First Do No Harm, But…
Toxicology Lessons in Psychopharmacology

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- With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between the party listed above (and/or spouse/partner/immediate family members) and any for-profit company in the past 24 months which could be considered a conflict of interest.
Disclaimer

The views presented herein are my own and do not reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.
What you’ll see…or won’t see…

- Sedative / Hypnotics
  - Benzodiazepines
  - Psychosomatic agents
- Antidepressants
  - SSRIs, TCAs, Mixed reuptake inhibitors
- Antipsychotics
  - Typical (old), Atypical (new)
- Mood Stabilizers
  - Antiepileptics, Lithium
- Stimulants
- Cognitive Enhancers
- And…

Why Talk About This?...

Drug toxicity appears on comprehensive differential diagnosis lists for most symptoms, physical and mental. Easily relegated low on lists…

- No single diagnostic test
- Syndromic states that mimic others
- Continuum rather than binary process
- Not trained to think treatments cause harm
- Self-induced symptoms are…complicated

So, we don’t talk about this!

Clinical suspicion & critical thinking
Toxicology Principles

- Presentation reflects clinical biochemistry through receptor mechanisms and drug properties
- Syndromes describe classic presentations
- Pattern recognition is useful, though some variability is not uncommon
- Targeted treatments are available and effective

Illustrative Case #1

- Bright first semester seminarian
- Kind, well-liked, socially conscious
- Brought by friends with concerns about his recently changed and odd behavior
- Stressed around exam time last week, despite getting through now ‘worse’
- Irritable, not sleeping, scared that stalkers are around the residence and people have been staining / stealing laundry
Physical

- Disheveled, mismatched clothes
- Sweat-like body odor
- Poor eye contact, pressured speech: can say he is nervous but “fine”
- T 37.2, R 12, P 110, BP 149 / 98
- Wide eyes, thin, tremulous, antsy, warm skin
- Paranoia precludes further exam

Psychostimulants

- Methylphenidate (Ritalin, Concerta)
- Dexamphetamine (Focalin)
- Dextroamphetamine (Dexedrine)
- Amphetamine/Dextroamphetamine (Adderall)
- Methamphetamine (Desoxyn)
- Pemoline (Cylert)
- Lisdexamfetamine (Vyvanse)
- Modafinil (Provigil)
- Armodafinil (Nuvigil)
- Caffeine…

Hypertension, tachycardia, confusion, seizure, psychosis
Sympathomimetic Toxicity

- Psychostimulants
- Enhanced catecholamine activity
- Cardiovascular effects
- Adrenergic receptor agonism
- Mydriasis, diaphoresis
- CNS effects include increased motivation and attention, nervousness, aggression, paranoia, hallucinosis

Toxicities: Everything Could be Data

Affective symptoms
- Depression, anxiety, lability, mania

Cognitive symptoms
- Concentration, attention, executive function, verbal memory, task switching

Perceptual / behavioral symptoms
- Hallucinosis, irritability, rage, lethargy
Vocabulary

- Delirium – Acute Brain Failure
  - Confusion / disorientation
  - Inattention → impaired consciousness
  - Memory impairment
  - Abnormal thought processes
  - Psychomotor disturbance
    Sometimes, psychotic symptoms

- Psychosis
  - Delusions, Hallucinations
Bedside Screening

♦ Registration (Immediate Recall)
  – Name 3 objects, ask patient to repeat back
  – Example – “Nickel, Pony, Chair”

♦ Orientation
  – Year, Date, Month, State, Town, Place

♦ Attention (Digit Span with increasing length)
  – 7 random numbers forward
    • 5, 8, 2, 9, 1, 3, 6
  – 5 random numbers backward
    • 7, 1, 4, 9, 2

