ANXIETY GUIDELINES 2014

PRINCIPLES OF DX AND MANAGEMENT

- Lifetime prevalence 31% - under-diagnosed and under-treated
- 40% of those diagnosed are untreated
- Generally women > men; phobia and separation d/o onset 7-14 yrs; GAD/PD/PTSD onset 24-50 yrs
- ***Suicide risk*** - increased for those with panic disorder, PTSD, and GAD

Initial Assessment

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

Adapted from reference [26].

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

Basic lab tests

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

If warranted

- Urine toxicology for substance use

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)

- Validated screening tools - macanxiety.com
- Risk factors:
  - Family/personal hx of mood/anxiety disorders → important predictor of anxiety sx
  - Family hx → more recurrent course, more impairment, greater service use
  - Personal hx of stressful life events (especially childhood abuse)
  - Loneliness, low education, adverse parenting, chronic somatic illness
- ***Comorbidity***: frequent, especially with mood and substance use disorders
  - >50% have multiple anxiety disorders (30% have 3+)
  - 50-60% of those with BD, MDD, and ADHD have comorbid anxiety disorder
  - More comorbidity associated with poorer treatment outcomes, greater severity, chronicity, impaired fn, service use, and treatment cost
  - Also associated with HTN, CV condition, GI disease, arthritis, thyroid disease, respiratory disease, migraines, and allergic conditions
- ***Treatment:*** all patients should receive psychoeducation and be encouraged to face their fears
  - Meta-analyses demonstrate efficacy for group and individual psychological tx
  - Psychotherapy and pharmacotherapy generally have **equivalent** efficacy
    - Inconsistent evidence to support combination

- ***Medications:*** SSRI/SNRI preferred initially
- Benzos may be useful as adjunctive therapy; best to be dose <u>regularly</u> rather than PRN
- *SSRI/SNRI:*
    - Side effects - Headache, irritability, GI sx, insomnia, sexual dysfunction, weight gain, increased anxiety, drowsiness, tremour
    - Usually occur early (first 2 weeks) and transient, except sexual dysfunction and weight gain
    - Increase risk of upper GI bleeding, lower BMD/# (SSRI), hypoNa (SSRI)
    - Risk for discontinuation syndrome - GI, psychiatric and vasomotor sx
    - FDA warning re: increased risk of suicidal ideation and behaviour in children and adolescents
- *Anxiolytics:*
    - Side effects - sedation, fatigue, ataxia, slurred speech, memory impair, weakness
    - Be careful in those with SUDs (dependence), older patients (falls, #, cognitive impair)
    - *Buspirone*: side effects - dizziness, drowsiness, nausea
- *Atypical antipsychotics*: variable data on cognitive effects
- *Anticonvulsants:* GI side effects, somnolence, weight gain, tremor, derm/heme issues

Table 9 Components of cognitive behavioral interventions

Exposure	• Encourage patients to face fears • Patients learn corrective information through experience • Extinction of fear occurs through repeated exposure • Successful coping enhances self-efficacy
Safety response inhibition	• Patients restrict their usual anxiety-reducing behaviors (e.g., escape, need for reassurance) • Decreases negative reinforcement • Coping with anxiety without using anxiety-reducing behavior enhances self-efficacy
Cognitive strategies	• Cognitive restructuring, behavioral experiments, and related strategies target patients' exaggerated perception of danger (e.g., fear of negative evaluation in SAD) • Provides corrective information regarding the level of threat • Can also target self-efficacy beliefs
Arousal management	• Relaxation and breathing control skills can help patient control increased anxiety levels
Surrender of safety signals	• Patient relinquishes safety signals (e.g., presence of a companion, knowledge of the location of the nearest toilet) • Patients learn adaptive self-efficacy beliefs

