Recognizing and Avoiding Adverse Drug Events

Let’s define our terms...

Adverse Drug Reaction

- a drug effect that is unwanted, unpleasant, noxious, or potentially harmful

Let’s define our terms...

Adverse Drug Events

- an injury resulting from medical drugs, including medication errors, ADRs, allergic reactions, overdoses

One more point...

ADRs can be a matter of perspective

- an “unwanted, unpleasant” reaction to one drug in one case can be the desired result in another.

Example: sedation can be an “adverse reaction”, or it can be the goal

Umm... wait, we aren’t physicians.

Did you know...

Only YOU can prevent ADEs!

- ADEs are common and commonly missed. The more eyes are on a patient, the more likely an ADE is recognized.
Role for psychologists

- Many ADRs are unpreventable
- Many medication errors caused by physician lack of knowledge or forgetting
- APA Guidelines on Psychopharmacology (2011)
  - prescribers
  - collaborators
  - information provider

Why are ADEs important?

- one of the leading causes of morbidity and mortality in health care—possibly the 4th leading cause of death
- over 4 billion prescriptions are filled every year
- the odds of an ADR increase significantly with 4 or more prescriptions
- Approximately 1.6 million hospital stays involving ADEs occurred in hospitals in 2014
- psychotropics accounted for 8.1% of hospital ADE stays in 2014

Adverse Drug Events account for what portion of ALL hospital adverse events?

1 in 3
1 in 9
1 in 20
1 in 50

Which class of medications is NOT among the top 5 for most preventable ADEs?

- analgesics
- antimicrobials
- antipsychotics
- diabetes medications
- cancer medications

# of ADR reports made to FDA

- 1995: 562,500
- 2000: 1,125,000
- 2005: 1,687,500
- 2010: 2,250,000
Reported ADRs are what estimated percentage of total ADRs?

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Number of ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5%</td>
<td></td>
</tr>
<tr>
<td>5-10%</td>
<td></td>
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<tr>
<td>50-55%</td>
<td></td>
</tr>
<tr>
<td>70-75%</td>
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<tr>
<td>75-80%</td>
<td></td>
</tr>
</tbody>
</table>

Most common ADRs of top 200 drugs

1. dizziness 11. thrombocytopenia 21. anxiety
2. nausea 12. abdominal pain 22. palpitation
3. headache 13. somnolence 23. tremor
4. vomiting 14. allergic reactions 24. arthralgia
5. diarrhea 15. dyspepsia 25. anorexia
6. rash 16. urticaria 26. nervousness
7. constipation 17. dyspnea 27. anaphylaxis
8. fatigue 18. hypotension 28. xerostomia
9. insomnia 19. depression 29. fever
10. pruritus 20. paresthesia 30. taste disturbance

But most of all beware of...

1. allergic reactions, rashes
2. altered consciousness
3. vomiting/eating problems
4. diarrhea, constipation
5. heartbeat changes
6. fainting or dizziness
7. muscle changes (rigidity, spasms, weakness)
8. yellowing of eyes, skin, or mouth
9. unusual bruising or bleeding
10. fever, feeling sick
11. sexual side effects

Yellowing of eyes skin mouth

- Jaundice (bilirubin not being filtered from the blood)
- hepatitis, alcoholic liver disease, blocked bile ducts, pancreatic cancer, meds (including acetaminophen, penicillin, birth control, steroids, Thorazine)

Sexual Side Effects

- Very common among psychotropics.
- Rates appear to be more drug related than class related
- Cause is usually unknown, studies are inconsistent, may not even be drug related
- Antidepressants, antipsychotics, mood stabilizers?, anxiolytics?

Acetylcholine (ACh)

- acetylcholine= central and peripheral nervous system neurotransmitter (GI tract, urinary tract, lungs, etc.)
- Anticholinergics can treat dizziness, extrapyramidal symptoms, GI disorders, insomnia, incontinence, respiratory problem, etc.
- Many psychotropics have incidental impacts on ACh
- FUN FACT: many of the finest chemical weapons are cholinergics!

