PSYCHOTROPIC UPDATE & PHARMACOGENETIC TESTING

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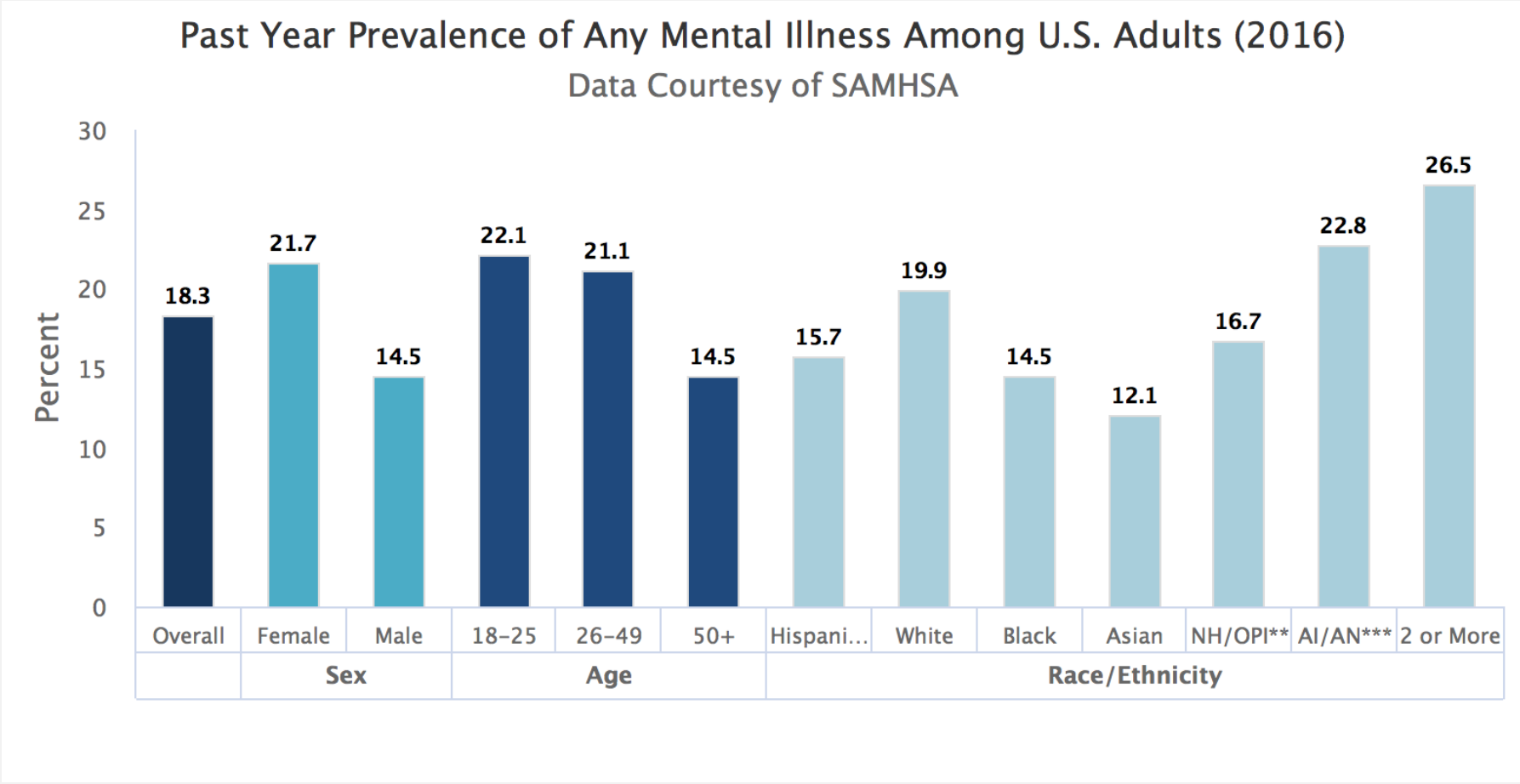
DISCLOSURE

- I have no conflicts of interest, financial or otherwise, to disclose.

OBJECTIVES

- Update on new psychotropic medications
  - Review basic psychopharm classes
  - Identify newest psychotropic meds available
  - Understand class, indications, dosing, & monitoring requirements for each
- Discuss pharmacogenetic testing
  - Controversies regarding usefulness & application
  - When to consider ordering
  - How to correctly interpret & apply results

IMPACT OF MENTAL ILLNESS

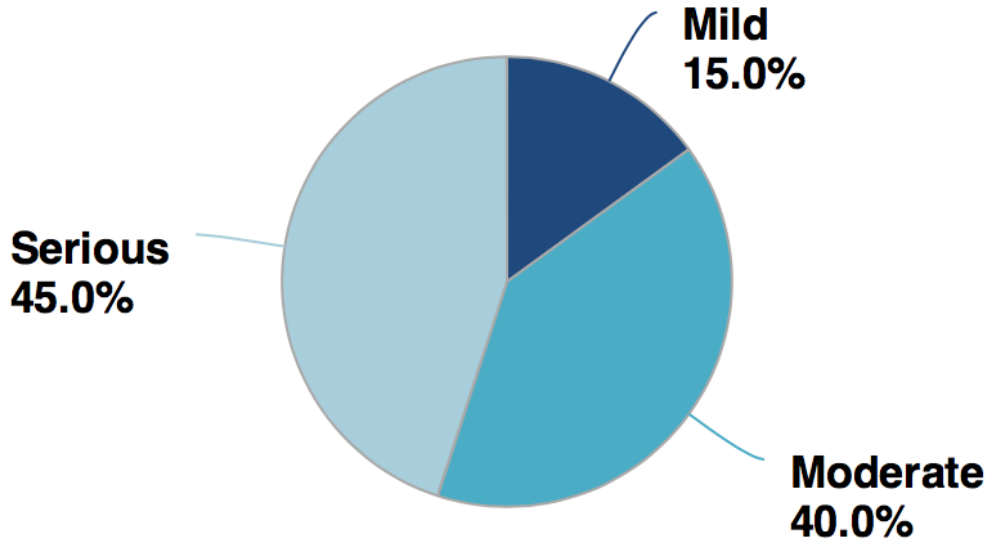


NIMH.NIH.GOV

IMPACT OF MENTAL ILLNESS

Past Year Severity of Any Mood Disorder Among U.S. Adults (2001–2003)

