Principles of Pharmacology

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Abstract

Understanding and being able to apply the principles of pharmacology is a key component in the treatment of patients' medical conditions. Pharmacokinetics describes the interaction of the body upon a drug and its pathway as it moves across cell membranes. Pharmacodynamics encompasses the relationship between drug concentration and the effect within the human body. In addition to pharmacokinetics and pharmacodynamics leading to individual responses to drug therapy, exploration of the genetic influence continues to be an area of intense research. Each individual has his or her own unique genetic code and how individual genetic variations affect drug response is referred to as pharmacogenetics. While the ability to take one's medication as directed seems like a simple concept, in actuality, adherence is complex and influenced by many factors. Medication selection and route of administration may be influenced by available formulation options and concomitant conditions. These concepts are reviewed in this chapter.

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Introduction

Having a working knowledge of pharmacology is an essential component in the appropriate treatment of patients. The goal of each medication prescribed should be maximizing treatment efficacy while minimizing the risk of adverse effects to the patient. Understanding the principles of drug pharmacokinetics and pharmacodynamics as well as the evolving field of pharmacogenetics and pharmacogenomics is the cornerstone to individualizing therapy. These concepts will be reviewed within this chapter. Not only do these concepts affect drug therapy

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selection, but other factors affect treatment outcomes and drug selection. Without patient adherence to therapy, efficacy cannot be achieved. A discussion of barriers and interventions to improve adherence is included as well as special considerations in patients with intellectual and developmental disabilities (IDD).

> PA was born full term via normal spontaneous vaginal delivery. The pregnancy was complicated by maternal pre-eclampsia and HELLP syndrome (hemolytic anemia, elevated liver enzymes, low platelet count). Neonatal course was complicated by PA developing venous sinus thrombosis. Further hematology and genetics evaluation revealed that PA had MTHFR (methyl tetrahydrofolate reductase) deficiency. PA, now 10 years old, has cerebral palsy with spastic quadriplegia, profound intellectual disability, cortical blindness, and seizures. He is total care dependent. He is fed and given medications via gastric tube. He is on baclofen, keppra, and Phenobarbital. He also receives albuterol and Pulmicort via nebulizer. His caregiver is also instructed in administration of diazepam rectally for acute seizure episodes if needed. To ameliorate excessive drooling PA is on dermal patch of gycopyrrolate.

Pharmacokinetics

Pharmacokinetics describes the interaction of the body upon a drug and its pathway as it moves across cell membranes. Pharmacokinetics involves absorption, distribution, metabolism and excretion (ADME) of a drug. These parameters can be affected by a variety of influences including sex, race/ethnicity, other medications, diet, comorbid disease states and genetics [1]. Differences with respect to child development are discussed but there are no known differences in regards to those with IDD. A detailed discussion of ADME is noted below.

Absorption

Absorption of a drug can occur via a variety of routes including gastrointestinal, transdermal, intramuscular, intravenous, and rectal. Drug absorption can be influenced by a variety of physiological and drug factors as noted in Table 141.1. Bioavailability of a drug refers to the extent at which it is available at its site of action [2]. A decrease in bioavailability can occur in those drugs that undergo extensive hepatic first pass metabolism due to enzymatic degradation in the intestines or liver [2]. Several mechanisms exist for drug transport across cell membranes to its site of action and include passive and active transport as well as facilitated diffusion [2] (see Table 141.2). Passive diffusion is the most common for drugs but transporters play an important role by enhancing or limiting drug absorption via uptake or efflux mechanisms (i.e. p-glycoprotein) [2]. Drug factors that affect the ability to cross cellular membranes and reach the target site

Table 141.1 Factors affecting gastrointestinal absorption of drugs [2]

Gastric factors	Gastric enzyme activity
	Gastrointestinal pH
	Dissolution rate (rate at which drug dissolves in GI tract)
Intestinal factors	Motility
	Regional blood flow
	Surface area for absorption
	Transit time
	Presence of food
	Presence of other medications
Drug properties	Polarity
	Water/lipid solubility
	pKa (Logarithmic measure of the acid dissociation. The larger the value, the weaker the acid)
	Degree of ionization
	Local drug concentration
	Dosage form

Table 141.2 Cellular membrane transport mechanisms [2]

Passive diffusion	Drug moves along a concentration gradient because of its lipid solubility properties
Active transport	Drug is transported by an energy dependent carrier against a concentration gradient (i.e. sodium-potassium ATPase)
Facilitated diffusion	Drug is transported by a non-energy dependent carrier and in the direction of the concentration gradient

include molecular size and shape of the drug, degree of ionization, solubility at the site of absorption and protein binding [2].

Developmental differences in absorption include an increase in intragastric pH for neonates [3]. This can lead to an increased need for higher doses of weak acids such as phenobarbital and phenytoin [3]. Gastric emptying is protracted in infancy and overall absorption rates of most drugs are slower in neonates and young infants [1, 3].

Some oral agents are available as controlled release products which provide a sustained response due to control of the dissolution rate. This allows for a more consistent therapeutic drug level and less frequent dosing. Controlled release mechanisms are most appropriate for those drugs with short half-lives [2]. Drug class examples include stimulants (i.e. methylphenidate ER), antidepressants (i.e. venlafaxine ER, buproprion XL) and anticonvulsants (i.e. carbamazepine ER).

Medications can also be administered topically and absorption is dependent on the surface area of the drug, duration of exposure and its lipid solubility [2]. Drug exposure can be increased in infants and young children due to increased body surface area compared to total body weight elevating the risks for toxicity [4]. Transdermal routes are more common for adult medications but do include methylphenidate for the pediatric population. Transdermal patches provide a sustained therapeutic effect due to their controlled-release mechanism.

Medication selection and route of administration may be influenced by timeframe needed to achieve a response, available formulation options and concomitant conditions. Often the gastrointestinal route is the most convenient and frequently used route within children. Enteric coated formulations can be useful for reducing the risk for gastrointestinal discomfort as well as those who get skin irritation due to dribbling from liquid preparations [5]. Liquid formulations are useful in those who have trouble swallowing pills, especially children, but may have to be extemporaneously compounded due to unavailability by the manufacturer. Rectal formulations give an alternative route when other routes are not available and typically provide rapid absorption [6]. Patient variability does exist and absorption can be delayed and reduced due to decreased rectal tone or presence of stool [6]. Transdermal and oral transmucosal provide additional administration routes for patients who have difficulty swallowing medications but are not available for many classes of medications.

