Antipsychotic Pharmacogenetics: CYP2D6 Drug-Gene Pair Proposal

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Antipsychotic Medications

- Originally indicated for the treatment of schizophrenia
- Growing list of other indications*
  - Augmentation with antidepressants for mood and anxiety disorders, Bipolar disorder, aberrant behavior in ASD/ID, Tourette's, Insomnia (quetiapine)
  - Growing utilization
  - E.g. Quetiapine (#57), aripiprazole (#98), risperidone (#154), olanzapine (#218), lurasidone (#237), all on 2018 top 300 prescribed drug list
  - 28,639,654 prescriptions in 2018
- 30-75% discontinuation rate of therapy within a year of starting a new medication
  - Adverse Events
  - Lack of efficacy

Aripiprazole and risperidone are significantly impacted by CYP2D6

Medical Expenditure Panel Survey (MEPS) 2008-2018. Agency for Healthcare Research and Quality (AHRQ), Rockville, MD.

*Specific indications may differ by drug

Antipsychotic Medications

- Antipsychotic pharmacology
  - Two primary categories
    - 1st and 2nd generation antipsychotics (also called typical and atypical antipsychotics)
  - Primary mechanism of action: dopamine-2 (D2) receptor antagonism
  - Blockade of D2 receptors accounts for the reduction of delusions and hallucinations
  - Serotonin-2A receptor (5HT2A) antagonism
    - Mostly 2nd generation agents
  - Other receptors antagonized depending on agent
    - Alpha1/2, H1/2, muscarinic, 5HT2C, D1 (Clozapine: 19+ receptors affected)

Antipsychotic Metabolism

First Generation (Typical) Antipsychotics

Drug	Metabolism Pathways
Chlorpromazine	CYP1A2, **CYP2D6,** CYP3A4
Fluphenazine	**CYP2D6**
Haloperidol	CYP1A2, **CYP2D6, CYP3A4**
Loxapine	CYP1A2, CYP2C19, CYP2D6, CYP3A4
Molindone	CYP2D6, CYP3A4
Perphenazine	CYP1A2, CYP2C9, CYP2C19, **CYP2D6,** CYP3A4
Pimozide	**CYP1A2, CYP2D6, CYP3A4**
Thioridazine	CYP2C19, **CYP2D6**
Thiothixene	**CYP1A2**
Trifluoperazine	**CYP1A2**

Second Generation (Atypical) Antipsychotics

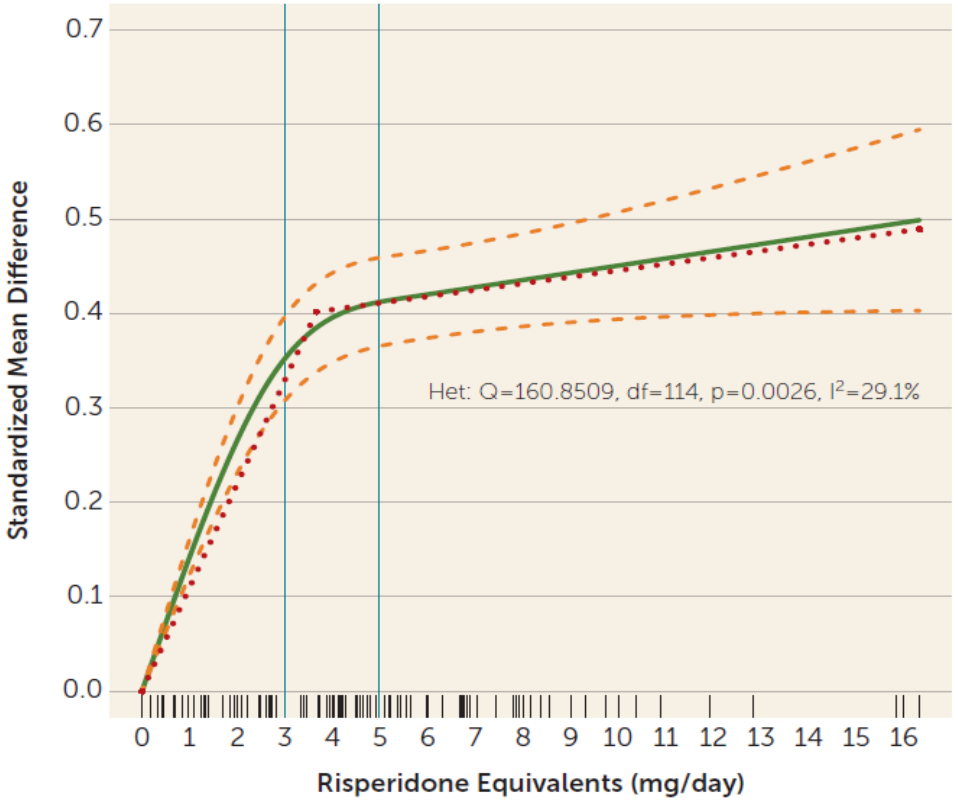
Drug	Metabolism Pathways
Aripiprazole	**CYP2D6, CYP3A4**
Asenapine	**CYP1A2, UGT1A4,** CYP2D6, CYP3A4
Brexpiprazole	**CYP2D6, CYP3A4**
Cariprazine	CYP2D6, **CYP3A4**
Clozapine	**CYP1A2, CYP2D6, CYP3A4**
Iloperidone	**CYP2D6, CYP3A4**
Lurasidone	**CYP3A4**
Olanzapine	Glucuronidation, **CYP1A2,** CYP2D6
Paliperidone	None significant/renal
Quetiapine	**CYP3A4**
Risperidone	**CYP2D6,** CYP3A4
Ziprasidone	CYP1A2, **CYP3A4**