Data from National Comorbidity Survey Replication (NCS-R)



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FDA-APPROVED MEDICATIONS FOR MDD

Amitriptyline	Bupropion
Citalopram	
Doxepin	Duloxetine
Escitalopram	Fluoxetine
Imipramine	
Mirtazapine	Nefazadone
Nortriptyline	Paroxetine
Quetiapine	Selegiline
Sertraline	Trazodone
Venlafaxine	

FDA-APPROVED MEDICATIONS FOR MDD

Amitriptyline	Bupropion
Citalopram	**DESVENLAFAXINE**
Doxepin	Duloxetine
Escitalopram	Fluoxetine
Imipramine	**LEVOMILNACIPRAN**
Mirtazapine	Nefazadone
Nortriptyline	Paroxetine
Quetiapine	Selegiline
Sertraline	Trazodone
Venlafaxine	**VILAZODONE**
VORTIOXETINE	

DESVENLAFAXINE (PRISTIQ®)

- Class: SNRI
- Indication: MDD
- Off label: GAD, Fibromyalgia, Social Anxiety, PTSD, Panic Disorder, PMDD
- Metabolite of Venlafaxine (Effexor ®)
  - 45% excreted unchanged into urine
    20% metabolized via UGT &
    only 5% CYP 3A4
- Forms: 25, 50, 100mg extended-release tablets
- Dose: 50mg is starting & therapeutic dose
- Taper off / Can take with or without food
- SE: hypertension, sedation, somnolence, constipation, dizziness, increased sweating, nausea, decreased appetite, sexual dysfunction, anxiety

DESVENLAFAXINE (PRISTIQ®)

USE IN SPECIFIC POPULATIONS

- Pregnancy: No controlled studies in humans → registry available
- Nursing: Mean RID = 6.8%
- Renal Impairment:
  - Moderate (clearance 30-50 mL/min) = 50mg
  - Severe (15-29 mL/min or below) = 25mg every day or 50mg every other
    - No supplemental dose after dialysis
- Hepatic Impairment: ↓ dose in mod to severe (Child Pugh 7-15) = 50mg highest
- Geriatric: Increased incidence of orthostatic hypotension

Package insert - Apr2018

DESVENLAFAXINE (PRISTIQ®)

- PATENT EXTENDER
- So why prescribe desvenlafaxine > venlafaxine?
  - Once daily dosing that does not require titration
  - Theoretically fewer DDI than venlafaxine
- Ultimately not any more effective than venlafaxine
- COST: GoodRx.com → $34.15 for #30 of 50mg @ Meijer

LEVOMILNACIPRAN (FETZIMA®)

- Class: SNRI
- Indication: MDD
- Off label: anxiety
- Enantiomer of milnacipran (Savella®)
- Forms: 20, 40, 80, 120mg XR capsule
- Dose: 20mg x 2 days → 40mg
  - Target 40-120mg once daily (can increase by 40mg q2 days)

- SE: *nausea*, constipation, sexual SE, increased sweating, urinary retention, hyponatremia, impaired platelet aggregation, mydriasis (tend to be dose dependent)
- Taper off / Best taken with food to ↓ nausea

LEVOMILNACIPRAN (FETZIMA®)

- USE IN SPECIAL POPULATIONS:
- Pregnancy: C – Based on animal data, may cause harm
- Nursing: No data available (registry available)
- Renal Impairment: predominant clearance
  - Mild → no dose change
  - Moderate → 80mg daily
  - Severe → 40mg daily (ESRD: not recommended)
- Hepatic Impairment: No dose change required
- Geriatric: No dose change required

Package Insert - Apr 2018; UpToDate

LEVOMILNACIPRAN (FETZIMA®)

- When to consider prescribing?
  - "Norepinephrine deficient depression" → poor concentration, amotivation, low energy, cognitive impairment compared to "serotonergic deficient depression" → anxiety, appetite changes, suicidality (Moret C et al, Neuropsychiatr Dis Treat 2011;7Suppl1:9–13; Nutt DJ, J Clin Psychiatry 2008;69SupplE1:4–7)
  - Chronic pain + depression
  - Pearls:
    - Avoid in patients with uncontrolled narrow angle glaucoma due to mydriasis
    - Careful if cardiovascular disease due to potent norepinephrine reuptake (increased HR, BP, orthostatic hypotension)
  - COST: GoodRx → $364.76 for #30 of 80mg @ Meijer

VILAZODONE (VIIBRYD®)

- Class: SPARI
- Off label: Anxiety
- Forms: 10, 20, 40mg tabs
- Dose: 10 x 7 days, 20 x 7 days, then 40mg daily
  - HAS TO BE TAKEN WITH FOOD (72% bioavailability after a meal)
- Half-life is 24 hours
- Taper off
- SE: nausea, diarrhea, increased sweating, dizziness, abnormal dreams, headache, sexual SE, hyponatremia, may impair platelet aggregation

Indication: MDD

VILAZODONE (VIIBRYD®)

- USE IN SPECIAL POPULATIONS:
  - Pregnancy: No adequate studies in women (registry available)
  - Nursing: No data available
  - Renal Impairment: No dose adjustment for mild to severe
  - Hepatic Impairment: No dose adjustment for mild to severe
  - Geriatric: No pharmacokinetic differences requiring dose change
  - Pearls:
    - If vilazodone is taken with a strong CYP3A4 inhibitor (e.g. some HIV antivirals, clarithromycin, itraconazole, ketoconazole, etc.), ↓ max dose to 20mg
    - If given with a strong CYP3A4 inducer (e.g., carbamazepine, barbiturates, etc.), max dose may need to be ↑ to 80mg

Package insert – April 2018; Simple a
Practical Mental Health

VILAZODONE (VIIBRYD®)

- When to consider prescribing?
  - Theoretically, partial agonism @ 5-HT1A may give vilazodone increased efficacy for the depressed, anxious patient
    - Need studies comparing it head to head with other antidepressants
  - May have additional benefit in the IBS-constipated patient given 5-HT4 action
- COST: GoodRx → $255.43 for #30 of 40mg @ Meijer