Distribution

Upon absorption, a drug reaches the blood stream and is distributed to interstitial and intracellular fluids. Medications can bind to a variety of proteins including lipoproteins, albumin (acidic drugs) and alpha-1-glycoprotein (basic drugs). The extent of binding is mediated by drug concentration in the blood, affinity to and availability of the binding sites [2, 7]. The volume of distribution (Vd) correlates the amount of drug in the body to the plasma concentration and provides an estimate of the amount of drug in the extravascular tissues [8]. A drug's volume of distribution can vary by age due to changes in body composition, age-related changes in protein binding capacity, membrane permeability and comorbid disease states [2]. The Vd will be relatively small for drugs contained in the vascular system compared to a relatively large Vd for those drugs bound to body tissues [8]. Protein-binding can affect volume of distribution. Phenytoin is highly bound to albumin and subsequently has a low Vd; displacement from albumin will increase plasma concentrations and increase the risk for toxicity. Other medications bound to the same protein can compete for the same binding site leading to drug displacement and a change in plasma concentrations [8]. The effect of drug displacement is more likely to be significant for medications that have a narrow therapeutic index [7]. The volume of distribution can be helpful in determining a loading dose or the dose needed to achieve a desired drug serum level [loading dose = desired drug serum concentration (mg/L) × Vd (L/kg) × patient's weight (kg)] [7].

Age-related physiologic changes include larger body water spaces and higher ratio of

water to lipid in adipose tissues in neonates and young infants [1, 3]. This results in decreased plasma levels for drugs that distribute to these areas and an increase in Vd (i.e. gentamicin) [4]. Due to reduced body fat in neonates, highly lipophilic drugs will have a reduced Vd compared to adults and can impact drug therapy [4]. Plasma protein concentrations are noted to be reduced in neonates and young infants [3, 4]. This leads to an increased free fraction of the drug in the serum and subsequently increased drug effect.

Metabolism

Enzyme systems within the liver, lungs, intestines and kidneys metabolize or transform drugs [9]. The resulting product can be biologically active or rendered inactive. First pass effect occurs when drugs are metabolized in the intestines or liver into inactive products reducing the amount that reaches the vascular system [10]. Most drug metabolism occurs in the liver and can undergo one or two types of reactions. Phase I reactions involve oxidation, reduction and hydrolysis of a drug to make it more water soluble. Phase II reactions involve conjugation with glucuronic acid, sulfate or acetate. These reactions produce compounds that are often biologically inactive and more readily excreted by the kidneys [9].

The cytochrome P450 (CYP 450) enzyme system serves a primary role in the biotransformation of drugs with wide ranging implications in efficacy, toxicity and drug interactions. CYP isoenzymes are compromised of various families and subfamilies with a CYP isoenzyme family having at least a 40 % homology in amino acid sequence and denoted by an Arabic number (i.e. CYP2) [11]. A CYP isoenzyme subfamily contains at least 55 % homology in amino acid sequence and is denoted by an upper case letter (i.e. CYP2D) [11]. The last number in the notation marks the individual isoenzyme (i.e. CYP2D6) [11]. Isoenzyme families CYP1, CYP2 and CYP3 are most often involved in drug metabolism and CYP 3A4 metabolizes over 50 % of prescription medications via the liver [11, 12]. Genetic variability can be seen with the CYP isoenzymes, particularly with CYP 2C9, CYP 2C19 & CYP 2D6, leading to interindividual variability [9]. A genetic defect in the isoenzyme gene leads to diminished drug metabolism and the patient is considered a "poor metabolizer" [9]. While this is not common, it can lead to toxicity from drug accumulation or lack of effect if the metabolite is the active moiety. Other factors besides ethnicity that affect drug metabolism include age, diet, presence of other drugs, comorbid disease states and environmental factors such as alcohol and tobacco [2, 9]. Knowing how a drug is metabolized by the CYP 450 isoenzyme system can be useful for predicting drug interactions. Medications can be selective for isoenzymes in either inhibiting metabolism (increasing drug effect) and/or inducing metabolism (decreasing drug effect) [9]. Drugs can also be a substrate for an isoenzyme as well as serve as an inducer or inhibitor for that same substrate [9]. Drug information monographs are useful in evaluating metabolism routes and potential drug interactions. A variety of drug information databases can also help determine potential drug-drug interactions. While not all drug interactions are clinically relevant, they can often be predicted and avoided.

Age-related physiologic changes are seen with metabolism of drugs in children. Overall, drug metabolism is reduced in neonates compared to children and adults [4]. Differences can be seen with various pathways including decreased glucuronidation compared to the sulfation pathway [4]. While drug metabolism by the cytochrome P450 enzyme system is reduced in neonates and infants, an increase in drug plasma clearance secondary to increased metabolism has been seen in prepubescent children [13]. Theophylline and carbamazepine, both metabolized by cytochrome P450 isoenzymes, have demonstrated greater clearance in children compared to adults [3, 4]. Specifically, CYP1A2, 2C9 and 3A4 activity surpasses adult levels until puberty is reached while no difference is seen with CYP 2C19 and 2D6 [13]. This may result in the need for higher drug doses or more frequent dosing with enhanced metabolic clearance.

Excretion

The kidneys serve as the major organ for drug elimination and compounds can be eliminated as unchanged product or as metabolites [8]. Hydrophilic compounds are more readily excreted compared to lipophilic agents. Conversion of lipophilic agents to a more polar water soluble compound enhances renal elimination [8]. Renal excretion consists of three components: filtration by the glomerulus, active tubular secretion and passive tubular reabsorption [8]. These processes are affected by fluid volume, unbound plasma drug concentrations, a drug's intrinsic clearance by transporters, transporter saturation, rate of drug delivery, protein binding, blood flow and number of functioning nephrons [2]. Age-related changes are seen with glomerular filtration and tubular secretion and maturation is noted by approximately 1 year of age [13]. Reduced dosing may be necessary in neonates and infants for drugs that are extensively renally eliminated to reduce the risk for toxicity [13].

