Canadian Anxiety 2014

Clinical Practice Guidelines

Slides: B Chow
Updates: L Jia 2021

Katzman *et al. BMC Psychiatry* 2014, **14**(Suppl 1):S1
http://www.biomedcentral.com/1471-244X/14/S1/S1

BMC Psychiatry

REVIEW Open Access

Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders

Martin A Katzman[1*], Pierre Bleau[2], Pierre Blier[3], Pratap Chokka[4], Kevin Kjernisted[5], Michael Van Ameringen[6], the Canadian Anxiety Guidelines Initiative Group on behalf of the Anxiety Disorders Association of Canada/ Association Canadienne des troubles anxieux and McGill University

Contents

1 Principles of Diagnosis & Management

Table 1 Levels of evidence

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

Table 2 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

- Prevalence (all anxiety and related disorders)
  - Lifetime prevalence = **31%** (higher than mood disorders, SUDs)
  - 12-month prevalence = **18%**
  - Higher in **women**

- Onset
  - Early → **specific phobias, separation anxiety** (7-14 yrs)
  - Later → **GAD, panic disorder, PTSD** (24-50 yrs)

- Suicide Risk
  - **1.7 – 2.5x** incr risk of suicide attempts
    - **Panic disorder, PTSD, GAD** → incr risk of SA + completion
      - (even without MDD)
  - **Comorbid mood disorder** → sig incr risk of suicidal behavior

Table 3 Overview of the management of anxiety and related disorders

- Screen for anxiety and related symptoms
- Conduct differential diagnosis (consider severity, impairment, and comorbidity)
- Identify specific anxiety or related disorder
- Psychological and/or pharmacological treatment
- Perform follow-up

Table 4 General screening questions

- During the past two weeks how much have you been bothered by the following problems?
    - Feeling nervous, anxious, frightened, worried, or on edge
    - Feeling panic or being frightened
    - Avoiding situations that make you anxious

Table 5 Screening questions for specific anxiety and related disorders

Panic disorder – MACSCREEN [29,30]
- Do you have sudden episodes/spells/attacks of intense fear or discomfort that are unexpected or out of the blue?

If you answered "YES" then continue
- Have you had more than one of these attacks?
- Does the worst part of these attacks usually peak within several minutes?
- Have you ever had one of these attacks and spent the next month or more living in fear of having another attack or worrying about the consequences of the attack?

SAD (Based on Mini-SPIN [28])
- Does fear of embarrassment cause you to avoid doing things or speaking to people?
- Do you avoid activities in which you are the center of attention?
- Is being embarrassed or looking stupid among your worst fears?

GAD [31]
- During the past 4 weeks, have you been bothered by feeling worried, tense, or anxious most of the time?
- Are you frequently tense, irritable, and having trouble sleeping?

OCD – MACSCREEN [29,30]

Obsessions:
- Are you bothered by repeated and unwanted thoughts of any of the following types:
  - Thoughts of hurting someone else
  - Sexual thoughts
  - Excessive concern about contamination/germs/disease
  - Preoccupation with doubts ("what if" questions) or an inability to make decisions
  - Mental rituals (e.g., counting, praying, repeating)
  - Other unwanted intrusive thoughts
- If you answered "YES" to any of the above… Do you have trouble resisting these thoughts, images, or impulses when they come into your mind?

Compulsions:
- Do you feel driven to perform certain actions or habits over and over again, or in a certain way, or until it feels just right? Such as:
  - Washing, cleaning
  - Checking (e.g., doors, locks, appliances)
  - Ordering/arranging
  - Repeating (e.g., counting, touching, praying)
  - Hoarding/collecting/saving
- If you answered "YES" to any of the above… Do you have trouble resisting the urge to do these things?

PTSD – MACSCREEN [29,30]
- Have you experienced or seen a life-threatening or traumatic event such as a rape, accident, someone badly hurt or killed, assault, natural or man-made disaster, war, or torture?

If you answered "YES" then continue
- Do you re-experience the event in disturbing (upsetting) ways such as dreams, intrusive memories, flashbacks, or physical reactions to situations that remind you of the event?

- Common risk factors in patients with anxiety disorders
  - **Family history** (more recurrent, impairment, service use)
  - **Personal history** of mood or anxiety disorders
  - **Stressful life events** (esp childhood abuse)
  - **Loneliness, low education, adverse parenting**
  - **Chronic somatic illness** (CVD, DM, asthma, obesity)
  - **Female**
  - **Behavioral inhibition**

Table 6 Common risk factors in patients with anxiety and related disorders

- Family history of anxiety [33]
- Personal history of anxiety or mood disorder [34,35]
- Childhood stressful life events or trauma [36,37]
- Being female [4,9]
- Chronic medical illness [34,40]
- Behavioral inhibition [41,42]

- Anxiety disorders often comorbid with other disorders
  - **>50%** have **2+ anxiety disorders**
  - **30%** have **3+ anxiety disorders**
  - **60% of MDD**
  - **52% of bipolar**
  - **47% of ADHD**

- Comorbidities associated with
  - Greater **severity, chronicity, impairment**
  - Worse **treatment outcomes**
  - Higher tx costs, higher health service use
  - Worse with more comorbidities

- Higher prevalence of medical comorbidities
  - Hypertension, other cardiovascular conditions
  - GI disease
  - Arthritis
  - Thyroid disease
  - Respiratory disease
  - Migraine headaches
  - Allergic conditions

- Impact
  - Incr risk of developing **comorbid MDD**
  - Incr **functional impairment** (with severity, # of anxiety disorders)
  - **Economic impact** (healthcare use, work productivity)
  - Of those dx with anxiety disorder → **40% untreated**

- Baseline Assessment
  - History
    - Review of systems
    - Meds, OTC
    - Alcohol, drugs
    - Caffeine
    - Anxiety symptoms
    - Functioning
  - Physical exam
  - Investigations

Table 7 Considerations for baseline laboratory investigations (as needed based on patient's presenting symptoms)

Basic lab tests

- Complete blood count
- Fasting lipid profile (TC, vLDL, LDL, HDL, TG)
- Electrolytes
- Fasting glucose
- Thyroid-stimulating hormone
- Liver enzymes

If warranted

- Urine toxicology for substance use

- Monitoring
  - Initially **q1-2weeks**
  - Then **q4weeks** → weight Δ, medication SE
  - Closer if: **age <10, older, medically ill, metabolic Δ, polypharmacy**

Table 8 Key features of specific anxiety and related disorders

Disorder	Key features
Panic disorder	• Recurrent unexpected panic attacks, in the absence of triggers • Persistent concern about additional panic attacks and/or maladaptive change in behavior related to the attacks
Agoraphobia	• Marked, unreasonable fear or anxiety about a situation • Active avoidance of feared situation due to thoughts that escape might be difficult or help unavailable if panic-like symptoms occur
Specific phobia	• Marked, unreasonable fear or anxiety about a specific object or situation, which is actively avoided (e.g., flying, heights, animals, receiving an injection, seeing blood)
Social anxiety disorder (SAD)	• Marked, excessive or unrealistic fear or anxiety about social situations in which there is possible exposure to scrutiny by others • Active avoidance of feared situation
Generalized anxiety disorder (GAD)	• Excessive, difficult to control anxiety and worry (apprehensive expectation) about multiple events or activities (e.g., school/work difficulties) • Accompanied by symptoms such as restlessness/feeling on edge or muscle tension
Obsessive–compulsive disorder (OCD)	• Obsessions: recurrent and persistent thoughts, urges, or images that are experienced as intrusive and unwanted and that cause marked anxiety or distress • Compulsions: repetitive behaviors (e.g., hand washing) or mental acts (e.g., counting) that the individual feels driven to perform to reduce the anxiety generated by the obsessions
Posttraumatic stress disorder (PTSD)	• Exposure to actual or threatened death, serious injury, or sexual violation • Intrusion symptoms (e.g., distressing memories or dreams, flashbacks, intense distress) and avoidance of stimuli associated with the event • Negative alterations in cognitions and mood (e.g., negative beliefs and emotions, detachment), as well as marked alterations in arousal and reactivity (e.g., irritable behavior, hypervigilance)

- Approach to Treatment
  - **Psychoeducation**
    - About anxiety disorders
    - Treatment choices, efficacy, tolerability
    - Aggravating factors
    - Signs of relapse
  - **Treatment choice factors**
    - Pt preference, motivation, ability to engage
    - Prev tx response
    - Illness severity, comorbidities
    - Clinician skill, clinician expertise

- Overview of psychological treatment
  - Meta-analyses → efficacy for **CBT protocols (exposure), MBCT**
  - For panic disorder, specific phobia, SAD, OCD, GAD, PTSD
  - CBT addresses factors that **cause + maintain** anxiety sx

- CBT delivery
  - **Group = individual**
  - **Self-directed** (bibliotherapy, internet/computer) → sig improve
  - **Virtual reality exposure (VRE) therapy** → EFFECTIVE
    - When real-life exposure difficult
    - (inconvenient, expensive, pt reluctance)

Table 9. Components of cognitive behavioral interventions	
Exposure	• Face fears through repeated exposure • Corrective info through exposure • Extinguish fears • Successful coping
Safety Response Inhibition	• Restrict anxiety-reducing BEHAVIORS • Decrease NEGATIVE reinforcement • Enhance self-efficacy
Surrender of Safety Signals	• Relinquish safety signals (PEOPLE/OBJECTS) • Learn adaptive self-efficacy beliefs
Cognitive Strategies	• Cognitive restructuring + behavioral experiments • Corrective info about threat • Target exaggerated sense of danger • Target self-efficacy beliefs
Arousal Management	• Relaxation • Breathing control

