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Drug Glucuronidation in Clinical Psychopharmacology

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Glucuronidation is a phase II metabolic process and one of the most common pathways in the formation of hydrophilic drug metabolites. At least 33 families of uridine diphosphate-glucuronosyltransferases have been identified *in vitro*, and specific nomenclature similar to that used to classify the cytochrome (CYP) P450 system has been established. The UGT1 and UGT2 subfamilies represent the most important of these enzymes in human drug metabolism. Factors affecting glucuronidation include the following: cigarette smoking, obesity, age, and gender. In addition, several drugs have been found *in vitro* to be substrates, inhibitors, or inducers of UGT enzymes. Induction or inhibition of both UGT and CYP isoforms may occur simultaneously. Some important drug interactions involving glucuronidation have been documented and others can be postulated. This review summarizes the relevant literature pertaining to drug glucuronidation and its implications for clinical psychopharmacology. (J Clin Psychopharmacol 2001;21:500–515)

THE BIOTRANSFORMATION OF xenobiotics and endogenous compounds is accomplished by a variety of enzymatic reactions. Given humans' exposure to an enormous variety of substances of varying molecular weight and solubility, it should be expected that numerous enzymes of differing and overlapping functional capacity be required to accomplish drug elimination. Depending on the types of mediated metabolic pathways, these reactions have traditionally been classified as phase I or phase II.

Phase I reactions include oxidative, reductive, and hydrolytic processes. These metabolic reactions result in the attachment of polar functional groups to substrates, for example, hydroxy or carboxyl groups produce more water-soluble compounds or provide a site for the attachment of a conjugate via a phase II reaction.[1] Of the phase I reactions, oxidative metabolism mediated by the cytochrome (CYP) P450 system, has stimulated the most recent research. Several reviews have summarized the drug interactions mediated by the CYP P450 system and the implications for clinical psychopharmacology.[2, 3]

Phase II reactions are conjugations. They include glucuronide (GLUC), sulfate, glycine and glutathione conjugation, acetylation, and methylation. Table 1 summarizes the characteristics of phase II drug metabolic reactions. Phase II processes, mediated by enzymes known as transferases, link a convenient moiety from a coenzyme to endogenous or exogenous substrates. Many drug metabolites undergo phase II conjugation after phase I reactions. For some drugs, conjugation can proceed without phase I functionalization of a drug molecule.[4, 5] Valproic acid (VPA), haloperidol, and olanzapine represent examples of psychotropic drugs that owe a significant portion of their metabolism to the direct glucuronidation of the parent compound.[6–8] The formation of GLUC conjugates represents the most important of the various phase II reactions because of the numerous functional groups that are acceptors for GLUCs, the quantity of drugs that form GLUCs, and the ubiquitous nature of these conjugates in most vertebrate species.

The importance of phase II metabolic reactions, as pathways for elimination of drugs, has received little emphasis in the clinical psychopharmacology literature. Relative to the CYP P450 enzymes, less is known about the specificity of individual uridine diphosphate (UDP)-glucuronosyltransferases (UDPGT) toward the glucuronidation of specific medications. However, several extensively used anxiolytics, antidepressants, mood stabilizers, and antipsychotics are predominantly eliminated in the urine as GLUC conjugates. It is likely that the functional capacity of glucuronidation is a contributing factor to inter- and intrasubject variability in response to these psychoactive drugs. The *in vitro* interindividual variation in glucuronidation catalytic activity from different liver

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TABLE 1. Characterization of phase II metabolic reactions[a]

Phase II Enzyme	Co-Factor	Location	Genetic Aspects	Common Reactions	Common Substrates	Inter-Hepatic Fold Activity Variation
UGT	UDPGA	Liver, kidney, intestine, lung, skin, prostate, brain	Mutations in exons UGT1A1, 2, 3, 4, and 5 associated with Crigler-Najjar type I and II and Gilbert syndrome Variant alleles exist for UGT2B7, and 2B15, no apparent effect on *in vitro* enzyme activity	Glucuronidation	Acetaminophen Bilirubin Ethinylestradiol Morphine Lorazepam Oxazepam Valproic acid Lamotrigine Olanzapine	3.1–10
SULT	PAPS	Liver, kidney, intestine	Variant alleles exist for SULT1A1 and 2A1, SULT1A1 genotype correlated with enzyme activity	Sulfgate conjugation	Acetaminophen Albuterol Terbutaline Methyldopa	2–13
GST	Glutathione	Liver, kidney	Null genotypes exist GSTM1 and GSTT1, may be markers for cancer susceptibility	Glutathione conjugation	Azathioprine 6-Mercaptopurine Nitroglycerin Organophosphates	2
NAT	Acetyl coenzyme A	Liver, lung, spleen, gastric mucosa, RBCs, lymphocytes	Variant alleles exist for NAT1 and NAT2, slow acetylator status associated with increased isoniazid toxicity	N-acetylation	Dapsone Hydralazine Isoniazid Phenelzine Procainamide	3–18
MT	SAM	Liver, kidney, lung, CNS	Genetic polymorphism demonstrated for Catechol *O*-MT, Thiopurine MT, and Thio MT, low enzyme activity associated with thiopurine toxicity	Methylation	Dobutamine Dopamine Levodopa Norepinephrime Serotonin	2

[a]UGT, glucuronosyltransferases; UDPGA, UDP-glucuronic acid; SULT, Sulfotransferases: PAPS, 3′-phosphoadenosine-5′-phosphosulfate; GST, Glutathione-*S*-transferases; NAT, *N*-acetyltransferases; RBC, red blood cell; MT, Methyltransferases; SAM, *S*-adenosyl-L-methionin; CNS, central nervous system.

banks was reported to range between 3.1- and 10-fold.[9] Table 1 lists the reported interindividual fold variation of phase II catalytic processes. The purpose of this review was to examine the available data relating to glucuronidation, emphasizing potential drug-drug interactions involving psychoactive drugs, and summarize the importance in clinical psychopharmacology. A description of glucuronidation characteristics is followed by an explanation of the classification system. Finally, factors that can affect glucuronidation are discussed.

Glucuronidation Characteristics

Glucuronidation is a major detoxification pathway in mammals and represents the most common metabolic pathway in the formation of hydrophilic drug metabolites for excretion by the kidney or through biliary processe, or both.[10] A general mechanism is shown in Figure 1 illustrating the metabolism of lamotrigine.[11] Uridine diphosphate glucuronic acid (UDPGA) mediates the conjugation of lamotrigine with glucuronic acid and acts as a cofactor. There is an attack at the activated UDPGA cofactor, resulting in the transfer of the glucuronyl moiety onto the substrate (aglycone), lamotrigine, with a subsequent release of UDP. The enzyme responsible for the formation of lamotrigine GLUC is UDPGT. UDPGTs are species-specific and vary widely in their substrate specificity. There is a large variability of functional groups that can be conjugated with glucuronic acid, including oxygen, nitrogen, sulfur, and carbon. Hydroxy and carboxy functional groups of primarily phenolic and alcoholic moieties form *O*-GLUCs. Many opioids and nonsteroidal antiinflammatory agents (NSAIDS) are primarily excreted as *O*-GLUCs. In general, planar phenolic molecules are glucuronidated more rapidly than drugs with bulkier structures.[12] Aromatic and aliphatic amines, amides, and sulfonamides can form *N*-GLUCs.[1, 13]

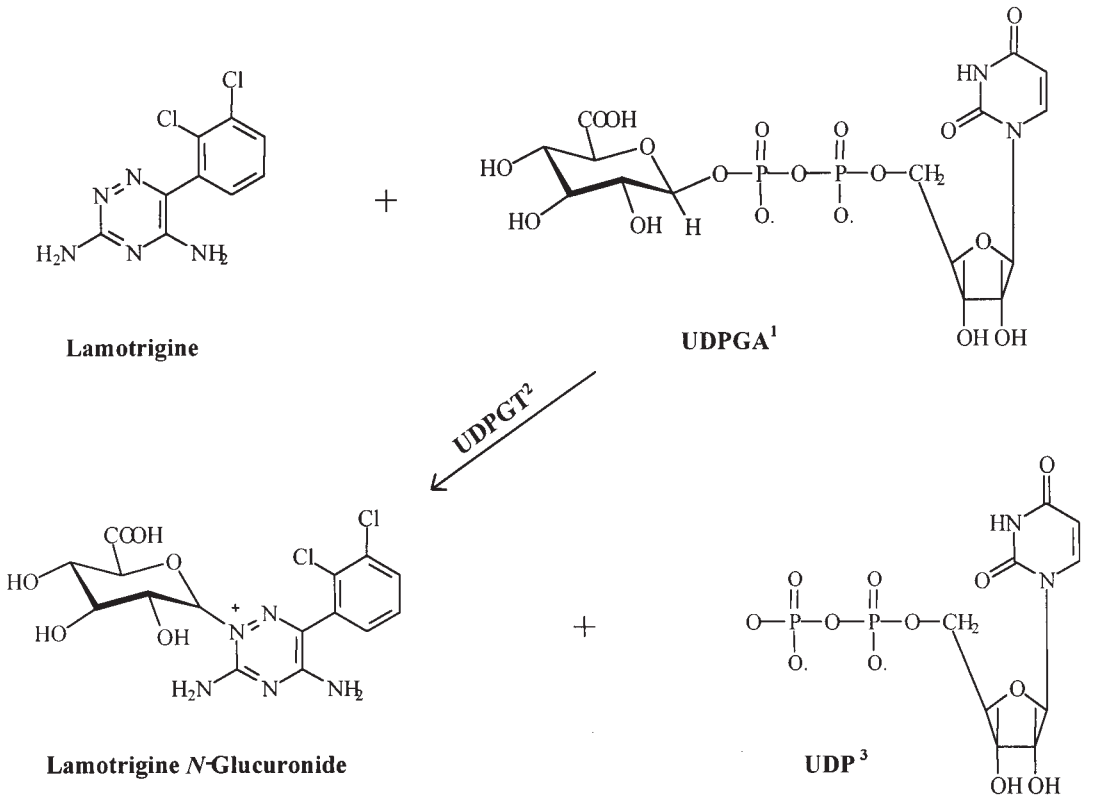

FIG. 1. Glucuronidation pathway of lamotrigine.

Tertiary amines including tricyclic antidepressants (TCAs), the atypical antipsychotics clozapine and olanzapine, the anticonvulsant lamotrigine, and the 5-hydroxytryptamine-2 antagonist cyproheptadine, form quaternary ammonium compounds via glucuronidation.[14–18] *S*-GLUC and *C*-GLUC products are generally recognized as less common glucuronidation pathways in drug metabolism.[1]

Although many pharmacologically active metabolites are known to be formed through phase I reactions, glucuronidated drugs have traditionally been regarded as inactive because of their hydrophilicity, low protein binding, and reduced volumes of distribution. Thus, GLUC metabolites have been often ignored in pharmacokinetic and pharmacodynamic studies. GLUCs can exert pharmacologic actions, and in some cases exhibit greater potency than the parent compound.[4] For example, morphine-6-glucuronide (M6G) is a potent receptor agonist,[19] digitoxin- and digoxin-GLUCs possess positive inotropic effects,[20] and fluorouracil GLUC was found to have antitumor activity.[21] The glucuronidation of morphine (MOR) is of particular interest in clinical psychopharmacology.