Clearance is an important pharmacokinetic parameter for determining drug maintenance dosing. Clearance is defined as the efficiency of drug elimination from the blood or plasma and is expressed in milliliters/minute (volume/unit of time) [8]. If clearance and desired steady state concentration (or therapeutic range) are known, a drug's maintenance dose can readily be calculated [8]. Steady state concentrations are achieved when drug elimination equals drug administration rate [8]. A majority of drugs follow linear pharmacokinetics where steady state drug plasma concentrations rise in proportion to drug dose [8]. Nonlinear pharmacokinetics occur when steady state plasma drug concentrations rise disproportionally to a change in drug dose [8]. The half-life of a drug is essential for determining the time required to reach steady state, drug elimination from the body and drug dosing interval. Three to five half-lives are generally needed to reach steady state and half-life is estimated from clinical pharmacokinetic drug studies [8].

Pharmacodynamics

Pharmacodynamics encompasses the relationship between drug concentration and the effect within the human body [9]. Quantifiable examples include blood pressure reduction with antihypertensives and temperature reduction with antipyretics. The effect of a drug is often mediated by its interaction with a receptor. A variety of drug receptors exist including regulatory proteins (determine the action of endogenous chemicals such as neurotransmitters and hormones), enzymes, transport proteins and structural proteins [15]. Factors that affect binding of the drug to a receptor and its ability to elicit a response include molecular size and shape, electrical charge, and affinity to the receptor [15]. A drug that acts as an agonist at a receptor site will promote the action of the receptor whereas an antagonist will prevent an agonist from binding or oppose the action of the receptor [15]. Antagonism can occur through several mechanisms including direct binding to the agonist, blocking the effects of an agonist, competitive receptor binding or binding to an alternative site [15]. An antagonist can be competitively reversible with sufficient concentrations of an agonist to overcome the antagonist or irreversible making it unavailable to an agonist [15]. A partial agonist produces an incomplete response despite adequate drug concentrations and complete receptor binding [15]. Partial agonist activity can be clinically useful when a drug produces less toxicity secondary to an incomplete response.

The chemical structure of a drug affects its potential binding, intrinsic activity and specificity for the target site. A drug can be selective for a specific receptor type (i.e. digoxin for the sodium-potassium ATPase pump) producing a discrete action or can affect a variety of receptors (i.e. amitriptyline inhibits reuptake of serotonin and norepinephrine and antagonizes acetylcholine) producing a range of physiologic responses [15]. A drug can also produce a range of therapeutic as well as toxic effects by being selective for one receptor type but the receptor is available on a variety of cells throughout the body (i.e.

oxybutynin and muscarinic receptors). Modifications of drug structure or development of new entities that have greater receptor selectivity can lead to enhanced efficacy and reduction in adverse effects (i.e. darifenacin for the muscarinic [M3] receptor) [15].

Individuals can vary in their magnitude and response to drug therapy and a variety of factors influence drug response including age, comorbid disease states, physiologic changes, genetics, other medications, adherence, diet and substance use (i.e. alcohol and tobacco) [15]. These factors in addition to pharmacokinetics, will influence the agent chosen as well as its dose and frequency in order to achieve an optimal therapeutic effect. The therapeutic index relates the amount of drug necessary to produce a desired response to that which would produce an untoward effect [14]. While an exact therapeutic index is often unknown, generally effective doses are determined from clinical studies and experience. Unfortunately, drug toxicity can overlap with typical therapeutic drug plasma concentrations as a result of pharmacodynamic differences within the population and therefore requires a practitioner to also utilize clinical and surrogate markers to evaluate for efficacy and toxicity [14].

Drug interactions can occur from pharmacokinetic, pharmacodynamic or a combination of both and can often be difficult to discern in a patient with multiple comorbidities and medications [14]. Pharmacokinetic drug interactions affect the ability of a drug to reach its target site and were previously discussed [14]. Pharmacodynamic drug interactions occur when one drug alters the response of another [14]. Examples of this include an increased risk for bleeding with the combination of warfarin and aspirin, risk of bradycardia with the combination of beta-blockers and acetylcholinesterase inhibitors and risk for serotonin syndrome when selective serotonin reuptake inhibitors (SSRIs) are combined with tramadol or dextromethorphan. While not all drug interactions are clinically significant most can be predicted. Therefore it is important for practitioners to be knowledgeable regarding a drug's pharmacokinetic and pharmacodynamic properties to maximize benefit and minimize the risk for toxicity.

Pharmacogenetics and Pharmacogenomics

In addition to pharmacokinetics and pharmacodynamics leading to individual responses to drug therapy, exploration of the genetic influence continues to be an area of intense research. While significant advances have been made in the field of genetic research, trying to determine the place that genetic testing plays in individualizing drug therapy remains a challenge.

Each individual has their own unique genetic code and how individual genetic variations affect drug response is referred to as pharmacogenetics [16]. On the other hand, pharmacogenomics entails the relationship between drug effect and variation seen within a number of genes (up to the whole genome) [17]. Differences within a specific gene among a population is referred to as a polymorphism (typically >1 % in a specific population) [17, 18]. These can occur in coding or noncoding regions and can be influenced by ethnicity [17]. The alteration in one nucleotide within a gene is referred to as a single nucleotide polymorphism (SNP) and is the most frequent type [17]. When a gene polymorphism exists, alternative forms of the gene are known as alleles [17]. Within a given region of the DNA, the alleles can be homozygous (identical) or heterozygous (different) [18].

Initial pharmacogenetic studies focused on polymorphisms within drug metabolizing enzymes but have expanded to include drug transporters and drug targets [18, 19]. One of the most extensively studied drug-metabolizing enzymes with regards to genetic variability is the CYP2D6 isoenzyme. Greater than 75 alleles have been described with CYP2D6 including SNPs in encoded proteins, altered RNA splicing, deletions and even multiple copies in ultrarapid metabolizers [20, 21]. Similar polymorphisms have also been identified for CYP3A5, 2C9 and 2C19 [20]. Some medications (i.e. codeine, tetrabenazine) now include dosage modifications and/or precautions in their package insert based on whether a patient is a rapid or poor metabolizer [22]. Alterations have also been seen in phase II hepatic reactions and one of the earliest examples was demonstrated with isoniazid. N-acetyltransferase

(NAT) is responsible for the metabolism of isoniazid [23]. Rapid metabolism of isoniazid, leading to decreased efficacy, has been observed in some populations (i.e. East Asians) due to a polymorphism in the NAT2 gene [20, 23].

