Psych Genes:
The Role of PGx in Treating Schizophrenia

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Learning Objectives

- Describe enzymes that metabolize psychotropic agents and notable enzyme variants
- Review current literature describing pharmacogenomic polymorphisms in the enzymes that metabolize psychotropic agents
- Explain recommendations for therapy management based on genetic polymorphism information

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- Kiara Wilson, Student Pharmacist
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Disease State Review – Schizophrenia

Trishia E. Shaw, PharmD, BCPS, BCACP

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Schizophrenia Disease State Review

- Chronic disorder characterized by disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect and impaired psychosocial functioning
- Usually presents in late adolescence or early adulthood; rarely occurs before adolescence or after the age of 40
- Development and progression thought to be due to decreases in gray matter in multiple brain areas, leading to dysregulation of dopamine synthesis and release in the subcortical areas
- First episode is usually preceded by withdrawn, suspicious, peculiar behavior, individual loses touch with reality and creates a false reality to replace it

Crimson, et al. Accessed June 14, 2022

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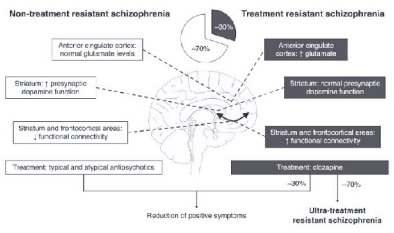
Physiology of Schizophrenia



Spark DL, et al. (2022)12:147

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Schizophrenia Associated Symptoms

Positive	Negative	Cognitive
• Suspiciousness • Delusions • Hallucinations • Conceptual disorganization	• Affective flattening • Alogia • Anhedonia • Avolition	• Impaired attention • Impaired working memory • Impaired executive function

Crimson, et al. Accessed June 14, 2022

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Receptor Targets for Antipsychotic Treatments

$5HT_7$
- Circadian rhythms, sleep, mood
- Thermoregulation
- Learning and memory
- Endocrine regulation

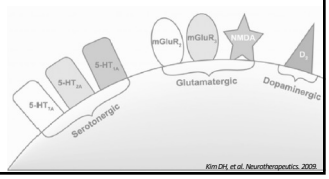
$5HT_{2A}$
- Excitation of cortical pyramidal neurons
- Excitation of glutamate release
- Inhibition of dopamine

$5HT_{1A}$
- Inhibition of cortical pyramidal symptoms
- Regulation of hormones
- Roles in depression,

$mGluR_2/mGluR_3$
- Presynaptic autoregulation of excitatory neurotransmission
- Neuroprotection
- Mood stabilization

NMDA
- Modulation of postsynaptic neurotransmission

D_2
- Mediation of positive symptoms
- Mediation of negative symptoms



Kim DH, et al. Neurotherapeutics. 2009

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Pharmacogenomic Basics – Drug Metabolizing Enzymes

Kiara Wilson, Student Pharmacist

Learning Objective: Describe enzymes that metabolize psychotropic agents and notable enzyme variants

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Metabolism of Psychotropic Drugs

Cytochrome P450

CYP1A2
18% of antipsychotics are major substrates

CYP2D6
40% of antipsychotics are major substrates

CYP3A4
23% of antipsychotics are major substrates

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Primary Enzyme Responsible for Metabolism	First Generation Antipsychotics	Second Generation Antipsychotics
CYP2D6	Chlorpromazine Fluphenazine Haloperidol Perphenazine Thioridazine	Aripiprazole Clozapine Olanzapine Risperidone
CYP3A4	Haloperidol Loxapine Pimozide	Aripiprazole Clozapine Iloperidone Lurasidone Quetiapine Risperidone Ziprasidone
CYP1A2	Chlorpromazine Loxapine Perphenazine Thioridazine Thiothixene Trifluoperazine	Clozapine Olanzapine

Poyurt et al. Dialogues Clin Neurosci. 2014; 16:555-566

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Genetic Phenotypes Based on Genetic Function

Term	Functional Definition
Ultra Rapid Metabolizer	Increased enzyme activity compared to rapid metabolizers
Rapid Metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultra-rapid metabolizers
Normal Metabolizer	Fully functional enzyme activity
Intermediate Metabolizer	Decreased enzyme activity (activity between normal and poor metabolizers)
Poor Metabolizer	Little to no enzyme activity

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CYP2D6

More than 1400 variants have been identified in CYP2D6 to date

- *CYP2D6*1*, *2, *33, and *35 are classified as active alleles
- *CYP2D6* alleles *9, *10, *17, *29, *36, and *41 cause decreased enzyme activity as a result of decreased gene expression or altered protein conformation.