MOR metabolism results in the formation of two major conjugates, M6G and morphine-3-glucuronide (M3G).[22] Approximately 66% to 70% of a MOR dose is excreted as these compounds.[23] M6G, a more potent analgesic than its parent drug, is 20-fold more active than MOR when injected into the periaqueductal gray matter of rats using the tailflick latency test.[19] M3G has been shown to antagonize the antinociceptive effect of both MOR and M6G when administered via the intravenous, intrathecal, or intracerebroventricular routes in rats.[24] The development of tolerance after the administration of MOR may partially be explained by the formation of this GLUC.

β-Glucuronidases, esterases, and serum albumin catalyze the hydrolysis of GLUCs, converting them to the active aglycone, thus contributing indirectly to pharmacologic activity through the release of parent compounds (enterohepatic recycling).[4, 25] β-Glucuronidase-resistant forms occur through the molecular rearrangement of primarily carboxylic acids containing GLUC conjugates. The intramolecular transesterification in hydroxyl groups of the glucuronic acid moiety is a phenomenon referred to as acyl migration.[25] Acyl GLUCs are reactive molecules that can bind irreversibly to plasma proteins.[26] This covalent protein binding can lead to toxicity and hypersensitivity reactions.[25] The acyl GLUC of zomepirac, an NSAID removed from the United States market because of a high incidence of anaphylaxis, undergoes irreversible protein binding *in vitro* and *in vivo*.[26]

Analogous to phase I metabolic processes, stereospecific glucuronidation has been observed in a number of compounds. This may prove to be of therapeutic significance for compounds administered as racemic mixtures.[10, 27–30] (+)MOR is preferentially glucuronidated over (−)MOR in human hepatic microsomes.[30] E-10-hydroxynortriptyline (E-10-OH-NT) undergoes stereoselective GLUC formation, with (+)E-10-OH-NT GLUC being preferentially formed in humans. Sixty-four percent of (+)E-10-OH-NT versus 35% of (−)E-10-OH-NT was recovered in the urine as GLUC conjugate after a 75-mg dose of 50:50 E-10-OH-NT racemate was administered to 10 healthy men. Comparably more (−)E-10-OH-NT was excreted unchanged.[28] *In vitro* analysis in human hepatic microsomal preparations demonstrated increased production of (*S*)-oxazepam over (*R*)-oxazepam GLUC. NSAIDS such as ketoprofen inhibited the formation of (*S*)-oxazepam over (*R*)-oxazepam significantly more than the (*R*)-isomer ($p < 0.01$).[29] Oxazepam pharmacodynamics could be altered in the presence of such inhibitors because the (*S*) enantiomer has been shown to be approximately 10 times more potent than the (*R*) enantiomer at inhibiting diazepam binding in rat synaptosomes.[31]

Glucuronidation is a low-affinity/high-capacity conjugative process[4, 5] and seems to be under dual regulation, that is, (1) specific isozyme expression and (2) modulation of their functional state.[32] The catalytic enzymes UDPGTs are located in the endoplasmic reticulum of cells of the liver, kidney, intestine, skin, lung, spleen, prostate, and brain.[13, 33] Quantitatively, hepatic glucuronidation is most important.[5, 13] Identification and classification of various UDPGTs has been accomplished in recent years.

UDPGT Classification

Thirty-three families of UDPGTs have been defined *in vitro* so far, and specific nomenclature similar to that used for the CYP P450 system has been established and recently refined.[34] The best examples are the mammalian UDPGTs and the three families of UGTs that have been identified in humans. As with the CYP P450 superfamily, the UGT superfamily is widely found among animals, plants, and bacteria, suggesting a common ancestral gene.[34, 35] Among the UGTs, the UGT1 and UGT2 families seem to be the most important in human drug metabolism and are the focus of this review. Table 2 summarizes substrates of individual UGT isoforms. For a complete review detailing the background and nomenclature of the UGT system, refer to Mackenzie and colleagues.[34]

UGT1 Family

At least 12 isoforms of UGT1 have been found to be encoded by this gene family[3, 35, 36] and they share in

TABLE 2. *In vitro* UGT1 and UGT2 family substrates

1A1	1A3	1A4	1A6	1A9	2B7	2B15
Bilirubin	Amitriptyline	Amitriptyline	Acetaminophen	Acetaminophen	Androsterone	Androstane 3α-diol
Buprenorphine	Buprenorphine	Chlorpromazine	5-Hydroxytriptophan	Dapsone	Buprenorphine	Dienestrol
Ethinylestradiol	Chlorpromazine	Clozapine	1-Naphthylamine	Ethinylestradiol	Chloramphenicol	Diethylstilbesterol
Irinotecan	Clozapine	Cyproheptadine	*N*-Hydroxynaphthylamine	Estrone	Codeine	6-Hydroxyquinoline
Nalorphine	Cyproheptadine	Desmethylclozapine		4-Hydroxyestrone	Clofibric acid	8-Hydroxyquinoline
Naltrexone	Doxepin	Doxepin		Furosemide	Fenoprofen	5-(*p*-Hydroxyphenyl)-5-phenylhydantoin
	Fenoprofen	Imipramine		Ibuprofen	5-Hyroxytriptophan	5-(*m*-Hydroxyphenyl)-5-phenylhydantoin
	Hydroxymorphone	Lamotrigine		Ketoprofen	Hydromorphone	SCH23390
	2-Hydroxyestrone	Loxapine		Labetalol	Ibuprofen	
	2-Hydroxyestriol	Olanzapine		Naproxen	Ketoprofen	
	Ibuprofen	Promethazine		Propranolol	Morphine	
	Imipramine	Retigabine		Propofol	Nalmefene	
	Ketoprofen			3,3′,5′-Triiodo-L-Thyronine	Nalorphine	
	Loxapine			Retinoic acid	Naloxone	
	Morphine				Naltrexone	
	Nalorphine				*S*-Naproxen	
	Naloxone				Oxazepam	
	Naproxen				Oxymorphone	
	Promethazine				Propranolol	
	Valproic Acid				Valproic acid	
					Temazepam	

common exons 2 through 5.[37] The UGT1 family includes enzymes that can glucuronidate bilirubin, quinone, and phenol derivatives such as anthraquinones, flavones, and estrogens.[37, 38]

At least five human UGT1A complementary deoxyribonucleic acids have been identified in hepatic tissue. They are UGT1A1, UGT1A3, UGT1A4, UGT1A6, and UGT1A9. UGT1A9 is also found in the kidney.[35, 37, 39, 40] The human colon has been found to express all isoforms present in the liver, in addition to UGT1A7, UGT1A8, and UGT1A10.[41, 42] UGT1A activities differ significantly depending on the location and substrate.

UGT1A1

UGT1A1, previously known as HUGBr1 or UGT1.1, is the enzyme catalyzing the glucuronidation of bilirubin.[37] This isoform is inducible by phenobarbital,[40] which has been used in the treatment of hyperbilirubinemia.[43] Human-expressed UGT1A1 was found to catalyze the glucuronidation of the opioids buprenorphine, nalorphine, and naltrexone. Of the compounds investigated, buprenorphine exhibited the most reactivity with UGT1A1, demonstrating a glucuronidation efficiency more than 1000-fold greater than that for naltrexone and nalorphine. Glucuronidation rates of buprenorphine were significantly reduced (75%) in liver microsomes from patients with type I Crigler-Najjar disease.[44] Type I Crigler-Najjar disease affects fewer than 1% of the population; however, it can lead to lethal hyperbilirubinemia as a result of defects in the UGT1A1 gene. Patients with Gilbert syndrome, a milder form of Crigler-Najjar, could potentially experience adverse effects from medications primarily metabolized by this isoform. This impairment does not generally seem to be of clinical significance[10]; however, two cases of severe toxicity characterized by neutropenia and diarrhea have been reported in patients with Gilbert syndrome after treatment with irinotecan, a chemotherapeutic agent.[45] UGT1A1 was found to catalyze the glucuronidation of irinotecan, which explains the observed toxicity in the two patients with Gilbert syndrome.[46]

Drugs sharing this metabolic pathway, such as ethynylestradiol (a component of most oral contraceptives [OCs]) and naltrexone,[38, 44] may competitively inhibit one another, resulting in pronounced or adverse pharmacologic effects. Likewise, drugs that inhibit UGT1A1 could result in hyperbilirubinemia or other adverse effects from coadministered drugs metabolized by this enzyme. Specific inhibitors of UGT1A1 that could be useful in human volunteer studies have not been identified.

Other xenobiotics glucuronidated by UGT1A1 include 2-hydroxyestrogenic catechols, anthraquinones, coumarins, flavonoids, and phenolic compounds.[38, 47] Many of these agents are components of herbal products, foods, and food preservatives and could also competitively inhibit the metabolism of UGT1A1 substrates such as bilirubin.[38]

UGT1A3

Human-expressed UGT1A3 catalyzes the glucuronidation of primary, secondary, and tertiary amines, coumarins, flavonoids, anthraquinones, estrones, and phenolic and carboxylic acid-containing substrates.[15, 39, 47] As with UGT1A1, 2-hydroxyestrone and 2-hydroxyestradiol are substrates of UGT1A3, whereas the 4-hydroxycatechol estrogens are not.[47] Apparent K_m values for primary amine substrates of UGT1A3 are approximately 100-fold higher than K_m values obtained for UGT1A4, making the glucuronidating ability of UGT1A3 one of low efficiency in comparison to UGT1A4. O-glucuronidated substrates of UGT1A3 include VPA; the opiates MOR, hydromorphone, nalorphine, buprenorphine, norbuprenorphine; the opioid antagonists naltrexone and naloxone; and various NSAIDS. Amitriptyline and cyproheptadine exhibited the greatest quaternary ammonium GLUC formation of the tertiary amines investigated by Green and associates.[15]

UGT1A4

Little structural difference exists between UGT1A4 and UGT1A3 with more than 90% similarity in their amino acid sequences.[34] Unlike UGT1A3, UGT1A4 exerts minimal activity toward phenolic compounds and is not involved in the metabolism of carboxylic acid-containing substrates such as NSAIDS.[15, 48] Green and colleagues,[14, 48] demonstrated that expressed human UGT1A4 protein efficiently catalyzes the N-glucuronidation of many primary, secondary, and tertiary amines. The highest glucuronidating efficiency has been demonstrated for the primary amines, 2- and 4-aminobiphenyl.[48]

UGT1A4 was found to catalyze the tertiary amines including imipramine, amitriptyline, doxepin, promethazine, chlorpromazine, loxapine, and cyproheptadine to quaternary ammonium GLUCs.[14,48] Olanzapine has also been found to be a UGT1A4 substrate in vitro.(personal communication, T. Tephly, 6/15/2001). Two *N*-GLUC metabolites of clozapine have been observed after incubation with human UGT1A4 protein.[48] Formation of the first GLUC likely resulted from glucuronidation at the secondary amine position, whereas the quaternary ammonium GLUC represented the second metabolite. The first reaction is kinetically favored, with a reaction rate approximately six times greater than that for the quaternary ammonium GLUC.[48] The primary metabolite of clozapine desmethyl clozapine, a secondary amine, was found also to be glucuronidated by UGT1A4, whereas nortriptyline and desipramine were not.[48] Similarly, the 10-*N*-GLUC of olanzapine has been found to be preferentially formed

over the quaternary ammonium GLUC and represents the predominant circulating metabolite in human plasma.[17] In contrast, another atypical antipsychotic, risperidone, is metabolized primarily by nonconjugative pathways, and its plasma concentration was not influenced by coadministration in human volunteers with probenecid, a broad-spectrum UGT inhibitor (Markowitz and associates, unpublished data).