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					

- ***Follow-up:***
    - Full medication response may take **up to 12+ weeks**, and continue for **12-24 months+**
    - Start at low dose, increase at 1-2 week intervals over 4-6 weeks
        - Improvement seen over the next 4-8 weeks
        - F/U should occur at 2-week intervals x 6 weeks, then monthly
    - Psychotherapy typically weekly x 12-20 weeks
        - F/U 4 weeks later, then q2-3 months
    - Treatment response typically = 25-50% reduction in symptoms
        - Remission = loss of diagnostic status, low score on specific scale, and no fn impair
    - Scales - Sheehan Disability Scale (functional impair), CGI, Hamilton Anxiety Rating Scale
    - **Weight monitoring** - initially q 1-2 weeks, then q 4 weeks

PANIC DISORDER AND AGORAPHOBIA

Epidemiology

- Lifetime prevalence of PD ~5% (29% for panic attacks); 12-month ~2.5%
- Lifetime prevalence of agoraphobia ~1.4%; 12-month 0.8%
- Risk of PD/A higher in women, middle-aged, widowed/divorced, low income
- ***Comorbidity*** - with another anxiety, mood, impulse-control or substance use disorder
    - MDD common, occurs in **35-40%** of those with PD
    - PD more prevalent in those with thyroid disease, cancer, chronic pain, cardiac disease, IBS, migraine, and allergic/respiratory diseases

Diagnosis

- *Panic attack* - abrupt surge of intense fear/discomfort, peaks within minutes, 4+/13 symptoms
- *PD* - recurrent, unexpected panic attacks and 1+ attacks followed by 1+ month of:
    - Persistent concern/worry about further attacks or their consequences AND/OR
    - Significant maladaptive behavioural change related to attacks
- *Agoraphobia* - marked fear/anxiety in **2+/5** situations:
    - Public transport, open space, closed space, line/crowd, outside the home alone
    - Thought that escape may be difficult or help unavailable if panic symptoms occur
    - Situations provide fear/anxiety, actively avoided, require companion, or endured
    - Fear/anxiety out of proportion to actual danger
    - Fear/anxiety/avoidance **lasts 6+ months** and cause distress/impairment

Psychological treatment

- **CBT:** Level 1, group or individual
    - Exposure and cognitive restructuring had most consistent evidence
        - Panic disorder - exposure most effective
            - Interoceptive exposure > relaxation therapy
        - Agoraphobia - combination more effective than single techniques (not effective)
    - Minimal intervention formats (bibliotherapy, phone/VC, internet-based) effective and low $
        - **NO** added benefit of EMDR
    - Predictors of decreased CBT response:
        - Severity of PD, strength of fears, earlier age of panic sx onset, comorbid social anxiety, and degree of agoraphobic avoidance
    - Changes in beliefs and avoidance behaviours = key process variables
- ***Combination of psychological and pharmacological treatment***
    - Acute phase: combination > either alone
    - After treatment termination: combined = psychotherapy > meds
    - CBT provided at time of medication d/c associated with lower relapse rate
    - *CBT alone or CBT + meds = first-line*
- ***Long-term effects of treatment***
    - At 6-24 mo F/U, remission/response rates combo > meds alone and psychotherapy

Pharmacological treatment (Health Canada approved = PSV)

- First-line: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine XR
- Second-line: TCAs-clomipramine, imipramine

    - Similar efficacy to SSRI, but more side effects and higher d/c rates
    - Also - reboxetine, mirtazapine, benzodiazepines (may hasten response at SSRI initiation)
- Third-line: MAOi/RIMAs - moclobemide, phenelzine, tranylcypromine; AAP - OLZ, QTP, RISP; table
- Adjuncts: Benzos at SSRI initiation
- NOT recommended: buspirone, propranolol, tiagabine, trazodone, carbamazepine