♦ Delayed Recall – 3 objects above

Etiologies of Delirium

Infection
  Pneumonia, UTI, meningitis, sepsis

Withdrawal (substances)
  BZDs, EtOH

Acute metabolic
  Renal failure, acid-base, electrolytes

Trauma
  Head injury, GI/GU obstruction

CNS pathology
  Tumor, abscess, inflammation

Hypoxia
  COPD, asthma, CHF, anemia

Deficiencies (vitamin/nutritional)
  B12, folate

Endocrine
  thyroid, cortisol, paraneoplastic

Acute vascular events
  CVA, MI

Toxins/Drugs
  Oh, it's quite a list …

Heavy metals
  Pb, Hg, Pt
Drugs and Toxins

- Anticholinergics
- Antihistamines
- Antiretrovirals
- Benzodiazepines
- Carisoprodol
- Chemotherapeutics
- Cocaine
- Interferons
- Lithium
- LSD
- MAOIs
- Methamphetamine
- PCP
- Propoxyphene
- Salicylates
- Sedative / EtOH withdrawal
- Serotonergics
- TCAs
- Tramadol

Illustrative Case #2

- 59 y/o female with PMH of bipolar disorder, HTN presents to PES ataxic, drowsy, confused, and difficult to comprehend (mumbling).
- Cough last month, progressed to pneumonia; 12 days ago Rx erythromycin – started to unravel…
- For mania, 6 days ago, psychiatrist increased quetiapine to from 100 mg qhs to 400 mg qhs and added carbamazepine 100 mg bid.

- OTHER MEDS: Fesoterodine, Lisinopril, Pantoprazole, Allopurinol, Paricalcitol, Lidoderm
Physical

- Restlessly picking at clothes and bedsheets
- Mildly shaky
- Skin warm, dry, intact
- Poor eye contact, normal pupils

- $T\ 36.1$, $R\ 14$, $P\ 88$, $BP\ 106/52$
- EKG rate 95, normal intervals & morphology
- CBZ level 12.1 µg/mL (ref 4-12 µg/mL)

Anticholinergic Toxicity

**Peripheral**
- Dry skin, membranes
- Flushing, Hyperthermia
- Urinary retention
- Constipation
- Mydriasis
- Lost accommodation
- Myoclonus, twitching
- Tachycardia

**Central**
- Ataxia
- Disorientation
- Inattention, amnesia
- Anxiety
- Hallucinosis
  - people, animals
- Agitation
- Lethargy
- Coma
The Usual, and Unusual Suspects

- Antihistamines
- OTC sleep aids
- Tricyclic antidepressants
- Antipsychotics
- Antiemetics
- Antispasmodics
- Cyclobenzaprine
- Carisoprodol
- Baclofen
- Botanicals
  - Jimson Weed
  - Belladonna
  - Mushrooms

-zines, -pines, -amines, et al.

ANTILIRIUM
(Physostigmine Salicylate)

FOR THE IMMEDIATE USE
IN REVERSING SUSPECTED DRUG OVERDOSE

ANTILIRIUM... "The drug of choice" in the emergency room for reversing overdoses of commonly used drugs, chemicals and plants with anticholinergic properties.

DRUGS AND CHEMICALS CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING:

- Neuroleptics
- Antihypertensives
- Anticholinergics
- Antipsychotics
- Antidepressants
- Benzodiazepines
- Botanicals

PLANTS CONTAINING ANTICHOLINERGIC ALKALOIDS

- Jimson Weed
- Belladonna
- Mushrooms

ANTILIRIUM REVERSES CNS ANTICHOLINERGIA
WHEREAS OTHER ANTICHOLINERGICS DO NOT

ANTILIRIUM, unlike other anticholinesterases including neostigmine does not have a quaternary nitrogen atom, but has a tertiary amine. For this reason it is not hydrolyzed and rapidly crosses the blood brain barrier.
A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning.

- Benzodiazepines did not control agitation well and had NO reversal of delirium
- Patients given physostigmine
  - Fewer complications, none serious
  - Shorter recovery period
  - Obviated the need for LP and Head CT
- **Safer and more effective than benzodiazepines in treating agitation and delirium caused by anticholinergic poisoning**

What went wrong?...

