Psychotropic Medication

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Part 2: Antipsychotics & Anxiolytics

with Terry Broda

Antipsychotic Drugs, Dose Equivalents, and Recommended Daily Dose Ranges

Drug	Relative Therapeutic Potency	Recommended Daily Dose Range (mg)
Chlorpromazine	100	25-800
Fluphenazine	2-3	1-60
Perphenazine	6-10	8-64
Trifluoperazine	3-5	4-60
Thioridazine	100	50-800
Mesoridaxine	50	24-400
Piperacetazine	10	10-160
Haloperidol	1.5-2	1-100
Thiothixene	2-4	5-120
Butaperazine	10-15	15-100
Loxapine	10-16	20-100
Molindone	7.5-12	15-200
Sulpiride	100	100-1000
Pimozide	1-2	2-20

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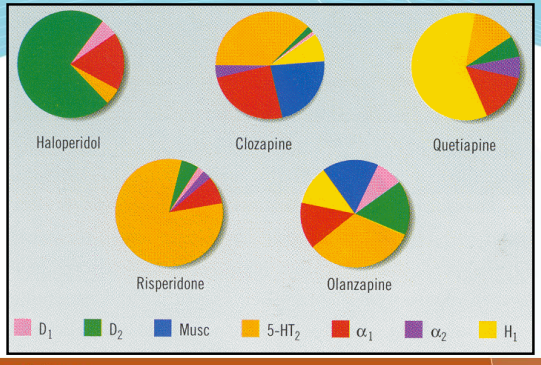
Binding Affinities of Antipsychotics



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Atypical Antipsychotics

Risperidone (Risperdal (M-tab) + Consta)
Clozapine (Clozaril)
Olanzapine (Zyprexa (Zydis))
Quetiapine (Seroquel)
Ziprasidone (Zeldox /Geodon)
Paliperidone (Invega + Sustenna)
Asenapine (Saphris –>S/L)
*Aripiprazole (Abilify)

- (form. dissoudre rapide)
- + IM LA
- * 3ieme génération

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Atypical Antipsychotics

Unique Properties

- Potent dopamine (D_2) and Serotonin (5-HT_2) antagonism
- Less occurrence of extrapyramidal adverse effects
- Decreased theoretical risk of Tardive Dyskinesia
- Greater impact on negative symptoms of schizophrenia

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Atypical Antipsychotics

Indications in Individuals with Developmental Disabilities

- Schizophrenia and related psychotic disorders
- Adjunctive mood stabilizers in Bipolar Disorder
- Adjunctive treatment in Obsessive-Compulsive Disorder
- Tic Suppression in Tourette's Syndrome
- Symptomatic treatment in Pervasive Developmental Disorders
- Conversion strategy to reduce risk of Tardive Dyskinesia

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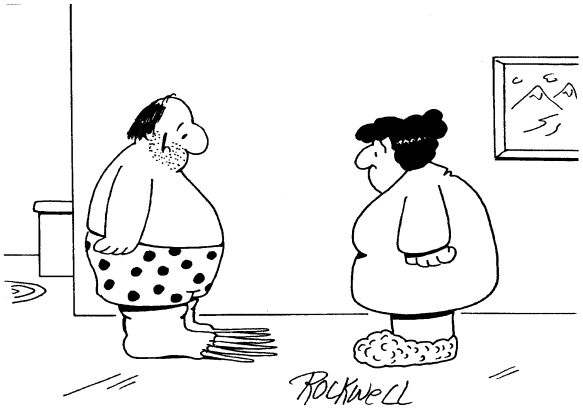
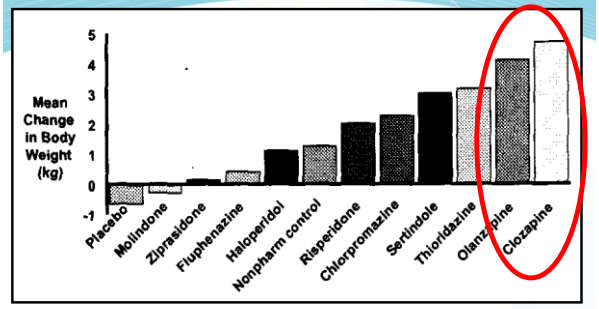


"I must be losing weight! I can see the tips of my toes."

