Psychiatry Clinical Reviews
Anxiety Disorder Updates

Katherine M. Moore, MD
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Intercontinental Chicago Magnificent Mile
Chicago, IL
Disclosure

Relevant Financial Relationships
None

Off-Label/Investigational Uses
Off-label uses of medications will be identified in the presentation.
Learning Objectives

After completion of this educational activity, participants will be able to:

• Describe evidence-based psychological and pharmacological treatment options for anxiety disorders
• Identify guidelines and web-based resources to support clinical care of patients with anxiety
Mr. GM

• 45-year-old professional presents with panic symptoms
• Remote history of similar presentation
• Pharmacotherapy initiated with sertraline & lorazepam
• Motivated for CBT—has had eight sessions
• Limited progress on sertraline 100 mg x 6 weeks and lorazepam 0.5 mg tid
• Wife calls in, “He is not any better.”
What is Your Next Step?
1. Increase sertraline to 150mg
2. Re-emphasize CBT approaches and give it more time
3. Re-evaluate diagnosis and co-morbidities
4. Change SSRI
5. Switch to clonazepam
6. Bang your head in frustration
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Which of the following components of CBT is most effective for anxiety symptoms?

1. Self-monitoring
2. Relaxation skills
3. Cognitive restructuring
4. Exposure
5. Distraction
Anxiety Presenting Over the Lifespan

Changes in anxiety disorder presentation across the lifespan

Anxiety Disorders: Prevalence and Impact

- Common
- Comorbidity
- Substantial functional impairment
- Approximately 40% of patients diagnosed with anxiety and related disorders are untreated.
- Suicide risk

Katzman MA et al. BMC Psychiatry 2014, 14(Suppl 1):S1
Psychiatric Comorbidities are Common

- Comorbidities extremely common
- Screening 1,127 outpatients with Anxiety Disorders Interview Schedule for DSMIV
  - Prevalence of additional Axis I disorder
    - Current 57%
    - Lifetime 81%
- Bipolar disorder: Increased risk for anxiety disorders RR 3.22 (2.41-4.29)

Pavlova. Lancet 2015
With Anxiety—We Tend to be “Splitters”

- Separation Anxiety Disorder
- Specific Phobia
- Social Anxiety Disorder (Social Phobia)
- Panic Disorder
- Agoraphobia
- Generalized Anxiety Disorder
- Substance/Medication-induced Anxiety Disorder
- Anxiety Disorder Due To Another Medical Condition
- Other Specified Anxiety Disorder
- Unspecified Anxiety Disorder
- Obsessive-compulsive Disorder
- Posttraumatic Stress Disorder
- Acute Stress Disorder

Leads to Challenges in Measurement

- Social Phobia Inventory (SPIN)
- Social Anxiety Questionnaire (SAQ-A3Q).
- Anxiety about Death Questionnaire
- Cardiac Anxiety Questionnaire
- Anxiety Sensitivity Index
- Trauma Symptom Checklist
- Anxiety and Preoccupation of Sleep Questionnaire
- Penn State Worry Questionnaire
- Yale-Brown Obsessive Compulsive Scale
- Pain Anxiety Questionnaire(s)
- And many others….

**Perfect vs Good Enough**

Screen and Monitor

- GAD-7 item (free, quick)
- At cut off of 10 or more…

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD</td>
<td>90%</td>
<td>79%</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>74%</td>
<td>81%</td>
</tr>
<tr>
<td>Social Anxiety</td>
<td>72%</td>
<td>80%</td>
</tr>
<tr>
<td>PTSD</td>
<td>66%</td>
<td>81%</td>
</tr>
<tr>
<td>Any Anxiety</td>
<td>68%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Spitzer. Arch Intern Med 2006 May 22;166(10):1092-1097
## GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling nervous, anxious or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Not being able to stop or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Being so restless that it is hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling afraid as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Total Score = Add Columns

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult
Anxiety Disorder Resources
Evidence-Based Practice

