Psychopharmacology Update 2023: A Comprehensive Look at the Neuroscience of Antidepressant Medications- Psychiatric Disorders Session I

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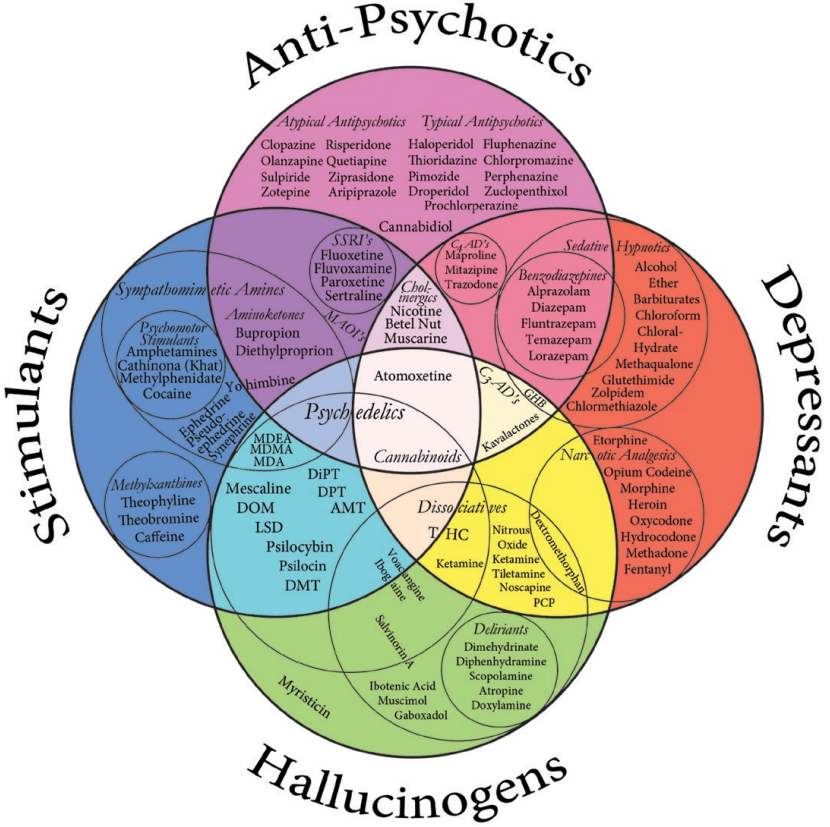
Today's Psychopharmacology – Can It Rescue A Drug Damaged Brain?



Basic points we'll cover today:

- **What's New In Psychopharmacology**
- **Updated Antidepressant Drug Drug Interactions**
- **Neurobiology of Depression**
- **Antidepressants**
- **Ketamine Psychopharmacology**
- **Antipsychotics**
- **ADHD Psychopharmacology and Medications**
- **SUDS/Trauma Psychopharmacology**
- **CBD and the Treatment of Mental Disorders**
- **Questions**

The Future of Behavioral Medicine – Digital Phenotyping?

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MindStrong

- Mindstrong has developed and patented a biomarker panel that measures brain function from interaction patterns captured passively and continuously from human-computer interfaces found in ubiquitous mobile technology.
- "The science in your smartphone"
- **How you use your smartphone**—typing, swiping, scrolling—is a new way to measure things like your mental health symptoms.
- **Passive & objective**. Measure your mental health symptoms automatically with your smartphone.
- **Personalized care.** Your measurements are shared with your clinical team so they can provide more personalized care.
- **Improving through information**. By adding these measurements to your care plan, you can easily track your progress over time.

https://mindstrong.com/our-services/

What's New in Psychopharmacology?

- **Aduhelm (aducanumab-avwa)** injection to treat **Alzheimer's disease.** This drug is the first therapy for Alzheimer's that targets the fundamental disease pathophysiology. Granted accelerated approval by the FDA. June 2021.
- **Azstarys (serdexmethylphenidate and dexmethylphenidate):** CNS stimulant capsule to treat **ADHD** in people 6 and older. June 2021.
- **Auvelity (Dextromethorphan and bupropion) March 2023** MDD
- **Caplyta (lumateperone):** antipsychotic approved to treat type 1 or 2 bipolar depression. *CAPLYTA is the only FDA-approved treatment for depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults as monotherapy and as adjunctive therapy with lithium or valproate*. December 2021.
- **Kloxxado (naloxone hydrochloride)** nasal spray to treat **opioid overdose** was approved in April 2021. 8 mg is a higher dose than Narcan (4 mg)
- **Lybalvi (olanzapine and samidorphan):** tablet to treat **schizophrenia and bipolar 1 disorder.** Antipsychotic + opioid antagonist. June 2021.
- **Nurtec ODT** (rimegepant) orally disintegrating tablets, originally approved in 2020 to treat acute migraine, received approval in 2021 to help reduce the frequency of **migraine attacks** in patients with episodic migraines.
- **Qelbree** (viloxazine) capsules to treat **attention deficit hyperactivity disorder (ADHD)** in patients aged 6 to 18. Qelbree is one of a few approved nonstimulant medications for **ADHD**. Selective norepinephrine reuptake inhibitor. April 2021.
- **Qulipta** (atogepant) tablets to help reduce the frequency of **migraine attacks** in patients with **episodic migraines**. CGRP receptor antagonist. September 2021.
- **Quviviq (daridorexant):** approved to treat insomnia. Daridorexant is a dual orexin receptor antagonist that blocks the binding of neuropeptides orexins, which is connected to sleep/wake regulation. The drug is thought to turn down overactive wakefulness, as opposed to sedating the brain. January 2022.
- **Zimhi (naloxone hydrochloride)** injection to treat **opioid overdose** was approved as a single-shot injection in October 2021. Higher dose of naloxone – 5 mg/0.5 mL
- https://www.fda.gov/media/155227/download

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Antidepressants

Agomelatine - A Possible New Type of Anti-Depressant

- Acts on Melatonegic MT_1 , MT_2 5-HT_{2B} and 5-HT_{2C} receptors
- 5-HT receptors are found in platelets, the linings of heart values, and blood vessels of the cardiovascular system.
- Believed to regulate pituitary release of melatonin activity
- Reduces sedation as a result of retina activity
- Increases norepinephrine release
- Increase dopamine release
- Depression has dysfunctional releases of NE and DA in prefrontal cortex which creates learned helplessness and chronic stress{anxiety}
- Medication stabilizes melatonin in midbrain and NE/DA in PFC
- Offsets jetlag effects

Spravato™ (Esketamine Nasal Spray) CIII

- **SPRAVATO™ is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults**
- **Nasal Spray: 28 mg of esketamine per device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine.**
- **Adults Induction Phase Day 1 starting dose: 56 mg**
- **Weeks 1 to 4:**
- **Administer twice per week Subsequent doses: 56 mg or 84 mg**

Maintenance Phase

Weeks 5 to 8:

- **Administer once weekly 56mg or 84mg**

Week 9 and after

Administer every 2 weeks 56 mg or 84 mg


100
mg/mL
EPIDIOLEX®
(cannabidiol) 100 mg/mL
Oral Solution
CAUTION: New Drug – Limited by Federal
(or United States) Law to
Investigational Use

Brexanolone (Zulresso)

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- **The U.S. Food and Drug Administration approved Zulresso (brexanolone) injection for intravenous (IV) use for the treatment of postpartum depression (PPD) in adult women. This is the first drug approved by the FDA specifically for PPD.**
- **Zulresso will be available only through a restricted program called the Zulresso REMS Program that requires the drug be administered by a health care provider in a certified health care facility. The REMS requires that patients be enrolled in the program prior to administration of the drug. Zulresso is administered as a continuous IV infusion over a total of 60 hours (2.5 days). Because of the risk of serious harm due to the sudden loss of consciousness, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring (monitors oxygen levels in the blood). While receiving the infusion, patients must be accompanied during interactions with their child(ren). The need for these steps is addressed in a Boxed Warning in the drug's prescribing information. Patients will be counseled on the risks of Zulresso treatment and instructed that they must be monitored for these effects at a health care facility for the entire 60 hours of infusion. Patients should not drive, operate machinery, or do other dangerous activities until feelings of sleepiness from the treatment have completely gone away.**

Efficacy and Tolerability of Combination Treatments for Major Depression: Antidepressants plus Second-Generation Antipsychotics vs. Esketamine vs. Lithium

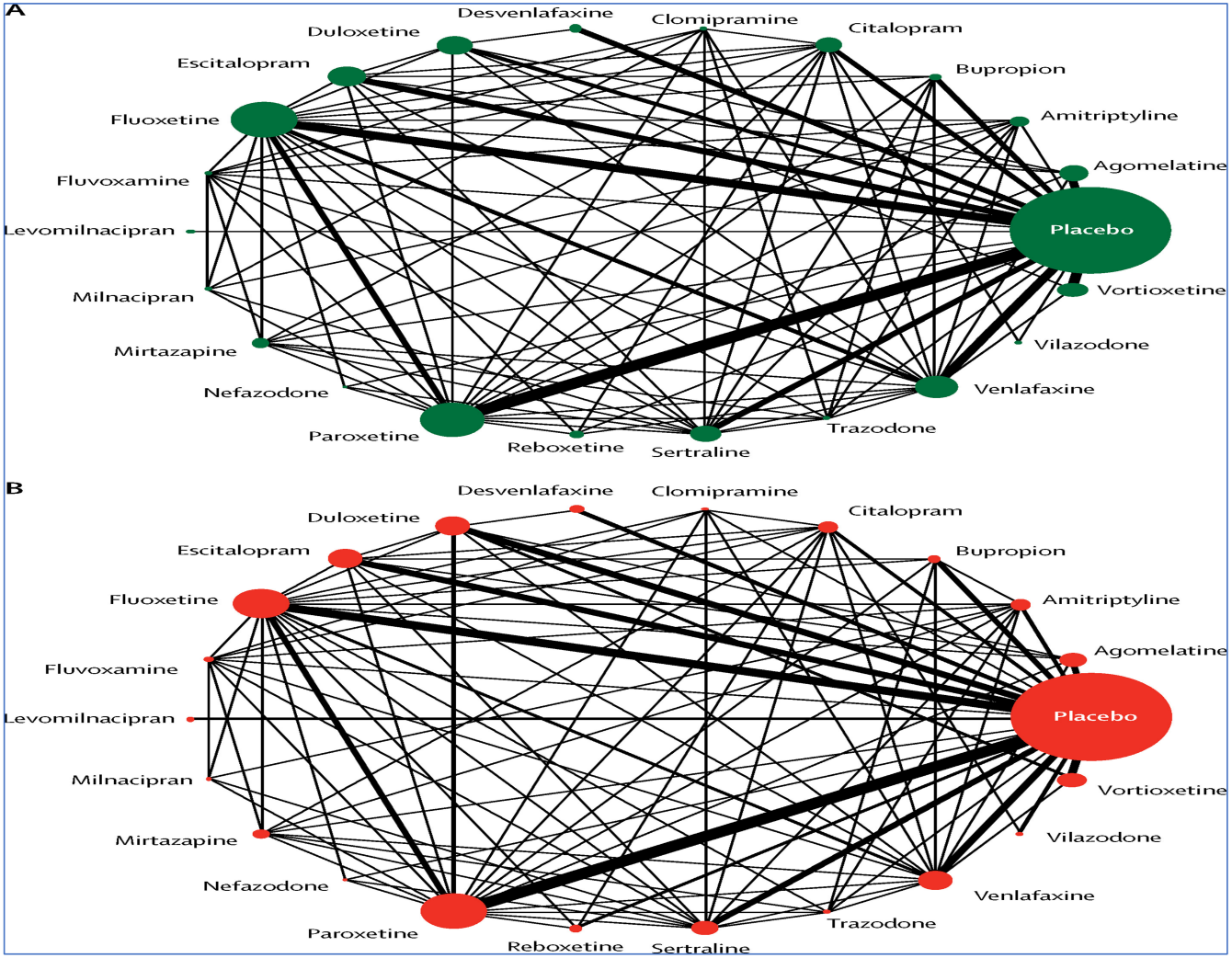
Gustavo H. Vazquez, Anees Bahji, Juan Undurraga, Leonardo Tondo, Ross J. Baldessarini

Journal of Psychopharmacology
Volume 35, Issue 8, Pages 890-900 (July 2021)
DOI: 10.1177/02698811211013579

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Andrea Cipriani, MD, Prof Toshi A Furukawa, MD, Georgia Salanti, PhD, Anna Chaimani, PhD, Lauren Z Atkinson, MSc, Yusuke Ogawa, MD, Prof Stefan Leucht, MD, Henricus G Ruhe, PhD, Erick H Turner, MD, Prof Julian P T Higgins, PhD, Prof Matthias Egger, PhD, Nozomi Takeshima, MD, Yu Hayasaka, MD, Hissei Imai, MD, Kiyomi Shinohara, MD, Aran Tajika, MD, Prof John P A Ioannidis, MD, Prof John R Geddes, MD

The Lancet
Volume 391, Issue 10128, Pages 1357-1366 (April 2018)
DOI: 10.1016/S0140-6736(17)32802-7



The Lancet
Volume 391, Issue 10128, Pages 1357-1366 (April 2018)
DOI: 10.1016/S0140-6736(17)32802-7

The most effective antidepressants for adults revealed in major review- 2018

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- **Researchers ranked drugs by effectiveness and acceptability after eight weeks of treatment. Several drugs were more effective and were stopped by fewer people than others:**
- **Escitalopram (Lexapro)**
- **Paroxetine (Paxil)**
- **Sertraline (Zoloft)**
- **Agomelatine (Vodoxan Europe and Australia - not in US.. yet!!!)**
- **Mirtazapine (Remeron and Remeron Soltab)**

A Cipriani, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. The Lancet. Feb 2018.