Estimated Weight Gain After 10 Weeks



Allison DB *et al.* (1999). *American Journal of Psychiatry, 156,* 1686-1696

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Weight Gain by Individual Atypical Antipsychotic Drug

	Weight gain(kg/month)
Olanzapine*	2,3
Quetiapine	1,8
Clozapine*	1,7
Risperidone	1,0
Ziprasidone	0,8

*Risk of dyslipidemia & diabetes also elevated, 2004

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Medical Hazards of Obesity

- Hypertension
- Blood Lipid abnormalities
- Coronary Heart Disease
- Diabetes Mellitus
- Gallbladder Disease
- Respiratory Disease
- Cancer
- Gout
- Arthritis
- (Low Self Esteem)
- (Birth Defects)

Monitoring

Table 3 – American Diabetes Association (ADA) and American Psychiatric Association (APA) consensus guidelines for baseline assessment and monitoring of patients receiving atypical antipsychotic medications [71][a].

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history[b]	X					X	
Weight (body mass index)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

[a] More frequent assessments may be warranted based on clinical status.
[b] Personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease.

SE Clozaril

- Agranulocytosis…FATAL!
- Regular bloodwork:
  - CBC & diff weekly X 26 weeks
  - Every 2 weeks thereafter
  - If stable after one year, every 4 weeks
- Important to check if person has a fever (symptom of infection)
- Constipation!

Considerations

- Ziprasidone WITH food
- Asenapine WITHOUT food, under the tongue & DO NOT SWALLOW!
- Avoid grapefruit juice
- Zydis -> aspartame

Typical Antipsychotics

- Haldol (haloperidol)
- Loxapac (loxapine)
- Largactil (chlorpromazine)
- Nozinan (methotrimeprazine)
- Clopixol (zuclopenthixol)

Abnormal Involuntary Movement Scale (AIMS)

Patient identification: _____ Date: _____

Rated by:

- Either before or after completing the examination, observe the patient unobtrusively at rest (*e.g.*, in waiting room).
- The chair to be used in this examination should be hard and firm, without arms.
- After observing the patient, he/she may be rated on a scale of 0 (none), 1 (minimal), 2 (mild), 3 (moderate), and 4 (severe), according to the severity of symptoms.
- Ask the patient whether there is anything in his/her mouth (*i.e.*, gum, candy, *etc.*) and, if there is, to remove it.
- Ask patient about the current condition of his/her teeth. Ask if he/she wears dentures, and if teeth or dentures bother the patient now.
- Ask patient whether he/she notices any movement in mouth, face, hands or feet. If yes, ask to describe and to what extent they currently bother patient or interfere with his/her activities.

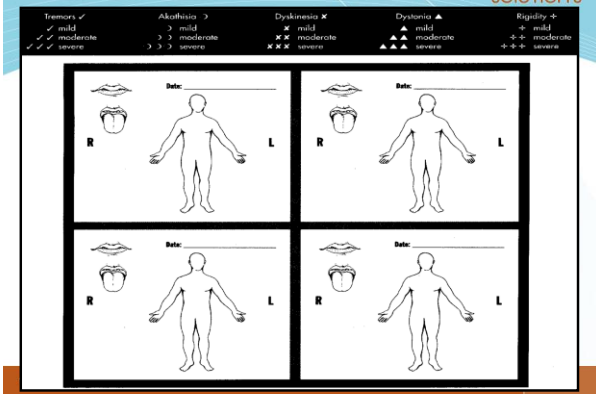
0 1 2 3 4	Have patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at entire body for movements while in this position)
0 1 2 3 4	Ask patient to sit with hands hanging unsupported. If male, between legs; if female and wearing a dress, hanging over knees. (Observe hands and other body areas)
0 1 2 3 4	Ask patient to open mouth. Do this twice. (Observe tongue at rest within mouth)
0 1 2 3 4	Ask the patient to protrude tongue. Repeat. (Observe abnormalities of tongue movement)
0 1 2 3 4	Ask the patient to tap thumb, with each finger, as rapidly as possible for 10-15 seconds; separately with right hand, then with left hand. (Observe facial and leg movements)
0 1 2 3 4	Flex and extend patient's left and right arms. (One at a time)
0 1 2 3 4	Ask patient to stand up. (Observe in profile; observe all body areas again, hips included)
0 1 2 3 4	Ask patient to extend both arms outstretched in front with palms down. (Observe trunk, legs and mouth)*
0 1 2 3 4	Have patient walk a few paces, turn and walk back to chair. Repeat. (Observe hands and gait)*