First line	**Second line**		**Third line**		**NOT recommended**
Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine (+CR) Sertraline Venlafaxine	Alprazolam Clonazepam Diazepam Lorazepam Clomipramine Imipramine Mirtazapine Reboxetine	Adjunct: Alprazolam Clonazepam	Bupropion Duloxetine Milnacipran Gabapentin Divalproex Levetiracetam Olanzapine Quetiapine Risperidone Moclobemide Phenelzine Tranylcypromine	Adjunct: Aripiprazole Divalproex Olanzapine Pindolol Risperidone	Buspirone *Carbamazepine* *Gabapentin* Propranolol Tiagabine Trazodone

- **Maintenance pharmacological treatment:**
    - Positive evidence for citalopram, fluoxetine, fluvoxamine, paroxetine, moclobemide, clomipramine, imipramine, venlafaxine, alprazolam/clonazepam
- Biological/alternative therapies: noninvasive brain stimulation, **rTMS**

SUMMARY:

- Initial tx - data supports meds, CBT alone, and CBT + meds
    - CBT alone insufficient if comorbid MDD, severe/frequent panic attacks, rapid worsening agoraphobia, SI, need rescue benzo, lack motivation for CBT, or fearful of exposure
- Follow-up - combined meds and psychotherapy > meds alone
- Patient who do not respond to first/second line agents - treatment-refractory illness
    - Reassess dx, consider comorbidities affecting tx response, and try third-line/alternatives

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SPECIFIC PHOBIA

Epidemiology - Lifetime prevalence **10-13%**; more common in adolescents, women

- Age of onset 5-12 years (**avg 7**) - animal/BII often in childhood, and situational later in life
- Comorbidities - often with other phobias, avg = 3
    - Often comorbid with SUDs, mood disorder, panic disorder, SAD, GAD, personality disorder

Diagnosis - specifiers = animal, natural environment, blood-injection-injury, situational, other

- Specific object/situation → provokes fear/anxiety → avoid/endure
- Fear/anxiety out of proportion to actual danger, is 6+ months, with distress/fn impair
- Distinguish from panic disorder by considering focus of apprehension (fear of crashing in car vs panic attack), expectedness of panic attack, and range of situations associated with fear/avoidance

Psychological treatment

- **Exposure-based interventions** = treatment of choice, with high degree of success, including VR
- More effective if:
    - Sessions grouped closely together
    - Exposure is prolonged, real, in multiple different settings
    - Some degree of therapist involvement
- No evidence that flooding vs gradual exposure more effective
- BII phobias - **exposure therapy + muscle tension exercises** (prevent fainting)
- ***Combined psychological and pharmacological treatment***:
    - Possible promise - adjunctive d-cycloserine (heights), cortisol, yohimbine (NE agonist)
    - Naltrexone - exposure therapy less effective
- Long-term treatment: rare; CBT has sustained benefit at LT F/U

Pharmacological treatment

- Minimal role, **not recommended** - some evidence for paroxetine, escitalopram, fluoxetine, fluvoxamine
- Benzodiazepines - NO additional benefit as adjunct to exposure therapy

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SOCIAL ANXIETY DISORDER

Epidemiology - **8-12%** life prevalence, women > men, more in developed countries

- Onset **~12 yrs old**; chronic, unremitting course
- Risk factors - low education, low SES, single/separated, comorbid MDD
- ***Comorbidity*** - common (72%), highest rates for MDD and other anxiety d/o
    - Avoidant PD, BDD, SUD, ADHD, SCZ also commonly occur with SAD

Diagnosis - fear/anxiety about social situations - possible scrutiny, negative evaluation, offending others

- Social situation ⟶ fear/anxiety ⟶ avoided/endured
- Fear/anxiety out of proportion to actual threat, 6+ months, distress/fn impair; spp - performance only

Psychological treatment

- **CBT** - gold standard; includes restructuring/challenging maladaptive thoughts and exposure
    - **CBT = meds** (efficacy) but gains achieved with CBT may persistent longer than those w/ meds
- Evidence for IPT is mixed - likely CBT > IPT > wait-list control
- CBT > MBT, but some improvement in SAD sx
- ***Combined psychological and pharmacological treatments:***
    - Pharmacotherapy has NOT been shown to add to benefit of CBT
    - D-cycloserine may enhance exposure exercises
- ***Long-term effects of psychological treatment:***
    - CBT benefits maintained - more enduring than meds

