New Frontiers in the Treatment of PTSD

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Disclosures

Consultant/ Speakers Bureaus	No Disclosures
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Off-label uses	No Disclosures

Objectives

1. To explain the potential role of Personalized Medicine in the therapeutic management of patients with PTSD.

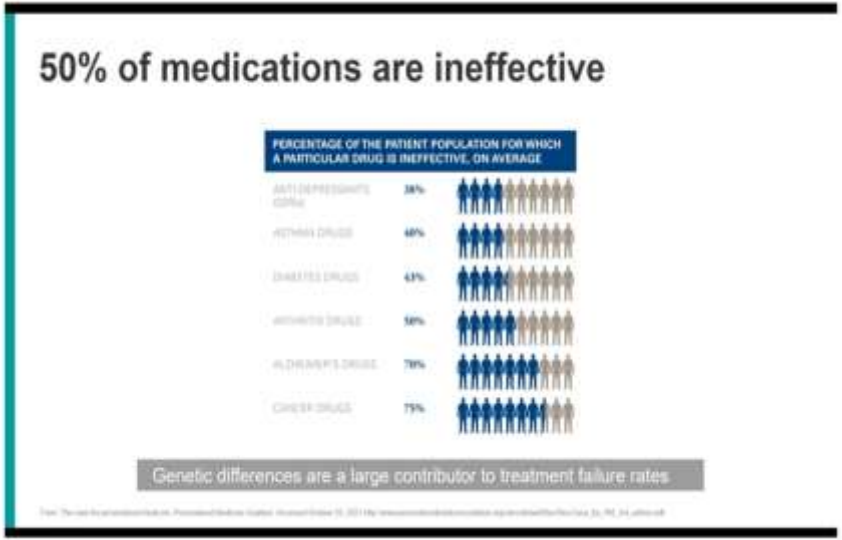
2. To discuss the emerging therapies in the management of PTSD.

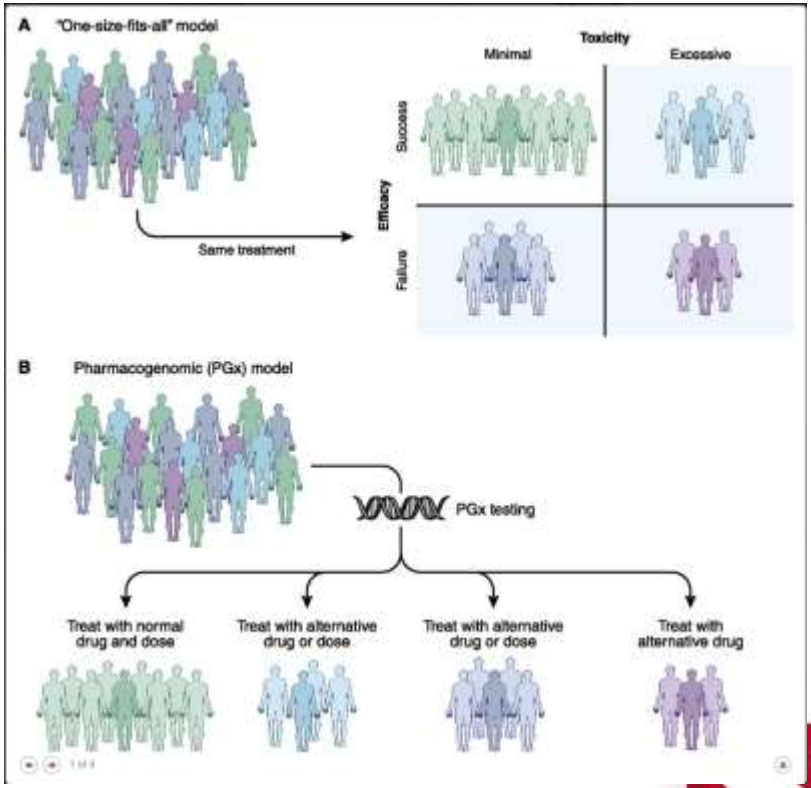
The “Promise” of Personalized Medicine

Personalized Medicine

- Pharmacogenetics
- Metabolomics
- Proteomics
- Epigenetics

Current Treatment Paradigm





Medications with PGX Impact

Expert consensus: PGx impacts many common medications

Behavioral health
Amitriptyline
Aripiprazole
Atomoxetine
Brexpiprazole
Citalopram
Clomipramine
Desipramine
Doxepin
Escitalopram
Fluvoxamine
Mipramine
Mirtazapine
Nortriptyline
Paroxetine
Protriptyline
Risperidone
Sertraline
Trimipramine
Venlafaxine
Vortioxetine

Cardiology
Clopidogrel
Quinidine
Simvastatin
Warfarin

Ear, eye, nose, throat
Dextromethorphan

Gastroenterology
Dexlansoprazole
Esomeprazole
Lansoprazole
Omeprazole
Ondansetron
Pantoprazole
Rabeprazole

Hematology/oncology
Belinostat
Capecitabine
Eliglustat
Fluorouracil
Irinotecan
Mercaptopurine
Tamoxifen
Thioguanine

Infectious disease
Abacavir
Atazanavir
Efavirenz
Nevirapine
Voriconazole

Neurology
Phenytoin
Siponimod
Pimozide

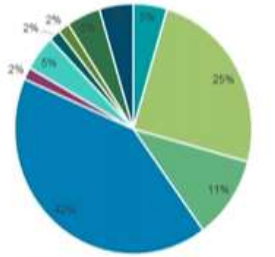
Pain management
Celecoxib
Codeine
Flurbiprofen
Ibuprofen
Meloxicam
Methadone
Oxycodone
Piroxicam
Tramadol

Rheumatology
Azathioprine

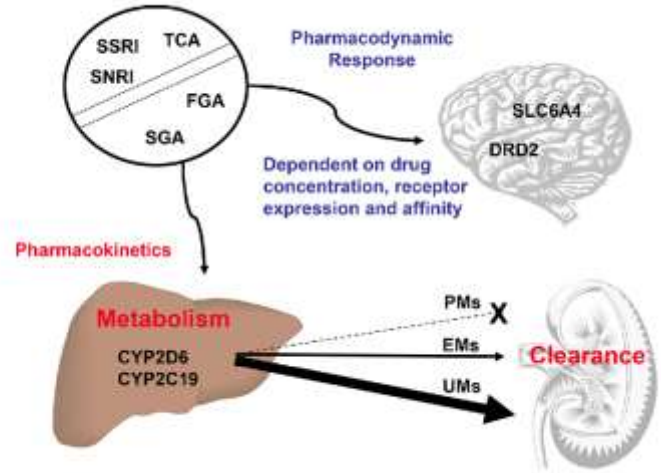
Transplant
Tacrolimus

And many more…

The same set of genes affects most medications



Impact of Pharmacokinetics and Pharmacodynamics



Pharmacokinetics: what the body does to the drug

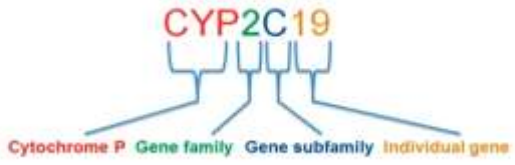
Pharmacodynamics: what the drug does to the body

Pharmacogenetic Nomenclature

Nomenclature

Genes encoding CYP450 enzymes

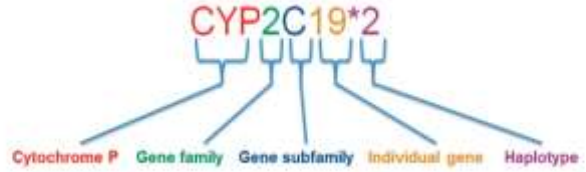
- Gene designated with the abbreviation CYP
- Number indicating the gene family
- Capital letter indicating the subfamily
- Numeral for the individual gene