VORTIOXETINE (TRINTELLIX®)

- Class: Multimodal agent Indication: MDD
  - Inhibits serotonin transporter
  - Post-synaptic antagonist effect on
    - 5-HT1D, 5-HT3A, 5-HT7
  - Partial agonism 5-HT1B
  - Agonist @ presynaptic somatodendritic 5-HT1A auto-receptors

- Off label use: Cognitive slowing, GAD
- Forms: 5, 10, 20mg tablet
- Dosing: Begin @ 10mg daily; can ↓ to 5mg or ↑ to 20mg as tolerated
- Half life is 66 hours; Take with or without food; Taper off

VORTIOXETINE (TRINTELLIX®)

- SE: nausea, constipation, sexual SE, SIADH, impaired platelet aggregation
- Unique in that it is the only antidepressant studied separately in geriatric patients and for its effect on cognitive deficits
- USE IN SPECIAL POPULATIONS:
  - Pregnancy: No controlled studies (registry available)
  - Nursing: No clinical data available
  - Renal Impairment: No dose change needed
  - Hepatic Impairment: No dose change needed
  - Geriatric: No pharmacokinetic differences requiring dose change
- With strong inhibitors of CYP2D6 (ie: bupropion), consider dosage reduction by half. If strong CYP inducers are coadministered for 14 days, consider increasing the dose (up to 3 times maximum).

Package insert – Apr 2018; Simple And Practical Mental Health

VORTIOXETINE (TRINTELLIX®)

- When to consider prescribing?
  - Depressed patients who have cognitive deficits, especially geriatric patrients
- Pearls:
  - Most studies suggest clinically meaningful advantage in tolerability over other serotonergic agents
  - Incidence of sexual SE appears low comparatively
  - No weight gain
  - Appears to ↑ frontal cortical activity differently than SSRIs/SNRIs
- COST: GoodRx → $351.45 for #30 of 20mg tabs @ CVS

KETAMINE

- Dissociative anesthetic with hallucinogenic properties
  - Recreational drug in US in mid 1990s with increasing abuse in other countries currently
  - At subanesthetic doses, it produces hallucinations (K-hole), mood changes, dissociation
  - Relatively short acting (30-60 minutes)
  - **Intravenous**, **intranasal**, oral, sublingual
- MOA: noncompetitive NMDA receptor antagonist with anti-inflammatory properties
  - Theoretically ketamine is a more direct and immediate way to target the glutamatergic system via NMDA receptor as opposed to traditional ADs that target the monoaminergic system upstream from CNS

KETAMINE

- APA Council of Research Task Force on Novel Biomarkers and Treatments Consensus Statement:
  - No clear indication for ketamine use → best evidence is MDD w/o psychosis
  - Many studies have shown positive effect over a few days, but increasing research showing that with repeated doses, benefit can persist for a few weeks
  - Esketamine is more commonly used (a stereoisomer) as it binds more potently & recent reports show may be effective short-term in intranasal formulation
  - Typical dose is 0.5mg/kg given IV over 40 minutes (subanesthetic dose)
  - Commercial ketamine clinics typically administer 3x/week; data is not showing benefit over 2x/week
  - Long-term benefit/safety have not yet been determined
  - Risks during infusion (autonomic instability, ↑ with BMI), dissociative/psychotomimetic SE

RECENT NEWS…

Articles

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

Summary

Background Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available; however, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, we aimed to update and expand our previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder.

Methods We did a systematic review and network meta-analysis. We searched Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, the websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomised controlled trials from their inception to Jan 8, 2016. We included placebo-controlled and head-to-head trials of 21 antidepressants used for the acute treatment of adults (≥18 years old and of both sexes) with major depressive disorder diagnosed according to standard operationalised criteria. We excluded quasi-randomised trials and trials

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See Comment page 1333

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BIPOLAR DISORDER	SCHIZOPHRENIA
Aripiprazole	Aripiprazole
Carbamazepine	
Divalproex Sodium	Chlorpromazine
Lamotrigine	Clozapine
Lithium	Fluphenazine
Olanzapine	Haloperidol
Quetiapine	Iloperidone
Risperidone	
Ziprasidone	Molindone
	Olanzapine
	Paliperidone
	Quetiapine
	Risperidone
	Ziprasidone

BIPOLAR DISORDER	SCHIZOPHRENIA
Aripiprazole	Aripiprazole
ASENAPINE	**ASENAPINE**
Carbamazepine	**BREXIPIPRAZOLE**
CARIPRAZINE	**CARIPRAZINE**
Divalproex Sodium	Chlorpromazine
Lamotrigine	Clozapine
Lithium	Fluphenazine
Olanzapine	Haloperidol
Quetiapine	**ILOPERIDONE**
Risperidone	**LURASIDONE**
Ziprasidone	Molindone
	Olanzapine
	Paliperidone
	Quetiapine
	Risperidone
	Ziprasidone

FDA APPROVED INDICATIONS IN BIPOLAR DISORDER WITH 2ND GEN ANTIPSYCHOTICS

	Aripiprazole	Asenapine	Olanzapine	Olanzapine/ fluoxetine	Quetiapine	Risperidone	Risperidone LAI	Ziprasidone	Lurasidone	Cariprazine
Manic/mixed monotherapy	X	X	X		X	X		X		X
Manic/mixed adjunctive	X	X	X		X	X				
Depression monotherapy				X	X				X	
Depression adjunctive					X				X	
Maintenance monotherapy	X		X		X		X			
Maintenance adjunctive	X				X		X	X		

Courtesy of Dr. William Resch

ANTIPSYCHOTIC MONITORING

Table 3—*Monitoring protocol for patients on SGAs

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status

DIABETES CARE, VOLUME 27, NUMBER 2, FEBRUARY 2004

PREGNANCY & ATYPICAL ANTIPSYCHOTICS

- National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/

ASENAPINE (SAPHRIS)

