

Inside the Black Box: What You Need To Know About Medication Interactions

Chitra Malur MD

Medical Director of Behavioral Health
East Orange General Hospital

Psychiatric Medication Interactions

WHY SHOULD I KNOW ABOUT THIS

I HAVE NOTHING TO DO WITH
PSYCHIATRY

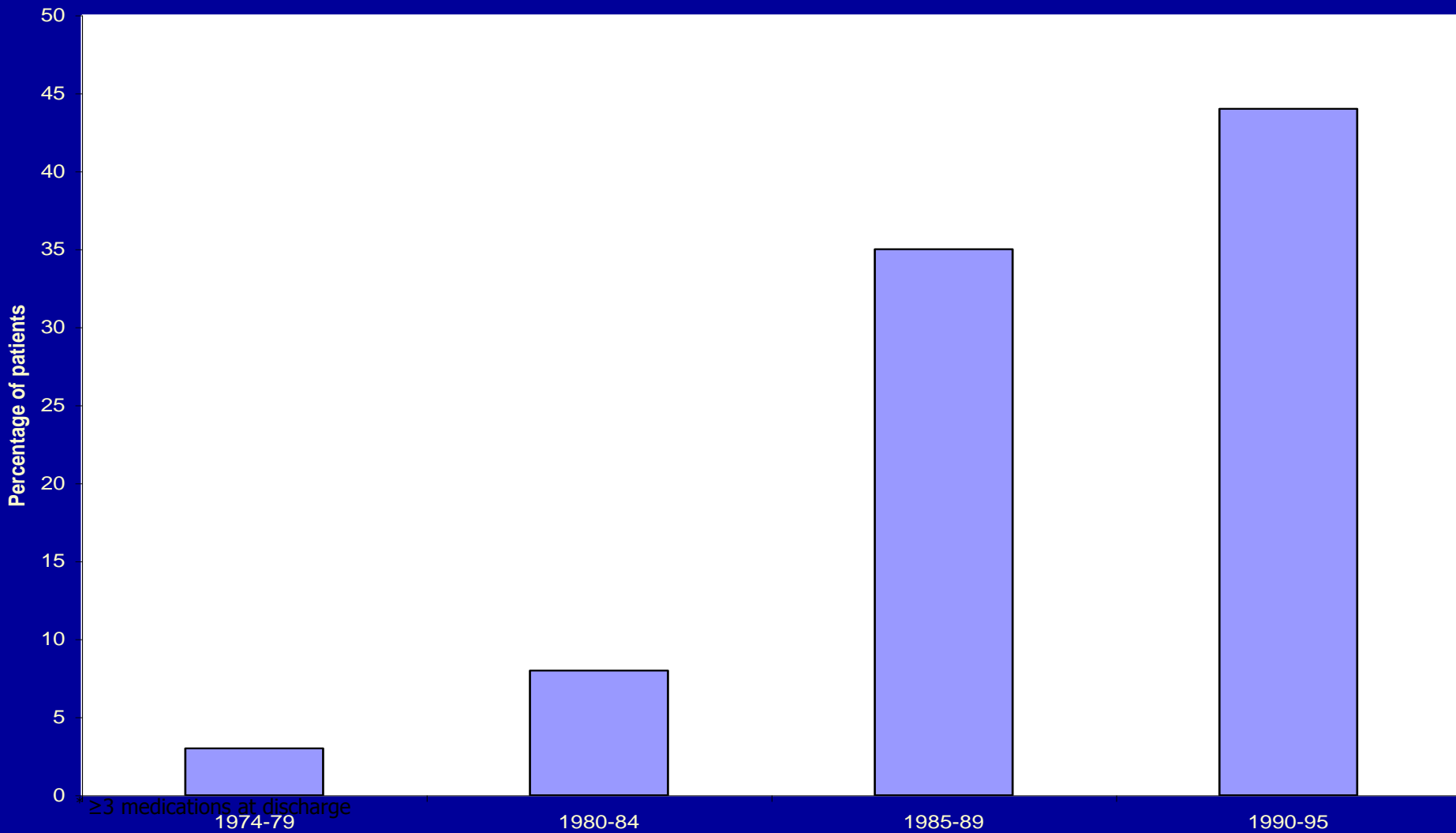
Psychiatric medication interaction: Why should we know about it