The most effective antidepressants for adults revealed in major review- 2018

A major review of 522 antidepressant trials found that all of the 21 drugs studied performed better than placebo, in short-term trials measuring response to treatment. However, effectiveness varied widely.

The review provides new evidence which may help people decide which antidepressant to choose first-line for moderate to severe depression. However, it did not assess antidepressants compared to other treatments such as cognitive behavioural therapy, or treatments in combination. Though there are some concerns over items not reported by individual trials, this review is likely to be reliable. It is extensive, included only placebo controlled double blind trials and searched successfully for unpublished trials.

A Cipriani, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. The Lancet. Feb 2018.

Updated Antidepressant Drug to Drug Interactions

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Drug To Drug Interactions

NSAIDs (non-steroidal anti- inflammatory drugs): Try to avoid SSRI's – but if no suitable alternatives can be identified, offer gastro-protective medicines (e.g. omeprazole) together with the SSRI5,11. Consider mirtazapine, moclobemide or trazodone

Warfarin or heparin: Do not normally offer SSRI's. Consider mirtazapine.

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Drug To Drug Interactions

Theophylline or methadone: Offer citalopram or sertraline (sertraline may increase methadone levels).

Clozapine: Consider citalopram or sertraline (small to modest increases in plasma clozapine levels may occur, particularly with sertraline)

'Triptan' drugs for migraine: Do not offer SSRI's, offer mirtazapine or trazodone.

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Drug To Drug Interactions

Aspirin: Use SSRI's with caution, if no suitable alternatives can be identified, offer gastro-protective medicines together with the SSRI. Consider trazodone when aspirin is used as a single agent, alternatively consider mirtazapine

Monoamine-oxidase B inhibitors, e.g. selegiline or rasagiline: inhibitors, e.g. selegiline or rasagiline: Do not normally offer SSRI's, offer mirtazapine or trazodone

Antidepressants and Opioid DDIs

Some selective serotonin reuptake inhibitors block the metabolism of opioids.
This may reduce the concentrations and analgesic effect of some opioids such as codeine and tramadol,and increase the concentrations and risk of adverse effects of other opioids such as methadone.
Some opioids such as tramadol, dextromethorphan and tapentadol increase serotonergic activity. Fentanyl and methadone also do this but to a lesser extent.
Fluoxetine and irreversible monoamine oxidase inhibitors – tranylcypromine and phenelzine – have prolonged actions and may interact for weeks after they have been discontinued.

Antidepressants and Opioid DDIs

Tramadol's main metabolite is an opioid agonist, it is remarkably similar in structure to venlafaxine, with similar inhibitory effects on noradrenaline and serotonin reuptake.

The combination of tramadol with an antidepressant is by far the most common serotonergic drug–drug interaction.

Fentanyl is a high-potency opioid agonist with no effect on serotonin reuptake and low affinity (relative to opioid receptor affinity) for postsynaptic serotonin receptors (5-HT1A and 5-HT2A). (Unless high doses are taken which increased risk of respiratory depression.)

Methadone has been associated with serotonin toxicity when given with other serotonergic medicines but the risk appears low.

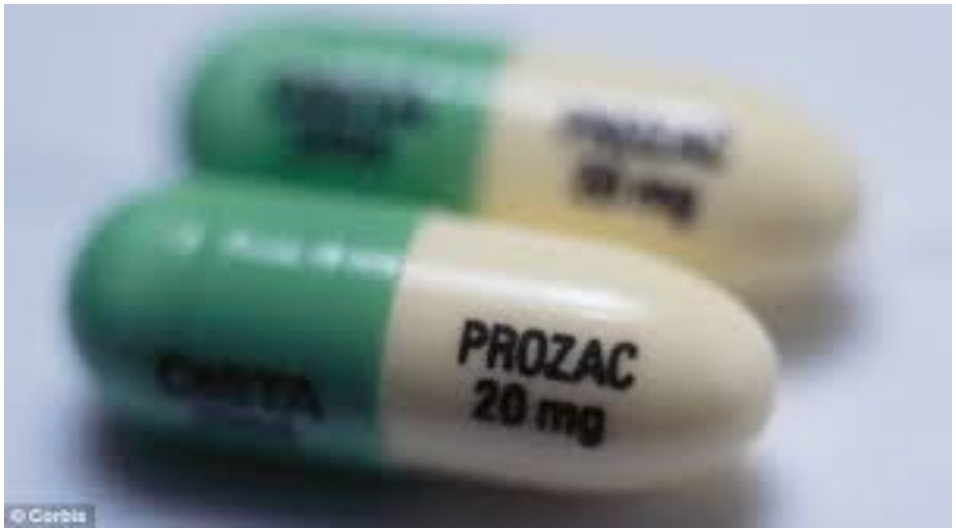
Dextromethorphan and Antidepressant DDI

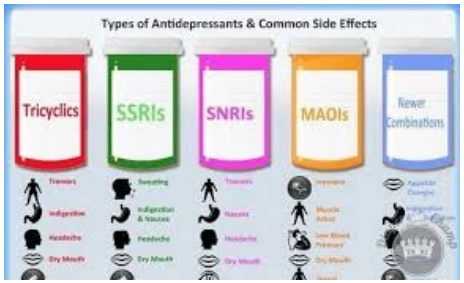
It is especially important that you do not use any medicine with dextromethorphan if you take a selective serotonin reuptake inhibitor (SSRI) such as Prozac (fluoxetine), Zoloft (sertraline), or Lexapro(escitalopram).

The combination can cause a serious interaction called serotonin syndrome.

Why Does the Current Antidepressant Pharmacotherapy Not Work for Over 45% of Patients?

The Neurobiology of Depression





Neurotransmitter Deficiency Hypotheses of Depression

- Serotonin
- Norepinephrine
- Dopamine
- Gamma-aminobutyric acid (GABA)
- Brain-derived neurotrophic factor (BDNF)
- Somatostatin

Low Serotonin Not Responsible for Depression????

- The new umbrella review -- an overview of existing meta-analyses and systematic reviews -- published in *Molecular Psychiatry*, suggests that depression is not likely caused by a chemical imbalance, and calls into question what antidepressants do.
- Most antidepressants are selective serotonin reuptake inhibitors (SSRIs), which were originally said to work by correcting abnormally low serotonin levels.
- There is no other accepted pharmacological mechanism by which antidepressants affect the symptoms of depression.
- Joanna Moncrieff, Ruth E. Cooper, Tom Stockmann, Simone Amendola, Michael P. Hengartner, Mark A. Horowitz. **The serotonin theory of depression: a systematic umbrella review of the evidence**. *Molecular Psychiatry*, 2022; DOI: 10.1038/s41380-022-01661-0

Updated Serotonin Deficiency Theory for Depression

- Surveys suggest that 80% or more of the general public now believe it is established that depression is caused by a “chemical imbalance” ;
- Despite the fact that the serotonin theory of depression has been so influential, no comprehensive review has yet synthesized the relevant evidence.
- Two meta-analyses of a total of 19 studies of 5-HIAA in CSF (seven studies were included in both) found no evidence of an association between 5-HIAA concentrations and depression.

- Moncrieff, J., Cooper, R.E., Stockmann, T. *et al.* The serotonin theory of depression: a systematic umbrella review of the evidence. *Mol Psychiatry* (2022). https://doi.org/10.1038/s41380-022-01661-0

Low Serotonin Not Responsible for Depression????

- "One interesting aspect in the studies we examined was how strong an effect adverse life events played in depression, suggesting low mood is a response to people's lives and cannot be boiled down to a simple chemical equation."
- "Our view is that patients should not be told that depression is caused by low serotonin or by a chemical imbalance, and they should not be led to believe that antidepressants work by targeting these unproven abnormalities.
- We do not understand what antidepressants are doing to the brain exactly, and giving people this sort of misinformation prevents them from making an informed decision about whether to take antidepressants or not."
- Joanna Moncrieff, Ruth E. Cooper, Tom Stockmann, Simone Amendola, Michael P. Hengartner, Mark A. Horowitz. **The serotonin theory of depression: a systematic umbrella review of the evidence**. *Molecular Psychiatry*, 2022; DOI: 10.1038/s41380-022-01661-0

Low Serotonin Not Responsible for Depression????

- The researchers say their findings are important as studies show that as many as 85-90% of the public believes that depression is caused by low serotonin or a chemical imbalance.
- A growing number of scientists and professional bodies are recognizing the chemical imbalance framing as an over-simplification.
- While the study did not review the efficacy of antidepressants, the authors encourage further research and advice into treatments that might focus instead on managing stressful or traumatic events in people's lives, such as with psychotherapy, alongside other practices such as exercise or mindfulness, or addressing underlying contributors such as poverty, stress and loneliness.
- Joanna Moncrieff, Ruth E. Cooper, Tom Stockmann, Simone Amendola, Michael P. Hengartner, Mark A. Horowitz. **The serotonin theory of depression: a systematic umbrella review of the evidence**. *Molecular Psychiatry*, 2022; DOI: 10.1038/s41380-022-01661-0

Findings of Review of Literature

- Fourteen different serotonin receptors have been identified, with most research on depression focusing on the 5-HT1A receptor;
- If depression is the result of reduced serotonin activity caused by abnormalities in the 5-HT1A receptor, people with depression would be expected to show increased activity of 5-HT1A receptors compared to those without;
- The majority of results across the two analyses suggested either no difference in 5-HT1A receptors between people with depression and controls, or a lower level of these inhibitory receptors, which would imply higher concentrations or activity of serotonin in people with depression.
- Moncrieff, J., Cooper, R.E., Stockmann, T. *et al.* The serotonin theory of depression: a systematic umbrella review of the evidence. *Mol Psychiatry* (2022). https://doi.org/10.1038/s41380-022-01661-0

Findings of Review of Literature

- Although changes in serotonin transport protein(SERT) may be a marker for other abnormalities, if depression is caused by low serotonin availability or activity, and if SERT is the origin of that deficit, then the amount or activity of SERT would be expected to be higher in people with depression compared to those without;
- The studies would suggest that depression is associated with higher concentrations or activity of serotonin
- This review suggests that the huge research effort based on the serotonin hypothesis has not produced convincing evidence of a biochemical basis to depression.
- This is consistent with research on many other biological markers. We suggest it is time to acknowledge that the serotonin theory of depression is not empirically substantiated.
- Moncrieff, J., Cooper, R.E., Stockmann, T. *et al.* The serotonin theory of depression: a systematic umbrella review of the evidence. *Mol Psychiatry* (2022). https://doi.org/10.1038/s41380-022-01661-0

