# Psychopharmacology of Anxiety Disorders

# Anxiety Disorders Are Common:

## National Comorbidity Survey Replication

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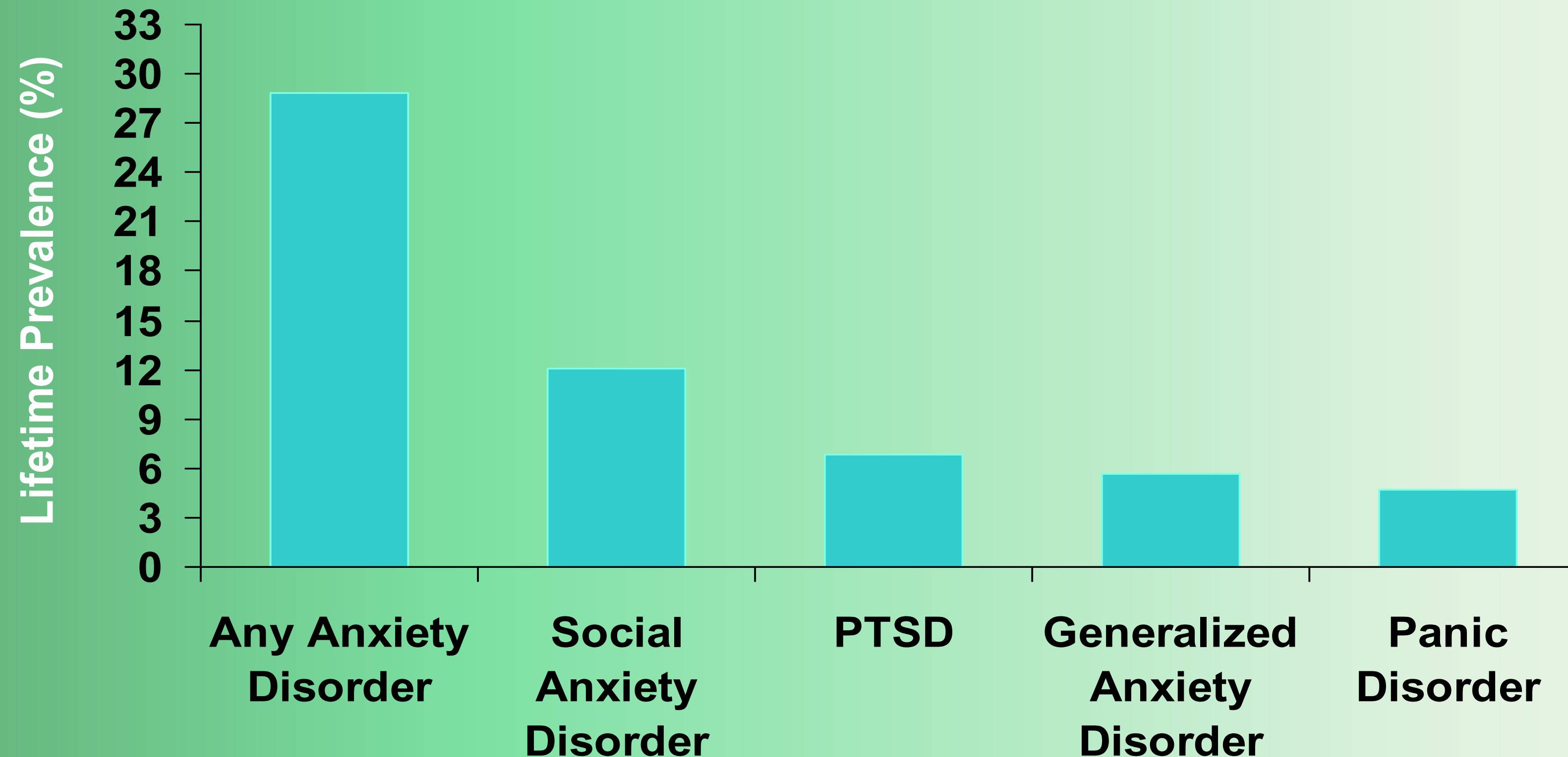