- “Appropriate” but ill-advised pharmacologic intervention for acute mania.
- Drugs combined without knowledge of their pharmacology
- Non toxic level of mood stabilizer, but still sick due to overall drug burden (CBZ, quetiapine, and fesoterodine)
Cognitive Enhancers

Cholinesterase Inhibitors
- Donepizil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne, Reminyl)
- Tacrine (Cognex)
  Bradycardia, hypersecretion, confusion

Catechol-O-methyltransferase (COMT) inhibitors
- Entacapone (Comtan)
- Tolcapone (Tasmar)

Glutamate antagonist
- Memantine (Namenda)

Illustrative Case #3
- Junior girl with a number of conditions
- Depression, fibromyalgia, migraines
- GERD, Mitral valve prolapse, IBS, sprue
- Frequent visits to clinic – seems lonely, sad
- Presents with a cough / URI x5 days, saying that she feels funny and can’t do any of her work or go to class
Physical

- Run-down appearing, wearing sweats and tee, having removed her hoodie
- Coughs, can’t seem to sit still
- Goes to restroom twice during clinic visit
- Diaphoretic with warm hands
- T 38.7, R 16, P 92, BP 130 / 108
- Poor focus, slow to respond to questions
- MS: Increased tone in lower ext.-- heel rises from the table with passive lift of thigh
- Neuro: DTRs symmetrically enhanced, slightly greater in lower extremities

Medications

- Paroxetine (Paxil) 60 mg daily
- Trazodone 50-100 mg nightly prn
- St. John’s Wort Supplement dose unknown
- Tramadol (Ultram) 50 mg TID prn
- Rizatriptan (Maxalt) 5-10 mg prn, up to 30 mg/d

Rx:

Robitussin DM or NyQuil

…used in accordance w/ package directions
Presentation of Severe Toxicity

Serotonin Syndrome Features

- Hypertension
- Tachycardia
- Hyperthermia
- Diaphoresis
- Tremor
- Increased GI motility
- Increased lower extremity tone
- Hyperreflexia...Clonus
- Altered mental status
Spectrum of Clinical Findings

Range from mild to severe, but not necessarily with consistent, inclusive progression

Serotonin Physiology

Toxicity generally results from excessive medication dosage, in combination
**Serotonergic Drugs**

- Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, *paroxetine*, citalopram
- Other antidepressant drugs: *trazodone*, nefazodone, buspirone, venlafaxine, *tricyclics* (clomipramine)
- Monoamine oxidase inhibitors: phenelzine, moclobemide, isocarboxazid, *selegiline*
- Analgesics: meperidine, fentanyl, *tramadol*, pentazocine
- Antimigraine drugs: sumatriptan, *rizatriptan*, and others
- Antimicrobials: *linezolid* (a monoamine oxidase inhibitor)
- Over-the-counter cough and cold remedies: *dextromethorphan*
- Drugs of abuse: MDMA, or “ecstasy”, lysergic acid diethylamide (LSD), Syrian rue, *K2/Spice*, synthetic stimulants (bath salts), cocaine
- Dietary supplements and herbal products: tryptophan, *Hypericum perforatum* (St. John’s wort), Panax ginseng (ginseng)

**Serotonin Syndrome Treatment**

- **Withdrawal of offending agents**
- **Supportive care**—fluids, cooling
- **Differentiate from anticholinergic syndrome**
  - Physostigmine trial
- **Benzodiazepines** (avoid physical restraint)
  - Sedation and seizure prevention
- **Aggressive care can be required to avoid**
  rhabdomyolysis, hyperthermia, and progression to seizures, coma, death
Illustrative Case #4

- Weary, aging businessman with financial stress and chronic back spasms
- Depressed, insomniac
- Drinking problems for a number of years, came to care – sobriety within the past few months
- Missed morning group treatment session in residential program
- Barely wakes up when shaken out of bed, slurs out a few words, can’t hold his head or stand