The glucuronidation of lamotrigine is also catalyzed by this isoenzyme (Fig. 1). Because lamotrigine possesses both heterocyclic nitrogen and an amine side chain, glucuronidation could occur at both sites. Previously, the quaternary ammonium GLUC has been isolated and shown to be the major metabolite in patients receiving lamotrigine.[11]

Additionally, UGT1A4 has been found to be the major isoform responsible for the N-glucuronidation of the structurally related anticonvulsant retigabine.[49] Significantly, human plasma concentrations of retigabine-*N*-GLUC exceeded those of the parent compound by a factor of 24, and the metabolite is likely to be subject to enterohepatic cycling.[49]

UGT1A6

UGT1A6 is involved in the glucuronidation of primarily planar phenols.[50] 2-Naphthylamine and 4-aminobiphenyl are two carcinogenic arylamines found in small quantities in cigarette smoke. Glucuronidation of these compounds may contribute to a reduction in toxicity or determine the target of adverse effects by hydrolysis to the parent compound or hydroxy metabolite in such environments as the urinary bladder.[51,52] Acetaminophen (APAP) glucuronidation rates were obtained in homogenates of both UGT1A6 and UGT1A9 transferred cells. APAP affinity was greater for UGT1A6 than UGT1A9 with K_m values of 2 mM and 50 mM, respectively.[50] Expression of UGT1A6 in the human central nervous system (CNS) has been demonstrated, specifically in the cerebellum.[53] King and associates[53] investigated whether the neurotransmitter 5-hydroxytryptamine was a potential substrate for this enzyme in HK293 cells. 5-Hydroxytryptamine was found to be efficiently glucuronidated by UGT1A6 with K_m and maximum velocity (V_{max}) values of 165 μM and 55 nmol·min^{-1}·mg^{-1}, respectively. The significance of this observation remains to be explained.

UGT1A9

Although UGT1A6 favors reactions with planar phenols, UGT1A9 has been shown to be conjugated with both planar and nonplanar phenols, anthraquinones, flavones, aliphatic alcohols, aromatic carboxylic acids, and steroids.[12] Pharmacologic agents that were found to be substrates of UGT1A9 expressed in Chinese hamster V79 cells included propranolol, labetalol, propofol, ethynylestradiol, 4-hydroxytamoxifen, ibuprofen, ketoprofen, naproxen, furosemide, and dapsone. Endogenous substrates, included 3,3′,5′-triiodo-L-thyronine, estrone, 4-hydroxyestrone, and retinoic acid.[12]

UGT2 Family

The UGT2 gene products, unlike UGT1, likely arise from separate genes.[54,55] The UGT2A subfamily represents glucuronosyltransferases present in rat and bovine olfactory systems that have not been well characterized.[56] The UGT2B family contains phenobarbital-inducible genes and others that are involved in the glucuronidation of endogenous steroids, biogenic amines, and various opioids.[54,55,57–60] Although the majority of enzyme activity rests within the liver, the presence of UGT2B7 has been found in human intestinal mucosa.[61]

UGT2B7

There is evidence to support genetic variants of UGT2B7, as well as UGT1A1. Two forms have been identified, UGT2B7Y contains a tyrosine, and UGT2B7H contains a histidine residue at position 268.[58,62]

MOR metabolism to both the M3G and M6G has been shown to be catalyzed by human embryonic kidney cells expressing UGT2B7.[57,58] Other opioids that are also glucuronidated by this enzyme include dihydrocodeine, hydromorphone, oxymorphone, nalorphine, nalmefene, buprenorphine, and the antagonists naloxone and naltrexone.[57,58] Codeine was found to be glucuronidated to the codeine-6-glucuronide (C6G), but at only 1% the rate of MOR.[57] The ratio of V_{max} for the formation of M3G versus M6G was found to be comparable to those reported in human hepatic microsomes. Because of this, it has been suggested that UGT2B7 is likely the major UGT that catalyzes MOR glucuronidation.[57] Like UGT1A6, UGT2B7 has also been isolated from the human brain and found to glucuronidate 5-hydroxytryptamine, although with much less efficiency.[53] Human brain microsomes were shown to catalyze the glucuronidation of naloxone and MOR.[63] This observed metabolism may contribute to the exertion and termination of opiate pharmacologic action within the CNS.

The UGT2B7 variant demonstrated specificity for a number of carboxylic acid substrates including various NSAIDS, VPA, and clofibric acid.[62] Other substrates not containing a carboxylic acid included propranolol, testosterone, temazepam, chloramphenicol, and oxazepam, although activities for these substrates was substantially reduced.[58,62]

UGT2B15

UGT2B15 expressed in HK293 cells was found to catalyze the glucuronidation of planar phenols, coumarins, anthraquinones, and flavonoids, as well as various andro-

genic and estrogenic steroids.[64] Other xenobiotics found to be substrates of this enzyme included a metabolite of diethylstilbestrol, dienestrol, the *para*- and *meta*-hydroxylated metabolites of phenytoin, 6- and 8-hydroxyquinoline, phenolphthalein, and the dopamine D_1 receptor antagonist SCH23390.[64] A variant of UGT2B15(D^{85}), UGT2B15(Y^{85}) has been characterized, and substrate specificity between the two forms was found to be similar.[65] The expression of the UGT2B15 gene was found in several extrahepatic tissues including kidney, testes, mammary glands, placenta, adipose, skin, uterus, prostate, and lung, suggesting it is a significant glucuronidating enzyme in humans.[65]

Genetic Polymorphism

Genetic polymorphism has been demonstrated for UGT1A1, UGT1A4, UGT2B15, and UGT2B7.[40, 65] Although little is known about the effects of mutations in the later three UGTs, UGT1A1 defects lead to hyperbilirubinemia conditions such as Crigler-Najjar disease and Gilbert syndrome.[66, 67] Studies in Japanese, Eastern Scottish, and Canadian Inuit populations have revealed differences in the percentage incidence of homozygous (TA_7)-TAA alleles associated with Gilbert syndrome of 3%, 12%, and 17%, respectively.[66, 68, 69]

Evidence supports polymorphic distribution of N-glucuronidation of nicotine and its principal metabolite, cotinine, in African American population.[70] The percentage of radiolabeled nicotine and cotinine excreted as the *N*-glucuronide was found to be 25% and 21%, respectively, in 51 African American subjects compared with 40% and 35%, respectively, in 57 Caucasian subjects. In addition, a trimodal distribution for nicotine and a bimodal distribution for cotinine N-glucuronidation was demonstrated in the African American group.[70] In a previous report, African Americans glucuronidated less of the carc-inogenic nicotine derivative, nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol NNAL).[71] A decrease in glucuronidating ability in African Americans is a potential cause of the increased incidence of lung cancer observed in this population. The specific UGT responsible for this observed genetic polymorphism has not yet been identified.

Yue and associates[72] compared codeine metabolism in 149 Swedish Caucasian patients and 133 Chinese. The mean proportion of C6G excreted by the Caucasian subjects was 62%. This was significantly higher than the 44% excreted by the Chinese subjects. Comparably, the Chinese group excreted more unchanged codeine, norcodeine, and less norcodeine-GLUC. These results parallel those found with the smaller codeine doses required to treat pain in the Chinese population. APAP clearance (CL) has also been demonstrated to be 20% lower in patients of Asian decent than those of European decent.[73]

The incidence of neonatal hyperbilirubinemia in the first few days of life was reported to be significantly higher in a group of Navajo American Indians than in a control group made up of African Americans, Hispanic Americans, and Caucasians. The breast milk of Navajo women was shown *in vitro* to significantly inhibit the glucuronidation of bilirubin; however, this alone could not account for the observed incidence of hyperbilirubinemia because several affected infants were bottle fed.[74]

Factors Affecting Glucuronidation

As noted above, ethnicity can impact glucuronidating ability. Other factors that have been shown to alter glucuronidation include age, gender, body habitus, some disease states, and cigarette smoking. Table 3 summarizes these factors and their effects.[75–99]

Inducers and Inhibitors of Glucuronidation

There are fewer data on drug-drug interactions involving glucuronidation in contrast to an extensive documentation for CYP P450-mediated drug interactions. One reason for this situation is the lack of specific marker substrates or inhibitors of individual UDPGT isoforms analogous to debrisoquine and quinidine, a substrate and inhibitor, respectively, of CYP2D6 used in urine CL studies. In addition, many drugs are metabolized through multiple pathways, and substantial overlap of substrate specificity of UGTs exists.

The following section discusses the glucuronidation of drug substrates by specific isoforms mainly in expressed human cells, as well as interactions reported *in vivo*. Potential drug-drug interactions associated with the UGT enzyme system are summarized in Table 4.

Any substrate of UDPGT has the potential to competitively inhibit glucuronidation of other substrates metabolized by the same enzyme. Unlike the CYP P450 system, no specific inhibitors of individual UGT isoforms have been identified that may be safely administered clinically for use in inhibition studies.[13, 100] Furthermore, no substrates that are glucuronidated exclusively are available for human studies. Although APAP is frequently used as a marker for glucuronidation activity, it is also subject to other metabolic pathways including sulfate conjugation and, to a minor degree, oxidation through the CYP P450 system.[101] Nonetheless, several examples of competitive inhibitors that have relevance to clinical psychopharmacology exist.