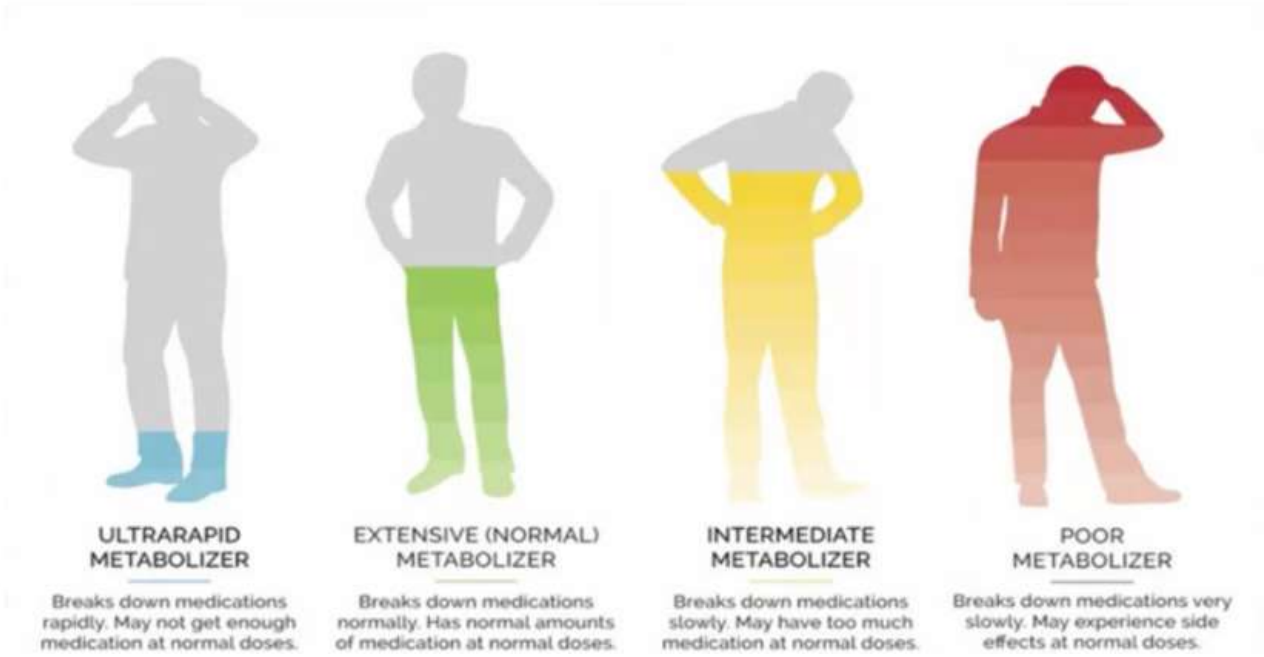
Nomenclature

* (star) alleles – pharmacogenomic haplotype

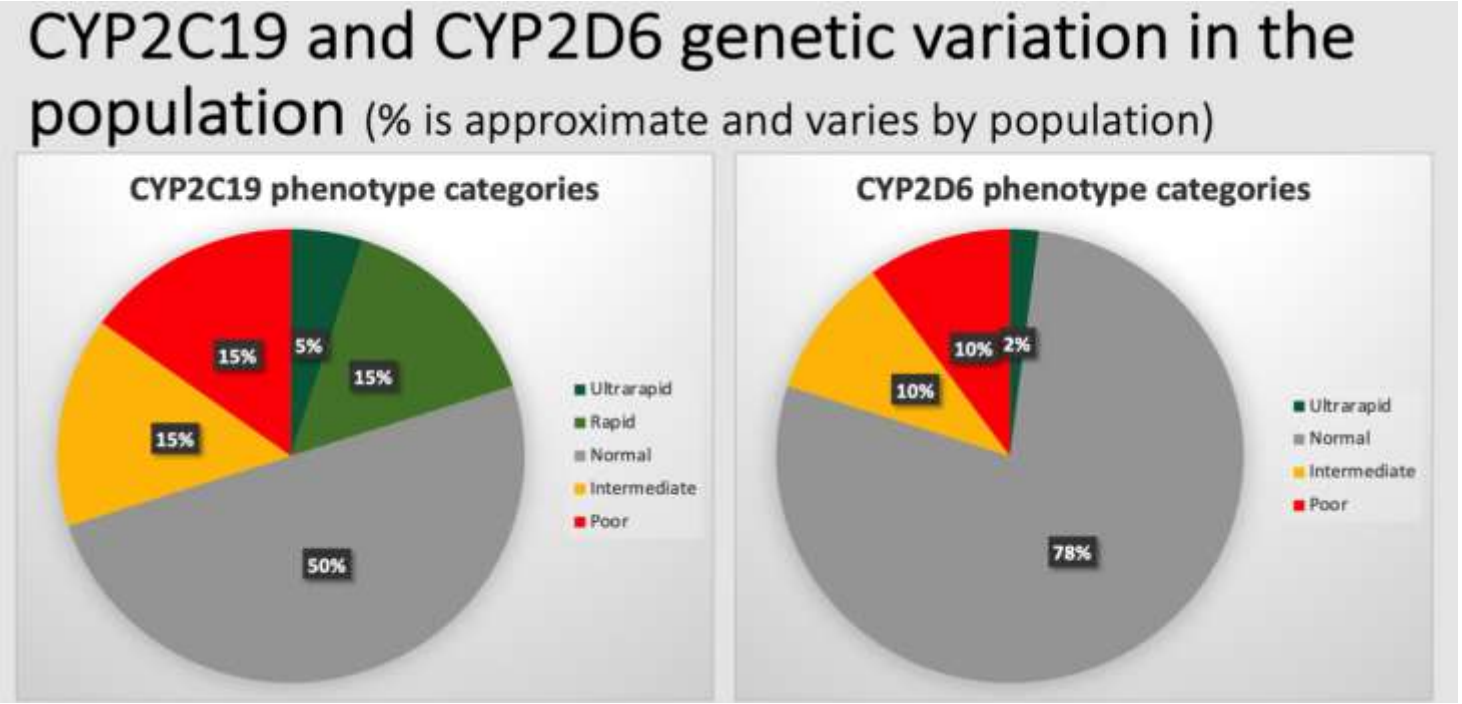
- Normal function/enzyme activity (wild type) denoted by *1
- Altered function variant: *2, *3, *4, etc.
  - *2x2 copy number variant
- Single genes (CYP2C19) have many star alleles (e.g., CYP2C19*2, CYP2C19*3)
- Results reported as diplotypes: CYP2C19*1/*17