Antipsychotic Medications: dosing and drug exposure are important

- Assessment of PBO-controlled dose finding studies of n=20 antipsychotics
- N=68 acute schizophrenia studies
  - Dose-response up to 95% effective doses then plateau
- Known dose-dependent side effects
  - Movement d/o, somnolence/sedation, anticholinergic
- Serum concentrations predict D2 receptor occupancy (optimal range: 60-80%)
- TDM guidelines recently published
  - Not done clinically due to logistics
  - Genotyping may be easier to apply

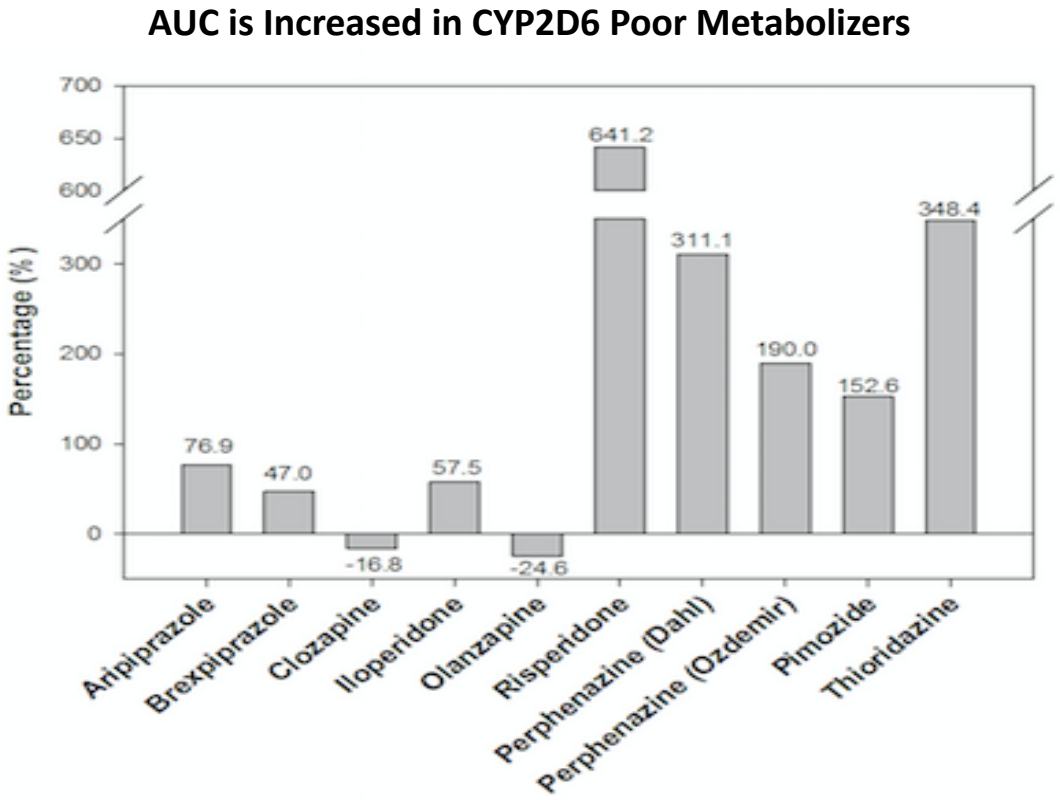
Leucht S. Am J Psychiatry 2020. PMID: 31838873
Schoretsanitis G. J Clin Psychiatry 2020. PMID: 32433836