*Activated movements

Videos

- http://www.youtube.com/watch?v=_dnK578aZdo
- http://www.youtube.com/watch?v=W_3bbpFjI68
- http://www.youtube.com/watch?v=FUr8ltXh1Pc

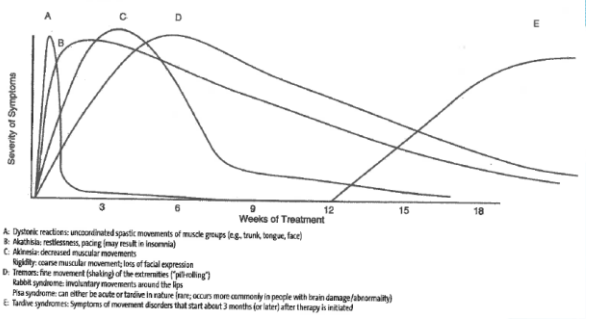
EPS Assessment



Examination & Checklist for EPS

Monitored on a regular basis means every person receiving drug therapy must be assessed at least once:

- Every 3 to 6 months
- After the initiation of a new psychotropic medication or a dose increase



A: Dystonic reactions: uncoordinated spastic movements of muscle groups (e.g., trunk, tongue, face)
B: Akathisia: restlessness, pacing (may result in insomnia)
C: Akinesia: decreased muscular movements
Rigidity: coarse muscular movement; loss of facial expression
D: Tremors: fine movement (shaking) of the extremities ("pill-rolling")
Rabbit syndrome: involuntary movements around the lips
Pisa syndrome: can either be acute or tardive in nature (rare; occurs more commonly in people with brain damage/abnormality)
E: Tardive syndromes: Symptoms of movement disorders that start about 3 months (or later) after therapy is initiated

Acute Dystonia

Clinical Signs/Symptoms

Motor Symptoms	Psychological Symptoms	Differential Diagnosis	Risk
Briefly sustained or fixed abnormal movement e.g., torticolis (30%) tongue (25%) trismus (14.6%) oculogyric crisis (6%) laryngospasm	• fear • anxiety	• malingering • seizure • catatonia	• high potency first-generation antipsychotics (FGAP) • young males • first exposure to FGAP

Treatments

- Lorazepam S/L
- Benztropine IM
- Diphenhydramine IM
- Rx antiparkinsonian as prophylaxis
- Decrease the dose
- Change Rx

Akathisia

Clinical Signs/Symptoms			
Motor Symptoms	**Psychological Symptoms**	**Differential Diagnosis**	**Risk**
• Foot shifting • Pacing • Rocking	• Agitation • Restlessness • Decreased concentration	• Psychotic exacerbation	• High potency first-generation antipsychotics (FGAP) • Elderly • Female • Anemia • SSRIs

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Treatments

- Antiparkinsonians NOT EFFECTIVE
- Diazepam, clonazepam, lorazepam
- ß-blocker
- Decrease the dose
- Change Rx