Reaction to the Review

- **“**The authors justify the need for such a review by saying that it is a public misconception that depression is caused by low brain serotonin.
- The main misconception is, however, that depression is a single disease with a single biochemical deficit.
- Today, it is largely accepted that depression is a heterogeneous disorder with potentially multiple underlying causes.
- The review aims to uncover existing evidence for a serotonergic deficit, but the studies included in the review use methodologies that only generate proxies for the real question which is if synaptic 5-HT concentration and release are altered in (subsets) of patients with major depression.”
- **Prof Gitte Moos Knudsen, Professor of Neurobiology and Chair of Department of Neurology and Neurobiology Research Unit, Copenhagen University Hospital, Denmark**

Neurotransmitter Excess Hypotheses of Depression

Acetylcholine

Substance P

Corticotrophin Releasing Hormone (CRH)

1. Neural Circuitry of Depression

Mayberg's model limbic-cortical dysregulation (1997)

Some mechanisms involving limbic structures (Krishnan and Nestler, 2008)

Specific role of the subgenual Anterior Cingulate Cortex (later, Drevets et al., 2008))

- **Implication of several brain regions and circuits regulating emotion, reward and executive functions:**
- **Structural findings in post-mortem studies & neuroimaging: ↓ grey matter & ↓ glial density in PFC & hippocampus**
  - **-> cognitive impairments in depression**
- **BUT: findings are not consistent, common problem: co-morbid diagnosis, medication history -> limited evidence for cause-effect relation**
- **Functional: activity in amygdala and subgenual cingulate cortex correlated with dysphoric emotions**

- **!! Caution with simplistic "localization of function" approach to examine limbic structures**

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2. The Role of Monoamines

- **« Monoamine Hypothesis »**

- **Decreased monoamine function in the brain**
  - **Monoamine neurotransmitters and neuromodulators include serotonin, dopamine, norepinephrine and epinephrine**
- **Antidepressant effects of iproniazid (irreversible and nonselective monoamine oxidase inhibitor (MAOI), discovered in the 1950, originally used as medication against tuberculosis) & imipramine (first tricyclic antidepressant, originally meant to be used as a neuroleptic to treat schizophrenia)**
- **Modern antidepressants = designed to increase monoamine transmission acutely by:**
  - **Inhibiting neuronal reuptake (SSRIs (selective serotonin reuptake inhibitors))**
  - **Inhibiting degradation (monoamine oxidase inhibitors (MAOI) -> tranylcypromine (Jatrosom))**

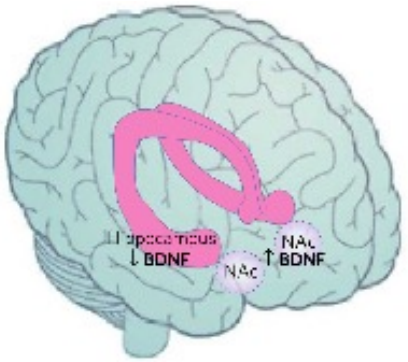
3. Neurotrophins and Neurogenesis

- **Neurotrophic factors: neurodevelopmentally expressed growth factors that also regulate plasticity within adult brain**

« BDNF hypothesis »

- **Brain-derived Neurotrophic Factor = abundantly expressed in adult limbic structures**
- **Preclinical studies show**
  - **Several forms of stress reduce BDNF-mediated signaling in the hippocampus**
  - **Chronic treatment with antidepressants increase BDNF-mediated signaling**

- **Post-mortem data from depressed humans**
  - **Decrease in the amount of BDNF in the hippocampus**
  - **Increase in the NAc**



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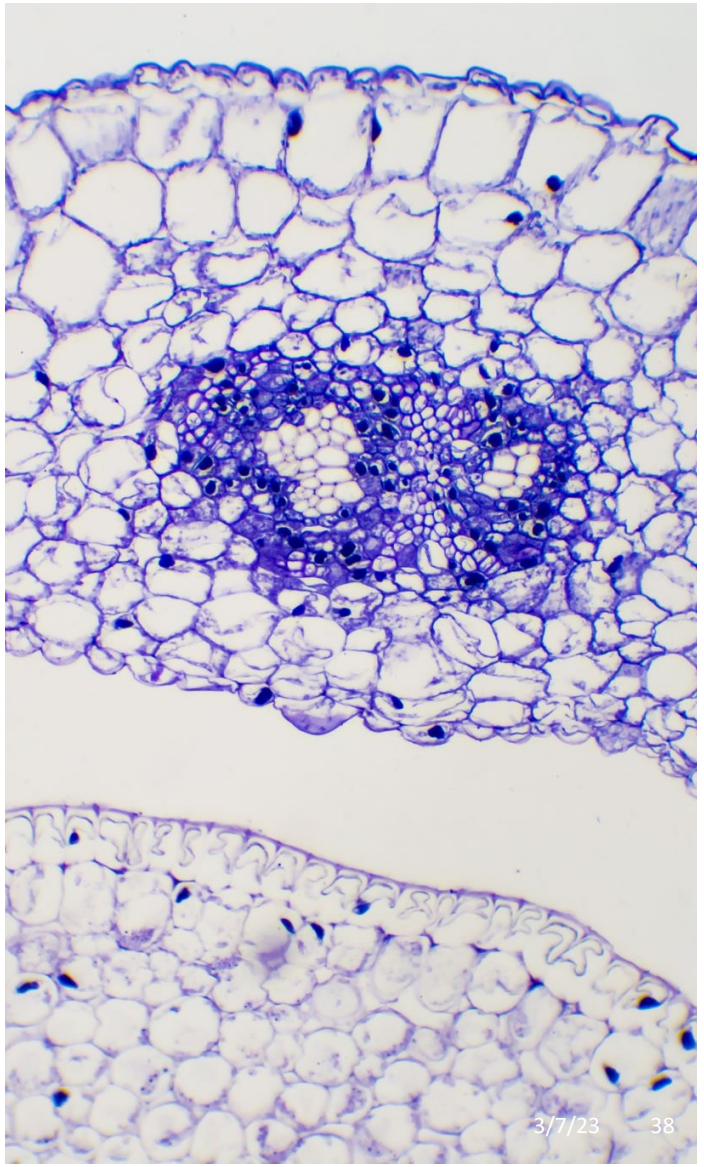
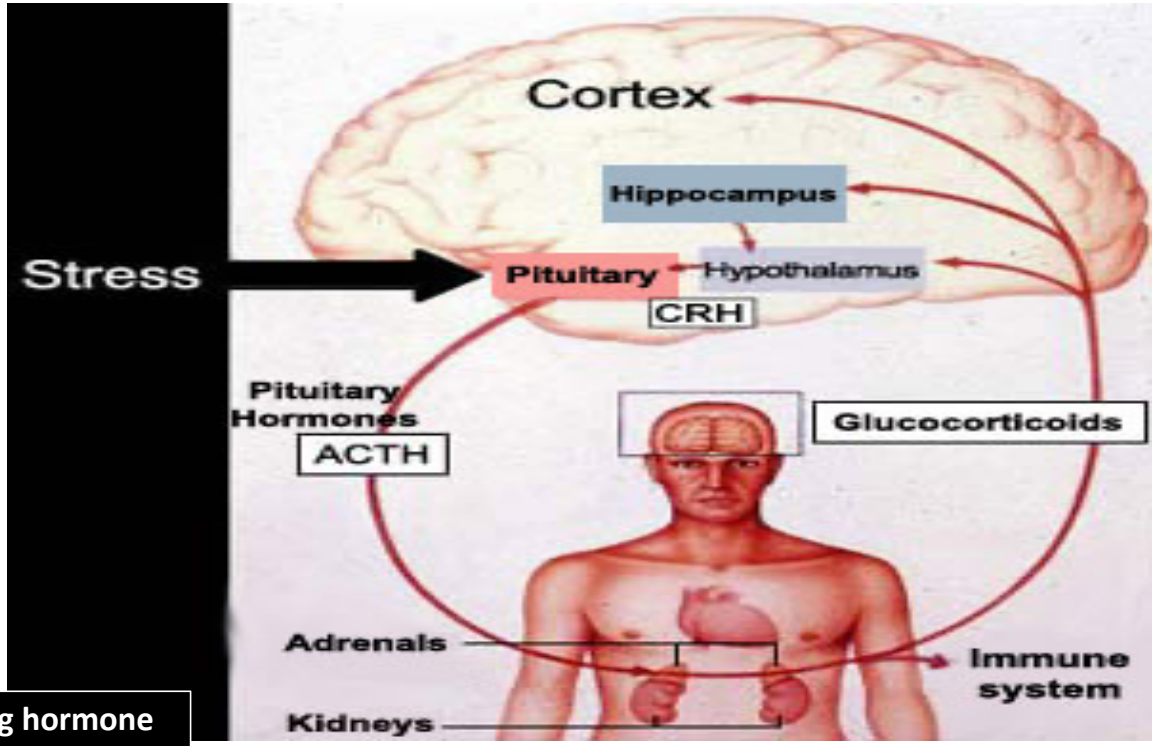
4. Neuroendocrine and Neuroimmune Interactions

- **Hypothalamic-pituitary-adrenal (HPA) axis dysfunction**
- **“Cytokine hypothesis”**



(a) Hypothalamic-pituitary-adrenal (HPA) axis dysfunction



CRH = Corticotropin-releasing hormone
ACTH = adrenocorticotropic hormone

Dysfunctional Hypothalamic-pituitary-adrenal (HPA) axis

- Chronic administration of glucocorticoids can lead to depression-like symptoms in rodents
- Excess in glucocorticoids can reduce subgranular zone proliferation (one of two major zones of adult neurogenesis) and produce atrophic changes in hippocampal subregions
  - this could lead to hippocampal volume reduction seen in depression
- Hypercortisolemia is manifest at many levels in depressed patients

- **Early adverse experiences** play a preeminent role in the development of mood and anxiety disorders
  - Association mediated by **corticotropin-releasing factor (CRF)** system?
  - Evidence from preclinical studies (rats, non-human primates): increased CRF may be the persisting neurobiological consequence of stress early in development

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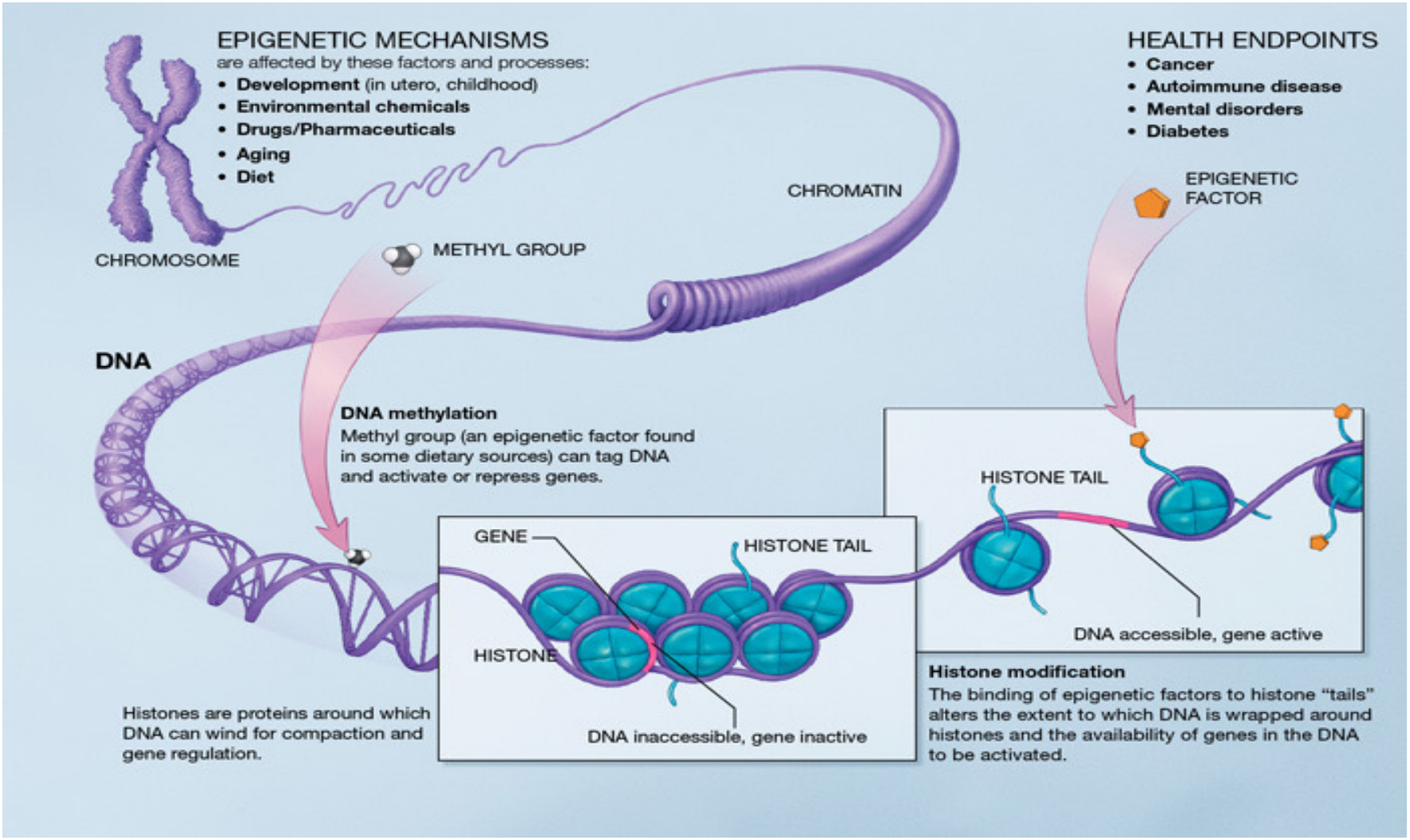
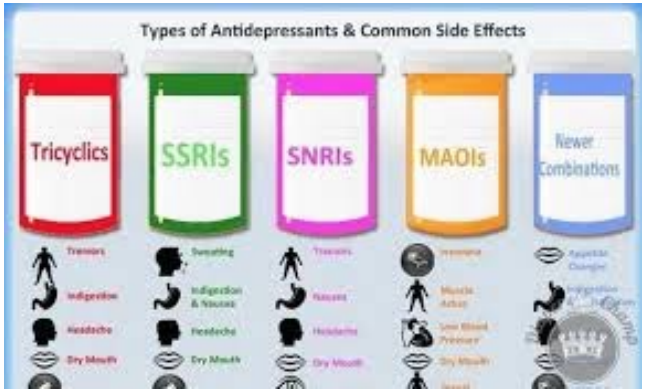
5. Epigenetic Mechanisms

