PGx Recommendations by CYP2D6 Genotype

CYP2D6 and Paroxetine and Fluvoxamine

Phenotype	Drug(s) being considered	Implication	Therapeutic Recommendation	Classification of Recommendation
Ultra-rapid metabolizer	Paroxetine	Increased metabolism to less active compounds when comapred to extensive metabolizers. Lower/undetectable plasma concentrations may increase probability of pharmacotherapy failure	Select alternative drug not predominantly metabolized by CYP2D6	Strong
	Fluvoxamine	No data available for fluvoamine	No recommendation for fluvoxmine due to lack of evidence	Optional
Extensive (normal) metabolizer	Fluvoxamine and paroxetine	Normal metabolism	Initiate therapy with recommended starting dose	Strong
Intermediate metabolizer	Fluvoxamine and paroxetine	Reduced metabolism compared to normal metabolizers. Higher plasma concentrations may increase the probability of side effects	Initiate therapy with recommended starting dose	Moderate
Poor metabolizer	Fluvoxamine and paroxetine	Greatly reduced metabolism compared to normal metabolizers. Higher plasma concentrations may increase the probability of side effects	Select alternative drug not predominantly metabolized by CYP2D6, if use is warranted consider a 50% reduction of initial dose	Optional

CYP2C19 Citalopram, Escitalopram, and Sertraline

Phenotype	Drug(s) being considered	Implication	Therapeutic Recommendation	Classification of Recommendation
Ultra-rapid metabolizer	Citalopram and escitalopram	Increased metabolism when comapred to extensive metabolizers. Lower plasma concentrations may increase probability of pharmacotherapy failure	Select alternative drug not predominantly metabolized by CYP2C19	Moderate
	Sertraline	Increased metabolism when compared to normal metabolizers	Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19	Optional
Extensive (normal) metabolizer	Citalopram, escitalopram, sertraline	Normal metabolism	Initiate therapy with recommended starting dose	Strong
Intermediate metabolizer	Citalopram, escitalopram, sertraline	Reduced metabolism compared to normal metabolizers.	Initiate therapy with recommended starting dose	Moderate
Poor metabolizer	Citalopram and escitalopram	Greatly reduced metabolism compared to normal metabolizers. Higher plasma concentrations may increase the probability of side effects	Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19	Moderate
	Sertraline			Optional

Pediatric SSRI PGx Cheat Sheet

SSRI Use in Pediatric/Adolescent Depression

Medication	FDA Approval in Pediactics	Recommend by:		
		AAP	GLAD-PC	TCCP
Citalopram		✓	✓++	✓
Fluoxetine	✓	✓	✓+	✓
Fluvoxamine		✓		
Paroxetine		✓		
Sertraline		✓	✓++	✓
Escitalopram	✓*	✓	✓++	