- Overview of pharmacological treatment
  - **SSRI/SNRIs** → preferred initial treatments (safer, tolerance)
  - Consider: efficacy, safety, tolerability, comorbidity

- Benzodiazepines
  - **Early adjunctive tx** → acute anxiety, acute crises
    - **Waiting for SSRI effects**
  - Concerns = dependency, sedation, cognitive impairment, SE
  - Short-term use, regular dosing

- Anticonvulsants, AAPs
  - Efficacy in some anxiety disorders
  - But **2nd or 3rd line, adjunctive tx** (due to SE, limited RCTs)

Table 10 Medications with Health Canada–approved indications for anxiety and related disorders

	Anxiety disorders	Panic disorder	Social anxiety disorder	Obsessive–compulsive disorder	Generalized anxiety disorder	Posttraumatic stress disorder
ANTIDEPRESSANTS						
SSRIs						
Escitalopram (Cipralex®)				X	X	
Fluoxetine (Prozac®)				X		
Fluvoxamine (Luvox®)				X		
Paroxetine (Paxil®)		X	X	X	X	X
Paroxetine CR (Paxil® CR)		X	X			
Sertraline (Zoloft®)		X		X		
TCAs						
Clomipramine				X		
Other antidepressants						
Venlafaxine XR (Effexor® XR)		X	X		X	
Duloxetine (Cymbalta®)					X	
AZAPIRONES						
Buspirone (BuSpar®, Buspirex®)					X	
BENZODIAZEPINES*	X					

Data from respective Canadian product monographs [84].

*Multiple generic and brand name products, consult product monographs: alprazolam, bromazepam, chlordiazepoxide, clorazepate, diazepam, lorazepam, and oxazepam are indicated for anxiety disorders; alprazolam is also indicated for panic disorder.

- Antidepressant Safety & SE
  - Most common BOTHERSOME SE of SSRI/SNRI:
    - **Sexual dysfunction, drowsiness, fatigue, weight gain**
  - Other common SE of SSRI/SNRI
    - Headache, irritability, anxiety, insomnia, tremor, GI sx
    - **Risk of UGIB** (esp with NSAIDs)
    - SSRI specifically → **low BMD, incr #, hyponatremia**
  - Usually **early + transient** (first 2 weeks)
    - Sexual dysfunction + weight gain can persist
  - **Discontinuation Syndrome:** GI, psychiatric, vasomotor sx
  - In C&A → **incr risk of SUICIDAL ideation/behavior**

- Antidepressant Safety & SE
  - SSRI/SNRIs → better tolerated/safer **than TCAs/MAOIs**
    - Less anticholinergic, toxicity, lethality
    - Less psychomotor/cognitive impairment
    - **MAOIs** → 2nd/3rd line (SE, drug interactions, diet restrictions)

- Anxiolytic Safety & SE
  - Benzodiazepines (most common SE)
    - **Sedation, fatigue, weakness**
    - **Slurred speech, ataxia**
    - **Memory impairment**
    - Also assoc with → **withdrawal, rebound, dependence**
      - Greater risk with short/intermediate-acting agents
      - Caution in pts with SUD
    - Older pts → risk of **falls + fractures**
      - **Cognitive impairment** may persist after cessation
      - Memory impairment assoc with high-dose/potency agents
  - Azapirones **(buspirone, 5HT1A agonist)**
    - Dizziness, drowsiness, nausea

- Atypical Antipsychotics Safety & SE
  - **Metabolic SE** (weight gain, DM2, glucose, lipids)
    - High → olanzapine
    - Med → risperidone, quetiapine
    - Lower → aripiprazole, asenapine, lurasidone, ziprasidone
  - **Sedation**
    - More → quetiapine, clozapine, olanzapine, asenapine
    - Less → risperidone, aripiprazole, ziprasidone, lurasidone
  - Because of risk of diabetes + weight gain + limited RCT evidence
    - AAP considered **2nd/3rd/adjunctive therapies**

- Anticonvulsants
  - GI, somnolence, weight gain, tremor
  - Dermatological
    - **Erythema multiforme, SJS, TENS**
  - Hematological

  - **Divalproex** → monitor drug levels + LFTs

- Follow-up
  - Pharmacological tx → **2-8 weeks to onset of sx relief**
    - Full response may take **12 weeks**
    - Continue for **12-24 months**
    - Longer-term therapy → continued sx relief, prevent relapse
  - Initiate at low dose
    - Titrate at **1-2 week intervals**, over 4-6 weeks
    - At therapeutic dose → improvement usually in **next 4-8 weeks**
    - Follow-up at 2 week intervals for first 6 weeks
    - Then monthly follow-up

- Assessing response to treatment
  - Response = **25-50% reduction in symptoms**
  - Remission
    - **Loss of diagnostic status**
    - Low score on anxiety scale (CGI, HARS)
    - No functional impairment (Sheehan Disability Scale, SF-36)

2 Panic Disorder & Agoraphobia

Table 11 DSM-5 criteria for panic attacks

• An abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and includes ≥4 of the following symptoms:
(1) Palpitations, pounding heart, or accelerated heart rate
(2) Sweating
(3) Trembling or shaking
(4) Sensations of shortness of breath or smothering
(5) Feelings of choking
(6) Chest pain or discomfort
(7) Nausea or abdominal distress
(8) Feeling dizzy, unsteady, light-headed, or faint
(9) Chills or heat sensations
(10) Paresthesias (numbness or tingling sensations)
(11) Derealization (feelings of unreality) or depersonalization (being detached from oneself)
(12) Fear of losing control or going crazy
(13) Fear of dying

Table 12 DSM-5 diagnosis of panic disorder

- The person has experienced both of the following:
  - Recurrent unexpected panic attacks
  - ≥1 of the attacks followed by ≥1 month of 1 or both of the following:
    - Persistent concern or worry about additional panic attacks or their consequences
    - Significant maladaptive change in behavior related to the attacks

Table 13 DSM-5 diagnosis of agoraphobia

- Marked fear or anxiety about ≥2 of the following 5 groups of situations:

(1) Public transportation (e.g., traveling in automobiles, buses, trains, ships, or planes)
(2) Open spaces (e.g., parking lots, market places, or bridges)
(3) Being in shops, theatres, or cinemas
(4) Standing in line or being in a crowd
(5) Being outside of the home alone in other situations

- The individual fears or avoids these situations due to thoughts that escape might be difficult or help might not be available in the event of panic-like symptoms
- The agoraphobic situations almost always provoke fear or anxiety
- The situations are actively avoided, require presence of a companion, or endured with marked fear or anxiety
- The fear or anxiety is out of proportion to actual danger posed by agoraphobic situation
- The fear, anxiety, or avoidance is persistent, typically lasting ≥6 months
- The fear, anxiety, and avoidance cause clinically significant distress or functional impairment

- Epidemiology

	Panic Disorder	Agoraphobia (without panic)	Panic Attacks
Lifetime	**5%**	1.4%	28%
12-month	**2.5%**	0.8%	6-11%

- Higher risk of ***panic disorder or agoraphobia*** if:
  - **Female**
  - **Middle-aged**
  - **Widowed/divorced**
  - **Low income**
  - (no difference if urban vs rural)

- Epidemiology
  - ***Panic disorder***
    - 40-70% have **nocturnal panic**
    - Negative impact on quality of life, function
      - Incr risk of **suicide attempts**
      - Worse cognitive + emotional dysfunction
  - ***Panic attacks***
    - Youth → often comorbid psychiatric disorders
    - Most general public will NOT develop psychopathology

- Comorbidity
  - Incr risk of comorbid disorder
    - Anxiety, mood, impulse-control, substance use
    - **35-40% have comorbid MDD**
    - Agoraphobia common
  - More prevalent among pts with **medical conditions**
    - Thyroid, cancer, cardiac disease
    - Chronic pain, migraine, IBS
    - Allergic, respiratory diseases
    - Assoc with **greater severity of panic disorder sx**

- Psychological Treatment
  - ***CBT for panic disorder*** → favored over medications
    - **Exposure** → MOST effective
      - Cognitive restructuring
      - Combined strategies more effective for agoraphobia
      - Interoceptive exposure → superior to relaxation
    - Homework + follow-up → improved effectiveness
    - **VR exposure effective**
    - **Minimal intervention CBT as effective** as face-to-face CBT
      - Bibliotherapy, telephone, videoconference, internet-based
    - **Usually 12-14 weekly sessions**
      - Briefer courses as effective (6-7 sessions)
      - **Changes in beliefs FIRST** (precede changes in symptoms)
      - Change in beliefs + avoidance = KEY process variables

- Psychological Treatment
  - **Predictors of POOR response to CBT**
    - Severity of panic disorder
    - Strength of blood/injury fears
    - Earlier onset of panic sx
    - Comorbid social anxiety
    - Degree of agoraphobic avoidance
  - *NO advantage of EMDR* (vs non-eye movement desensitization)

- Combined psychological + pharmacological treatment
  - Combination CBT + pharmacotherapy for PANIC DISORDER
    - Superior during **acute treatment phase**
      - (vs CBT or pharmacotherapy alone)
    - **Equal to psychotherapy** after termination of treatment
      - (still more effective than pharmacotherapy alone)
    - Cost effective

  - ***CBT alone or combination*** → **FIRST-LINE treatment**
    - NO benefit with *self-administered CBT + SSRI*
    - NO long-term benefit with *buspirone + CBT (only short-term)*
    - NO benefit with *combined benzos or D-cycloserine*

  - **Provide CBT at time of med d/c** → lower relapse rates
    - CBT may help benzo discontinuation