Pharmacological treatment (Health Canada approved - PV)

First line	Second line	Third line		NOT recommended
Escitalopram Fluvoxamine (+CR) Paroxetine (+CR) Sertraline Venlafaxine Pregabalin	Alprazolam Bromazepam Clonazepam Citalopram Gabapentin Phenelzine	Atomoxetine Bupropion Duloxetine Fluoxetine Mirtazapine Clomipramine Moclobemide Selegiline Olanzapine Divalproex Topiramate Tiagabine	Adjunct: Aripiprazole Buspirone Paroxetine Risperidone	Atenolol Propranolol (except performance) Buspirone Imipramine Levetiracetam Quetiapine Pergolide St. John's Wort Adjunct: clonazepam, pindolol

- **First-line:** SSRIs, SNRIs, pregabalin (>600 mg/d)
- **Second-line:** Meta-analysis found benzos as effective as SSRIs, but higher risk
- *Maintenance:* significant reduction in relapse rate with continued SSRI (escitalopram, fluvox, venlafaxine)
- *Biological/alternative therapies:* St. John's Wort is NOT recommended

SUMMARY

- CBT and exposure therapy alone = effective first-line options
    - VRE and internet-based programs also effective
    - CBT benefits maintained over 1-5 years F/U
- CBT and meds have similar efficacy for acute tx, but after d/c, gains from CBT persist longer
    - Adding meds do not increase benefit of CBT

GENERALIZED ANXIETY DISORDER

Epidemiology - **6%** lifetime prevalence (DSM = 9%), more often in Caucasians, women, older adults

- Onset ~ 32 years old (may be bimodal- late teens/early 20s, then 30-40s; for C&A onset 10-14)
- Comorbidity - frequent - other anxiety disorders and MDD, ***pain*** syndromes, HTN, CV/GI conditions

Psychological treatment

- **CBT** - very effective; comparable efficacy to medications
  - Group = individual, though individual may lead to earlier improvement
  - Meta-analyses → CBT = relaxation therapy…
  - Evidence-based protocols focus on intolerance of uncertainty, poor problem-solving, and metacognitive beliefs about the fn/utility of worry
    - Led to development of acceptance-based, meta-cognitive, MBCT
- Psychodynamic may be beneficial - research unclear
- Pre-CBT motivational interviewing may help reduce resistance and improve compliance
- ***Psychological and pharmacological treatment*** - no evidence to support the routine combination
- Psychological benefits are maintained in f/up

Pharmacological treatment (Health Canada approved - PV DEB)

First line	**Second line**		**Third line**		**NOT recommended**
Agomelatine Escitalopram Paroxetine (+CR) Sertraline Venlafaxine Duloxetine Pregabalin	Alprazolam Bromazepam Diazepam Lorazepam Bupropion Buspirone Hydroxyzine Imipramine Vortioxetine	Adjunct: Pregabalin	Citalopram Fluoxetine Mirtazapine Trazodone Divalproex chrono	Adjunct: Aripiprazole Olanzapine Quetiapine (+XR) Risperidone	Beta blockers Pexacerfont Tiagabine *Memantine* *Bright light therapy* Adjunct: Ziprasidone

- **First-line:** SSRI and SNRI efficacy similar
- **Second-line:** Buspirone has limited effectiveness clinically
- **Adjuncts:** Data on antipsychotics inconsistent - only of highly tx-resistant
- **Not recommended:** Table, also memantine and bright light therapy
- **Maintenance:** Significant reduction in relapse w/ continued SSRI tx
- **Biological/alternative:** rTMS, lavender oil, passion flower, weight-lifting, meditation/yoga

SUMMARY

- **CBT** = effective first-line option for tx of GAD, and = to pharmacotherapy
- Evidence does not support CBT + meds, but when patients don't benefit from one try the other
- Meds - start with SSRI, SNRI, agomelatine or pregabalin
  - If no response to multiple courses of tx → tx-refractory illness → third line/alternative tx

