- Aviaphobia is a common simple phobia, if avoidant can cripple people's careers, isolate from distant family
- Responds well to to Exposure Therapy, sometimes provided in groups
- People without SUD may benefit from episodic use of a benzodiazepine for short term use, also consider propranolol or Hydroxyzine
### Social Anxiety Disorder (formerly social phobia)

- 7% prevalence, decreases with age
- High comorbidity with MDD if chronic isolation, explains higher suicide rate than other anxiety disorders, frequently comorbid with bipolar disorder and body dysmorphic disorder
- Marked fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others
- Individual fears showing anxiety or being negatively evaluated, social situations almost always provoke fear or anxiety

### Social Anxiety Disorder

- Social situations almost always provoke fear and anxiety
- Social situations avoided or endured with intense fear or anxiety
- Fear is out of proportion to threat, persistent, lasting for 6 months or more, not attributable to the effects of a substance, not better explained by another mental disorder
- If another medical condition is present, fear, anxiety, or avoidance is unrelated or excessive
- Specify if performance only - fear is restricted to speaking or performing in public

### Generalized Anxiety Disorder

- 12 month prevalence 6.8% in adolescents, 2.9% among adults, peaks in middle age. Commonly comorbid with unipolar depression, which increases suicide risk
- Excessive anxiety, worry more days than not for at least 6 months about a number of events or activities
- Difficult to control worry (pervasive, pronounced, global, frequently without precipitants)
- Clinically significant distress or impairment in social, occupational, or other areas of functioning
- Associated with three or more of the following (one required in children)
  - Restlessness, fatigue, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance
- Excessive anxiety, worry more days than not for at least 6 months about a number of events or activities
- Difficult to control worry (pervasive, pronounced, global, frequently without precipitants)
Generalized Anxiety Disorder

+ Not attributable to physiological effects of substance or another medical condition
+ Not better explained by another mental disorder
+ Associated features:
  + Trembling, twitching, feeling shaky, muscle aches or soreness
  + Sweating, nausea, diarrhea
  + Exaggerated startle
  + Accelerated heart rate, shortness of breath, dizziness are less prominent in GAD than in panic disorder
+ Associated medical stress conditions: irritable bowel, headaches

Other Specified Anxiety Disorder

+ Clinically significant distress or impairment in social, occupational, or other important areas of functioning but do not meet full criteria for any of the disorders in the anxiety disorders class
+ Used when clinician chooses to communicate the reason the presentation does not meet criteria for limited symptoms attacks.
  + Limited-symptom attacks
  + Generalized anxiety not occurring more days than not

Unspecified Anxiety Disorder

+ Symptoms characteristics of an anxiety disorder that case clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the anxiety disorders in the anxiety disorders class
+ The clinician chooses not to specify the reason that criteria are not met for a specific anxiety disorder, and includes presentations in which there is insufficient information to make a more specific diagnosis
Workup for Anxiety Symptoms

- GAD-7, Beck Anxiety Inventory
- SCARED for children
- CBC, TSH if none recent, urine drug screen if substance use suspected
- Review medication list for anxiety inducing medications, alcohol and substance use
- Medical hx to o/o anxiety inducing medical conditions
- Panic Attack with chest pain, consider chest pain workup if risk factors present

Current Treatments for GAD

- FDA-Approved Medications:
  - SSRI: Escitalopram, Paroxetine
  - SNRI: Duloxetine, Venlafaxine
- Off-Label Medications:
  - Fluoxetine, Sertraline, Citalopram, TCAs, MAOI's, Mirtazapine, Pregabalin, Gabapentin, Hydroxyzine, Antipsychotics: Quetiapine
- Psychotherapy: CBT
- First-Line: SSRI or SNRI
- Second-Line: Buspirone, TCAs Pregabalin, CBT
- Benzodiazepines: for short term use only if no hx of addiction, avoid in elderly, children and adolescents, pregnancy
- Return monthly for medication check until symptoms manageable or remitted