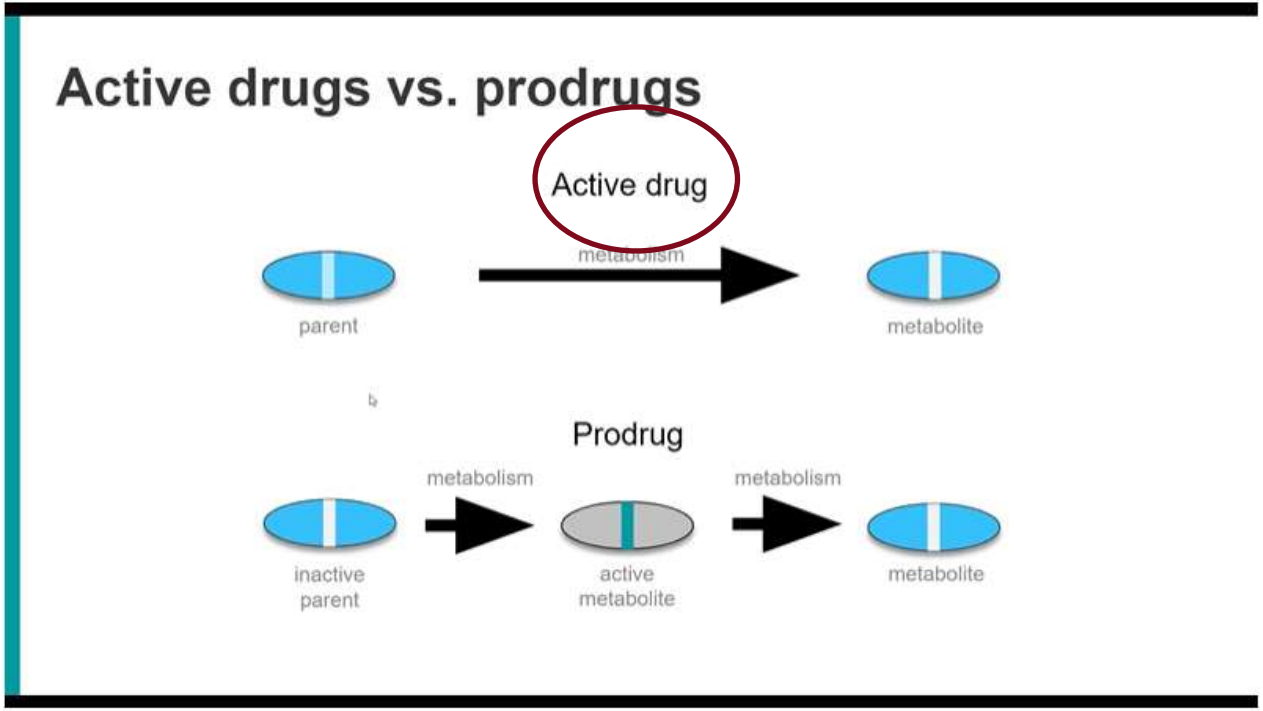
Definitions of Metabolic Status



Prevalence of PGX Polymorphisms



Pharmacology of Active vs Pro-drugs

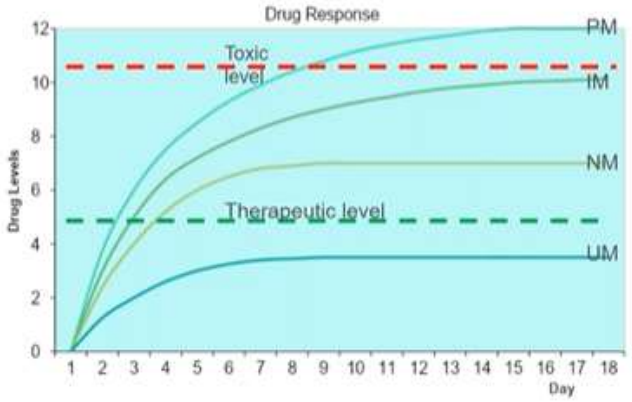


Impact of PGX on Drug Concentrations

Drug response: Active drug

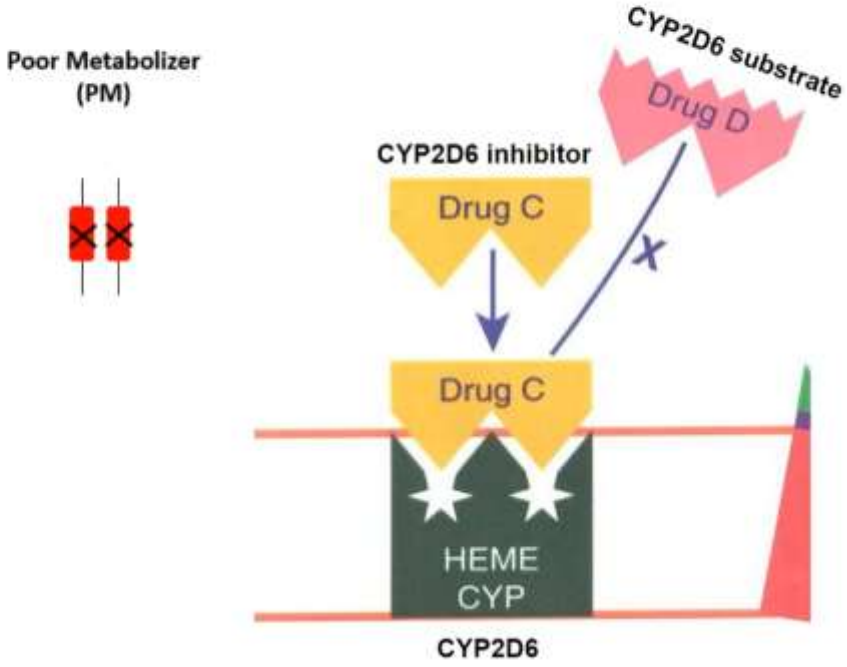
At steady state, we expect:

- **PM** – low-absent enzymatic activity; more likely to experience adverse effects due to high levels of unmetabolized drugs
- **IM** – possibly more adverse effects compared to NM due to decreased enzymatic activity
- **NM** – typical response at standard doses
- **UM** – less likely to experience therapeutic effect at standard doses due to increased enzymatic activity

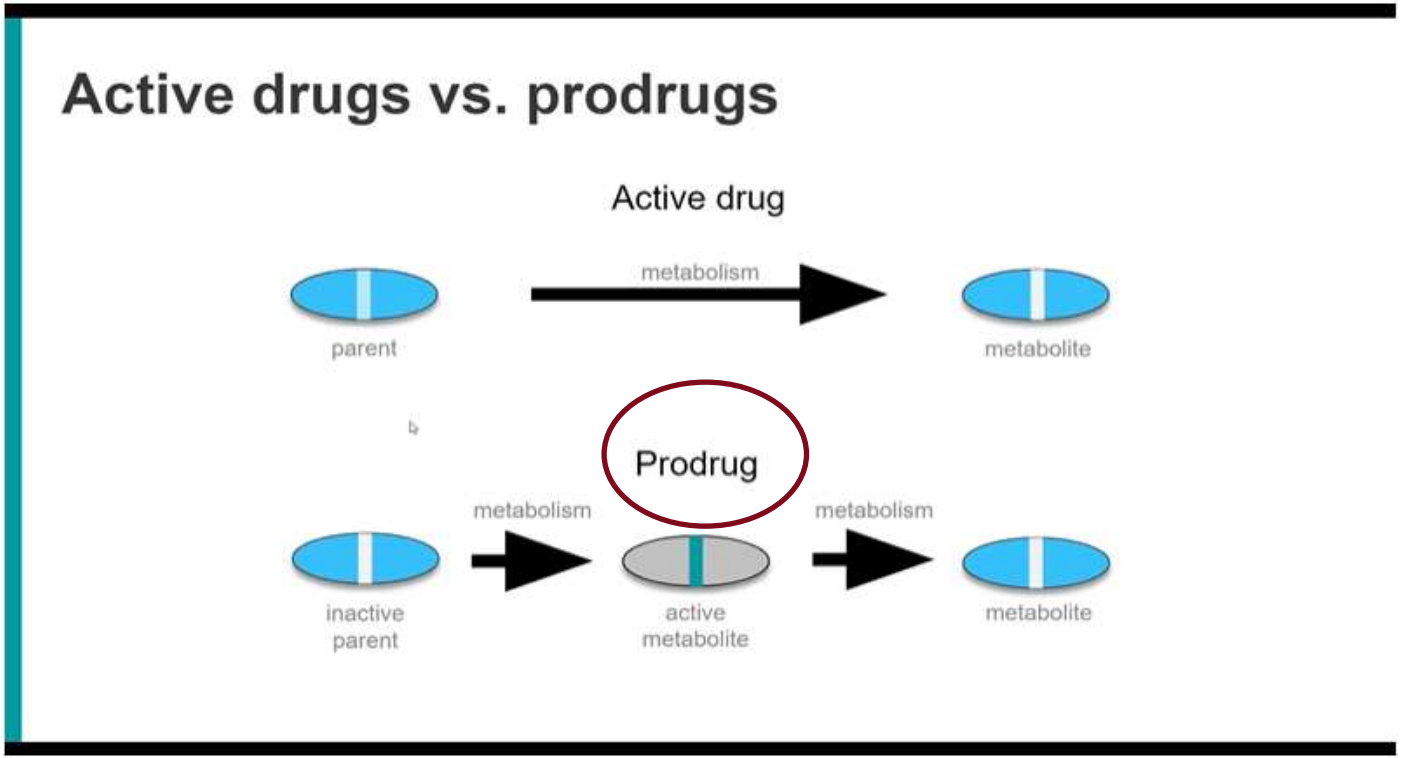


Similar response

There is a similar response for potent inhibitors and poor metabolizers.



