


 **Antihistamines and Antidepressants**

Sabra Jones, PhD, D-ABFT-FT
Regional Toxicology Liaison, NHTSA Region 8




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Disclosures 



I have no relevant financial or nonfinancial relationships to disclose.

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Learning Objectives 



- Understand the therapeutic uses of antidepressants and antihistamines identified in impaired driving cases
- Review definitions applicable to this lecture
- Identify drugs and the characteristics in the different generations of antidepressants and antihistamines
- Know the adverse effects, toxicity and impairment characteristics associated with their use

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Experimental Data on Driving Impairment DRUG IMPAIRMENT.COM



- On-road or simulator studies
- Examine a variety of metrics (SDLP etc.)
- Most use "healthy" volunteers
- Some use "patients" vs "healthy controls"
- Dosing regimens: Acute / Sub-chronic / Chronic
- Some use nocturnal dosing

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Experimental Data DRUG IMPAIRMENT.COM

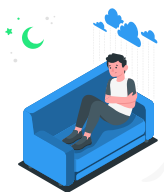
- 280 million people in the world have depression. Source: World Health Organization, Depressive Disorder March 2023
- During 2015 – 2018: 13.2% of Americans 18 and older reported antidepressant use in last 30 days. Source: CDC / National Health and Nutrition Examination Survey
- Over 33 million American adults on antidepressants

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Crash Risk & ADs DRUG IMPAIRMENT.COM


Epidemiological Data

- Odds ratios ranging from 1.10-3.10 for antidepressant users.
- Modest increases may be seen in young to middle-age drivers.
- Younger populations range from "none" to "minor" increases.
- Elderly users of sedating antidepressants have greater than 2-fold increase in crash risk.
- Data for all groups is confounded by the potential influence of disease states, comedications, comorbidities, withdrawal effects, etc.



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Antihistamines and Antidepressants



What are the most common Antihistamines and Antidepressants in impairment cases?


Antihistamines	Antihistamines (Continued)	Antidepressants
Diphenhydramine ^b	Chlorpheniramine ^b	Citalopram
Dextromethorphan ^b	Hydroxyzine ^b	Tricyclic Antidepressants
Doxylamine ^b	Phenylpropanolamine	Sertraline
	Pseudoephedrine	Venlafaxine

^bTier II Compounds


D'Orazio AL, Mohr ALA, Chan-Hoosokwee A, Harzer C, Huestis MA, Limoges JT, Miles AK, Scamro CE, Kerrigan S, Liddcoat LJ, Scott KS, Logan BK. Recommendations for Toxicological Investigation of Drug-Impaired Driving and Motor Vehicle Fatalities: 2021 Update. J Anal Toxicol. 2021 Jul 10;45(6):529-536. doi: 10.1093/jat/btab064. PMID: 34086916; PMCID: PMC8272528.

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Depression and Driving Impairment




Depressed patients may have psychomotor disturbances that affect driving




Cognitive Function



Daytime Alertness



Impaired Sleep



Vigilance

Increased crashes, less lane control, and slowed steering reaction in simulator studies
 Perform poorly compared to healthy controls in experimental studies
 Treatment may improve performance – not necessarily equal to healthy controls

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Therapeutic Use of Antidepressants



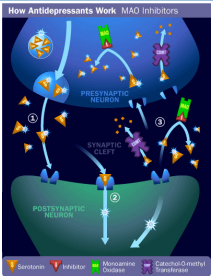

- Major Depressive Disorder (MDD)
- Obsessive Compulsive Disorder (OCD)
- Generalized Anxiety Disorder (GAD)
- Post-Traumatic Stress Disorder (PTSD)
- Bipolar I
- Chronic Musculoskeletal Pain
- Diabetic Peripheral Neuropathy
- Fibromyalgia
- Panic Disorder
- Premenstrual Dysphoric Disorder
- Social Anxiety Disorder
- Seasonal Affective Disorder

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Monoamine Oxidase Inhibitors (MAOIs)