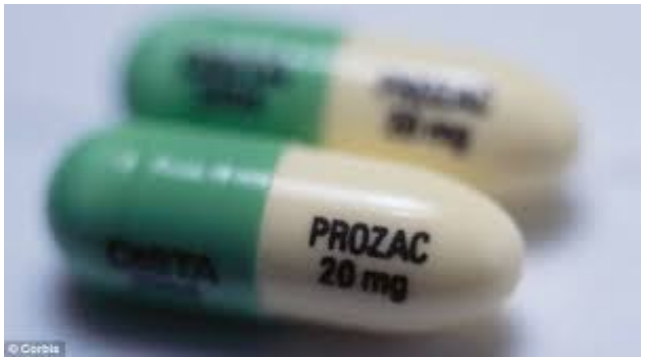
- **Epigenetics** -> study of heritable changes in gene expression or cellular phenotype, caused by mechanisms other than changes in the underlying DNA sequence
  - **E.g. DNA methylation and histone modification -> alteration of gene expression without altering the underlying DNA sequence**
- **Epigenetic changes** -> mechanisms by which environmental experiences can modify gene function in absence of DNA sequence changes
  - **-> might help to explain largely inconsistent genetic association studies of depression**

- **Epigenetic modifications in the pathophysiology of depression ?**
  - **Covalent changes to DNA (e.g. DNA methylation)**
  - **Post-translational modifications of histone N-terminal trials (e.g. acetylation and methylation)**
  - **Non transcriptional gene-silencing mechanisms (e.g. RNAs)**


EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
HISTONE TAIL
DNA accessible, gene active
DNA inaccessible, gene inactive
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Antidepressant Medication Classifications





Purpose

Antidepressant medications are used to treat a variety of mental health conditions including depression, bipolar illness, and anxiety disorders.

Most antidepressants must be taken for a period of 3 to 4 weeks to begin to reduce or take away the symptoms of depression, but a full therapeutic effect may not be present for several months.

Antidepressant Classifications

SSRIs — Selective Serotonin Reuptake Inhibitors	
citalopram	Celexa
escitalopram	Lexapro
fluoxetine	Prozac, Prozac Weekly, Sarafem
fluvoxamine	Luvox
paroxetine	Paxil, Paxil CR
sertraline	Zoloft
vilazodone	Viibryd
vortioxetine (Brintellix) 2016-Renamed Trintellix	

Antidepressant Classifications

Tricyclics & quatracyclics	amitriptyline	Elavil
	amoxapine	Asendin
	clomipramine	Anafranil
	desipramine	Nopramin
	doxepin	Sinequan
	imipramine	Tofranil
	maprotiline	Ludiomil
	nortriptyline	Aventyl, Pamelor
	protriptyline	Vivactil
	trimipramine	Surmontil

Antidepressant Classifications

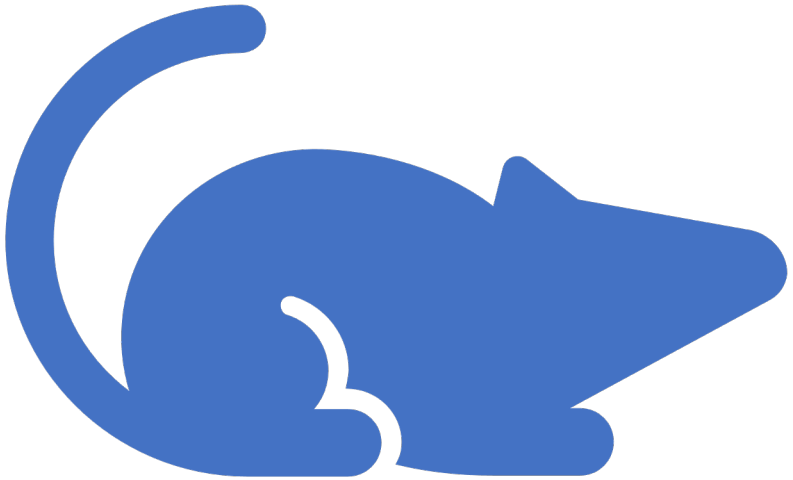
SNRIs — Serotonin Norepinephrine Reuptake Inhibitors	**desvenlafaxine**	**Pristiq**
	duloxetine	**Cymbalta**
	levomilnacipran	**Fetzima**
	venlafaxine	**Effexor, Effexor ER**

Antidepressant Classifications

Monoamine Oxidase (MAO) Inhibitors	**isocarboxazid**	**Marplan**
	phenelzine	**Nardil**
	Selegiline	**Generic**
	transdermal patch	**EMSAM**
	tranylcypromine	**Parnate**

In the Pipeline

- **ALKS 5461-combination of Suboxone and Samidorphan**
- **“Triple Reuptake Inhibitors” a.k.a. SNDRIs** (Serotonin-Norepinephrine-Dopamine Reuptake Inhibitors)
- **Ketamine nasal spray - approved 2019**
- **Psilocybin Mushrooms**



Clinical Pearls Series: Ketamine

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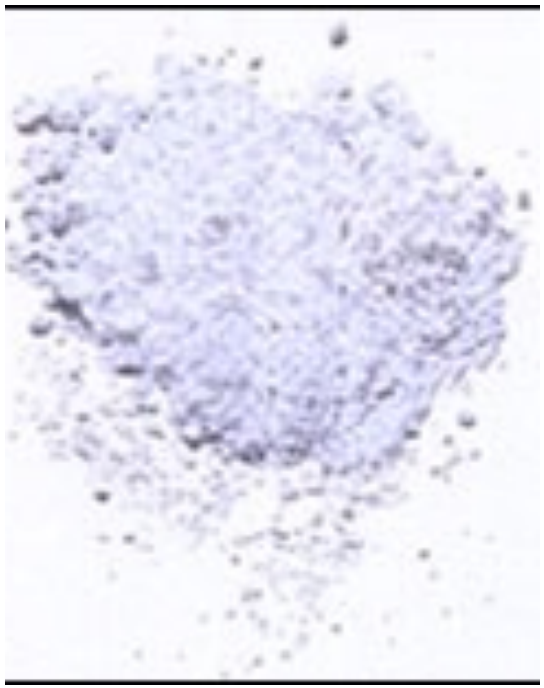
Ketamine

- Today, Ketamine is considered a threat due to its potentially addictive and harmful side effects.
- In the early 1990's Ketamine became a popular drug of abuse among the rave and techno scene due to its hallucinogenic properties.



Ketamine

- **Ketamine appears as a white or off-white powder, resembling cocaine and crystal methamphetamine.**
- **It is also available in liquid form that is commonly injected intramuscularly. Because it has no odor or color, Ketamine in liquid form closely resembles water.**

Ketamine and the Treatment of Resistant/refractory Depression

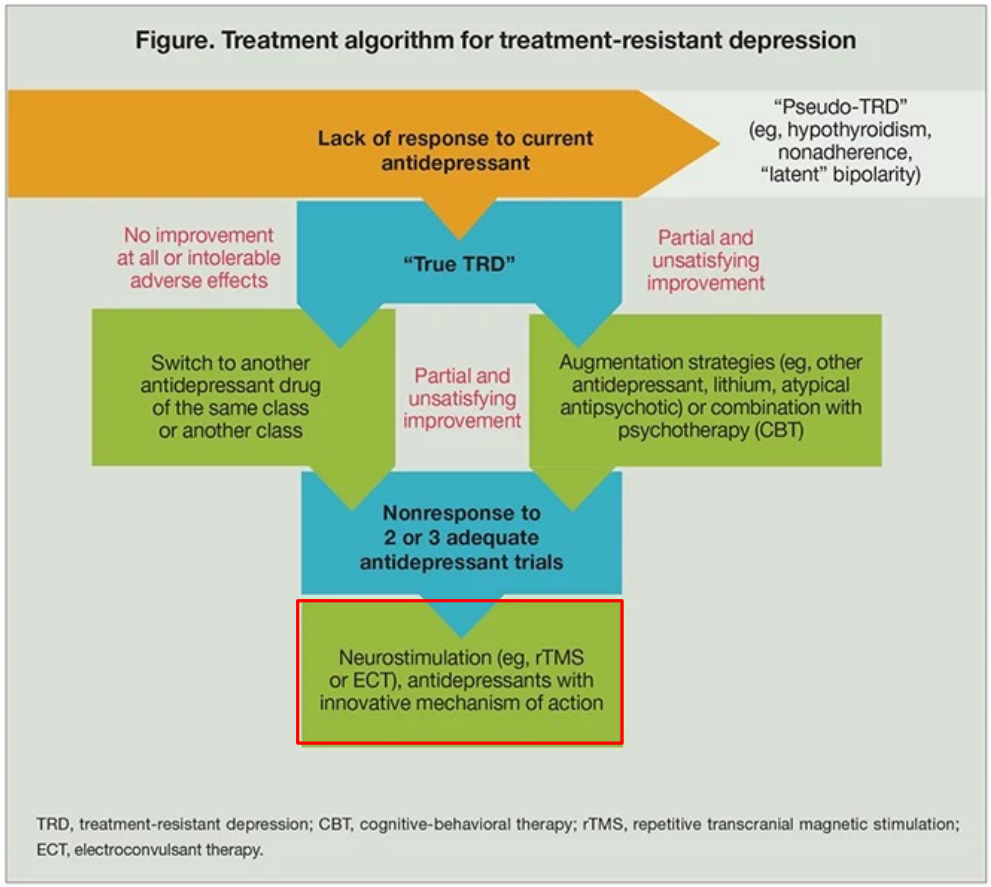
What is Refractory Depression?