Best Practice Guidelines

• Canadian Clinical Practice Guidelines for the Management of Anxiety, Posttraumatic Stress, and Obsessive Compulsive Disorders (www.biomedcentral.com)

• National Institute for Health and Care Excellence (NICE: www.org.uk/guidance)

• AHRQ National Guideline Clearinghouse (www.guideline.gov)
Algorithms for Pharmacotherapy

- Canadian Clinical Practice guidelines for the management of anxiety, posttraumatic stress and obsessive compulsive disorders
  - Katzman et al. BMC Psychiatry 2014, 14(Suppl 1):S1
- American Psychiatric Association
  - OCD (2007) update 2013
  - Panic(2009)
- National Institute for Health and Care Excellence (NICE)
  - GAD and Panic - 2011
  - OCD - 2005
  - PTSD - 2005
  - https://www.nice.org.uk/guidance/qs53
Where to Find CBT?

• Know the providers who have an expertise in cognitive behavioral therapy (CBT) and exposure therapy

• CBT therapist locator websites:
  www.adaa.org
  www.abct.org
Treatment Approaches: What We Know

• Pharmacotherapy and cognitive behavioral therapy (CBT) are effective

• Multiple low-step to high-step intervention choices available

• Patient choice enhances outcomes
Treatment Approaches: What We Know

• Majority are not offered / able to access evidence-based treatments for anxiety

• Multiple individual, provider, and systems-based barriers to accessing evidence-based treatments

• Majority of patients prefer CBT over pharmacotherapy
Treatment Approaches: What We Know

- CBT tends to show a more durable treatment response
- Component control studies note exposure as the most effective component in CBT
- Skills that are the least effective for anxiety are used most frequently
- Exposure is the most effective approach for anxiety but used least frequently
Gold Standard Patient Care

“All patients being treated with pharmacotherapy should be instructed to gradually face their fears (exposure to decrease avoidance).”

Canadian Clinical Practice Guidelines for the Management of Anxiety, Posttraumatic Stress and Obsessive Compulsive Disorders

Katzman, et al. 2014
Exposure

- Encourages the participant to face the fear(s)
- Patients learn corrective information through experience
- Repeated exposure leads to extinction of fear
- Successful coping improves self-efficacy
# FDA-Labeled Anxiety Indications

<table>
<thead>
<tr>
<th></th>
<th>GAD</th>
<th>OCD</th>
<th>Panic</th>
<th>PTSD</th>
<th>Social Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Paroxetine CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Canadian Clinical Practice Guidelines for the Management of Anxiety, Posttraumatic Stress, and Obsessive-Compulsive Disorders:

Levels of Evidence

• Meta-analysis or at least 2 randomized controlled trials (RCTs) that included a placebo condition
• At least 1 RCT with placebo or active comparison condition
• Uncontrolled trial with at least 10 subjects
• Anecdotal reports or expert opinion

*Levels of evidence do not assume positive or negative or equivocal results, they merely represent the quality and nature of the studies that have been conducted.

Katzman MA et al. BMC Psychiatry 2014; 14(Suppl 1):S1
Canadian Clinical Practice Guidelines for the Management of Anxiety, Posttraumatic Stress, and Obsessive-compulsive Disorders:

Treatment Recommendation Summary

• First-line: Level 1 or Level 2 evidence plus clinical support for efficacy and safety

• Second-line: Level 3 evidence or higher plus clinical support for efficacy and safety

• Third-line: Level 4 evidence or higher plus clinical support for efficacy and safety

• Not recommended: Level 1 or Level 2 evidence for lack of efficacy
Recommendations for Pharmacotherapy for Panic Disorder

• First-line: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, paroxetine CR, sertraline, venlafaxine XR
• Second-line: alprazolam, clomipramine, clonazepam, diazepam, imipramine, lorazepam, mirtazapine, reboxetine
• Third-line: bupropion SR, divalproex, duloxetine, gabapentin, levetiracetam, milnacipran, moclobemide, olanzapine, phenelzine, quetiapine, risperidone, tranylcypromine
• Adjunctive therapy
  • 2nd line: alprazolam ODT, clonazepam
  • 3rd line: aripiprazole, divalproex, olanzapine, pindolol, risperidone
• Not recommended: buspirone, propranolol, tigabine, trazodone