Dose-response curve across antipsychotic drugs converted to risperidone equivalents



Premise: antipsychotic dosing and drug exposure are important…and impacted by genetics

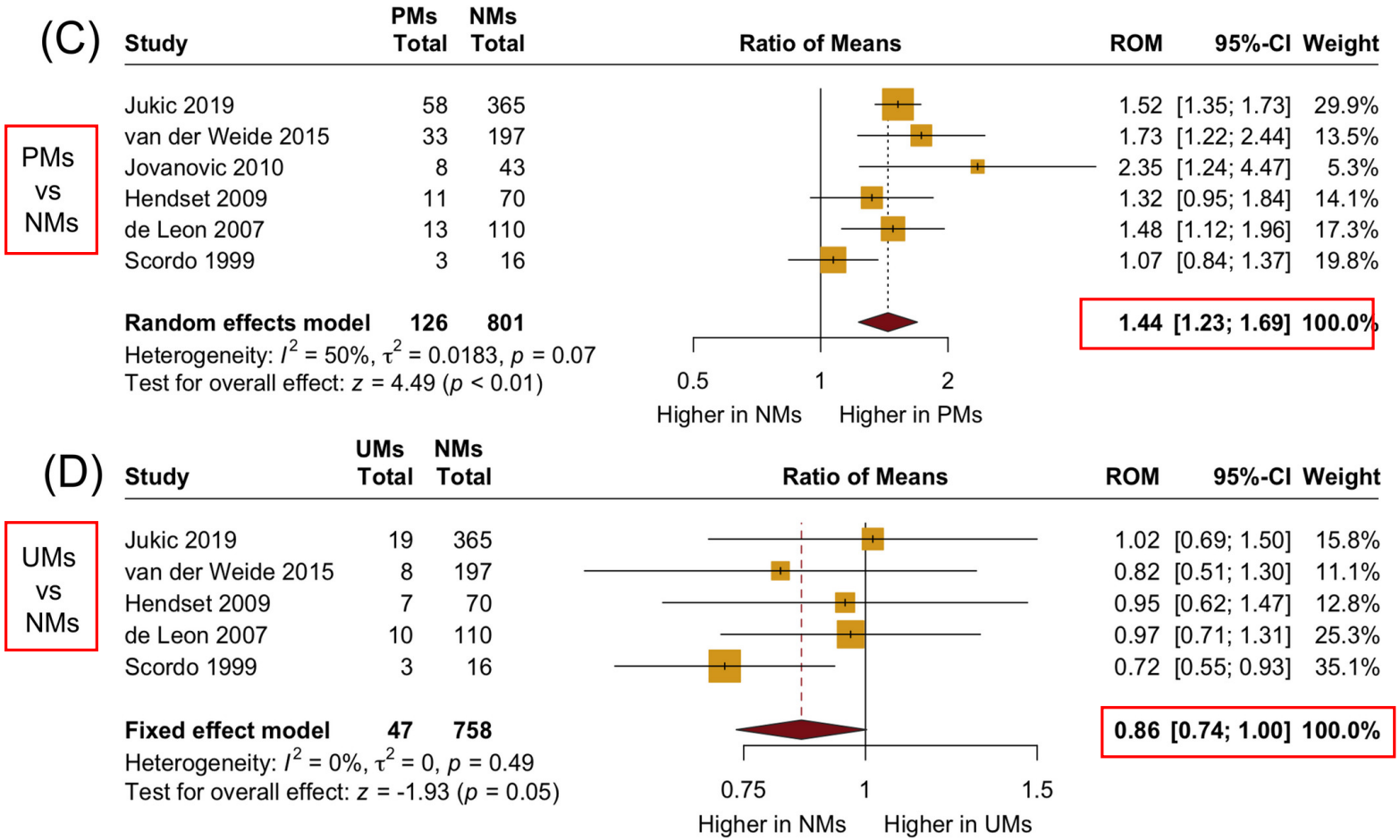
- Examples of dose-dependent side effects
  - Movement disorder
  - Anticholinergic
  - sedation/somnolence
  - Prolactin
  - Hypotension
  - QTc prolongation



