PREGNANCY: NOTE – PATIENT COMPLIANCE SHOULD BE TAKEN INTO ACCOUNT (as many as 60% of pregnant women don't take their meds as prescribed)

ABSORPTION	GIT TRANSIT	• **Both rate of gastric emptying & rate of mortality in small intestine can be decreased up to 50%** o Due to effects of progesterone on smooth muscle contractility o Can cause greater drug exposure due to increased GIT transit time
DISTRIBUTION	PASSAGE ACROSS ALVEOLAR MEMBRANES	• **Cardiac output is increased by 30%** = greater pulmonary flow o Favours uptake of substances across the alveolar membranes of the lung o Can also promote absorption of compounds across intestine (not been documented to require clinical dosage adjustment) • Increased breaths/minute (caused by greater progesterone levels) and an increase in tidal volume may also promote alveolar passage of substances into the system
	PROTEIN BINDING	• By end of first trimester, **plasma albumin decreases to approx. 75% of normal & stabilizes at this level** o May confer higher plasma unbound fraction for drugs that bind to albumin (generally weak bases) after they are absorbed o Only likely of significance for highly protein bound drugs, potential for drug toxicity (rare) ▪ Single trial in literature: re: cisplatin
	ACROSS PLACENTA	• Fetal compartment is more acidic than maternal = ionization can differ on either side of the membrane o Placental partitioning of drugs occur to some extent **based on drug's acid:base properties** (ion trapping) as has been for salicylate and several other weak bases o This prolongs the exposure of the fetus to the drug, but is toxicological in nature – drug dosing in the mother is not usually adjusted
METABOLISM	HEPATIC ENZYMES	• Hepatic CYP1A2, 2B6, 2C9, 2D6 are induced • Hepatic CYP2C19 is suppressed NOTE: **differences in drug metabolism between men & women** are coming to light (irrespective of pregnancy) • Several studies have demonstrated that CYP3A4 activity is constitutively higher in women than in men • Activity of hepatic CYP2C19 and CYP1A2 appear to be higher in men than women • At present, this has not translated into sex-specific differences in drug dosing and it is believed that most drug-drug interactions in pregnancy are pharmacodynamic in nature, not pharmacokinetic
	PLACENTAL METABOLISM	• Placental metabolism and transport may also affect both maternal and embryonic/fetal levels of drugs • Placental drug metabolizing enzyme expression & activity can vary across gestation, as can the expression pattern of placental active transporters o Same exposure at different times in pregnancy can have differential fetal effects
ELIMINATION	RENAL	• **50% increase in renal plasma flow, GFR and endogenous CrCl** o Increases clearance of compounds that are orally ingested & predominantly renally eliminated o Causes decrease in their plasma concentrations and may require increased drug dosage to maintain therapeutic concentrations

NEONATE:

ABSORPTION	pH DEPENDENT PASSIVE DIFFUSION (GIT absorption)	• Neutral gastric pH (6-8) at birth is related to presence of amniotic fluid in stomach o Postnatally, gastric acid secretory capacity appears after the first 24-48h of life, and gastric acidity decreases during the first weeks to months of life (adult values approached by 3 months) ▪ In premature infants, gastric pH may remain elevated due to immature acid secretion • Higher gastric pH may explain higher serum concentrations of acid-labile drugs (ex// ampicillin, penicillin, nafcillin) observed in premature neonates as compared to children and adults
	GASTRIC EMPTYING (GIT absorption)	• Rate of gastric emptying during neonatal period is both variable & prolonged o Gestational age and postnatal age both affect gastric emptying rate (prolonged emptying times in premature infants) • Absorption of phenobarbital, digoxin & xylose demonstrate that although prolonged gastric emptying is present in neonates, it doesn't completely account for the delays in gastric absorption of these compounds
	OTHER FACTORS	• Age-dependent differences in absorption rate remain even after stimulation of intestinal motility • Decreased capacity of enteral absorption in neonates • **Pancreatic enzyme function & bile acid secretion** are also diminished in neonates (and affect GI absorption)
DISTRIBUTION	PROTEIN BINDING	• Binding of drugs to plasma protein is important and may be immature in the neonate o Plasma albumin, total protein concentrations, and alpha-1-acid glycoprotein are decreased and don't approach adult values until about 1 year of age • Competition for binding sites by: o Increased circulatory concentrations of endogenous bilirubin and free fatty acids o Qualitatively different albumin seen during neonatal period • Alone or in concert, these may all affect drug protein binding
METABOLISM	ENZYMES	• Hepatic enzyme activity & plasma/tissue esterase activity both reduced during neonatal period • Most enzymatic microsomal systems responsible for drug metabolism are present at birth and their activities increase with advancing gestational and postnatal age
ELIMINATION	RENAL	• Significant age-dependent changes in renal function affect the elimination of drugs & their metabolites o At birth, glomerular function is more advanced than tubular function (and this persists until 6 month) o At birth, GFR is 2-4 mL/min in term neonates, and as low as 0.6-0.6 mL/min in premature infants ▪ Dramatic increases occur during the first 72 hour of life where GFR may increase 4-fold o Clearance of renally eliminated drugs can be compromised in the neonate

