U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

CLINICIAN GUIDE

Applying Pharmacogenomics (PGx) to the Treatment of Major Depressive Disorder (MDD)

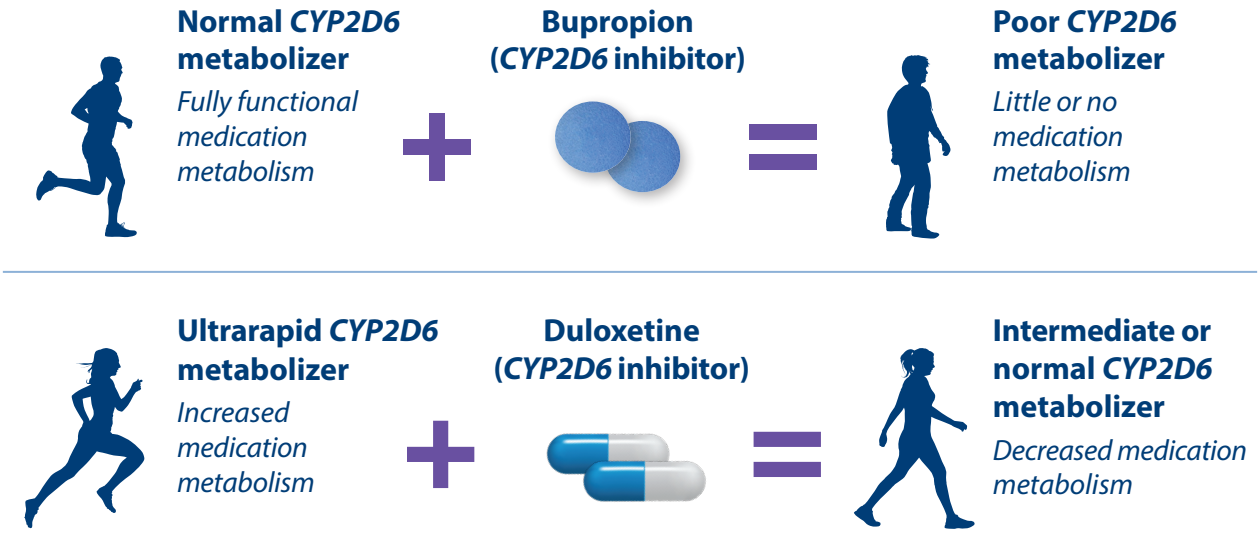
PGx can help optimize pharmaceutical treatment of MDD

MDD is a leading cause of disability and one of the most common mental health disorders.[1] Remission can only be expected in around 30% of patients, with the odds decreasing with each treatment trial.[2,3] If depression persists after two or more proven treatment modalities, it is considered treatment resistant depression (TRD).[4-6]

30% of patients with TRD are estimated to have at least one suicide attempt.[7]

- Provision of PGx testing can reduce the use of medications with predicted drug-gene interactions and may initially increase symptom remission rates.[8,9]
- Variations in DNA coding for *CYP2D6, CYP2C19,* and *CYP2B6* enzymes may result in individual differences in drug exposure.[10,11] **This variability may influence tolerability and treatment discontinuation.**

Phenoconversion+ occurs when factors such as drug-drug interactions modify a genotype-expected phenotype. This effect depends on the strength, duration of therapy, and innate metabolism phenotype.[12] Adjustments in therapy may be needed. Example phenoconversions:



+Phenoconversion is commonly seen with *CYP2D6, CYP2C19,* and *CYP2B6*. For clinical *CYP2D6* phenoconversion guidance, see the *CYP2D6 Phenoconversion Calculator*: precisionmedicine.ufhealth.org/phenoconversion-calculator.

Utilize PGx testing to streamline antidepressant selection or optimize therapy.

The charts below help identify recommendations for antidepressant selection and dosing based on the Veteran's phenotype. **Remember to consider the possibility of phenoconversion** *(see page 1)* when reviewing these tables. For currently prescribed treatments, adjustment is only indicated if the patient is experiencing side effects or not responding to therapy as expected.

Table 1. *CYP2D6* recommendations: fluvoxamine, paroxetine, venlafaxine, vortioxetine[12]

CYP2D6 phenotype	Recommendation	Alternatives
Ultrarapid or rapid	**Paroxetine:** Select alternative antidepressant *(right column)*. **Vortioxetine:** Select alternative antidepressant *(right column)* or if use is warranted, initiate therapy at standard starting dose and titrate accordingly. Increasing target maintenance dose by 50% or more may be needed for efficacy.	• citalopram • duloxetine+ • escitalopram • mirtazapine • levomilnacipran • sertraline • trazodone • vilazodone
Normal	Initiate at usual starting dose and titrate to response.	
Intermediate	Initiate at usual starting dose and titrate to response. **Paroxetine:** Consider lower starting dose and slower titration schedule.	
Poor	**Fluvoxamine:** Consider a 25-50% reduction of recommended starting dose and titrate to response or use alternative antidepressant *(right column)*. **Paroxetine:** Consider a 50% reduction in recommended starting dose, slower titration schedule, and a 50% lower maintenance dose. **Venlafaxine:** Consider alternative antidepressant *(right column)*. **Vortioxetine:** Initiate with 50% of starting dose (e.g., 5 mg) and titrate to the maximum recommended dose of 10 mg or consider alternative antidepressant *(right column)*.	