- Long-term effects of psychological treatment
  - Benefits of CBT → maintained for **up to 3 years**
    - Lower relapse rates
  - If panic-free with exposure therapy
    - **93% remission** after 2 years
    - 62% remission after 10 years
  - Remission/response rates better with **combination**
    - (vs psychotherapy or pharmacotherapy alone)

Table 15. Recommendations for pharmacotherapy for panic disorder

	SSRIs, SNRIs, others	*TCAs, MAOIs, others*	*Benzos, AED, AAPs*
FIRST-LINE	• **All 6 SSRIs** (CEFFPS) • Venlafaxine		
SECOND-LINE	• Mirtazapine • Reboxetine	• Clomipramine • Imipramine	• Alprazolam • Clonazepam • Diazepam • Lorazepam
THIRD-LINE	• Bupropion • Duloxetine • Milnacipran	• Moclobemide • Phenelzine • Tranylcypromine	• Divalproex • Gabapentin • Levetiracetam • Olanzapine • Quetiapine • Risperidone
Adjunctive therapy	• *Second-line*: **alprazolam** ODT, **clonazepam** • *Third-line:* aripiprazole, olanzapine, risperidone, divalproex, pindolol		
NOT recommended	• Buspirone, propranolol, tiagabine, trazodone		

Table 15 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	**Second-line**: alprazolam ODT, clonazepam **Third-line**: aripiprazole, divalproex, olanzapine, pindolol, risperidone
Not recommended	Buspirone, propranolol, tiagabine, trazodone

CR = controlled release; ODT = orally disintegrating tablets; SR = sustained release; XR = extended release.

- Pharmacological Treatment
  - ***First-line agents***
    - **SSRIs** → improved panic, agoraphobic, anxiety, depressive sx
      - Similar effects to TCA (but lower dropout rates with SSRIs)
    - **SNRIs** → decr panic disorder sx
  - ***Second-line agents***
    - TCAs → **clomipramine, imipramine**
      - Less tolerated, higher discontinuation (vs SSRIs)
    - **Reboxetine** → SE dry mouth, constipation, insomnia
    - **Mirtazapine** → less evidence, as effective as fluoxetine
    - **Benzos** → short-term, severe agitation
  - ***Third-line agents***
    - **MAOIs, RIMAs** → may be useful in treatment-resistant pts
    - **AAPs**, others → some evidence for efficacy

- Pharmacological Treatment
  - **Adjunctive treatments**
    - Adjunctive benzos may lead to more rapid response
    - Adjunctive AAP for treatment-resistant pts
  - **NOT RECOMMENDED treatments**
    - Buspirone, propranolol, tiagabine, trazodone, carbamazepine
    - NO evidence for efficacy
- Maintenance Pharmacological Treatment
  - SSRIs, venlafaxine, TCAs → prevent relapse
  - Benzos → only short-term use

- Biological Therapies
  - Radioelectric asymmetric conveyor (level 3)
  - rTMS for comorbid (level 4)

- Alternative Therapies
  - **Capnometry-assisted respiratory training** (level 2)
  - Aerobic exercise (level 3)
  - *NOT breathing training (negative level 2)*
  - *NOT group exercise (negative level 2)*

Summary of Panic Disorder

- **40%** of gen pop have a panic attack in lifetime
- Evidence for tx: **pharmacotherapy, CBT alone, or combination**

- <u>Psychological strategies for panic disorder</u>
  - Panic sx → **exposure**
  - Agoraphobia → **combined strategies**

  - CBT equally effective in **individual = groups**
    - Also self-help books, virtual reality, internet-based CBT

  - CBT effects **maintained during follow-up**
    - Combination tx may be superior to pharmacotherapy alone

Summary of Panic Disorder

- Indications for pharmacotherapy in panic disorder
  - CBT alone may be insufficient if:
    - Comorbid mod-severe **major depression**
    - **Severe + frequent** panic attacks
    - Rapid **worsening of agoraphobia**
    - **Suicidal ideation**
  - Preference for pharmacotherapy
    - Pt **not motivated** to participate in CBT
    - Pt **too fearful** to engage in exposure
  - While waiting for first-line pharmacotherapy to be effective
    - Could consider **initial rescue benzo** (first 4-12 weeks)

Summary of Panic Disorder

- First-line agents
  - **All 6 SSRIs, venlafaxine**
  - Optimize dose, switch to another first-line if not tolerated

- Second-line agents
  - **Mirtazapine**
  - TCAs **(clomipramine, imipramine)**
  - Benzos **(clonazepam, lorazepam, diazepam, alprazolam)**
  - **Reboxetine**

- If no response to first- or second-line → **tx-refractory**
  - Reassess dx, comorbidities
  - Consider third-line agents, adjunctive therapies, alternatives

3 Specific Phobia

Table 16 DSM-5 diagnosis of specific phobia

- Marked fear or anxiety about a specific object or situation (e.g., flying, seeing blood)
- The phobic object or situation almost always provokes immediate fear or anxiety and is actively avoided or endured with marked fear or anxiety
- The fear or anxiety is out of proportion to the actual danger posed by the specific object or situation
- The fear, anxiety, or avoidance is persistent, typically ≥6 months
- There is marked distress or functional impairment

Table 17 Specific phobia specifiers in DSM-5

Specifier	Examples
Animal	Spiders, insects, dogs
Natural environment	Heights, storms, water
Blood-injection-injury	Needles, invasive medical procedures
Situational	Airplanes, elevators, enclosed spaces
Other	Choking or vomiting. In children, loud sounds or costumed characters

- Epidemiology
  - Lifetime prevalence = **10-13%** (adolescents 36.5%)
  - 12-month prevalence = 7-9% (adolescents 27.3%)
  - More common in **WOMEN**
  - Age of onset → **5-12 years** (school-age)
    - Animal, B-I-I → childhood
    - Situational → late adolescent, early adulthood

- Comorbidities
  - Tend to co-occur with **other specific phobias (>90%)**
    - Average 3 fears
  - Often other psychiatric disorders
    - Other anxiety disorders (panic, SAD, GAD)
    - SUDs, mood disorders, personality disorders

- Psychological Treatment
  - ***Psychological tx PREFERRED***
    - Esp **exposure-based tx**
    - High degree of success in providing **remission**
    - Both ***in vivo*** **+ virtual reality exposure** EFFECTIVE
  - ***Exposure-based therapy MORE effective if:***
    - **Grouped closely together**
    - **Prolonged exposure**
    - **Real** (not imagined)
    - Provided in **different settings**
    - Some degree of **therapist involvement**
  - NO evidence that flooding vs gradual exposure more effective
    - But **progressive exposures** generally more tolerable

Table 18. Psychological treatments with demonstrated efficacy in specific phobias	
Psychological treatment	*Phobia*
Exposure-based treatments	• All specific phobias
Virtual reality exposure	• Flying • Spiders • Heights • Claustrophobia
Computer-based self-help programs	• Flying • Spiders • Small animals
Applied muscle tension (+ exposure)	• Blood-injection-injury type
Cognitive therapy & exposure	• Dental • Flying

- Combined psychological + pharmacological treatment
  - **Adjunctive D-cycloserine** (NMDA receptor partial agonist)
    - Enhanced exposure therapy (heights, not spiders)
  - **Adjunctive cortisol**
    - Enhances exposure therapy (spider, heights)
  - **Adjunctive yohimbine**
    - Enhanced VRE for claustrophobia
  - Adjunctive naltrexone LESS effective

- Long-term effects of psychological treatment
  - **Sustained benefits** at long-term follow-up
  - (long-term treatment is rare)

- Pharmacological Treatment
  - **MINIMAL ROLE**
    - (success of exposure therapy, lack of med research)
  - Some evidence for SSRI
  - *NO benefit for benzos as adjunct to exposure therapy*
    - May be necessary for acute sx relief
    - Nasal midazolam for claustrophobia + MRI

Summary of Specific Phobia

- Quite common, esp among **adolescents**

- Most common phobia types
  - **Animal**
  - **Natural environment**
  - **Situational**
  - **Blood-injection-injury**

- Foundation of treatment
  - **Exposure-based techniques** (incl VRE)
  - *Pharmacotherapy NOT recommended usually (unproven)*

4 Social Anxiety Disorder

Table 19 DSM-5 diagnosis of SAD (social phobia)

- Marked fear or anxiety about social situations in which the person may be exposed to scrutiny by others
- Fear that actions or showing anxiety symptoms will cause negative evaluation (e.g., embarrassment, humiliation) or offend others
- The social situation:
  - Almost always provokes fear or anxiety
  - Is actively avoided or endured with marked fear or anxiety
- The fear, anxiety, or avoidance:
  - Is out of proportion to the actual threat posed by the social situation
  - Is persistent, typically ≥6 months
  - Causes significant distress or functional impairment
- If another medical condition is present (e.g., stuttering, obesity), the disturbance is unrelated or out of proportion to it
- Specify "performance only" if the fear is restricted to speaking or performing in public

- Epidemiology
  - Lifetime prevalence = **8-12%**
  - Earlier onset → typically during **adolescence** (mean age 12)
  - **Chronic + unremitting course**

- Factors for higher prevalence
  - More common in **WOMEN**
  - **Single** or separated
  - **Comorbid MDD**
  - More common in **developed countries** (6% vs 2% developing)
  - **Low educational** achievement
  - **Low SES**

- Functional Impairment
  - Education, occupation, family, overall quality of life

- Economic burden
  - Work day missed
  - Health care costs
  - More likely to report disability days

- Psychiatric comorbidity
  - **72%** with another psychiatric disorder
  - MOST common → **MDD, other anxiety disorders**
  - Other common
    - Avoidant PD
    - Body dysmorphic disorder
    - ADHD
    - Schizophrenia

