A Closer Look at the Central Nervous System PRN

Overview of the PRN

The Central Nervous System Practice and Research Network (CNS PRN) provides a forum to encourage networking among pharmacists specializing in CNS disorders, increase high-quality programming on CNS diseases, and foster an arena where young professionals can develop leadership and presentation skills. The CNS PRN has committees related to Annual Meeting programming, awards and nominations, and trainee travel awards.

Membership Overview:

Total Members: 322
Student Members: 160
Resident Members: 8
Fellow Members: 4

Opportunities for Student, Resident, and Fellow Members

The CNS PRN encourages the participation of students, residents, and fellows. One of the easiest ways to get involved is to serve on one of its committees. Membership for committees is usually discussed at the CNS PRN business meeting at the ACCP Annual Meeting. However, individuals interested in committee involvement who cannot attend the Annual Meeting are encouraged to contact the current officers about opportunities for involvement at any time. The CNS PRN usually offers a travel award each year. Currently, this is available to students, though eligibility has varied over the years for residents and fellows. Awardees generally receive a monetary award to help support attendance to the meeting as well as an opportunity to present their research or a clinically related project at the CNS PRN business meeting.

With 322 members, the CNS PRN is very accessible for networking. The CNS PRN business meeting welcomes student, resident, and fellow members, which, in the PRN's experience, provides an excellent opportunity for trainees to get to know current members. Attendance at the business meeting is well diversified across those in psychiatric and neurologic clinical practice as well as among researchers.

Current Clinical Issue: Pharmacogenomic Testing

Use of pharmacogenomic (PGx) information to tailor medication therapy to individuals is a technology now available to clinicians and patients with growing interest in the fields of psychiatry and neurology. Over 140 medications mention PGx information in the FDA product labeling. Moreover, almost one-third of the medications for which PGx information is listed as potentially "actionable" are used for the treatment of neurologic or psychiatric illnesses.[1] Use of PGx information in both inpatient and outpatient settings is growing, with many commercial clinical laboratories providing PGx test panels targeting genes thought to be meaningful in guiding dosing or drug selection decisions. What remains unknown are *how* and *when* it is best to implement this information and whether PGx-informed treatment decisions improve patient outcomes relative to standard of care.

So what *is* known with respect to PGx technology in psychiatry and neurology? Much research has investigated the relationships between genes and drug response, tolerability, and pharmacokinetic factors.[2] There are clear associations between pharmacodynamic genes (encoding transporters and receptors that are medication targets) and pharmacokinetic genes (e.g., drug metabolism genes) and different types of drug outcomes. Most of this information comes from secondary genetic analyses of clinical trials or practice-based intervention studies. Some drug-gene relationships are included in Table 1. This particular list comes from the product labeling for neuropsychiatric medications. Although not comprehensive, the list shows important relationships between drug metabolism and aspects of dosing for some drugs. In addition, for some medications such as carbamazepine and phenytoin, genetic factors may predispose certain populations to deadly hypersensitivity reactions. Although the scientific findings have evolved, the new challenge is to determine if and how this information is clinically helpful for guiding drug selection and dosing decisions.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is a multidisciplinary international group that creates evidence-based guidelines specifying how to use or consider PGx information *when it is available*. However, the CPIC guidelines *do not* recommend to clinicians when they should or should not order testing, or even how many clinic patients receiving testing will have "actionable/useful" polymorphisms that may change their initial medication and/or dose selection. Nevertheless, publications from this group are a good source

of consensus evaluations of data for specific drug-gene pairs. Currently, there are CPIC guidelines related to medications used in neurologic and psychiatric practice. These include tricyclic antidepressants,[3] selective serotonin reuptake inhibitors,[4] phenytoin,[5] carbamazepine,[6] and warfarin.[7]

The consensus guideline process is very time-consuming, and other genes are known to be relevant and useful. For example, Table 1 highlights many neuropsychiatric medications with PGx information included in the labeling and potential clinical considerations.[8] Perhaps a bigger challenge is that commercially available testing panels often include a variety of genes with recommendations related to drug selection and dosing. Some information represents what has been evaluated by consensus guideline groups or is included in the product labeling, but some are genes with unclear clinical implications.[1] Determining which information to use is challenging.

An additional challenge related to the evolving nature of scientific data in the field of genomics is financial reimbursement for these tests and their interpretation. Genomics is evolving at a rapid pace, and the evidence for gene-outcome relationships is growing all of the time. Related to this, reimbursement patterns also appear to be evolving and, in the PRN's experience, are often different across drug and diagnosis groups as well as region of the country.