- Class: Atypical Antipsychotic
- Indication: Schizophrenia/Bipolar I
- Forms: 2.5, 5, 10mg SL tablets
- Dosing: 5mg SL BID, titrate to 10mg SL BID
  - Range 10-20mg BID; Taper off
- Must be given SL to achieve ~35% with 5mg dose (PO <2
  - NPO x 10 minutes after taking SL tab
  - Black cherry flavor
- SE: TD, TdP, NMS, Seizures, Metabolic Syndrome, EPS, sedation/somnolence, increased appetite, weight gain, akathisia, oral hypoesthesia, hyperprolactinemia, neutropenia/agranulocystosis

ASENAPINE (SAPHRIS®)

- USE IN SPECIAL POPULATIONS:
  - Pregnancy: No human studies; May cause EPS/withdrawal in neonates with 3TM exposure; Risk of birth defect and miscarriage unknown → Registry available
  - Nursing: No studies available
  - Renal Impairment: No dose requirements needed
  - Hepatic Impairment: Contraindicated in Child-Pugh C; no dose adjustment for mild-moderate impairment
  - Geriatric: No specific studies. Black Box for CVA in patients with dementia
  - COST: GoodRx→ $1,200.95 for #60 of 10mg tabs 😬

BREXPIPRAZOLE (REXULTI®)

- Class: Atypical Antipsychotic
- Indication: Schizophrenia; Adj tx for MDD
- Forms: 0.25, 0.5, 1, 2, 3, 4mg tablet
- Dosing: MDD= 0.5-1mg daily; target 2mg, max 3
  Schizophrenia= 1mg x 4d, 2mg x 3 days, then 4m
- Taken with or without food; 91 hour half-life*
- SE: Akathisia, weight gain, EPS, headache, seda
  anxiety, restlessness, NMS, Seizures, metabolic changes
- Dose changes: adjustments are recommended for poor metabolizers on the CYP450 2D6 isoenzyme; 2D6 & 3A4 inhibitors can ↑ levels; 3A4 inducers can ↓ levels

BREXPIPRAZOLE (REXULTI®)

- USE IN SPECIAL POPULATIONS:
  - Pregnancy: No human studies; May cause EPS/withdrawal in neonates with 3TM exposure; Risk of birth defect and miscarriage unknown → Registry available
  - Nursing: No studies available
  - Renal Impairment: Moderate, severe or end-stage renal impairment (CL_{cr}<60 mL/min), max dosage = 2 mg for MDD and 3 mg for schizophrenia
  - Hepatic Impairment: Moderate to severe (Child-Pugh score ≥7), max dosage 2 mg for MDD and 3 mg for schizophrenia
  - Geriatric: No specific studies. Black Box for CVA in patients with dementia

BREXPIPRAZOLE (REXULTI®)

- Pearls:
  - Compared with aripiprazole, has ↓ activity at the D_2, ↑ antagonism at 5-HT_{2A} & NET & ∴ ↓ potential to induce D3 partial agonist mediated adverse effects (akathisia, restlessness, insomnia, and nausea)
  - No associated hyperprolactinemia
  - No identified QTc changes
  - Lower risk for EPS
- COST: GoodRx → $1,040.21 for #30 of 3mg tabs @ Meijer 😢

CARIPRAZINE (VRAYLAR®)

- Class: Atypical Antipsychotic
- Indications: Schizophrenia & Bipolar I Acute Mania/Mixed
- Off label: Behavioral and Psychological Sx of dementia
- Forms: 1.5, 3, 4.5, 6mg cap
- Dosing: Start at 1.5mg qd → Schizophrenia range is 1.5-6

  1.5mg dose may be therapeutic; Bipolar range is 3-6mg
- Dose Change: 3A4 inhibitors can ↑ levels; 3A4 inducers can ↓ levels
- SE: Sedation, constipation, **akathisia**, dyspepsia, restlessness, **EPS**, Metabolic syndrome, TD, NMS, seizures, GI discomfort

CARIPRAZINE (VRAYLAR®)

- USE IN SPECIAL POPULATIONS:
  - Pregnancy: No human studies; May cause EPS/withdrawal in neonates with 3TM exposure; Risk of birth defect and miscarriage unknown → Registry available
  - Nursing: No studies available
  - Renal Impairment: No dose adjustment needed
  - Hepatic Impairment: No change for mild to moderate (Child-Pugh score 5-9)
    - Not recommended for severe (Child-Pugh 10-15)
- Geriatric: No specific studies. Black Box for CVA in patients with dementia

CARIPRAZINE (VRAYLAR®)

- Pearls:
  - Half-life of the parent drug and its two active metabolites is ~1 week
  - Shows preference for D3 > D2 receptors (D3 → cognition, mood, emotions, and reward/substance abuse; D2 → antipsychotic, emotional blunting, and cognitive problems, EPS, increased prolactin)
  - Minimal effect on prolactin
  - Theoretically low risk for metabolic impact, including weight gain
- COST: GoodRx → $1,200.95 for #30 of the 3mg caps

ILOPERIDONE (FANAPT®)

- Class: Atypical Antipsychotic
- Indication: Schizophrenia
- Off label: agitation & aggression in dementia
- Forms: 1, 2, 4, 6, 8, 10, 12mg tabs
- Dosing: Start 1mg BID; Target 6-12mg BID by ↑ 1-2mg BID/q24h up to max 12mg BID (24mg/day)
- Taper off

- 2D6 and 3A4 inhibitors can ↑ levels; 3A4 inducers can ↓ levels
- SE: Hypotension, TdP, NMS, seizures, metabolic changes, sedation, dizziness, xerostomia, diarrhea, tachycardia, hypotension, EPS, weight gain, priapism

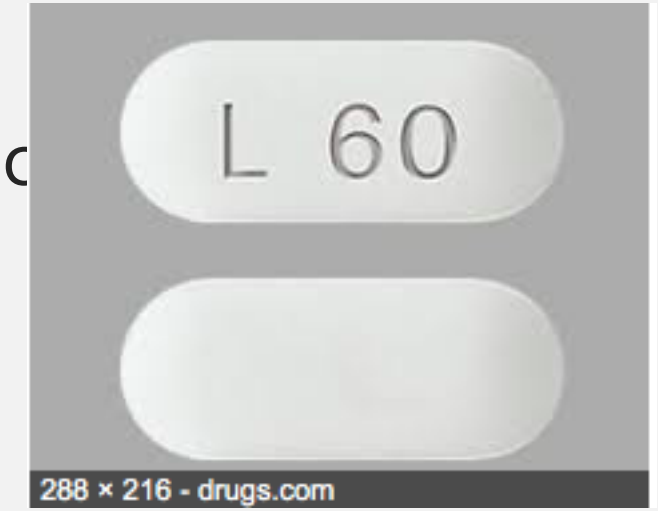
ILOPERIDONE (FANAPT®)