- Selegiline
- Moclobemide
- Tranylcypromine
- Isocarboxazid
- Phenelzine



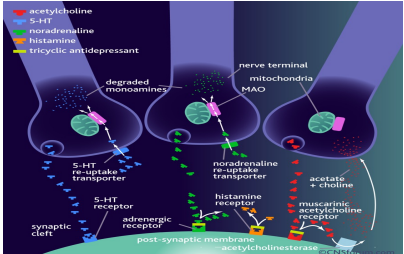
- MAOIs were the first class of antidepressants to be developed.
- MAOIs elevate the levels of norepinephrine, serotonin, and dopamine by inhibiting an enzyme called monoamine oxidase.
- Concerns about interactions with certain foods and numerous drug interactions.
- Overdoses

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Tricyclic Antidepressants (TCAs)




- Treat depression
- Treatment of other mood disorders
- Chronic nerve-related pain
- Reduce bed-wetting
- Manage obsessive compulsive behaviors
- Prevent migraines

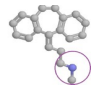


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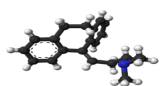
TCAs Adverse Effects and Toxicity



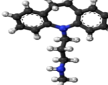
Nortriptyline



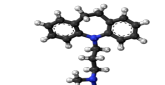
Amitriptyline









Desipramine



Imipramine




Therapeutic Levels:

-  Hypotension
-  Dry Mouth
-  Blurred Vision
-  Drowsiness
-  Confusion
-  Motor incoordination

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Serotonin Modulators Adverse Effects and Toxicity DRUG IMPAIRMENT.COM



- Gastrointestinal (GI) side effects
 - Nausea, diarrhea, dry mouth, constipation and vomiting
- Central Nervous System Adverse Reactions
 - Dizziness (Most Common)
 - Insomnia
 - Restlessness
 - Somnolence (Sleepiness)
 - Paresthesia (Tingling/Pin Prick Feelings)

Trazodone Nefazodone
Vilazodone Vortioxetine

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Selective Serotonin Re-uptake Inhibitors (SSRIs) DRUG IMPAIRMENT.COM




"In 2010, over 24.4 million prescriptions for fluoxetine were filled in the U.S." - "Top 200 Generic Drugs by Units in 2010"

- Sertraline
- Fluvoxamine
- Fluoxetine
- Paroxetine
- Citalopram
- Escitalopram

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SSRIs Adverse Effects and Toxicity DRUG IMPAIRMENT.COM



- Sleep disturbances, weight changes, anxiety, dizziness, xerostomia/dry mouth, headache, nervousness, and motor agitation
- Black Box warning due to possible increased risk of suicidality among pediatric and young adult populations
- Serotonin Syndrome/Toxicity

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Serotonin/Norepinephrine Reuptake inhibitors (SNRIs)



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- Venlafaxine
- Desvenlafaxine
- Duloxetine
- Levomilnacipran
- Milnacipran*

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SNRI Adverse Effects and Toxicity

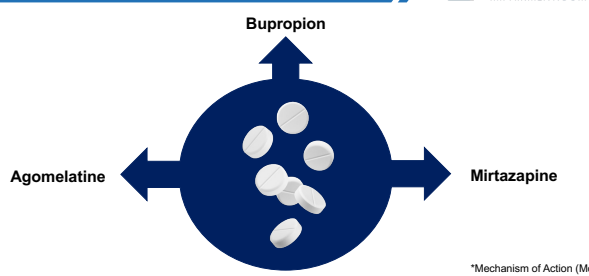


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- Drug-Drug Interactions
- Serotonin Syndrome
 - Anxiety
 - Agitation
 - **High Fever/Sweating***
 - Confusion
 - **Tremors***
 - Restlessness
 - **Lack of Coordination***
 - **Major changes in blood pressure and rapid hear rate***

