

 **DRUG**
IMPAIRMENT.COM


Pharmacology of Antihistamines and Antidepressants


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



1

Disclosures


 **DRUG**
IMPAIRMENT.COM




I have no relevant financial or nonfinancial relationships to disclose.

2

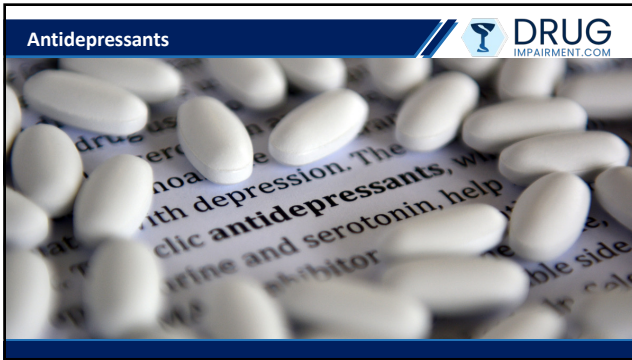
Learning Objectives

 **DRUG**
IMPAIRMENT.COM



- Review the most common antidepressants and antihistamines identified in impaired driving cases
- Review definitions applicable to this lecture
- Understand the pharmacology of antidepressants and antihistamines identified in impaired driving cases
- Learn what neurotransmitters and enzymes are targeted that modulate mood and behavior
- Review the major mechanisms of action for antidepressants and antihistamines

3



4



5

Antihistamines and Antidepressants DRUG IMPAIRMENT.COM

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

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

^aTier II Compounds

D'Orazio AL, Mohr ALA, Chan-Hoackwae A, Harzer C, Huestis MA, Limoges JF, Miles AK, Scamro CE, Kerrigan S, Liddicoat 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/biab064. PMID: 34086916; PMCID: PMC8272528.

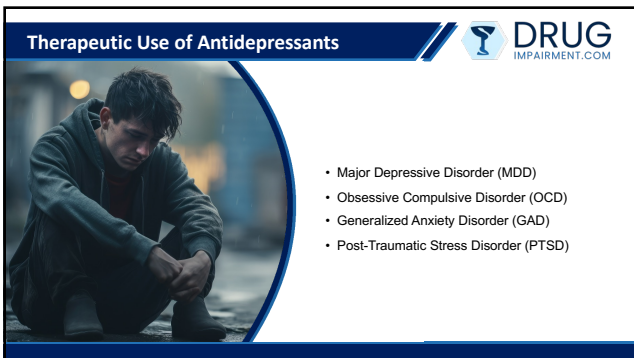
6



7




8



9

Therapeutic Use of Antidepressants DRUG IMPAIRMENT.COM



- Bipolar I
- Chronic Musculoskeletal Pain
- Diabetic Peripheral Neuropathy
- Fibromyalgia

10

Therapeutic Use of Antidepressants DRUG IMPAIRMENT.COM



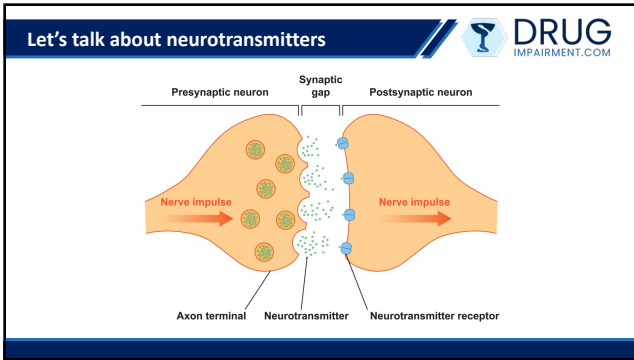
- Panic Disorder
- Premenstrual Dysphoric Disorder
- Social Anxiety Disorder
- Seasonal Affective Disorder

11

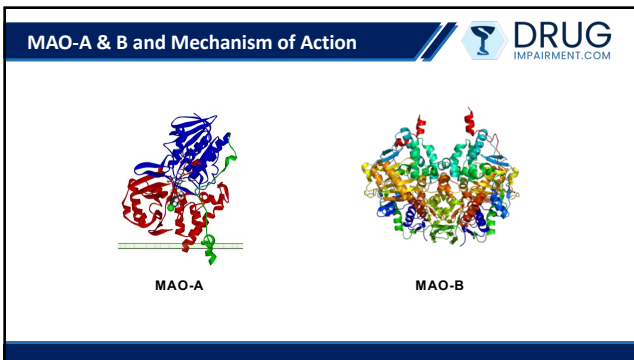
How Antidepressants Work DRUG IMPAIRMENT.COM