Kim Jong-nam
Killed with VX gas—an acetylcholinesterase inhibitor, which causes involuntary contraction of all muscles leading to cardiac and respiratory failure.

Sergei Skripal
almost killed with Novichok powder—another acetylcholinesterase inhibitor

which of our patients take acetylcholinesterase inhibitors?

- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)

“Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.”

– Paracelsus (1493-1541)

Anticholinergic drugs

- First-gen antihistamines
  - diphenhydramine, hydroxyzine, meclizine, promethazine
- Anti-Parkinson’s drugs
  - benztropine (Cogentin)
- Antidepressants
  - TCAs, Paxil
- Antipsychotics
  - Clozapine, olanzapine, thioridazine
- And many more!
<table>
<thead>
<tr>
<th>Anticholinergic symptoms</th>
<th>Anti-depressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>sedation</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>dry mouth</td>
<td>SSRI’s</td>
</tr>
<tr>
<td>blurred vision</td>
<td>SNRI’s</td>
</tr>
<tr>
<td>dizziness</td>
<td>NDRT’s</td>
</tr>
<tr>
<td>urinary retention</td>
<td>NaSSA’s</td>
</tr>
<tr>
<td>confusion/ delirium</td>
<td>TCA’s</td>
</tr>
<tr>
<td>constipation</td>
<td>MAO’s</td>
</tr>
<tr>
<td>hallucinations</td>
<td>atypicals</td>
</tr>
<tr>
<td>reduced sweating and higher body temp</td>
<td></td>
</tr>
</tbody>
</table>
Anti-depressant ADE’s

- GI related ADE’s:
- Nausea
- Vomiting
- Weight Gain
- Insomnia
- Sexual effects
- Agitation/drowsiness
- restlessness/racing thoughts
- Suicide....?
- Tardive dysphoria (TDp) ...
- Drug interactions
- And more! (tremor, night-sweats...)

Serotonin Syndrome

- caused by over activation of 5HT-1A and 5HT-2A
- result of...
  - a single drug used appropriately
  - an overdose
  - two serotonergic drugs (most common)

Serotonin Syndrome

<table>
<thead>
<tr>
<th>Symptom Cluster</th>
<th>Symptomatology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered Mental Status</td>
<td>Agitation</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Disorientation</td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td>Neurovascular Abnormalities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Muscle rigidity</td>
</tr>
<tr>
<td></td>
<td>Bilateral Babinski signs</td>
</tr>
<tr>
<td></td>
<td>Akathisia</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td>Tachypnea</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Multinodules</td>
</tr>
<tr>
<td>Autonomic Hyperactivity</td>
<td>Hyperpyrexia</td>
</tr>
<tr>
<td></td>
<td>Diaphoresis</td>
</tr>
<tr>
<td></td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td>Shivering</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Diaphoresis</td>
</tr>
</tbody>
</table>


Serotonin Syndrome

onset usually within 24 hours of medication change, mild cases often undiagnosed

1. agitation
2. hyperreflexia
3. diaphoresis (excessive sweating)
4. tremor
5. mental status changes
6. shivering
7. myoclonus (involuntary muscle twitching)
8. diarrhea
9. poor coordination
10. fever

Withdrawning from antidepressants

- Not a topic that has had much attention until recently, some denial in the field
- symptoms of withdrawal include insomnia, anxiety, depressed mood, lability, “brain zaps” (parasthesias)
- Multiple studies now suggesting SSRIs should be drawn down over months to years, maybe to 1/40 dose before d/c


Anxiolytics

- benzodiazepines
  - Xanax, Valium, Ativan, Clonazepam, etc.
  - BuSpar
  - Prazosin
  - Propranolol

Anxiolytics ADE’s

- Benzodiazepines (GABA agonists)
  - sedation
    - memory impairment, slurred speech, grogginess, confusion
    - incoordination (risk of falls in elderly)
  - dependence
  - paradoxical agitation
  - respiratory depression (avoid with apnea, alcohol, other sedatives)

