Specific Populations: Pediatrics, Pregnancy, Renal and Hepatic Impairment

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Objectives

- Awareness of physiological changes associated with specific populations and implications for drug dosing
- Be able to describe types of studies commonly done to determine dosing recommendations for specific populations

Overview

- Investigational drugs are typically studied in a fairly homogeneous population of healthy adults to evaluate pharmacokinetics, tolerability, food effect, etc
- Efficacy and safety studies in the disease population are less homogeneous but may still exclude a significant share of the population
  - Pediatrics, pregnant women, elderly, etc
- It may not be feasible to conduct efficacy and safety studies within each specific population. Efficacy and safety are first established in the general population.
- Dosing requirements are often determined for subgroups by comparing pharmacokinetics (PK) within the subgroup to PK within the general population

Overview

Specific populations that will be discussed

- Pediatrics
- Pregnancy
- Lactation
- Renal Impairment
- Hepatic Impairment
- Geriatrics

Specific populations that will not be discussed

- Sex
- Race
- Obesity
- Genetics

Pediatrics

- Developmental physiological changes during infancy and childhood have implications for drug dosing

Physiologic Factors	Difference Compared to Adults	PK Implications	Example Drug
Oral absorption			
Gastric pH	↑	↓ Bioavailability (weak acids)	Phenytoin, phenobarbital, ganciclovir
		↑ Bioavailability (weak bases)	Penicillin G, ampicillin, nafcillin
Gastric emptying time	↑	Delayed absorption	Phenobarbital, digoxin and sulfonamides
Intestinal CYP3A4	↓	↑ Bioavailability	Midazolam
Intestinal GST	↑	↓ Bioavailability	Busulfan
Intestinal drug transporters	↓	↓ Bioavailability	Gabapentin
Percutaneous absorption			
Hydration of epidermis	↑	↑ Bioavailability	Steroids
Intramuscular absorption			
Skeletal muscle blood flow	Variable	Unknown	n.a.
Distribution			
Body water : fat ratio	↑	↑ Volume of distribution (hydrophilic drugs)	Gentamicin, linezolid, phenobarbital, propofol
		↓ Volume of d istribution (lipophilic drugs)	Diazepam, lorazepam
Protein binding	↓	↑ Free fraction of drugs	Sulfonamides
Hepatic metabolism			
Phase I enzyme activity	↓	↓ Hepatic clearance	Theophylline, caffeine, midazolam
Phase II UGT enzyme activity	↓	↓ Hepatic clearance	Morphine
Renal excretion			
Glomerular filtration rate	↓	↓ Renal clearance	Aminoglycosides
Renal tubular absorption and secretion	↓	↓ Renal clearance	Digoxin

↑, changes increased in values; ↓, changes decreased in values; GST, glutathione S-transferase; n.a., not available; PK, pharmacokinetic; UGT, UDP glucuronosyltransferase.

Lu et at, JPPT, 2014

Pediatrics

- Pediatric participants can be included in clinical pharmacology studies if there is “no more than minimal risk” or a “minor increase over minimal risk”
- Patient population is enrolled (no healthy volunteer pediatric studies)
- Where disease course and drug response can be assumed to be similar in adults and the pediatric population, a PK and safety study may suffice for pediatric approval
- The purpose of the pediatric PK study is to identify the dose that results in similar exposures (Cmax, AUC, etc) as observed in adults in order to extrapolate efficacy from adults to pediatrics

General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products
https://www.fda.gov/media/90358/download

Pediatrics – example study

- Extrapolation of adult efficacy was used for adolescent approval of atazanavir (ATV) in combination with cobicistat (COBI) and darunavir (DRV) in combination with COBI for treatment of HIV
- Approved adult dosages were administered to adolescents with HIV
- Exposure differences in adolescents vs adults were observed (↑ATV, ↓DRV, comparable for COBI), but were deemed not clinically significant