CYP2D6 metabolizer status strongly influences the metabolism of antipsychotics, leading to changes in pharmacokinetic parameters, including overall exposure by……

- the area under the concentration time curve (AUC)
- half-life
- clearance
- steady-state concentration

CYP2D6 Poor Metabolizers (PM)

Aripiprazole, Brexpiprazole, Haloperidol, Iloperidone, Risperidone

Aripiprazole	Doses must be decreased by 50% or maximum oral dose of 10mg/day
Brexpiprazole, Iloperidone	Doses must be decreased by 50%
Haloperidol, Risperidone	Doses must be decreased by 50% or may be best to select another alternative antipsychotic

Eum S. Dialogues in Clinical Neuroscience 2016;18(3):323-337.

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CYP1A2

CYP1A2 activity can be strongly influenced by environmental factors (tobacco, caffeine and diet)

- *CYP1A2*1F* increase gene function by induction of expression
- *CYP1A2*1K, *4, *7, *8, *11, *15, and *16 decrease enzyme activity

Polymorphisms, CYP21A2*7 and CYP1A2*6, which are thought to confer decreased activity are found predominantly in individuals of European ancestry.

Low activity alleles, specifically the *8, *15, *16, and *11 alleles, confer "poor metabolizer" phenotype and are found in individuals of East Asian ancestry.

CYP1A2 Poor Metabolizers (PM)

Clozapine, Olanzapine

Clozapine, Olanzapine	Poor metabolizer dose must be decreased by 25-50% Rapid metabolizer dose must be increased by 25-30%

Eum S. Dialogues in Clinical Neuroscience 2016;18(3):323-337.

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Literature Review – Polymorphisms and Psychotropic Medications

Trishia E. Shaw, PharmD, BCPS, BCACP

Learning Objective: Review current literature describing pharmacogenomic polymorphisms in the enzymes that metabolize psychotropic agents

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A pharmacogenetic intervention for the improvement of the safety profile of antipsychotic treatments

Arranz MJ, et al. Translational Psychiatry. (2019)9:177

Objectives

- Evaluate the clinic benefits of a pharmacogenetic intervention (PI) for the personalization of antipsychotic treatment
- Pharmacogenetic information in key CYP polymorphisms was used to adjust clinical doses in a group of patients who started or switched results were compared with a group of patients treated following existing clinical guides

Methods

- 290 patients with a diagnosis of schizophrenia, schizoaffective or delusional disorders completed the study
- Randomized to the pharmacogenetic intervention (PharmG+) or usual treatment (PharmG-)
- 123 patients were genotyped using a pharmacogenetic test at the beginning of treatment with a new antipsychotic and clinical doses adjusted accordingly when required
- 167 patients were treated following standard clinic practice
- The positive and negative syndrome scale for schizophrenia (PANSS) and the UKU-side effect rating scale were obtained in all patients at the beginning and after 12 weeks

Results

- CYP minor allele frequencies observed those described in European populations
- No significant difference in the PANSS scores at 12 weeks
  - 26.81 ± 1.3 score reduction (PharmG+) vs 26.6 ± 1 score reduction (PharmG-)
- Significant difference when analysing PANSS score improvement between PharmG+ patients (26.6 ± 3.5) and PharmG- patients (28.63 ± 3.7) when treated with CYP2D6 substrates
  - Dose and gender not PI
- Slightly higher improvement in the PharmG+ group vs the PharmG- group with respect to side effects

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Genetic testing for CYP2D6 and CYP2C19 suggests improved outcome for antidepressant and antipsychotic medication

Walden LM, et al. Psychiatry Research. (2019)279:111-115.