Physical

- Very groggy, voices no complaints
- Falls back asleep whenever not stimulated
- T 36.7, R 10, P 65, BP 108 / 59
- Pupils normal appearing, slow to react to light – nystagmus
- Hands go to the face when awake
- Sluggish, generally weak appearing
Sedative Effects

- Sleep aids, anxiolytics, muscle relaxants
- Reduce catecholamine activity
- Euphoria, well-being, reduced self-control
- Over-relaxation...
- CNS effects include decreased motivation and attention, disinhibition, amnesia, confusion...progressing to LOC

...Alcohol is well-understood as a short-acting, non-specific sedative

Sedative / Hypnotic Toxicity

- Within 60-120 minutes of exposure
- Ataxia, dysarthria → lethargy → coma
  - Occasional disinhibition
- Relaxed autonomic indices
  - Low / normal HR and BP
- Fatigue and hyporeflexia
- Diminished (not ablated) respiratory drive
- Miosis or Normal pupil size

Synergistic effects...but rarely fatal
Benzodiazepines

GABA-A receptor agonism
- Lorazepam (Ativan)
- Oxazepam (Serax)
- Temazepam (Restoril)
- Alprazolam (Xanax)
- Clonazepam (Klonopin)
- Diazepam (Valium)
- Triazolam (Halcion)
- Chlordiazepoxide (Librium)

Sedatives

GABA-A receptor agonism, etc.
- Zolpidem (Ambien)
- Zaleplon (Sonata)
- Eszopiclone (Lunesta)
- Ramelteon (Rozerem)
- Sodium Oxybate (Xyrem)
- Baclofen (Lioresal)
- Carisoprodl (Soma)
- Cyclobenzaprine (Flexeril)
- Metaxalone (Skelaxin)
**Flumazenil**

- Competitive antagonist at the benzodiazepine receptor binding site

- **Indications**
  - Extubate / avoid intubation in toxic sedation threatening airway loss
  - Diagnostic aid in coma
Mood Stabilizers

Antiepileptics
- Valproic Acid (Depakote, Depakene, Depacon)
- Carbamazepine (Tegretol)
- Oxcarbazepine (Trileptal)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
- Gabapentin (Neurontin)
- Zonisamide (Zonegran)
- Pemoline (Cylert)

Selective Na+ channel, Ca++ channel blockade produce sedation, ataxia, dysarthria…and potentially, SZ

Remember our old soldier...
- Weary, aging businessman with financial stress and chronic back spasms
- Depressed, insomniac
- Drinking problems for a number of years, came to care – sobriety within the past few months
- Missed morning group treatment session in residential program
- Completely unresponsive
Physical
- Barely breathing
- Cool to the touch
- T 35.1, R 2, P 38, BP 81 / 40
- Pupils constricted
- Comatose
- Urine drug screen positive only for benzodiazepines

Opioid Toxicity
- CNS Depression / Coma
- Respiratory Depression
- Miosis
- Hypotension
- Bradycardia
- Ileus, hypothermia, multiple organ damage and failure
Opioids

- Heroin™ (diacetylmorphine)
- Morphine
- Codeine
- Hydrocodone (Vicodin)
- Oxycodone (Percocet, Oxycontin)
- Hydromorphone (Dilaudid)
- Meperidine (Demerol)
- Fentanyl (Duragesic)…and more and more…

And More and More…

Figure 2: Unintentional drug overdose deaths by major type of drug, United States, 1999-2006

Source: National Vital Statistics System
Naloxone (Narcan)

- Texts and practice sometimes suggest utilizing large doses of naloxone (2-10 mg)
- Opiate dependent patients risk acute withdrawal
- Toxicology references recommend small starting doses of naloxone (0.05-0.2 mg)
- Some drugs are semi-resistant to naloxone
  - Buprenorphine (Suboxone / Subutex)
  - Pentazocine (Talwin)

Dosing of Naloxone

- Initial dose of 0.2-0.4 mg (0.1 mg in users), then escalate to 1 mg, then 2 mg
  - Consider diluting 2mg in 10 cc syringe and titrating
- Consider other causes if no response to 2 mg
- Buprenorphine, clonidine, and pentazocine may require 2-4 mg, and up to 10 mg total
- No evidence that fentanyl, propoxyphene, or oxycodone require high doses
- Initial dose should never be 2 mg
Some problems are fairly obvious...