Antidepressants

The 10-hydroxy metabolites of nortriptyline are often found in higher concentration than the parent drug in humans.[102] The elimination of the E-10-hydroxy metabolite is primarily through glucuronidation.[102] *In vitro* inhibition

TABLE 3. Factors affecting glucuronidation[a]

Factor	Effect on Glucuronidation	Drugs or Compounds Affected
Age		
Infant	⇑	Chloramphenicol, MOR, APAP, bilirubin, steroids.[75–78]
Elderly	⇔ or ⇑	No change found for APAP, oxazepam, temazepam, or propranolol; decreased CL found for C6G and decreased unbound CL for oxazepam in the very elderly.[79–83]
Gender		
Men	⇑	CL higher in men for APAP, oxazepam, temazepam, and propranolol. Possible additive
Women	⇓	role with CYP1A2 resulting in higher clozapine and olanzapine concentrations in women.[80,81,84–90]
Body habitus		
Overweight	⇑	CL of lorazepam, oxazepam, temazepam, and APAP, likely the result of an increase in liver size and quantity of enzyme.[91]
Underweight, malnourished	⇓	Chloramphenicol, APAP.[92]
Disease states		
Fulminant hepatitis, cirrhosis	⇓	Zidovudine, oxazepam, lamotrigine (glucuronidation by affected liver microsomes).
Hypothyroidism	⇓	Oxazepam, APAP.[94]
HIV	⇓	APAP.[95]
Cigarette smoking	⇑	Propranolol, oxazepam, lorazepam, APAP.[80,86,96,97] Possible additive role with CYP1A2 induction resulting in decreased clozapine and olanzapine concentration.[88,89,98]
Ethanol	⇓	*In vitro* inhibition of harmol, 2-naphthol, 4-methylumbelliform, phenothalein[99]

[a]MOR, morphine; APAP, acetaminophen; CL, clearance; C6G, codeine-6-glucuronide; HIV, human immunodeficiency virus.

studies were performed on the formation of (+)-E-10-hydroxynortriptyline GLUC in human liver microsomes. Both amitriptyline and 2-hydroxydesipramine inhibited the glucuronidation of (+)-E-hydroxynortriptyline.[103]

In human hepatic microsomes, nortriptyline noncompetitively inhibited the formation of M3G and M6G, whereas amitriptyline and clomipramine exerted competitive or mixed inhibition of MOR glucuronidation.[104] The K_i values for nortriptyline, amitriptyline, and clomipramine for the formation of M3G were 0.033, 0.160, and 0.090 mM, respectively. Amitriptyline has previously been shown to inhibit the glucuronidation of both codeine and MOR in human liver microsomes.[105] In 24 patients with cancer, the mean MOR area under the curve (AUC) was shown to increase approximately 2-fold after the addition of either clomipramine or amitriptyline.[106, 107] Inhibition of glucuronidating enzymes by TCAs may contribute to the potentiation of opioid analgesic, as well as adverse effects.[107]

In human liver microsomes, both amitriptyline and imipramine were found to inhibit testosterone UDPGT activity with percentage inhibitions of 75% and 68%, respectively.[108] Androsterone UDPGT activity was inhibited by 70% and 45% by amitriptyline and imipramine, respectively. Other endogenous substrates including estriol and 1-naphthol were also inhibited, although to a lesser degree. The inhibition of amitriptyline seemed to be noncompetitive, whereas that of imipramine was competitive.[108] Alterations in endogenous steroid metabolism may play a role in the occurrence of adverse effects related to sexual function often associated with these agents.

Two cases of drug-drug interactions involving sertraline and lamotrigine have been reported suggesting sertraline inhibition of lamotrigine glucuronidation.[109] Lamotrigine concentration doubled after the addition of sertraline in the first case. In the second case lamotrigine concentration decreased from 19.3 μg/mL to 9.8 μg/mL when the sertraline dose was reduced to 50 mg/day despite a simultaneous increase in the lamotrigine dose.[109] Although sertraline possesses mild CYP2D6 inhibitory capability, lamotrigine is primarily metabolized by glucuronidation, making inhibition of this pathway a potential explanation.[110] A single case report involving citalopram suggests the selective serotonin reuptake inhibitor (SSRI) may inhibit the glucuronidation of 8-hydroxydesmethylclomipramine (8-OHDCMI). After the addition of 40 mg of citalopram, a 5-fold increase in the 8-OHDCMI concentration was observed. Only slight increases occurred in the clomipramine, desmethylclomipramine, and 8-hydroxyclomipramine concentrations. The increase in the 8-OHDCMI metabolite was observed despite a decrease in the patient's clomipramine dose from 150 mg/day to 75 mg/day. Because CYP P450 does not further metabolize 8-OHDCMI, citalopram may have inhibited the glucuronidation of this metabolite.[111]

Anticonvulsant and antimanic agents

The majority of anticonvulsants undergo partial glucuronidation in the course of hepatic metabolism. Gabapentin and lithium, the only significantly renally eliminated agents in this class, seem devoid of the potential for drug-drug interactions associated with glucuronidation.[112] VPA is a widely used anticonvulsant

TABLE 4. Potential *in vitro* and *in vivo* substrates, inhibitors, and inducers of glucuronidation

Substrate	Inhibitor	Inducer
Morphine	Amitriptriptyline	Rifampin
	Clomipramine	
	Clonazepam	
	Diazepam	
	Flurnitrazepam	
	Lorazepam	
	Nitrazepam	
	Oxazepam	
Oxazepam	Ethinylestradiol	Phenobarbitone
	Fenoprofen	Phenytoin
	Ibuprofen	
	Ketoprofen	
	S-Naproxen	
(+)-E-10-Hydroxynortriptyline	Amitriptyline	Pentobarbital
	2-Hydroxydesipramine	
Bilirubin		Phenobarbital
Acetaminophen	Ethinylestradiol	
	Probenecid	
	Propranolol	
Androsterone	Promethazine	
	Chlorpromazine	
Carbamazepine-10,1 1-transdiol	Valproic acid	
Codeine	Amitriptyline	
Lamotrigine	Sertraline	
	Valproic acid	
Lorazepam	Ethinylestradiol	
	Probenecid	
	Valproic acid	
Temazepam	Probenecid	
Testosterone	Amitriptyline	
	Chlorpromazine	
	Imipramine	
	Promethazine	
Zidovudine	Probenecid	
	Valproic acid	

and antimanic agent implicated as a broad inhibitor of drug metabolism, including glucuronidation. VPA undergoes extensive glucuronidation with approximately 20% to 70% of a daily dose excreted in the urine as the GLUC.[6] The percentage of the drug and GLUC excreted seems to increase with increasing dose, whereas oxidative metabolism decreases.[113] The half-life ($t_{1/2}$) of lamotrigine was found to be 164% higher in subjects who were coadministered VPA (69.6 vs. 26.4 hours).[114] The manufacturer's product information for lamotrigine recommends that the dose of lamotrigine be reduced to half of the normal dose in patients who are concurrently receiving VPA.[115] The clinical importance of this interaction is the potentiation of the development of a severe rash or Stevens-Johnson syndrome when these agents are combined, because this dermatologic effect is proposed to be dose- or concentration-mediated.[116]

Combining anticonvulsant medications in the treatment of affective disorders has become more prevalent. The coadministration of VPA and carbamazepine caused an increase in plasma concentrations of carbamazepine-10,11-epoxide. This was attributed to VPA inhibition of epoxide hydrolase; however, VPA also seems to inhibit the glucuronidation of carbamazepine-10,11-trans-diol.[117] Because increased plasma concentration of the epoxide is associated with potential toxicity, careful monitoring of this combination is necessary.

The percentage of dose excreted as *p*-hydroxyphenobarbitone GLUC was similar between patients treated with and without VPA. However, the percentage of drug excreted as unconjugated metabolite significantly increased, (5.7% to 16.0%). In addition, the excretion of phenobarbitone *N*-glucoside was significantly decreased with concomitant VPA therapy (16.2% vs 1.9%).[118] The potential mechanism for this observation may be depletion of both UDP-glucuronic acid and UDP-glucose by VPA.

The effects of VPA were studied on the disposition of amitriptyline in healthy volunteers.[119] A 50-mg dose of amitriptyline was given with and without VPA 500 mg, twice daily. Subjects demonstrated a 31% mean increase in the AUC of amitriptyline and a 55% increase in its principal metabolite, nortriptyline.[119] Both nortriptyline and

amitriptyline are partially eliminated by glucuronidation. The observed effects of VPA suggest inhibition of oxidative metabolism, conjugation, or both.

Recently, a case report documented increased clomipramine and desmethylclomipramine concentrations associated with adverse effects in a 46-year old woman, after the addition of VPA. The authors postulated the observed increase was caused by the inhibition of CYP2C or UGT by VPA.[120]

In healthy subjects, VPA has been shown to decrease lorazepam CL by 40% and lead to increased lorazepam plasma concentration and decreased lorazepam GLUC formation.[121] Samara and co-workers[122] confirmed these findings in a randomized, double-blind, placebo-controlled crossover study. Under concomitant treatment with VPA 500 mg twice daily, subjects demonstrated increases in the lorazepam maximum concentration (8%), AUC (20%), and trough lorazepam plasma concentration (31%). Despite these increases, sedation scales revealed no significant effect under coadministration conditions. The disposition of VPA was not affected by lorazepam.[122]

Significant sedation, confusion, and slurred speech was reported in a patient receiving clozapine, lithium, and VPA. Symptoms resolved after discontinuation of VPA but emerged again when the anticonvulsant was reintroduced.[123] A separate investigation reported a mean 41% decrease in total clozapine concentration after the initiation of VPA in four patients.[124] The combination of clozapine plasma protein-binding displacement and the inhibition of GLUC formation may explain the emergence of adverse effects reported above because of a potential increase in the unbound fraction of clozapine.[123]

Like probenecid, VPA has been proposed to inhibit the glucuronidation of zidovudine. Because there is a higher frequency of adverse effects including bone marrow suppression associated with increased plasma zidovudine concentration, the significance of this interaction has been studied *in vitro* and correlated with *in vivo* data. VPA at a concentration level of 100 μg/mL, a concentration comparable to levels achieved *in vivo* for the treatment of acute mania, produced 50% inhibition of zidovudine glucuronidation in human hepatic microsomes.[125] Inhibition of zidovudine glucuronidation occurred in a concentration-dependent manner with complete blockade of glucuronidation by VPA at a concentration of 1,000 μg/mL.[125] At least one report demonstrated a significant increase in both plasma and cerebrospinal zidovudine concentrations, after the addition of VPA. Peak plasma zidovudine concentration levels increased to 344 ng/mL from a baseline of 119 ng/mL and cerebrospinal fluid concentration levels increased to 47 ng/mL from a baseline of 26 ng/mL. This change was accompanied by a zidovudine GLUC plasma concentration reduction of 50%.[126]