Transporters play an important role in the pharmacokinetic regulation of many medications and polymorphisms in these genes have led to variability in drug response [19]. P-glycoprotein is responsible for efflux of a variety of medications including digoxin, glucocorticoids, several anticancer drugs, and some immunosuppressive agents [19]. Single-nucleotide polymorphisms in the MDR1 gene that encodes P-glycoprotein has produced greater bioavailability for digoxin and decreased levels of fexofenadine [19, 24, 25]. Polymorphisms have also been identified for a variety of drug targets. One of the most notable affecting drug therapy is the VKORC1 which encodes a region of the vitamin K epoxide reductase complex [17]. Alterations in the CYP2C9 enzyme was thought to account for differences in response to warfarin but discovery of polymorphisms in the target site, VKORC1, demonstrated greater variability than that of the drug-metabolizing enzyme [17]. The warfarin labeling has been updated twice in the past and now includes precautions for those with genetic polymorphisms may be at an increased risk of bleeding and may require lower doses as well as recommendations for maintenance doses in those with CYP2C9 and VKORC1 polymorphisms [22, 26]. Polymorphisms in genes not directly related to drug transport or target have even been show to alter drug response in selected situations. Genetic mutations in KCNE2, which encodes for potassium channels, may increase the risk for a prolonged QT interval and life-threatening torsades de pointe when taking some types anti-infective or antipsychotic agents [19, 27].

The field has expanded tremendously from evaluating single gene polymorphisms to whole genome-wide studies (see Fig. 141.1). Candidate gene and pathway approaches offer the advantage of testing genes with known functional relevance but has the disadvantage of important genes that may be missed [26]. Decreased cost has allowed for more genome-wide studies to be performed which provides a more comprehensive approach and allows for detection of rare polymorphisms [26]. Unfortunately, genome-wide studies require increased sample sizes, can result in a large number of false positives and may provide rare variants with unknown functional significance [26]. The next generation of sequencing has reduced the time and cost of genome sequencing but continues to have some of the same challenges of genome-wide association studies [26].

Ideally, pharmacogenomics will be utilized to individualize drug therapy in order to enhance efficacy and reduce the risk for toxicity. Significant gains have been made within this field but many challenges continue to exist and must be overcome in order for this to become part of mainstream medicine. Table 141.3 provides a list of medicines that have had FDA-required labeling changes due to identified polymorphisms [22, 28]. Unfortunately, not all provide guidance as to changes in drug dosing or monitoring parameters. The challenges associated with the clinical relevance of pharmacogenetic testing have recently been published. Several large multicenter, randomized, controlled trials demonstrated that genotype-guided initial warfarin dosing provided no benefit or marginal benefit compared to clinical-guided dosing when assessing time within therapeutic range [29–31]. Not only genetic factors, but nongenetic factors such as medication adherence, concurrent medications and substance use serve as important factors and should be considered when initiating drug therapy [32]. Additional challenges associated with the clinical implementation of pharmacogenetics includes cost, feasibility, evidence to support, alternative biomarkers and practitioner knowledge. The 1200 Patients Project is currently evaluating a model to overcome some of these barriers to facilitate use within the clinical setting [33]. The project is providing comprehensive genotype testing up front along with an interactive Web-based system to provide guidance in interpreting results and drug dosing [33]. The primary outcomes are to assess providers' use of the information and its ability to alter prescribing practices for patients who may be at high risk [33]. As research moves forward, it is essential that we expand our knowledge within this area to meet the ever-changing requirements in drug therapy management.

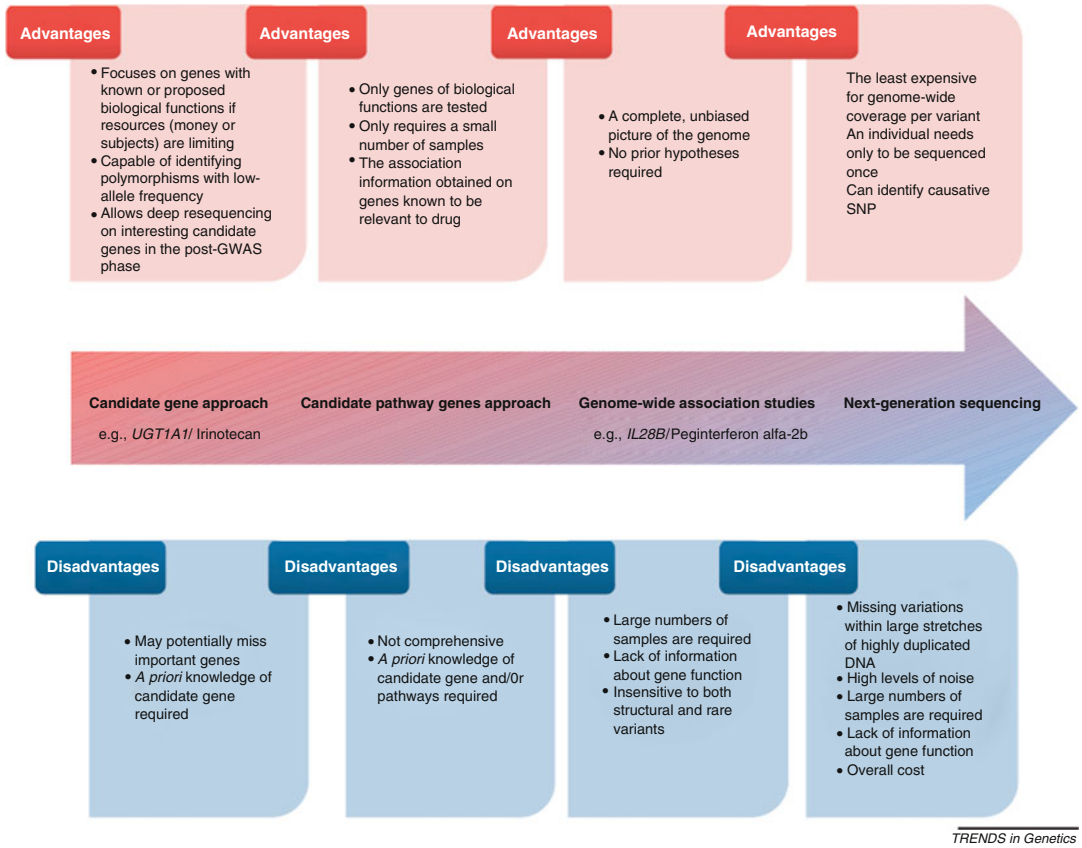

Fig. 141.1 The evolution of pharmacogenetics (Reprinted from Ref. [26] with permission from Elsevier)