Katzman MA et al. BMC Psychiatry 2014, 14(Suppl 1):S1
Back to our Case Sample…

• Patient had AUDIT score of 6 on initial evaluation
• Laboratory evaluation not completed
• After phone call…. Wife reports that husband has been heavily drinking but that she has been hesitant to tell anyone
• Referred for treatment of alcohol dependence
• Resolution of symptoms with treatment plan after alcohol dependence treated
Recent Meta-Analysis Pooling all Anxiety

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRIs</td>
<td>23</td>
<td>2.25</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>42</td>
<td>2.15</td>
</tr>
<tr>
<td>CBT + drug</td>
<td>16</td>
<td>2.12</td>
</tr>
<tr>
<td>SSRIs</td>
<td>62</td>
<td>2.09</td>
</tr>
<tr>
<td>TCAs</td>
<td>15</td>
<td>1.88</td>
</tr>
<tr>
<td>Relaxation</td>
<td>17</td>
<td>1.36</td>
</tr>
<tr>
<td>CBT/exposure, individual</td>
<td>93</td>
<td>1.30</td>
</tr>
<tr>
<td>Pill placebo</td>
<td>111</td>
<td>1.20</td>
</tr>
<tr>
<td>CBT, group</td>
<td>18</td>
<td>1.22</td>
</tr>
<tr>
<td>Psychodynamic therapy</td>
<td>5</td>
<td>1.17</td>
</tr>
<tr>
<td>Non-face-to-face therapies</td>
<td>34</td>
<td>1.18</td>
</tr>
<tr>
<td>Psychological placebo</td>
<td>16</td>
<td>0.83</td>
</tr>
<tr>
<td>Waiting list</td>
<td>50</td>
<td>0.20</td>
</tr>
</tbody>
</table>

### Dosing of Antidepressants & Benzodiazepines for Panic Disorder

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose and Incremental Dose (mg/day)</th>
<th>Usual Therapeutic Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>10</td>
<td>20-40</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5-10</td>
<td>10-20</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>5-10</td>
<td>20-40</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>25-50</td>
<td>100-200</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10</td>
<td>20-40</td>
</tr>
<tr>
<td>Paroxetine CR</td>
<td>12.5</td>
<td>25-50</td>
</tr>
<tr>
<td>Sertraline</td>
<td>25</td>
<td>100-200</td>
</tr>
<tr>
<td><strong>SNRIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>20-30</td>
<td>60-120</td>
</tr>
<tr>
<td>Venlafaxine ER</td>
<td>37.5</td>
<td>150-225</td>
</tr>
<tr>
<td><strong>TCAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>10</td>
<td>100-300</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>10-25</td>
<td>50-150</td>
</tr>
<tr>
<td>Despiramine</td>
<td>25-50</td>
<td>100-200</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>25</td>
<td>50-150</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.75-1.0[^b]</td>
<td>2-4[^b]</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5-1.0[^c]</td>
<td>1-2[^c]</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1.5-2.0[^b]</td>
<td>4-8[^b]</td>
</tr>
</tbody>
</table>

[^a]: Higher doses are sometimes used for patients who do not respond to the usual therapeutic dose.
[^b]: Usually split into three or four doses given throughout the day.
[^c]: Often split into two doses given morning and evening.
Benzodiazepines

• What role in treating anxiety disorders?