The ratio of chloramphenicol GLUC to total nitro-compounds excreted in the urine was shown to be significantly higher in two of six patients with schizophrenia receiving both a phenothiazine and phenobarbital.[127] The average phenobarbital dose for the group was 62 mg/day. The chloramphenicol $t_{1/2}$ in these two patients was 45 and 95 minutes compared to an average $t_{1/2}$ of 130.6 minutes in the control group.[127]

The *in vitro* glucuronidation rate of (+)-E-10-hydroxy-nortriptyline in human hepatic microsomes was found to be higher in livers from two patients who had received prior treatment with pentobarbital.[103] GLUC formation was 31 pmol/mg per minute and 23.8 pmol/mg per minute, respectively, versus the mean activity of 18.8 pmol/mg per minute found in microsomes from all 13 patients studied.[103] Phenobarbital induces the glucuronidation of endogenous bilirubin catalyzed by UGT1A1[40] and is used therapeutically in the treatment of hyperbilirubinemia in newborns.[43]

Phenytoin alone and in combination with phenobarbitone significantly increased oxazepam CL in nine patients with epilepsy.[128] Average phenytoin and phenobarbitone doses were 267 mg and 100 mg, respectively. Mean oxazepam AUC and $t_{1/2}$ were significantly reduced from matched controls (1864 vs. 1030 ng/mL and 6.99 vs. 3.31 hours, respectively) after a 15-mg dose. Bilirubin concentrations were also significantly lower in treated patients than in controls (6.1 vs. 10.9 μmol/L) reflecting phenobarbitone or phenytoin induction of UGT1A1.[128]

Antipsychotics

Promethazine and chlorpromazine were both found to inhibit testosterone, androsterone, estriol, and 1-naphthol activity in human hepatic microsomes.[108] Chlorpromazine exhibited the most profound inhibition of testosterone, androsterone, and 1-naphthol with inhibition values of 77%, 86%, and 62%, respectively. Inhibition of testosterone and androsterone UDPGT activity by promethazine was 56% and 59%, respectively.[108] The mean circulating concentrations of haloperidol GLUC (35.4 ng/mL) have been shown to be higher than those of the parent drug (16.2 ng/mL), reduced haloperidol (14.1 ng/mL) or reduced haloperidol GLUC (12.7 ng/mL) in 39 hospitalized patients with schizophrenia.[7] Increased extrapyramidal symptoms (EPS) were reported after the addition of olanzapine to existing haloperidol treatment in a 67-year old man.[129] The increase in EPS may be explained by a pharmacodynamic interaction at the D_2 receptor level; however, inhibition of haloperidol conjugative or oxidative metabolism could also be involved.[129]

The plasma nortriptyline concentration was doubled to 185 ng/mL in a 38-year old man with schizoaffective disorder after the addition of clozapine.[130] The patient demonstrated symptoms congruent with an anticholinergic delirium including confusion, slurred speech, and

short-term memory loss. Both drugs were discontinued, and clozapine was gradually reinstituted after 5 days. Ten days after the discontinuation of nortriptyline, the plasma concentration was 44 ng/mL. Concentration of the 10-hydroxy metabolite was not measured.[130] Competitive inhibition of oxidative enzymes might have accounted for the observed increase in plasma nortriptyline concentration; however, inhibition of glucuronidation is also possible. Although the affinity of the 10-hydroxynortriptyline metabolite for muscarinic receptors is approximately one ninth and one eighteenth that of nortriptyline's for the Z-10 and E-10-hydroxy metabolite, respectively,[102] excessive concentrations of these metabolites, secondary to reduced GLUC formation, could have contributed to the adverse effects.

Antihypertensives

The β-adrenergic antagonist, propranolol is used in the treatment of cardiovascular disorders, performance anxiety, and in the symptomatic management of antipsychotic-induced akathisia.[131] When administered at a dosage of 80 mg, twice daily, during a 4-day period, it was found to inhibit both the oxidation and glucuronidation of APAP in 10 healthy volunteers. Propranolol decreased the formation of the APAP GLUC by 27%, whereas sulfation was unaffected.[132] Propranolol had no effect on the pharmacokinetics of lorazepam; however, CL was prolonged for diazepam, which undergoes metabolism through several oxidative pathways.[133]

Guanfacine, a centrally acting α_2 agonist, is used in the treatment of disruptive and impulsive behavior in children.[134] It undergoes both oxidative and conjugative metabolism with 3-hydroxy guanfacine GLUC and sulfate conjugates accounting for approximately 50% of the metabolites found in the urine.[135] In a case report, VPA plasma concentration was found to decrease by 20% to 40% when guanfacine was decreased in two children and resulted in the reemergence of symptoms in one patient. This interaction may reflect competitive inhibition of glucuronidation.[136]

Benzodiazepines

Diazepam inhibited codeine glucuronidation when incubated with UDP-glucuronic acid in human liver and kidney microsomes.[105] In addition, diazepam and oxazepam were found to inhibit the formation of both M3G and M6G. The degree of inhibition was concentration-dependent, with the most profound inhibition occurring with diazepam at a concentration of 1,000 μM. The observed percentage of control activity in the presence of diazepam was 13% and 9% for the formation of M3G and M6G, respectively.[105] In separate studies, oxazepam has also been shown to competitively inhibit MOR glucuronidation in human fetal and adult liver microsomes.[30, 137] Oxazepam was found to preferentially inhibit the formation of M3G of the (−)enantiomer, although it had the least inhibitory effect on the formation of (+)M6G.[30]

An apparent pharmacodynamic interaction occurred after the addition of lorazepam to existing clozapine treatment in two patients. Marked sialorrhea and ataxia occurred with combined therapy. Previous administration of lorazepam with haloperidol in one of the patients had not resulted in such adverse effects. Although clozapine concentration was not measured, lorazepam may have competitively inhibited the glucuronidation pathway of clozapine.[138]

NSAIDS

(*S*)-Oxazepam was found in one study to be preferentially glucuronidated over the (*R*)-isomer by a variant of UGT2B7,[29, 139] although others have found low activity for UGT2B7 toward oxazepam.[58, 62] Ketoprofen was found to competitively inhibit the glucuronidation of (*S*)-oxazepam to a greater degree than (*R*)-oxazepam.[29] Other NSAIDS that have demonstrated competitive inhibition included (*S*)-naproxen, ibuprofen, and fenoprofen.[29]

Oral contraceptives

Ethynylestradiol is a substrate of UGT1A1[37] and has been found to participate in interactions of agents subject to glucuronidation. The effect of OCs on the pharmacokinetics of lorazepam, oxazepam, and chlordiazepoxide was investigated in eight healthy women who had been receiving OCs for a period of 6 months.[140] The CLs of lorazepam and oxazepam were significantly enhanced in the OC users compared with nonusers (288.9 vs. 77.5 mL/min for lorazepam ($p < 0.01$) and 251.2 vs. 97.86 mL/min for oxazepam) ($p < 0.01$). The CL of chlordiazepoxide, which undergoes oxidative metabolism, was found to be significantly impaired. It seems that OCs induced the glucuronidation of lorazepam and oxazepam, whereas the oxidative metabolism of chlordiazepoxide was inhibited.[140] In contrast, Abernethy and coworkers[141] found OCs had no effect on the pharmacokinetics of either lorazepam or oxazepam in 17 women who had received OCs containing 50 μg of ethynylestradiol or less for a minimum of 3 months. The larger sample of women in this study or the inclusion of subjects receiving less than 50 μg of ethynylestradiol may reflect the absence of effect on benzodiazepine CL. Fifty μg of ethynylestradiol taken alone or in combination with norethindrone for 21 days increased propranolol CL through glucuronidation significantly.[142] Propranolol GLUC CL in women receiving ethynylestradiol alone

was 71% higher, whereas those receiving the combination of ethynylestradiol with norethindrone experienced a 32% increase in propranolol glucuronidation, suggesting that the progestin component exerts an inhibitory effect on glucuronidation.[142]

OCs were also found to have an impact on APAP CL.[143] OC users had a higher CL rate of the analgesic (5.81 mL/min) compared with controls (4.12 mL/min). Likewise, OCs were found to impair the oxidative metabolism of antipyrine.[143] Given the widespread use of OCs concomitantly with psychotherapeutic agents, the potential significance of OC drug interactions deserves additional investigation.[144]

Probenecid

Probenecid is a uricosuric agent used in the treatment of gout to competitively inhibit the reabsorption of uric acid in the renal proximal convoluted tubule. It also inhibits the active tubular secretion and urinary excretion of penicillin and cephalosporin antibiotics. Besides undergoing oxidative metabolism, approximately 20% of a probenecid dose is glucuronidated into the acyl-GLUC.[145]

The glucuronidation of APAP and lorazepam was competitively inhibited *in vitro* by probenecid in hepatic microsomes.[146] In 11 patients who received concurrent probenecid and APAP, APAP CL was decreased from 329 to 178 mL/min ($p < 0.001$).[140] The 24-hour urinary excretion of APAP GLUC decreased from 260 to 84 mg, whereas the APAP sulfate excretion was increased proportionally so that the sum of the two conjugated metabolites remained constant. Similarly lorazepam CL decreased from 80.3 to 44.7 mL/min ($p < 0.001$) in nine subjects who received probenecid.[147]

The pharmacokinetics of nitrazepam and temazepam were investigated after the addition of probenecid in 16 healthy subjects.[148] The total CL of antipyrine and nitrazepam were decreased by 22% and 25%, respectively. For norantipyrine and 4-OH-antipyrine, this decrease was caused by a reduction in GLUC formation. The sulfate fraction of norantipyrine and 4-OH-antipyrine was found to be increased. The fraction of temazepam excreted as GLUC was decreased by 33%; however, no changes in the pharmacokinetic parameters of temazepam were observed, as a result of increases in both the parent and sulfate fractions.[148]

The antiretroviral zidovudine undergoes extensive glucuronidation. The exact isoforms responsible for the glucuronidation of zidovudine are unknown, but UGT1A6 and UGT2B7 have been excluded.[10] Seven patients with AIDS-related complex who were receiving treatment with zidovudine were administered probenecid. The mean AUC of zidovudine doubled, along with a decrease in CL and an increase in $t_{1/2}$ after the coadministration of probenecid.[149] Theoretically, psychoactive drugs extensively glucuronidated, including clozapine, olanzapine, and lamotrigine, could be similarly affected by probenecid.