Useful resources include Pharmacogenomics Education Program (http://pharmacogenomics.ucs.edu), Genetics Home Reference by the US National Library of Medicine (http://ghr.nlm.nih.gov/glossary), CDC's National Office of Public Health (http://www.cdc.gov/genomics) and Pharmacogenomics Knowledge Base (http://pharmgkb.org) [32].

Adherence

While the ability to take one's medication as directed seems like a simple concept, in actuality, adherence is complex and influenced by many factors. Adherence is often arbitrarily defined as taking 80 % or more of intended doses, is often dismally low and tends to be higher with acute vs. chronic medical conditions [34, 35]. Adherence has been found to be the lowest in adolescence and may be related to a variety of psychosocial factors including increased independence, risk-taking behavior, peer influence, family conflict and fluctuating schedules [36, 37]. The most frequent form of nonadherence is missing a dose due to forgetfulness or a delay in taking a dose [34, 36, 38].

Measuring adherence can be challenging for practitioners and the consequences of nonadherence can be quite significant for both the patient and the healthcare system. Adherence can be measured directly through direct observation or the use of blood levels [34]. While advantageous, these are not always practical or available for all medicines. Methods of indirect measurement include self or caregiver report, physician estimates, pill counts, refill history, clinical response, physiologic markers, and electronic monitoring

Table 141.3 Examples of FDA labeling incorporating pharmacogenomics [22, 28]

Drug	Gene	Labeling information
Carbamazepine	HLA-B*1502	Those with Asian decent should be tested prior to initiation of therapy; increased risk for adverse effects; avoid if positive result
Tetrabenazine	CYP2D6	Test when requiring doses >50 mg/day. Maximum dose 50 mg/day for poor vs. 100 mg/day for extensive/intermediate metabolizers
Dapsone	G6PD	Cautious use in patients with G6PD deficiency; test prior to initiation of therapy
Azathioprine	TMPT	Increased risk for myelosuppression with absent, low and intermediate TMPT activity; recommend dosage reduction with decreased activity
Abacavir	HLA-B*5701	Test prior to start of therapy; increased risk for hypersensitivity reactions; avoid use if positive result
Irinotecan	UGT1A1*28	Homozygous for allele: increased risk for neutropenia; adjust starting dose by one dose level (reduced dose)
		Heterozygous for allele: may have increased risk; most tolerate usual initial doses
Clopidogrel	CYP2C19*2 or*3	Decreased efficacy with one or more alleles; may consider testing in those at moderate to high risk for negative outcomes; optimal dose is unknown in poor metabolizers
Maraviroc	CCR5	Test prior to start of therapy; lack of efficacy in those with CXCR4 or dual tropic HIV infection
Carglumic acid	NAGS	Indicated for those with N-acetylglutamate synthase deficiency

HLA-B Human leukocyte antigen-B, *G6PD* glucose-6-phosphate dehydrogenase, *TMPT* thiopurine s-methyltransferase, *UGT* UDP-glucuronosyl transferase, *CCR5* chemokine (C-C motif) receptor 5, *NAGS* N-acetylglutamate synthase

devices [34, 36]. While many of these are simple and easy to perform, they all have caveats to their use rendering no one method as ideal. Adherence is often under-recognized by providers, tends to be overestimated by patients and caregivers, clinical response and physiologic markers may be influenced by other factors and pill counts and refill history do not equate to taking the medicine [34]. Numerous consequences can occur as a result of nonadherence and include suboptimal or lack of treatment efficacy, repeat physician visits, change in dose or additional prescriptions and increased length of illness [39]. Undoubtedly, adherence contributes to an increase in healthcare costs and utilization as well as patient morbidity and mortality [34]. Understanding the factors and barriers that contribute to adherence can provide insight into strategies for improving patient medication adherence and ultimately treatment efficacy.

Several patient and family factors can influence adherence and include health literacy, education and cultural beliefs [39]. With technology and increased use of the internet for health care information, it is important to assess background information and any potential misperceptions due to outside sources [39]. Cultural and health beliefs regarding disease and treatment is an important perspective to evaluate since they can influence the treatment selection as well as ability to adhere to provider recommendations [39]. Family influences can also affect adherence, especially in pediatrics. Children who split their time between different households, varying

weekly schedules due to school and outside activities, dysfunctional households and poor communication between caregivers can all contribute to nonadherence [36].

In addition to patient and family, factors related to the medication can influence the choice of treatment and ability to adhere to therapy. Cost, insurance coverage, duration of treatment, dosing frequency, taste, ability to swallow and side effects can all affect adherence [39]. Cost of an agent can influence whether a patient or caregiver fills a prescription and formulary restrictions may restrict or prohibit the use of more patient-friendly options. Increased daily dosing frequency has shown a correlation to reduced adherence. A systematic review demonstrated that adherence with once daily dosing produced compliance rates of ~79 % compared to ~51 % with four times daily dosing [40]. Most patients and caregivers prefer fewer doses and avoiding daytime dosing with children in school can enhance adherence and lessen social stigma [36]. Dosage form of the medication can influence a patient's ability to comply with a regimen. Large tablet sizes making it difficult to swallow, extended-release formulations not able to be crushed and poor taste of liquid formulations can lead to nonadherence. This can be especially troublesome for parents of children who resist therapy and don't understand the purpose of the treatment [36]. Last but not least, medication side effects can lead to nonadherence as well as medication discontinuation [39, 41]. This can be especially significant for adolescents where adverse effects, such as weight gain, can be stigmatizing [36].