*≥ 12 years old; + first line; ++ second line

AFP Questions to Guide Initiation of Pharmacotherapy

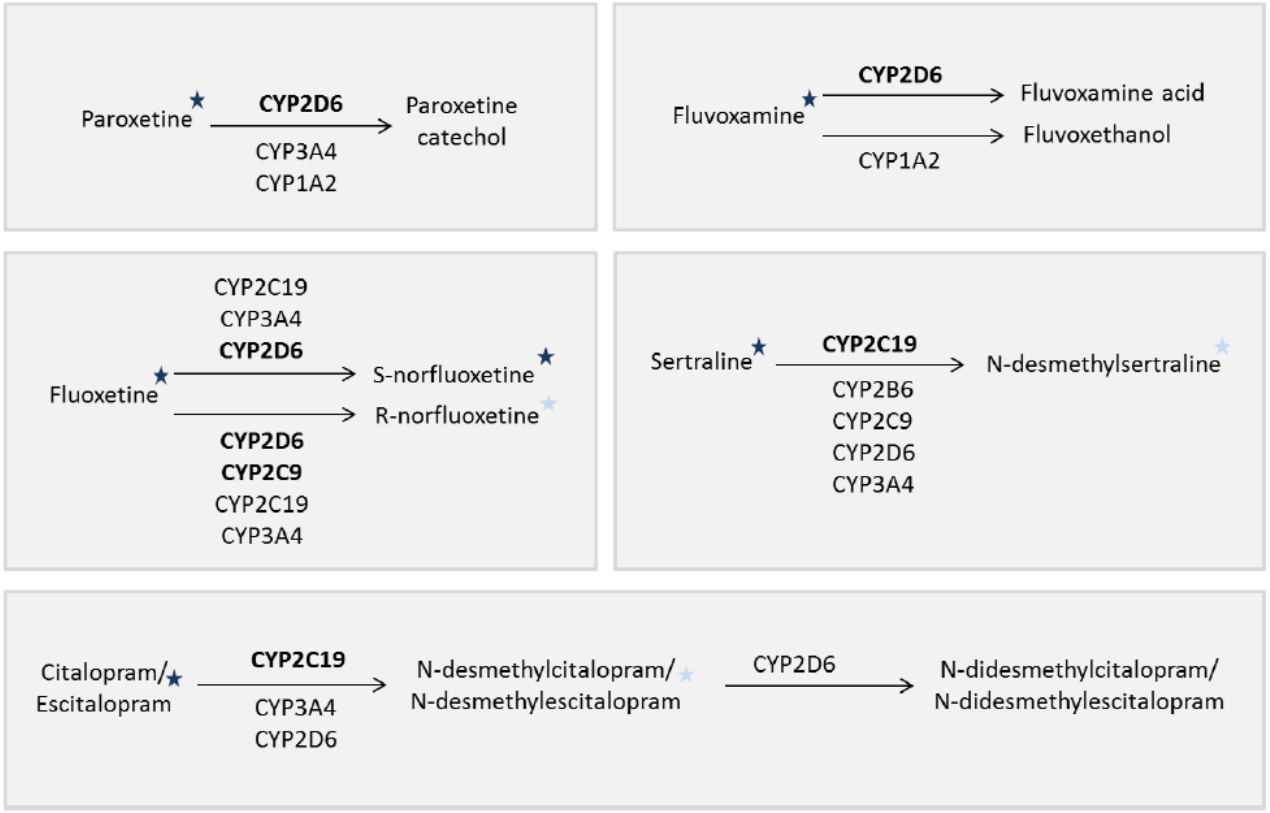
Is the depression of moderate to severe severity?
Has there been a prior episode of depression?
Has the patient been treated for depression with medication in the past?
Is there a family history of depression?
Is there a family history of depression with significant response to medication?
Have environmental stressors been modified with no associated improvements in mood?
Has evidence-based psychotherapy (i.e., cognitive behavior therapy, interpersonal therapy) been attempted without success?

General SSRI Information

Medication	Starting Dose, mg/d	Increments, mg	Effective Dose, mg	Maximum Dose	Affected by CYP2D6	Affected by CYP2C19
Citalopram	10	10	20	60		✓
Fluoxetine	10	10-20	20	60		
Fluvoxamine	50+	50	150	300	✓	
Paroxetine	10	10	20	60	✓	
Sertraline	25	12.5-25	50	200		✓
Escitalopram	5	5	10	20		✓

Per AAP Depression Guidelines and GLAD-PC

GLAD-PC update suggests a starting dose of 25 mg/d



SUPPLEMENTAL FIGURE S1. METABOLISM OF SSRIs, WHERE BOLDED ENZYMES REPRESENT A MAJOR METABOLIC PATHWAY.

★ Active ☆ Less active metabolite

Drug	Gene(s)/Level of evidence	Guidelines/Supporting Studies*	FDA Label Information	Additional Information/Comments
Haloperidol	CYP2D6 (3) SLC6A5 (3)	2D6: DPWG guidelines • Reduce dose by 50% in PMs	--	
Aripiprazole	CYP2D6 (3)	2D6: DPWG guidelines • Reduce maximum dose to 10 mg/day (67% of max recommended daily dose).	2D6 FDA label: Decrease dose by half in 2D6 PMs; decrease to one-quarter of usual dose in 2D6 PMs who are taking a 3A4 inhibitor (Dosage and Administration)	
Risperidone	CYP2D6 (2A, 3) HTR2C (3) HTR2A (3)	2D6: DPWG guidelines • Insufficient data to allow dosage adjustment	2D6 FDA label: Although 2D6 EMs have lower risperidone and higher 9- hydroxyrisperidone concentrations than PMs, PK of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in EMs PMs. (Clinical Pharmacology)	
Paliperidone		--	--	A few small studies show that genotype MCR4 AA linked to increase risks of weight gain Gene not included on clinical panels
Ziprasidone		--	--	CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on in vivo abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction by aldehyde oxidase.
Clozapine	HTR2C (2B) MTHFR (3) HTR3A (3) CYP1A2 (3)	2D6: DPWG • no recommendations for dose change	Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these patients. (Dosage and administration, use in specific populations)	
Fluphenazine	CYP1A2 (3)	--	--	2 small studies: Genotypes CC + AC are associated with increased QT interval when treated with chlorpromazine in people with Schizophrenia as compared to genotype AA