- USE IN SPECIAL POPULATIONS:
- Pregnancy: May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure.
- Nursing: Manufacturer advises “because of potential for serious adverse reactions in breastfed infants, advised to not breastfeed while taking.”
- Renal Impairment: No dose requirements needed (<1% excreted in urine)
- Hepatic Impairment: Mild – no dose change required; Moderate may require dose reduction but level not specified; Severe – use not recommended.
- Geriatric: No specific studies. Black Box for CVA in patients with dementia

ILOPERIDONE (FANAPT®)

- Pearls:
  - Very low level of EPS
  - Low level of dyslipidemia
  - Moderate weight gain
  - High potential for orthostatic hypotension
  - Strong α1 blockade may confer some efficacy in treating nightmares (similar to Prazosin)
- COST: GoodRx→ $1,139.77 for #60 of the 6mg tabs 😗

LURASIDONE (LATUDA®)



- Class: Atypical Antipsychotic
- Indications: Schizophrenia & Bipolar Depression (Mo
  And Adjunct to lithium or valproate)
- Off label: Bipolar II; Depression
- Forms: 20, 40, 60, 80, 120mg tabs
- Dose: Schizophrenia = start @ 40mg with max 160mg daily; Bipolar = start @ 20mg and max dose is 120mg daily. Taper off.
- Dose changes: 3A4 inhibitors ↑ levels; 3A4 inducers can ↓ levels
- SE: Sedation, dizziness, akathisia, agitation, EPS, rhinorrhea, NMS, seizures, Metabolic changes, TD

LURASIDONE (LATUDA®)

- USE IN SPECIAL POPULATIONS:
  - Pregnancy: No studies in pregnant women. No teratogenic effects in rats/rabbits. Neonates at risk for EPS and/or withdrawal symptoms after delivery.
  - Nursing: No lactation studies done; present in rat milk.
  - Renal Impairment: For mod to severe (CLcr <50 mL/min), reduce starting to 20mg daily and max 80mg/day
  - Hepatic Impairment: For mod to severe, start @ 20mg daily. Max dose in moderate = 80mg/day. Max dose in severe = 40mg/day.
  - Geriatric: No specific studies. Black Box for CVA in patients with dementia

LURASIDONE (LATUDA®)

- Pearls:
  - Has to be taken with at least 350 calories; ↑ bioavailability up to 60%
  - Minimal sedation
  - One of the few metabolically friendly antipsychotics (neutral for weight gain, lipids, and glucose)
  - Weight neutral is due to its lack of affinity for H1 and low affinity for 5-HT2C receptors
  - No QTc warning & minimal EPS
  - Half life of 18 hours so can be prescribed in once daily dosing
- COST: GoodRx→ $1,223.39 for #30 of the 60mg tabs ☺

PIMAVANSERIN (NUPLAZID®)

- Class: Atypical Antipsychotic*
  - Inverse agonist & antagonist at 5-HT2A>5-HT2C
    No appreciable D2 activity
- Indication: Hallucinations & Delusions in Parksinson's **
- Off label: Agitation in Alzheimer's
- Forms: 17mg tabs
- Dose: 34mg once daily *Start directly at full dose/no titration
  - No dose adjustment needed when given with carbidopa/levodopa; with or without food
- DDI: 3A4 inhibitors ↑ levels so reduce dose by ½ ; 3A4 inducers ↓ levels
- SE: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis
  - QT prolongation; peripheral edema; gait disturbances; confusions, nausea, orthostatic hypotension

PIMAVANSERIN (NUPLAZID®)

- FDA APPROVAL STUDY BACKGROUND:
  - One phase II and two phase III clinical trials showed trends for pimavanserin to be efficacious but the results were not statistically significant. Thus, the FDA-approval is based on just the third phase III, randomized, placebo-controlled clinical trial (Cummings et al., 2014). The primary analysis in that study included data on 185 patients. Given the importance of the topic, the FDA agreed that this single study was enough to approve the medication.
- How well did pimavanserin work in this study?
  - 100% improvement in psychosis occurred in 13.7% of patients on pimavanserin versus 1.1% of patients on placebo.
  - Representatives of the FDA point out (Mathis et al., 2017) that a substantial difference between pimavanserin and placebo is demonstrated by the following: an 8 point improvement on the Scale for Positive Symptoms (modified for Parkinson's disease psychosis) in over 40% of patients on pimavanserin versus in about 20% of patients on placebo.

PIMAVANSERIN (NUPLAZID®)

FDA worried drug was risky; now reports of deaths spark concern

By Blake Ellis and Melanie Hicken, CNN Investigates

Updated 6:00 AM ET, Mon April 9, 2018

(CNN) — Two years ago, Brendan Tyne pleaded with the Food and Drug Administration to approve a drug that he was hopeful could finally bring his mother some peace.

CNN.com

- Institute for Safe Medical Practices reported that 244 deaths had been reported between launch & March 2017
- FDA data now shows deaths > 700
- Concern about risk > benefit?
- FDA states that cases are typically elderly patients with comorbidities, who are taking other meds that can increase risk of death
- Based on these data, the FDA has, at this time, not identified a specific safety issue that is not already adequately described in the product labeling,

PIMAVANSERIN (NUPLAZID®)

- USE IN SPECIAL POPULATIONS:
  - Pregnancy: No data in pregnant women. No teratogenic effect in animal studies.
  - Nursing: No information available
  - Renal Impairment: No dose change in mild to moderate; use with caution in severe/ESRD
  - Hepatic Impairment: No dosage adjustment is recommended in patients with hepatic impairment based on the exposure differences observed in patients with and without hepatic impairment in a hepatic impairment study
  - Geriatric: No dose adjustment just based on age. Mean age in trials was 71.
  - COST: GoodRx→ $2,844.06 for #60 of 17mg **
    - Nuplazid Connect™ → Care Coordinator + Nurse Educator