Modulating Effects <ul style="list-style-type: none">• Agonist• Antagonist• Reuptake Inhibitor• Inhibiting Biotransformation• Other	of	Neurotransmitters & Their Receptors <ul style="list-style-type: none">• Serotonin (5HT)• Norepinephrine (NE)• Dopamine (DA)
--	----	--

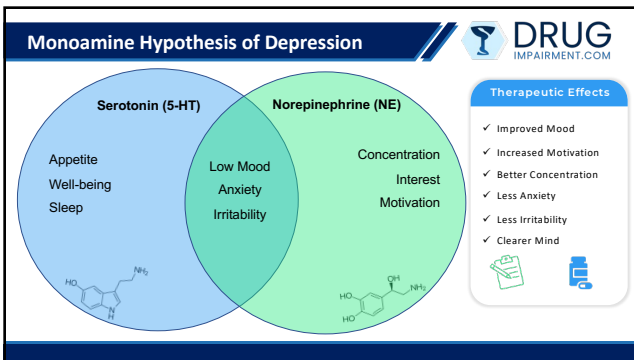
12



13



14



15

Ancillary Targets May Be Affected DRUG IMPAIRMENT.COM

Acetylcholine
 Primary neurotransmitter of the parasympathetic nervous system
 Activates muscles at neuromuscular junction

Diverse actions in CNS:
 Arousal
 Attention
 Memory

Anticholinergic Effects:

1. Parasympathetic Inhibition	6. Cognitive Impairment
2. Mydriasis	7. Psychomotor Slowing
3. Cycloplegia	8. Confusion
4. Tachycardia	9. Delirium
5. Dry Mouth	

16

Ancillary Targets May Be Affected DRUG IMPAIRMENT.COM

Histamine
 Diverse functions in modulating immune response to pathogens

CNS:
 Sleep/Wake Cycle
 Appetite
 Cognition

Anticholinergic Effects:

1. Sedation	3. Dizziness
2. Vasoconstriction	4. Insomnia

*Varies depending upon histamine receptor type (H1 – H4) and ability to cross blood brain barrier

Periphery:
 Vasodilation
 Itch perception
 Bronchoconstriction
 Stomach acid

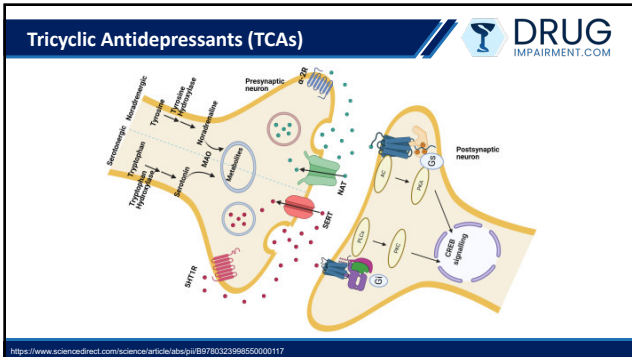
17

Monoamine Oxidase Inhibitors DRUG IMPAIRMENT.COM

Copyright © 2008 Nature Publishing Group
 Nature Reviews | Neuroscience

- Selegiline
- Moclobemide
- Tranylcypromine
- Isocarboxazid
- Phenelzine

18



19

Tricyclic Antidepressants Pharmacology

DRUG IMPAIRMENT.COM

- TCAs increase levels of norepinephrine and serotonin by inhibiting their reuptake, and also block the actions of another neurotransmitter, acetylcholine.
- Affinities for these neurotransmitters differ among various TCAs
- Some TCAs are more effective than others for certain conditions or are more likely than others to cause side effects such as constipation, dry mouth, and sedation.

20

Serotonin Modulators

DRUG IMPAIRMENT.COM

- Nefazodone
- Trazodone
- Vilazodone
- Vortioxetine

21

Selective Serotonin Re-uptake Inhibitors (SSRIs)

DRUG IMPAIRMENT.COM

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

23

SSRI Pharmacology

DRUG IMPAIRMENT.COM

Credit: Blambi/Shutterstock.com

24

Serotonin/Norepinephrine Reuptake inhibitors (SNRIs)

DRUG IMPAIRMENT.COM

- Levomilnacipran
- Venlafaxine
- Milnacipran*
- Desvenlafaxine
- Duloxetine

25

Atypical Antidepressants DRUG IMPAIRMENT.COM

Bupropion

Agomelatine

Mirtazapine

*Mechanism of Action (MoA)