Anxiolytics ADE’s

- BuSpar (buspirone) 5HT1A partial agonist
  - dizziness
  - nervousness
  - nausea
  - headache
  - jitteriness
Anxiolytics ADE’s

- Prazosin (Alpha-1 adrenergic antagonist)
- sleepiness, dizziness, headache, weakness
- priapism rarely reported
- caution when adding to other hypertensives

Anxiolytics ADE’s

- Inderal (propranolol) (beta-1 and beta-2 adrenergic antagonist)
- dizziness
- fatigue
- bradycardia
- hypotension

Stimulants

- The Amphetamines
  - amphetamine (Evekeo)
  - dextroamphetamine (Dexedrine)
  - lisdexamfetamine (Vyvanse)
- The Methylphenidates
  - methylphenidate (Ritalin)
  - dexamethasone (Focalin)

Stimulants

- Dry mouth/thirst
- Decreased Appetite
- Nausea/Vomiting
- Abdominal Pain/Cramps
- Growth delay
- Constipation or diarrhea
- Heart rhythm changes (QT prolongation)—probably not as risky as we used to think, when taken as prescribed.

Stimulant ADE’s

- Tension
- Agitation
- Irritability
- Mood Swings
- Tics
- Insomnia
- Seizures (unlikely at normal doses)
- Psychosis (.21% amphetamine vs. .1% methylphenidate ages 13-25)
**QT prolongation**

- Drugs that cause it:
  - CNS stimulants, chlorpromazine, haloperidol, thioridazine, quetiapine, risperidone, ziprasidone, fluoxetine, paroxetine, sertraline, citalopram/escitalopram (over 40mg), venlafaxine, TCAs, antibiotics, anti-fungals, sodium channel blockers, potassium channel blockers
  - [www.qtdrugs.org](http://www.qtdrugs.org)
  - Risk factors: women, older, family history, heart disease, renal or hepatic disease, drug interactions, bradycardia, extremely low or high weight

**Torsades de pointes**

![Diagram of Torsades de pointes]

- Pro tip...
  - Get an EKG before and after starting a drug with QT potential

**Antipsychotics**

- Dopamine and serotonin antagonists
- Typicals
  - Haldol, Mellaril, Moban, Navane, Prolixin, Seta
dize
- Atypical
  - Clozaril, Risperdal, Latuda, Zyprexa, Seroquel, Abilify
- Better to compare each drug on its own terms
### Antipsychotics

Diagrams showing brain regions involved with various antipsychotic actions.

### Antipsychotic ADEs

- Dry mouth
- Weight gain
- Hyperglycemia (high blood sugar)
- Increased prolactin
- QTc prolongation
- ACh symptoms
- **Metabolic syndrome**

### Antipsychotic ADEs

<table>
<thead>
<tr>
<th>Antipsychotic Name</th>
<th>Weight gain</th>
<th>Dry mouth</th>
<th>Metabolic syndrome</th>
<th>QTc prolongation</th>
<th>Sedation</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>氯丙嗪 (chlorpromazine)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>氯氮平 (clozapine)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>奥氮平 (olanzapine)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>利培酮 (risperidone)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>阿立哌唑 (aripiprazole)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>氟哌啶醇 (haloperidol)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>拉莫三嗪 (lamotrigine)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>喹硫平 (quetiapine)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>奥氮平 (olanzapine)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Antipsychotic ADEs

- **Metabolic syndrome**
  - Cluster of metabolic risks
  - Increased blood pressure
  - Increased triglycerides
  - Insulin resistance
  - Obesity
  - Decreased high-density lipoprotein (HDL) cholesterol
  - Increased risk of CV disease and diabetes

### Antipsychotic ADEs

- Dizziness (orthostatic hypotension)
- Blurred vision
- Motor restlessness
- Mental restlessness
- Drowsiness
- Apathy
- Dementia in elderly
- Increased mortality in elderly
- Neuroleptic Malignant Syndrome

### Pro tip...

**Metabolic syndrome**
- Monitor weight/lipids
- Behavioral changes to reduce calorie intake
- Metformin
Neuroleptic malignant syndrome