OCD

Epidemiology

- Lifetime prevalence **1 - 2.3%**, mean age of onset **~20 years old** (sx often occur <10 years old)
- Under-recognized and under-treated, up to ¼ attempt suicide
- Risk factors: social isolation, hx physical abuse, negative emotionality
- Comorbidity - high, occur in 60-90%, namely mood, anxiety, somatoform, SUDs, psychotic, bipolar d/o's

Diagnosis → Obsessions AND/OR compulsions; note specifier - tic-related

Psychological treatment

- CBT + ERP, usually with emphasis on cognitive elements, especially in those without overt compulsions
  - CBT is EQUIVALENT or SUPERIOR to meds
  - Generally group = individual; but group → **group encouragement, reciprocal support, imitation,** and **interpersonal learning** → increase motivation, decrease tx discontinuation
- Intensity and duration of tx is a consideration - can also consider step-care (low-intensity → standard)
- Other techniques - ACT, modular cognitive therapy, organizational training, mindfulness
  - Generally MI has mixed data, and EMDR NOT recommended
- Therapist-guided is better than self-exposure; can consider telephone-based, bibliotherapy, iCBT
- Target <u>family accommodation</u> to improve treatment outcomes
- For hoarding - <u>group</u> CBT helpful, bibliotherapy and home assistance NOT helpful
- ***Combined psychological and pharmacological treatment***
  - Combination is SUPERIOR to meds alone, NOT CBT alone
  - Thus if meds required/preferred, adding CBT may enhance response
  - NO contraindication to combining CBT with meds - may improve relapse prevention
  - D-cycloserine may hasten improvements with ERP
- ***Long-term effects of psychological tx*** - CBT benefits maintained at 1-5 yr f/up

Pharmacological treatment (Health Canada approved - all SSRI + clomipramine)

First line		**Second line**		**Third line**		**NOT recommended**
Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	<u>Adjunct:</u> Aripiprazole Risperidone	Citalopram Clomipramine Mirtazapine Venlafaxine	<u>Adjunct:</u> Memantine Quetiapine Topiramate	Citalopram IV Clomipramine IV Duloxetine Phenelzine Tramadol Tranylcypromine	<u>Adjunct:</u> Amisulpride Celecoxib Citalopram Granisetron Haloperidol Ketamine IC Mirtazapine NAC Olanzapine Ondansetron Pindolol Pregabalin Riluzole Ziprasidone	Clonazepam Clonidine Desipramine *Bupropion* *Naltrexone* <u>Adjunct:</u> Buspirone, clonazepam, lithium, morphine

- **First-line:** SSRI response x2 of placebo (**40-60%** vs. <20%); similar efficacy to clomipramine w/ less SE
  - Symmetry and hoarding less responsive to SSRI - may be mediated by **dopamine** system
  - Aggressive/sexual/religion → better outcomes (aggression mediated by **serotonin** system)
- **Second-line:** Clomipramine has good evidence, but SE → anticholinergic, arrhythmias, sz, interactions
- **Adjunctive therapy:** Typically for those with inadequate response to SSRI
- **NR:** Bupropion and naltrexone not effective (not in the chart)
- ***Maintenance pharmacological treatment*** - continued SSRI treatment → reduced relapse rates
  - Evidence for - escitalopram, paroxetine, sertraline, fluoxetine (basically all first line options)
- **Biological/alternative therapies**: rTMS; DBS may help (up to ⅔), capsulotomy/cingulotomy = last resort

SUMMARY

- CBT + ERP first-line, benefits maintained over 1-5 year f/up
- Adding CBT to meds may yield better long-term outcomes