Rifamycins

Rifampin is an antimicrobial known to induce drug metabolism through effects on human CYP isoforms, resulting in the increased CL of several drugs including OCs, warfarin, quinidine, digoxin, cyclosporine, protease inhibitors, nortriptyline, midazolam, and triazolam.[150] Interactions with zidovudine have also suggested an inductive effect on glucuronidation.[151] The CL of nitrazepam was increased by 83% in healthy subjects who received rifampin at a dosage of 600 mg/day for 7 days. However, the pharmacokinetics of temazepam were not significantly affected by concurrent rifampin treatment.[148] The percentage of dose excreted as propranolol GLUC did not change after 22 days of treatment with rifampin 600 mg/day.[152] This was noted in both extensive and poor metabolizers of debrisoquine; however, the fractional CL of propranolol glucuronidation increased after treatment because of a higher total propranolol CL.[152] After 13 days of treatment with rifampin, analgesic effects of MOR were lost as measured by the cold pressor test in 10 subjects.[113] Furthermore, MOR AUC values were significantly reduced by nearly 28% with proportional reductions in both M3G and M6G AUCs. The urinary recovery of the MOR GLUCs was also reduced.[153]

Clozapine serum concentrations were significantly decreased (600%) after the addition of rifampin for the treatment of tuberculosis in a 33-year-old patient with schizophrenia. This reduction resulted in the reemergence of psychotic symptoms.[154] Clozapine undergoes both oxidative and conjugative metabolism; therefore, it is unlikely that the observed decrease in clozapine concentration can be solely accounted for by rifampin's induction of CYP P450 isozymes.

Conclusion

Relative to published clinical investigations of phase I metabolic processes and interactions, there has been less systematic study of changes in the pharmacokinetic parameters of psychotropic agents as a result of inhibition or induction of phase II processes. Substantial inter- and intra-individual variability in the pharmacokinetics of many psychotropic drugs has come to be a widely recognized, yet frequently unexplained phenomena associated with psychotropic drug therapy. The identification of genetic polymorphisms in CYP isoforms has explained the causes of significant variability in drug metabolism and response to many drugs, yet does not adequately

explain all observations. Glucuronidation as a major metabolic pathway is being increasingly recognized as a source of variability in the dose/concentration/effect relationship of several psychoactive drugs. The UGT enzyme system can be inhibited or induced and at least some UGT isoforms seem to be subject to genetic polymorphism. Additionally, stereospecific conjugation has been observed for a number of compounds. Taken together, these factors likely contribute to intersubject variability in psychoactive drug metabolism and, potentially, important drug-drug interactions.

The ability of some xenobiotics to simultaneously *coinduce* or *coinhibit* both UGT and CYP isoforms (i.e., polycyclic aromatic hydrocarbons) seems to be a potential confound to accurate interpretation of drug-drug interactions. Even drug interaction case reports suggestive of cimetidine inhibition of clozapine metabolism[155] and rifampin induction of clozapine metabolism,[153] purportedly through CYP mechanisms, could also represent inhibitory[139] and inductive[151] effects of these drugs on glucuronidation, respectively. Most SSRI antidepressants are likewise subject to extensive glucuronidation and may also affect the disposition of coadministered medications.[108] This is an intriguing possibility that has undergone little study. Future *in vitro* and *in vivo* drug interaction studies involving both old and new drug entities will undoubtedly investigate the effects and consequences of glucuronidation on psychotropic medications.

References

1. Low LK, Castagnoli N Jr. Metabolic changes of drugs and related organic compounds. In: Delgado JN, Remers WA, ed. Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry. Philadelphia: J.B. Lippincott Co., 1991:45–127.
2. von Moltke LL, Greenblatt DJ, Harmatz JS, et al. Cytochromes in psychopharmacology. J Clin Psychopharmacol 1994;14:1–4.
3. Nemeroff CB, DeVane CL, Pollock BG. Newer antidepressants and the cytochrome P450 system. Am J Psychiatry 1996;153: 311–20.
4. Kroemer HK, Klotz U. Glucuronidation of drugs, a re-evaluation of the pharmacological significance of the conjugates and modulating factors. Clin Pharmacokinet 1992;23:292–310.
5. Miners JO, Mackenzie PI. Drug glucuronidation in humans. Pharmacol Ther 1991;51:347–69.
6. Chapman A, Keane PE, Meldrum BS, et al. Mechanism of anticonvulsant action of valproate. Prog Neurobiol 1982;19:315–59.
7. Someya T, Shibasaki M, Noguchi T, et al. Haloperidol metabolism in psychiatric patients: importance of glucuronidation and carbonyl reduction. J Clin Psychopharmacol 1992;12:169–74.
8. Kassahun K, Mattiuz E, Nyhart E Jr, et al. Disposition and biotransformation of the antipsychotic agent olanzapine in humans. Drug Metab Dispos 1997;25:81–93.
9. Iyer KR, Sinz MW. Characterization of phase I and phase II hepatic drug metabolism activities in a panel of human liver preparations. Chem Biol Interact 1999;118:151–69.
10. Burchell B, Brierley CH, Rance D. Specificity of human UDP-glucuronosyltransferases and xenobiotic glucuronidation. Life Sci 1995;57:1819–31.
11. Sinz MW, Remmel RP. Isolation and characterization of a novel quaternary ammonium-linked glucuronide of lamotrigine. Drug Metab Dispos 1991;19:149–53.
12. Ebner T, Burchell B. Substrate specificities of two stably expressed human liver UDP-glucuronosyltransferases of the UGT1 gene family. Drug Metab Dispos 1993;21:50–7.
13. Dutton GJ. Glucuronidation of drugs and other compounds. Boca Raton: CRC Press, 1980.
14. Green MD, Bishop WP, Tephly TR. Expressed human UGT1.4 protein catalyzes the formation of quaternary ammonium-linked glucuronides. Drug Metab Dispos 1995;23:299–302.
15. Green MD, King CD, Mojarrabi B, et al. Glucuronidation of amines and other xenobiotics catalyzed by expressed human UDP-glucuronosyltransferase 1A3. Drug Metab Dispos 1998;26:507–12.
16. Green MD, Tephly TR. Glucuronidation of amine substrates by purified and expressed UDP-glucuronosyltransferase proteins. Drug Metab Dispos 1998;26:860–7.
17. Kassahun K, Mattiuz E, Franklin R, et al. Olanzapine 10-*N*-glucuronide, a tertiary *N*-glucuronide unique to humans. Drug Metab Dispos 1998;26:848–55.
18. Luo H, Hawes EM, McKay G, et al. N^+-glucuronidation of aliphatic tertiary amines in human: antidepressant versus antipsychotic drugs. Xenobiotica 1995;25:291–301.
19. Pasternak GIW, Bodnar RJ, Clark JA, et al. Morphine-6-glucuronide, a potent MU agonist. Life Sci 1987;41:2845–9.
20. Scholz H, Schmitz W. Positive inotropic effects of digitoxin- and digoxin-glucuronide in human isolated ventricular heart muscle preparations. Basic Res Cardiol 1984;79[suppl]:134–9.
21. Arakawa M, Shimizu F, Sdasagawa K, et al. Antitumor activity of methyl (5-fluoro-1H-2-oxo-4-pyrimidinyl β-D-glucopyranosid) uronate against various experimental tumors. Gann 1981;72: 220–5.
22. Osborne R, Joel S, Trew D, et al. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. Clin Pharmacol Ther 1990;47:12–9.
23. Brunk SF, Delle M. Morphine metabolism in man. Clin Pharmacol Ther 1974;16:51–7.
24. Ekblom M, Gardmark M, Hammarlund-Udenaes M. Pharmacokinetics and pharmacodynamics of morphine-3-glucuronide in rats and its influence on the antinociceptive effect of morphine. Biopharm Drug Dispos 1993;14:1–11.
25. Spahn-Langguth H, Benet LZ. Acyl glucuronides revisited: is the glucuronidation process a toxification as well as a detoxification mechanism? Drug Metab Rev 1992;24:5–48.
26. Smith PC, McDonagh AF, Benet LZ. Irreversible binding of zomepirac to plasma protein in vitro and in vivo. J Clin Invest 1986; 77:934–9.
27. Miners JO, Lillywhite KJ, Birkett DJ. *In vitro* evidence for the involvement of at least two forms of human liver UDP-glucuronosyltransferase in morphine 3-glucuronidation. Biochem Pharmacol 1988;37:2839–45.
28. Dahl-Puustinen ML, Perry TL, Dumont E, et al. Stereoselective disposition of racemic E-10-hydroxynortriptyline in human beings. Clin Pharmacol Ther 1989;45:650–6.
29. Patel M, Tang BK, Kalow W. (S)oxazepam glucuronidation is inhibited by ketoprofen and other substrates of UGT2B7. Pharmacogenetics 1995;5:43–9.
30. Wahlström A, Pacifici GM, Lindström B, et al. Human liver morphine UDP-glucuronyl transferase enantioselectivity and inhibition by opioid congeners and oxazepam. Br J Pharmacol 1988;94:864–70.
31. Waddington JL, Owen F. Stereospecific benzodiazepine receptor binding by the enantiomers of oxazepam sodium hemisuccinate. Neuropharmacology 1978;17:215–6.
32. Guéraud F, Paris A. Glucuronidation: a dual control. Gen Pharmacol 1998;31:683–8.
33. Meech R, Mackenzie PI. Structure and function of uridine diphosphate glucuronosyltransferases. Clin Exp Pharmacol Physiol 1997; 24:907–15.
34. Mackenzie PI, Owens IS, Burchell B, et al. The UDP glycosyltransferase gene superfamily: recommended nomenclature update based on evolutionary divergence. Pharmacogenetics 1997;7:255–69.
35. Wooster R, Sutherland L, Ebner T, et al. Cloning and stable expression of a new member of the human liver phenol/bilirubin: UDP-glucuronosyltransferase cDNA family. Biochem J 1991;278:465–9.