Chlorpromazine	CYP1A2 (3)	--	--	2 small studies: Genotypes CC + AC are associated with increased QT interval when treated with chlorpromazine in people with Schizophrenia as compared to genotype AA.
Iloperidone	CYP2D6 (3)	--	FANAPT dose should be reduced by one-half for poor metabolizers of CYP2D6 (dosage and administration)	
Olanzapine		2D6: DPWG • no dosing recommendations for olanzapine based on CYP2D6 genotype.		
Perphenazine	--	--	CYP2D6 is involved in the pharmacokinetics of perphenazine. Poor metabolizers demonstrate higher plasma concentrations of antipsychotic drugs at usual doses, which may correlate with emergence of side effects. Prospective phenotyping of elderly patients prior to antipsychotic treatment may identify those at risk for adverse events. (clinical pharmacology)	No studies on PharmGKB with 2D6; 2 lower level clinical annotations with RGS4 (level 3)
Quetiapine	CYP3A5 (3) SLC6A4 (3)	--	--	--
Thioridazine	CYP1A2 (3) CYP2D6 (3)	--	Contraindicated in CYP2D6 PMs (contraindications, warnings, and precautions)	Small study (n = 61) patients showed variability in thioridazine: mesoridazine ratio in different CYP2D6 genotypes
**Asenapine, lurasidone, thiothixene are included in the GeneSight panel but do not have clinically relevant data per PharmGKB.*				
Antidepressants				
Citalopram	CYP2C19 (1A) SLC6A4 (2A) HTR2A (2B) CYP2D6 (3)	2C19: DPWG, CPIC Guideline provides dose recommendations • CPIC • UM: Consider alt drug • EM, IM: No change • PM: Consider alt drug or consider 50% dose reduction • DPWG: • UM: Titrate to max of 150% of normal dose or select alt drug • PM, IM: No recommendation	2C19 FDA label: 20 mg/day is the maximum recommended dose in PMs (Dosage and Administration)	
Escitalopram	CYP2C19 (1A, 2A, 3) SLC6A4 (2A, 3)	2C19: DPWG, CPIC Guideline provides dose recommendations • CPIC	--	

	CYP2D6 (3) HTR2A (3) CYP1A2 (3)	• UM: Consider alt drug • EM, IM: No change • PM: Consider alt drug or consider 50% dose reduction • DPWG: • UM: Titrate to max of 150% of normal dose or select alt drug • PM, IM: No recommendation 2D6 - No PGx studies. PK studies show lack of interaction		
Paroxetine	CYP2D6 (1A, 3) HTR2A (3, 4) CYP1A2 (3) SLC6A4 (3) HTR1A (2B, 3) HTR1B (3) HTR3B (3)	2D6: DPWG, CPIC Guideline provides dose recommendations based on CYP2D6 • CPIC: • UM: Select alt drug • EM, IM: No change • PM: Select alt drug or consider 50% dose reduction • DPWG: • UM: insufficient data • PM, IM: No recommendation	2D6 FDA label: Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment (Clinical Pharmacology)	
Sertraline	CYP2C19 (1A) CYP2D6 (3) SLC6A4 (3) HTR1A (3)	2C19: DPWG, CPIC Guideline provides dose recommendations • CPIC • UM: Initiate therapy as normal, consider alt drug is no response • EM, IM: No change • PM: Consider alt drug or consider 50% dose reduction • DPWG: • UM: no recommendation • PM: Reduce dose by 50% • IM: insufficient data	--	
Venlafaxine	CYP2D6 (2A, 3) HTR2A (3) CYP2C19 (4) HTR1B (3)	2D6: DPWG guideline • PM, IM: insufficient data • UM: Titrate to max of 150% of normal dose or select alt drug	2D6 FDA label: Label states venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. "Additionally, in a clinical study involving CYP2D6-poor and extensive metabolizers, the total concentration of active compounds (venlafaxine plus ODV), was similar in the two metabolizer groups. Therefore, no	I've checked the pdf drug label and the full label on daily med and I can't find the study this is referencing.

			dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor."	
Amitriptyline	CYP2D6 (1A) CYP2C19 (1A, 3)	2D6: CPIC and DPWG guidelines • DPWG: UM & PM insufficient data for dose calculation; select alt drug. IM reduce dose by 25% or select alt drug. • CPIC: • UM: Avoid TCA. Select alt drug. If TCA needed increase starting dose • EM: No change • IM: Consider 25% reduction in start dose • PM: Avoid TCA. If TCA needed, consider 50% starting dose reduction 2C19: CPIC guideline • UM: Consider alt drug • EM, IM: No change • PM: Consider 50% reduction in starting dose	2D6 FDA Label: CYP2D6 poor metabolizers may have higher plasma concentrations of tricyclic antidepressants, and the label suggests monitoring of plasma levels if this drug is co-administered with a CYP2D6 inhibitor.	CPIC neuropathic pain: Due to lower dosages it is less likely for 2D6 or 2C19 IM or PM to experience adverse effects. Recommend no dose modifications in these instances.
Nortriptyline	2D6: Level 1A SLC39A14: Level 3	2D6: CPIC and DPWG guidelines • DPWG: PM reduce dose by 60%. IM reduce dose by 40%. UM select alt drug or increase dose by 60%. • CPIC: • UM: Avoid TCA. Select alt drug. If TCA needed increase starting dose • EM: No change • IM: Consider 25% reduction in start dose • PM: Avoid TCA. If TCA needed, consider 50% starting dose reduction	2D6 FDA Label: CYP2D6 poor metabolizers may have higher plasma concentrations of tricyclic antidepressants, and the label suggests monitoring of plasma levels if this drug is co-administered with a CYP2D6 inhibitor.	
Clomipramine	CYP2D6 (1A) CYP2C19 (2A) SLC6A4 (3)	2D6: DPWG guidelines	2D6 FDA Label: CYP2D6 poor metabolizers may have higher plasma concentrations of tricyclic antidepressants, and the label suggests	CPIC guideline use amitriptyline as model drug but state that tricyclics have comparable pharmacokinetic profiles and it

	HTR1B (3)	• PM reduce dose by 50%. IM insufficient data. UM select alt drug. 2D6 and 2C19: CPIC guideline Recommendations for amitriptyline may apply	monitoring of plasma levels if this drug is co-administered with a CYP2D6 inhibitor.	may be reasonable to apply the guideline to other tricyclics
Desipramine	CYP2D6 (1A, 2A)	2D6: CPIC guideline Recommendations for nortriptyline may apply.	2D6 FDA Label: Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs), such as desipramine, when given typical doses.	Model drug: Nortriptyline
Doxepin	CYP2D6 (1A, 2A) CYP2C19 (3) CYP2C9 (3)	2D6: DPWG guidelines • PM reduce dose by 60%. IM reduce dose by 20%. UM select alt drug or increase dose by 100%. 2D6 and 2C19: CPIC guideline Recommendations for amitriptyline may apply	2D6 and 2C19 FDA Label: CYP2D6 and CYP2C19 poor metabolizers have higher than expected plasma concentrations of doxepin when given typical doses.	Model drug: Amitriptyline
Imipramine	CYP2D6 (1A, 2A) CYP2C19 (2A, 3)	2D6 and 2C19: CPIC and DPWG guidelines • DPWG 2D6: PM reduce dose by 70%. IM reduce dose by 30%. UM select alt drug or increase dose by 70%. • DPWG 2C19: PM reduce dose by 30% or select alt drug. IM insufficient data. UM no recommendation • CPIC: Recommendations for amitriptyline may apply	2D6 FDA Label: CYP2D6 poor metabolizers may have higher plasma concentrations of tricyclic antidepressants, and the label suggests monitoring of plasma levels if this drug is co-administered with a CYP2D6 inhibitor.	Model drug: Amitriptyline
Trimipramine	CYP2D6 (1A, 2A) CYP2C19 (2A) CYP2C9 (3)	2D6 and 2C19: CPIC guideline Recommendations for amitriptyline may apply	2D6 FDA label: PMs have higher than expected plasma concentrations of TCAs when given usual doses. Depending on the fraction of drug metabolized by 2D6, the increase in plasma concentration may be small, or large (8 fold increase in plasma AUC of the TCA) (Drug Interactions).	Model drug: Amitriptyline
Bupropion	CYP2C19 (3) CYP 2B6 (3)	--	--	*
Desvenlafaxine	--	--	--	Major active metabolite of Venlafaxine