…and some not...

What’s Wrong with this EKG?
Where it’s headed…

- K+ rectifier inhibition
- Delay in onset
  - Careful monitoring
  - Repeat / late EKGs
- Management
  - NOT Bicarb
  - Mg++
  - Antiarrhythmics
  - Overdrive pacing

Myocardial Cell Electrophysiology
Antipsychotic (Neuroleptic) Medications

- Inhibit Dopamine (D2 > D1) receptors
- Mesolimbic – therapeutic effect
- Nigrostriatal – movement side effects
  - Dystonia, Akathisia, Tardive Dyskinesia…NMS
- Tuberoinfundibular – sexual side effects
- Chemoreceptor trigger zone – therapeutic effect
- Other toxicities:
  - Hypotension, Sedation/ACS, Arrhythmia
Conventional Agents

**Butyrophenones**
- Haloperidol (Haldol)
- Droperidol (Inapsine)

**Phenothiazines**
- Fluphenazine (Prolixin)
- Chlorpromazine (Thorazine)
- Perphenazine (Trilafon)
- Thiothixene (Navane)
- Trifluoperazine (Stelazine)
- Thioridazine (Mellaril)
- Mesoridazine (Serentil)

Typical Antipsychotics

Dopamine (D2) Antagonism, and…
- Haloperidol (Haldol) 2
- Fluphenazine (Prolixin) 2
- Chlorpromazine (Thorazine) 100
- Perphenazine (Trilafon) 10
- Thiothixene (Navane) 5
- Thioridazine (Mellaril) 100
- Pimozide (Orap) 1

Anticholinergic activity increases sedation, decreases risk of EPS, and generally accompanies α blockade w/ orthostasis (exc. risperidone)
Extra Pyramidal Side Effects

- EPS is a group of sustained-movement disorders ranging from akathisia, to acute dystonias, to parkinsonism, to tardive dyskinesia, to the most severe form, neuroleptic malignant syndrome.*

- Approximately 30% of patients given neuroleptics experience one or more of these adverse effects at some time during treatment.


A tangled neurochemical web…

Akathisia

*Definition:* subjective sensation of motor restlessness, characterized by a compelling need to move and inability to maintain a stable position or posture for several minutes.

- **Prophylaxis:** Anticholinergics
  - Diphenhydramine, Benztropine, or Trihexyphenidyl
- **Treatment:**
  - Benzodiazepines
  - Propranolol (10 - 20 mg BID – TID)
  - Clonidine (0.05 - 0.1 mg BID – TID)

Dystonia

*Definition:* sustained muscle contractions resulting in abnormal posturing of the eyes, face, tongue, jaw, neck, and back.

- Characterized by a patient *awake and alert.*
- Less common in agents w/ anticholinergic activity
- Death may rarely occur from impaired respiration caused by dystonia of pharyngeal and laryngeal muscles.

- **Prophylaxis** and **Treatment:** Anticholinergics
  - Diphenhydramine or Benztropine
**Parkinsonism**

*Definition:* syndrome of bradykinesia (slow movement), masked facies, cogweel muscle rigidity, tremors (e.g., pill rolling), gait and postural instability, bradyphrenia (slow thinking), and cognitive impairment.

- Typically a reversible/treatable intermediate-stage extrapyramidal syndrome.
- **Prophylaxis/Alleviation:** Dose reduction
- **Treatment:** Anticholinergics relieve movement side effects, but cognitive impairments remain and may worsen
  - Amantadine

**Tardive Dyskinesia**

*Definition:* stereotyped, involuntary, repetitive painless movements of the face, eyelids, mouth, tongue, extremities, or trunk.