36. Cho J, Gholami N, Owens IS. Diversity and independent regulation at the novel human UGTI locus encoding 12 UDP-glucuronosyltransferase isozymes through duplication of both exon 1 and the upstream regulatory region [abstact]. FASEB J 1995;9:A1268.
37. Ritter JK, Chen F, Sheen YY, et al. A novel complex locus UGTI encodes human bilirubin, phenol and other UDP-glucuronosyltransferase isozymes with identical carboxyl termini. J Biol Chem 1992;267:3257–61.
38. Senafi SB, Clarke DJ, Burchell B. Investigation of the substrate specificity of a cloned expressed human bilirubin UDP-glucuronosyltransferase: UDP-sugar specificity and involvement in steroid and xenobiotic glucuronidation. Biochem J 1994;303:233–40.
39. Mojarrabi B, Butler R, Mackenzie PI. cDNA cloning and characterization of the human UDP glucuronosyltransferase, UGT1A3. Biochem Biophys Res Commun 1996;225:785–90.
40. Bock KW, Gschaidmeier H, Heel H, et al. Functions and transcriptional regulation of pah-inducible human UDP-glucuronosyltransferases. Drug Metab Rev 1999;31:411–22.
41. Strassburg CP, Nguyen N, Manns MP, et al. UDP-glucuronosyltransferase activity in human liver and colon. Gastroenterology 1999;116:149–60.
42. Cheng Z, Radominska-Pandya A, Tephly TR. Cloning and expression of human UDP-glucuronosyltransferase (UGT) 1A8. Arch Biochem Biophys 1998;356:301–5.
43. Perucca E. Drug metabolism in pregnancy, infancy, and childhood. Pharmacol Ther 1987;34:129–43.
44. King CD, Green MD, Rios GR, et al. The glucuronidation of exogenous and endogenous compounds by stably expressed rat and human UDP-glucuronosyltransferase 1.1. Arch Biochem Biophys 1996;332:92–100.
45. Wasserman E, Myara A, Lokiec F, et al. Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. Ann Oncol 1997;8:1049–51.
46. Iyer L, King CD, Whitington PF, et al. Genetic predisposition to the metabolism of irinotecan (CPT-11)—role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. J Clin Invest 1998;101:847–54.
47. Cheng Z, Rios GR, King CD, et al. Glucuronidation of catechol estrogens by expressed human UDP-glucuronosyltransferases (UGTs) 1A1, 1A3, and 2B7. Toxicol Sci 1998;45:52–7.
48. Green MD, Tephly TR. Glucuronidation of amines and hydroxylated xenobiotics and endobiotics catalyzed by expressed human UGT1.4 protein. Drug Metab Dispos 1996;24:356–63.
49. Hiller A, Nguyen N, Strassburg CP, et al. Retigabine *N*-glucuronidation and its potential role in enterohepatic circulation. Drug Metab Dispos 1999;27:605–12.
50. Bock KW, Forster A, Gschaidmeier H, et al. Paracetamol glucuronidation by recombinant rat and human phenol UDP-glucuronosyltransferases. Biochem Pharmacol 1993;45:1809–14.
51. Bock KW. UDP-glucuronosyltransferases and their role in metabolism and disposition of carcinogens. Adv Pharmacol 1994;27:3 67–83.
52. Orzechowski A, Schrenk D, Bock-Hennig BS, et al. Glucuronidation of carcinogenic arylamines and their *N*-hydroxy derivatives by rat and human phenol UDP-glucuronosyltransferases of the UGT1 gene complex. Carcinogenesis 1994;15:1549–53.
53. King CD, Rios GR, Assouline JA, et al. Expression of UDP-glucuronosyltransferases (UGTs) 2B7 and 1A6 in the human brain and identification of 5-hydroxytryptamine as a substrate. Arch Biochem Biophys 1999;365:156–62.
54. Monaghan G, Clarke DJ, Povey S, et al. Isolation of a human YAC contig encompassing a cluster of UGT2 genes and its regional localization to chromosome 4q 13. Genomics 1994;23:496–9.
55. Monaghan G, Povey S, Burchell B, et al. Localization of a bile acid UDP-glucuronosyltransferase gene (UGT2B) to chromosome 4 using the polymerase chain reaction. Genomics 1992;13:908–9.
56. Lazard D, Zupko K, Poria Y, et al. Odorant signal termination by olfactory UDP-glucuronosyltransferase. Nature 1991;349:790–3.
57. Coffman BL, Rios GR, King CD, et al. Human UGT2B7 catalyzes morphine glucuronidation. Drug Metab Dispos 1997;25:1–4.
58. Coffman BL, King CD, Rios GR, et al. The glucuronidation of opioids, other xenobiotics and androgens by human UGT2B7Y(268) and UGT2B7H(268). Drug Metab Dispos 1998;26:73–7.
59. Chen F, Ritter JK, Wang MG, et al. Characterization of a cloned human dihydrotestosterone/androstanediol UDP-glucuronosyltransferase and its comparison to other steroid isoforms. Biochemistry 1993;32:10648–57.
60. Münzet PA, Schmohl S, Heel H, et al. Induction of human UDP glucuronosyltransferases (UGT1A6, UGT1A9, and UGT2B7) by *t*-butylhydroquinone and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in cao-2 cells. Drug Metab Dispos 1999;27:569–73.
61. Radominskapandya A, Little JM, Pandya JT, et al. UDP-glucuronosyltransferases in human intestinal mucosa. Biochim Biophys Acta 1998;1394:199–208.
62. Jin C, Miners JO, Lillywhite KJ, et al. Complementary deoxyribonucleic acid cloning and expression of a human liver uridine diphosphate-glucuronosyltransferase glucuronidating carboxylic acid-containing drugs. J Pharmacol Exp Ther 1993;264:475–9.
63. Wahlström A, Winblad B, Bixo M, et al. Human brain metabolism of morphine and naloxone. Pain 1988;35:121–7.
64. Green MD, Oturu EM, Tephly TR. Stable expression of human liver and UDP-glucuronosyltransferase (UGT2B15) with activity toward steroid and xenobiotic substrates. Drug Metab Dispos 1994;22:799–805.
65. Lévesque E, Beaulieu M, Green MD, et al. Isolation and characterization of UGT2B15(Y^{85}): a UDP-glucuronosyltransferase encoded by a polymorphic gene. Pharmacogenetics 1997;7:317–25.
66. Monaghan G, Ryan M, Seddon R, et al. Genetic variation in bilirubin UDP-glucuronosyltransferase gene promoter and Gilbert's syndrome. Lancet 1996;347:578–81.
67. Ciotti M, Obaray R, Martin MG, et al. Genetic defects at the UGT1 locus associated with Crigler-Najjar type I disease, including a prenatal diagnosis. Am J Med Genet 1997;68:173–8.
68. Monaghan G, Foster B, Jurima-Romet M, et al. UGT1*1 genotyping in a Canadian Inuit population. Pharmacogenetics 1997;7: 153–6.
69. Ando Y, Chida M, Nakayama K, et al. The UGT 1A1*28 allele is relatively rare in a Japanese population. Pharmacogenetics 1998;8: 357–60.
70. Benowitz NL, Perez-Stable EJ, Fong I, et al. Ethnic differences in glucuronidation of nicotine and cotinine. J Pharmacol Exp Ther 1999;291:1196–203.
71. Richie JP Jr, Carmella SG, Muscat JE, et al. Differences in the urinary metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in black and white smokers. Cancer Epidemiol Biomarkers Prev 1997;6:783–90.
72. Yue QY, Svensson JO, Alm C, et al. Interindividual and interethnic differences in the demethylation and glucuronidation of codeine. Br J Clin Pharmacol 1989;28:629–37.
73. Mucklow JC, Fraser US, Bulpitt CJ, et al. Environmental factors affecting paracetamol metabolism in London factory and office workers. Br J Clin Pharmacol 1980;10:67–74.
74. Saland J, McNamara H, Cohen Mi. Navajo jaundice: a variant of neonatal hyperbilirubinemia associated with breast feeding. J Pediatr 1974;85:271–5.
75. McRorie TI, Lynn AM, Nespeca MK, et al. The maturation of morphine clearance and metabolism. Am J Dis Child 1992;146: 972–6.
76. Mulhall A, de Louvois J, Hurley R. The pharmacokinetics of chloramphenicol in the neonate and young infant. J Antimicrob Chemother 1983;12:629–39.
77. Levy G, Khanna NN, Soda DM, et al. Pharmacokinetics of acetaminophen in the human neonate: formation of acetaminophen glucuronide and sulfate in relation to plasma bilirubin concentration and D-glucaric acid excretion. Pediatrics 1975;55:818–25.
78. Lietman PS. Chloramphenicol and the neonate—1979 view. Clin Perinatol 1979;6:151–62.
79. Herd B, Wynne H, Wright P, et al. The effect of age on glucuronidation and sulphation of paracetamol by human liver fractions. Br J Clin Pharmacol 1991;32:768–70.
80. Greenblatt DJ, Divoll M, Harmatz JS, et al. Oxazepam kinetics: effects of age and sex. J Pharmacol Exp Ther 1980;215:86–91.