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Parkinsonism

Clinical Signs/Symptoms			
Motor Symptoms	**Psychological Symptoms**	**Differential Diagnosis**	**Risk**
• Tremor • Bradykinesia • Rigidity • Akinesia (masked facies, decreased arm swing) • Pill rolling movements	• Poor concentration attention • Bradyphrenia	• Depression • Negative symptoms of psychosis	• High potency first-generation antipsychotics (FGAP) • Elderly • Female • Neurological disorders

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Treatments

- Decrease the dose
- Change Rx
- Antiparkinsonian
  - Caution side effects: anticholinergic symptoms, exacerbation of psychosis, decrease cognition, unmask / ↑ TD
  - Less use of anticholinergic medication w/ Olanzapine, Seroquel

Classification of Movement Disorders

Type	Characteristics
Classical Tardive Dyskinesia	Lip smacking and pursing Tongue side to side movement (bon-bon) Tongue protrusion (Fly-catcher) Chewing movements Respiratory Dyskinesia Pelvic thrusting Choreoathetoid limb movements Tapping, side to side foot movements Marching in place
Tardive Dystonia	Similar to Idiopathic Torsion Dystonia Generalized or Focal/Segmental
Tardive Tic	Motor and Vocal Tics
Tardive Akathisia	Subjective restlessness or need to move
Withdrawal Emergent Syndrome	Transient, 6-12 weeks duration Begins immediately following abrupt discontinuation of neuroleptics Children > Adults Generalized Chorea

Tardive Dyskinesia (TD)

Diagnostic Criteria:

- History of three months total cumulative neuroleptic use
- Dyskinesia of lingual-facial-buccal muscle (most common), upper face, limb, trunk
- Movements which are repetitive, stereotyped in appearance and distribution
- Most common is choreoathetoid movements (classical TD)
- Motor impersistence is NOT a feature
- Gait is usually not affected

Tardive Dyskinesia Risk Factors

Variable	Factor	Determinant of Increased Risk
Patient Characteristics	• Age • Gender • Diagnosis • Previous EPS • Diabetes Mellitus (NIDDM)	• Increased risk with age (>55 years) • Female (slightly higher) • Affective disorder • Risk 2 to 3 times higher • Risk 50-100% higher
Drug Characteristics	• Type of neuroleptic • Dose/Duration • Continuous vs. intermittent	• Typical neuroleptics have similar liability • Positive correlation with total drug exposure • Higher with intermittent treatment

Epidemiology (TD)

	AP-1G	AP-2G
Incidence (per year)	5 %	0 - 2 %
Prevalence	25 % (elderly:50 - 60 %)	? 0 - 3 % (elderly: ? 0 - 5 %)

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Treatment for TD

- Change to 2nd /3rd generation AP
- Pyridoxine up to 400 mg/jr
- Clonazepam 0.5 - 6 mg/jr
- Tetrabenazine 25 - 75 mg/jr
- Clonidine 0.05 - 0.2 mg/jr

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Tardive Dystonia

Clinical Signs/Symptoms		Risks
Motor • Sustained muscle contractions • Blepharospasm • Sustained jaw opening (83%) • Torticollis (50-65%) • Arm hyperextension (42%) • Back arching/flexion/leaning (35%) • Hand flexion/grasp-like	**Psychological** • Distress • Mobility dysfunction • Embarrassment	• Abnormal birth • Abnormal development • Neurological disorders • Mental retardation • Male, younger age • Earlier onset

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NMS : F-E-V-E-R

(d/t blockage of dopamine receptors)

- **F**ever: hyperthermia & diaphoresis
- **E**ncephalopathy: abrupt onset confusion, stupor
- **V**ital sign instability: BP unstable, tachycardia
- **E**nzyme elevation: CPK (creatinine phosphokinase, hepatic enzymes)
- **R**igidity: "lead pipe" rigidity (generalized)

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Anticholinergic Side Effects

- Blurry vision
- Nasal congestion
- Dry mouth
- Urinary retention
- Constipation*

(*deaths with Clozapine)

Rx : tricyclic antidepressants, antipsychotics

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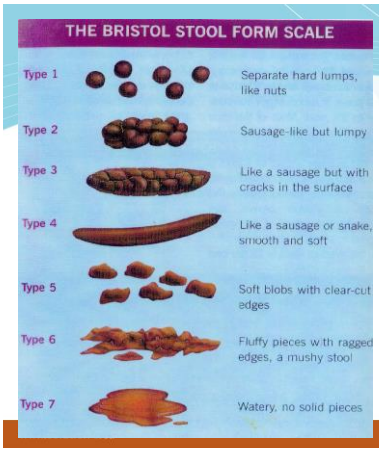

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IDEAL : Type 4, Type 3 also OK

« glides out easily with no fuss whatsoever !»