Pharmacology of Active vs Pro-drugs



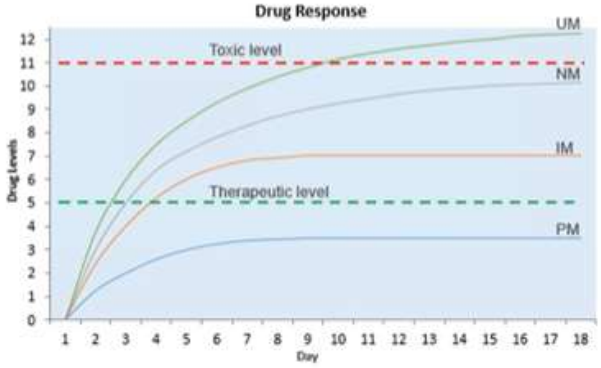
Impact of PGX on Drug Concentrations

Drug response: Prodrug

A prodrug is a biologically inactive precursor drug that must undergo chemical conversion before becoming an active pharmacological agent (active metabolite).

At steady state, we expect:

- **UM** – more likely to experience adverse effects due increased/rapid formation of active metabolites
- **NM** – typical response at standard doses, possibly more adverse effects
- **IM** – typical response at standard doses; possibly less therapeutic effects
- **PM** – less likely to experience therapeutic effect since the inactive parent compound is not been converted to the active form



Regulatory Guidelines

Pharmacogenomic-guided antidepressants

- CPIC Guidelines are currently available to guide selective serotonin reuptake inhibitors and tricyclic antidepressants
- Guidance available for other psychotropic medications, including certain antipsychotics through FDA and mood stabilizers through CPIC

	Actionable Guideline Available[2]		Product Label[3]
Antidepressant	**CPIC**	**DPWG**	**FDA**
Amitriptyline	CYP2C19, CYP2D6	CYP2D6	CYP2D6
Amoxapine	–	–	CYP2D6
Citalopram	CYP2C19	CYP2C19	CYP2C19
Clomipramine	CYP2C19, CYP2D6	CYP2D6	CYP2D6
Desipramine	CYP2D6	–	CYP2D6
Doxepin	CYP2C19, CYP2D6	CYP2D6	CYP2C19, CYP2D6
Duloxetine	–	–	CYP2D6
Escitalopram	CYP2C19	CYP2C19	–
Fluvoxamine	CYP2D6	–	CYP2D6
Imipramine	CYP2C19, CYP2D6	CYP2C19, CYP2D6	CYP2D6
Nortriptyline	CYP2D6	CYP2D6	CYP2D6
Paroxetine	CYP2D6	CYP2D6	–
Protriptyline	–	–	CYP2D6
Sertraline	CYP2C19	CYP2C19	–
Trimipramine	CYP2C19, CYP2D6	–	CYP2D6
Venlafaxine	–	CYP2D6	CYP2D6
Vortioxetine	–	–	CYP2D6

Hicks JK et al. Clin Pharmacol Ther . 2017 Jul;102(1):37-44.
Hicks JK et al. Clin Pharmacol Ther. 2015 Aug;98(2):127-34.

Incorporation into Clinical Decision Support

Selective serotonin reuptake inhibitors (SSRI)

Medication	Gene
Citalopram*¥	CYP2C19
Escitalopram*	CYP2C19
Sertraline*	CYP2C19
Paroxetine*	CYP2D6
Fluoxetine*	CYP2D6/CYP2C9
Fluvoxamine*	CYP2D6
Vortioxetine¥	CYP2D6

*Medications with CPIC guidelines
¥Medications with actionable FDA labeling

CYP2D6 Phenotype	Therapeutic recommendation for PAROXETINE*	Classification of recommendation
Ultra-rapid metabolizer	Select alternative drug not predominantly metabolized by CYP2D6	Strong
Normal metabolizer	Initiate therapy with recommended starting dose	Strong
Intermediate metabolizer	Initiate therapy with recommended starting dose	Moderate
Poor metabolizer	Select alternative drug not predominantly metabolized by CYP2D6 or if paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response.	Optional

Hicks JK et al. Clin Pharmacol Ther. 2015 Aug;98(2):127-34.

USF Health · Society for Birth Defects Research & Prevention · OTIS

Current applications of PGx: Psychiatry

Drug class	Gene(s)	CPIC level
Tricyclic antidepressants (TCAs)		A
Amitriptyline (Elavil)	CYP2D6/CYP2C19	
Clomipramine (Anafranil)	CYP2D6	
Doxepin (Silenor)	CYP2D6	
Imipramine (Tofranil)	CYP2D6	
Trimipramine (Surmontil)	CYP2C19	
Selective serotonin reuptake inhibitors (SSRIs)		A
Paroxetine (Paxil)	CYP2D6	
Fluvoxamine (Luvox)	CYP2D6	
Citalopram (Celexa)	CYP2C19	
Escitalopram (Lexapro)	CYP2C19	
Sertraline (Zoloft)	CYP2C19	

Current applications of PGx: Psychiatry

Drug class	Gene(s)	CPIC level
Antipsychotics Aripiprazole (Abilify) Brexpiprazole (Rexulti) Pimozide (Orap) Risperidone (Risperidone) Iloperidone (Fanapt) Perphenazine (Trilafon) Clozapine (Clozaril) Haloperidol (Haldol) Olanzapine (Zyprexa) Thioridazine (Mellaril) Zuclopenthixol (Clopixol)	CYP2D6	B

European Psychiatric Association (EPA) 2022 Congress: Abstract Evaluation of the Utility and Cost-Effectiveness of Pharmacogenetic Testing Based on CYP2D6 e CYP2C19 Profiling in Antidepressant Treatment. Presented June 4, 2022.

Pharmacogenomic Impact in Psychiatry

- Improved antidepressant efficacy and adherence:
  2.52-fold greater chance of remission for major depressive disorder[1]
- Reduced pharmacy costs:
  $1035.60 lower total medication costs over one year[2]
- Reduced length of stay in a psychiatric hospital:
  36.3 days vs. 46.6 days[3]

[1]Singh AB. *Clin Psychopharmacol Neurosci*. 2015;13(2):150–6.
[2]Winner JG, *et al*. *Curr Res Med Opin*. 2015;31(9):1633–43. doi: 10.1185/03007995.2015.
[3]Bättig VAD, *et al*. *Pharmacopsychiatry*. 2020;53(4):185–92. doi: 10.1055/a-1096-1171.

It’s not just the genes..

Personalized Medicine and Pharmacogenomics are just one piece of the puzzle.