Kessler et al. *Arch Gen Psychiatry*. 2005;62:593-602

# DSM-5 reorganized Anxiety Cluster

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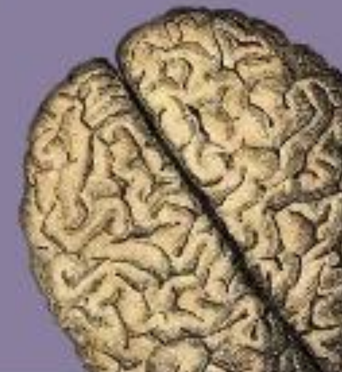
## DSM-5 Disorders

### Anxiety Disorders

- Separation Anxiety Disorder
- Selective Mutism
- Specific Phobia
- Social Anxiety Disorder (Social Phobia)
- Panic Disorder
- Panic Attack (Specifier)
- Agoraphobia
- Generalized Anxiety Disorder
- Substance/Medication-Induced Anxiety Disorder
- Anxiety Disorder Due to Another Medical Condition
- Other Specified Anxiety Disorder Unspecified Anxiety Disorder



*www.slideshare.com, SMR Grey*

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# *Anxiety Disorder Treatment Options*

**PSYCHOSOCIAL**

- **Exposure-Based**
- **Cognitive Behavioral Therapy**
- **Other psychotherapies**
- **Relaxation/mindfulness**

**PHARMACOLOGICAL**

- **SSRIs/SNRIs**
- **Benzodiazepines**
- **Mood Stabilizers**
- **Antipsychotics**
- **Adrenergic Blockers**
- **Sleep agents**

# Anxiety Disorders Management

- Exercise, mindfulness, diet, time in nature
- Evaluate medical/psychiatric/substance comorbidity
- RCT data together suggest comparable efficacy for SSRIs, SNRI, TCAs (except SAD, PTSD), Benzos (except PTSD), and CBT
  - SSRI/SNRIs and CBT are first line due to side effects and broad spectrum efficacy
  - Longer acting high potency benzos optimal (but not PTSD)
- Anticipate side-effect sensitivity
- Mixed support combining CBT and meds first line (benzos may interfere CBT, esp. prn)
- → anticipate plan to d/c meds if start together
- Encourage return to avoided situations for all

# Generalized Anxiety Disorder

Severe anxiety → Consider adjunctive prn Benzodiazepine: Clonazepam or Lorazepam; ideally <4 weeks *SOR A*

Psychotherapy:
1. Cognitive behavioral therapy (*SOR A*)
2. Acceptance and commitment therapy (*SOR B*)

Combination

Comorbid depression?

No → Buspirone *SOR A* / SSRI/SNRI *SOR A*

Buspirone offers more benign SE profile

Less effective with hx of Benzodiazepine use

Yes → SSRI or SNRI *SOR A*

Follow up and titrate dose as appropriate q 1-2 weeks for active medication management

Adequate response (≥ 50% decrease in symptoms)

Inadequate response (< 50% improvement)

Partial Response

Max dose NOT achieved due to side effects

Max dose achieved with inadequate response (<50% improvement)

Buspirone montherapy?

Yes → Switch to SSRI/SNRI

No → First time failing an SSRI or SNRI?

Yes → Trial of different medication

No → Discontinue current medication

Partial Response

On SSRI/SNRI? → Continue SSRI/SNRI; augment with Buspirone

On buspirone monotherapy? → Continue Buspirone; add SSRI/SNRI

Maintain effective pharmacotherapy for minimum of 12 months; if asymptomatic for 4-6 months, consider slow taper *SOR A*

Follow up and titrate dose as appropriate q 1-2 weeks for active medication management

Adequate response (≥ 50% decrease in symptoms)

Partial response

Continue SSRI/SNRI and Buspirone

Begin Mirtazapine *SOR B*

Inadequate response

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response

Begin Mirtazapine
*SOR B*

Continue SSRI/SNRI and Buspirone

Inadequate response

Stop Mirtazapine and start either:

Quetiapine
*SOR A*

Pregabalin/Gabapentin
*SOR A*

Inadequate response

Try other agent

Inadequate response after trying both agents

Stop above agent and start either:

TCA
*SOR C*

Consider TCA prior to chronic benzodiazepines

Benzodiazepine

Imipramine most studied, other TCAs reasonable

Clonazepam

Lorazepam

# Medications for Anxiety Disorders

**Antidepressants**

- Serotonin Selective Reuptake Inhibitors (SSRIs)
- Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
- Atypical Antidepressants
- Tricyclic Antidepressants (TCAs)
- Monoamine Oxidase Inhibitors (MAOIs)

**Benzodiazepines**

- High Potency Benzodiazepines
- Low Potency Benzodiazepines

**Other Agents**

- Azaspirones
- Beta blockers
- Anticonvulsants
- Atypical Antipsychotics

# SSRI and SNRI Antidepressants First Line for Anxiety Disorders

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- Due to safety and tolerability and broad efficacy
- No clear within-class efficacy differences anxiety disorders
- Start low, go slow, but go
  - start citalopram 10 mg, sertraline 25 mg, venlafaxine 37.5 mg
  - -Minimize early exacerbation of anxiety and overlapping side effects, but MAY NEED HIGHER DOSES
- Lack abuse but serotonin withdrawal, initial activation, insomnia, sexual dysfn, GI, weight gain
- AUGMENTATION STRATEGIES: Adjunctive benzodiazepine, beta-blocker, anticonvulsant

# Tricyclic Antidepressants and Anxiety

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- No longer first line due to side effect profile (e.g., cardiovascular, anticholinergic) and lethal in overdose
- Imipramine most RCT data in panic
- No evidence lesser efficacy SSRIs/SNRIs panic but lack efficacy Social Anxiety Disorder
- No RCT refractory data but clinical SSRI augmentation
- Initial anxiety worsening (initiate with "test" dose - e.g., 10 mg/d imipramine)

Bakker A et al. *Acta Psychiatrica Scand*. 2002.

**This information concerns a use that has not been approved by the US FDA.**

# Buspirone

- Non-benzodiazepine anxiolytic
- Non-sedating
- Effects on serotonin and dopamine receptors
- Indicated for generalized anxiety; weak antidepressant effects at higher doses but generally reserve milder cases or if no depression comorbidity
- Potentially useful as augmentation  GAD or augment:
  - Panic
  - Social phobia
  - Depression
  - Sexual dysfunction
- Dosing: 30-60 mg/d

This information concerns a use that has not been approved by the US FDA.

# Beta-Blockers

- Propranolol: 10-40 mg PO QD
- Atenolol: 50-150 mg PO QD
- Effective for discrete "performance anxiety" taken 1-2 h before event
- Propranolol meta-anal. panic (n=130), social (n=16), spec phobia (n=37) found <u>insufficient evidence for anxiety disorders</u>[1]
- Not effective for depression/comorbidities
- Decreases physiologic symptoms of arousal, not emotional experience of anxiety

This information concerns a use that has not been approved by the US FDA

[1]Steenen et al . J psychopharmacology, 2016

# Anticonvulsants for SAD

- None "first line"
- Some RCT support for:
  - Gabapentin (900-3600 mg/d)
  - Pregabalin (at 600 mg)
- Other anticonvulsants have demonstrated possible efficacy for SAD on the basis of open and anecdotal experience
  - Valproate
  - Tiagabine
  - Negative results for Levetiracetam (3,000 mg/day)

This information concerns a use that has not been approved by the US FDA.

Pande et al. J Clin Psychopharmacol. 1999:19:341; Pande. J Clin Psychopharmacol. 2004.
Feltner et al. Int Clin Psychopharmacol. 2011 26;213-220

# Atypical Antipsychotics: Role Refractory Anxiety?

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- NOT a first line intervention!
- May have role for refractory patients or more complex comorbidity:
  → bipolar and anxiety
- Better side effect and safety profiles than typicals but not side effect free
- Caution re: weight gain and metabolic syndrome

**Krystal et al JAMA. 2011 Aug 3;306(5):493-502.**

**This information concerns a use that has not been approved by the US FDA.**

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# Pharmacotherapy Augmentation: Limited Data

- Potential benefits
  - Enhance initial partial response
  - No lost time tapering
  - Combine agents differing in mechanism
- Potential downsides
  - Side-effect burden
  - Cost
  - Unclear which drug to discontinue and when