- approximately 1% of people taking APS drugs
- high fever
- confusion
- rigid muscles
- variable blood pressure
- sweating
- fast heart rate
- seizures

Neuroleptic malignant syndrome

- risk of death 10-20%
- onset usually in less than 3 days, at beginning of treatment
- first signs are muscle cramps, tremor, fever, unstable blood pressure, agitation, delirium
- risk is higher with Lewy body dementia
- higher risk with high potency drugs, rapid increase in dose, long-acting forms

Mood stabilizers

- neuromodulators, ant-convulsants, anti-epileptics
- Lithium, Lamictal, Depakote, Trileptal, Tegretol, Dilantin
- Seroquel, Latuda, Abilify, Symbyax (fluoxetine/olanzapine) for bipolar depression

Mood stabilizer ADE’s

- Suicide…? (incidence rate of thoughts/behaviors: .43% vs. .24% anticonvulsants vs. placebo)
- Drug Rash with Eosinophilia and Systemic Symptoms (DRESS): fever, rash, and/or lymphadenopathy, signs of multiple organ systems affected
  - onset 2-8 weeks after exposure, chronic course
- Stevens-Johnson syndrome (10% of body)
  - onset 1-39 days post exposure, median 5 days
- Toxic Epidermal Necrosis (TEN) (30% of body)
  - fever > flu-like symptoms > rash usually around face then mucus membranes of eyes, mouth, genitals > blisters, peeling > necrosis

SJS/TEN is LEAST likely to be caused by

- allopurinol
- anticonvulsives
- antibiotics
- antipsychotics
- NSAIDs
- sulfa drugs
Mood stabilizer ADE’s

- Learning difficulties
- Mental fogginess (e.g., Topamax AKA “Dope” amax)
- Nausea/vomiting
- Indigestion
- Polydipsia (increased thirst) and Polyuria (more urine)
- Increased weight gain
- Thyroid problems

Mood stabilizer ADE’s

- Lithium toxicity
  - Risk increased by...
    - Drugs altering renal function (NSAID, ACE inhibitors, thiazides)
    - Decreased circulating volume (great heat, sauna)
    - Infections (viral infections, gastroenteritis with diarrhea and vomiting)
    - Fever
    - Decreased oral intake of water
    - Renal insufficiency
    - Nephrogenic diabetes insipidus

**but how do I know it’s an ADE?**

“have you noticed any physical or mental changes?”

---

Clinical Effects of Lithium Toxicity

<table>
<thead>
<tr>
<th>Effect</th>
<th>Acute Poisoning</th>
<th>Chronic Poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>None</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>GI</td>
<td>Nausea, vomiting</td>
<td>Minimal</td>
</tr>
<tr>
<td>CV</td>
<td>Prolonged QT interval, ST and T wave changes</td>
<td>Myocarditis</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Leukocytosis</td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight</td>
<td>Fine tremor, lightheadedness, weakness</td>
<td>Same</td>
</tr>
<tr>
<td>Moderate</td>
<td>Ataxia, drowsiness, hyperreflexia, muscle twitching, slurred speech, tinnitus</td>
<td>Same</td>
</tr>
<tr>
<td>Severe</td>
<td>Choreoathetoid movements, clumsiness, coma, confusion, muscular irritability, seizures</td>
<td>Memory deficits, Parkinson’s disease</td>
</tr>
<tr>
<td>Neuronalocular</td>
<td>Myopathy, peripheral neuropathy</td>
<td>Same</td>
</tr>
<tr>
<td>Renal</td>
<td>Urine concentrating defect</td>
<td>Chronic interstitial nephritis, nephrogenic diabetes insipidus, renal failure</td>
</tr>
<tr>
<td>Skin</td>
<td>None</td>
<td>Dermatitis, localized edema, ulcers</td>
</tr>
</tbody>
</table>