- Psychological Treatment
  - ***CBT*** = gold-standard non-pharm treatment
    - **Restructuring**, challenging maladaptive thoughts
    - **Exposure therapy** (some evidence for just exposure therapy)
    - Similar efficacy vs pharmacotherapy
      - But **more PERSISTENT gains**
    - No difference between group or individual
  - CBT variants
    - **CBT + VRE** → as EFFECTIVE as imagined/in vivo exposure
    - **Internet CBT** → more EFFECTIVE than waitlist control
    - *Videotaped feedback does NOT enhance exposure*
  - **IPT** → LESS effective than CBT, more effective than waitlist control
  - **Mindfulness-Based Therapy (MBT)** → LESS effective than CBT

- Combined psychological + pharmacological treatments
  - **Mixed results** for additional benefit of pharmacotherapy
  - D-cycloserine may enhance exposure therapy

- Long-term effects of psychological treatment
  - Benefits of CBT maintained **at 6-12 months → up to 5 years**
  - Longer lasting effects than pharmacotherapy

Table 21. Recommendations for pharmacotherapy for SAD

	SSRIs, SNRIs, others	*TCAs, MAOIs, others*	*Benzos, AED, AAPs*
FIRST-LINE	• **4 SSRIs → EFvPS** • Venlafaxine	• Pregabalin	
SECOND-LINE	• **Citalopram**	• Gabapentin • Phenelzine	• Alprazolam • Bromazepam • Clonazepam
THIRD-LINE	• **Fluoxetine** • Duloxetine • Bupropion • Mirtazapine	• Clomipramine • Selegiline • Moclobemide • Atomoxetine	• Olanzapine • Divalproex • Tiagabine • Topiramate
Adjunctive therapy	• *Third-line:* aripiprazole, risperidone, buspirone, paroxetine,		
NOT recommended	• **Quetiapine**, buspirone, imipramine, levetiracetam, propranolol, atenolol • *Adjunct:* clonazepam, pindolol		

Table 21 Recommendations for pharmacotherapy for 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, tiagabine, topiramate
Adjunctive therapy	**Third-line:** aripiprazole, buspirone, paroxetine, risperidone **Not recommended:** clonazepam, pindolol
Not recommended	Atenolol*, buspirone, imipramine, levetiracetam, propranolol*, quetiapine

CR = controlled release; SR = sustained release; XR = extended release.

*Beta-blockers have been successfully used in clinical practice for performance situations such as public speaking.

Note: although there is limited evidence for citalopram in SAD, it is likely as effective as the other SSRIs, in contrast there are negative trials of fluoxetine in SAD suggesting it may be less effective than other SSRIs [382,449].

- Pharmacological Treatment
  - ***First-line agents***
    - **SSRIs → EFvPS** (NOT citalopram or fluoxetine)
    - **Venlafaxine**
    - **Pregabalin**
  - ***Second-line agents***
    - **Citalopram** (less evidence)
    - **Benzos** (as effective as SSRIs, but abuse potential)
    - **Gabapentin**
    - **Phenelzine** (safety)
  - ***Third-line agents*** → for refractory pts
    - **Fluoxetine** (some negative trials)
    - Moclobemide, mirtazapine (mixed results)
    - Duloxetine (limited effect)
    - Bupropion, clomipramine, divalproex, topiramate, tiagabine, olanzapine, selegiline, atomoxetine → open-label/small studies

- Adjunctive Therapy
  - *Third-line adjunctive* (open-label studies)
    - **Aripiprazole, risperidone**, buspirone, paroxetine
  - NOT RECOMMENDED adjunctive
    - Clonazepam + paroxetine
    - Pindolol + paroxetine

- NOT RECOMMENDED treatments
  - Atenolol, propranolol (clinically used in performance situations)
  - Buspirone, quetiapine, imipramine, levetiracetam, pergolide

- Maintenance pharmacological treatment
  - **Continued SSRI for 3-6 months** → reduced relapse rates (NNT 3.6)
  - **Pregabalin** reduced relapse over 6 months

- Biological therapies
  - **Neuro-psycho-physical optimization radio electric asymmetric conveyor (NPPO-REAC)**
    - As effective as sertraline

- Alternative therapies
  - *St. John's wort NOT recommended*

Summary of SAD

- SAD one of the most common anxiety disorders
  - More often in WOMEN

- **CBT & exposure therapy ALONE** → effective first-line tx

- CBT vs pharmacotherapy → **similar efficacy for ACUTE SAD**
  - But gains with **CBT persist longer**
  - Adding pharmacotherapy does not increase benefits of CBT

- Pharmacotherapy
  - First-line → **EFFPS, venlafaxine, pregabalin**
  - Second-line → **citalopram, benzos, gabapentin**, phenelzine

5 Generalized Anxiety Disorder

Table 22 DSM-5 diagnosis of GAD

- Excessive anxiety and worry (apprehensive expectation) about a number of events or activities (e.g., school/work performance)
- The individual finds it difficult to control the worry
- Excessive anxiety and worry are associated with ≥3 of the following symptoms (with at least some occurring more days than not for ≥6 months):
    - Restlessness or feeling keyed-up or on edge, being easily fatigued, difficulty concentrating, irritability, muscle tension, or sleep disturbance
- The disturbance causes clinically significant distress or functional impairment

- Epidemiology
  - Lifetime prevalence = **6%**
  - 12-month prevalence = 1-4%
  - Later onset → **age 31** (but may be bimodal)
    - May be more common in older adults
  - More frequent in **CAUSASIANS** (2-3x)
  - More frequent in **WOMEN**
- Children & Adolescent GAD
  - Children 3%
  - Adolescents 11%
  - Onset between **age 10-14**

- Impairment
  - Functional, occupational, quality of life, economic costs

- Comorbidity
  - Often other **anxiety disorders, MDD**
  - Incr risk of medical conditions
    - Pain syndromes
    - HTN, CV, GI
    - Increases severity of illness, functional impairment, costs

- Psychological Treatment
  - ***CBT*** significantly reduces GAD sx
    - Comparable with pharmacotherapy
    - Individual + group equally effective
      - Individual therapy may have earlier improvement
    - **<8 sessions still effective**
      - But more sessions may improve worry/depression more
    - ICBT → more effective than waitlist, prolonged benefits
    - *NO benefit from adding interpersonal + emotional processing*

  - **Relaxation therapy** → limited efficacy
  - **Balneotherapy (spas)** → some evidence
  - **Psychodynamic therapy** → unclear benefits, some evidence
  - Some efficacy for ACT, meta-cognitive therapy, CBT targeting intolerance of uncertainty, adjunctive MBCT

- Psychological + Pharmacological Treatment
  - Combination CBT + pharmacotherapy
    - More effective only post-treatment, **NOT after 6 months**
  - Conflicting results about adjunctive psychotherapy
  - **NO current evidence to support routine combination**

- Long-term effects of psychological treatment
  - Benefits maintained **1-3 years after treatment**

- Pharmacological Treatment
  - ***First-line agents***
    - SSRIs → **EPS (escitalopram, paroxetine, sertraline)**
    - SNRIs **(venlafaxine, duloxetine)**
    - **Agomelatine, pregabalin**
  - ***Second-line agents***
    - **Bupropion** (less data)
    - **Quetiapine** (side effects)
    - **Vortioxetine** (mixed results)
    - **Buspirone** (limited effectiveness)
    - **Benzos** (short-term use)
    - **Imipramine** (side effects)
    - **Hydroxyzine** (limited clinical experience)
  - ***Third-line agents***
    - **Citalopram, fluoxetine, mirtazapine** (open-label/case series)
    - Trazodone, divalproex chrono (not widely available)

- Pharmacological Treatment
  - *Adjunctive second-line therapy*
    - **Pregabalin**
  - *Adjunctive third-line therapy*
    - **Risperidone, quetiapine** (mixed results)
    - **Olanzapine, aripiprazole** (weaker data)
    - AAP side effects → only for treatment-refractory cases
  - NOT recommended adjunctive
    - Ziprasidone

- NOT recommended treatments
  - *Propranolol*, pexacerfont, tiagabine, memantine

- Maintenance pharmacological treatment
  - **SSRIs, SNRIs, pregabalin, quetiapine** reduce relapse at 6 months

Table 24. Recommendations for pharmacotherapy for GAD

	SSRIs, SNRIs, others	*TCAs, MAOIs, others*	*Benzos, AED, AAPs*
FIRST-LINE	• **3 SSRIs → EPS** • Duloxetine • Venlafaxine	• Agomelatine • Pregabalin	
SECOND-LINE	• Vortioxetine • Bupropion	• Imipramine • Buspirone • Hydroxyzine	• Alprazolam • Bromazepam • Clonazepam • Lorazepam • Quetiapine
THIRD-LINE	• **Citalopram** • **Fluoxetine** • Mirtazapine • Trazadone		• Divalproex chrono
Adjunctive therapy	• *Second-line:* **pregabalin** • Third-line: aripiprazole, olanzapine, quetiapine, risperidone		
NOT recommended	• Beta blockers (propranolol), pexacerfont, tiagabine • *Adjunct:* ziprasidone		

Table 24 Recommendations for pharmacotherapy for 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, divalproex 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

CR = controlled release; XL = extended release; XR=extended release.

*Note: These have distinct mechanisms, efficacy and safety profiles. Within these second-line agents, benzodiazepines would be considered first in most cases, except where there is a risk of substance abuse, while bupropion XL would likely be reserved for later. Quetiapine XR remains a good choice in terms of efficacy, but given the metabolic concerns associated with atypical antipsychotic, it should be reserved for patients who cannot be provided antidepressants or benzodiazepines. Please refer to text for further rationale for the recommendations.