- Late-appearing but potentially irreversible
- Orofacial movements earliest and most frequent
- Occurs in 12 to 25% of patients who receive long term neuroleptic treatment, with increasing incidence each year on drug
- **Prophylaxis:** Minimizing doses, vigilant exams
- **Treatment:** None consistently effective
Neuroleptic Malignant Syndrome

*Definition:* sub-acute, life threatening syndrome characterized by fever, rigidity, mental status changes, and autonomic instability.

- **Distinguishing characteristics**
  - Early WBC and LFT elevations
  - Severe rigidity, equal in all extremities
  - Normal or diminished reflexes
  - Bradykinesia

- **Treatment:** Remove offending agents
  - Supportive care: Benzodiazepines, bromocriptine, cooling, dantrolene, and/or neuromuscular blockade

Dopamine

- Central and peripheral neurotransmitter
- **Wakefulness, motivation, pleasure and sensation, movement, vasoactivity**
- **Agonism**
  - Arousal / Vigilance / Psychosis
  - Stimulated hyperkinesis / Akathisia
  - Autonomic instability
- **Antagonism**
  - Sedation
  - Bradykinesia / Akathisia
  - Hypotension
Atypicality

- Serotonin (5-HT2A) antagonism in mesocortical, mesolimbic, and nigrostriatal pathways*
- Preferentially antagonize mesolimbic D2 receptors over those in the nigrostriatum and prefrontal cortex*
  - Reduced overall D2 receptor affinity
  - Reduced D2 receptor occupancy: <70%**


Atypical Antipsychotics – 5-HT

- **clozapine** (Clozaril) 25-600 mg/d (po)
  - agranulocytosis, seizures
- **risperidone** (Risperdal) 1-6 mg/d (po)
  - postural hypotension, less weight gain
- **olanzapine** (Zyprexa) 5-20 mg/d (po, im)
  - weight gain, hyperglycemia
- **ziprasidone** (Geodon) 40-280 mg/d (po, im)
  - low sedation, akathisia, QTc prolongation
- **quetiapine** (Seroquel) 25-900 mg/d (po)
  - lowest EPS, postural hypotension, sedation
- **aripiprazole** (Abilify) 5-30 mg/d (po, im)
  - low sedation, but can activate uncomfortably
Me, Too…

- Paliperidone (Invega)
  - 2D6 metabolite of risperidone
- Iloperidone (Fanapt)
  - Risperidone derivative
  - 2D6 and 3A4 substrate
- Lurasidone (Latuda)
  - Ziprasidone analog
  - 3A4 substrate
- Asenapine (Saphris)
  - Structure similar to olanzapine & quetiapine
  - Likely less anticholinergic

Antipsychotic Pharmacology

Manifestations of Toxicity

- Peak effects typically evident within **2 to 6 hours**
- Most common clinical manifestations:
  - **Dopamine (and histamine) blockade**: slurred speech, ataxia, lethargy, sedation, and **coma**
  - **α Adrenergic blockade**: tachycardia and **hypotension**
  - **Muscarinic blockade**: tachycardia, **delirial agitation**, hallucinations, blurry vision, retention, and sicca
  - **Potassium Channel Antagonism**: arrhythmias

EPS may be the only presenting manifestation especially in children (rigidity, bradykinesia, tremors and/or akathisia).