Source: Heaton KW, et al. Gut. 1992;33:818-824

Other Side Effects (SE)

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- Sedation
- Orthostatic Hypotension
- Prolongation of QTc interval (dizziness, fainting, palpitations, N & V)
- Galactorrhea / increased prolactin
- Sexual dysfunction
- Sun hypersensitivity

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Withdrawal Symptoms

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- N & V, diaphoresis, myalgia, insomnia, anxiety, confusion (rebound cholinergic effects) (within days after D/C)
- Psychosis (2-3 weeks after D/C)
- Dyskinesia (2-4 weeks after D/C)
- Dystonia, parkinsonism, akathesia (within days after D/C)

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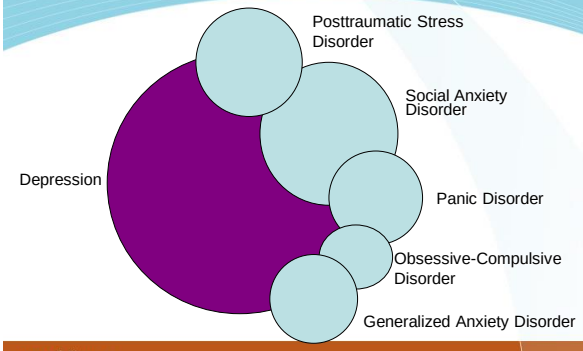
Spectrum of Depression and Anxiety Disorders



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ANXIOLYTICS (*benzodiazepines)

- Valium*
- Ativan*
- Rivotril*
- Serax*
- Xanax*
- Lectopam*
- Dalmane*
- Restoril*
- Librium*

- Diazepam
- Lorazepam
- Clonazepam
- Oxazepam
- Alprazolam
- Bromazepam
- Flurazepam
- Temazepam
- Chlordiazepoxide

- *Buspar*
- *Buspirone*

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Indications for use of benzodiazepines

Clear Indications	Probable Indications	Possible Indications
• Panic • Generalized anxiety • Social Phobia • Mania/agitated schizophrenia	• Coping difficulties with anxiety • Acute insomnia related to stress • Sleep-wake cycle disturbance	• Akathisia • Tourette Syndrome • Severe agitation (emergency/ crisis)

Use of Benzodiazepines

- Useful by NOT recommended as first-line
- For short periods (less than 4 months)
- Side effect profile
  - Sedation
  - Reduced coordination
  - Impaired cognition
- Risk of dependency/tolerance
- Withdrawal symptoms/rebound anxiety

****(decrease gradually: 10 - 25% every 1 - 4 weeks.)**

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Benzodiazepines

Class	Medication
1. Long half-life (>13hrs) & high potency	Clonazepam (Rivotril) Clobazam (Frisium) (*AED)
2. Long half-life (>13hrs) & low potency	**Chlordiazepoxide (Librium) **Diazepam (Valium) **Flurazepam (Dalmane) Nitrazepam (Mogadon) ***(**active metabolites)***
3. Short half-life (<13hrs) & high potency	Lorazepam (Ativan) Alprazolam (Xanax)
4. Short half-life (<13hrs) & low potency	Oxazepam (Serax) Temazepam (Restoril)

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Risks and Side Effects Associated with Anxiolytics