- Major Depressive Disorder
- Refractory = Treatment resistant
- Once 2 adequate antidepressant pharmacotherapy trials have been unsuccessful, the illness is termed treatment-resistant depression (TRD)

Incidence of TREATMENT RESISTANT DEPRESSION (TRD)

- **15.7 million** U.S. adults aged 18 and older had at least one major depressive episode during the past year (6.7% of all U.S. adults)
- **TRD occurs in 10-30% of patients with Major Depressive Disorder (MDD)**
- TRD patients have double the hospitalization rate and more outpatient and emergency room (ER) visits compared with non-TRD (nTRD) and non-MDD patients from the general population

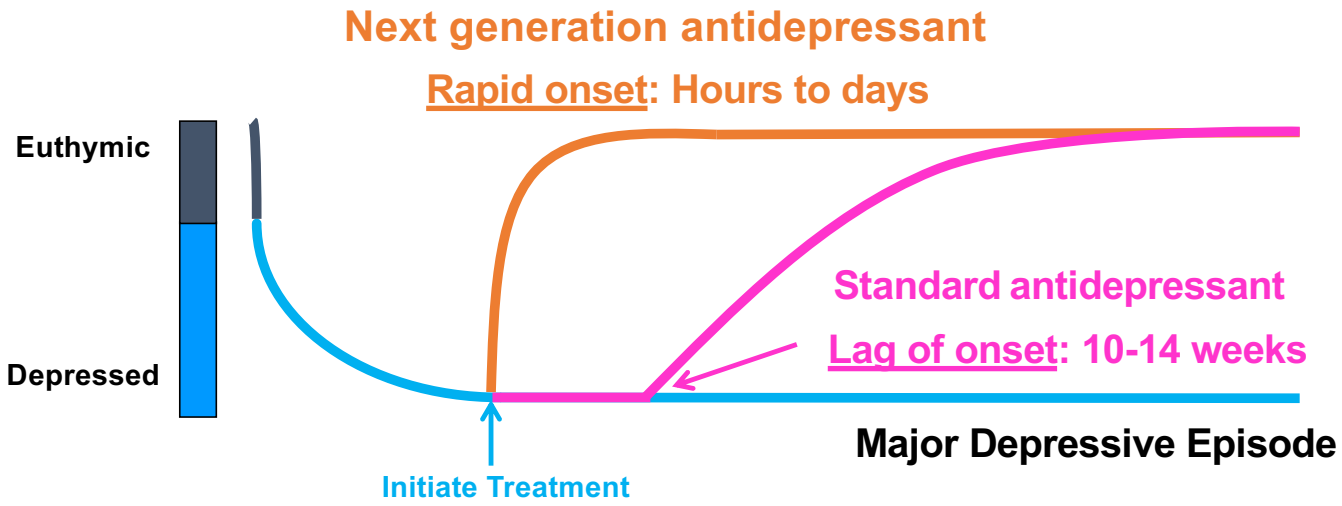
Algorithm for TRD Treatment



Depression: The Need for Improved Treatments

Problems with Current Antidepressants:

- Low remission rates
- Lag of onset of antidepressant effects



Courtesy of Carlos Zarate Jr, MD

Depression

REVIEW

Synaptic Dysfunction in Depression: Potential Therapeutic Targets

Ronald S. Duman* and George K. Aghajanian

Basic and clinical studies demonstrate that depression is associated with reduced size of brain regions that regulate mood and cognition, including the prefrontal cortex and the hippocampus, and decreased neuronal synapses in these areas. Antidepressants can block or reverse these neuronal deficits, although typical antidepressants have limited efficacy and delayed response times of weeks to months. A notable recent discovery shows that ketamine, a *N*-methyl-D-aspartate receptor antagonist, produces rapid (within hours) antidepressant responses in patients who are resistant to typical antidepressants. Basic studies show that ketamine rapidly induces synaptogenesis and reverses the synaptic deficits caused by chronic stress. These findings highlight the central importance of homeostatic control of mood circuit connections and form the basis of a synaptogenic hypothesis of depression and treatment response.

"Recent studies report what is arguably the most important discovery in half a century: ketamine produces rapid antidepressant action in treatment resistant depressed patients."

Spravato™ (Esketamine nasal spray) CIII

- **SPRAVATO™ is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults**
- **Nasal Spray: 28 mg of esketamine per device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine.**
- **Adults Induction Phase Day 1 starting dose: 56 mg**
- **Weeks 1 to 4:**
- **Administer twice per week Subsequent doses: 56 mg or 84 mg**

Maintenance Phase

Weeks 5 to 8:

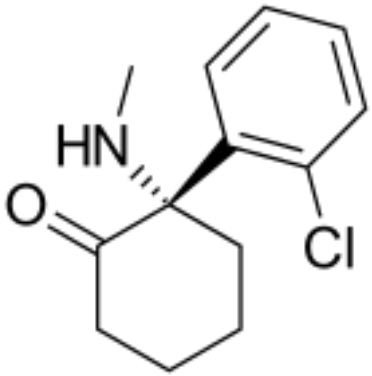
- **Administer once weekly 56mg or 84mg**

Week 9 and after

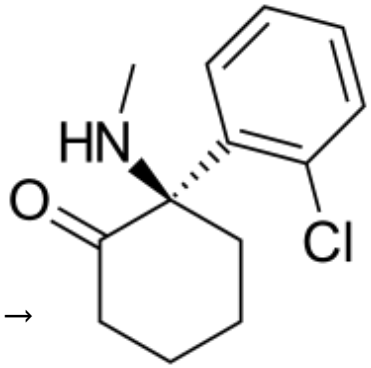
- **Administer every 2 weeks 56 mg or 84 mg**

Esketamine!
(Spravato Nasal Spray)

- **“Watershed” moment in the treatment of depression**
- **First “rapid-acting” medication for depression**
- **NMDA-receptor antagonist**
- **Indicated WITH an oral antidepressant, for the treatment of treatment-resistant depression**
- **Must be administered under the direct supervision of a healthcare provider**
- **Treatment session consists of nasal administration of Spravato and post-administration observation under supervision**



Esketamine ↑



Arketamine →

Esketamine (Spravato)

- **Avoid food for at least 2 hours before administration, and avoid drinking liquids at least 30 minutes prior to administration (some experience N/V)**
- **Assess BP prior to dosing**
  - **If > 140 mmHg SBP or > 90 mmHg DBP weigh risks and benefits**
  - **Do not administer if increase in BP or intracranial pressure poses a serious risk**
  - **Reassess BP 40 minutes after administration (correlates with Cmax)**
  - **DC patient after two hours if BP normal**

Treatment Resistant Depression and Suicide

- **30% of patients with treatment-resistant depression (TRD) attempt suicide at least once during their lifetime**

Practicality of Ketamine Use

- Price to treat
  - $400-$800 per infusion of ketamine
  - $240 per dose of esketamine
- Dosing schedules
  - 6 treatments over 2 – 3 weeks
  - 4 treatments over 1 – 2 weeks
- Requirements for TRD use
  - You've already tried different medication combinations or dosages without any relief in your symptoms
  - You've tried other therapies, including TMS (Transcranial Magnetic Stimulation)
  - You haven't responded fully to a group or individual CBT or therapy
  - You don't have any of the contraindications

Psilocybin

Psilocybin – “Magic Mushrooms”

- “teonanacatl” or flesh of the Gods

- Used by indigenous cultures – Mazotec in Mexico. In 50s, Maria Sabina shares with Gordon Wasson who reports experience in LIFE magazine.

- 1959 Albert Hoffman synthesizes psilocybin
- 1962 Good Friday Experiment = Mystical Experience can be prompted by Psilocybin

- Positive outcomes for end of life anxiety, depression, anxiety, OCD, nicotine & alcohol addiction .

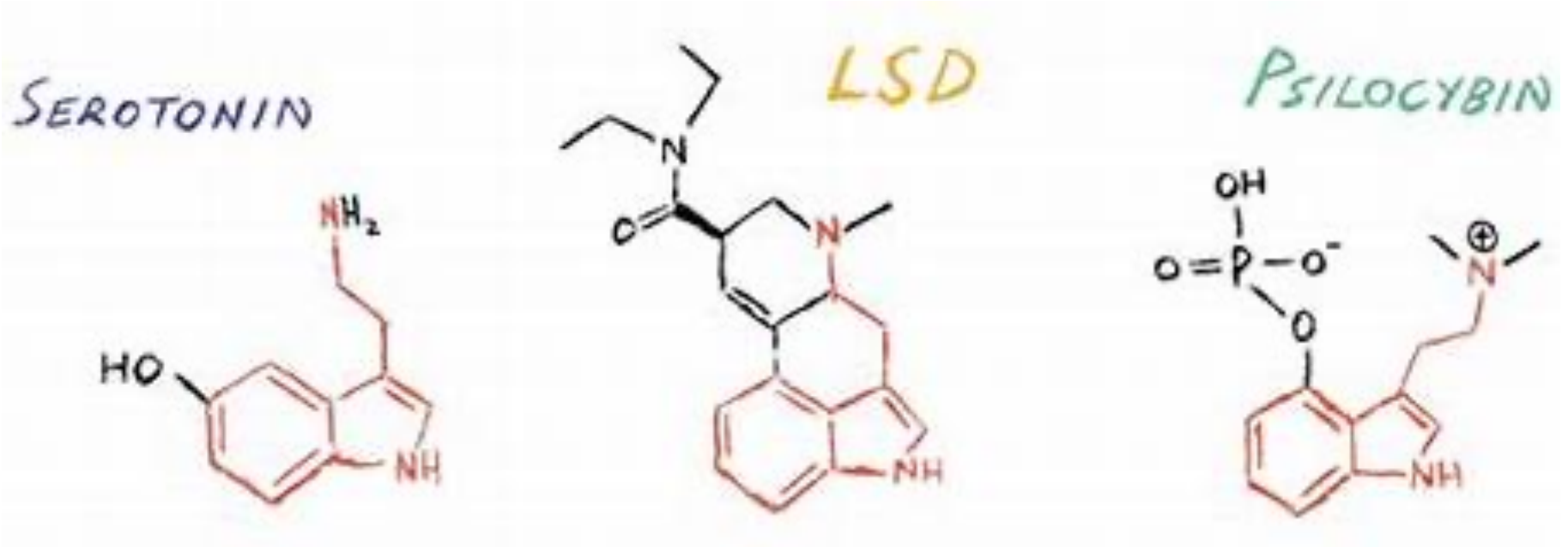
What is Psilocybin?

- **Psilocybin is a form of mushrooms that contain hallucinogenic properties.**
- **Also known as *magic mushrooms*, psilocybin is classified by the DEA as a Schedule 1 Controlled Substance.**
- **Hallucinogenic mushrooms have, historically, been used by several cultures during their religious rituals.**

How is Psilocybin Consumed?

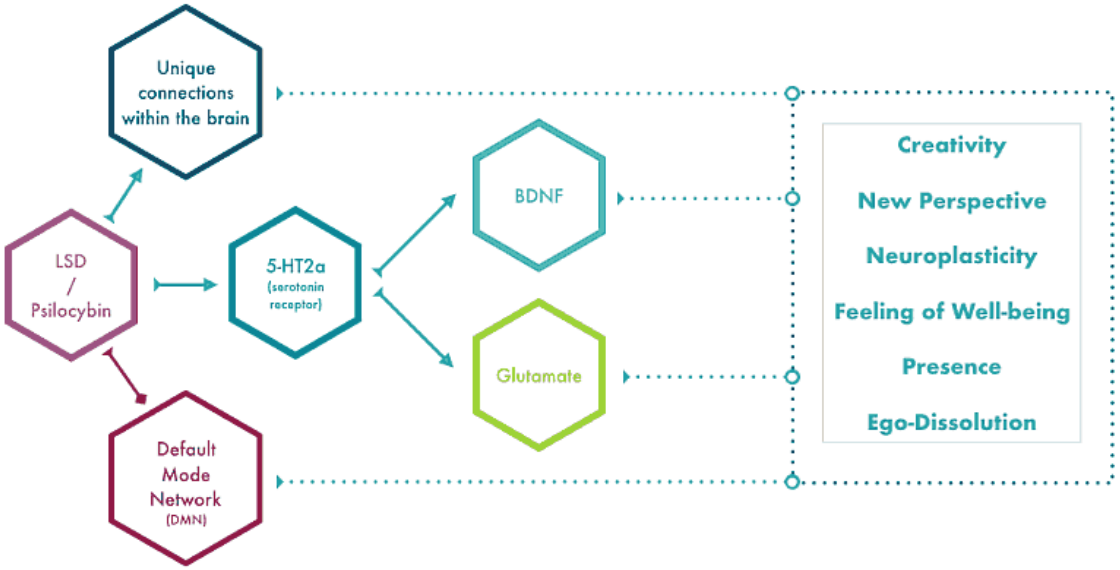
- <u>Eaten</u> – While the mushrooms are usually dried prior to sale and/or consumption, they can be eaten raw or cooked like regular mushrooms.
- <u>Drank</u> – Heated with water to make a tea or a soup.
- <u>Smoked</u> – The mushroom is ground into a fine powder and often smoked on top of marijuana.