Panic Attack Specifier

- A panic attack is not a mental disorder and cannot be coded as such
  - Prevalence rate is 1.2x, increased likelihood of later anxiety disorders, depressive disorders, bipolar disorder
- Abrupt surge can occur from a calm state or an anxious state—four or more symptoms
  - Palpitations, pounding heart, or accelerated heart rate
  - Sweating
  - Trembling or shaking
  - Sensation of choking or smothering
  - Feeling of losing control or going crazy
  - Chest pain or discomfort
  - Nausea or abdominal distress
  - Dizzy, unsteady, light-headed, or faint
  - Chills or heat
  - Paresthesias
  - Derealization or depersonalization
  - Fear of losing control or going crazy
  - Fear of dying
Panic Attacks

Peak in minutes

Panic Disorder

- Prevalence: 12.3%. In context of comorbidity with mood disorders, psychosis, SUD, personality disorders, have increased suicidality and poor treatment response, more disability, poor quality of life
- Recurrent unexpected panic attacks
  - Surge of intense fear or intense discomfort that reaches a peak within minutes, during which time panic attack specifier symptoms occur
- At least one of the attacks has been followed by 1 month or more of the following
  - Persistent concern or worry about additional panic attacks or their consequences
  - A significant maladaptive change in behavior related to the attacks, such as avoidance of unfamiliar situations
  - Not attributed to a substance or medical condition
  - Not better explained by another mental disorder

Current Treatments for Panic Disorder

- FDA-Approved Medications: SSRI: Fluoxetine, Paroxetine, Sertraline; SNRI: Venlafaxine XR; Benzodiazepines: Clonazepam, Alprazolam; TCAs: Clomipramine, Imipramine
- Off-Label Medications: SSRI: Escitalopram; SNRI: Duloxetine, Desvenlafaxine; TCAs, MAOIs: Phenaamine, Gabapentin, Benzodiazepines: lorazepam
- Psychotherapy: CBT, Psychodynamic
- First Line: CBT or SSRl, SNRI, or combination
- Monthly follow-up until panic attacks remitted or patient finds them manageable
- Refer for severe disorder or no response to treatment, comorbidities
Agoraphobia

- Incidence 1.7% adolescents and adults
- 30-50% co-occurrence with panic disorder, majority have other anxiety disorders or mental illnesses, depressive disorder and SUD secondary to agoraphobia
- Marked fear of two or more: Public transportation, being in open spaces, being in enclosed places, standing in line or being in a crowd, being outside of the home alone
- Fears or avoids these situations, almost always provide anxiety, actively avoided, or are endured with intense fear

Agoraphobia

- Persistent for 6 months causing clinically significant distress in social, occupational, or other important areas of functioning
- If another medical condition is present, the fear, anxiety, or avoidance is clearly excessive
- Not better explained by another mental disorder
- Refer for psychiatric evaluation, therapy, consider starting SSRI prior to appointment

Anxiety Disorder due to Another Medical Condition

- Panic attacks or anxiety is predominant in the clinical picture
- There is evidence from hx, PE, or lab findings that the disturbance is the direct pathophysiological consequence of another medical condition
- Not better explained by another mental disorder
- Does not occur exclusively during a delirium
- Causes clinical significant clinical distress or impairment in social, occupational, or other important areas of functioning
- Include name of medical condition in dx
Anxiety Disorder due to Another Medical Condition

+ Cardiovascular: Angina, Arrhythmias, Heart Failure, Myocardial Infarction, Syncope, Valvular Disease, Shock
+ Hematologic: Anemia
+ Immunologic: Anaphylaxis, Systemic Lupus Erythematosus
+ Metabolic: Hyperadrenalism (Cushing's), Hyperkalemia, Hyperthermia, Hypereotyroidism, Hypocalcemia, Hyperglycemia, Hyponatremia, Menopause
+ Neurologic: Encephalopathies, Essential Tremor, Intracranial Mass Lesions, Post Concussive Syndrome, Seizure Disorders, especially Temporal Lobe, Vertigo

Anxiety Disorder due to Another Medical Condition

+ Respiratory: Asthma, Chronic obstructive pulmonary disease, pneumonia, pneumothorax, pulmonary edema, pulmonary embolism
+ Secreting tumors: Carcinoid, Insulinoma, Pheochromocytoma
+ Mental health:
  + In bipolar disorder high anxiety can occur during episodes of mania or hypomania
  + GAD or panic disorder may rarely signal emergent schizophrenia