Primary care providers and their office practices can influence adherence to treatment. Lack of a continuity provider, disorganized offices, poor communication by physician and office staff and inability to access office for questions or concerns can contribute to frustration and nonadherence [39]. Providers can also contribute to nonadherence by prescribing complex treatments and not taking into account patient preferences [34]. The ability to establish an effective relationship by the provider can positively influence adherence [39, 42].

With all the barriers noted above, multiple interventions have been proposed to enhance adherence and ultimately treatment efficacy. Providing patients with the simplest and most efficacious treatment regimen with ideally once daily dosing can ease treatment burden [39]. Use of longer-acting agents (i.e. Depo-Provera®, Prolia®) that reduce dosing frequency and are more forgiving may be beneficial for selected patients. Having knowledge of patient preferences, medication financial constraints and insurance coverage should be accounted for when selecting a medication [39]. Developing a treatment plan with the patient taking into account these factors as well as cultural beliefs can enhance patient-provider relationship and adherence. Improving communication between the physician, office staff and patient/caregiver can significantly aide adherence [39]. Assessing whether the patient can adhere to the proposed regimen and providing adequate medication education regarding the indication, dosing, administration, common side effects and expected benefits is essential. Providing the information in writing along with contact information for any follow-up questions would be ideal and beneficial to the patient/caregiver. Time constraints within the office setting may not always allow for this type of extended intervention. Incorporating the patient into the decision-making process and encouraging self-management can aide adherence and allow the patient to take a greater role in their care [39]. Utilizing technology to enhance adherence can be beneficial for many patients. Medications that ease administration (i.e. insulin pens, one step inhalers), devices that simplify use (i.e. aerochambers), automated, alarmed pill boxes and medication-dose packs can all influence treatment adherence. Many individuals communicate nonverbally with the use of texting and emailing. Online communication between providers and patients can enhance communication and promote adherence [39].

Assessing nonadherence is an important component to patient care and providers should have a high suspicion when patients miss appointments, are not refilling medications on a timely

basis or are not achieving efficacy when expected [34]. Questioning patients and/or caregivers about treatment adherence is the simplest approach and performing in a non-threatening and judgmental manner is the most useful [36]. Asking open-ended questions, providing reference points ("have you missed any doses in the last 4–7 days") and discerning any adverse effects may help elicit details regarding nonadherence.

Adherence is a well recognized problem that can contribute to significant morbidity and mortality and research has identified a variety of barriers to therapy [34]. Perfect adherence may not be achievable due to human error and unfortunately, no one single intervention to improve adherence is useful for all circumstances [36]. A combination of approaches is recommended and is likely to be the most successful in encouraging compliance to therapy [34].

Special Considerations

Patients with IDD often have coexisting medical conditions including seizures, spasticity, behavioral disorders, cognitive dysfunction, swallowing impairment, gastroesophageal reflux disease, constipation, and urinary tract infections [5]. Medications used to treat symptoms related to IDD as well as concomitant conditions can exacerbate other coexisting disorders. Detailed treatment for individual disorders is reviewed in other chapters within the book; the following section briefly highlights some of the special considerations.

Polypharmacy

As noted above, those with IDD often end up taking multiple medications due to concurrent medical comorbidities. The prevalence of polypharmacy varies widely based on the definition used and the population studied. Polypharmacy has often been defined in the literature as the use of multiple medications (ranging from 2 to 9), but this use may be appropriate in a patient with numerous medical conditions [43]. Most studies evaluating polypharmacy have been in the geriatric population with pediatric studies focusing on psychotropic use. A study by Spencer et al. [44] evaluated the use of psychotropic medications in patients with autism spectrum disorder (ASD) utilizing medical and pharmacy claims data. Psychotropic medications included anticonvulsants, antidepressants, antipsychotics, anxiolytics, attention-deficit disorder (ADD) medications, lithium and antiparkinsonian medications [44]. A total of 33,565 patients were evaluated: 64 % had at least one psychotropic medication fill and 35 % having psychotropic polypharmacy (≥2 psychotropic medications filled simultaneously) [44]. Factors associated with psychotropic polypharmacy included concomitant disorders, older age, southern United States (US) region, white race and psychiatry visit [44].

A more appropriate and practical definition of polypharmacy is the utilization of medications that are not indicated [43]. This may include medications that are ineffective, lack an indication or are duplicative of another agent [43]. The Medication Appropriateness Index is a ten item tool that can be used to assess appropriate prescribing [45, 46]. Three of the items (indication, efficacy and duplication) can be used alone to detect polypharmacy (see Box 141.1) [45]. Risk factors for polypharmacy include poor health, multiple chronic conditions, multiple providers, lack of communication between health providers, patient/caregiver expectation of a prescription with a medical visit and self-treatment [47].

Unfortunately polypharmacy is not without its consequences and include the potential for adverse drug reactions, drug-drug or drug-disease interactions, nonadherence, decreased functional capacity and increased use of healthcare resources [43]. It is important that providers take the time to assess each patient's medical regimen to evaluate for polypharmacy and reduce inappropriate medications so that therapy can be optimized and the risk for adverse events is minimized.

Epilepsy

Antiepileptics are frequently used due to a high prevalence of seizures in those with intellectual

Box 141.1: Medication Appropriateness Index [45]

Is there an indication for the drug?
Is the medication effective for the condition?
Is the dosage correct?
Are the directions correct?
Are the directions practical?
Are there clinically significant drug-drug interactions?
Are there clinically significant drug-disease/condition interactions?
Is there unnecessary duplication with other medications?
Is the duration of therapy acceptable?
Is this drug the least expensive alternative compared to others of equal utility?

From: Hanlon et al. [45]
Italicized lines can be used to detect for polypharmacy

and developmental disabilities [5]. All antiepileptics can exacerbate or cause cognitive slowing with some newer agents possibly having a better cognitive profile than older agents [48]. Multiple antiepileptics and higher doses have been shown to be risk factors for antiepileptic-induced cognitive impairment [48]. Some antiepileptics as well as benzodiazepines have sedating properties which can lead to gait instability. This can be especially significant for those with motor impairments secondary to developmental delays or physical deformities [5].