Parameter Geometric Mean (CV%)	Cobicistat		Atazanavir	Darunavir
Treatment Administered	**TYBOST + Atazanavir**	**TYBOST + Darunavir**	**TYBOST + Atazanavir**	**TYBOST + Darunavir**
Pediatric Subjects[a]	N=12	N=7	N=12	N=7
AUC_{tau} (mcg·hr/mL)	12.11 (44.7)	8.33 (34.9)	49.48 (49.1)	77.22 (29.5)
C_{max} (mcg/mL)	1.28 (31.7)	1.10 (20.0)	4.32 (49.9)	7.32 (21.7)
C_{tau} (mcg/mL)	0.09 (156.2)	0.02 (123.9)[b]	0.91 (96.4)	0.68 (91.6)
Adults[c,d]	N=30[c]	N=21[d]	N=30[c]	N=21[d]
AUC_{tau} (mcg·hr/mL)	9.65 (41.8)	7.69 (43.9)	39.96 (52.1)	90.56 (45.3)
C_{max} (mcg/mL)	1.28 (35.6)	1.04 (35.3)	3.54 (45.8)	8.34 (33.3)
C_{tau} (mcg/mL)	0.04 (112.7)	0.02 (135.1)[e]	0.58 (84.7)	1.00 (108.0)

Source: Tybost® labeling

Pregnancy

- Physiological changes during pregnancy in general peak during the second trimester and have implications for drug dosing

System (reference)	Parameter	Non-pregnant	Pregnant
Cardiovascular[64,71,72]	Cardiac output [L/min]	4.0	6.0
	Heart rate [beats per min]	70	90
	Stroke volume [mL]	65	85
	Plasma volume [L]	2.6	3.5
Respiratory[73,74]	Total lung capacity [mL]	4225	4080
	Residual volume [mL]	965	770
	Tidal volume [mL]	485	680
Liver[75]	Portal vein blood flow [L/min]	1.25	1.92
	Hepatic artery blood flow [L/min]	0.57	1.06[a]
Renal[76]	Glomerular filtration rate [mL/min]	97	144
	Serum creatinine [mg/dL]	0.7	0.5

[a]Not statistically significant.

Enzyme (references)	Pregnancy-induced change	Potential substrates in obstetrics
CYP3A4[19,20,77,78]	Increased	Glyburide, nifedipine, and indinavir
CYP2D6[77,79]	Increased	Metoprolol, dextromethorphan, paroxetine, duloxetine, fluoxetine, and citalopram
CYP2C9[18,80]	Increased	Glyburide, NSAIDs, phenytoin, and fluoxetine
CYP2C19[18,80]	Decreased	Glyburide, citalopram, diazepam, omeprazole, pantoprazole, and propranolol
CYP1A2[17,23,77,81]	Decreased	Theophylline, clozapine, olanzapine, ondansetron, and cyclobenzaprine
UGT1A4[82–84]	Increased	Lamotrigine
UGT1A1/9[25]	Increased	Acetaminophen
NAT2[17,24,85]	Decreased	Caffeine