Seenae Eum, MS, PharmD

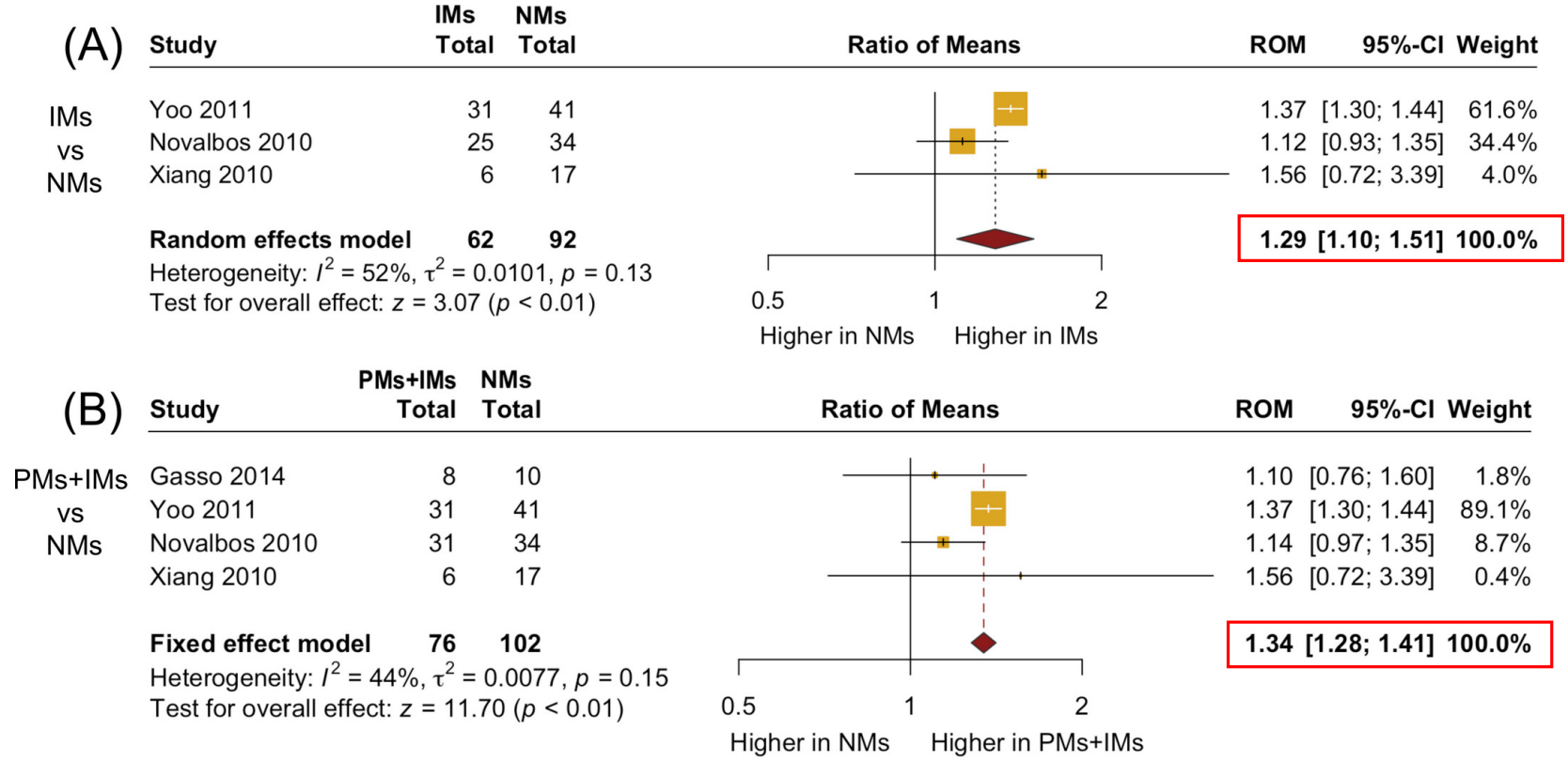
Eum, Lee, and Bishop. *Dialogues Clin Neurosci* 2016. PMID:277757066