VALBENAZINE (INGREZZA®)

- Class: VMAT2 Antagonist Indication: Tardive Dyskinesia
- Off Label: Tourette's
- Forms: 40, 80mg capsules
- Dosing: 40mg qd x 1 week, then increase to 80mg daily; wi
  or without food

Drugs.com

- DDI: 2D6 and 3A4 inhibitors ↑ levels ; 3A4 inducers ↓ levels. Don't exceed 40mg if taking 3A4 inhibitors (e.g.: luoxetine, sertraline, haloperidol, aripiprazole)
- SE: Prolonged QT, sedation, akathisia

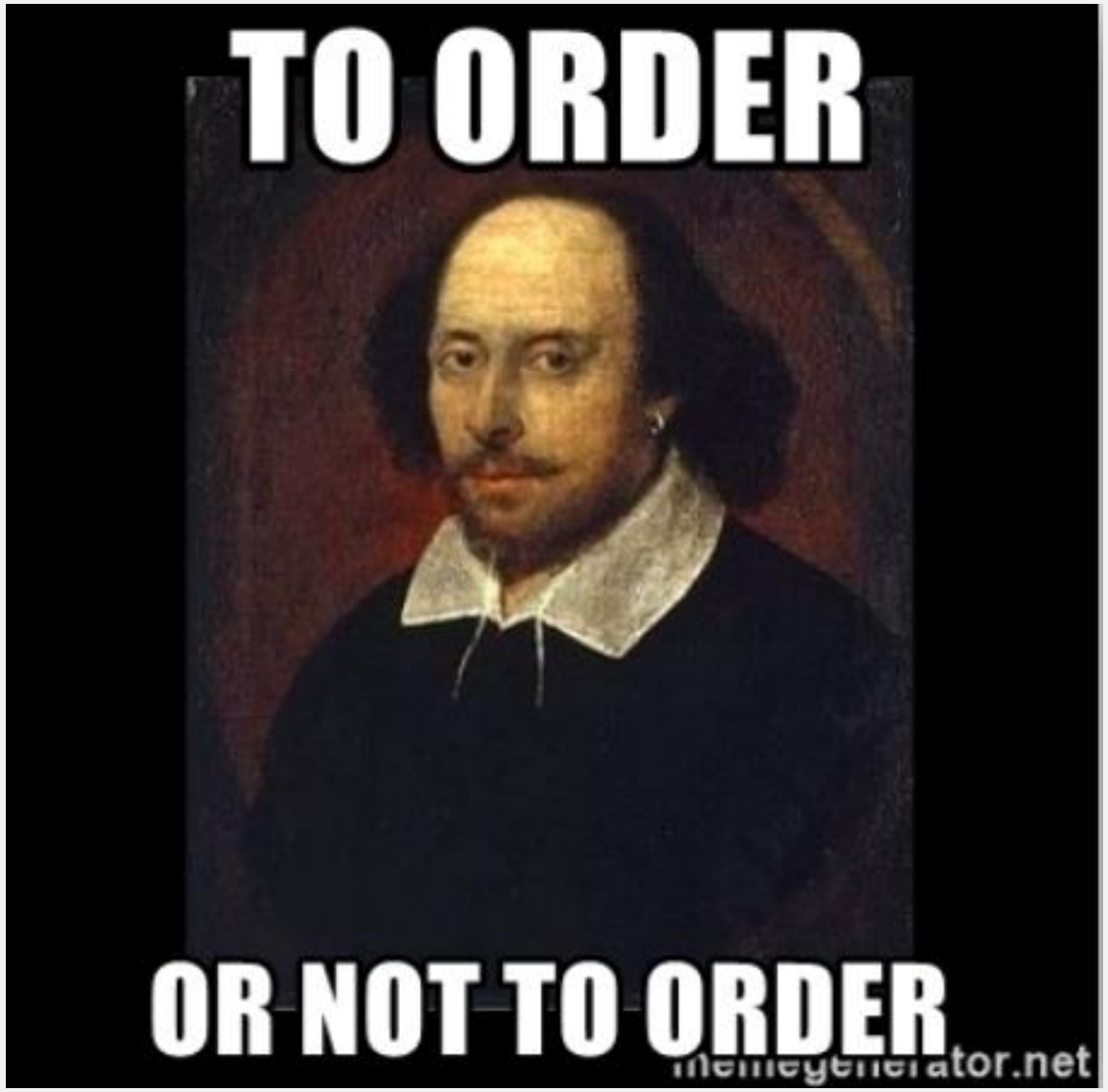
VALBENAZINE (INGREZZA®)

- USE IN SPECIAL POPULATIONS:
  - Pregnancy: May cause fetal harm
  - Nursing: Advised to not breastfeed for 5 days after last dose
- Renal Impairment: No dose adjustment in mild to moderate impairment; Not recommended for severe impairment
- Hepatic Impairment: 40mg/day recommended for mod to severe (Child-Pugh 7-15)
- Geriatric: No dose adjustment required
- Poor CYP2D6 metabolizers → 40mg/day max dose

VALBENAZINE (INGREZZA®)

- Pearls:
  - Currently only FDA-approved med for TD
  - Fewer tolerability issues than with tetrabenazine
  - During initial studies valbenazine appeared to have no effect on depression, suicidality, and there were no clinically significant changes in measures of schizophrenia symptoms
  - Lack of multiple daily dosing and possible need for 2D6 genotyping involved with tetrabenazine prescribing
- COST: GoodRx → #30 of 40mg is $5,875.50 😟 😬

PHARMACOGENETIC TESTING


TO ORDER
OR NOT TO ORDER

PHARMACOGENOMICS BASICS

Ultra-Rapid Metabolizer	Extensive Metabolizer	Intermediate Metabolizer	Poor Metabolizers
• Metabolic capacity greater than normal • 3 or more active genes coding for production of drug-metabolizing enzyme ∴ ↑ metabolic capacity • Likely require higher dose • Typically non-responders due to drug not reaching therapeutic levels	• Represent normal metabolic capacity • 2 active functional forms of gene producing full-drug metabolizing capacity • "Wild type" • Most common in Caucasians • Normal activity • Standard dosing practices	• Decreased (but not absent) metabolic capacity • 1 active or functional form of gene producing drug-metabolizing enzyme ∴ ↓ metabolic capacity • One non-functional allele • May require doses lower than average	• Absent metabolic capacity • Genes code for producing inactive enzyme • Two nonfunctional alleles ∴ unable to metabolize substrates through affected enzymatic pathway • At risk for accumulating med &. Experiencing SE