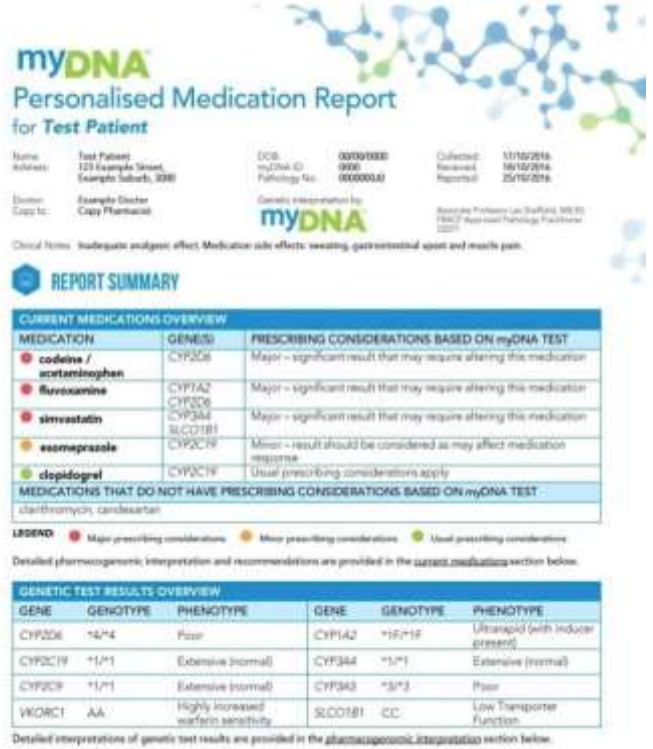
<u>Still have:</u>

- Drug-drug interactions
- Drug-disease interactions
- Drug-nutrient interactions
- Drug-genetic interactions

An additional piece of data to assist the clinician for the best therapeutic plan for the patient!

Pharmacogenetics Clinic
Medical Geneticist
Genetic Counselor
Pharmacologist

Pharmacogenetics
& Direct To Consumer genetic testing



myDNA

Personalised Medication Report

for **Test Patient**

Name: Test Patient
Address: 123 Example Street, Example Suburb, 3000

DOB: 00/00/0000
myDNA ID: 0000
Pathology No: 00000000

Collected: 17/10/2016
Received: 18/10/2016
Reported: 25/10/2016

Doctor: Example Doctor
Copy to: Copy Pharmacist

Genetic interpretation by: myDNA

Associate Professor Lee Stafford, MB BS FRACP Accredited Pathology Practitioner 12345

Clinical Notes: Inadequate analgesic effect. Medication side effects: sweating, gastrointestinal upset and muscle pain.

REPORT SUMMARY

CURRENT MEDICATIONS OVERVIEW		
MEDICATION	GENE(S)	PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST
codeine / acetaminophen	CYP2D6	Major – significant result that may require altering this medication
fluvoxamine	CYP1A2 CYP2D6	Major – significant result that may require altering this medication
simvastatin	CYP3A4 SLCO1B1	Major – significant result that may require altering this medication
esomeprazole	CYP2C19	Minor – result should be considered as may affect medication response
clopidogrel	CYP2C19	Usual prescribing considerations apply
MEDICATIONS THAT DO NOT HAVE PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST		
clarithromycin, candesartan		

LEGEND: Major prescribing considerations; Minor prescribing considerations; Usual prescribing considerations

Detailed pharmacogenomic interpretation and recommendations are provided in the current medications section below.

GENETIC TEST RESULTS OVERVIEW					
GENE	GENOTYPE	PHENOTYPE	GENE	GENOTYPE	PHENOTYPE
CYP2D6	*4/*4	Poor	CYP1A2	*1F/*1F	Ultrarapid (with inducer present)
CYP2C19	*1/*1	Extensive (normal)	CYP3A4	*1/*1	Extensive (normal)
CYP2C9	*1/*1	Extensive (normal)	CYP3A5	*3/*3	Poor
VKORC1	AA	Highly increased warfarin sensitivity	SLCO1B1	CC	Low Transporter Function

Detailed interpretations of genetic test results are provided in the pharmacogenomic interpretation section below.

Pharmacogenetics
& Clinical Laboratores

GENOMIND®

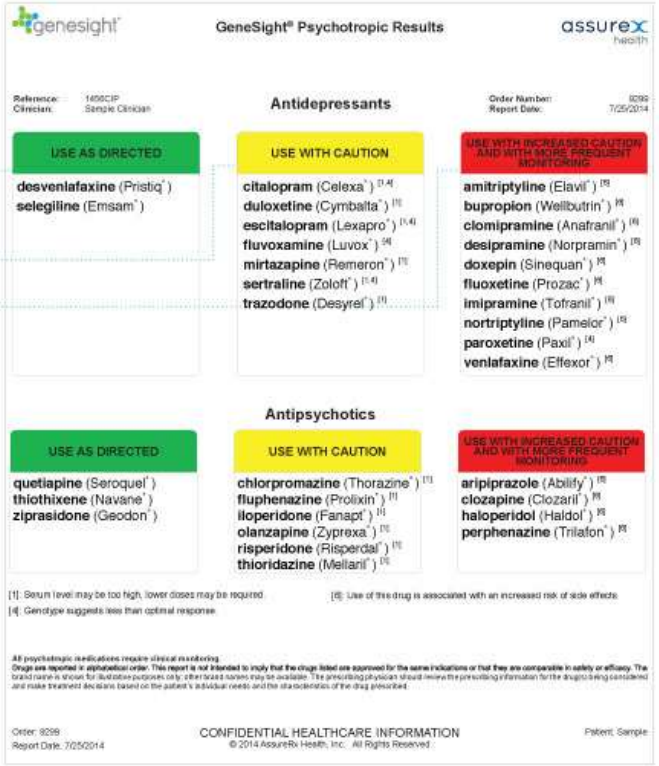
n of One™
Powering Precision Medicine™

Genesight Sample Report

Green: Medications may be used as directed

Yellow: Use medications with caution

Red: Use medications with increased caution and more frequent monitoring



genesight

GeneSight® Psychotropic Results

assurex health

Reference: 1456CIP
Clinician: Sample Clinician

Order Number: 8299
Report Date: 7/25/2014

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
desvenlafaxine (Pristiq®)	**citalopram** (Celexa®) [1,4]	**amitriptyline** (Elavil®) [5]
selegiline (Emsam®)	**duloxetine** (Cymbalta®) [1]	**bupropion** (Wellbutrin®) [4]
	escitalopram (Lexapro®) [1,4]	**clomipramine** (Anafranil®) [5]
	fluvoxamine (Luvox®) [4]	**desipramine** (Norpramin®) [5]
	mirtazapine (Remeron®) [1]	**doxepin** (Sinequan®) [5]
	sertraline (Zoloft®) [1,4]	**fluoxetine** (Prozac®) [4]
	trazodone (Desyrel®) [1]	**imipramine** (Tofranil®) [5]
		nortriptyline (Pamelor®) [5]
		paroxetine (Paxil®) [4]
		venlafaxine (Effexor®) [5]

Antipsychotics

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
quetiapine (Seroquel®)	**chlorpromazine** (Thorazine®) [1]	**aripiprazole** (Abilify®) [6]
thiothixene (Navane®)	**fluphenazine** (Prolixin®) [1]	**clozapine** (Clozaril®) [6]
ziprasidone (Geodon®)	**iloperidone** (Fanapt®) [1]	**haloperidol** (Haldol®) [5]
	olanzapine (Zyprexa®) [1]	**perphenazine** (Trilafon®) [5]
	risperidone (Risperdal®) [1]	
	thioridazine (Mellaril®) [1]	

[1]: Serum level may be too high, lower doses may be required.

[4]: Genotype suggests less than optimal response.

[5]: Use of this drug is associated with an increased risk of side effects.