- Psychiatric medications are more being prescribed by health care providers from other disciplines
- Psychiatric medications are used for other indications, e.g. pain management
- Medical issues in patients with psychiatric history

Medication trends in the United States for 2009

- Antipsychotics- \$ 14.6 Billion
- Acid Reflux drugs- \$ 13.6 Billion
- Lipid regulators- \$ 13.6 Billion
- Antidepressants- \$ 9.9 Billion

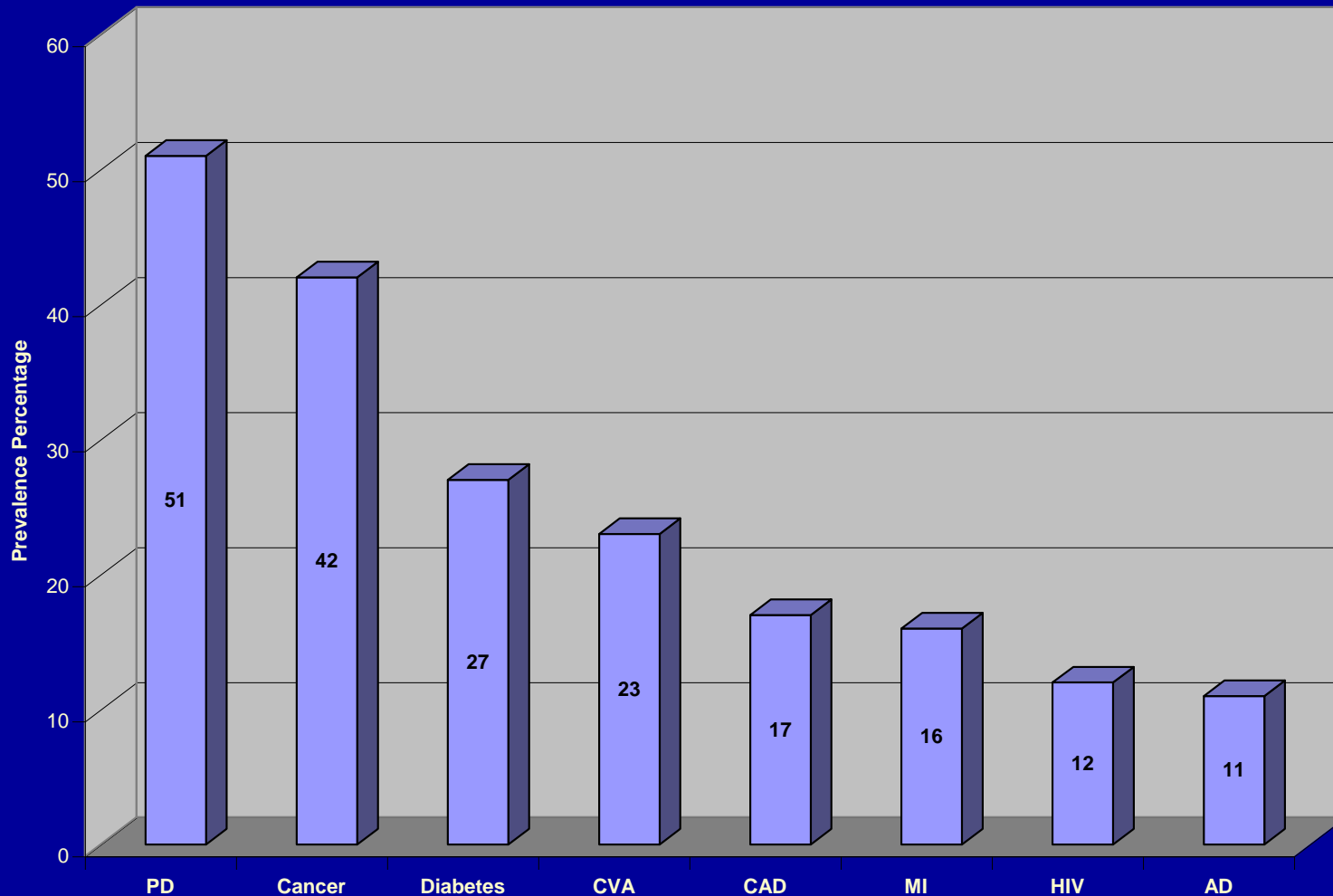
Increasing use of Polypharmacy* at the NIMH Biological Psychiatry Branch between 1974- 1996