Malik and Azeem. Psychiatr Ann. 2016;46(1):52-57

IDEAL PHARMACOGENETIC-BASED DECISION TREE

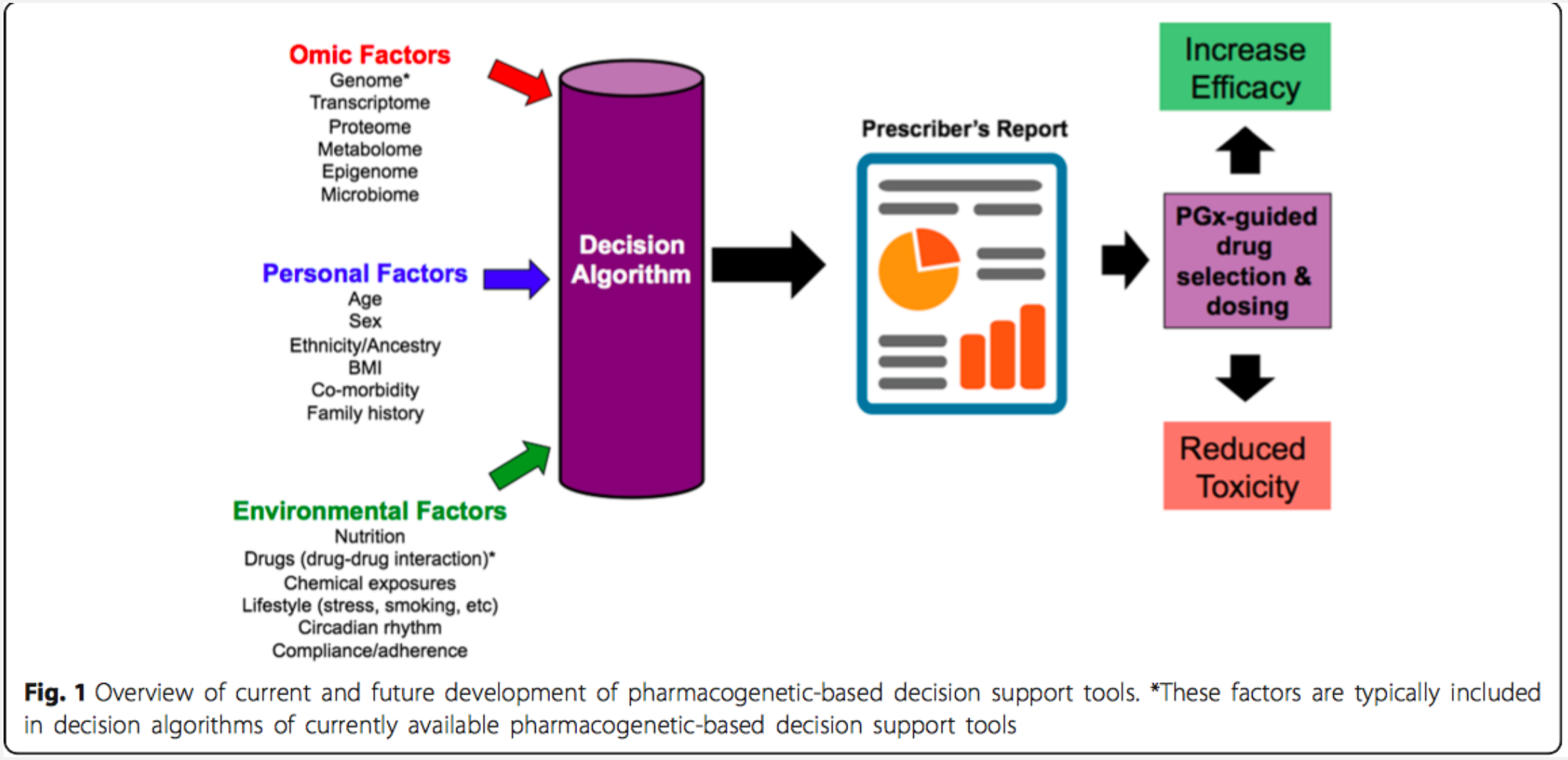


Fig. 1 Overview of current and future development of pharmacogenetic-based decision support tools. *These factors are typically included in decision algorithms of currently available pharmacogenetic-based decision support tools

Bousman et al. BMC Psychiatry (2017)

CURRENT STATE OF TOOLS IN PRACTICE

- Menu of commercial testing companies depends on geographical location
  - In US, 19 different companies available
- Physician ordered > direct-to-consumer testing
- Companies want physicians to order prior to medication prescribing & claim increased treatment adherence, decreased SE, and reduced health care costs
- EBM
  - <20% of current pharmacogenetic tools have been empirically evaluated
    - Suggested benefit but huge gap in literature
    - No independent, non-industry sponsored large studies available backing up claims
- Clinical Pharmacogenomics Implementation Consortium (CPIC) does not recommend testing as a standard

QUESTIONS FOR CONSIDERATION

- Based on Oxford Centre for Evidence-Based Medicine Levels of Evidence
  - 1) Do you have good reason to believe that your patients are sufficiently similar to the patients in the studies?
    - Most pharmacogenetic tests were developed and tested in Caucasian populations and may not include alleles that are rare in Caucasians but frequent in Asian/African descent
  - 2) Does the tool have a clinically relevant benefit that outweighs the harms?
    - Benefit: Potential for increased remission, reduced SE, test itself is of low risk (typically cheek swab)
    - Harm: Significant concern for delaying initiation of med pending results, COST, loss of genetic privacy (especially as some tools measure genetic variation in apolipoprotein E)

  3) Is another tool better?
    - No comparative effectiveness between tools

  4) Are the patient's values and circumstances compatible with use of pharmacogenetic decision support tools?