All psychotropic medications require clinical monitoring.
Drugs are reported in alphabetical order. This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed.

Order: 8299
Report Date: 7/25/2014

CONFIDENTIAL HEALTHCARE INFORMATION

Patient: Sample

GENOMIND® PROFESSIONAL PGx EXPRESS

I. PHARMACODYNAMIC GENE VARIATIONS

GENE RESULT	THERAPEUTIC IMPLICATIONS	GUIDE	CLINICAL IMPACT
SLC6A4 S/S [Low Activity]	***Serotonin Transporter (SLC6A4)*** *is a synaptic transporter protein responsible for serotonin reuptake* • SSRIs act by blocking this transporter to produce a therapeutic response • In Caucasians, **lower likelihood of remission and increased side effect risk with SSRIs** • Potential for increased cortisol release in response to stress		**Assess alternatives to SSRIs** in Caucasians **Therapeutic options: SNRIs** or other **non-SSRI antidepressants** may be considered if clinically indicated
BDNF Val/Met [Altered BDNF secretion]	***Brain-derived Neurotrophic Factor (BDNF)*** *is a protein involved in neuronal development and neural plasticity* • Studies have shown that **Met carriers of *Caucasian ancestry*** may have a **poorer response to SSRIs**, and **improved response to SNRIs or TCAs**. Further studies need to confirm these findings • Studies show that **Met carriers of *Asian ancestry*** may have an **improved response to SSRIs** • **Exercise** has been linked to improvements in cognition and stress response, with **Met carriers showing a more pronounced response**		**Therapeutic options:** increased levels of **physical activity/exercise** if clinically appropriate **Ethnicity dependent antidepressant response**
MTHFR C677T: C/T A1298C: A/C [Low to intermediate activity]	***Methylenetetrahydrofolate Reductase (MTHFR)*** *is an enzyme responsible for the conversion of folic acid to methylfolate, which is a cofactor needed for serotonin, norepinephrine, and dopamine synthesis* • Risk for reduced MTHFR enzyme activity and reduced methylfolate production • **L-methylfolate supplementation** of SSRIs and SNRIs may result in greater symptom reduction compared to SSRIs/SNRIs alone in major depressive disorder • L-methylfolate may be an effective monotherapy for patients with major depressive disorder		**Therapeutic options: L-methylfolate** may be used if clinically indicated

GENOMIND PROFESSIONAL PGx EXPRESS

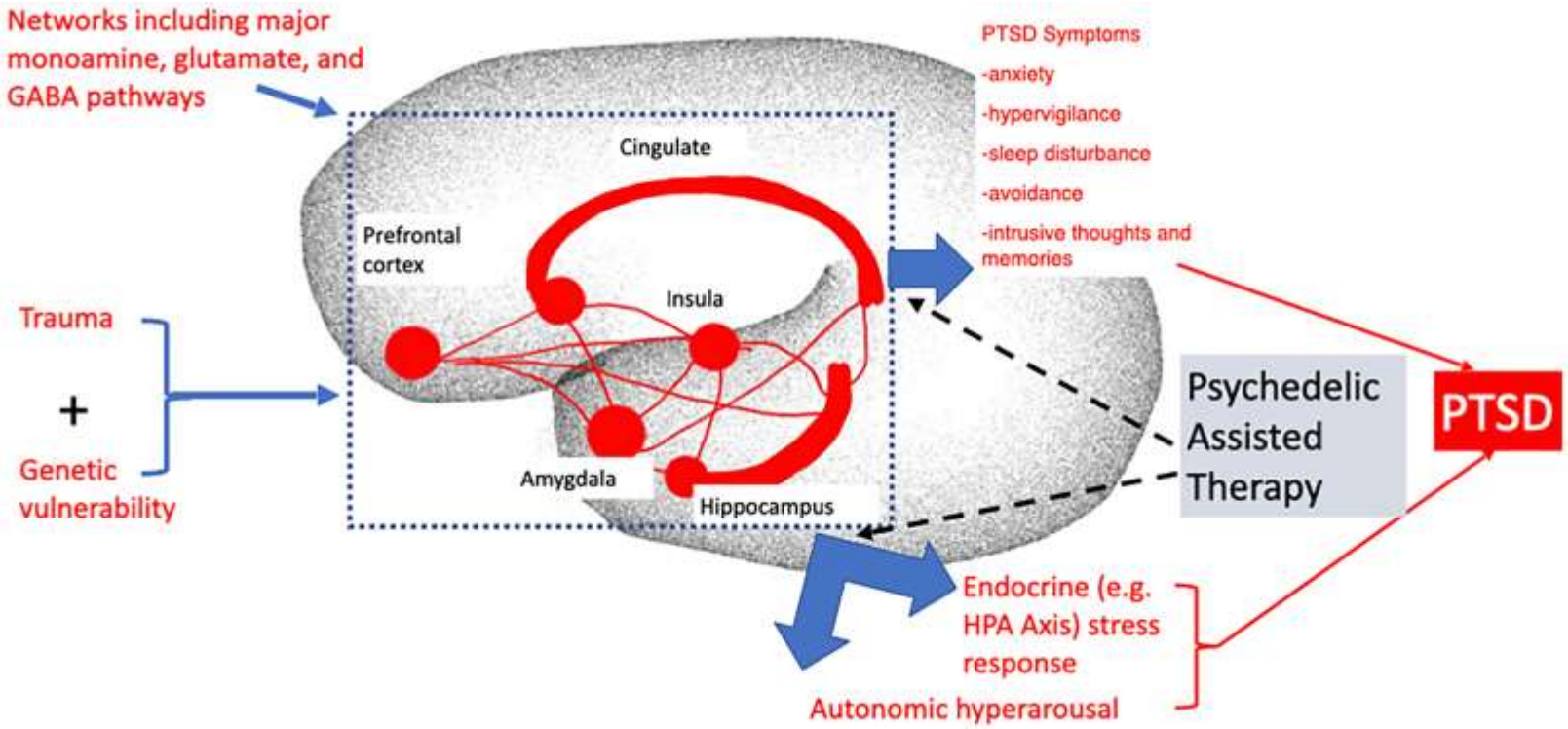
III. GENE DRUG INTERACTION SUMMARY

CLASS	MEDICATION	PHARMACODYNAMIC ASSOCIATIONS	PHARMACODYNAMIC GENE	DRUG EXPOSURE	PHARMACOKINETIC GENE
ANTIDEPRESSANTS					
SSRIs	**Citalopram** (Celexa®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF		2C19
	Escitalopram (Lexapro®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF		2C19
	Fluoxetine (Prozac®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2D6, 2C9
	Fluvoxamine (Luvox®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2D6, 1A2
	Paroxetine (Paxil®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2D6
	Sertraline (Zoloft®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF		2C19, 2B6

"Here is my DNA sequence.."
(New Yorker 2000)

Emerging Psychedelic Therapy in PTSD

Pathophysiology of PTSD



Henner, Keshavan, Hill: J Neuro Sci 439 (2022)

MDMA (3,4 methylenedioxymethamphetamine)

Status: Most advanced in clinical research for PTSD.

Mechanism: Enhances feelings of trust and emotional safety; reduces fear response; facilitates therapeutic processing of trauma.

Evidence:

- **Phase 3 clinical trials** (sponsored by MAPS) have shown **significant reductions in PTSD symptoms**, with many participants no longer meeting PTSD criteria after treatment.
- **FDA granted "Breakthrough Therapy" designation**.

Therapy format: MDMA is used **in conjunction with psychotherapy**.