Substance/Medication-Induced Anxiety Disorder

+ Panic attacks or anxiety is predominant in the clinical picture
+ There is evidence from hx, physical exam, or lab findings of:
  + Symptoms developed during or soon after substance intoxication or withdrawal or after exposure to a medication
  + The involved substance/medication is capable of producing the symptoms
  + Disturbance is not better explained by an anxiety disorder that is not substance-induced, persist for about one month after cessation of withdrawal or intoxication
  + Does not occur exclusively during the course of delirium
  + Causes significant distress or impairment in social, occupational, or other areas of fx
Substance/Medication-Induced Anxiety Disorder

CAFFEINE
Legal stimulant, FDA recommends no more than 400mg per day
Studies show connection with caffeine consumption and increased stress and anxiety
Caffeine increasingly added to foods such as gums, candies, marshmallows
Aging causes increased half life, up to 9 hours, can cause worsening sleep with same caffeine consumption in the elderly

Substance/Medication-Induced Anxiety Disorder

What makes 400 mg of caffeine?

- 5 shots (2-oz) of espresso
- 47 cups (8-fl oz) of drip coffee
- 6 cans (12 oz) of energy drinks

Or

Or

Substance/Medication-Induced Anxiety Disorder

+ Stimulants: Amphetamine, Aminophylline, Caffeine, Cocaine, Methylphenidate, Theophylline
+ Sympathomimetics: Ephedrine, Epinephrine, Pseudoephedrine
+ Miscellaneous: Baclofen, Cycloserine, Hallucinogens, Indomethacin, Steroids
+ Drug Withdrawal: Opioids, Benzodiazepines, Alcohol, Sedatives, Barbiturates
+ Anticholinergics: Benztropine, Diphenhydramine, Merperidine, Oxybutynin, Tricyclic Antidepressants, Trihexphenidyl
Substance/Medication-Induced Anxiety Disorder

- Dopaminergics: Amantadine, Bromocriptine, Levodopa, Levodopa-Carbidopa, Metoclopramide, Neuroleptics
- Medication related: Akathisia due to antipsychotics, Digitalis Toxicity, Hypotensive medications

Use of Medication in the Elderly

- BEERS Criteria for Geriatric > 65 yo
  - Reduce or avoid anticholinergic, hypotensive medications or benzodiazepines
  - SSRIs preferred over Tricyclics
  - Paroxetine last choice due to higher anticholinergic properties
  - SSRIs can contribute to falls-evaluate all meds for fall risk, can switch to SNRI if necessary
  - Check sodium level due to increased risk of SIADH including Mirtazapine
  - Duloxetine may use if $\text{CrCl} > 30 \text{ml/min}$
  - Escitalopram max dose 10mg q hs, Citalopram 20mg per day due to risk of QTC lengthening

In Pregnancy

- Mothers with high anxiety are at risk of low birthweight newborn
- Babies of mothers anxious during pregnancy cry more
- Assess for domestic abuse-elevated risk in pregnancy
- Utilize therapy if possible
- Do not give Paxil-category D or TR, no benzodiazepines
- SSRIs are generally safe, full disclosure of potential side effects and fetal effects to mother
Children and Adolescents

- Current community standard is to refer for mental health evaluation of child or adolescent
- Many PCP's are not starting SSRI's in children and adolescents due to black box warning for suicide
- Sertraline is often a first choice for GAD and Panic Disorder. Can give false positive for Benzodiazepines UTOX
- In specialty care child and family also engaged in therapy
  - (J. Baldrias, PMHNP-BC personal communication, May 9, 2017). Pacific Clinics Child Adolescent Behavioral Health

Anxiety Treatment in Substance Use Disorder or long term

- SSRIs, SNRI's
- Antihistamine-Hydroxyzine prn
- Anticonvulsant-Gabapentin prn

Evidenced Based Therapy

- Generalized Anxiety Disorder-Cognitive Behavioral Therapy
- Panic Disorder-CBT, Psychodynamic
- Social Anxiety Disorder-Exposure Therapy, CBT
- Specific Phobias-Exposure Therapy
Alternative Therapies