Objectives

- Assess the implementation of pharmacogenetic testing by following patients before and after their physician received their genetic report, and evaluating physicians' and patients' opinions of pharmacogenetic testing

Methods

- Patients enrolled via referral from their treating physician and followed prospectively over three months at baseline, 6 weeks and 12 weeks
- Study population included drug-naïve, chronically ill, and treatment resistant patients
- For the first 45 patients, six CYP2D6 (*3, *4, *5, *10, *17, and *41) and 3 CYP2C19 alleles (*2, *3, and *17) were analyzed
- For the remaining 35 patients, nine CYP2D6 alleles (*2, *3, *4, *5, *6, *10, *17, *29 and *41; gene copy number) were analyzed
- Physicians were provided a genetic analysis that colored coded commonly prescribed antidepressants (n=18) and antipsychotics (n=10) into three groups
  - Red – should be avoided due to phenotype
  - Yellow – should be taken with caution and frequent monitoring
  - Green – can be taken in standard doses
- Assessed treating physicians' opinions about clinical status using the Pharmacogenetics in Psychiatry Follow-Up Questionnaire (PIP-FQ)
- Secondary outcome ® assessment of side effects using a modified UKU side effect scale

Results

- Sample size of 80 patients diagnosed with schizoaffective disorder or schizophrenia (n=43), depression or anxiety (n=32) or other psychiatric disorders (n=5).
- Majority of patients were either CYP2D6 EM's (82.5%) and CYP2C19 EM's (72.5%)
- Physicians reported that their patients either improved (n=14, 23%) or did not change (n=25, 41%) after treatment changes based on their CYP2D6 or CYP2C19 genotype
- No physicians reported a worse outcome following changes based on pharmacogenetic testing
- There were no statistically significant difference between UKU scores between NM's, IM's, UM's and PM's for both CYP2D6 and CYP2C19

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Effect of Routine Cytochrome P450 2D6 and 2C19 Genotyping on Antipsychotic Drug Persistence in Patients with Schizophrenia – A Randomized Clinical Trial

Jurgens G, et al. JAMA Network Open. 2020;3(12):e2027909

Objectives

- Aim was to assess whether routine genetic testing for CY2D6 and CYP2C19 improves antipsychotic drug treatment n patients with schizophrenia in terms of improved drug persistence, a surrogate for tolerability and effectiveness, compared with clinically guided treatment

Methods

- Prospective, single-masked, 3-group randomized clinical trial
- Patients were included consecutively from pool of 1406 potentially eligible patient form 12 psychiatric clinics in Capital Region, Denmark
- Inclusion criteria
  - 18 years or older
  - Diagnosed within the schizophrenia spectrum
  - Not previously CYP tested
- 2 intervention groups, where treatment was guided by CYP testing (CTG) or structured clinical monitoring (SCM) and 1 control group
- All samples were genotyped for CY2D6*3, *4, *5 and *6 as well as CYP2C19*2 and *3
- Primary outcome: antipsychotic treatment persistence
- First secondary outcome: number of drug changes and number of drug and dose changes combined

Results

- Patients were enrolled between July 2008 and December 2009
- 311 patients were included in trial, of which 61 (20%) ExM's
  - CYP2D6 PM's – N=41 (67%)
  - CYP2D6 UM's – N=12 (20%)
  - CYP2C19 PM's – n=8 (13%)
- Persistence in the CTG and SCM group were similar
- ExM's in the CTG and SCM group experienced fewer drug and dose changes combined that patients in the control arm

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Treatment Recommendations Based on Polymorphic Information

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Learning Objective: Explain recommendations for therapy management based on genetic polymorphism information