Increased enzyme activity = faster metabolism = higher dose needed

Feghali et al, Semin Perinatol, 2015

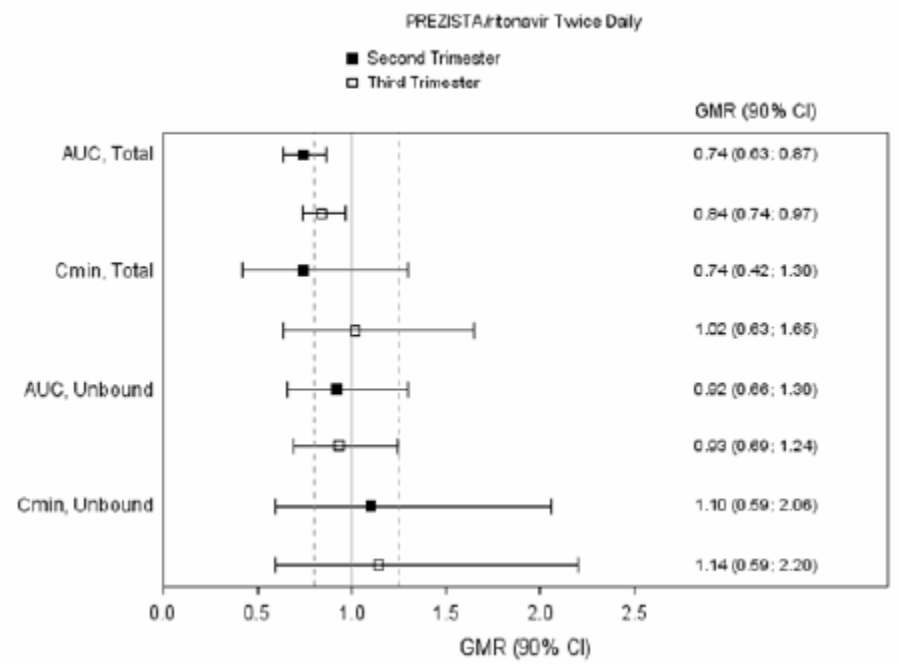
Pregnancy

- Pregnant women can be included in PK studies if prior animal and human studies demonstrate minimal risk to the fetus
- Patient population is enrolled (no healthy volunteer studies)
- To determine the need for dose adjustment during pregnancy, the recommended study design is to compare drug pharmacokinetics (PK) during pregnancy compared to baseline.
  - Baseline is typically postpartum
  - For highly protein bound drugs it is recommended to measure unbound drug concentrations

Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling
https://www.fda.gov/media/71353/download

Pregnancy – example study

- The PK of darunavir (DRV) in combination with ritonavir (RTV) was evaluated in pregnant women with HIV
- The approved dose for non-pregnant adults was administered during pregnancy and postpartum. Total and unbound DRV was measured.
- Based on the observation of similar unbound exposure during pregnancy vs postpartum, DRV twice daily with RTV is approved for use during pregnancy



Source: Prezista® labeling. GMR = geometric mean ratio; CI = confidence interval

Lactation

- Women take an average of four medications during lactation
- Decisions regarding drug therapy and continuation of breastfeeding during therapy are often made in the absence of data
- Clinical lactation studies are recommended where the drug is expected or known to be used by women of reproductive age or lactating women

Wang et al, 2017, CPT

Clinical Lactation Studies: Considerations for Study Design
https://www.fda.gov/media/124749/download

Lactation

- The Pregnancy and Lactation Labeling (Drugs) Final Rule, effective 2015, requires a summary of known data regarding the following (or a statement that the information is unknown):
  - Presence of a drug and/or its active metabolite(s) in human milk
  - The effects of a drug and/or its active metabolite(s) on the breastfed child
  - The effects of a drug and/or its active metabolite(s) on milk production

Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format
https://www.fda.gov/media/90160/download

Lactation – recommended study design

- FDA recommends a milk-only study in lactating women. If clinically relevant drug concentrations are found in breast milk, further studies may be needed.
- Goals of the milk-only study are to quantify the amount of a drug transferred into breast milk and evaluate effect of a drug on milk production
- Generally, it is recommended to collect the entire milk volume from both breasts over 24 hours at steady state

Clinical Lactation Studies: Considerations for Study Design
https://www.fda.gov/media/124749/download

Lactation – recommended study design

- Daily infant dosage from breastfeeding should be reported using either of the following methods:
  - Drug concentration in milk **X** milk volume consumed per day
  - Maternal milk-to-plasma concentration ratio **X** average maternal plasma concentration **X** daily infant milk intake volume
- Relative infant dose (infant dosage/maternal dosage) should be reported. Or if the drug is approved for infants, estimated daily infant dosage from breastfeeding should be compared to the approved dose.

Clinical Lactation Studies: Considerations for Study Design
https://www.fda.gov/media/124749/download