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Atypical Antidepressants



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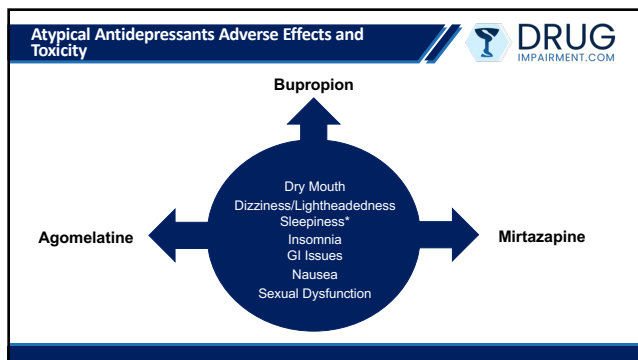
Bupropion

Agomelatine

Mirtazapine

*Mechanism of Action (MoA)

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NMDA Receptor Antagonists DRUG IMPAIRMENT.COM

- Esketamine
- Dextromethorphan/bupropion fixed drug combination
- Sertraline and escitalopram

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NMDA Receptor Antagonists Adverse Effects and Toxicity DRUG IMPAIRMENT.COM

Dizziness/Confusion/
Headache Hypertension Dyspnea

Somnolence Syncope Fatigue

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H-1 Compounds

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H-1 Antihistamines 1 st Gen.	H-1 Antihistamines (Cont.) 1 st Gen.
Diphenhydramine	Phenindamine
Brompheniramine	Cyproheptadine
Chlorpheniramine	
Cyclizine	H-1 Antihistamines 2 nd Gen.
Dimenhydrinate*	Cetirizine
Hydroxyzine	Azelastine
Meclizine	Loratadine
Clemastine	Desloratadine
Doxylamine	Fexofenadine

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H-2 Compounds

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H-2 Antihistamines
Cimetidine
Famotidine*
Ranitidine (removed from market)
Nizatidine
Roxatidine (not available in the USA)

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H-1 Antihistamines (1st Generation) Adverse Effects and Driving

- Drowsiness
- Dizziness and headache
- Rapid heart rate
- Dry mouth, dry eyes
- Low blood pressure
- Difficulty urinating and constipation
- Blurred or double vision
- Mucous thickening in the airways

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H-1 Antihistamines (1st Generation) Adverse Effects and Driving




- Headache
- Cough
- Tiredness
- Sore throat
- Abdominal pain or discomfort
- Nausea or vomiting


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Summary-Antidepressants

- Used in the treatment: Major Depressive Disorder, Obsessive Compulsive Disorder, Generalized Anxiety Disorder, and Post-Traumatic Stress Disorder
- Earlier generations resulted in more adverse effects, drug-drug interactions, drug-food interactions, and drug overdoses
- Drowsiness, confusion, dizziness, insomnia, motor incoordination, and agitation
- We detect Citalopram, Sertraline, Venlafaxine, and Tricyclic Antidepressants most often in our impaired driving case work. However, not all antidepressants may be within the scope of testing.

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Summary-Antihistamines 



- H-1 receptor antihistamines will generally cause adverse effects (dose-dependent)
- These side effects are far more commonly seen in first-generation antihistamines.
 - Sedation/Drowsiness*
- Second-generation antihistamines do not easily cross the blood-brain barrier, and therefore their side effect profile is far more limited.
- In contrast to H-1 receptor antihistamines, H-2 receptor antihistamines do not commonly cause adverse effects except for cimetidine.
- We detect Diphenhydramine, Chlorpheniramine, Dextromethorphan, Hydroxyzine, Doxylamine, Phenylpropranolamine, and Pseudoephedrine most often in our impaired driving case work. However, not all antihistamines may be within the scope of testing.

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THANK YOU

Sabra Jones – Regional Toxicology Liaison, Region 5 sabra@soft-tox.org	National Safety Council's Alcohol, Drugs, and Impairment Division- Immediate Past-Chair	Academy Standards Board- Toxicology Consensus Body-Vice Chair
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