Many different types of psychotropic drugs are now available to treat a wide variety of mental disorders. Why some patients respond to a particular drug and others do not, or why some patients tolerate a drug well and others do not, is an important clinical issue. Genetic differences among patients may contribute to variations in medication response as well as the development of adverse effects (Malhotra, Murphy, & Kennedy, 2004). The term “pharmacogenetics” refers to the use of molecular genetic approaches to understand differences in psychotropic drug response and tolerability. One approach to understanding pharmacogenetic differences is through pharmacokinetics (Weinshilboum, 2003).

PHARMACOGENETICS AND PHARMACOKINETICS

Pharmacokinetics refers to the body’s absorption, distribution, metabolism, and excretion of drugs (Brunton, Lazo, Parker, Buxton, & Blumenthal, 2006). The metabolism of drugs through the liver is the most clinically relevant pharmacokinetic process. The cytochrome P-450 (CYP-450) system is a group of enzymes, each produced by a different gene, which metabolize drugs in the liver. They account for the metabolism of approximately 60% of commonly prescribed drugs. Multiple CYP-450 enzymes exist in the liver and are classified into different families, subfamilies, and subforms according to a standardized nomenclature.
tature. The major drug-metabolizing CYP-450 subforms of interest in clinical psychopharmacology are CYP-1A2, CYP-2B6, CYP-2C9, CYP-2C19, CYP-2D6, and CYP-3A4 (Shader, 2003). A drug is referred to as a "substrate" of a CYP-450 enzyme if it binds to the enzyme and is metabolized by it. Drugs can be a substrate for one, or more than one, of these enzymes.

Slight variations in a particular gene are referred to as "genetic polymorphisms." Genetic polymorphisms occur with each of these CYP-450 genes and affect the enzyme activity, which can influence how a person metabolizes certain drugs (Weinshilboum, 2003). The metabolic activity of CYP-450 enzymes can be categorized as ultra-rapid, extensive, intermediate, or poor. Poor metabolism is characterized by the absence of enzyme activity, whereas ultra-rapid metabolism is characterized by excessive enzyme activity. Extensive metabolism is considered to be mostly normal enzyme activity, and intermediate metabolism is considered to be slightly decreased enzyme activity. Patients with poor or intermediate metabolic activity have higher serum concentrations of some drugs that also linger in the body for longer periods of time. As a result, these patients may experience more adverse effects. For example, decreased CYP-2D6 activity has been associated with more parkinsonian side effects with the use of risperidone (Risperdal®) (de Leon et al., 2005) and has been associated with an increased risk of tardive dyskinesia (de Leon, Susce, Pan, Koch, & Wedlund, 2005). Such patients may require lower dosage of medications to achieve acceptable levels of tolerability. However, lower doses, although better tolerated, may not be as effective, and patients may not be able to tolerate higher dosages that would be considered therapeutical.

By contrast, patients with ultra-rapid metabolic activity have much lower serum concentrations of some drugs. As a result, they may not respond to usual dosages of a drug. For example, increased CYP-2D6 activity has been associated with a poor response to some antidepressant drugs (Rau et al., 2004). These patients may require higher than usual drug dosages to achieve some therapeutic benefit. They may also seem to tolerate a drug at a dosage that would be considered excessive and intolerable to other patients.

Some drugs may be metabolized into compounds ("metabolites") that are physiologically active or inactive. The best example is the narcotic codeine, which is physiologically inactive and must be metabolized by CYP-2D6 into the active metabolite morphine (Brunton et al., 2006). Hence, patients with poor metabolic activity do not respond adequately to any dosage of codeine, while patients with ultra-rapid metabolic activity may not only show an analgesic response but may also be prone to side effects, such as sedation or even intoxication, with usual clinical dosages.

Other preliminary studies have examined this issue by investigating genetic variability in the metabolism of different antidepressant drugs (Kircheiner et al., 2003). These studies have found that some drugs may be transformed into multiple metabolites, some of which are therapeutically active (i.e., have antidepressant effects), while some are inactive (i.e., have no antidepressant effects). Similarly, some drugs may be transformed into multiple metabolites, some of which are benign (i.e., have no significant adverse effects) and some of which are potentially toxic (e.g., have cardiotoxic effects). An important implication of this work is that some patients may not respond to a particular antidepressant drug (or drug class) because their unique CYP-450 enzyme system preferentially transforms the drug into an inactive metabolite. Similarly, some patients may be prone to adverse or toxic effects because they preferentially transform a drug to a toxic metabolite. Therefore, genetic polymorphisms among the different CYP-450 en-
zymes may offer one explanation for differences in response, tolerability, and safety among patients taking the same drug.