PTSD

Epidemiology - **9.2%** lifetime prevalence

- Most common forms resulting in PTSD - unexpected death, sexual assault, serious illness/injury, child with serious illness, and beaten by partner/caregiver
- Onset mid-to-late 20s, 2W:1M
- Associated with chronic pain, sleep problems, sexual dysfunction, cognitive dysfunction, and alexithymia
- Suicide attempts increased x2-3
- Comorbidity - 75% have another psychiatric d/o - especially another anxiety d/o, MDD, ODD, ADHD, SUD

Diagnosis

- **E**xposure to trauma (death, injury, sexual violation - direct experience, witnessed, occurred to close family/friend, or repeat exposure to details)
    - → 1+ **I**ntrusion sx (memories, dreams, dissociative rxn, psych/physiological distress)
    - → 1+ Persistent **a**voidance of stimuli (avoid memories/feelings and external reminders)
    - → 2+ **N**egative **a**lteration in cognition/mood (impaired recall, detached from others, negative beliefs, blame, negative emotions)
    - X 1 month, cause distress/impair fn, *spp*: with dissociative sx or delayed expression (6+ mo after)

Prevention and early intervention

- NO evidence for individual debriefing post-trauma to prevent PTSD (may have adverse effect)
    - Insufficient evidence for group debriefing
    - Instead - screen and treat appropriate individuals
- TF-CBT has benefit for those with ASD (acute stress d/o) and PTSD
    - Brief TF-CBT may **prevent** chronic PTSD in those with ASD/acute PTSD (vs. waitlist/supportive counselling)
- Benzo post-trauma was NOT beneficial, may INCREASE risk of developing PTSD
    - Gabapentin and pregabalin had NO effect on developing PTSD
- Conflicting data on propranolol (one RCT - decr PTSD sx severity and development), SSRI, morphine

Psychological treatment

- Include education about disorder/tx AND exposure to cues
- Significant efficacy, though meta-analysis suggests maybe **LESS effective than meds** in improving PTSD/depression symptoms
- + evidence for TF-CBT (individual and group), EMDR, stress management
    - Non-trauma focused tx (supportive, psychodynamic) did NOT reduce sx as significantly
    - Individual TF-CBT = EMDR, but **EMDR resulted in faster recovery**
    - **I-TF-CBT, EMDR > stress management**
- **Cognitive processing therapy (CPT)** = cognitive therapy + written account; effective
- **Prolonged exposure** (PE, a CBT approach) = **CBT, CPT, EMDR > waitlist or placebo**
- Imaginal exposure as effective as *in vivo* exposure
- Limitations - ⅓ to ½ continue to experience substantial residual sx and fn impair post-CBT
    - May require booster sessions
- DBT can help PTSD

- ***Combined psychological and pharm tx*** - needs more study; combo likely > or = CBT, and > meds
    - **Adjunct propranolol** with trauma-reactivation tx may **prevent reconsolidation** of traumatic memory; adjunct d-cycloserine NOT helpful
- ***Long-term effects of psychological tx*** - benefits maintained at 6-18 mo f/up
    - EMDR effect maintained at 3 yrs, CPT and PE effect maintained over 5-10 years

Pharmacological treatment (only HC approved med - Paroxetine)

First line	Second line		Third line		NOT recommended
Fluoxetine Paroxetine Sertraline Venlafaxine	Fluvoxamine Mirtazapine Phenelzine	Adjunct: Eszopiclone Olanzapine Risperidone	Amitriptyline, Desipramine Imipramine Aripiprazole, Risperidone Quetiapine Bupropion SR, Buspirone, Duloxetine, Escitalopram, Moclobemide, Reboxetine, Trazodone Carbamazepine, Lamotrigine, Memantine, Tianeptine, Topiramate	Adjunct: Aripiprazole Clonidine Gabapentin Levetiracetam Pregabalin Quetiapine Reboxetine Tiagabine	Alprazolam Citalopram Clonazepam Desipramine Divalproex Olanzapine Tiagabine Adjunct: Bupropion, guanfacine, topiramate, zolpidem