Reasons for Polypharmacy

- To speed up the onset of response
- To boost or augment response
- To treat an adverse effect
- To treat a concomitant illness

Prevalence of depression in patients with chronic illnesses



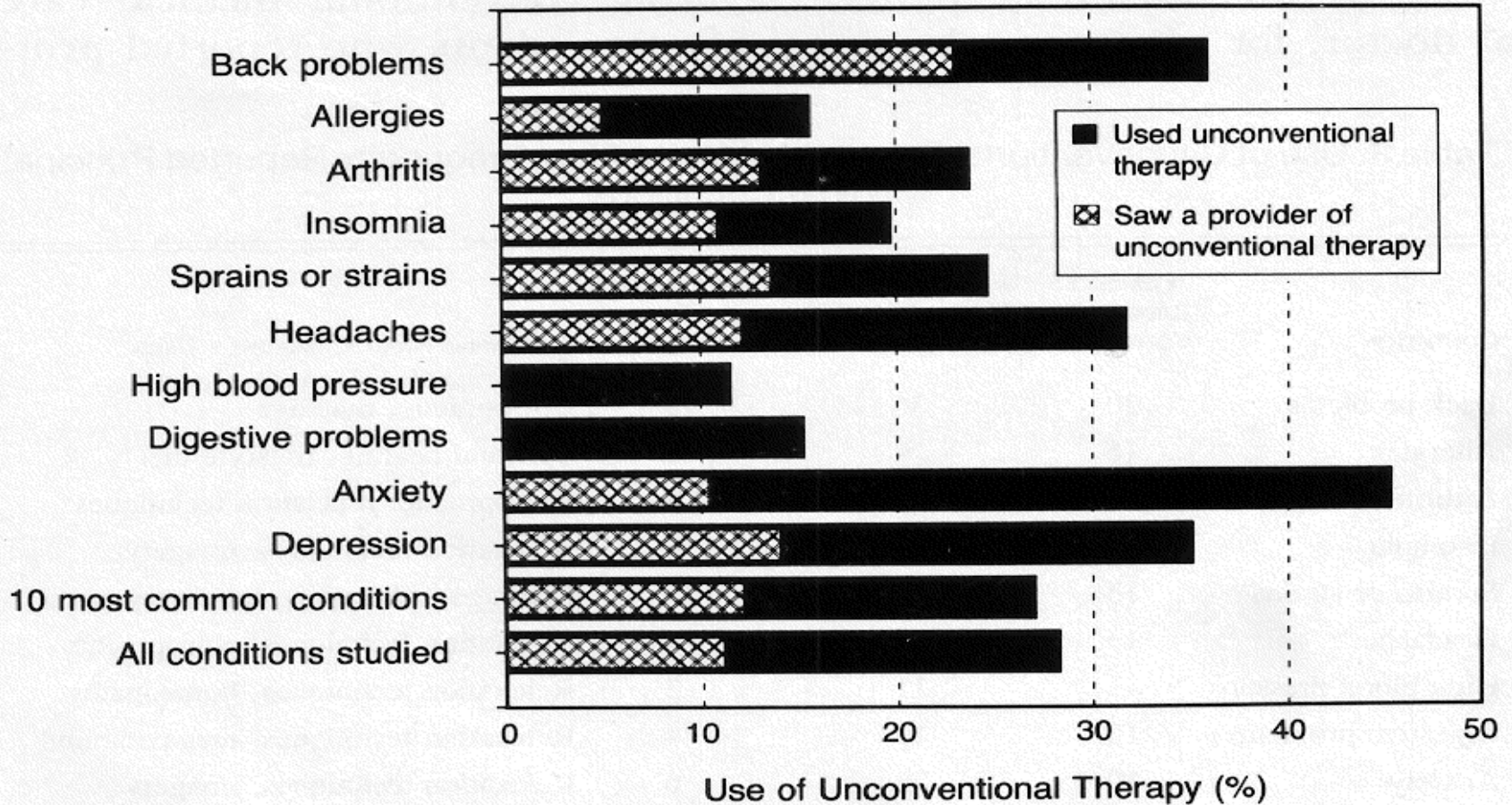
What is a Drug-Drug Interaction

- A Drug-Drug Interaction (DDI) occurs when one drug exerts an influence upon the action of another drug