Different drugs also may bind to one (or more than one) CYP-450 enzyme and either "inhibit" or "induce" its activity, without being metabolized by the enzyme(s). Thus, metabolic drug-drug interactions can occur when a drug that inhibits or induces a CYP-450 enzyme is combined with a drug that is a substrate for that enzyme. For example, the anticonvulsant agent carbamazepine (Equetro®, Tegretol®) induces CYP-3A4 activity, which can lead to increased metabolism, decreased serum levels, and reduced clinical efficacy of drugs that are substrates for this enzyme (Shader, 2003). By contrast, drugs that inhibit CYP-450 enzymes can result in decreased metabolism, increased serum levels, and greater side effects of drugs that are enzyme substrates. For example, the antidepressant agent paroxetine (Paxil®) inhibits CYP-2D6. Combining paroxetine with substrates such as tricyclic antidepressant agents or the antipsychotic thioridazine (Mellaril®) can result in higher serum concentrations of these drugs, both of which have potentially serious adverse cardiac effects (Shader, 2003).

In addition to inter-individual differences, genetic polymorphisms of CYP-450 enzymes may also exist between different ethnic groups (Ng, Schweitzer, Norman, & Eastal, 2004). For example, approximately 5% to 10% of Caucasian individuals can be characterized as having poor metabolic activity of CYP-2D6, and approximately 20% of Asian individuals have poor metabolic activity of CYP-2C19 (Ng et al., 2004). This phenomenon may explain differences in drug response or tolerability that have been described in some clinical treatment studies conducted in various patient populations. Because the activity of CYP-450 enzymes is genetically determined, and therefore heritable, it is possible that drug response and tolerability may be predicted based on family history. Indeed, although how various clinical variables (e.g., ethnicity, family history, gender) may be markers for underlying genetic differences that contribute to variability in drug response, tolerability, and safety (Weinshilboum, 2003).

**CLINICAL APPLICATIONS OF PHARMACOGENETICS AND PHARMACOKINETICS**

The AmpliChip CYP450 Test (Roche Diagnostics) is the first commercially available product approved by the U.S. Food and Drug Administration that analyzes genetic polymorphisms in two CYP-450 enzymes: CYP-2D6 and CYP-2C19 (Jain, 2005). The AmpliChip can identify 29 known CYP-2D6 polymorphisms and two known CYP-2C19 polymorphisms. A blood sample is taken and sent to a laboratory capable of performing genetic analyses. DNA from the blood sample is "amplified" using standardized molecular genetic techniques and is then applied to a microchip approximately the size of a thumbnail. This DNA binds to pre-determined DNA test fragments on the microchip, which is analyzed by computer. The entire process takes approximately 8 hours.

The AmpliChip determines the patient’s particular CYP-2D6 and 2C19 polymorphisms, as well as their metabolic activity status for each enzyme. With this test, CYP-2D6 metabolic activity is characterized as poor, intermediate, extensive, or ultra-rapid, and CYP-2C19 activity as poor or extensive. The laboratory generates a report with this information, which can be used by the treating clinician to make clinical decisions about the use of drugs that are substrates, inhibitors, and/or inducers of CYP-2D6 or CYP-2C19.

Approximately 25% of all drugs are substrates of these two enzymes. CYP-2D6-dependent

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**Nurses will play an important role in educating patients and their families about the benefits and limitations of pharmacogenetic testing related to their treatment.**
drugs include many antidepressants, antipsychotic, anti-arrhythmic, beta-blocking, analgesic, and anti-emetic agents, as well as cancer drugs. CYP-2C19 dependent drugs include many anticonvulsant, proton pump-inhibiting, benzodiazepine, and anti-malarial agents. Comprehensive lists of drugs that are substrates, inhibitors, or inducers of these enzymes are widely and readily available from many Internet and print sources. These sources are periodically updated with new data about existing and newly available drugs.

CONCLUSION
Pharmacogenetics and pharmacokinetics are part of a rapidly evolving field. Nurses should be familiar with the use of pharmacogenetics technology and information in the care of patients receiving drug therapy (Lea, 2005).

Although much work needs to be done to fully realize the clinical potential of pharmacogenetics testing (Epstein, 2004), such information will be increasingly important not only for choosing among different drug therapies, but also for monitoring their effectiveness, tolerability, and safety. Nurses will play an important role in educating patients and their families about the benefits and limitations of pharmacogenetic testing related to their treatment.

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IN THE NEWS
FDA SAYS: LONG-TERM EFFECTIVENESS NOT NECESSARY FOR APPROVAL OF PSYCHIATRIC DRUGS

The U.S. Food and Drug Administration (FDA) unanimously rejected a proposal to require drug makers to provide evidence of the long-term effectiveness of certain drugs before they can be sold. The decision is not binding, but Dr. Thomas Laughren, acting director of the FDA’s division of psychiatry products, said he would not pursue the issue given the committee’s decision, which was also supported by both drug companies and mental health advocates because delaying approval would delay patient access, as well as further slow an already lengthy approval process. In addition, the decision does not affect long-term safety studies, which are already required.

Laughren had asked the committee to consider whether to require long-term studies, as drugs for most chronic psychiatric illnesses are prescribed for at least 4 to 6 months. However, drug companies only have to show their drugs are effective through short-term trials.

The FDA usually asks drug companies to complete long-term efficacy studies after a drug is approved, and most companies comply. Most of the studies have shown long-term effectiveness, but it can be 4 to 5 years before the studies are available. Drug companies estimated that requiring long-term studies before approval would add another year or more to development, and could also discourage companies from conducting research in what is already a challenging area.