Table 1-2. Naranjo ADR Probability Scale

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Do Not Know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3. Did the adverse reaction appear when the drug was discontinued or a specific agent was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4. Did the adverse event appear when the drug was withdrawn?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5. Are these adverse reactions caused by other drugs?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous experience?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total Score  ADR Probability Classification
9  Highly Probable
5–8  Probable
1–4  Possible
0  Doubtful


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**Once again...**

1. allergic reactions, rashes
2. altered consciousness
3. vomiting/eating problems
4. diarrhea, constipation
5. heartbeat changes
6. fainting or dizziness
7. muscle changes (rigidity, spasms, weakness)
8. yellowing of eyes, skin, or mouth
9. unusual bruising or bleeding
10. fever, feeling sick
11. sexual side effects

---

**Be informed**

- Ask patients what medications they are taking
- Ask patients about the dosages
- Ask patients about how they actually take it
- Ask about herbals and supplements
- Remember to ask: “have you noticed any physical or mental changes?”

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**how am I supposed to remember all that?**

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**what should I do?**

---

**don’t overlook long-term patients especially as they enter their 60’s**
Be informed

- Be aware of higher risk groups
  - Elderly
    - less weight, less water, more fat
    - decreased liver, kidney functioning
    - trouble regulating blood pressure, temp (ACh)
    - more drugs
  - Children
    - drugs understudied in children
    - ADRs may be attributed to normal childhood fluctuations

Be informed

- Be aware of higher risk groups
  - people taking multiple medications
    - risk of interaction effect increases
  - use an online interaction checker (but respond cautiously to results)

Be informed

- Be aware of higher risk groups
  - poor CYP metabolizers and ultra-rapid metabolizers
    - wave of the future?
    - either direction may require changes in dosage

Educate

- Talk to patients about the meds they are taking or going to take—answer questions, look up information in session, inform them of risk and benefits the MD may not have covered
- Don’t be afraid to educate MDs about psychotropics. Do it respectfully (don’t demand, give options, etc). Advocate for smart prescribing practices like pre/post EKG, systematic drug on-boarding/tapering, limited prescribing of addictive meds, lab work

What is the average level of medication adherence?

- 10%
- 30%
- 50%
- 75%
- 90%
Reporting suspecting ADEs

- Option 1: discuss the concern with the patient
- Option 2: contact the patient’s PCP to discuss concern
- Option 3: send the patient to the ER
- Option 4: consider reporting ADR to MedWatch Voluntary Reporting system
  - https://www.fda.gov/Safety/MedWatch/default.htm

Case Example

- 45-year old man referred for psychotherapy for depression
  - history of chronic back pain
  - meds: oxycontin, amitriptyline, Flexeril, clonazepam (for anxiety), mirtazapine (for sleep)

Case Example

- 30-year old woman
- self-admitted for suicidal ideation, taken off Prozac and placed on Cymbalta, released after 5 days, within 4 days calls to complain of NO sleep for 4 days, visual hallucinations, shakiness, elevated heart rate, elevated temperature (100), dizziness, sense of slowed time, no evidence of impaired judgment, cognition seems normal

Case Example

- A 65-year old man, recently divorced, complains of severe depressed mood for at least six months. Reports anhedonia, lethargy, occasional agitation, frequent dizziness, substantial weight gain, excessive sleep, no suicidal ideation. No similar episodes prior to this. Attributes his symptoms to the divorce which has been very hard for him to cope with, but suspects his depression precedes the divorce.
- Known medical issues: High blood pressure, high cholesterol, seasonal allergies
- Medications include: Valium, PRN for agitation; fluoxetine, qam for depression; atorvastatin for cholesterol; Clonidine, BID for hypertension; Dmphehydramine OTC, daily, for allergies; drinks several cups of coffee throughout the day

Additional Resources

- Stephen Stahl “Essential Psychopharmacology”
- The Carlat Report
- The Psychopharmacology Institute
- Medscape or Epocrates Interaction Checker

That’s it!

Dr. Tony Ragusa
E-mail: anthony.ragus@evanhospital.com
Evangelical Community Hospital
Lewisburg, PA