Public Perception of Mental Illness

- 71 % Due to emotional weakness
- 65 % Caused by bad parenting
- 45 % Victim's fault: can will it away
- 43 % Incurable
- 35 % Consequence of sinful behavior
- 10 %** Has a biological basis: involves the brain

Prevalence of Unconventional Therapy



Herbal & Supplements	Interacting Drugs	Clinical Implications
Echinacea	Drugs metabolized by 3A4	Increased hepatic 3A4 activity
Ginseng	MAOI	CNS effects (e.g. manic symptoms, tremulousness)
Kava	Benzodiazepines	CNS effects increased
St. John's Wort	SSRI	Serotonin syndrome
	TCA	Plasma concentration is decreased
	Alprazolam	Increases clearance twofold
	Methadone	Action of methadone is decreased
Valerian	Sedative hypnotics	Excessive sedation
	MAOIs	Reversal of antidepressant activity
	Phenytoin	Antagonism of anticonvulsant activity

Drug- Drug Interaction- Case 1

A 45 year old construction worker is hospitalized after his arm is mutilated by a lawn mower. Upon intake in the ER he reports that he has difficulty with his “nerves” and is in treatment. In the week following surgery, he has intermittent fevers. Blood cultures are positive for MRSA. Vancomycin is started . His fever abates. 4 days later his fevers return. Blood cultures are done.

Drug- Drug Interaction- Case 1

The blood culture is positive for
Vancomycin-resistant Enterococcus
bacteremia

Vancomycin is discontinued and
Zyvox (linezolid) is started

Drug- Drug Interaction- Case 1

Two days later-

The patient is delirious, febrile,
hypertensive, vomiting and
experiencing myoclonus

WHAT WENT WRONG

Cautionary Drug- Drug Interactions Medication List

Common medication interactions

Medication	Rationale
Intramuscular Olanzapine and Lorazepam	Drop in Blood Pressure if given within 3 hours
Carbamazepine and SSRIs Or SGAs	Decrease in efficacy of the SSRI or SGA
Clozapine and SSRI	SSRIs can increase the blood level of clozapine
SSRIs and MAOIs	Hypertensive Crisis
Intramuscular Chlorpromazine	Hypotension
Carisoprodol and alprazolam	CNS Depression, monitor for respiratory depression
Buprenorphine & Methadone or ultram	Withdrawal symptoms
Fluconazole/voriconazole/Itraconazole and alprazolam	Increases alprazolam toxicity
Lithium and NSAIDS	Lithium toxicity

Cautionary Medication List- 1

Intramuscular Olanzapine and Lorazepam

Separate lorazepam (Ativan®) IM use by 3 hours when using Olanzapine (Zyprexa®) IM., Drop in blood pressure if given within 3 hours

Cautionary Medication List- 2

Carbamazepine and Selective Serotonin Reuptake Inhibitors (SSRI) (or) 2nd generation antipsychotics

Concurrent use can decrease the efficacy of antipsychotics such as Quetiapine

Case Study- 2

A 54 year old man with Chronic Paranoid Schizophrenia whose psychotic symptoms were stable on clozapine 600 mg/day was admitted to the hospital for complaints of Right Lower Lobe Pneumonia. The Resident Physician working with the patient notices that the patient has a sad affect and asks the patient if he was feeling depressed. The patient responds that he feels sad when he thinks of his deceased mother. The Resident Physician feels that he has nothing to lose by treating the patient's depression and decides to start the patient on Paxil 10 mg a day

Case Study- 2

4 days later the patient is walking towards the nursing station when he falls to the ground and has a Grandmal seizure.

What went wrong?

Cautionary Medication List- 3

Clozapine and SSRI (or) Carbamazepine

Concurrent administration of carbamazepine and clozapine should be avoided due to increased risk of agranulocytosis.