- Biological therapies
  - **rTMS** → EFFECTIVE (as monotherapy or adjunct to SSRIs)
    - Improvements maintained 6 months after

- Alternative therapies
  - Lavender oil (silexan) → comparable to lorazepam
  - Galphimia glauca extract → comparable to lorazepam
  - Passion flower → as effective as benzos
  - Valerian → comparable to diazepam
  - NOT recommended due to poor standardization

  - **Resistance or aerobic exercise** → more effective than waitlist
  - **Adjunctive meditation/yoga** → may be useful
  - Acupuncture → insufficient evidence

  - *Bright light therapy NOT recommended*

Summary of GAD

- Lifetime prevalence = **6%**
  - More frequent in WOMEN
  - **Bimodal** distribution (early 20s, then 30-40s)

- **CBT** → effective **FIRST-LINE** tx
  - As effective as pharmacotherapy
  - NO evidence for routine combination tx

- Pharmacotherapy
  - **FIRST-LINE** → **EPS, venla/dulox, pregabalin, agomelatine**
  - **SECOND-LINE** → bupropion, buspirone, benzos, quetiapine, vortioxetine, imipramine, hydroxyzine

6 OCD

Table 25 DSM-5 diagnosis of OCD

- Presence of either obsessions, compulsions, or both
  - Obsessions are defined by the following:
    - Recurrent and persistent thoughts, urges, or images that are experienced as intrusive and unwanted and that cause marked anxiety or distress
    - The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with other thoughts or actions
  - Compulsions are defined by the following:
    - Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rigid rules
    - Compulsions are aimed preventing or reducing anxiety or preventing some dreaded situation or event; however, they are not connected in a realistic way with what they are designed to neutralize or are clearly excessive
- The obsessions or compulsions are time-consuming (e.g., take >1 h/day) or cause clinically significant distress or functional impairment
- Specify patient's degree of insight as to reality of OCD beliefs:
  - Good or fair insight (i.e., definitely or probably not true)
  - Poor insight (i.e., probably true)
  - Absent insight (i.e., completely convinced beliefs are true)
- Specify if "tic-related" OCD

- Epidemiology
  - Lifetime prevalence = **1.0 – 2.3%**
  - 12-month prevalence = 0.7 – 1.2%
  - Onset → **age ~20** (can occur age <10)

- Risk factors
  - **Social isolation**
  - **Hx physical abuse**
  - **Negative emotionality**

- Comorbidity
  - **60-90% have comorbidity** (3x higher than if NO OCD)
  - Common comorbidities
    - Mood, anxiety, somatoform disorders
    - SUDs, psychotic disorders, bipolar disorders

- Impairment
  - Cognitive, social, occupational, quality of life
  - **Up to 25% attempt suicide**
  - Incr health care utilization

- Psychological Treatment
  - ***CBT + exposure response prevention (ERP)***
    - Superior/equivalent to pharmacotherapy
    - ERP emphasis similar results to cognitive emphasis
    - **Therapist-guided exposure better**
  - **"Danger Ideation Reduction Therapy" (DIRT)**
    - Addresses fear of contamination without direct exposure
    - MORE efficacious than ERP
    - Combined *in vivo* + imagined better than just *in vivo*
  - No differences between group vs individual CBT
    - Individual therapy → dysfunctional beliefs
    - Group therapy → encouragement, reciprocal support, imitation, interpersonal learning
      - Group CBT can reduce hoarding sx

- Psychological Treatment
  - Other techniques
    - ACT, CT addressing OCD beliefs, CT addressing obsessional doubt, organizational training, mindfulness training
    - Bibliotherapy better than waitlist control
    - *EMDR NOT recommended for OCD*
  - **ICBT** → more effective than supportive therapy
  - Target family accommodation (assoc with poorer response)

- Combined psychological + pharmacological treatment
  - **Combination NOT superior to CBT alone**
    - Combination superior to medication alone
  - D-cycloserine may hasten improvement of ERP

- Long-term effects of psychological treatment
  - Benefits of CBT **maintained at 1-5 years**

- Pharmacological treatment
  - ***First-line agents***
    - **SSRIs → EFFPS** (NOT citalopram)
  - ***Second-line agents***
    - **Citalopram** (less effective than psychotherapy)
    - **Clomipramine** (similar efficacy to SSRIs, but SE/tolerability)
    - **Venlafaxine, mirtazapine**
  - ***Third-line***
    - IV clomipramine, IV citalopram
    - Duloxetine
    - Tramadol
    - Tranylcypromine, phenelzine

- Adjunctive therapy
  - *First-line adjunctive*
    - **Aripiprazole, risperidone**
  - *Second-line adjunctive*
    - **Quetiapine, topiramate**, memantine
  - *Third-line adjunctive*
    - Olanzapine, amisulpride, ziprasidone, haloperidol
    - Mirtazapine, citalopram
    - Lamotrigine, pregabalin

- NOT recommended
  - *Clonazepam, clonidine, desipramine (negative, level 2)*
  - *Bupropion, naltrexone (negative, level 3)*
  - Adjunctive buspirone, clonazepam, lithium

Table 27. Recommendations for pharmacotherapy for OCD

	SSRIs, SNRIs, others	*TCAs, MAOIs, others*	*Benzos, AED, AAPs*
FIRST-LINE	• **5 SSRIs → EFFPS**		
SECOND-LINE	• **Citalopram** • Venlafaxine • Mirtazapine	• **Clomipramine**	
THIRD-LINE	• IV citalopram • Duloxetine	• IV clomipramine • Phenelzine • Tranylcypromine • Tramadol	
Adjunctive therapy	• *First-line:* **aripiprazole, risperidone** • *Second-line:* memantine, quetiapine, topiramate • *Third-line:* amisulpride, celecoxib, citalopram, granisetron, haloperidol, IV ketamine, mirtazapine, NAC, olanzapine, ondansetron, pindolol, pregabalin, riluzole, ziprasidone		
NOT recommended	• Clonazepam, clonidine, desipramine • *Adjunct:* buspirone, clonazepam, lithium, morphine		

Table 27 Recommendations for pharmacotherapy for 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

IV = intravenous; XR = extended release.

- Maintenance pharmacological treatment
  - SSRI reduces relapse rates over 6-12 months
  - Mirtazapine, clomipramine → continued improvement x 12 mos

- Biological therapies
  - Adjunctive rTMS
  - DBS
  - **Capsulotomy, cingulotomy** → usually last resorts

- Alternative therapies
  - Meditation therapies (transcendental, Kundalini yoga)
  - Adjunctive moderate-intensity aerobic exercise
  - Milk thistle, valerian root, St. John's wort → poorly standardized

Summary of OCD

- Relative rare → onset in 20s or earlier

- **CBT & ERP** → effective **FIRST-LINE** tx
  - Equivalent or superior to pharmacotherapy
  - Individual, group, self-exposure, self-help, telephone, internet
    - ALL EFFECTIVE
  - Benefits maintained for 1-5 years

- Combination → **superior to meds only** (not better than CBT alone)

- Pharmacotherapy
  - **FIRST-LINE** → **EFFPS**
  - **SECOND-LINE** → **citalopram, clomipramine**, venla, mirtaz
  - Adjunctive first-line → **risperidone, aripiprazole**

7 PTSD

Table 28 DSM-5 diagnosis of PTSD

- The person has been exposed to actual or threatened death, serious injury, or sexual violation in ≥1 of the following ways:
  - Directly experienced or witnessed the traumatic event, learned that trauma occurred to close family member or friend (actual or threatened death must have been violent or accidental), experienced repeated exposure to aversive details of trauma
- Presence of ≥1 of the following intrusion symptoms associated with the trauma:
  - Recurrent, involuntary, and intrusive distressing memories, distressing dreams, dissociative reactions (e.g., flashbacks), psychological or physiological distress at reminders of trauma
- Persistent avoidance of stimuli associated with the trauma, including ≥1 of the following:
  - Avoidance of distressing memories or feelings and external reminders (e.g., people, places) of the trauma
- Negative alterations in cognitions and mood associated with the trauma, including ≥2 of the following:
  - Inability to recall important aspect of the trauma, diminished interest or participation in activities, feeling of detachment or estrangement from others, persistent negative beliefs, distorted blame, and negative emotional state
- Marked alterations in arousal and reactivity associated with the trauma, including ≥2 of the following:
  - Irritable or aggressive behavior, reckless or self-destructive behavior, hypervigilance, exaggerated startle response, problems with concentration, sleep disturbance
- Duration of disturbance >1 month
- Symptoms cause clinically significant distress or impaired functioning
- Specify whether with dissociative symptoms (depersonalization or derealization) or with delayed expression (full criteria not met until at least 6 months after the event)

- Epidemiology
  - Lifetime prevalence = **9.2%** (Canada)
  - 12-month prevalence = 1.1 – 3.5% (US, EU)
  - Onset → **mid-late 20s**
  - More common in **WOMEN** (2x)

  - **76%** of Canadians exposed to sig traumatic event
  - Most common forms of trauma
    - Unexpected death of someone close
    - Sexual assault
    - Serious illness or injury to someone close
    - Having a child with serious illness
    - Being beaten by a partner or caregiver

- Impairments
  - QoL, functional → incr sx severity
    - Chronic pain, sleep, sexual function, cognitive, alexithymia
    - Longer hospitalizations, more use of mental healthcare
  - **Incr SUICIDE attempts** (2-3x)

  - Among Canadian military personnel, **greater MH care use** assoc:
    - Cumulative lifetime trauma exposure, index trauma type
    - PTSD sx interference, suicidal ideation, female gender
    - Comorbid MDD