CHILDREN AND ADOLESCENTS:

- PK parameters in male and female children under the age of 12 years normalized for body size are generally similar
- Prior to onset of puberty, children are at a steroidal nadir with vanishingly low levels of steroids expressed
- At pubertal onset, as hormones arise, we might consider PK effects similar to the lens for pregnancy (e.g. higher levels of progesterone increase gut motility
- PK data collected strictly in the adolescent population are limited, however clinical data indicates important differences between the adolescent and both younger pediatric patients and adults
  - Studies in pediatric cancer pts have shown distinct PK differences in three broad age groups: children < 12 years old, children 12-18 years, and adults
  - A study specifically designed to determine effect of puberty on antipyrine clearance in 17 healthy subjects (6-21 yrs) showed changes in antipyrine clearance related to the adolescent growth spurt
    - Suggested that Tanner stages of adolescent development correlate better with a decline in apparent renal tubular clearance that is known to occur at the onset of adolescence
  - A study of Busulfan (anti-cancer) showed clearance was 8.4 mL/min/kg in children in 4 years, 4.4 mL/min/kg in adolescents, 2.5 mL/min/kg in adults
  - Preliminary PK data for HIV-infected children suggest a substantially different average AUC for zidovudine/AZT in adolescent patients as compared to the average values for all pediatric patients
- The puberty-associated hormonal changes occurring with the onset of gender differentiation are a potentially importance source of PK variability in adolescents
- Dosage adjustment for pediatric patients is performed by weight or BSA, however no such guideline are available specifically for puberty or adolescence

OLDER AND ELDERLY:

- Ageing is involved with the accumulation of both random and progressive changes to physiological systems
- The average life expectancy is ~ 85 years and at present, it is believed that maximum life span cannot go beyond ~ 122 years
- Changes in physiology in the elderly, necessarily confer PK differences

AGE RELATED ASSOCIATED WITH THE FOLLOWING CHANGES:

CV System		• Reduced elasticity and compliance of the aorta and great arteries
		  ○ Higher systolic arterial pressure, increased difficulty with left ventricular ejection → left ventricular hypertrophy & interstitial fibrosis
		• A decrease in the rate of myocardial relaxation
		  ○ Left ventricle becomes stiffer and takes longer to relax and fill in diastole, affecting timing for atrial contraction & normal end-diastolic volume
		• Prolonged isotonic contraction
		• Reduced intrinsic heart rate
		• Increased sinoatrial node conduction time
		• Less sensitive response to postural changes
		  ○ Young subjects maintained cardiac output by increasing HR whereas elderly subjects increase in stroke volume to compensate

Renal		• Renal mass decreases with age and is made of:
		  ○ Reduction in nephrons
		  ○ Intra-renal vascular changes, primarily reduced blood flow in the afferent arterioles in the cortex
		• Plasma flow and GFR decline with age
		• Acid-base is maintained under physiological conditions but a reduced response to stress is revealed by inability to deal with acid loads
		• Ability to concentrate the urine during water deprivation is reduced
		• **All together, most drugs that are renally excreted are dosage-adjusted over the age of 65**

GIT	**Stomach & duodenum**	• The main change are decreased secretion of HCl acid & pepsin; currently considered that this is a combination of:
		  ○ Changes in the enzyme secreting cells and organs
		  ○ Hormonal and neural regulatory differences
		• In contrast, gastric emptying in elderly subjects is similar to that of young patients

	Small Intestine	• Advancing age is accompanied by reduced absorption of many endogenous compounds & drugs (ex// sugar, calcium, iron, lansoprazole, cefpodoxime) but digestion and motility remain relatively unchanged

	Colon	• Studies of colonic differences in the elderly are conflicting:
		  ○ In one study, elderly subjects had a slower colonic transit time of radiolabelled particles than young subjects
		  ○ No significant age-related changes in colonic transit time have been observed in a recent study comparing young and middle-aged subjects

	Pancreas	• Of the major digestive enzymes: amylase remains constant but lipase & trypsin decrease dramatically
	Liver	• Advancing age is associated with a progressive reduction in liver volume and liver blood flow • Alteration of hepatic structure and enzymatic functions with ageing is moderate • In the healthy elderly person, routine tests of liver function do not show significant differences between individuals aged 50-69 and 70-89 years • Unless liver disease is present, drug dosing is seldom adjusted

PK IMPLICATIONS OF THESE CHANGES:

- Early studies showed reduced gastric emptying, reduced splanchnic blood flow and reduced absorptive capacity of the small intestine
  - However this was likely due to the effects of disease states, as more recent reports have not confirmed these findings in healthy subjects

OLDER AND ELDERLY CONTINUED:

ABSORPTION	CONFLICTING RESULTS IN STUDIES	• While some studies have not shown SS age-related differences in absorption rates for different drugs: o **Absorption of vit B12, iron and calcium through active transport mechanisms is reduced** o **Absorption of levodopa is increased** (likely due to a reduced amount of dopadecarnoxylase in the gastric mucosa, rather than a structural difference)
DISTRIBUTION	VOLUME OF DISTRIBUTION	• As a consequence of the age-related changes in body composition, polar drugs that are mainly water soluble tend to have smaller Vd, resulting in higher serum levels in older people o Gentamicin, digoxin, ethanol, theophylline, and cimetidine are affected ▪ Ex// loading doses of digoxin needs to be reduced to accommodate these changes • On the other hand, non-polar compounds tend to be lipid soluble and so their Vd increases with age = causes increased half-life o Diazepam, thiopentone, lignocaine & chlormethiazole are affected and dosing frequency is adjusted
METABOLISM	FIRST PASS METABOLISM	• Ageing associated with reduction in 1st pass metabolism (probably d/t reduction in liver mass & blood flow) o Bioavailability of drugs undergoing extensive first-pass metabolism (ex// propranolol and labetalol) can be significantly increased o On the other hand, several ACEI (ex// enalapril and perindopril) are prodrugs and need to be activated in the liver = 1st pass activation can be slowed or reduced
ELIMINATION	RENAL	• Reduction in renal function in elderly subjects (particularly GFR) affects clearance of many drugs such as water-soluble antibiotics, diuretics, digoxin, water-soluble beta blockers, lithium & NSAIDs • Clinical importance of reduced renal excretion is dependent on therapeutic index o Drugs with a narrow therapeutic index like aminoglycosides, digoxin, and lithium dosage adjusted, especially > 65 years
	HEPATIC	• Drugs can be classified into three groups according to their extraction rate: o <u>High > 0.7:</u> chlormethiazole, dextropropoxyphene, glyceryl nitrate, lignocaine, pethidine, propranolol o <u>Intermediate 0.3 – 0.7:</u> aspirin, codeine, morphine, triazolam o <u>Low < 0.3:</u> carbamazepine, diazepam, phenytoin, theophylline, warfarin • Several studies have shown reductions in clearance of drugs metabolized by phase-1 pathways in liver o Critical factor is probably age-related changes in liver size and hepatic blood flow o Activity of drug metabolizing enzymes is generally preserved

SPECIFIC DISEASE STATES IN THE ELDERLY:

CONGESTIVE HEART FAILURE	Digoxin	• Well-absorbed in the GIT, however in the elderly: o The time to peak plasma concentrations increases with age from 38h in younger pts to 69 h o Time to reach Css increases from 7 to 12 days o Vd is decreased • As a result, loading doses should be reduced by approx. 20% and daily doses are reduced
	Furosemide	• Vd similar in older subjects as compared with younger individuals • Reduced renal clearance and prolonged half-life • Reduced effects of furosemide with ageing seem to be due mainly to a decrease in tubular secretion, probably caused by reduction in renal plasma flow
	ACEI	• Common ACEI are activated in liver (i.e. enalapril, perindopril) – might be impaired in pts with severe CHF and hepatic congestion • Similarly, most ACEIs are excreted through kidney by glomerular filtration & tubular secretion o In presence of renal impairment, their plasma concentration increases = dose adjustments need to occur (especially when CrCl < 30 mL/min) • Newer ACEI (benazepril, fosinopril, spirapril, and zofenopril) are excreted through the bile route o Swapping drug regimens can be beneficial
ANTICOAGULANTS	Warfarin	• Higher inhibition of Vitamin K-dependent clotting factors at similar plasma concentrations of warfarin in elderly • Exact mechanisms responsible for the increased sensitivity are unknown
	Heparin	• Relationship between plasma heparin concentration & anticoagulant effect does not change
CV & RESP DRUGS	Verapamil	• Elderly are less sensitive to effect of verapamil on cardiac conduction, but effect on BP and HR tends to be greater in older than in younger patients
	Beta adrenorceptor	• Reduced beta adrenoreceptor function is observed with age • Elderly patients are less sensitive to the chronotropic effect of isoprenaline o Impaired response is due primarily to an age-related difference in reflex (vagal) CV effects on HR rather than b-adrenoreceptor sensitivity • Both salbutamol (b-2 adrenoreceptor agonist) & propranolol (beta adrenoreceptor antagonist) show reduced responses with age due to lower levels of 2nd messengers (not receptors or physiology) • Alpha adrenoreceptor drugs do not change
PSYCHOTROPIC DRUGS	• Elderly patients are particularly vulnerable to AEs from neuroleptics, including: delirium, EPS, arrhythmias, postural hypotension • Advancing age also associated with increased sensitivity to CNS effects of benzodiazepines o Sedation is induced by diazepam at lower doses and lower plasma concentrations in elderly subjects o Advancing age also associated with increased sensitivity to effects of nitrazepam, flurazepam, and loprazolam • Exact mechanism responsible for increased sensitivity are unknown	
DRUG INTERACTIONS	• Drug-drug interactions are more common in the elderly, as they become more co-morbid and take more drugs • The incidence of DDI increased exponentially with the number of drugs taken o At >4 drugs, DDI are almost certain to occur o Severity of DDI that requires monitoring and attention	