81. Divoll M, Greenblatt DJ, Harmatz JS, et al. Effect of age and gender on disposition of temazepam. J Pharm Sci 1981;70:1104–7.
82. Bochner F, Chen ZR, Young G, et al. Codeine metabolism and disposition: comparison in young and elderly subjects. Eur J Pharmacol 1990;183:630–1.
83. Sonne J, Loft S, Døssing M, et al. Single dose pharmacokinetic and pharmacodynamics of oral oxazepam in very elderly institutionalized subjects. Br J Clin Pharmacol 1991;31:712–22.
84. Abernethy DR, Divoll M, Greenblatt DJ, et al. Obesity, sex, and acetaminophen disposition. Clin Pharmacol Ther 1982;31: 783–90.
85. Miners JO, Attwood J, Birkett DJ. Influence of sex and oral contraceptive steroids on paracetamol metabolism. Br J Clin Pharmacol 1983;16:503–9.
86. Bock KW, Schrenk D, Forster A, et al. The influence of environmental and genetic factors on CYP2D6, CYP1A2, and UDP-glucuronosyltransferases in man using sparteine, caffeine, and paracetamol as probes. Pharmacogenetics 1994;4:209–18.
87. Walle T, Walle K, Cowart D, et al. Pathway-selective sex differences in the metabolic clearance of propranolol in human subjects. Clin Pharmacol Ther 1989;46:257–63.
88. Haring C, Meise U, Humpel C, et al. Dose-related plasma levels of clozapine: influence of smoking behavior, sex, and age. Psychopharmacology (Berl) 1989;99:S38–S40.
89. Patel BR, Nyhart EH, Callaghan JT, et al. Combined population analysis of olanzapine in healthy volunteers [abstract]. Pharm Res 1995;12: S–415.
90. Wrighton SA, Ring BJ. Predicting drug interactions and pharmacokinetic variability with in vitro methods: the olanzapine experience. Drug Metab Rev 1999;31:15–28.
91. Abernethy DR, Greenblatt DJ, Divoll M, et al. Enhanced glucuronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen. J Lab Clin Med 1983;101:873–80.
92. Ashton M, Bolme P, Alemayehu E, et al. Decreased chloramphenicol clearance in malnourished ethiopian children. Eur J Clin Pharmacol 1993;45:181–6.
93. Furlan V, Demirdjian S, Bourdon O, et al. Glucuronidation of drugs by hepatic microsomes derived from healthy and cirrhotic human livers. J Pharmacol Exp Ther 1999;289:1169–75.
94. Sonne J, Boesgaard S, Poulsen HE, et al. Pharmacokinetics and pharmacodynamics of oxazepam and metabolism of paracetamol in severe hypothyroidism. Br J Clin Pharmacol 1990;30:737–42.
95. Esteban A, Pérez-Mateo M, Boix V, et al. Abnormalities in the metabolism of acetaminophen in patients infected with the human immunodeficiency virus (HIV). Methods Find Exp Clin Pharmacol 1997;19:129–32.
96. Fleischmann R, Remmer H, Stärz U. Induction of cytochrome P-448 iso-enzymes and related glucuronyltransferases in the human liver by cigarette smoking. Eur J Clin Pharmacol 1986;30: 475–80.
97. Walle T, Walle UK, Cowart EC, et al. Selective induction of propranolol metabolism by smoking: additional effects on renal clearance of metabolites. J Pharmacol Exp Ther 1987;241: 928–33.
98. Hasegawa M, Gutierrez-Esteinou R, Way L, et al. Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. J Clin Psychopharmacol 1993; 13:383–90.
99. Lieber CS. Interaction of alcohol with other drugs and nutrients: implications for the therapy of alcoholic liver disease. Drugs 1990;40:23–44.
100. Golovinsky E, Naydenova Z, Grancharov K. UDP-glucuronosyltransferase inhibitors. Eur J Drug Metab Pharmacokinet 1998;23: 453–6.
101. Forrest JAH, Clements JA, Prescott LF. Clinical pharmacokinetics of paracetamol. Clin Pharmacokinet 1982;7:93–107.
102. Nordin C, Bertilsson L. Active hydroxymetabolites of antidepressants. Emphasis on E-10-hydroxy-nortriptyline. Clin Pharmacokinet 1995;28:26–40.
103. Dumont E, von Bahr C, Perry TL, et al. Glucuronidation of the enantiomers of E-10-hydroxy-nortriptyline in human and rat liver microsomes. Pharmacol Toxicol 1987;61:335–41.
104. Wahlström A, Lenhammar L, Ask B, et al. Tricyclic antidepressants inhibit opioid receptor binding in human brain and hepatic morphine glucuronidation. Pharmacol Toxicol 1994;75:23–7.
105. Yue Q, von Bahr C, Odar-Cederlöf I, et al. Glucuronidation of codeine and morphine in human liver and kidney microsomes: effect of inhibitors. Pharmacol Toxicol 1990;66:221–6.
106. Ventafridda V, Ripamonti C, De Conno F, et al. Antidepressants increase bioavailability of morphine in cancer patients [letter]. Lancet 1987;1:1204.
107. Ventafridda V, Bianchi M, Ripamonti C, et al. Studies on the effects of antidepressant drugs on the antinociceptive action of morphine and on plasma morphine in rat and man. Pain 1990;43: 155–62.
108. Sharp S, Mak LY, Smith DJ, et al. Inhibition of human and rabbit liver steroid and xenobiotic UDP-glucuronosyltransferases by tertiary amine drugs—implications for adverse drug reactions. Xenobiotica 1992;22:13–25.
109. Kaufman KR, Gerner R. Lamotrigine toxicity secondary to sertraline. Seizure 1998;7:163–5.
110. Cohen AF, Land GS, Breimer DD, et al. Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. Clin Pharmacol Ther 1987;42:535–41.
111. Haffen E, Vandel P, Bonin B, et al. Citalopram pharmacokinetic interaction with clomipramine. UDP-glucuronosyltransferase inhibition? A case report. Therapie 1999;54:767–70.
112. McLean MJ. Clinical pharmacokinetics of gabapentin. Neurology 1994;44:[6 suppl 5]:S17–S22.
113. Dickinson RG, Hooper WD, Dunstan PR, et al. Urinary excretion of valproate and some metabolites in chronically treated patients. Ther Drug Monit 1989;11:127–33.
114. Yau MK, Wargin WA, Wolf KB, et al. Effect of valproate on the pharmacokinetics of lamotrigine [abstract]. Epilepsia 1992;33 [suppl 3]:82.
115. Lamictal (lamotrigine) (product information). London, England: GlaxoWellcome Inc., 1999.
116. Schlienger RG, Shapiro LE, Shear NH. Lamotrigine-induced severe cutaneous adverse reactions. Epilepsia 1998;39[suppl 7]: S22–S26.
117. Bernus I, Dickinson RG, Hooper WD, et al. The mechanism of the carbamazepine-valproate interaction in humans. Br J Clin Pharmacol 1997;44:21–7.
118. Bernus I, Dickinson RG, Hooper WD, et al. Inhibition of phenobarbitone N-glucosidation by valproate. Br J Clin Pharmacol 1994;38:411–6.
119. Wong SL, Cavanaugh J, Shi H, et al. Effects of divalproex sodium on amitriptyline and nortriptyline pharmacokinetics. Clin Pharmacol Ther 1996;60:48–53.
120. Fehr C, Gründer G, Hiemke C, et al. Increase in serum clomipramine concentrations caused by valproate. J Clin Psychopharmacol 2000;20:493–4.
121. Anderson GD, Gidal BE, Kantor ED, et al. Lorazepam-valproate interaction: studies in normal subjects and isolated perfused rat liver. Epilepsia 1994;35:221–5.
122. Samara EE, Granneman RG, Witt GF, et al. Effect of valproate on the pharmacokinetics and pharmacodynamics of lorazepam. J Clin Psychopharmacol 1997;37:442–50.
123. Costello LE, Suppes T. A clinically significant interaction between clozapine and valproate. J Clin Psychopharmacol 1995;15:139–41.
124. Finley P, Warner D. Potential impact of valproic acid therapy on clozapine disposition. Biol Psychiatry 1994;36:487–8.
125. Trapnell CB, Klecker RW, Jamis-Dow C, et al. Glucuronidation of 3'-azido-3'-deoxythimidine (zidovudine) by human liver microsomes: relevance to clinical pharmacokinetic interactions with atovaquone, fluconazole, methadone, and valproic acid. Antimicrob Agents Chemother 1998;42:1592–6.
126. Akula SK, Rege AB, Dreisbach AW, et al. Valproic acid increases cerebrospinal fluid zidovudine levels in a patient with AIDS. Am J Med Sci 1997;313:244–6.
127. Watanabe A. Effect of chronic administration of centrally acting compounds on chloramphenicol metabolism in schizophrenic patients. Pharmacology 1974;11:253–6.
128. Scott K, Khir ASM, Sreele WH, et al. Oxazepam pharmacokinetics in patients with epilepsy treated long-term with phenytoin

alone or in combination with phenobarbitone. Br J Clin Pharmacol 1983;16:441–4.
129. Gomberg RF. Interaction between olanzapine and haloperidol. J Clin Psychopharmacol 1999;19:272–3.
130. Smith T, Riskin J. Effect of clozapine on plasma nortriptyline concentration. Pharmacopsychiatry 1994;27:41–2.
131. Fleischhacker WW, Roth SD, Kane JM. The pharmacologic treatment of neuroleptic-induced akathisia. J Clin Psychopharmacol 1990;10:12–21.
132. Baraka OZ, Truman CA, Ford JM, et al. The effect of propranolol on paracetamol metabolism in man. Br J Clin Pharmacol 1990;29: 261–4.
133. Ochs HR, Greenblatt DJ, Verburg-Ochs B. Propranolol interactions with diazepam, lorazepam, and alprazolam. Clin Pharmacol Ther 1984;36:451–5.
134. Hunt RD. An open trial of guanfacine in the treatment of attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1995;34:50–4.
135. Kiechel JR. Pharmacokinetics and metabolism of guanfacine in man: a review. Br J Clin Pharmacol 1980;10[suppl 1]:25S–32S.
136. Ambrosini PJ, Sheikh RM. Increased plasma valproate concentrations when coadministered with guanfacine. J Child Adolesc Psychopharmacol 1998;8:143–7.
137. Pacifici GM, Rane A. Inhibition of morphine glucuronidation by oxazepam in human fetal liver microsomes. Drug Metab Dispos 1981;9:549–72.
138. Cobb CD, Anderson CB, Seidel DR. Possible interaction between clozapine and lorazepam. Am J Psychiatry 1991;148:1606–7.
139. Patel M, Tang BK, Grant DM, et al. Interindividual variability in the glucuronidation of (S) oxazepam contrasted with that of (R) oxazepam. Pharmacogenetics 1995;5:287–97.
140. Patawardhan RV, Mitchell MC, Johnson RF, et al. Differential effects of oral contraceptive steroids on the metabolism of benzodiazepines. Hepatology 1993;3:248–53.
141. Abernethy DR, Greenblatt DJ, Ochs HR, et al. Lorazepam and oxazepam kinetics in women on low-dose oral contraceptives. Clin Pharmacol Ther 1983;33:628–32.
142. Walle T, Fagan TC, Walle UK, et al. Stimulatory as well as inhibitory effects of ethinyloestradiol on the metabolic clearances of propranolol in young women. Br J Clin Pharmacol 1996;41:305–9.
143. Abernethy DR, Divoll M, Ochs HR, et al. Increased metabolic clearance of acetaminophen with oral contraceptive use. Obstet Gynecol 1982;60:338–41.
144. Thürmann PA, Hompesch BC. Influence of gender on the pharmacokinetics and pharmacodynamics of drugs. Int J Clin Pharmacol Ther 1998;36:586–90.
145. Cunningham RF, Israili ZH, Dayton PG. Clinical pharmacokinetics of probenecid. Clin Pharmacokinet 1981;6:135–51.
146. von Moltke LL, Manis M, Harmatz JS, et al. Inhibition of acetaminophen and lorazepam glucuronidation *in vitro* by probenecid. Biopharm Drug Dispos 1993;14:119–30.
147. Abernethy DR, Greenblatt DJ, Ameer B, et al. Probenecid impairment of acetaminophen and lorazepam clearance: direct inhibition of ether glucuronide formation. J Pharmacol Exp Ther 1985;234:345–9.
148. Brockmeyer NH, Mertins L, Klimek K, et al. Comparative effects of rifampin and/or probenecid on the pharmacokinetics of temazepam and nitrazepam. Int J Clin Pharmacol Ther Toxicol 1990; 28:387–93.
149. de Miranda P, Good SS, Yarchoan R, et al. Alteration of zidovudine pharmacokinetics by probenecid in patients with AIDS or AIDS-related complex. Clin Pharmacol Ther 1989;46:4 94–500.
150. Strayhorn VA, Baciewicz AM, Self TH. Update on rifampin drug interactions, III. Arch Intern Med 1997;157:2453–8.
151. Burger DM, Meenhorst PL, Koks CH, et al. Pharmacokinetic interaction between rifampin and zidovudine. Antimicrob Agents Chemother 1993;37:1426–31.
152. Shaheen O, Biollaz J, Koshakji RP, et al. Influence of debrisoquin phenotype on the inducibility of propranolol metabolism. Clin Pharmacol Ther 1989;45:439–43.
153. Fromm MF, Eckhardt K, Schänzle G, et al. Loss of analgesic effect of morphine due to coadministration of rifampin. Pain 1997;72:261–7.
154. Joos AAB, Frank UG. Pharmacokinetic interaction of clozapine and rifampicin in a forensic patient with an atypical mycobacterial infection. J Clin Psychopharmacol 1998;18:83–5.
155. Szymanski S, Lieberman J, Picou D, et al. A case report of cimetidine-induced clozapine hepatotoxicity. J Clin Psychiatry 1991; 52:21–2.