Concurrent administration of clozapine and SSRI can increase clozapine blood levels

Cautionary Medication List- 4

SSRI and Monoamine Oxidase Inhibitors (MAOIs)

Concurrent administration of SSRIs and MAOIs can result in hypertensive crisis

Cautionary Medication List- 5

**Intramuscular
chlorpromazine**

Can produce
hypotension

Cautionary Medication List- 6

Carisoprodol and Alprazolam

CNS depression, monitor for respiratory depression when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary

Cautionary Medication List- 7

Buprenorphine and Methadone / Ultram

Concomitant administration of an opioid analgesic and an opioid agonist/antagonist may result in withdrawal symptoms.

Cautionary Medication List- 8

Fluconazole/Voriconazole/Itraconazole and Alprazolam

Increase alprazolam (Xanax®) concentrations and potential alprazolam toxicity (excessive sedation, fatigue, ataxia, slurred speech, slowed reactions and prolonged hypnotic effects)

Cautionary Medication List- 9

Lithium and NSAID/Metronidazole

Concurrent use of metronidazole (Flagyl®) with lithium may provoke lithium toxicity due to reduced renal clearance.

Cautionary Medication List- 10

Depakote and Lamotrigine

The elimination half-life of lamotrigine can increase from 26 to 70 hours with valproate co-administration (a 165% increase) The dose of lamotrigine should be reduced when co-administered with valproate. Serious skin reactions (such as Steven-Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration.

Case study- 3

- A 47 year old attorney with Bipolar Disorder is admitted to the medical floor for pneumonia. His Bipolar Disorder has been well controlled on lithium. He complains of a headache. The Attending Physician orders Tylenol PRN. He continues to approach the nursing station several times reports that he is still in pain. The nurse pages the resident on call to see if another pain medication can be given. The resident orders Ibuprofen PRN. The patient receives several doses of Ibuprofen .

Case study- 3

Two days later, the patient falls while walking to the bathroom, his speech is slurred and he is confused

WHAT WENT WRONG

Cytochrome - P 450 system

The Cytochrome P 450 (CYP) system is a family of hemoproteins predominantly located in the liver and responsible for biotransformation of >60 % of the commonly prescribed drugs

Most common Cytochrome P-450 system involved in psychiatric medication interactions

CYP 1A2

CYP 2D6

CYP 3A4

Inducers
Cigarette smoke
Omeprazole

Inhibitors
SSRI
Fluroquinolones(cipro)

CYP 1A2

Clozapine
Olanzapine
Imipramine

Inducers
Dexamethasone

Inhibitors
Quinidine
Fluoxetine
Ticlopidine
Bupropion
Pindolol

CYP 2D6

**Risperidone
Venlafaxine
Thioridazine**

Inducers

St. John's wort
Carbamazepine
Modafanil
Dexamethasone

Inhibitors

Fluoxetine, paroxetine
Ciprofloxacin
Verapamil

CYP 3A4

**Buspirone
Mirtazapine
Haloperidol
Aripiprazole
Quetiapine**

**The Pharmacy and
Therapeutics Committee at
East Orange General Hospital**

Drug	Caution	DI (*cannot use together)
aripiprazole (Abilify)	Weight gain	Carbamazepine
clozapine (Clozaril)	Agranulocytosis, anticholinergic effects, seizures, thromboembolism, weight gain	BZDs, carbamazepine, cimetidine, codeine, macrolide antibiotics, SSRI,
haloperidol (Haldol)	Qtc prolongation, anticholinergic effects, myelosuppression, pigmentary retinopathy	Alfuzosin, carbamazepine, chlorpromazine, ciprofloxacin, codeine, eplerenone, gadobutrol, maraviroc, nilotinib*, quinidine, qtc prolongation agents, pimecrolimus, pramlintide, ranolazine*, salmeterol, SSRI, tamoxifen, thioridazine*, tramadol, ziprasidone*
olanzapine (Zyprexa)	Qtc prolongation, rash, weight gain	Fluvoxamine, lamotrigine, pramlintide
quetiapine (Seroquel)	Anticholinergic effects, blood dyscrasias, cataracts, hyperlipidemia, weight gain	Alfuzosin, ciprofloxacin, gadobutrol, nilotinib, phenytoin, pramlintide, thioridazine*, ziprasidone*
risperidone (Risperdal)	Anticholinergic effects, priapism, weight gain	Alfuzosin, carbamazepine, ciprofloxacin, gadobutrol, nilotinib*, pramlintide, SSRI: except fluvoxamine, valproic acid, verapamil, thioridazine*, ziprasidone*
ziprasidone (Geodon)	Qtc prolongation, rash, weight gain	Alfuzosin, antifungals, carbamazepine, ciprofloxacin, gadobutrol, nilotinib*, qtc prolongation agents*, thioridazine*
The following precautions and drug interactions are common to all drugs listed in this chart.	Cardiac, EPS, esophageal dysmotility, hyperglycemia, NMS, orthostatic hypotension, sedation, temperature irregularity	Alcohol, amphetamines, antiparkinson's drugs, CNS depressants, CYP int., lithium, tetrabenazine

