# Pharmacological Treatment of Anxiety Disorders

**Paul Cannistraro, MD**
*Director, Clinical Psychopharmacology*
*Obsessive-Compulsive Disorders Clinic*
*Massachusetts General Hospital*
*Instructor in Psychiatry*
*Harvard Medical School*

# Medications Used for Anxiety Disorders

Antidepressants

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

Benzodiazepines

Other Agents

- Beta blockers
- Anticonvulsants
- Other strategies

# Serotonin Selective Reuptake Inhibitors (SSRIs)

- Fluoxetine (Prozac), 20-80mg/d – start 5-10mg/d
- Sertraline (Zoloft), 50-200mg/d – start 25-50mg/d
- Paroxetine (Paxil), 20-50 mg/d – start 10mg/d
- Fluvoxamine (Luvox), 50-300 mg/d – start 25mg/d
- Citalopram (Celexa), 20-60mg/d – start 10-20mg/d
- Escitalopram (Lexapro), 10-20mg/d – start 5-10mg/d

# Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

- Venlafaxine (Effexor) 75-300 mg/d
  - Initiate with 37.5 mg/d
- Desvenlafaxine (Pristiq) 50-100 mg/d
  - Initiate with 50mg/d
- Duloxetine (Cymbalta) 20-80 mg/d
  - Initiate with 20-30 mg/d

# Side effects of SSRIs and SNRIs

- Acute anxiogenic effect
- Nausea, vomiting
- Diarrhea
- Insomnia
- Decreased libido
- Sexual dysfunction such as anorgasmia
- Agitation
- SNRIs tend to be more activating than SSRIs, and can be more likely to cause an acute anxiogenic effect, agitation, or insomnia. They are often good choices for depression with somnolence.

# Atypical Antidepressants

- Bupropion (Wellbutrin)
  - Norepinephrine/Dopamine reuptake inhibitor
  - Based on limited data, considered less effective for panic and other anxiety disorders
- Trazodone
  - Based on limited data, considered less effective for panic and other anxiety disorders
  - Most commonly used as a sleep aid

# Tricyclic Antidepressants

- Imipramine (Tofranil)
- Nortriptyline (Pamelor)
- Desipramine (Norpramin)
- Amitriptyline (Elavil)
- Doxepin (Sinequan)
- Clomipramine (Anafranil)

- Effective in anxiety with or without comorbid depression
- Recommended dosage 2.25 mg/kg/d Imipramine or its equivalent for panic

# Tricyclic Antidepressants (cont)

- Clomipramine (Anafranil), 25-250 mg/d
  - Initiate with 25 mg/d
  - Not an SSRI, but a Tricyclic antidepressant (TCA) with serotonin reuptake inhibition comparable to SSRIs

# Tricyclic Antidepressants (cont)

- Typical TCA side effects
  - anticholinergic effects (dry mouth, blurred vision, constipation)
  - orthostatic hypotension
  - cardiac conduction disturbance
  - weight gain
  - sexual dysfunction
- Lethal in overdose
- Weight gain and sedation often become increasingly problematic over time
- Efficacy: PDAG, GAD, PTSD

# Monoamine Oxidase Inhibitors

- Phenelzine (Nardil) 45-90 mg/d
- Tranylcypromine (Parnate) 30-60 mg/d
- Isocarboxacid (Marplan) 10-30 mg/d
- Initial worsening of anxiety is unusual
- Side effects: light-headedness, neurological symptoms, weight gain, sexual dysfunction, edema
- Dietary restrictions/Hypertensive crisis
- Risk of lethal overdose and toxicity
- Generally reserved for refractory cases
- Efficacy: PDAG, SP, OCD, PTSD

# Benzodiazepines

- Potency was considered critical determinant of anti-panic efficacy
  - Alprazolam (Xanax)
  - Clonazepam (Klonopin)
  - +/- Lorazepam (Ativan)
- But comparable doses of diazepam as effective as alprazolam
- All benzodiazepines effective for generalized anxiety

# Potential Benefits of Benzodiazepines

- Effective
- Short latency of therapeutic onset
- Well tolerated
- Rapid dose adjustment feasible
- Can be used as needed for situational anxiety