- Good evidence = fluoxetine, paroxetine, sertraline, venlafaxine XR
- **First-line:** data on fluoxetine and sertraline is mixed
- ***Adjunctive therapies*** - consider for those w/ treatment-resistant PTSD
- ***Treatment for specific PTSD-associated symptoms***:
    - Prazosin - reduce trauma nightmares and improve sleep quality
    - Naltrexone - reduce flashbacks
    - Fluphenazine - reduce re-experiencing
- ***Maintenance pharmacological treatment:***
    - RCT d/c studies of fluoxetine and sertraline → lower relapse rates over 6 months
    - F/U studies of paroxetine and sertraline (meds cont) → con't improvement over 6-12 months

Biological and alternative therapies

- rTMS, ECT, acupuncture, hypnotherapy, meditation

SUMMARY

- Lifetime prevalence 6-9%, F>M, mid-to-late 20s
- Associated with fn impair, somatic sx, SI, comorbid psych d/o
- NO support for early intervention to prevent PTSD, especially debriefing and medications
- First-line - **CBT** (TF-CBT, EMDR, PE, stress management therapy) - ICBT and VRE have benefit
    - Maintained at 1-10 yr f/up
    - Limited data on combo meds + psychotx
- Meds - try first line → switch to alternative first/second-line, or add second-line agent
    - Tx is difficult - preserve small gains w/ initial therapy, and augmenting may be important early in treatment

SPECIAL POPULATIONS

PERIPARTUM WOMEN

- Overall anxiety d/o prevalence in pregnancy **unchanged** - maybe higher risk of GAD
    - Similar findings for postpartum, but maybe higher GAD, OCD, and PTSD (if traumatic pregnancy)
- Maternal anxiety associated with shorter GA, preterm delivery, elective c/s, depressive sx, SUD, anemia
    - No relationship with perinatal outcomes
    - May affect parenting, childs' cognitive development, childs' future anxiety development
- Treatment - CBT likely effective, some evidence in BII phobia and OCD
    - Meds - weight risks/benefits… lots of mixed data - avoid paroxetine in pregnancy, consider PNAS due to antidepressants, and benzos may lead to cleft palate
        - Breastfeeding - sertraline and paroxetine preferred

CHILDREN AND ADOLESCENTS

- Most common psych d/o in this group - **32% lifetime prevalence**
- Specific phobias - very common in children, BII and animals most common
- OCD - 0.25% in kids, 1-2% in adolescents
- Separation anxiety and phobia onset 7-14 yrs old; OCD/GAD/PD/PTSD onset 20-30 yrs old
- Highly comorbid with MDD, other anxiety d/o, SUDs, somatic sx, sleep problems, SI, and function
- Prevention strategies - **psychoed programs** for C&A - small but significant effect
    - Indicated program > universal program (but both beneficial)
- Treatment - **CBT effective** - esp "coping cat" program = SSRI < combo
    - Family involvement encouraged
    - CBT benefit sustained
    - Psychological tx generally preferred over meds, though combo is an option
        - SSRI preferred (**bolded** = level 1)
        - OCD - **fluoxetine**, citalopram, fluvoxamine, paroxetine, sertraline, **clomipramine**
        - SAD - **fluoxetine**, fluvox, paroxetine, escitalopram, sertraline, venlafaxine, mirtazapine
        - Separation anxiety - fluoxetine, fluvox, sertraline, citalopram
        - PTSD - **sertraline NOT recommended**
        - Benzos NOT recommended (<u>except</u> in panic disorder, 4th line)
    - Combo of **sertraline and psychological tx** recommended in **separation anxiety, GAD and SAD**
    - Most common AD side effects in children = activation, vomiting; adolescents = somnolence

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]	

ELDERLY

- Prevalence 14% (lifetime), 7% (12-mo) in those 65+ → Lower than general population (28%, 18%)
- Generally prevalence declines with age, F>M, but underdx
- Comorbidity - depression most common
    - Higher rates of diabetes, GI issues, dementia
    - Issues i.e. urinary incontinence, hearing impair, HTN, respiratory dz, poor sleep associated with elevated rates of anxiety d/o