Lactation – example study

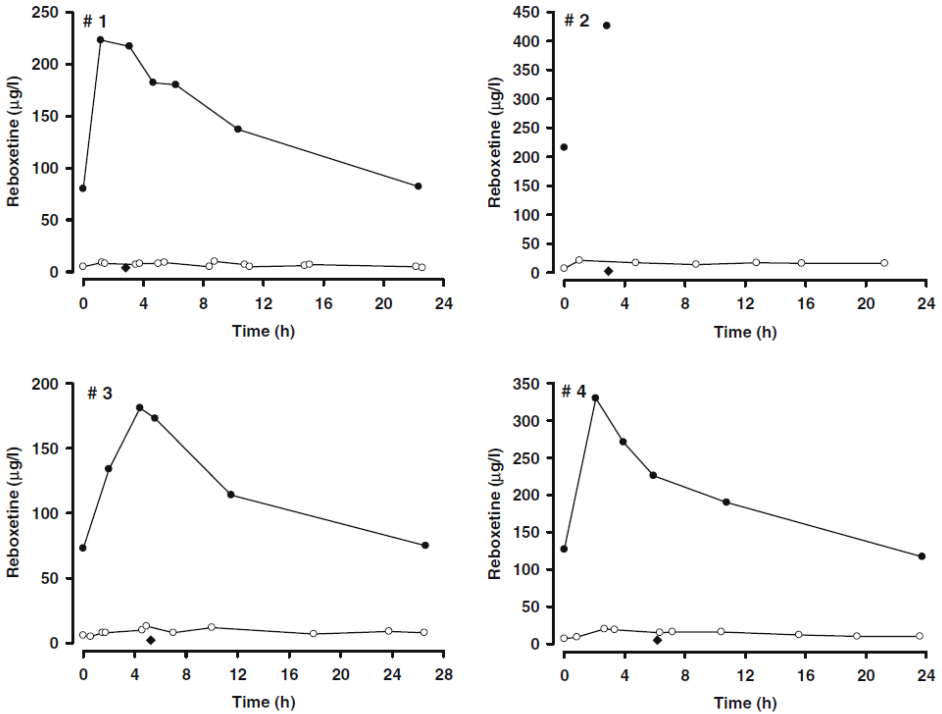


Fig. 1 Milk (○)and plasma (●) concentration-time profiles over a dose interval at steady-state following the morning reboxetine dose (time zero) in patients 1, 2, 3, and 4. The concentration of reboxetine in the breastfed infant's plasma is also shown relative to the mother's reboxetine dose (◆). Note that the value for the infant of patient 2 is shown as the LOD for the sample (4 µg/l)

Study enrolled four breastfeeding women treated with reboxetine (antidepressant not approved in the US) for post-natal depression

Hackett et al, 2006, Eur J Clin Pharmacol

Lactation – example study

Table 2 Reboxetine C_{max}, t_{max} and C_{av} for milk and plasma, and M/P_{AUC} estimates

Patient	Milk			Plasma			M/P_{AUC}
	C_{max} (µg/l)	t_{max} (h)	C_{av} (µg/l)	C_{max} (µg/l)	t_{max} (h)	C_{av} (µg/l)	
1	10	8.8	6.7	223	1.2	142	0.05
2	21	1.0	16.3	–[b]	–[b]	321[c]	0.05
3	12.5	5.8	8.9	181	4.2	115	0.08
4	20	2.7	13.5	330	2.1	191	0.07
Mean	16	4.3	11.3	245	2.1	192	0.06
(95% CI)	(7, 25)	(1.9, 7.3)[a]	(4.4, 18.2)	(54, 436)	(1.4, 3.7)[a]	(37, 337)	(0.03, 0.09)

[a]Median (25th and 75th percentiles); [b] insufficient data to estimate values; [c] mean of 2 observations

Table 3 Maternal dose of reboxetine, absolute and relative infant doses, and infant plasma concentrations of reboxetine

Patient	Maternal dose (µg/kg/day)	Absolute infant dose (µg/kg/day)	Relative infant dose (%)[a]	Infant plasma concentration (µg/l)
1	44	1.0	2.3	<4.0
2	172	2.4	1.4	2.6
3	54	1.3	2.5	2.3
4	104	2.0	2.0	5.0
Mean	79	1.7	2.0	
(95%CI)	(49, 138)[b]	(0.7, 2.7)	(1.3, 2.7)	

[a]Calculated from the primary data, [b] median (25th and 75th percentiles)

Hackett et al, 2006, Eur J Clin Pharmacol

Renal Impairment

- In adults, renal function decreases with age
- For drugs eliminated renally, to avoid adverse events dose adjustments may be needed for patients with renal impairment. However, regardless of how the drug is eliminated, renal impairment can affect drug metabolism and transport.
- Because exposures of both renally and non-renally eliminated drugs can be impacted by renal impairment, renal impairment PK studies are recommended for most drugs intended for chronic use.
- Typically single dose studies. Enrollment of those with renal impairment (mild, moderate, and/or severe) and a group of controls with similar demographics (such as age and gender). Primary endpoint is PK.