- Yoga – effective for anxiety disorder symptom reduction
- Mindfulness – effective for anxiety disorder symptom reduction

New Medications and Old Herbal Supplements

- Desvenlafaxine – SNRI new generation Venlafaxine, MDD indication with potential for use as an antianxiety agent.
- Herbal/supplement
  - Kava – there is evidence to support use of Kava, separates from placebo for GAD, SE - Risk of liver damage

Medication Pipeline

- Vilazodone – SSRI Approved for MDD, phase 3 GAD, phase 5 PTSD with co-morbid depression
- Agomelatine – Melatonin-1/Melatonin-2 agonist and 5HT2C receptor antagonist effective for GAD and lower rate of relapse but no further studies
- Glutamate Modulators – ADX-71149 and mGluR2, phase 2 MDD with anxiety TGH-618 for unspecified anxiety
- D-cycloserine – NMDA partial agonist, facilitates fear extinction used to augment exposure or CBT, social phobia
Medication Pipeline

- Anticonvulsants:
  - Pregabalin approved for use for GAD in Europe, but FDA did not approve in 2009. Studies have shown efficacy for social anxiety at 450mg to 600mg per day.
  - Neuropeptides: analgesia, reward, social behaviors, learning, memory, modulate anxiety and fear.
  - Oxytocin: Plays role in attachment and prosocial behavior. Positive effect on emotion modulation. In high stress individuals it can reduce negative cognitive appraisals elicited by high-stress tasks. Clinical trial for nasal spray effect on social anxiety.
  - Several other neuropeptides are being studied.

Research

- Microbiome Studies:
  - Chronic stress or depression can alter the Microbiome
  - Administration of probiotics:
    - B-GOS reduced cortisol awakening response
    - Lactobacillus reduced anxiety scores in patients with chronic fatigue
  - Medications Under Development
    - SNDRIs (Triple Reuptake Inhibitors)

The Amygdala
Stress and Cardiovascular disease

- Heightened activity in the amygdala is associated with a greater risk of heart disease and stroke, according to a study published in The Lancet.
- 293 patients were given a combined PET/CT scan of brain, bone marrow and spleen activity and inflammation of their arteries.
- Tracked for an average of 3.7 years, 22 patients had cardiovascular events.
- Those with higher amygdala activity had a greater risk of subsequent cardiovascular disease and developed problems sooner.
- Patients who fear their stress response have more constricted arteries in response to stress.
- Chronic stress is a risk factor for acute cardiovascular syndromes.

How to reduce stress related illness

- Stressful events cause the amygdala to release:
  - Norepinephrine, causing rapid heartbeat, vasoconstriction, and over long periods of time arterial inflammation.
  - Oxytocin, which causes people to seek support and is cardioprotective, even contributing to healing of cardiac cells.
  - Make stress your friend. People who see stressful situations as a welcome challenge experience a tachycardia but no related arterial constriction, the non-lethal cardiovascular equivalent of excitement or joy.

- Perception of stress can change by changing posture and facial expression.
- Seek social support. Engaging with others and mutual support increases oxytocin activity.
- Care for others. People who were stressed but cared for others in some way had reduced risk of cardiovascular events.

VA Resources-Manage Stress Workbook

- Manage Stress Workbook
Using Character Based Traits to Reduce Stress

- Self-selected Character Strengths identified by questionnaire.
- People are challenged to build areas of strengths to meet challenges. Builds self-esteem, feelings of competence, enhances happiness and success, reduces stress.
- Strengthening Character Based Strength of Love
  - Those who love you are not fooled by mistakes you have made or dark images you hold about yourself. They remember your beauty when you feel ugly; your wholeness when you are broken; your innocence when you feel guilty; and your purpose when you are confused - African saying.

There’s an APP for that

- Pacifica App Description
- Pacifica App
- Mayo Clinic Anxiety Coach - one of highest rated
Therapeutic Lifestyle Practices

Caring for Others Service

Therapeutic Lifestyle Practices

Recreation

Make Every Day a Masterpiece
Bibliography (cont)