Similar Molecules



How Do They Work?

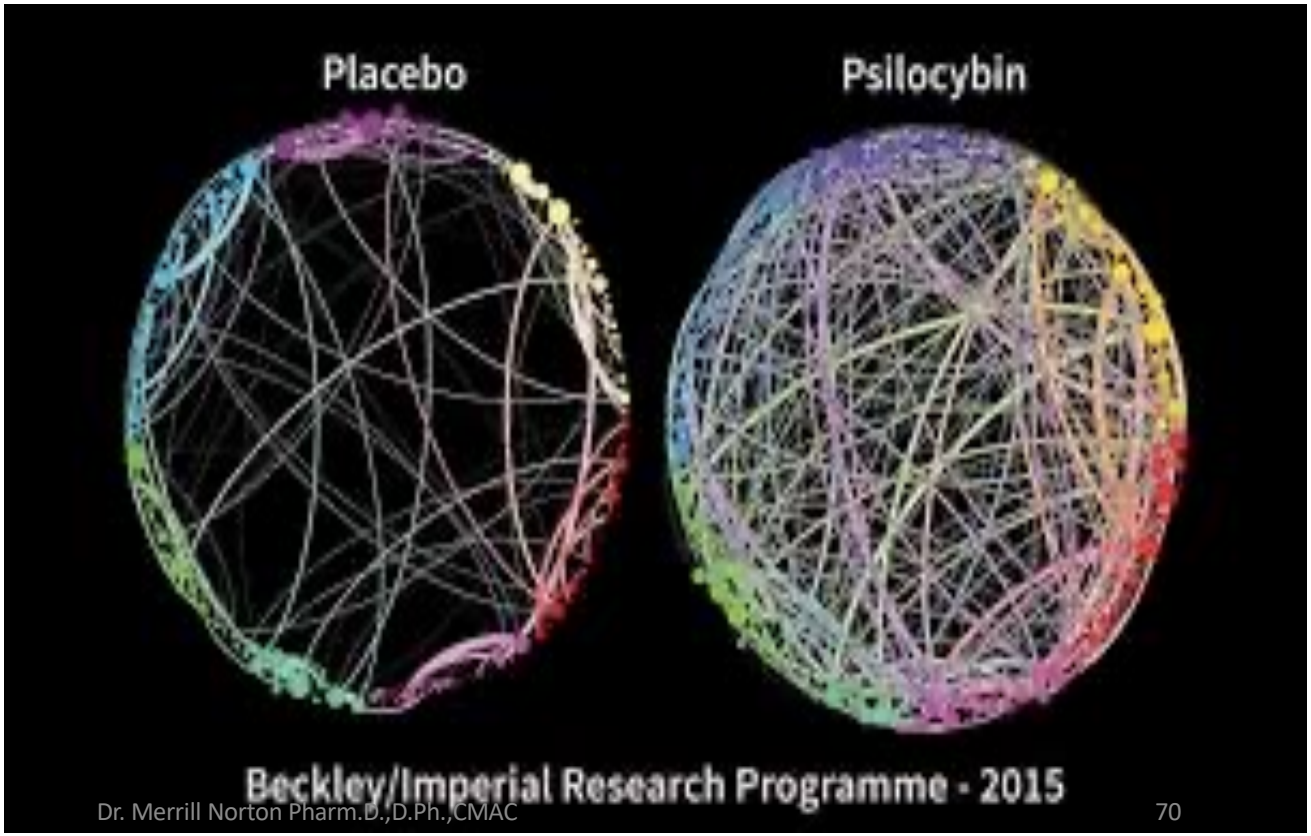
- https://thethirdwave.com



How do they work?

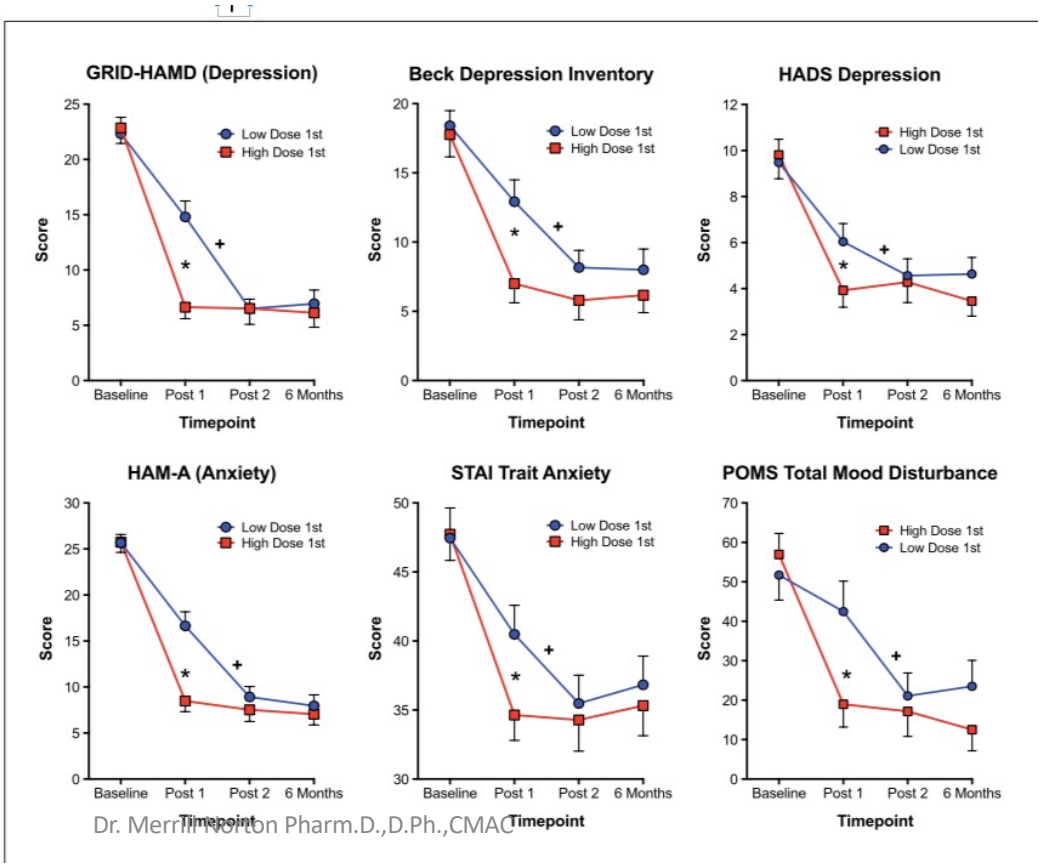
Increased connectivity.

Parts of the brain that don’t usually speak to each other connect.

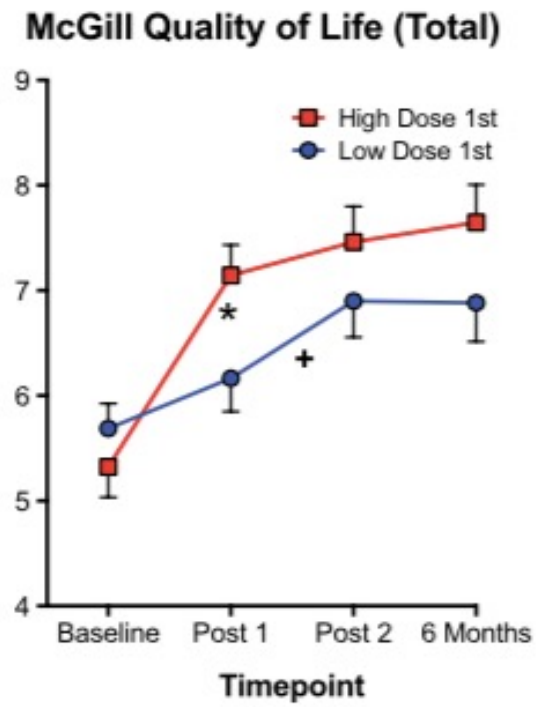


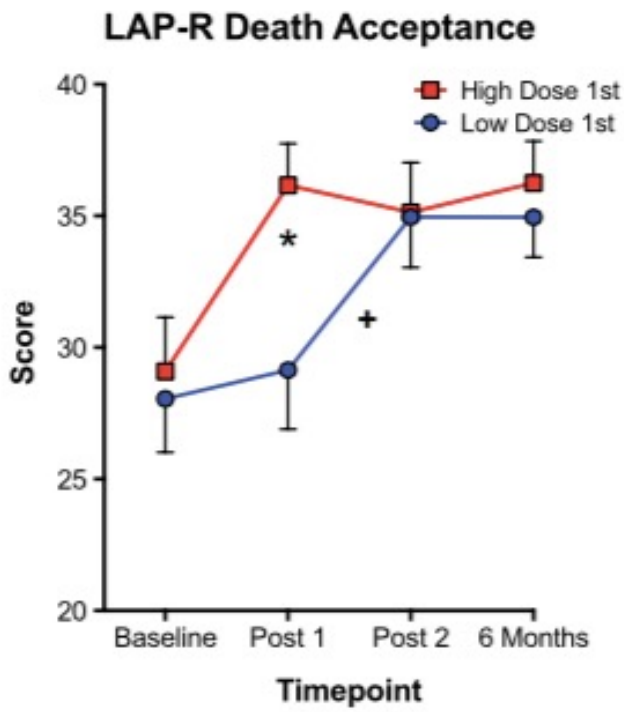
Psilocybin Study with Cancer Patients

- 51 Patient with life-threatening cancer.
- 80% decreases in anxiety and depression & improvement in attitude, mood, relationship& spirituality
- TRAIT anxiety decreases!
- (Griffiths, et al. 2016)



Quality of Life and Death Acceptance






Pharmacogenomic Testing for
Psychotropics 2022

Pharmacogenetic versus Pharmacogenomic

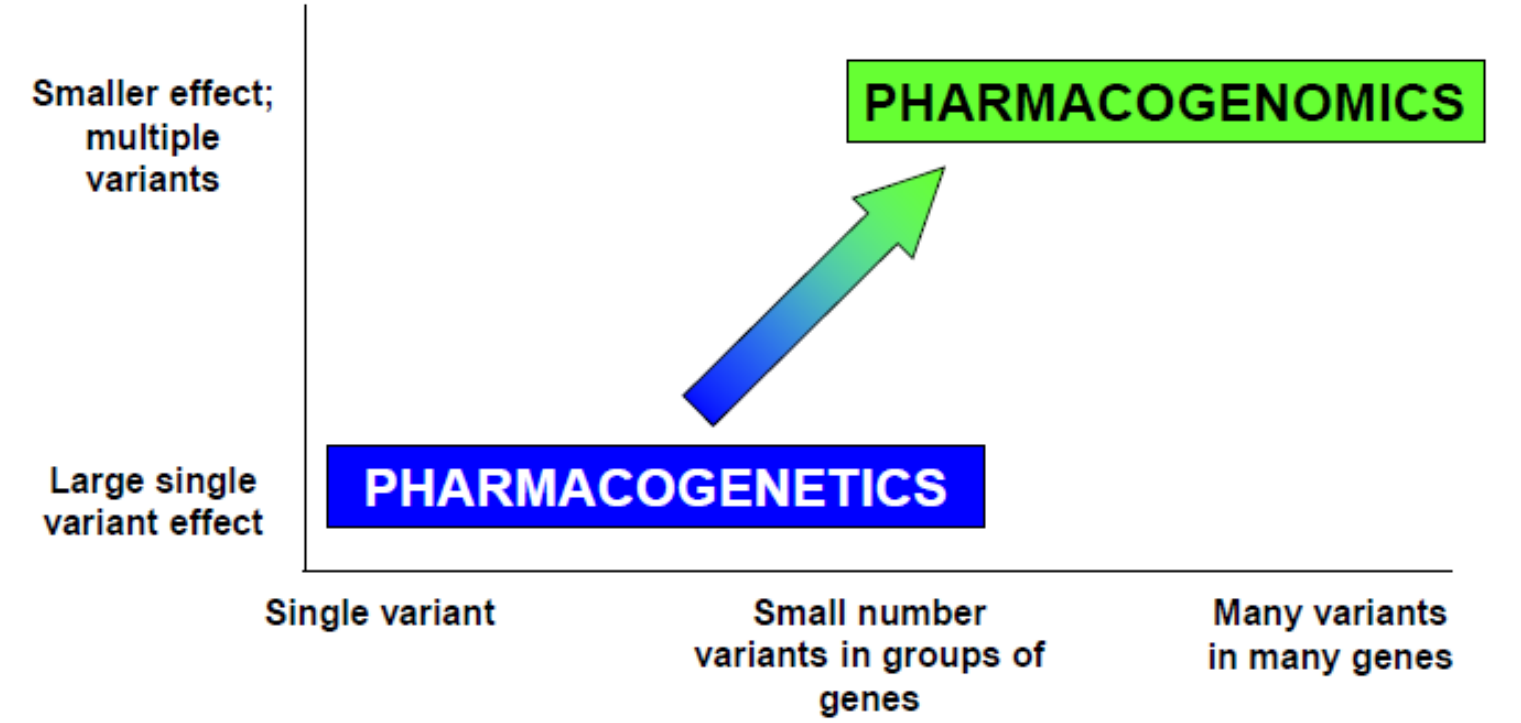
- No universally accepted definitions of either
- Often used interchangeably
- *Pharmacogenetics* used for more than 40 years to denote the science about how heritability affects the response to drugs.
- *Pharmacogenomics is new science about how the systematic identification of all the human* genes, their products, interindividual variation, intraindividual variation in expression and function over time affects drug response/metabolism etc.
- The term pharmacogenomics was coined in connection with the human genome project
- Most use pharmacogenetics to depict the study of single genes and their effects on interindividual differences in (mainly) drug metabolising enzymes, and pharmacogenomics to depict the study of not just single genes but the functions and interactions of all genes in the genome in the overall variability of drugs response