Emerging evidence: risperidone+ 9-OH Risp Steady State Concentrations increased in CYP2D6 PMs and decreased in UMs



Zhang L et al. *Pharmacotherapy*. 2020; PMID: 32519344

Emerging evidence: risperidone+ 9-OH Risp AUC_{0-t} greater in CYP2D6 IMs and PMs



Zhang L et al. *Pharmacotherapy*. 2020; PMID: 32519344

Emerging evidence: meta-analysis of CYP2D6 and antipsychotic exposure across studies

Table 3. Detailed Statistical Report of the Association of Metabolism Status With Antipsychotic and Antidepressant Exposure

Drug	Enzyme	No. of studies	No. of patients by metabolism group		RoM (95% CI)	*P* value	I^2 value, %
			Reference	Comparator			
Antipsychotics							
Aripiprazole	CYP2D6	5	693 NM	90 PM	1.51 (1.38-1.65)	<.001	0
	CYP2D6	9	664 NM	134 IM	1.47 (1.38-1.57)	<.001	65
	CYP2D6	12	814 NM	224 PM plus IM	1.48 (1.41-1.56)	<.001	56
Clozapine	CYP2D6	1	22 NM	4 PM	1.00 (0.43-2.32)	>.99	NA
	CYP2D6	2	33 NM	15 IM	1.22 (0.79-1.88)	.51	0
	CYP2C19	2	70 NM	8 PM	1.92 (1.32-2.79)	.008	0
	CYP2C19	4	127 NM	65 IM	1.00 (0.84-1.19)	.84	10
Haloperidol	CYP2D6	4	267 NM	46 PM	1.68 (1.40-1.91)	<.001	21
	CYP2D6	9	265 NM	158 IM	1.14 (1.05-1.25)	.003	0
Quetiapine	CYP2D6	1	171 NM	20 PM	1.32 (1.10-1.58)	<.001	NA
Risperidone	CYP2D6	13	937 NM	172 PM	1.40 (1.30-1.50)	<.001	17
	CYP2D6	11	469 NM	186 IM	1.31 (1.20-1.43)	<.001	44
	CYP2D6	23	1134 NM	358 PM plus IM	1.36 (1.28-1.44)	<.001	34

Milosavljević F et al. *JAMA Psychiatry*. 2020; PMID: 33237321

Antipsychotic Metabolism and PGx Implications on Dosing

Drug	Metabolism Pathways	Guideline or Regulatory Information	PGx Dosing Implications
Aripiprazole	**CYP2D6, CYP3A4**	Dutch and FDA (CYP2D6)	**Yes: ½ of usual dose in known CYP2D6 PM[1,2]**
Asenapine	**CYP1A2, UGT1A4,** CYP2D6, CYP3A4		No
Brexpiprazole	**CYP2D6, CYP3A4**	Dutch and FDA (CYP2D6)	**Yes: ½ usual dose in known CYP2D6 PM[1]**
Cariprazine	CYP2D6, **CYP3A4**		No
Clozapine	**CYP1A2, CYP2D6, CYP3A4**	Dutch no; FDA (CYP2D6)	**FDA: Yes, Dutch: No**
Iloperidone	**CYP2D6, CYP3A4**	FDA (CYP2D6)	**Yes: ½ of usual dose in known CYP2D6 PM[1]**
Lurasidone	**CYP3A4**		No
Olanzapine	Glucuronidation, **CYP1A2,** CYP2D6		No
Paliperidone	None significant		No
Quetiapine	**CYP3A4**		No
Risperidone	**CYP2D6,** CYP3A4	Dutch (CYP2D6); FDA no	**Yes: ~½ of usual dose in known CYP2D6 PM[2,4]; FDA: No**
Ziprasidone	CYP1A2, **CYP3A4**		No