Risk Factors	Side Effects		
	CNS Depressants	Anticholinergics	Atypical
Dose	"Intoxication"	Excitement	Dysphoria
Duration	Coma/Death	Delirium	Dizziness
Age (extremes)	Aggression	Cognitive Impairment	Insomnia
Developmental Level	Cognitive Impairment	Parasympathetic (reduced activity)	Nausea
Brain Damage	Depression	Synergism	
Personality	Dependence		
Social Ambience	Withdrawal		
Familial	Synergism		
Drug Interactions			
Coexistent Disease			
Idiosyncratic			

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Benzodiazepines

Persons with IDD are at an increased risk of exhibiting behavioral side effects, possibly due to :

- Decreased tolerance threshold to frustration
- More stressful living environments (group homes lacking privacy, with rigid structure, & limited trained staff) in combination with their own limited social skills & coping strategies
- **These side effects can appear from the 2nd to the 7th day or up to 55 days after starting/increasing the Rx (average = 23 days)

Buspirone

Indications

- Anxiolytic
- Anti-aggressive properties
- Anti-depressant and anti-obsessional properties
- No anticonvulsant properties

Dosage

- Begin 5 mg bid – tid
- Max. 45-60 mg/day
- Takes effect in 2-4 weeks
- *NOT effective as a PRN

Pharmacology

- 5HT1A partial agonist

Adverse Effects

- Little sedation
- Headaches, dizziness, GI upset
- No tolerance to date
- May precipitate hypomania in the elderly

Interactions

- Increased neuroleptic serum levels (+ risk EPS)
- Increased benzodiazepine levels
- Case reports of Serotonin syndrome with SSRIs & trazodone.

Surprising Drug Interactions

Grapefruit & Grapefruit Juice

- Fresh or frozen, it can increase or less frequently, decrease the effects of certain drugs by interfering with their metabolism & elimination, **resulting in serious adverse reactions.**
- As little as 250 ml (1 cup) can cause significant increased blood levels of certain drugs
- **These effects can last up to 3 days or longer!**

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Medications to avoid with GRAPEFRUIT

- *Amiodarone p.o. (Cordarone)
- Aripiprazole (Abilify)
- Atorvastatin (Lipitor)
- Buspirone (Buspar)
- Carbamazepine(Tegretol)
- Clomopramine (Anafranil)
- Dextromethorphane (DM)
- *Diazepam p.o. (Valium)
- *Erythromycin p.o.
- Estrogens
- Fluvoxamine (Luvox)
- Fluoxetine (Prozac)
- Itraconazole (Sporanox)
- Lovastatin (Mevacor)
- Methadone
- *Methylprednisolone p.o.
- *Midazolam p.o. (Versed)
- Montelukast (Singulair)
- Nifedipine (Adalat)
- Pimozide (Orap)
- Quetiapine (Seroquel)
- Risperidone (Risperdal)
- Sertraline (Zoloft)
- Sildenafil (Viagra)
- *Simvastatin p.o. (Zocor)
- Tamoxifen
- Trazodone (Desyrel)
- Ziprasidone (Zeldox)

***if given IV, no interaction noted**

Effects of Tobacco on Rx

- Increased metabolism of fluvoxamine by 25% (via CYP182)
- Increased clearance of cyclic anti-depressant (induction via CYP182)
- Decreased plasma levels of chlorpromazine, haloperidol, fluphenazine, thiothixene, clozapine & olanzapine by 20-100% (induction)
- Increased clearance of diazepam & chlordiazepoxide (induction)

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Effects of Caffeine on Psychotropics (coffee, tea, cola)

With SSRIs:

- Increased jitteriness & insomnia
- Increased caffeine levels with fluvoxamine, half-life increased from 5hr to 31hr !

With antipsychotics:

- Increased akathisia & agitation
- Increased levels of clozapine (competition for metabolism via CYP1A2)

Effects of Caffeine on Psychotropics (coffee, tea, cola)

With drugs that treat EPS:

- May offset benefits of Rx by increasing tremor & akathisia

With anxiolytics & sedatives:

- May counteract sedation & increase insomnia

With lithium:

- Increased renal excretion of lithium resulting in decreased plasma levels
- May increase lithium tremor

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