- ***Diagnosis -*** more likely to present with "concerns" (not worries), harder to detect avoidance/excess anxiety, attribute sx to physical illness, have difficulty remembering sx
    - Late-onset anxiety unusual - investigate for causative factors
- ***Psychological tx -*** relaxation training, CBT, supportive tx, CT
    - **Similar efficacy to meds**
    - May benefit from adding learning- and memory-aids to CBT
- ***Pharmacological tx*** - data mainly in GAD: pregabalin, duloxetine, venlafaxine, citalopram, sertraline
    - Panic disorder - paroxetine, escitalopram and citalopram, fluvoxamine
    - **Mirtazapine** can have anxiolytic effect
- ***Safety -*** psychotropic meds associated with risk of # (SSRI, benzo, antipsychotics, AEDs)
    - No different between different AAPs
    - Risk of increased mortality and antipsychotics, greater than FGA than SGA

COMORBIDITIES

- 60-80% with anxiety d/o have at least one comorbidity - another anxiety d/o, MDD, bipolar, ADHD, SUD
- Associated with poorer tx outcomes, more fn impair, poorer QoL, increase SI risk
- Often see medical issues and chronic pain
- +MDD: Anxiety pts with MDD = 20-36%; MDD pts with anxiety = 60%
    - More severe sx, less likely remission, more impair, more SI
    - Tx: **SSRI, SNRI, quetiapine monotherapy**
- +BD: Anxiety pts with BD = 14%; BD pts with anxiety = 52%
    - +SCZ and related d/o pts with anxiety = 10-15%
    - Tx: **AAP; some data on adjunct valproate and gabapentin (reduce anxiety sx)**
- +ADHD: ADHD pts with anxiety = 47% (SAD > phobia > PTSD > PD > GAD)
    - Tx: atomoxetine may improve ADHD, anxiety, and depression
        - However generally prioritize sx severity
- +Medical conditions: common in GAD, PD, PTSD
    - Chronic pain and migraines common
        - Tx: Duloxetine, TCAs
    - CV disease is 2-3x more likely in pts with anxiety

	First-line	Not recommended	Psychotherapy
Panic disorder and agoraphobia	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine (+CR) Sertraline Venlafaxine	Buspirone *Carbamazepine* Propranolol Tiagabine Trazodone	CBT - with exposure and interoceptive exposure Acute: combo > meds or CBT Maintenance: combo = CBT > meds
Specific phobia	Not recommended	Benzo as adjunct	Exposure-based interventions
SAD	Escitalopram Fluvoxamine (+CR) Paroxetine (+CR) Sertraline Venlafaxine Pregabalin	Atenolol Propranolol (except performance) Buspirone Imipramine Levetiracetam Quetiapine Pergolide <u>Adjunct</u>: clonazepam, pindolol	CBT and exposure therapy Acute: CBT = meds Meds do NOT add benefit to CBT
GAD	Agomelatine Escitalopram Paroxetine (+CR) Sertraline Venlafaxine Duloxetine Pregabalin	Beta blockers Pexacerfont Tiagabine *Memantine* *Bright light therapy* <u>Adjunct:</u> Ziprasidone	CBT Meds = psychotx, no evidence for routine combination
OCD	Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline <u>Adjunct:</u> Aripiprazole Risperidone	Clonazepam Clonidine Desipramine <u>Adjunct:</u> Buspirone, clonazepam, lithium, morphine	CBT + ERP Combo = CBT Combo > meds
PTSD	Fluoxetine Paroxetine Sertraline Venlafaxine	Alprazolam Citalopram Clonazepam Desipramine Divalproex Olanzapine Tiagabine <u>Adjunct:</u> Bupropion, guanfacine, topiramate, zolpidem	TF-CBT, EMDR, PE, stress management Combo > or = CBT Combo > meds