CPIC gene/drug combinations with guidelines for psychiatry[a]

Gene	Drug(s)
CYP2D6	Amitriptyline, fluvoxamine, nortriptyline, paroxetine, clomipramine, desipramine, doxepin, imipramine, trimipramine
CYP2C19	Amitriptyline, citalopram, escitalopram, clomipramine, doxepin, imipramine, trimipramine, sertraline
HLA-B	Carbamazepine

[a]As of April 2017

CPIC: Clinical Pharmacogenomics Implementation Consortium; CYP: cytochrome P450; HLA-B: human leukocyte antigen complex B

FOR DOCTOR/PATIENT CONSIDERATION

- Patient needs to understand prior to ordering that these tests help physicians understand how the liver is processing medications NOT whether there will be a clinical response to medication
- Don’t switch a patient’s medications based on test results if patient is already doing well
- Testing is not available for all medications
- Early findings that testing resulted in cost saving for some individuals, but did not demonstrate cost-effectiveness for population as whole
- Where are you going to put this info in the EMR?
- How do you provide other physicians with this information?
- Insurance impact: Federal law states that health insurance companies aren’t allowed to discriminate based on genetic information, but there is no protection for life insurance, disability insurance, or or long-term care coverage discrimination

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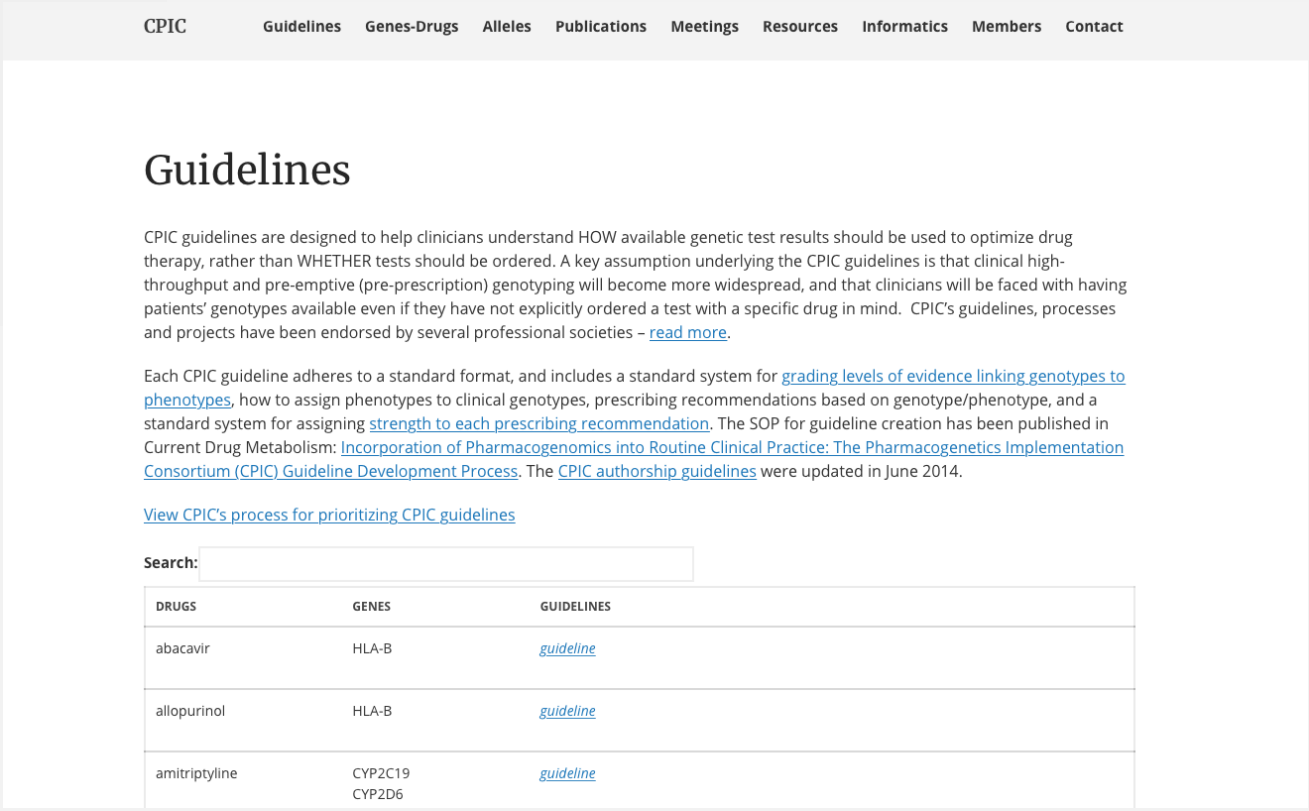

CPIC Guidelines Genes-Drugs Alleles Publications Meetings Resources Informatics Members Contact

Guidelines

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A key assumption underlying the CPIC guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. CPIC's guidelines, processes and projects have been endorsed by several professional societies – read more.

Each CPIC guideline adheres to a standard format, and includes a standard system for grading levels of evidence linking genotypes to phenotypes, how to assign phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and a standard system for assigning strength to each prescribing recommendation. The SOP for guideline creation has been published in Current Drug Metabolism: Incorporation of Pharmacogenomics into Routine Clinical Practice: The Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process. The CPIC authorship guidelines were updated in June 2014.

View CPIC's process for prioritizing CPIC guidelines

Search:

DRUGS	GENES	GUIDELINES
abacavir	HLA-B	*guideline*
allopurinol	HLA-B	*guideline*
amitriptyline	CYP2C19 CYP2D6	*guideline*

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Psychopharmacopeia.com is a progressive web application aimed at providing clinicians with fast access to psychiatric drug information.

Psychopharm Trivia

Paul Janssen's observation of amphetamine-intoxicated Belgian cyclists gave him the idea to test haloperidol on amphetamine-intoxicated mice, thinking 'finding a treatment for amphetamine intoxication would provide a cure for paranoid schizophrenia.'

Cytochrome P450 Table

Tweets by @psypharmacopeia

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Digital Doctor
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Apple's EHR feature launched last week. Here's what that looks like for patients and providers dlvr.it/QNcQ9p @MobiHealthNews

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