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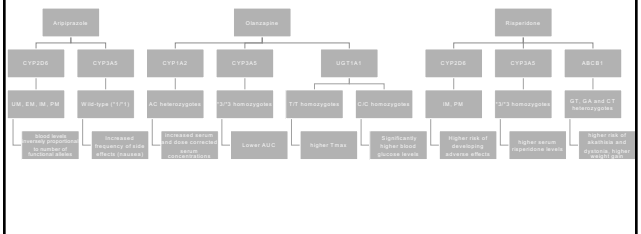
Impact of Gene Polymorphisms on Specific Medications



Plaza O, et al. Biomedicines 2022, 10, 3165

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Recommendations by Various Agencies

FDA	• Actionable PGx (Aripiprazole, Brexpiprazole, Clozapine, Iloperidone, Perphenazine, Thioridazine • Testing Required (Pimozide) • Informative PGx (Risperidone)
EMA	• Actionable PGx (Aripiprazole) • Informative PGx (Olanzapine)
HCSC	• Actionable PGx (Aripiprazole) • Informative PGx (Risperidone)
PMDA	• Actionable PGx (Perphenazine)
PGx drug dosing guidelines	• Aripiprazole • Clozapine • Haloperidol • Olanzapine • Risperidone

Yoshida K. Mol Neuropsychiatry 2019;5(suppl 1):1-26.

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Questions

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References

- Arranz MJ, Gonzalez-Rodriguez A, Perez-Blanco J, Penades R, Gutierrez B, Ibanez L, *et al.* A pharmacogenetic intervention for the improvement of the safety profile of antipsychotic treatments. Transl Psychiatry. 2019;9:177. https://doi.org/10.1038/s41398-019-0511-9.
- Crismon M, Smith TL, Buckley PF. Schizophrenia. In: DiPiro JT, Yee GC, Michael Posey LL, Haines ST, Nolin TD, Ellingrod VL. eds. *DiPiro: Pharmacotherapy A Pathophysiologic Approach, 12e*. McGraw Hill; 2021. Accessed June 14, 2022. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=267918845
- Eum S, Lee AM, and Bishop JR. Pharmacogenetic tests for antipsychotic medications: clinical implications and considerations. Dialogues in Clinical Neuroscience. 2016;18(3):323-337. doi:10.31887/DCNS.2016.18.3/jbishop
- Jurgens G, Andersen SE, Rasmussen HB, Werge T, Jensen HD, Kaas-Hansen BS, et al. Effect of Routine Cytochrome P450 2D6 and 2C19 Genotyping on Antipsychotic Drug Persistence in Patients with Schizophrenia – A Randomized Clinical Trial JAMA Network Open. 2020;3(12):e2027909. https://doi.org/10.1001/jamanetworkopen.2020.27909
- Kim DH, Maneen MJ, Stahl SM. Building a better antipsychotic: receptor targets for the treatment of multiple symptom dimensions of schizophrenia. *Neurotherapeutics*. 2009;6(1):78-85. doi:10.1016/j.nurt.2008.10.020
- Plaza O, Galecki P, Orzechowska A, Galecka M, Sobolewka-Nowak J, and Szulc A. Pharmacogenetics and Schizophrenia – Can Genomics Improve the Treatment with Second-Generation Antipsychotics? Biomedicines. 2022;10:3165. https://doi.org/10.3390/biomedicines10123165
- Pouget JG, Shams TA, Tiwari AK, Müller DJ. Pharmacogenetics and outcome with antipsychotic drugs. Dialogues Clin Neurosci. 2014 Dec;16(4):555-66. doi: 10.31887/DCNS.2014.16.4/jpouget.
- Spark DL, Fornito A, Langmead CJ, and Stewart GD. Beyond antipsychotics: a twenty-first century update for preclinical development of schizophrenia therapeutics. Transl Psychiatry. 2022;12:147.
- Yoshida K, Muller DJ. Pharmacogenetics of Antipsychotic Drug Treatment: Update and Clinical Implications. Mol Neuropsychiatry. 2019;5(suppl 1):1-26.
- Walden LM, Brandl EJ, Tiwari AK, Cheema S, Freeman N, Braganza N, et al. Genetic testing for CYP2D6 and CYP2C19 suggests improved outcome for antidepressant and antipsychotic medication. Psychiatry Research. 2019;279:111-115.

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