# Side Effects of Benzodiazepines

- Limited clinical efficacy in certain diseases
- Sedation
- Muscle relaxant effect
- Anticonvulsant effect
- Tolerance
- Dependence
- Significant withdrawal reactions
- Impact on Memory, particularly in the elderly
- Interaction with ethanol

# Alprazolam (Xanax)

- As effective as anti-depressants for panic
- Advantages: rapid onset of effect, lacks typical antidepressant side effects
- Disadvantages: short duration of effect (i.e., multiple dosing, interdose rebound), discontinuation syndromes, early relapse, abuse potential, disinhibition
- Dosing: anticipate initial sedation
- Range: 2-10 mg/d (4-6 mg/d usual) (QID dosing)

# Clonazepam (Klonopin)

- As effective as alprazolam for panic; issue of potency for anti-panic efficacy
- Advantages: Pharmacokinetic: longer duration of effect results in less frequent dosing, interdose symptoms, early relapse, or acute withdrawal symptoms. Slower onset of effect diminishes abuse potential
- Disadvantages: disinhibition, headaches
- Dosing: anticipate initial sedation (initiate at 0.25-0.5 mg qhs)
- Range: 1-5 mg/d (BID dosing)

# Combining Antidepressants with Benzodiazepines

- Provides rapid anxiolysis during antidepressant lag
- Decreases early anxiety associated with initiation of antidepressant
- Treats residual anxiety with antidepressant treatment
- Prevents and treats depression on benzodiazepines

# Buspirone (BuSpar)

- Non-benzodiazepine anxiolytic
- Non-sedating, muscle relaxant, anticonvulsant
- Effects on serotonin and dopamine receptors
- Indicated for GAD; weak antidepressant effects
- Useful as SSRI augmentation for panic, social phobia, depression, sexual dysfunction
- Dosing: 30-60 mg/d

# Beta Blockers

- Decrease autonomic arousal
- May be useful as adjunct for somatic symptoms of panic and GAD but not as primary treatment
- Useful for non-generalized social phobia, performance anxiety subtype
- Propranolol 10-60 mg/d;Atenolol 50-150 mg/d

# Anticonvulsants

- Valproate (Depakote/Depakene) and gabapentin (Neurontin) are effective for anxiety
- Gabapentin effective for social phobia
- Gabapentin (600-5400 mg/d) used as alternative to benzodiazepine
- Valproate, Carbamazepine (Tegretol), Gabapentin, Pregabalin (Lyrica), Topiramate (Topamax) and Lamotrigine (Lamictal)

# Strategies for Refractory Anxiety Disorders

- Maximize dose
- Combine antidepressant and benzodiazepine
- Administer cognitive-behavioral therapy
- Attend to psychosocial issues

# Strategies for Refractory Anxiety Disorders

- Augmentation
  - Anticonvulsants
    - Gabapentin
    - Valproate
    - Topiramate
  - Beta blocker
  - Buspirone
  - Clonidine/Guanfacine
  - Dopaminergic agonists (e.g., Ropinirole) for social phobia
  - Cyproheptadine (Periactin)
- Combined SSRI/TCA
- Alternative antidepressant
  - Clomipramine
  - MAOI
- Other
  - Atypical neuroleptics
    - Quetiepine (Seroquel)
    - Risperidone (Risperdal)
    - Paliperidone (Invega)
    - Olanzapine (Zyprexa)
    - Ziprasidone (Geodon)
    - Aripiprazole (Abilify)

# Discontinuation of Treatment

- Withdrawal/rebound more common with Bzd than other anxiolytic treatment
- Relapse: a significant problem across treatments. Many patients require maintenance therapy
- Bzd abuse is rare in non-predisposed individuals
- Clinical decision: balance comfort/compliance/ comorbidity during maintenance treatment with discontinuation-associated difficulties

## Strategies for Discontinuation of Anxiolytics

- Slow taper
- Switch to longer-acting agent for taper
- Adjunctives
  - Antidepressant
  - Anticonvulsant
  - Other –e.g., clonidine, beta blockers, buspirone
- Cognitive-Behavioral therapy