In conclusion, genetic polymorphisms appear to be important contributors to interindividual variation in medication response and tolerability. Currently, over 30 commonly used CNS-active medications contain PGx information in the product labeling that is relevant to drug selection, dosing, and monitoring. Most of this information references genetic variation in drug metabolism. Notable exceptions include markers for hypersensitivity reactions to some antiepileptic drugs. Pharmacogenomic studies of drug pharmacodynamics have yielded important information on drug mechanisms, but the clinical utility of this information is not yet clear. There is currently a need to better clarify how and when using PGx test information improves patient outcomes over standard clinical practice. As the cost of genetic analysis continues to decline, PGx testing will become more accessible, requiring clinicians to better understand the underlying science and clinical relevance of specific drug-gene pairs. Neurologic and psychiatric disorders are challenging to treat and often require long-term medication use. Pharmacogenomics is one way to better understand the potential sources of variability in response that will benefit greatly from the involvement of psychiatric and neurologic pharmacy specialists.

Table 1. Clinical Considerations or Implications of Pharmacogenomic Information Contained in Drug Product Labeling or Clinical Guidelines

Drug	Gene	Referenced Subgroup	Labeling Sections	Clinical Considerations or Implications
Amitriptyline	*CYP2D6*	*CYP2D6* poor metabolizers	Precautions	Lower dose may be required in *CYP2D6* or *CYP2C19* poor metabolizers. Consider alternative agents in *CYP2D6* ultrarapid metabolizers
	CYP2C19	*CYP2C19* poor metabolizers		
Aripiprazole	*CYP2D6*	*CYP2D6* poor metabolizers	Clinical Pharmacology, Dosage and Administration	Use lower dose in *CYP2D6* poor metabolizers
Atomoxetine	*CYP2D6*	*CYP2D6* poor metabolizers	Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology	Use lower dose in *CYP2D6* poor metabolizers
Azathioprine	*TPMT*	*TPMT* intermediate or poor metabolizers	Dosage and Administration, Warnings and Precautions, Drug Interactions, Adverse Reactions, Clinical Pharmacology	Lower dose required in intermediate metabolizers. Consider alternative agents in poor metabolizers
Brexpiprazole	*CYP2D6*	*CYP2D6* poor metabolizers	Dosage and Administration, Drug Interactions	Lower dose in *CYP2D6* poor metabolizers
Carbamazepine	*HLA-B*	*HLA-B*1502* allele carriers	Boxed Warning, Warnings and Precautions	Genetic testing is recommended in individuals of Asian ancestry. Treatment with carbamazepine is not recommended in *HLA-B*1502*
	HLA-A	*HLA-A*3101* allele carriers		
Citalopram	*CYP2C19*	*CYP2C19* poor metabolizers	Drug Interactions, Warnings	Maximum recommended daily dose in *CYP2C19* poor metabolizers is 20 mg/day
Clobazam	*CYP2C19*	*CYP2C19* poor metabolizers	Clinical Pharmacology, Dosage and Administration, Use in Specific Populations	In *CYP2C19* poor metabolizers, concentrations of *N*-desmethylclobazam, clobazam's active metabolite, are increased. Therefore, in patients known to be *CYP2C19* poor metabolizers, the starting dose should be 5 mg/day, and dose titration should continue slowly according to weight, but to half the usual target dose
Clomipramine	*CYP2D6*	*CYP2D6* poor metabolizers	Drug Interactions	Lower dose may be required in *CYP2D6* or *CYP2C19* poor

				metabolizers. Consider alternative agents in *CYP2D6* ultrarapid metabolizers
Clopidogrel	*CYP2C19*	*CYP2C19* intermediate or poor metabolizers	Boxed Warning, Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology	Consider alternative antiplatelet therapy in *CYP2C19* intermediate or poor metabolizers
Clozapine	*CYP2D6*	*CYP2D6* poor metabolizers	Drug Interactions, Clinical Pharmacology	Lower dose may be required in *CYP2D6* poor metabolizers
Desipramine	*CYP2D6*	*CYP2D6* poor metabolizers	Drug Interactions	Lower dose may be required in *CYP2D6* poor metabolizers. Consider alternative agents in *CYP2D6* ultrarapid metabolizers
Dextromethorphan and quinidine	*CYP2D6*	*CYP2D6* poor metabolizers	Clinical Pharmacology, Warnings and Precautions, Drug Interactions	*CYP2D6* poor metabolizers may be at greater risk of adverse effects
Doxepin	*CYP2D6*	*CYP2D6* poor metabolizers	Precautions	Lower dose may be required in *CYP2D6* or *CYP2C19* poor metabolizers. Consider alternative agents in *CYP2D6* ultrarapid metabolizers
Fluvoxamine	*CYP2D6*	*CYP2D6* poor metabolizers	Drug Interactions	*CYP2D6* poor metabolizers are known to have altered pharmacokinetic properties (i.e., increased AUC, Cmax, and half-life) compared with extensive metabolizers
Galantamine	*CYP2D6*	*CYP2D6* poor metabolizers	Special Populations	There is a 25% decrease in clearance in poor metabolizers compared with extensive metabolizers
Iloperidone	*CYP2D6*	*CYP2D6* poor metabolizers	Clinical Pharmacology, Dosage and Administration, Drug Interactions, Specific Populations, Warnings and Precautions	Lower dose may be required in *CYP2D6* poor metabolizers
Imipramine	*CYP2D6*	*CYP2D6* poor metabolizers	Drug Interactions	Lower dose may be required in *CYP2D6* or *CYP2C19* poor metabolizers. Consider alternative agents in *CYP2D6* ultrarapid metabolizers
Nortriptyline	*CYP2D6*	*CYP2D6* poor metabolizers	Drug Interactions	Lower dose may be required in *CYP2D6* or *CYP2C19* poor metabolizers. Consider