Pharmacogenetics

- "Pharmacogenetics is the study of how **genetic variations** affect the **disposition** of drugs, including their **metabolism and transport and their safety and efficacy"**
    - **J. Hoskins et. al NRC 2009**

Pharmacogenetics involves both PK and PD

- **P**harmaco**k**inetic
  - "The process by which a drug is absorbed, distributed, metabolized, and eliminated by the body"
- **P**harmaco**d**ynamic
  - "the biochemical and physiological effects of drugs and the mechanisms of their actions"

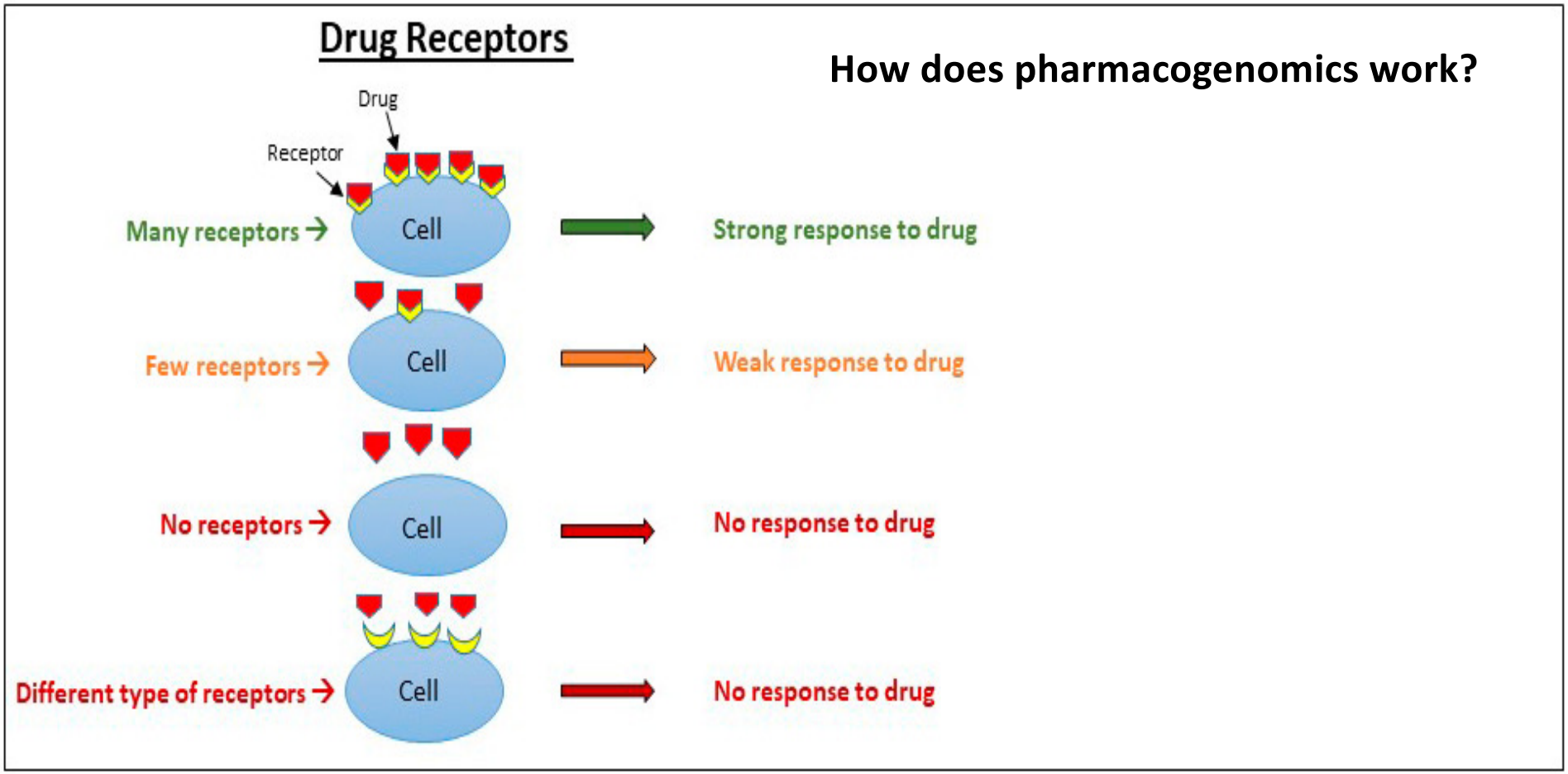


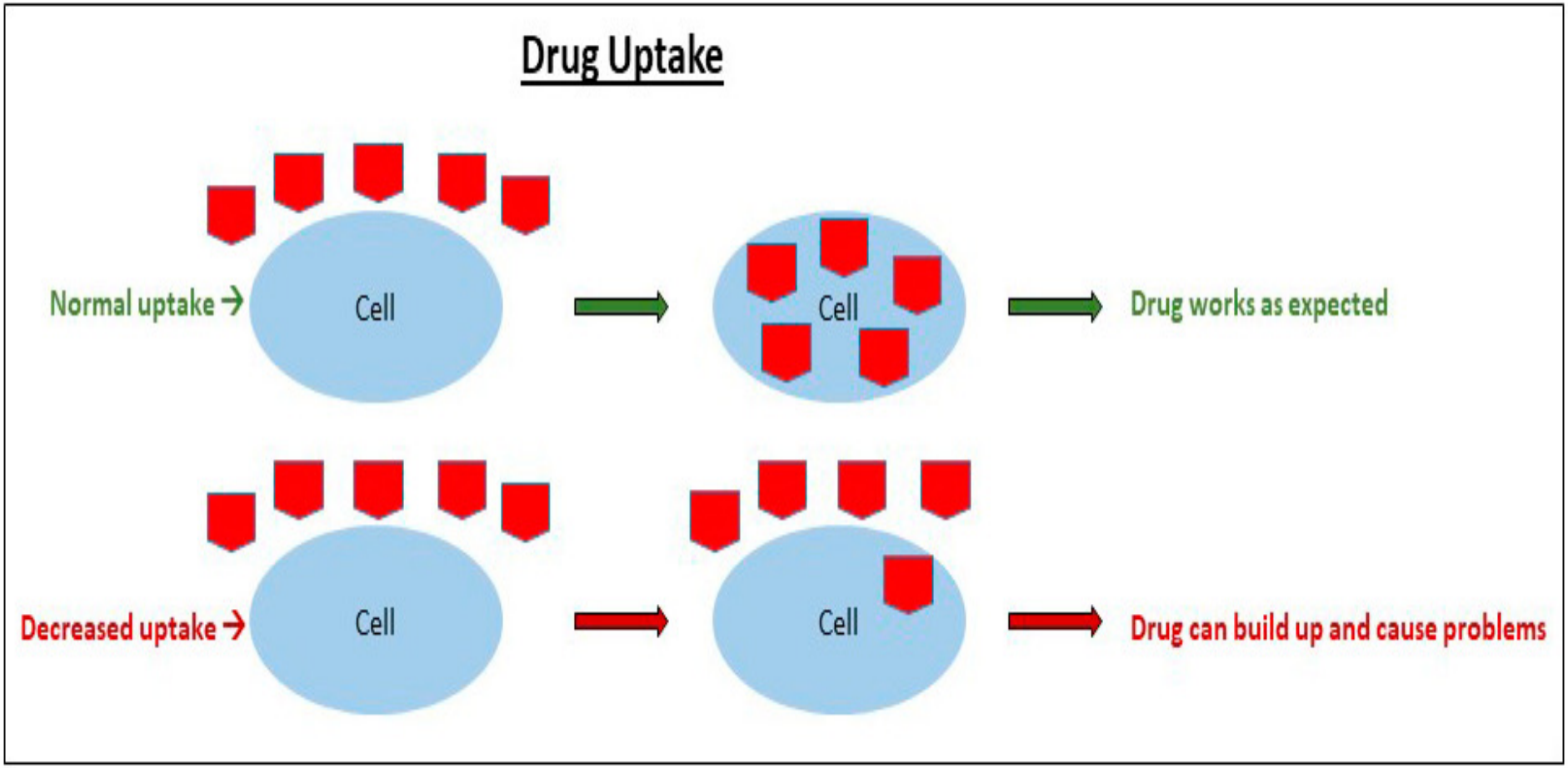
Adapted from The Pharmacogenetics Research Network Investigators, Ann Int Med, 2006