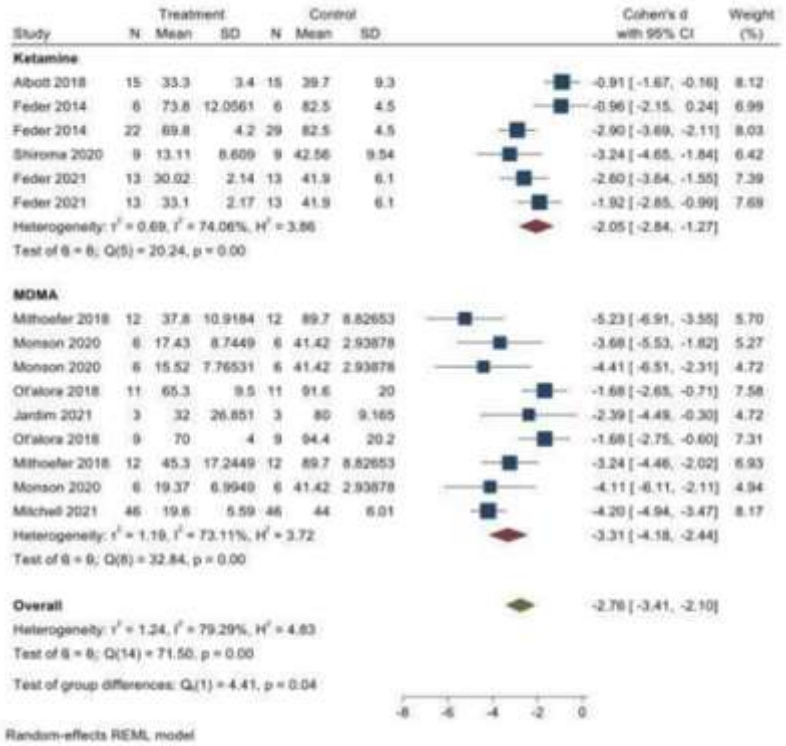
MDMA (3,4 methylenedioxymethamphetamine)

Therapeutic Rationale	Increases release of serotonin, dopamine, norepinephrine, oxytocin, prolactin, vasopressin, and cortisol.
	Increases fear extinction, reduces amygdala activity
	Reopens critical period for social reward learning
	Reduces fear response and shame
	Increases openness and interpersonal trust
	Increases emotional empathy and improves processing traumatic memories

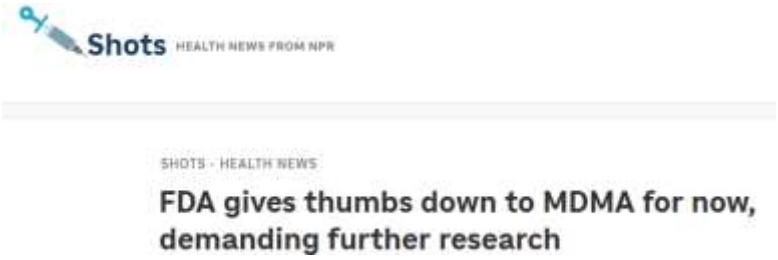
MDMA (3,4 methylenedioxymethamphetamine)

Administration

- Oral dose 75-125 mg
- Duration of Action: 4-8 hours
- Multiple administration (typically 3 sessions) spaced 2 month apart along with psychotherapy



AlFardan, Rose, et al. IJEMHHR 25, 2023



Concerns about the trial design and data integrity:

- Blinding issues: It was difficult to ensure that both participants and therapists remained unaware of who was receiving MDMA or a placebo due to the drug's noticeable effects, potentially introducing bias.
- Misconduct allegations: Accusations of misconduct and bias in the trials raised concerns about the validity of the results.
- Prior MDMA use: Up to 40% of participants had prior experience with MDMA, which could have influenced their responses and skewed the data.

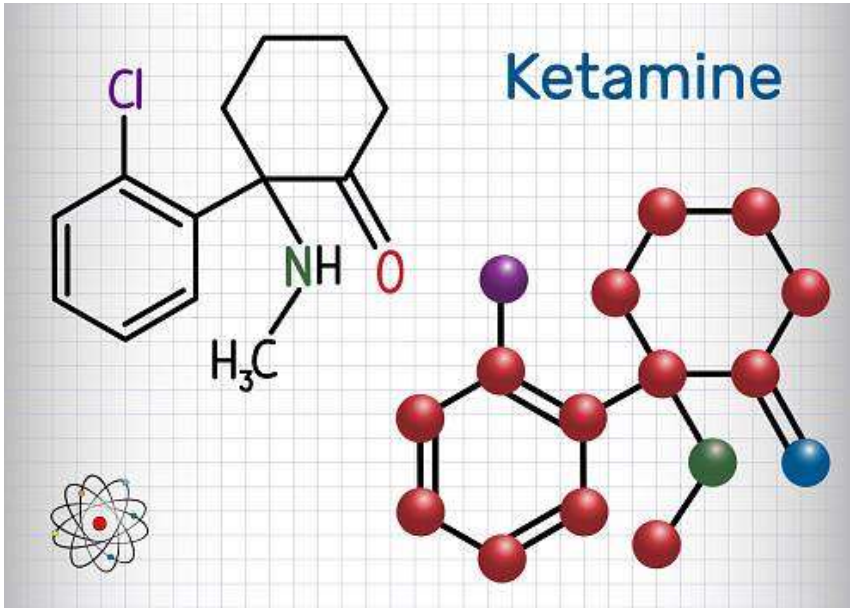
Potential safety concerns:

- Abuse potential: Concerns were raised about the potential for abuse and lack of safeguards to prevent it.
- Cardiovascular risks: There were concerns about potential health risks, including heart problems, which the studies did not adequately measure.

Ketamine

Therapeutic Rationale

- NMDA receptor antagonist
- Rapid symptom reduction
- May serve as a catalyst to psychotherapy-increases receptivity to therapeutic interventions
- Increases synaptic plasticity
- Facilitates fear extinction and blocks memory reconsolidation
- May improve ability to process traumatic memories



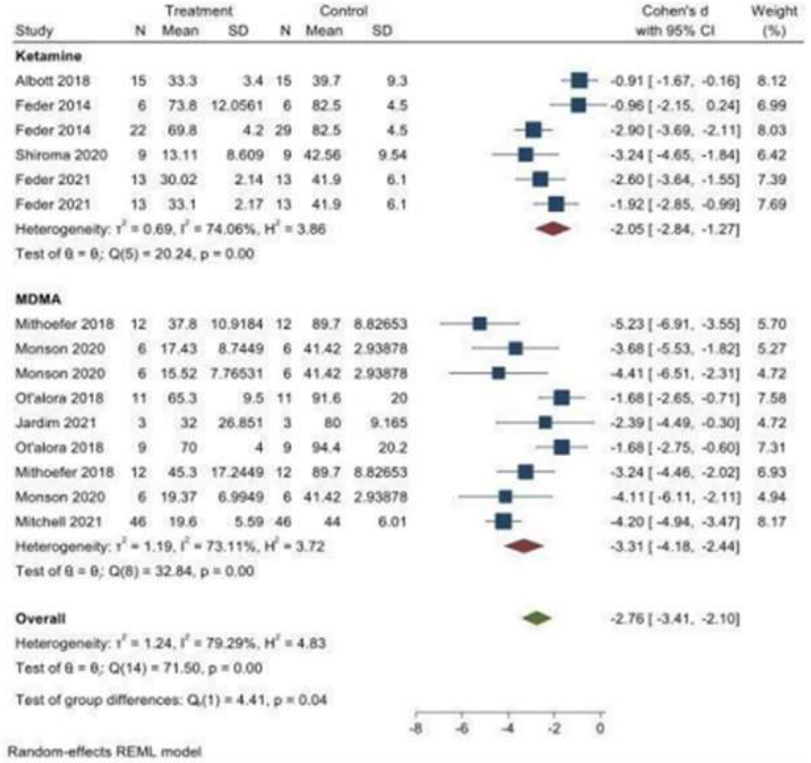
Ketamine

Administration

- Routes of administration: IV, IM, intranasal, oral
- Dose: 0.5 mg/kg over 40 minutes
- Duration of action: 40-70 minutes
- Administration at start of treatment, beginning of session, after memory retrieval, or without psychotherapy
- Single or multiple administration spaced days to weeks apart.