- Comorbidity
  - **75% have another psychiatric disorder**
    - Esp anxiety disorders, MDD, ODD, ADHD, SUD, AUD, BPD
  - **Comorbid BPD** → poorer QoL, more comorbidity, incr SA

- Prevention & Early Intervention
  - *Do NOT recommend individual psychological debriefing*
    - Insufficient evidence for group debriefing

  - ***Trauma-focused CBT (TF-CBT)*** → more effective than controls
  - *Propranolol* → may decr severity of PTSD
  - Morphine during trauma care may reduce risk

  - *Early use of benzos* → NOT beneficial, may incr risk of PTSD
  - *Gabapentin, pregabalin* → NO effect on PTSD development
  - *SSRIs* → better from parent report, but NOT child report

- Psychological treatment
  - Education
  - Psychotherapy → effective, but maybe less than pharmacotherapy

Effective CBT Approaches for PTSD	
TF-CBT	• Gradual recovery (individual = group)
EMDR	• Faster recovery (vs TF-CBT)
Stress Management	• Effective (but less than TF-CBT, EMDR)
Cognitive Processing Therapy (CPT)	• Cognitive therapy + written accounts • Effective (but no diff vs components alone)
Prolonged Exposure (PE)	• As effective as CBT, EMDR, CPTs • Imaginal = *in vivo*
Virtual Reality Exposure (VRE)	• Some utility
Internet CBT	• More effective than control
Cognitive Restructuring	• Mixed data • May improve non-fear problems
Social Emotional Rehabilitation	• Improved social function in male veterans • Did NOT improve PTSD sx

- CBT delivery
  - Individual = group
  - Face-to-face = video-conference
  - Telehealth less effective, but still better than pre-treatment

- CBT limitations
  - **Residual sx/impairment** in 33-50% of pts
  - **?external validity** → more complex pts in practice

- **DBT → reduced self-harm** when used as pre-treatment

- Non-trauma psychological tx NOT effective
  - *Supportive tx, non-directive counseling*
  - *Psychodynamic therapy, hypnotherapy*

- Combined psychological + pharmacological treatment
  - Combined **SSRI + psychotherapy** → **mixed results** for superiority
  - **Adjunctive propranolol** → may be effective
    - Prevented reconsolidation of traumatic memory
    - Decr physiological response + PTSD sx
  - D-cycloserine → did NOT enhance effects of exposure therapy
    - May decr response to psychotherapy
- Long-term effects of psychological treatment
  - Benefits maintained at **6-18 months**
  - **EMDR** → benefits at **3 years**
  - **CPT, PE** → benefits at **5-10 years**

- Pharmacological Treatment
  - ***First-line agents***
    - SSRIs → **FtPS (fluoxetine, paroxetine, sertraline)**
    - **Venlafaxine**
  - ***Second-line agents***
    - **Fluvoxamine** (lower quality evidence)
    - **Mirtazapine** (lower quality evidence)
    - **Phenelzine** (dietary restrictions, drug interactions)
  - ***Third-line agents***
    - **Escitalopram, duloxetine, bupropion** (less evidence)
    - **Aripiprazole, risperidone, quetiapine** (less evidence)
      - AAP may be helpful for **intrusion symptoms**

- Pharmacological Treatment
  - *Adjunctive second-line*
    - **Risperidone, olanzapine**, eszopiclone
  - *Adjunctive third-line*
    - Quetiapine, aripiprazole
    - Gabapentin, pregabalin, clonidine

- NOT RECOMMENDED treatment
  - ***Citalopram,*** *desipramine*
  - *Clonazepam, alprazolam*
  - *Olanzapine, divalproex, tiagabine*
  - *Cyproheptadine* (may exacerbate sleep disturbance)

  - *NOT RECOMMENDED adjunctive*
    - Guanfacine, bupropion, zolpidem, topiramate (negative)

Table 30. Recommendations for pharmacotherapy for PTSD

	SSRIs, SNRIs, others	*TCAs, MAOIs, others*	*Benzos, AED, AAPs*
FIRST-LINE	• **3 SSRIs → FtPS** • Venlafaxine		
SECOND-LINE	• **Fluvoxamine** • Mirtazapine	• Phenelzine	
THIRD-LINE	• Bupropion • Duloxetine • **Escitalopram** • Reboxetine • Trazodone • Tianeptine	• Amitriptyline • Imipramine • Desipramine • Buspirone • Memantine • Moclobemide	• Aripiprazole • Quetiapine • Risperidone • Carbamazepine • Lamotrigine • Topiramate
Adjunctive therapy	• *Second-line:* **risperidone**, **olanzapine,** eszopiclone • *Third-line:* quetiapine, aripiprazole, gabapentin, pregabalin, clonidine, levetiracetam, reboxetine, tiagabine		
NOT recommended	• **Citalopram,** clonazepam, alprazolam, desipramine, olanzapine, divalproex, tiagabine • *Adjunct:* bupropion SR, guanfacine, topiramate, zolpidem		

Table 30 Recommendations for pharmacotherapy for core symptoms of 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

SR = sustained release; XR = extended release.

- Treatment for specific PTSD sx
  - **Prazosin** → trauma nightmares, sleep quality
  - **Naltrexone** → reduce flashbacks
  - **Fluphenazine** → trauma re-experiencing symptoms

- Maintenance pharmacological treatment
  - SSRI → reduces relapse rates

- Biological therapies
  - **rTMS** → as effective as monotherapy or adjunct to SSRIs (level 1)
  - **Adjunctive ECT** → may be helpful in refractory PTSD

- Alternative therapies
  - **Acupuncture** → better than waitlist, equal to group CBT
  - Adjunctive hypnotherapy, mantra repetition, transcendental meditation → improved PTSD sx (weaker evidence)

Summary of PTSD

- Lifetime prevalence = **6-9%**
  - More frequent in **WOMEN** → onset in **mid-late 20s**
  - Increased **suicide risk**

- No evidence for widespread use of early intervention
  - **Screening + treating appropriate individuals** preferred
  - *Debriefing all trauma victims* **NOT RECOMMENDED**
  - Limited evidence for *preventative pharmacotherapy*

- **CBT** → effective **FIRST-LINE** tx
  - TF-CBT, EMDR, stress mgmt, PE, VRE, ICBT → all effective
  - Benefits up to 1-10 years
  - *Limited evidence for combination*

- Pharmacotherapy
  - **FIRST-LINE** → **FtPS, venlafaxine**
  - **SECOND-LINE** → fluvoxamine, mirtazapine, phenelzine

8 Pregnancy & Postpartum Period

- Epidemiology
  - Women at **HIGHER risk** for anxiety disorders
  - Overall prevalence during pregnancy **UNCHANGED**
    - May have incr risk for **GAD, OCD**
    - PTSD can develop if traumatic pregnancy complications

- Negative impact of anxiety disorders in peripartum
  - Shorter gestational age, **premature** delivery, **elective C-section**
  - **Depressive sx**, **substance use**, anemia, less prenatal vitamins

- Anxiety disorders during parenting
  - Less promoting of **psychological autonomy** (of child)
  - Assoc with **behavioral/emotional problems** in childhood
  - **Subsequent anxiety disorder** in child

- Treatment issues
  - CBT → **lacking available evidence** in perinatal women
    - Benefits for B-I-I phobias in pregnancy
    - Benefits for postnatal OCD
    - Exposure-based CBT, behavioral therapy → safe in pregnancy
  - Risk/benefit of pharmacotherapy (pregnancy, breastfeeding)

- Antidepressants in pregnancy
  - Congenital malformations
    - Esp **paroxetine → cardiac defects**
  - May have risk of **spontaneous abortions, preterm birth, SGA, LBW**
  - At delivery → risk of **NAS, PPH**
  - NOT assoc with long-term neurocognitive/behavioral development

- Antidepressants in breastfeeding
  - Majority of antidepressants excreted in breast milk (low amounts)
  - **Sertraline or paroxetine preferred**

- Benzos
  - Limited data
  - Meta-analysis → not incr risk for major malform, cardiac defects
  - Case-control study → incr risk of **oral cleft defects** (<1%)
  - **Neonatal withdrawal/toxicity** described
  - Excreted into **breast milk** (low levels)
    - Caution with sedation in infant

- Atypical antipsychotics
  - Not incr risk of malformations (but inconsistent data)
  - ?incr/decr birth weight, incr risk of **preterm birth**
  - AAP in 3rd trimester → risk of abn muscle movement, withdrawal
  - Metabolic syndrome/diabetes in mother
  - **Low levels in breast milk**

Summary for Perinatal Anxiety Disorders

- Antidepressants
  - Generally LOW teratogenic risk, adverse delivery outcomes
  - Counsel about **NAS + management**

- Less data about exposure to benzos, AAP

- Poorly treated psychiatric illness carries short + long-term risk

9 Children & Adolescents

Table 31 Prevalence estimates of anxiety and related disorders among youths in the NCS-A (age 13-18 years)

Anxiety and related disorder	Estimated prevalence (%)	
	12-month	Lifetime
Any anxiety disorder	24.9	31.9
Separation anxiety disorder	1.6	7.6
Specific phobia	15.8	19.3
Social anxiety disorder	8.2	9.1
Posttraumatic stress disorder	3.9	5.0
Panic disorder	1.9	2.3
Generalized anxiety disorder	1.1	2.2

Adapted from references [1155,1156]. NCS-A = National Comorbidity Survey-Adolescent supplement

- Epidemiology
  - **Specific phobias** very common
    - 77% at least one fear (but not necessarily disorder)
    - Lifetime prevalence → **10-35%**
    - **Blood-injection-injury & animal fears** → most common
  - **OCD** → 0.25% children, 1-2% adolescents (similar to adults)