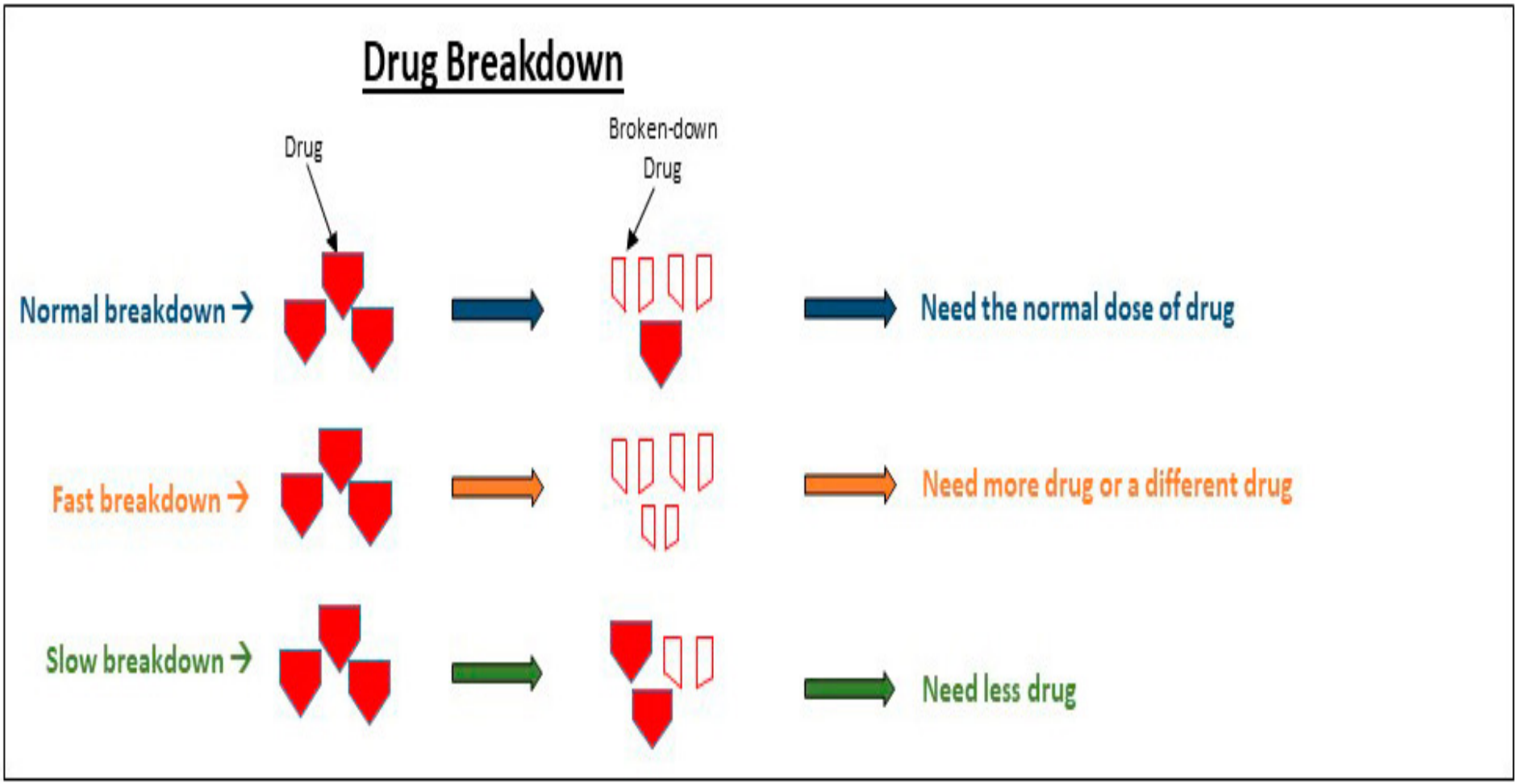
How Does Pharmacogenomics Work?

- Drugs interact with your body in numerous ways, depending both on how you take the drug and where the drug acts in your body. After you take a drug, your body needs to break it down and get it to the intended area.
- Your DNA can affect multiple steps in this process to influence how you respond to the drug:
- Drug Receptors
- Drug Uptake
- Drug Breakdown

How does pharmacogenomics work?




Drug Uptake
Normal uptake →
Cell
Cell
Drug works as expected
Decreased uptake →
Cell
Cell
Drug can build up and cause problems


Drug Breakdown
Drug
Broken-down Drug
Normal breakdown →
Need the normal dose of drug
Fast breakdown →
Need more drug or a different drug
Slow breakdown →
Need less drug

Goals of Pharmacogen(**et**ics)**om**ics

- Maximize drug efficacy
- Minimize drug toxicity
- Predict patients who will respond to intervention
- Aid in new drug development

This is the Hope/Hype

"Here's my sequence..."

New Yorker, 2000

Why is Pharmacogenomics Not Widely Utilized in the Clinic

- It required a shift in clinician attitude and beliefs "not one dose fits all"
- Paucity of studies demonstrating improved clinical benefit from use of pharmacogenomic data
  - Still much to be learned
    - Even some of the black block warnings currently on drug labels may be overcalls of importance
- Genome wide interrogation will likely be important to get the entire picture

SSRI'S – HOPE FOR LESS TRIAL AND ERROR?

- A cohort study of 1202 patients suggests sertraline dose reductions of 60% and 25% in poor metabolizers and intermediate metabolizers, respectively (Braten et al., 2019).
- Additional studies provide dosing recommendations for citalopram, escitalopram, fluvoxamine, and paroxetine based on pharmacogenomic testing.
- Bråten, L.S., Haslemo, T., Jukic, M.M. et al. Impact of CYP2C19 genotype on sertraline exposure in 1200 Scandinavian patients. Neuropsychopharmacol. (2019) doi:10.1038/s41386-019-0554-x
- 1. Kaye, A. D., Garcia, A. J., Hall, O. M., Jeha, G. M., Cramer, K. D., Granier, A. L., ... Urman, R. D. (2019). Update on the pharmacogenomics of pain management. Pharmacogenomics and personalized medicine, 12, 125–143. doi:10.2147/PGPM.S179152

Resources

- https://www.cdc.gov/genomics/disease/pharma.htm
- Tier-Classified Guidelines Database
- NIH Genetics Home Reference - Pharmacogenomicsexternal icon
- Clinical Pharmacogenetics Implementation Consortium (CPIC)external icon
- Search our Public Health Genomics Knowledge Base for the latest information and publications on the role of pharmacogenomics for specific medications

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Ketamine for suicidal ideation in bipolar disorder (March 2022)**
- Suicidal ideation in bipolar disorder that does not respond to standard treatments may resolve with ketamine.
- In a placebo-controlled randomized trial of 52 patients with bipolar depression hospitalized for suicidal ideation and receiving usual pharmacotherapy, two doses of add-on ketamine resulted in a higher rate of remission of suicidal ideas at day 3 (85 versus 28 percent), and the benefit appeared to persist at the six-week follow-up [1].
- Ketamine was well tolerated and did not induce switching to mania.
- However, the rate of suicide attempts was similar for both groups.
- Ketamine remains an investigational treatment for bipolar depression due to limited evidence of efficacy and concerns about adverse effects, including addiction

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Lumateperone for bipolar depression (January 2022)**
- Drawbacks to antipsychotics currently used for treatment of bipolar disorder include poor efficacy for associated depression, which often accounts for a high proportion of morbidity in such patients, and frequent undesirable side effects.
- In a clinical trial of individuals with type I or II bipolar depression, lumateperone, an antipsychotic with a novel mechanism, led to greater rates of response (51 versus 37 percent) and remission (40 versus 34 percent) compared with placebo [2].
- Treatment emergent side effects occurred at similar rates to placebo. While lumateperone may be a promising new option with minimal side effects for the treatment of bipolar disorder, further studies are needed in order to define its optimal role.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Prenatal antipsychotics and psychopathology in the offspring (September 2021)**
- Maternal use of antipsychotics during pregnancy does not appear to increase the risk of psychopathology in offspring.
- A retrospective study of electronic medical records identified over 400,000 mother-child pairs in which 706 had gestational exposure to antipsychotics.
- After adjusting for potential confounding factors, the risks of attention-deficit hyperactivity disorder and autism spectrum disorder in the exposed and nonexposed children were comparable.
- These results are reassuring for pregnant patients with bipolar disorder who require antipsychotics.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Rise in functional tics in adolescents and young adults (January 2022)**
- An increase in functional tics has been observed during the COVID-19 pandemic.
- Cases have been referred to as "TikTok tics," as affected individuals have commonly viewed online videos depicting tic-like behaviors.
- Most patients are females between 15 and 25 years of age.
- Symptom onset is usually acute, with complex vocal and motor tics involving large-amplitude arm movements, self-injury, and a wide range of odd words or phrases, often with obscenities.
- The stresses of the pandemic are believed to be contributing, and comorbid depression and anxiety disorders are common.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Omega-3 fatty acids and depression (March 2022)**
- Marine omega-3 fatty acids may have a limited adjunctive role in treatment of selected patients with acute major depression; however, recent evidence indicates that they do not prevent depression.
- A five-year randomized trial compared omega-3 fatty acids with placebo in more than 18,000 patients (mean age 68 years) without depression.
- Active treatment consisted of eicosapentaenoic acid 465 mg/day and docosahexaenoic acid 375 mg/day.
- Onset of depressive symptoms was comparable in the two groups.
- Thus, we recommend not prescribing omega-3 fatty acids to prevent depression.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Treatment of major depression after acute coronary syndrome (March 2022)**
- Major depression is common following acute coronary syndrome; safety of antidepressants in this setting is an important consideration.
- In a meta-analysis that included five trials of 891 patients with coronary artery disease and depressive syndrome, many with recent acute coronary syndrome, treatment with a selective serotonin reuptake inhibitor (SSRI; citalopram, escitalopram, fluoxetine, or sertraline) resulted in a higher depression response rate than placebo (odds ratio 2.7).
- Although noncardiac adverse effects were more likely with antidepressants, cardiac safety (eg, as measured by echocardiograms, electrocardiograms, and cardiac biomarkers) did not differ between the two groups.
- These data support our recommendation that treatment of depression following acute coronary syndrome include an SSRI.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Varenicline ineffective in the treatment of cocaine use disorder (March 2022)**
- Cocaine use and cocaine use disorder continue to be substantial public health concerns with limited treatment options. Varenicline, a selective nicotinic acetylcholine receptor agonist used for smoking cessation, showed mixed results in previous trials of treatment of cocaine use disorder.
- In a recent placebo-controlled trial that randomly assigned 156 individuals with cocaine use disorder to 12 weeks of psychotherapy with versus without varenicline, both groups had similar rates of cocaine abstinence (as measured by urine drug screen), severity of cocaine withdrawal, and symptoms of cocaine craving.
- These results do not support use of varenicline for the treatment of cocaine use disorder.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Varenicline for cannabis use disorder (December 2021)**
- Cannabis use disorder (CUD) can cause substantial psychosocial disability; however, few medications are effective in its treatment.
- Varenicline, a selective nicotinic acetylcholine receptor agonist used for smoking cessation, is a candidate agent for CUD treatment. In a trial of 72 individuals with CUD, six weeks of varenicline resulted in higher abstinence rates at each study visit (17 versus 5 percent at week six) and greater decrease in cannabis use (42 versus 27 percent fewer days) compared with placebo.
- Additional and larger trials are warranted to confirm this effect of varenicline in patients with CUD.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Impact of extended opioid agonist take-home doses during the COVID-19 pandemic (March 2022)**
- Concerns about disruption of therapy for opioid use disorder during the COVID-19 pandemic have led to loosening of opioid agonist dispensing restrictions on take-home doses.
- In an observational study of over 20,000 individuals on opioid agonist therapy, extension of take-home methadone doses was associated with a lower risk of treatment discontinuation or interruption, and extension of take-home buprenorphine/naloxone doses was associated with a lower risk of treatment interruption.
- An increase in opioid-related overdoses due to loosened restriction was not reported at six months' follow-up.
- These findings have implications on whether to return to treatment regulations in place prior to the COVID-19 pandemic.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Dental problems associated with oral dissolving buprenorphine (January 2022)**
- There are >300 reports of dental problems associated with use of buprenorphine formulations dissolved in the mouth, including the buccal formulation and sublingual tablets.
- Reported problems include dental caries, abscesses, and damaged teeth, many of which have required tooth removal.
- The incidence of dental problems with buprenorphine is unknown. Patients who use orally dissolving buprenorphine should swish and swallow water after the drug has dissolved, see a dentist soon after starting the drug, and make sure the dentist knows they are taking the drug.
- The US Food and Drug Administration (FDA) has issued a related safety advisory and will mandate a label change.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Daridorexant for treatment of insomnia in adults (January 2022)**
- Daridorexant, a dual orexin receptor antagonist (DORA), has been approved by the US Food and Drug Administration (FDA) for treatment of insomnia in adults.
- Like lemborexant and suvorexant, daridorexant improves both subjective and objective measures of sleep onset and sleep maintenance compared with placebo.
- Among the three DORAs, daridorexant has the shortest half-life (approximately eight hours).
- For adults who fail or do not have access to cognitive behavioral therapy, we consider DORAs to be an acceptable first-line option for sleep maintenance insomnia, along with benzodiazepine receptor agonists (BZRAs) and low-dose doxepin; for sleep-onset insomnia, we prefer trying medications with shorter half-lives first.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

What's New from UptoDate

- **Electroconvulsive therapy and risk of serious medical events (September 2021)**
- Electroconvulsive therapy (ECT) is underutilized due to stigma and concerns about medical complications.
- However, in a retrospective cohort study of over 10,000 patients hospitalized for depression, the rate of serious medical events was low and trended lower among those exposed to ECT compared with a propensity score-matched unexposed group (0.25 versus 0.33 events per person-year).
- Serious medical events were defined as a composite of hospitalization for nonpsychiatric reasons and non-suicide mortality within 30 days of the exposure date or corresponding index date.
- Clinicians can use these findings and previous data to reassure candidates for ECT that it is one of the safest procedures performed under general anesthesia.

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Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

Questions ???????