Neurobehavioral Disorders

Medications used to treat behavioral disturbances including stimulants, antipsychotics, antidepressants, anxiolytics and mood stabilizers can also produce cognitive impairment, sedation and gait instability which can exacerbate underlying conditions (see Table 141.4). Risk versus benefit should always be assessed prior to initiation with monitoring throughout therapy to reduce the risk for unwanted side effects.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is common in those with significant neurodevelopmental disorders and can be secondary to constipation, diminished lower esophageal sphincter tone and increased intra-abdominal pressure [5]. Medications can also contribute to GERD symptoms by lowering esophageal sphincter tone and include theophylline, anticholinergic agents, benzodiazepines and beta-adrenergic agonists and should be avoided if possible [49].

Constipation

Constipation is another frequent comorbidity in those with neurological dysfunction and has been associated with limited mobility, reduced fiber and liquid intake due to dysphagia, and diminished lower bowel movements [5, 50]. Anticholinergic properties are found in many medications and can worsen or precipitate constipation; see Table 141.5 for examples. Ideally, anticholinergic agents should be avoided in those with a history of constipation and frequently alternative agents are available.

Spasticity

Spasticity can limit function, and medications are often used to help decrease tone and control spasticity. One of the most commonly used medications is baclofen. Baclofen binds to gamma-amino butyric acid (GABA) receptors in the spinal cord inhibiting reflexes that lead to increased tone [51]. Baclofen may be administered orally or via an intrathecal pump. Side effects include sedation, confusion, nausea, dizziness, and muscle weakness. Intrathecal administration requires lower dosing and may help decrease side effects, particularly sedation. Patients and families should be cautioned against abruptly discontinuing baclofen. Withdrawal can result in seizures, rebound hypertonia, fever, and death.

Table 141.4 CNS medications and neurological adverse effects [22, 55–58]

Medication class	Examples	Adverse effects
Benzodiazepines	Clonazepam, diazepam, lorazepam, alprazolam	CNS depression, irritability, hyperactive, aggressive behavior, physical and psychological dependence, sedation, anterograde amnesia, ataxia,alter sleep architecture, cognitive dysfunction, slowed reaction time, withdrawal
Atypical antipsychotics	Olanzapine, risperidone, quetiapine, aripiprazole	Cognitive dysfunction, sedation, fatigue, anxiety, dizziness, gait impairment, headache, drooling, parkinsonism, seizures
SSRI/SNRI	Sertraline, escitalopram, paroxetine, duloxetine, venlafaxine	Headache, sedation, insomnia, dizziness, agitation, suicidal ideations, serotonin syndrome, withdrawal syndrome
Benzodiazepine receptor agonists	Zolpidem, zaleplon, eszopiclone	Sedation, ataxia, tolerance, dependence, withdrawal, delayed reaction time, anterograde amnesia, disinhibition reactions, sleep-related activities (eating, driving, cooking while asleep)
Antiepileptic	Phenytoin	Behavior changes, suicidal ideations, concentration-related: ataxia, dizziness, sedation, confusion, slurred speech
Antiepileptic	Carbamazepine, oxcarbazepine	Sedation, fatigue, dizziness, vertigo, ataxia, blurred vision, psychomotor retardation, cognitive impairment, gait disturbances, suicidal ideation
Antiepileptic	Valproic acid	Sedation, dizziness, ataxia, tremor, abnormal thinking, suicidal ideation
Antiepileptic	Gabapentin, pregabalin, lamotrigene, levetiracetam, tiagabine, topiramate, lacosamide, rufinamide	Sedation, dizziness, ataxia, fatigue, nervousness, blurred vision, cognitive impairment, suicidal ideation
Stimulants	Methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, lisdexamfetamine	Insomnia, anxiety, nervousness, aggression, dizziness, blurred vision, dependency, withdrawal, lower seizure threshold

CNS central nervous system, *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor

Diazepam also inhibits reflexes that lead to increased tone by facilitating post-synaptic binding of GABA in the brain stem and spinal cord [52]. Side effects include sedation, decreased motor coordination, impaired attention and memory. Both overdoses and withdrawal can occur. The sedative effect is significant, and generally limits use of diazepam to severely involved children [51].

Clonidine and tizanidine are alpha2-agonists that act in the brain and spinal cord to decrease tone by presynaptic inhibition of reflexes that lead to increased tone. Frequent side effects include dry mouth and sedation.

Table 141.5 Medications with anticholinergic properties [22]

Pharmacological category	Examples	Indication
1st generation antihistamine	Hydroxyzine, chlorpheniramine, diphenhydramine, cyproheptadine, meclizine	Allergic disorder, pruritis, vertigo
Antiemetic	Prochlorperazine, promethazine	Nausea, vomiting
Urinary antimuscarinic	Oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine	Urinary incontinence
Tricyclic antidepressant	Amitriptyline, nortriptyline, doxepin	Depression, neuropathy
Selective serotonin reuptake inhibitor	Paroxetine	Depression, anxiety
Skeletal muscle relaxant	Carisprodol, cyclobenzaprine, orphenadrine	Muscle spasms
Anti-Parkinson's	Benztropine, trihexphenidyl	Parkinson's disease
Typical antipsychotic	Chlorpromazine, thioridazine, fluphenazine	Schizophrenia, psychosis
Atypical antipsychotic	Clozapine, olanzapine	Bipolar 1 disorder, depression, schizophrenia
Antidiarrheal	Diphenoxylate/atropine	Diarrhea
Anticholinergic	Hyoscyamine, scopolamine	Gastrointestinal disorders, motion sickness

Bradycardia, hypotension, constipation and depression occur with clonidine. Tizanidine may cause visual hallucinations and elevated liver enzymes [51].

Dantrolene inhibits calcium ion release from the sarcoplasmic reticulum in skeletal muscle by inhibiting ryanodine receptor calcium channel function, decreasing the force produced during contraction [53]. It may also rarely cause hepatotoxicity, and requires monitoring of liver function tests [51].

Botulinum toxin blocks the presynaptic release of acetylcholine required for neuromuscular transmission, reversibly denervating muscle [51]. Effects may last up to 3–6 months. Adverse effects are usually minor and include injection site pain, generalized weakness, and fever. Rarely, systemic effects similar to botulism may occur, including unexpected muscle weakness, hoarseness, difficulty breathing or swallowing, loss of bladder control, blurred vision, and ptosis. This prompted the FDA to include a warning on the labeling of botulinum toxin products in 2009, however, botulinum toxin continues to be widely used, and the American Academy of Neurology and the Practice Committee of the Child Neurology Society Practice Parameter classifies it as level A recommendation for localized/segmental spasticity [54].