  - Anxiety disorders **earlier onset** than other psychiatric disorders
    - Earliest onset → **separation anxiety, specific phobia**
    - Later onset → OCD, GAD, panic disorder, PTSD

  - Anxiety disorders in C&A
    - Incr risk of MDD, other anxiety disorders, SUD in adulthood
    - High rates of comorbidity
      - Psychiatric, SUD, sleep problems, somatic sx
      - **SUICIDALITY,** cognition/attention, academics, peer r/s

Child Relevant Criteria for Anxiety Disorders	
Separation Anxiety Disorder	• >4 weeks duration
Selective Mutism	• Consistent failure to speak in social situations when expected
Specific Phobia	• Fear or anxiety may be crying, tantrums, freezing or clinging
SAD	• Anxiety must occur in peer settings, not just with adults • Fear or anxiety may be crying, tantrums, freezing, clinging, shrinking or failure to speak in social situations
GAD	• Only 1/6 assoc ITCHES symptoms (vs 3/6 for adults)
Panic Disorder	• No pediatric specific criteria
OCD	• No pediatric specific criteria
PTSD	• Trauma may be enacted/expressed in play • May be frightening dreams without recognizable content • Specific subtype for children age <6

- Prevention strategies
  - Psychoeducational programs
    - **Universal + indicated prevention** → benefits
    - Indicated prevention → LARGER effect than universal

  - *Ineffective prevention strategies*
    - *Early psychological intervention* after traffic accidents FAILED
    - Burn victims → *sertraline* effective per parents, NOT child
    - Data does NOT support *propranolol* for preventing PTSD/ASD in pediatric injury patients

- Psychological treatment issues
  - Adapt to chronological + developmental ages
  - Include parental involvement

  - **CBT effective in C&A**
    - Separation anxiety disorder, SAD, panic disorder, OCD, PTSD,
    - Also school refusal
    - Group, individual, computer, internet all effective
    - "Coping Cat" program → as effective as SSRI

Additional specific psychological approaches with efficacy in C&A	
Specific Phobia	• Exposure therapy
SAD	• Attention bias modification • MBCT • Social effectiveness therapy (SET)
OCD	• ERP • Family-based CBT • Meta-cognitive therapy
PTSD	• Exposure therapy • EMDR • Cognitive behavioral writing therapy (CBWT) • Spiritual-hypnosis assisted therapy (SHAT) • Emotional regulation therapy

- Psychological treatment issues
  - **Involving parents/family** → may have additional benefit
    - Esp if parents also suffer from anxiety
    - Parent training only has evidence
  - **Comorbidities** → negative impact on CBT efficacy
    - Integrated CBT protocols available (ADHD, aggression, SUD)
  - **Sustained benefits of CBT** → 2-7 years post-treatment

- Pharmacological treatment
  - **Psychological treatments generally preferred**
    - Combination therapy may be option (equal/superior)
    - Pharmacotherapy if severe impairment **(SSRI preferred)**
  - **Benzos** → little data, limited utility
    - May be useful for short-term therapy in specific situations
      - Allow for exposure therapy (panic disorder, school refusal)
  - Other treatments
    - Treatment-resistant OCD → adj aripiprazole, riluzole

Pharmacotherapy in C&A anxiety disorders		
Separation	• **Fluoxetine, fluvoxamine**	• *NOT clonazepam*
Panic		• *?clonazepam, ?alprazolam*
SAD	• **Fluoxetine, fluvoxamine** • Escitalopram, paroxetine, sertraline • Venlafaxine, mirtazapine	• *NOT alprazolam*
GAD	• **Fluoxetine, fluvoxamine** • Sertraline	• *NOT alprazolam*
OCD	• **Fluoxetine, fluvoxamine** • Citalopram, paroxetine, sertraline • Clomipramine	• Adjunctive aripiprazole • *?riluzole*
PTSD	• *NOT sertraline* • *NOT adjunctive sertraline*	
School refusal	• *?citalopram* • *?adjunctive imipramine + CBT*	• *NOT alprazolam*

Table 33 Strength of evidence of treatments for anxiety and related disorders in children and adolescents

Disorder	Antidepressants	Benzodiazepines and other treatments
OCD	Fluoxetine (Level 1) [1264-1269]	**Antipsychotics**
	Clomipramine (Level 1) [1274-1276]	Adjunctive aripiprazole (Level 3) [1293]
	Citalopram (Level 2) [1264,1270]	**Other**
	Fluvoxamine (Level 2) [1271]	Riluzole (Level 4) [1294]
	Paroxetine (Level 2) [1272]	
	Sertraline (Level 2) [1273]	
Panic disorder		**Anxiolytics**
		Clonazepam (Level 4) [1287,1288]
		Alprazolam (Level 4) [1289]
SAD	Fluoxetine (Level 1) [1227,1277]	**Anxiolytics**
	Fluvoxamine (Level 2) [1278]	Alprazolam (Level 2, -ve) [1290]
	Paroxetine (Level 2) [1279]	
	Venlafaxine XR (Level 2) [1282]	
	Escitalopram (Level 3) [1280]	
	Sertraline (Level 3) [1281]	
	Mirtazapine (Level 3) [1283]	
Separation anxiety disorder	Fluoxetine (Level 2) [1277]	**Anxiolytics**
	Fluvoxamine (Level 2) [1278]	Clonazepam (Level 2, -ve) [1292]
GAD	Fluoxetine (Level 2) [1277]	**Anxiolytics**
	Fluvoxamine (Level 2) [1278]	Alprazolam (Level 2, -ve) [1290]
	Sertraline (Level 2) [1284]	
School-refusal	Citalopram (Level 4) [1285]	**Anxiolytics**
	Adjunctive imipramine (Level 2) [1259]	Alprazolam (Level 2, -ve) [1291]
PTSD	Sertraline (Level 2, -ve) [1286]	
	Adjunctive sertraline (Level 2, -ve) [946]	

XR = extended release; (-ve) = negative.

- Combination psychological + pharmacological therapies
  - **Sertraline + CBT** → SUPERIOR for separation, SAD, GAD
  - **SSRI + CBT** → SUPERIOR for OCD
  - *NOT D-cycloserine + CBT*

- Alternative therapies
  - Little evidence for exercise → may have small effect for PTSD

- Safety issues with antidepressants in C&A
  - MOST common SE
    - Children → **activation, vomiting**
    - Adolescents → **somnolence**
  - Activating SE of SSRIs
    - Insomnia, anxiety, agitation, tremor
  - **Incr SUICIDALITY risk** (age <19)
    - Lower risk than SSRIs in MDD
    - BUT anxiety disorders themselves incr suicidality risk in C&A
      - 8x suicidal ideation
      - 6x suicide attempts

Summary for C&A Anxiety Disorders

- **Developmentally appropriate** assessment with collateral
- Children may have **different manifestations** of anxiety

- **Psychological therapies generally preferred** for C&A
  - Often need **adaptation** to chronological/developmental age
  - Include **parental involvement**
  - **Combination therapy** may be option

- If pharmacotherapy warranted
  - **SSRIs generally preferred**
  - Use antidepressants with caution

10 Elderly

- Epidemiology

	Elderly	Adults
Lifetime	**14%**	28%
12-month	**7%**	18%

- Prevalence **declines with age**
- Still higher in **WOMEN**
- Underdiagnosis is common

- Higher rates of **sleep disturbances**
- Greater **cognitive impairment**
- Impaired **physical function, mobility, QoL**

- Comorbidities
  - **Depression** → poorer outcomes for both disorders
  - **80% of ALL older adults have chronic medical condition**
    - If anxiety disorder → HIGHER risk chronic medical condition
      - Esp **DM2, GI, dementia**
      - HTN, respiratory disease
      - Chronic urinary incontinence
      - Poor sleep, hearing impairment
      - **Increased MORTALITY** (esp if CV disease)

- Diagnostic issues
  - Often present differently → **concerns** (vs worries)
    - Attribution to physical illness
    - Difficulty remembering sx
  - Functional changes may be complicated
    - Change in **responsibilities**
    - Ask about **older adult activities**
    - Avoidance may be harder to detect due to **physical limitations**
  - **Chronic medical illness or medications**
  - Late-onset anxiety disorders → **less common**
    - Rule out other causes

- Psychological treatment
  - **Similar efficacy to pharmacotherapy**
  - Evidence for **CBT**
    - But CBT may be LESS effective compared to adults
      - May benefit from learning/memory aids
      - Efficacy for **GAD, panic disorder**
  - Also cognitive therapy, supportive therapy, relaxation training
  - **Exposure therapy** (w/o CBT) → EFFICACY in PTSD, specific phobia
  - **Regular exercise** → decr risk of developing anxiety disorders

- Pharmacological treatment
  - **Antidepressants, anticonvulsants** → as effective as in adults
    - Mirtazapine → anxiolytic effects in MDD
  - **High rates of benzos** in older adults with anxiety disorders
    - *NOT preferred long-term treatment strategy*

Pharmacotherapy for anxiety disorders in elderly patients	
Panic	• Paroxetine, citalopram, escitalopram, fluvoxamine
GAD	• Sertraline, citalopram, escitalopram, fluvoxamine • Venlafaxine, duloxetine • Pregabalin, buspirone
OCD	• Fluvoxamine

- Safety issues
  - More susceptible to SE + drug-drug interactions
    - Age-related physiological changes
      - **Decr volume of distribution**
      - **Decr hepatic/renal function**
    - Frailty, decr homeostatic mechanisms
    - Psychosocial issues
  - **Drug-drug interactions** → more meds
  - **Increased risk of fractures**
    - ADs, SSRIs, benzos, anticonvulsants, antipsychotics
  - Antipsychotics in dementia → **increased mortality risk**
  - SSRIs in CHD + depression → lower mortality!