PM: poor metabolizer, **Bold:** primary metabolism pathway, AUC: area under the concentration curve, T1/2: elimination half-life

1. Drugs@FDA http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
2. Swen JJ et al. *Clin Pharmacol Ther*. 2011. PMID: 21412232
3. Bishop JR. Pharmacogenetics. Handb Clin Neurol. 2018; PMID: 29325628
4. Zhang L et al. Pharmacotherapy. 2020; PMID: 32519344

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Chlorpromazine	CYP1A2, **CYP2D6**, CYP3A4		Unclear/little data
Fluphenazine	**CYP2D6**		Unclear/little data
Haloperidol	CYP1A2, **CYP2D6**, **CYP3A4**	Dutch (CYP2D6)	**Yes: ½ usual dose in known CYP2D6 PM[2]**
Loxapine	CYP1A2, CYP2C19, CYP2D6, CYP3A4		No
Molindone	CYP2D6, CYP3A4		Unclear/little data
Perphenazine	CYP1A2, CYP2C9, CYP2C19, **CYP2D6**, CYP3A4	FDA (CYP2D6)	**Yes: CYP2D6 PM may have greater overall exposure[3]**
Pimozide	**CYP1A2, CYP2D6, CYP3A4**		**Yes: CYP2D6 PM max dose of 0.05 mg/kg/day for children and 4 mg/day for adults[1]**
Thioridazine	CYP2C19, **CYP2D6**	FDA (CYP2D6)	**Yes: CYP2D6 PM may have greater overall exposure and should not be used in PMs[4]**
Thiothixene	**CYP1A2**		Unclear
Trifluoperazine	**CYP1A2**		Unclear

1. Drugs@FDA http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
2. Swen JJ et al. *Clin Pharmacol Ther*. 2011. PMID: 21412232
3. Bishop JR. Pharmacogenetics. Handb Clin Neurol. 2018; PMID: 29325628

PM: poor metabolizer, **Bold:** primary metabolism pathway, AUC: area under the concentration curve, T1/2: elimination half-life

Other drug metabolism genes

- CYP1A2
  - Important for the metabolism of many antipsychotics
    - Less evidence linking genotype to antipsychotic pharmacokinetics or outcomes
    - Smoking may account for more variance in metabolism than genotype for some substrates
    - Genotype corrected for inhibitors and smoking may be relevant to clozapine exposure and symptoms

- CY3A4/3A5
  - Important for the metabolism of many antipsychotics
  - Mixed results of effects of reduced function 3A5 variants on pharmacokinetic properties of quetiapine and olanzapine
  - Rare no function CYP3A4 alleles may impact quetiapine

Eum S et al. *Dialogues Clin Neurosci* 2016. PMID:277757066
Lesche D et al. Pharmacogenomics Journal 2020. PMID: 31616047

CYP2D6 clinical relevance: relationships with genotype, dose, and switching (Adults)

- Retrospectively obtained patient data from a routine therapeutic drug monitoring database (Oslo, Norway)
- 1288 risperidone-treated, and 1334 aripiprazole-treated patients with CYP2D6 genotypes; 725 risperidone and 890 aripiprazole treated patients with serum data+genotype
- Examined pharmacokinetics and treatment switching after 1 year