				alternative agents in *CYP2D6* ultrarapid metabolizers
Perphenazine	*CYP2D6*	*CYP2D6* poor metabolizers	Clinical Pharmacology, Drug Interactions	*CYP2D6* poor metabolizers have higher plasma concentrations of perphenazine at usual doses, which may lead to a higher incidence of adverse effects
Phenytoin	*CYP2C9*	*CYP2C9* intermediate or poor metabolizers	Clinical Pharmacology	Lower doses in *CYP2C9* intermediate and poor metabolizers
	HLA-B	*HLA-B*1502* allele carriers	Warnings	Phenytoin should be used with caution in *HLA-B*1502* carriers
Pimozide	*CYP2D6*	*CYP2D6* poor metabolizers	Warnings, Precautions, Contraindications, Dosage and Administration	Concentrations in poor *CYP2D6* metabolizers are similar to those in extensive *CYP2D6* metabolizers. Time to achieve steady-state pimozide concentrations is expected to be longer (about 2 wk) in poor *CYP2D6* metabolizers because of the prolonged half-life
Protriptyline	*CYP2D6*	*CYP2D6* poor metabolizers	Precautions	Lower dose may be required in *CYP2D6* or *CYP2C19* poor metabolizers. Consider alternative agents in *CYP2D6* ultrarapid metabolizers
Risperidone	*CYP2D6*	*CYP2D6* poor metabolizers	Drug Interactions, Clinical Pharmacology	Pharmacokinetic parameters are altered in *CYP2D6* poor metabolizers
Tetrabenazine	*CYP2D6*	*CYP2D6* poor metabolizers	Dosage and Administration, Warnings, Clinical Pharmacology	Population pharmacokinetic analysis showed a 25% decrease in median clearance in poor metabolizers compared with extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers because the drug dose is individually titrated to tolerability
Thioridazine	*CYP2D6*	*CYP2D6* poor metabolizers	Precautions, Warnings, Contraindications	Greater drug exposure in poor metabolizers, which may increase risk of adverse effects
Trimipramine	*CYP2D6*	*CYP2D6* poor metabolizers	Drug Interactions	Lower dose may be required in *CYP2D6* or *CYP2C19* poor metabolizers. Consider alternative agents in *CYP2D6* ultrarapid metabolizers

Valproic acid	*POLG, NAGS, CPS1, ASS1, OTC, ASL, ABL2*	Urea cycle enzyme deficient	Boxed Warning, Contraindications, Warnings and Precautions, Adverse Reactions, Medication Guide	(1) Avoid use in patients with urea cycle disorders. Evaluation for genetic abnormalities (including ornithine transcarbamylase and carbamoyl-phosphate synthetase) should be considered in high-risk patients before initiating therapy (2) Genetic testing is required for patients with suspected mitochondrial DNA polymerase or "*POLG*-related" disorder
Vortioxetine	*CYP2D6*	*CYP2D6* poor metabolizers	Dosage and Administration, Drug Interactions, Clinical Pharmacology	Maximum recommended daily dose is 10 mg/day in *CYP2D6* poor metabolizers
Warfarin	*CYP2C9*	*CYP2C9* intermediate or poor metabolizers	Dosage and Administration, Drug Interactions, Clinical Pharmacology, Warning and Precautions	Starting doses may depend on the combination of *CYP2C9* and *VKORC1* genotypes
	VKORC1	*VKORC1* rs9923231 A allele carriers		
	PROC	Protein C deficient		

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