Trazodone	--	--	--	*
Vilazodone	--	--	--	*
Selegiline	--	--	--	*
Fluvoxamine	CYP2D6 (1A, 3) HTR2A (3, 4) SLC6A4 (3) HTR1A (3)	2D6: CPIC guideline • UM: No recommendation • EM, IM: No change • PM: Consider alt drug or consider 25-50% dose reduction	2D6 FDA Label: Caution should be used in treating patients with low CYP2D6 activity and those receiving other medication known to inhibit CYP2D6.	
Duloxetine	--	2D6: DPWG guideline provides no dosing recommendations. No evidence for IM and UM. PM has non-statistically significant clinical effect.	--	
Fluoxetine	CYP2D6 (3) SLC6A4 (3, 4) HTR1A (3)	2D6 & 2C19: CPIC guideline states lack of data and provides no recommendations.	2D6 FDA Label: Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Prescribing information states caution is warranted in situations that may prolong QT such as "conditions that predispose to increase fluoxetine exposure (overdose, hepatic impairment, use of CYP2D6 inhibitors, CYP2D6 poor metabolizer status, …"	
Mirtazapine	CYP2D6 (2A) SLC6A4 (3) CYP2B6 (3)	2D6: DPWG guideline provide no dose recommendations	--	
Vortioxetine	CYP2D6 (3)	--	2D6 FDA Label: Maximum recommended dose in patients who are known CYP2D6 poor metabolizers is 10 mg/day.	
Atomoxetine	CYP2D6 (2A) SLC6A2 (3)	2D6: DPWG Guideline • PMs: Dose increase probably not necessary; be alert to ADEs.	2D6 FDA label: Dosing adjustment is recommended in patients known to be poor CYP2D6 metabolizers (Dosage and	

		• UMs: Be alert to reduced efficacy or select alternative drug (e.g., methylphenidate, clonidine).	Administration; Warnings and Precautions; Clinical Pharmacology).	
Diazepam	CYP2C19 (3)	--	2C19, 3A4: FDA label: The marked inter-individual variability in clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 and CYP3A4 (Clinical Pharmacology)	Single study of 63 asian patients showed that CYP2C19 *2 + *3 is associated with decreased metabolism of diazepam as compared to CYP2C19 *1.
Lorazepam		--	--	Small study of 14 Asian patients with UGT2B7 (evidence level 3)
Oxazepam	UGT2B15 (2B)	--	--	
Alprazolam	--	--	--	
Clonazepam	--	--	--	

CPIC = Clinical Pharmacogenetics Implementation Consortium; DPWG = Dutch Pharmacogenetics Working Group
*See accompanying for PharmGKB Levels of Evidence definitions and a complete listing of CPIC guidelines

PharmGKB Levels of Evidence Definitions

Evidence Level	Definition
1A	Annotation for a variant-drug combination in a CPIC or medical society-endorsed PGx guideline, or implemented at a PGRN site or in another major health system.
1B	Annotation for a variant-drug combination where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p-values, and preferably will have a strong effect size.
2A	Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.
2B	Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.
3	Annotation for a variant-drug combination based on a single significant (not yet replicated) or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association.
4	Annotation based on a case report, non-significant study or in vitro, molecular or functional assay evidence only.

Available CPIC Guidelines

Drug	Gene
Clopidogrel	CYP2C19
Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, trimipramine	CYP2C19, CYP2D6
Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline	CYP2C19, CYP2D6
Codeine	CYP2D6
Phenytoin	CYP2C9, HLA-B
Warfarin	CYP2C9, VKORC1
Ivacaftor	CFTR
Capecitabine, 5-FU, tegafur	DPYD
Rasburicase	G6PD
Abacavir	HLA-B
Allopurinol	HLA-B
Carbamazepine	HLA-B
Azathioprine, 6-MP, thioguanine	TPMT
Boceprevir, peg-interferon, ribavirin, telaprevir	IFNL3
Simvastatin	SLCO1B1

CYP2D6

CYP2C19

CYP2C9

CYP1A2

SLC6A4

HTR2A