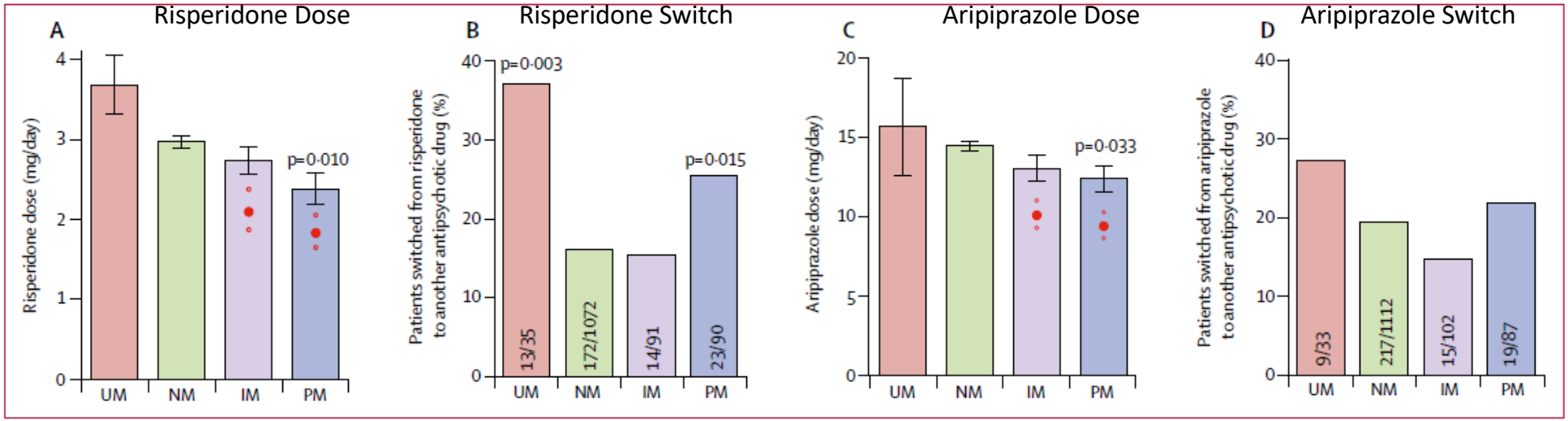


***Figure 2*: Effect of CYP2D6 metaboliser status on risperidone and aripiprazole dose and treatment failure rates**
In **A** and **C**, the dose reductions needed to compensate for the increase of risperidone exposure in patients who were intermediate metabolisers (IM) and poor metabolisers (PM; 95% CI) are indicated by red dots. Data are mean (SE). NM is the reference subgroup in all graphs. UM=ultrarapid metabolisers. NM=normal metabolisers.

Jukic et al. *Lancet Psychiatry*. 2019 PMID: 31000417

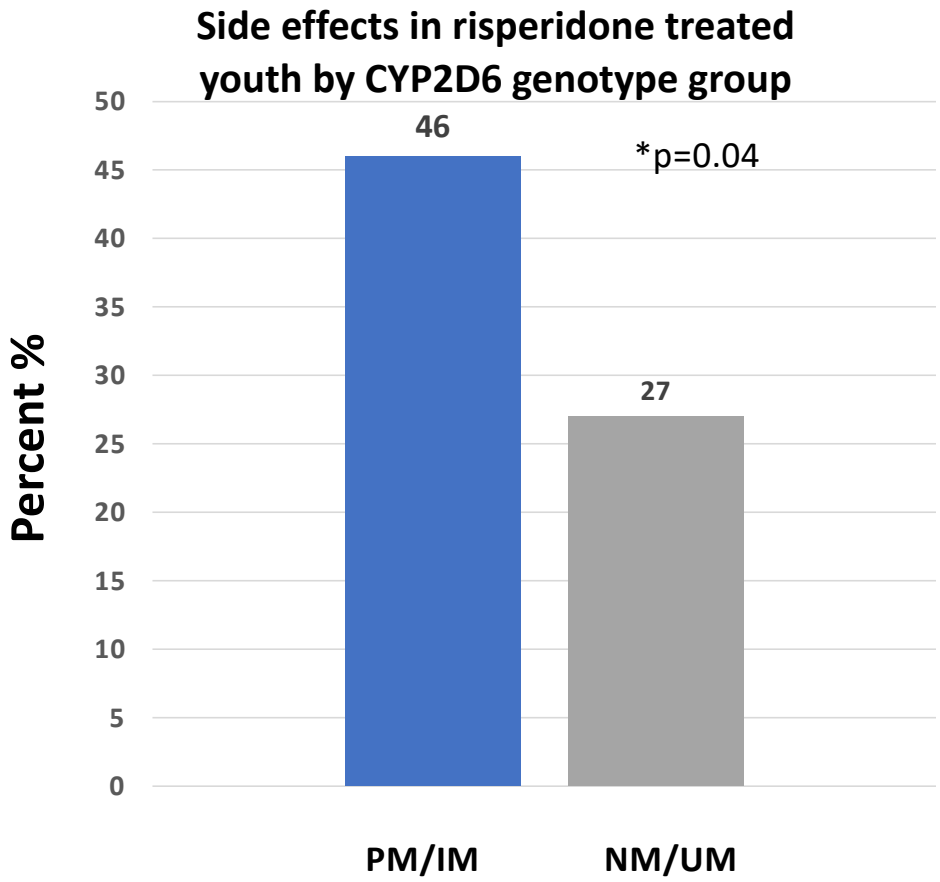
CYP2D6 clinical relevance: relationships with genotype, dose, and switching (children and adolescents)