26

Atypical Antidepressants Pharmacology DRUG IMPAIRMENT.COM

Bupropion

Agomelatine

Mirtazapine

- MoA: melatonergic agonist and a 5HT_{2a} antagonist

*Mechanism of Action (MoA)

27

Atypical Antidepressants Pharmacology DRUG IMPAIRMENT.COM

Bupropion

Agomelatine

Mirtazapine

- MoA: Not fully understood, Monamine, Norepinephrine and Dopamine, Nicotinic and Serotonin

*Mechanism of Action (MoA)

28

Atypical Antidepressants Pharmacology DRUG IMPAIRMENT.COM

Bupropion

Agomelatine

Mirtazapine

- MoA: inhibits alpha-2-adrenergic receptors resulting in increase in serotonin and norepinephrine

*Mechanism of Action (MoA)

29

NMDA Receptor Antagonists DRUG IMPAIRMENT.COM

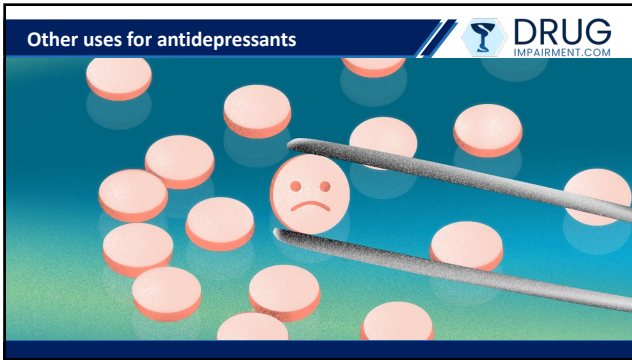
- Esketamine
- Dextromethorphan/bupropion fixed drug combination
- Sertraline and escitalopram

30

NMDA Receptor Antagonists MoA DRUG IMPAIRMENT.COM

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

31



32



33

H-1 Antihistamines DRUG IMPAIRMENT.COM

<ul style="list-style-type: none"> • Allergic rhinitis • Allergic conjunctivitis • Allergic dermatological reaction(s) • Sinusitis • Urticaria • Angioedema • Atopic dermatitis • Bronchitis • Motion sickness • Nausea • Vomiting 	<ul style="list-style-type: none"> • Diphenhydramine¹ • Cetirizine² • Chlorpheniramine¹ • Cyclizine¹ • Dimenhydrinate¹ (incorporates diphenhydramine and a stimulant compound) • Doxylamine¹ • Brompheniramine¹ • Hydroxyzine¹ • Meclizine¹ • Fexofenadine² • Loratadine²
---	---

¹First Generation
²Second Generation

34

H-2 Antihistamines 



- Peptic ulcer
- Acid reflux
- Gastritis
- Zollinger Ellison Syndrome


- Cimetidine
- Famotidine (most common H-2 antihistamine that is used in the United States)
- Ranitidine (removed from market)
- Nizatidine
- Roxatidine (not available in the USA)

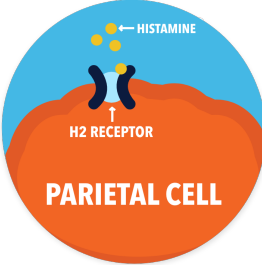
35

Mechanism of Action H1 





36

Mechanism of Action H2 



37



Summary-Antidepressants

- Antidepressants are a type of medicine used to treat clinical depression. They can also be used to treat a number of other conditions, including: obsessive compulsive disorder (OCD) generalized anxiety disorder, post-traumatic stress disorder (PTSD)
- Antidepressants target certain neurotransmitters and enzymes that modulate mood and behavior
 - Monoamine Oxidase
 - Serotonin, Norepinephrine, or both
 - Dopamine
- Antidepressants modulate NE, DA, and 5HT in a several ways, such as inhibiting reuptake, inhibiting enzymes that terminate their action, and a variety of receptor-mediated effects.

38

Summary-Antidepressants

- Antihistamine drugs that bind to H-1 receptors are generally used to treat allergies and allergic rhinitis. Drugs that bind to H-2 receptors can treat upper gastrointestinal conditions that are caused by excessive stomach acid.
- H-1 Antihistamines are most commonly used by people who have allergic reactions to pollen and other allergens.
- H-2 Antihistamines are used to treat Peptic ulcer, Acid reflux, Gastritis, and Zollinger Ellison syndrome.
- 1st generation H-1 antihistamines more easily cross the blood-brain barrier into the central nervous system where adverse or intended effects like drowsiness can occur, whereas 2nd generation H-1 antihistamines do not

39



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



40