Phenol is injected perineurally to denervate by axonal degeneration. In addition to denervation atrophy, it may also cause direct muscle necrosis. The effect lasts months to years until functional reinnervation occurs [52]. Phenol is best used to treat exclusively motor nerves, as there is a significant risk of long term pain and paresthesia when treating mixed motor/sensory nerves. Electrical stimulation is used to localize the intended nerve for injection. This is poorly tolerated in children, so injections are typically performed under sedation or anesthesia [52].

Generic and Brand Drugs

According to the United States drug regulatory agency, Food and Drug Administration (FDA), nearly eight in ten prescriptions filled in the United States are for generic drugs. The use of generic drugs is expected to grow over the next few years as a number of popular drugs come off patent through 2015 [59]. A generic drug is identical – or bioequivalent – to a brand name drug in

dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price. According to the United States Congressional Budget Office, generic drugs save consumers an estimated $8–10 billion a year at retail pharmacies and much more in the hospital use in the United States.

Health professionals and consumers can be assured that FDA approved generic drugs have met the same rigid standards as the innovator drug. To gain FDA approval, a generic drug must:

- contain the same active ingredients as the innovator drug (inactive ingredients may vary)
- be identical in strength, dosage form, and route of administration
- have the same use indications
- be bioequivalent
- meet the same batch requirements for identity, strength, purity, and quality
- be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products

The following FACTS are based on the information disseminated by the FDA [59].

FACT: FDA requires generic drugs to have the same quality and performance as brand name drugs.

- When a generic drug product is approved, it has met rigorous standards established by the FDA with respect to identity, strength, quality, purity, and potency. However, some variability can and does occur during manufacturing, for both brand name and generic drugs. When a drug, generic or brand name, is mass-produced, very small variations in purity, size, strength, and other parameters are permitted. FDA limits how much variability is acceptable.
- Generic drugs are required to have the same active ingredient, strength, dosage form, and route of administration as the brand name product. Generic drugs do not need to contain the same inactive ingredients as the brand name product.
- The generic drug manufacturer must prove its drug is the same as (bioequivalent) the brand name drug. For example, after the patient takes the generic drug, the amount of drug in the bloodstream is measured. If the levels of the drug in the bloodstream are the same as the levels found when the brand name product is used, the generic drug will work the same.
- Through review of bioequivalence data, FDA ensures that the generic product performs the same as its respective brand name product. This standard applies to all generic drugs, whether immediate or controlled release.
- All generic manufacturing, packaging, and testing sites must pass the same quality standards as those of brand name drugs, and the generic products must meet the same exacting specifications as any brand name product. In fact, many generic drugs are made in the same manufacturing plants as brand name drug products.

FACT: Research shows that generics work just as well as brand name drugs.

- A study evaluated the results of 38 published clinical trials that compared cardiovascular generic drugs to their brand name counterparts. There was no evidence that brand name heart drugs worked any better than generic heart drugs.

FACT: FDA does not allow a 45 % difference in the effectiveness of the generic drug product.

- FDA recently evaluated 2,070 human studies conducted between 1996 and 2007. These studies compared the absorption of brand name and generic drugs into a person's body. These studies were submitted to FDA to support approval of generics. The average difference in absorption into the body between the generic and the brand name was 3.5 %. Some generics were absorbed slightly more, some slightly less. This amount of difference would be expected and acceptable, whether for one

batch of brand name drug tested against another batch of the same brand, or for a generic tested against a brand name drug. In fact, there have been studies in which brand name drugs were compared with themselves as well as with a generic. As a rule, the difference for the generic-to-brand comparison was about the same as the brand-to-brand comparison.

- Any generic drug modeled after a single, brand name drug must perform approximately the same in the body as the brand name drug. There will always be a slight, but not medically important, level of natural variability – just as there is for one batch of brand name drug compared to the next batch of brand name product.

FACT: When it comes to price, there is a big difference between generic and brand name drugs. On average, the cost of a generic drug is 80–85 % lower than the brand name product.

- In 2010 alone, the use of FDA-approved generics saved $158 billion, an average of $3 billion every week.

FACT: Cheaper does not mean lower quality.

- Generic manufacturers are able to sell their products for lower prices because they are not required to repeat the costly clinical trials of new drugs and generally do not pay for costly advertising, marketing, and promotion. In addition, multiple generic companies are often approved to market a single product; this creates competition in the market place, often resulting in lower prices.

FACT: FDA monitors adverse events reports for generic drugs.

- The monitoring of adverse events for all drug products, including generic drugs, is one aspect of the overall FDA effort to evaluate the safety of drugs after approval. Many times, reports of adverse events describe a known reaction to the active drug ingredient.
- Reports are monitored and investigated, when appropriate. The investigations may lead to changes in how a product (brand name and generic counterparts) is used or manufactured.

FACT: FDA is actively engaged in making all regulated products – including generic drugs – safer.

- FDA is aware that there are reports noting that some people may experience an undesired effect when switching from brand name drug to a generic formulation or from one generic drug to another generic drug. FDA wants to understand what may cause problems with certain formulations if, in fact, they are linked to specific generic products.
- FDA is encouraging the generic industry to investigate whether, and under what circumstances, such problems occur. The Agency does not have the resources to perform independent clinical studies and lacks the regulatory authority to require industry to conduct such studies. FDA will continue to investigate these reports to ensure that it has all the facts about these treatment failures and will make recommendations to healthcare professionals and the public if the need arises.

Conclusions

Medication selection for a patient can be challenging and numerous factors need to be considered when choosing an agent. As previously discussed, pharmacokinetics and pharmacodynamics are important considerations as well as pharmacogenetics when applicable. The continued exploration and incorporation of pharmacogenetics into the field of medicine will require providers to stay up to date with the latest advances. Patients with developmental disabilities are often taking several medications and drug interactions should be evaluated as well as the risk for additive adverse effects. Concomitant disorders, diet, age and ethnicity may also influence the choice of therapy and need to be given careful consideration. Last but not least, the medicine only works when the patient takes the medicine (or is given to the patient when a caregiver is involved); barriers to adherence should be evaluated and interventions implemented to minimize the risk.

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