- Retrospective reviews of electronic medical record data for patients <18 years of age with a mood disorder, receiving oral aripiprazole, and CYP2D6 genotyped as part of routine care.
- Assessed dosing, discontinuation, reported side effects and measures of clinical improvement
- Results: Phenoconverted CYP2D6PMs (genotype+DIs) more likely to d/c (67% PM vs 51% IM & 57% NM) and more likely to have weight gain

Jallaq SA et al. *Journal of Child and Adolescent Psychopharmacology.* 2020. PMID: 32845723

CYP2D6 clinical relevance: relationships with genotype, dose, and switching (children and adolescents)

- N=257 Children ≤18 years with at least 4 weeks of risperidone exposure were identified using a de-identified DNA biobank linked to EHR data.
- The primary outcome = side effects
- PMs/IMs 2.4x more likely to have side effects
  - Weight gain, sedation, movement disorder

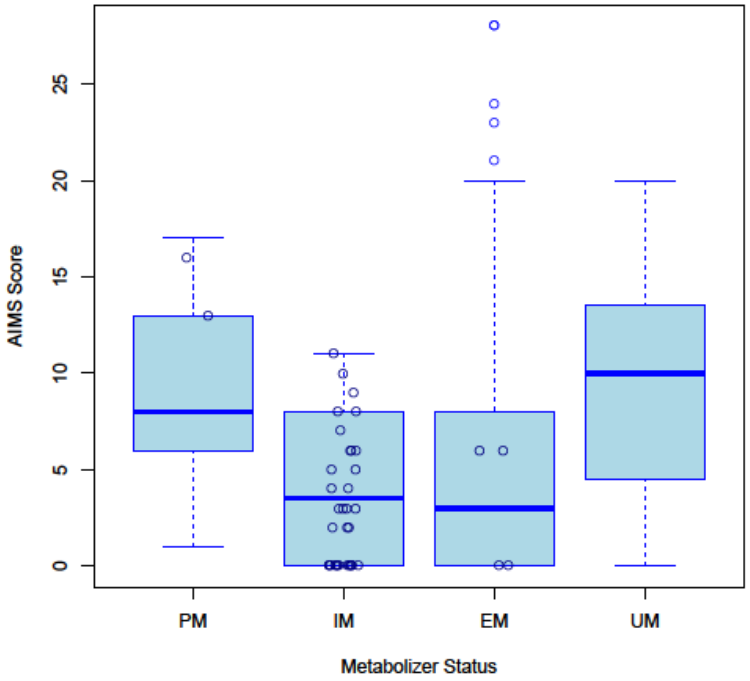


Kazeem A et al. *Ped Res.* 2019. PMID: 30661084

Tardive dyskinesia and CYP2D6

- Tested CYP2D6 metabolizer phenotype with TD occurrence and severity in our two samples of European chronic schizophrenia patients (total n = 198, of which 82 had TD).
- TD occurrence associated with extreme metabolizer phenotype, controlling for age and sex (p = 0.012).

CYP2D6 metabolizer phenotype vs Abnormal Involuntary Movement Scores (AIMS)



Lu JY et al. Pharmacogenomics 2020 PMID: 32969762

Good timing to consider a CPIC antipsychotic x CYP2D6 guideline?

- Recent International Society of Psychiatric Genetics (ISPG) consensus review on PGx testing in psychiatry (Bousman et al 2020 PMID: 33147643)
- CYP2D6 genetics, CPIC, PharmGKB, and PharmVar referenced in latest (copyright 2020) American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia)
- Meta-analyses in 2020 establishing CYP2D6 relationships with exposures to select substrates
- Recent data linking metabolizer genotypes with clinical outcomes
  - Adults and younger persons
- Not all antipsychotics impacted by CYP2D6 metabolism = clinical alternatives
- Many labs offer PGx results and guidance for antipsychotics
  - Lack of clarity from prescribers how to consider these

Thank you!

Questions?