• 2 agents: alprazolam, clonazepam FDA-approved for panic disorder

• Positives: rapid onset, effective, often tolerated well

• Negatives: oversedation, cognitive impairment, psychomotor incoordination, potential withdrawal symptoms, potential for dependence, dangerous in overdose

Barker, et al. CNS Drugs 2004
Benzodiazepines (cont’d)

• Short-term use during initiation of an SSRI can be very useful: Provides initial symptom relief, decreases initial activating side effects of antidepressant agents, may hasten response to SSRI

• Populations with special consideration: History of substance abuse, geriatric

• Vital to screen and evaluate for substance misuse at initial appt and in follow-up if not improving as expected

• Be vigilant for benzodiazepine dependence if used for over 4 months after starting treatment

Katzman MA et al. BMC Psychiatry 2014, 14(Suppl 1):S1
Katon WJ. NEJM 2006;354:2360-7
Recommendations for Pharmacotherapy for Social Anxiety Disorder (SAD)

• First-line: escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR

• Second-line: alprazolam, bromazepam, citalopram, clonazepam, gabapentin, phenelzine

• Third-line: atomoxetine, bupropion SR, clomipramine, divalproex, duloxetine, fluoxetine, mirtazapine, moclobemide, olanzapine, selegiline, tigabine, topiramate

• Adjunctive therapy
  • Third-line: aripiprazole, buspirone, paroxetine, risperidone
  • Not recommended: clonazepam, pindolol

• Not recommended: atenolol*, buspirone, imipramine, levetiracetam, propranolol*, quetiapine

(*Beta blockers have been successfully used in clinical practice for performance situations such as public speaking)
Recommenations for Pharmacotherapy for Generalized Anxiety Disorder (GAD)

• First-line: agomelatine, duloxetine, escitalopram, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
• Second-line: alprazolam, bromazepam, bupropion XL, buspirone, diazepam, hydroxyzine, imipramine, lorazepam, quetiapine XR, vortioxetine
• Third-line: citalopram, divalproox chrono, fluoxetine, mirtazapine, trazodone
• Adjunctive therapy:
  • Second-line: pregabalin
  • Third-line: aripiprazole, olanzapine, quetiapine, quetiapine XR, risperidone
  • Not recommended: ziprasidone
• Not recommended: Beta blockers (propranolol), pexacerfont, tiagabine

Katzman MA et al. BMC Psychiatry 2014; 14(Suppl 1):S1
Recommendations for Pharmacotherapy for Obsessive-compulsive Disorder (OCD)

- First-line: escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
- Second-line: citalopram, clomipramine, mirtazapine, venlafaxine XR
- Third-line: IV citalopram, IV clomipramine, duloxetine, phenelzine, tramadol, tranylcypromine

Adjunctive therapy
- First-line: aripiprazole, risperidone
- Second-line: memantine, quetiapine, topiramate
- Third-line: amisulpride, celecoxib, citalopram, granisetron, haloperidol, IV ketamine, mirtazapine, N-acetylcysteine, olanzapine, ondansetron, pindolol, pregabalin, riluzole, ziprasidone
- Not recommended: buspirone, clonazepam, lithium, morphine
- Not recommended: clonazepam, clonidine, desipramine

Katzman MA et al. BMC Psychiatry 2014, 14(Suppl 1):S1
Recommendations for Pharmacotherapy for Core symptoms of Posttraumatic Stress Disorder (PTSD)

- First-line: fluoxetine, paroxetine, sertraline, venlafaxine XR
- Second-line: fluvoxamine, mirtazapine, phenelzine
- Third-line: amitriptyline, aripiprazole, bupropion SR, buspirone, carbamazepine, desipramine, duloxetine, escitalopram, imipramine, lamotrigine, memantine, moclobemide, quetiapine, reboxetine, risperidone, tianeptine, topiramate, trazodone
- Adjunctive therapy
  - Second-line: eszopiclone, olanzapine, risperidone
  - Third-line: aripiprazole, clonidine, gabapentin, levetiracetam, pregabalin, quetiapine, reboxetine, tiagabine
  - Not recommended: bupropion SR, guanfacine, topiramate, zolpidem
  - Not recommended: alprazolam, citalopram, clonazepam, desipramine, divalproex, olanzapine, tiagabine

Katzman MA et al. BMC Psychiatry 2014, 14(Suppl 1):S1
Which of the following components of CBT is most effective for anxiety symptoms?

1. Self-monitoring
2. Relaxation skills
3. Cognitive restructuring
4. Exposure
5. Distraction
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