Ketamine

- Rapid (temporary) reduction in PTSD and depressive symptoms.
- Increasing evidence for use in depression



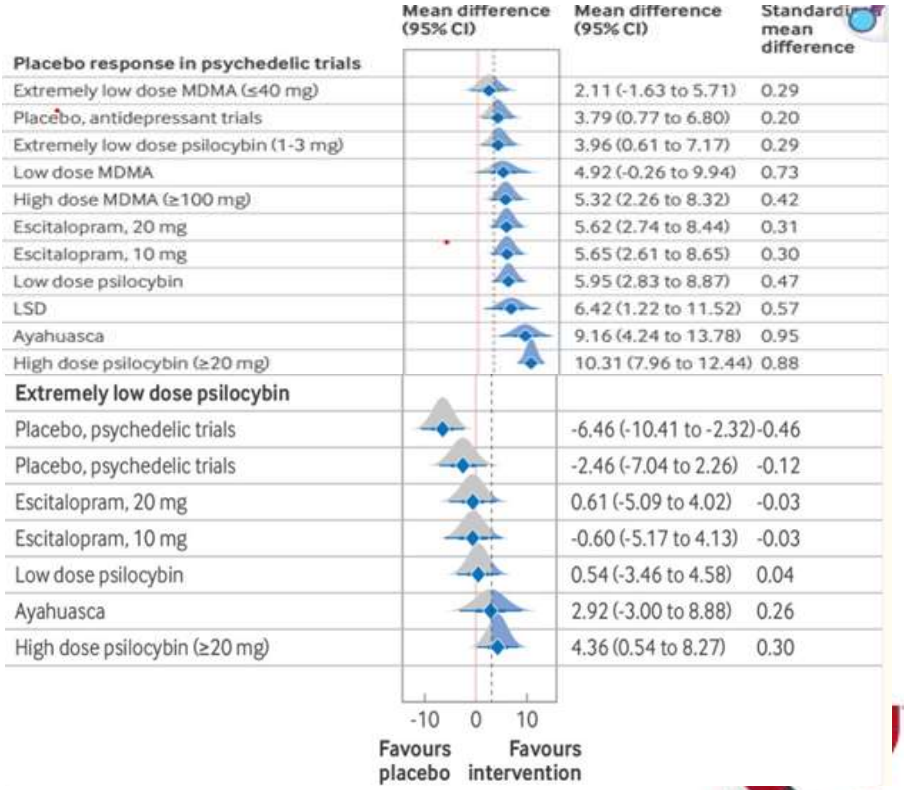
AlFardan, Rose, et al. IJEMHHR 25, 2023

Classic Psychedelics (Psylocibin, LSD, Ayahuasca)

Therapeutic Rationale	5-HT2A receptor agonist
	Serves as a catalyst for psychotherapy
	Can reduce amygdala reactivity during emotional processing.
	Increases insightfulness and introspection.
	Increases divergent thinking and mindfulness-related capacities.
	May reduce avoidance and resolve existential distress
	Can increase emotional empathy, induce emotional breakthrough experiences
	May increase access to traumatic memories.

Psylocibin and LSD

- Dose: Psylocibin 10-25 mg oral; LSD 50-200 ug
- Duration of action: 4-12 hours
- Administer at beginning of therapy session
- Single or multiple administration (typically not more than 3) spaced weeks to month apart.



Hsu, Tsai et al. BMJ 386:2024

Psilocin Dose-Concentrations in Health Individuals

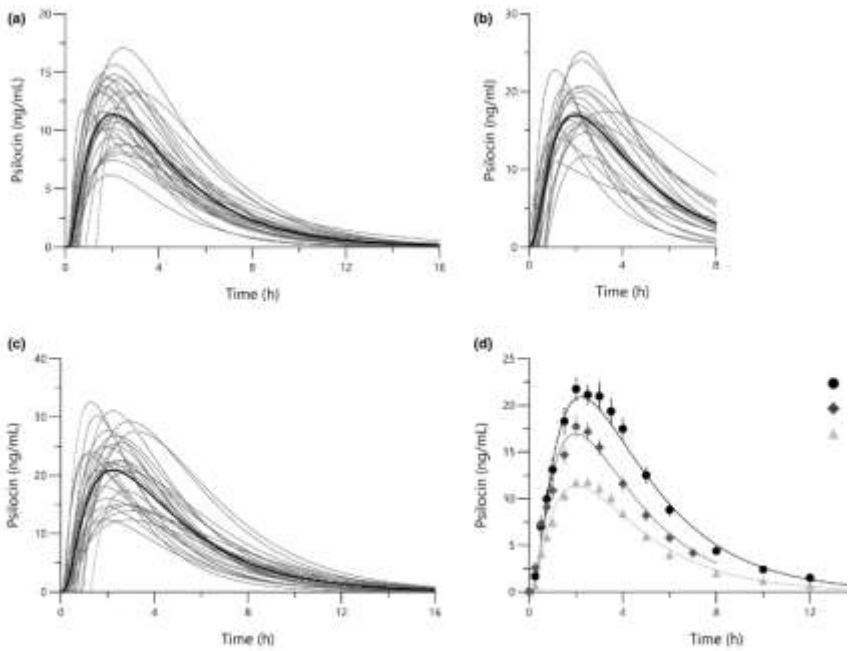


Figure 1 Pharmacokinetics (PKs) of 3 doses of psilocybin, 15, 25, and 30 mg, in 28, 22, and 28 subjects, respectively. (**a–c**) Predi individual plasma psilocin concentration-time curves shown separately for each subject, with the mean marked in bold to illustrate between-subject variability of psilocin concentrations after the administration of **a** 15 mg, **b** 25 mg, and **c** 30 mg psilocybin. (**d**) Plas concentration-time curves that represent the mean of individual PK model predictions. The observed data are expressed as symbol mean ± SEM. Dose-linear increases in psilocin concentrations were observed. Psilocybin was administered at t = 0 hours. PK param listed in **Table 1**.

Holze, Becker, et al. J Clin Pharm 2023

- PK profile in health individuals
- Role of CYP metabolism?
- Natural vs Synthetic Products?
- Assumes normal liver function, what does PK profile look like in hepatic dysfunction?

Cannabidiol (CBD)

Therapeutic Rationale

- Anxiety reduction by interacting with the body's endocannabinoid system
- Sleep improvement
- Reduction in flashback and intrusive memories
- Mood stabilization
- Neuroprotection

Cannabidiol (CBD)

Mild Symptoms (e.g., mild anxiety or mild pain)

- Low dose: 5–10 mg per day.

Moderate Symptoms (e.g., moderate anxiety, mild PTSD symptoms)

- Moderate dose: 15–30 mg per day.

Severe Symptoms (e.g., chronic pain, severe anxiety, or PTSD)

- High dose: 30–50 mg or more per day. Some people use doses upwards of 100 mg per day for severe conditions

Summary

- Significant opportunities in the pharmacologic treatment of PTSD are beginning to emerge.
- Pharmacogenetics can assist with some treatment resistant patients, especially those experiencing adverse events with traditional therapy.
- Psychedelic therapy is rapidly evolving, exploring agents historically “off-limits” from clinical research.
- Understanding the PK/PD profile of these agents will be important to potentially optimize therapy.

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