Due to insufficient evidence, fluoxetine is not included in the CPIC guidelines.
+Duloxetine is a substrate of *CYP2D6*, but evidence does not demonstrate a clinically meaningful impact of *CYP2D6* and therefore, CPIC provides no recommendation.[12]

Table 2. *CYP2C19* recommendations: citalopram,§ escitalopram[12]

CYP2C19 phenotype	Recommendation	Alternatives
Ultrarapid	Consider alternative antidepressant *(right column)*. If deemed clinically appropriate, and adequate efficacy is not achieved at standard maintenance dose, consider titrating to a higher maintenance dose.	• bupropion • duloxetine • fluoxetine • fluvoxamine • levomilnacipran • mirtazapine • nortriptyline • paroxetine • trazodone • venlafaxine • vilazodone • vortioxetine
Rapid	Initiate at usual starting dose. If adequate efficacy is not achieved at standard maintenance dose, consider titrating to a higher dose or alternative antidepressant *(right column)*.	
Normal	Initiate at usual starting dose and titrate to response.	
Intermediate or likely intermediate	Initiate at usual starting dose and consider slower titration and lower maintenance dose.	
Poor or likely poor	Consider alternative antidepressant *(right column)*. If deemed clinically appropriate, consider a lower starting dose, slower titration schedule, and 50% reduction of the standard maintenance dose. **Citalopram:** Not to exceed 20 mg/day **Escitalopram:** Not to exceed 10 mg/day	

§ If > 60 years old, hepatic impairment, poor *CYP2C19* metabolizer, or on cimetidine, the maximum dose is 20 mg daily.

Table 3. *CYP2C19* and *CYP2B6*⁺ dosing recommendations: sertraline[12]

Phenotype	*CYP2B6* ultrarapid or rapid	*CYP2B6* normal	*CYP2B6* intermediate	*CYP2B6* poor
***CYP2C19* ultrarapid or rapid**	Initiate at usual starting dose. If adequate efficacy is not achieved at standard maintenance dose, consider titrating to a higher dose or switching to an antidepressant not predominantly metabolized by *CYP2C19*.	Initiate at usual starting dose and titrate to response.		
***CYP2C19* normal**	Initiate at usual starting dose and titrate to response.		Initiate at usual starting dose and titrate to response. Consider slower titration and lower maintenance dose.	Consider lower starting dose, slower titration, and 25% reduction of standard maintenance dose or select an alternative antidepressant not predominantly metabolized by *CYP2B6*.
***CYP2C19* intermediate or likely intermediate**	Initiate at usual starting dose and titrate to response.	Initiate at usual starting dose and titrate to response. Consider slower titration and lower maintenance.		Consider lower starting dose, slower titration, and 50% reduction of standard maintenance dose.
***CYP2C19* poor or likely poor**	Consider lower starting dose, slower titration, and 50% reduction of standard maintenance dose, or use an antidepressant not predominantly metabolized by *CYP2C19*.			Select antidepressant not primarily metabolized by *CYP2C19* or *CYP2B6*.

⁺Antidepressants metabolized by *CYP2B6*–Major: bupropion; minor: vortioxetine, fluoxetine, amitriptyline.[13] If only *CYP2C19* phenotype is known, proceed as if *CYP2B6* is normal.

Ultrarapid or rapid metabolizer | Concerns for efficacy due to increased medication metabolism
Normal metabolizer | Fully functional medication metabolism
Intermediate metabolizer | Concerns for safety due to decreased medication metabolism
Poor metabolizer | Concerns for safety due to little or no medication metabolism

Tricyclic antidepressants (TCA)

TCA metabolism can be impacted by both *CYP2C19* and *CYP2D6* enzymes. TCAs are often prescribed at lower doses for indications like sleep, pain, and migraine prophylaxis. PGx dosing recommendations apply to higher initial doses of TCAs for treatment of depression.[14]

Table 4. Dual-gene (*CYP2D6/CYP2C19*) recommendations for the treatment of depression: amitriptyline, clomipramine, doxepin, imipramine, trimipramine[14]

<table>
<tr><th>Phenotype</th><th>CYP2D6
ultrarapid or rapid</th><th>CYP2D6
normal</th><th>CYP2D6
intermediate</th><th>CYP2D6
poor</th></tr>
<tr><td>CYP2C19
ultrarapid
or rapid</td><td rowspan="3">Avoid use+</td><td colspan="2">Consider alternative drug not metabolized by CYP2C19.</td><td rowspan="3">Avoid use+</td></tr>
<tr><td>CYP2C19
normal</td><td rowspan="2">Initiate at usual starting dose and titrate to response.</td><td rowspan="2">Consider a 25% reduction in recommended starting dose.</td></tr>
<tr><td>CYP2C19
intermediate</td></tr>
<tr><td>CYP2C19 poor</td><td>Avoid use+ If warranted, consider a 50% reduction in starting dose.</td><td>Avoid use+</td></tr>
</table>

+If use is warranted, consider ordering a pharmacy PGx consult. If using higher doses of TCAs, consider recommendations for monitoring therapeutic blood levels.

Clinical pharmacist practitioners (CPP)

PGx CPPs are Advanced Practice Providers who are highly trained members of the healthcare team with additional education or experience in pharmacogenomics.

Consult services are available in the electronic medical record orders package for providers to request CPP assistance. CPPs can evaluate antidepressant pharmacotherapy based on the PGx test results, make adjustments if needed, and contact patients for follow-up education.

For more information

RESOURCES:

National Pharmacogenomics SharePoint: http://tinyurl.com/bdft5zd8
For up to date testing capabilities and PGx CPP contact information

VA Formulary Advisor: https://www.va.gov/formularyadvisor/
For questions about medication formulary status

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