General Warnings

- Antipsychotics have an increased risk of death among elderly patients with dementia.
- FDA warns about hyperglycemia and diabetes
- Weight gain is more in second generation vs. first generation
- Concomitant use with an acetylcholinesterase inhibitor may cause more EPS
- Do not administer intramuscular ativan and zyprexa together
- Check QTC interval before medicating patient with an antipsychotic
- Benzodiazepines can cause respiratory suppression

Preventive Measures for Agitation/Delirium

- Identify and remove or treat underlying cause(s)
- Reorient to new surroundings
- Quiet, well-lit surroundings
- Familiar faces at bedside for reassurance
- Sitters
- Prevent dehydration: Monitor labs BUN/Serum Creatinine
- Correct sensory deficits (ex. Eyeglasses, Cerumen removal, Hearing aids or amplification device)
- Promote normal sleep

EAST ORANGE GENERAL HOSPITAL

Agitation Management Guidelines

Benzodiazepines

Lorazepam (Ativan) (rapid onset of action and a short half-life). (Half life- 12 hours). Usual daily dose is 0.5 to 2 mg IM. Average total dose- 4-8 mg

Diazepam (Valium) (half life- 20-40 hrs), Usual daily dose- 5-10 mg, average total dose-20- 60 mg

Midazolam (Versed) (more rapid onset than lorazepam but a shorter duration of action) (half life- 1- 4 hrs). The usual dose is 2.5 to 5 mg IM.

Antipsychotics

Olanzapine (Zyprexa): IM may cause more anticholinergic and hypotensive effects
(The dose is 5- 10 mg, Max Daily dose = 30mg (no more than 3 doses given 2 to 4 hours apart)

Ziprasidone (Geodon): Can cause cardiac conduction delays. The dose of ziprasidone is 10 to 20 mg IM, Max Daily dose = 40 mg)

Haloperidol (Haldol): IM, or orally used. It is usually given in doses of 2.5 to 10 mg. The onset of action-30 to 60 minutes. Decrease dose by one half in the elderly. Haloperidol should be avoided if possible in pregnant and lactating females, phencyclidine overdose, withdrawal and anticholinergic drug intoxication.
(Max Daily dose- 30 mg)

Fluphenazine (Prolixin): The dose is 2.5- 5mg ,Max Daily dose- 40 mg.
Can cause cardiac conduction abnormalities. May cause anticholinergic effects, orthostatic hypotension and Extrapyrimal symptoms

Preventing DDI

Ask your patient:

- Are there any medications we should not give you for any reason?
- Are there any medications we should not discontinue?

Alternative therapies:

- **Vitamins, Herbs and supplements:** Do you take any herbal medications?
- **OTC:** Do you take any over-the-counter medications?

Research interactions:

- Use available literature and a database to check for interactions.

Drug- Drug Interactions- *what have we learned*

- Familiarity with a particular medication's pharmacodynamic and pharmacokinetic profile is important
- Know all the medications that a patient is on before adding another one
- If you have a question,

DO NOT HESITATE TO ASK FOR HELP

**WE WORK AS A TEAM WITH A COMMON GOAL TO TAKE
CARE OF OUR PATIENTS**