Treatments

- **Supportive care**
- **Hypotension**: IV crystalloids → vasoconstrictive pressors
- **QT prolongation**: Mg++, K+ → Overdrive pacing +/- lidocaine
- **Anticholinergic delirium**: Physostigmine q1-2 hours PRN
- **Seizures**: Benzodiazepines +/- barbiturates
- **QRS prolongation** (Mesoridazine, Thoridizine): NaHCO₃

Most neuroleptics are highly lipophilic & protein bound

Large $V_d$ with relatively low plasma concentrations

All require P450 enzymes, >50% of them by CYP2D6 – so liver disease may prolong clearance and recovery
One Last Story…

Lithium

Pro-serotonergic w/ multiple cellular mechanisms of action
- Lithium carbonate, Eskalith, Lithobid
- Handled like sodium—distribution, effects, elimination
  - CNS, PNS, Cardiac, Renal

Serum Levels vs. Acute Toxicity vs. Chronic Toxicity
- Not bound by AC
- Decontamination with WBI
- Aggressive saline hydration
- Hemodialysis
- Time…
**Psychopharmacology Summary**

- Knowledge of mechanisms and kinetics
  - Guides therapeutic use
  - Predicts toxicity
  - Frames assessment
    - Vital signs
    - Mental status – arousal, attention, orientation, memory, understanding, judgment, choice…all data!
- Drug interactions, including non-prescribed
- Antidotes make sense when the pattern fits
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Questions?

Supplementary Material Follows
Selective Serotonin Reuptake Inhibitors

Inhibit Serotonin Uptake
- Fluvoxamine (Luvox) – shortest t½
- Fluoxetine (Prozac) – longest t½
- Paroxetine (Paxil) – mildly anticholinergic
- Escitalopram (Lexapro)
- Sertraline (Zoloft)
- Citalopram (Celexa)

All produce lethargy, ataxia, tachycardia, and in large ingestion seizures and QT prolongation

Serotonin Norepinephrine Reuptake Inhibitors

Inhibit 5-HT & Norepi Uptake
- Venlafaxine (Effexor)
- Duloxetine (Cymbalta) – pain indications
- Milnacipran (Savella) – fibromyalgia indication

All produce lethargy, ataxia, tachycardia, hypertension, and in large ingestion seizures, QT prolongation, and possibly Na+ channel blockade
Other Antidepressants

Alter Serotonin and Norepinephrine Activity

- Nefazodone (Serzone)
- Trazodone (Desyrel) – mild hypotension, brady
- Buspirone (Buspar)
- Bupropion/Budeprion (Wellbutrin, Zyban) – severe
- Vilazodone (Viibryd) – 5-HT Reuptake and agonism
- Atomoxetine (Strattera)
- Mirtazapine (Remeron) – mildly anticholinergic

Tricyclic Antidepressants

Inhibit Serotonin and Norepinephrine Uptake

- Amitriptyline (Elavil)
- Doxepin (Sinequan, Adapin, Silenor)
- Clomipramine (Anafranil)
- Imipramine (Tofranil, Janimine)
- Protriptyline (Vivactil)
- Nortriptyline (Pamelor, Aventyl)
- Desipramine (Norpramin, Pertofrane)
- Maprotiline (Ludiomil)
- Amoxapine (Asendin)
Monoamine Oxidase Inhibitors

Inhibit 5-HT, Norepi, Epi, DA Breakdown

- Isocarboxazid (Marplan)
- Phenelzine (Nardil)
- Tranylcypromine (Parnate)
- Selegiline (Emsam, Eldepryl, Zelapar)
TCA Toxicity

- Anticholinergic/Antihistaminergic
  - Somnolence, Confusion, Tachycardia
- α Adrenergic blockade
  - Hypotension
- GABA Antagonist
  - Seizures
- Sodium Channel Blockade
  - Myocardial Depression, Dysrhythmias
- Monoamine Reuptake Inhibition
  - Autonomic instability, Hyperreflexia
- Potassium Channel Antagonism
  - QT prolongation, arrhythmias

Myocardial Cell Electrophysiology
Wide QRS

- Rec Rx NaHCO3 when > 115 msec
- > 130 msec predictive of seizures
- > 160 msec predictive of dysrhythmias
Sodium Bicarbonate

- Place patient on monitor
- Administer bolus of 1 mEq/kg
- Observe for QRS narrowing
- Keep pH 7.5-7.55

NaHCO₃