# Focus on Remission: Pharmacotherapy Options for Patients Remaining Symptomatic

- Optimize dose, duration, and tolerability
- Augmentation
- Switch

Pharmacotherapeutic treatment regimen should reflect the adequacy of prior treatments and other patient variables (such as comorbidity)

# Social Anxiety and Pharmacotherapy Meta-analysis (n = 52 studies)

**Pooled effect sizes for pharmacotherapy trials by drug category**

| Drug Category (Type) | Pooled Effect Size (*g*) | No. Studies |
|---|---|---|
| **SSRI** (Paroxetine, Fluvoxamine, Sertraline, Fluoxetine, Citalopram, Escitalopram) | 0.44 | 26 |
| **SNRI** (Venlafaxine ER) | 0.45 | 5 |
| **MAOI** (Phenelzine, Moclobemide) | 0.36 | 9 |
| **MAO-A** (Brofaromine) | 0.60 | 6 |
| **Benzodiazepines** (Clonazepam, Alprazolam) | 0.82 | 2 |
| **Antipsychotics** (Olanzapine) | 0.72 | 1 |
| **Anticonvulsant** (Gabapentin, Pregabalin, Levetiracetam) | 0.21 | 5 |
| **Beta-blockers** (Atenolol) | 0.08 | 1 |
| **Herbal** (St. John's Wort) | -0.07 | 1 |
| **NaSSA** (Mirtazapine) | 0.13 | 1 |
| **NK1** (Gr205171) | 0.46 | 1 |

Curtiss J et al. Exp. Opin. Pharmacother. 2017;18:243-251.

# Panic, Social, & GAD Meta-Analysis RCTS

**Fig. 2**

| Treatment | *n* | *d* |
|---|---|---|
| SNRIs | 23 | 2.25 |
| Benzodiazepines | 42 | 2.15 |
| CBT + drug | 16 | 2.12 |
| SSRIs | 62 | 2.09 |
| TCAs | 15 | 1.83 |
| Relaxation | 17 | 1.36 |
| CBT/exposure, individual | 93 | 1.30 |
| Pill placebo | 111 | 1.29 |
| CBT, group | 18 | 1.22 |
| Psychodynamic therapy | 5 | 1.17 |
| Non-face-to-face therapies | 34 | 1.18 |
| Psychological placebo | 16 | 0.83 |
| Waiting list | 50 | 0.20 |



Bandelow B et al. Int Clin Psychopharmacol. 2015;30:183-92.

# Cost

| Drug[a] | Average Daily Dose (mg) | Cost Per Day ($) | References |
|---|---|---|---|
| **Antidepressant** | | | |
| Escitalopram | 19.1 | 3.60 | 6, 7, 8, 13 |
| Fluoxetine | 37.8 | 1.17 | 6, 7, 8, 13 |
| Paroxetine | 44.3 | 0.57 | 6, 7, 8, 13 |
| Sertraline | 142.8 | 0.76 | 6, 7, 8, 13 |
| Venlafaxine XR | 209.1 | 9.60 | 6, 7, 8, 13 |
| All antidepressants | | 4.13[b] | |
| Aripiprazole with ADT | 9.2 | 20.31 | 6, 7, 8, 13 |
| Quetiapine 150 mg with ADT | 150.0 | 12.28 | 9,13 |
| Quetiapine 300 mg with ADT | 300.0 | 15.90 | 10,13 |
| Olanzapine/fluoxetine | 8.6/48.8[c] | 19.21 | 11,13 |
| **Pharmacotherapy for akathisia** | | | |
| Lorazepam | 1.0 | 0.14 | 13 |
| Propranolol | 10.0 | 0.04 | 13 |
| Benztropine mesylate | 1.0 | 0.12 | 13 |

ADT = antidepressant therapy; XR = extended release.
[a]Aripiprazole, dosage 2-20 mg/day; olanzapine/fluoxetine, fixed-dose combination of 6-18/50 mg/day.
[b]Calculated by weighting the mean dosages of the antidepressants by the proportion of patients receiving each agent.

# Thank you!