Summary of Older Adult Anxiety Disorders

- Late-life onset of anxiety disorders → UNCOMMON
  - Can present differently

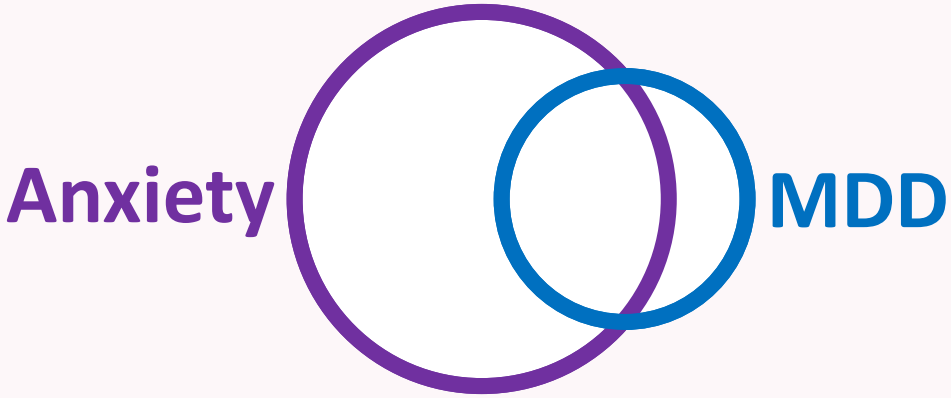
- **Psychological vs pharmacotherapy** → similarly effective

- Pharmacotherapy considerations in elderly
  - Body mass
  - Hepatic/renal function
  - Comorbidities
  - Polypharmacy

11 Anxiety with Comorbid Conditions

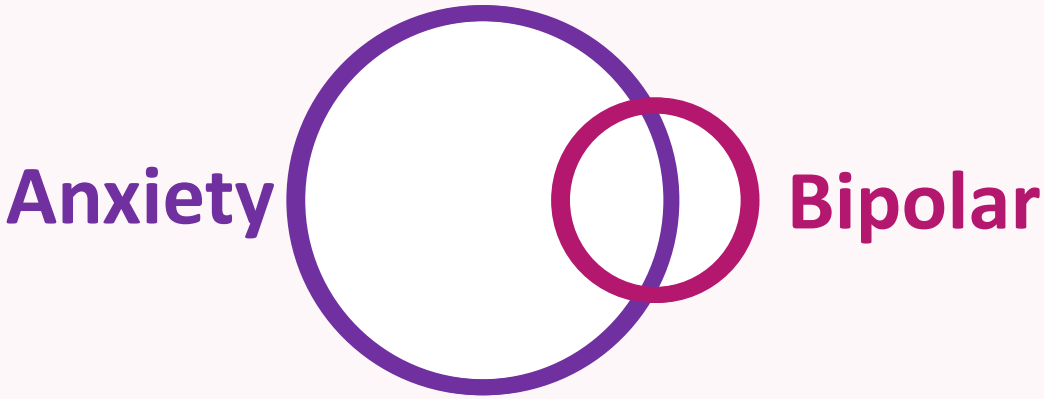
- Comorbidity common
  - **60-80% → comorbid psychiatric condition**
    - Another anxiety disorder, MDD, bipolar, ADHD, SUD
  - NEGATIVE impact
    - More severe sx, worse tx outcomes
    - Greater impairment, worse QoL
    - **Incr SUICIDE RISK**
  - **Medical + pain disorders also common**
    - CV, GI, arthritis, respiratory, thyroid, migraine, allergy
    - Incr disability, more psychiatric comorbidity
    - More depressive sx, worse interpersonal function
  - If **chronically painful conditions** → 2-4x risk of anxiety disorder
    - Esp panic or PTSD
  - Consider interventions beneficial for both conditions

- Comorbid MDD
  - Common → **MDD in 20-36% of pts with anxiety**
    - 60% pts with MDD have anxiety disorder
  - More severe sx, lower remission rates, more impairment
  - **Incr risk of suicide**, incr risk of another anxiety disorder

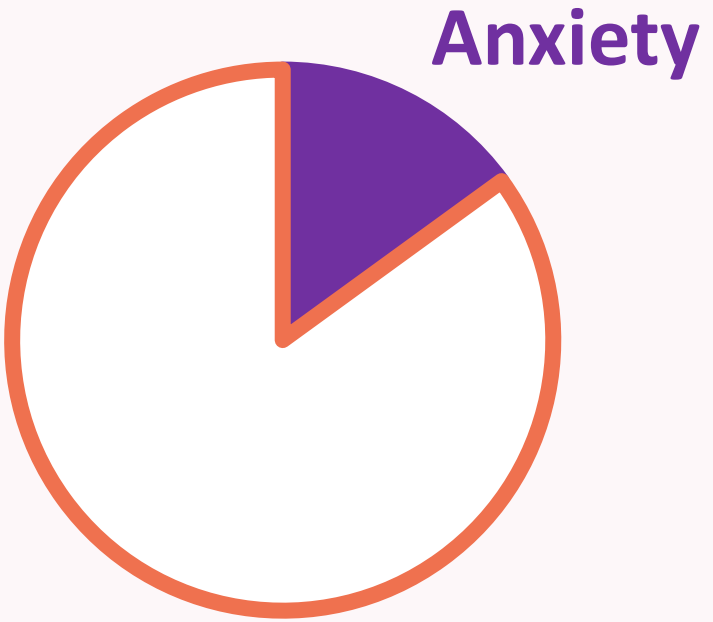


  - Pharmacological treatment
    - **SSRI/SNRIs FIRST-LINE**
    - Quetiapine, risperidone
    - Aripiprazole augmentation

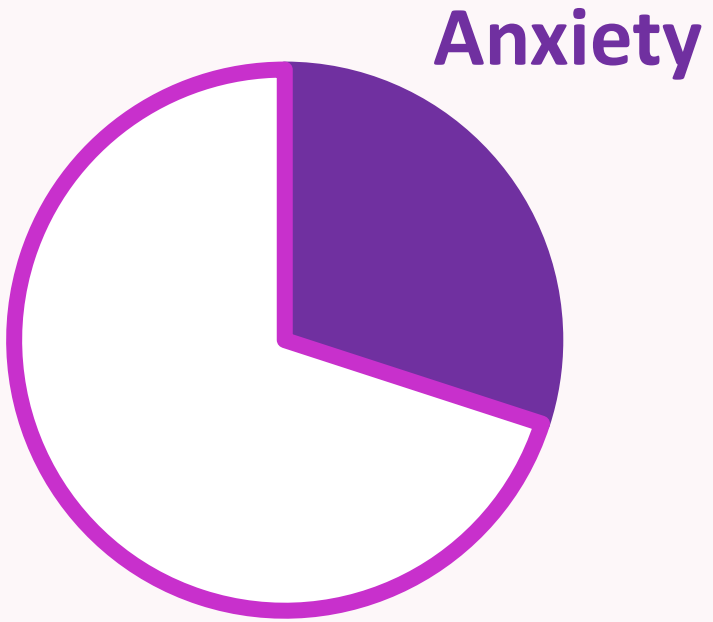
- Bipolar disorder & anxiety
  - 14% of pts with anxiety met criteria for Bipolar I/II
  - Anxiety disorders MOST COMMON comorbidity in bipolar disorder
    - **Lifetime comorbidity rate = 52% of bipolar**
  - Incr risk of MDD/SUD, worse course of bipolar
  - Lower QoL, lower psychosocial functioning
  - Mixed results about suicide risk



- Schizophrenia & anxiety
  - **10-15% of pts with schizophrenia**
    - 30% of pts with schizoaffective
  - More SUD, lower social adjustment, worse QoL
  - **Incr suicidality**



Schizophrenia



Schizoaffective

- Bipolar disorder & Psychosis
  - Pharmacological treatment
    - **AAP** for bipolar/schizophrenia alone
    - If comorbid anxiety
      - **Olanzapine/lamotrigine + lithium** (anxiety in bipolar)
      - **Adjunctive VPA or gabapentin** (panic disorder in bipolar)
      - **Aripiprazole** (SAD + schizophrenia)

- ADHD
  - **47% of ADHD** met criteria for anxiety disorder
    - **SAD 29% (most common)**
    - Specific phobia 23%, PTSD 12%, panic disorder 9%, GAD 8%
  - If anxiety disorder → **4x likelihood of ADHD**

  - Treatment factors
    - Stimulants may have role in managing ADHD with anxiety sx
    - Atomoxetine has some evidence for improving both sx
    - For comorbid **anxiety DISORDER + ADHD**
      - **Determine treatment priority**
      - Limited evidence for stimulants
      - Open trial evidence for **adj atomoxetine**, adj Ritalin

- Medical comorbidities
  - Common → **>60% of pts with anxiety**
    - Most common if **GAD, panic disorder, PTSD**
  - More psychiatric comorbidity, depressive sx
  - More severe anxiety sx, worse functioning

  - Chronically painful conditions
    - GAD + pain → **duloxetine**
    - Migraines, neuropathic pain → **TCAs** (less evidence SSRIs)

  - Comorbid CV disease → anxiety **incr risk of CV disease** (2-3x)
    - Incr risk of CV hospitalization, mortality risk
    - Consider impact on HR, BP, lipids

  - Comorbid DM2/metabolic → anxiety **incr risk of DM2**
    - Metabolic effects of AAPs
    - Weight gain (amitriptyline, mirtazapine, paroxetine)