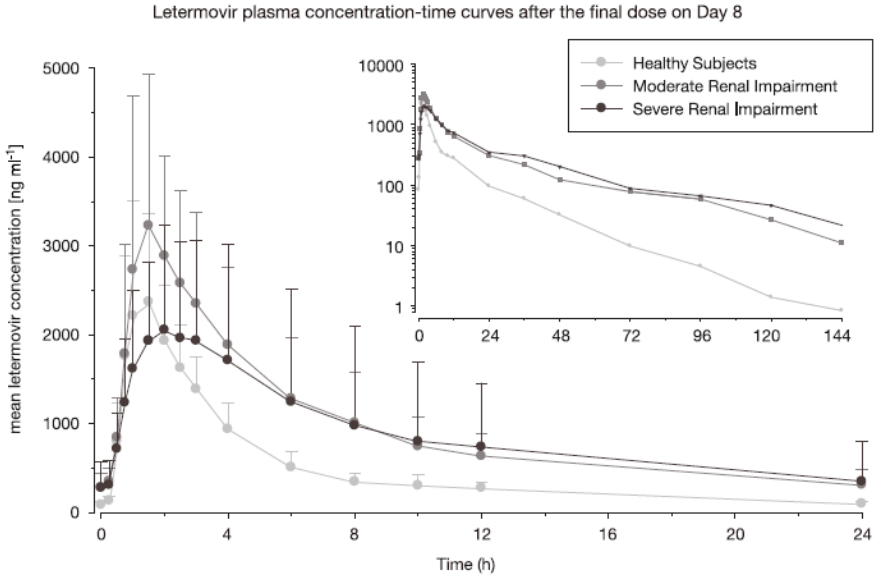
Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling
https://www.fda.gov/media/78573/download

Renal Impairment – example study

- Dedicated PK study in the non-disease population: The PK of total and unbound letermovir was evaluated in subjects with moderate or severe renal impairment, in comparison to subjects with normal renal function. Despite <2% of the dose being excreted in urine (drug is primarily eliminated by metabolism), higher exposures were observed in subjects with renal impairment (see figure).

- Phase 3 study in the transplant population: No adverse events were identified as being associated with drug exposure. Renal impairment (mild and moderate) was not associated with exposure changes in the phase 3 study.

- Despite ~2-fold higher exposures in renal impairment, no dose adjustment is recommended



Sources: Prevymis® labeling, NDA 209939 Clinical Pharmacology Review (https://www.accessdata.fda.gov/scripts/cder/daf/), Kropeit et al, Br J Clin Pharmacol, 2017

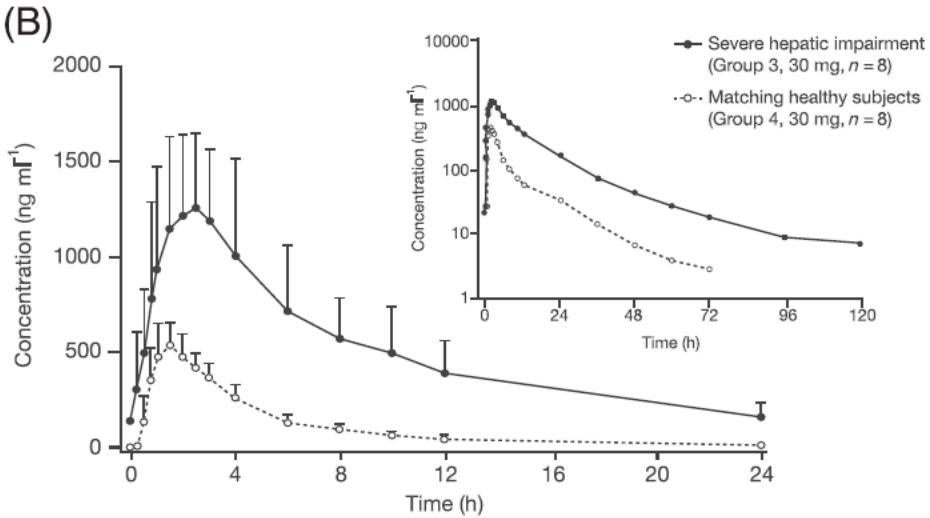
Hepatic Impairment

- Many drugs are primarily eliminated by metabolism. Liver disease can result in reduced metabolism and resulting increased drug exposures.
- A hepatic impairment PK study is recommended for drugs where hepatic metabolism and/or excretion accounts for >20% of total elimination
- Degree of liver function estimated according to Child-Pugh category
- Single dose study is acceptable if the drug has dose-proportional kinetics. Enrollment of those with hepatic impairment (mild, moderate and/or severe) and matched controls.

Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling
https://www.fda.gov/media/71311/download

Hepatic Impairment – example study

- The PK of total and unbound letermovir was evaluated in subjects with moderate or severe hepatic impairment, in comparison to subjects with normal hepatic function
- ~60% higher mean total exposures in moderate hepatic impairment vs healthy subjects (not statistically significant, data not shown). No dose adjustment recommended.
- Mean 3.8-fold higher total exposure in severe hepatic impairment vs healthy subjects (see figure). Use in severe hepatic impairment not recommended.



Sources: Prevymis® labeling, NDA 209939 Clinical Pharmacology Review (https://www.accessdata.fda.gov/scripts/cder/daf/), Kropeit et al, Br J Clin Pharmacol, 2017

Geriatrics

- Small molecule drugs are eliminated by renal and/or hepatic elimination
- Decreases in renal function and decreased function of certain drug metabolizing enzymes have been associated with aging

Route of inactivation	Change
Renal	
Filtration	↓
Secretion	↓
Reabsorption	↓
Hepatic	
Oxidation (CYP)	↓↔
CYP1	?↓
CYP2C, CYP2D, CYP2E	?↓
CYP3A	↓
Conjugation	↔

Schwartz et al, 2009, CPT

Geriatrics

- Age-related changes in the central nervous system and autonomic responses have also been observed
- These changes may be responsible for the following in older patients:
  - Benzodiazepines: Sedation and cognition
  - Opiate agonists: CNS depression
  - Antihistamines and neuroleptics: Delirium and disorientation

Effector	Change
Central nervous system	
Dopaminergic D_1, D_2	↓
Serotonergic $5HT_{1A}$, $5HT_{2A}$	↓
Muscarinic cholinergic M_1	↓
Acetylcholinesterase	↓
β-Adrenergic	↓
α-Adrenergic	↔
GABAergic	?
Enkephalin/endorphin	?
Autonomic nervous system	
β_1,β_2-Adrenergic	↓
α_1-Adrenergic	↔↓
Dopaminergic	↓
Parasympathetic responses	↓
Baroreflex function	↓↓

Schwartz et al, 2009, CPT

Geriatrics – example study

- Zolpidem (sedative-hypnotic) labeling specifies lower doses for elderly or debilitated patients, females and patients with hepatic impairment
- Elderly patients “may be especially sensitive to the effects of zolpidem”
- In one study, higher exposures in the elderly were observed among females but not males

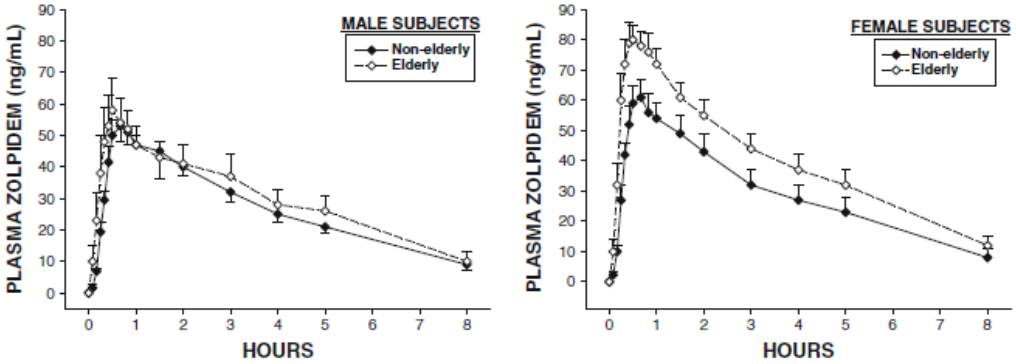


Fig. 1 Mean (± standard error) plasma zolpidem concentrations for the first 8 h after a 3.5 mg dose of zolpidem administered as sublingual zolpidem tablets (ZST) to healthy elderly and non-elderly male (*left*) and female (*right*) volunteers

Ambien® labeling
Greenblatt et al, 2014, Drugs Aging

Conclusions

- In comparison to past decades, increasing attention is paid to the need to include patients from all segments of society into clinical studies so that there are fewer gaps in drug labeling recommendations

- With the exception of geriatrics, FDA guidance documents are available to assist investigators in designing studies in the specific populations described in this talk

Challenge Question 1

- Name two assumptions that should be justified to extrapolate adult efficacy to the pediatric population

Challenge Question 2

- Total drug concentrations are typically measured in PK studies. What additional type of drug concentrations may also need to be measured in pregnancy or organ impairment PK studies?