ACoP8 October 16, 2017

Quantification of Covariate Effects for Labeling

Points to Consider when Making Inferences about Covariates

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Informing the Drug Label: Dosage and Administration

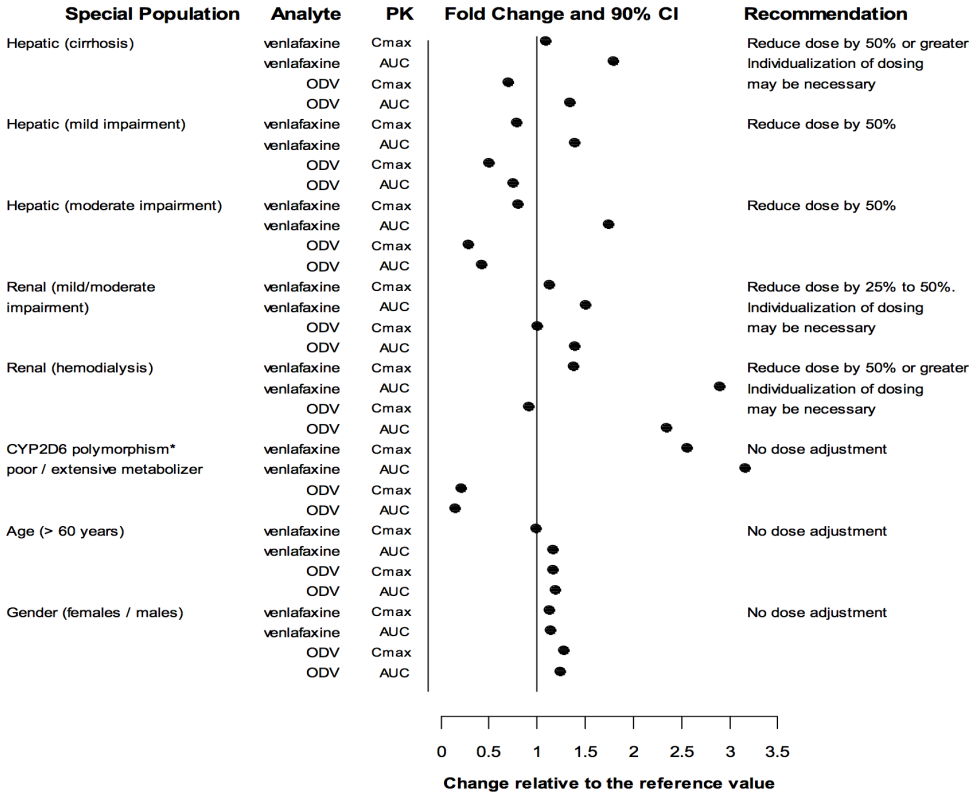
---------- DOSAGE AND ADMINISTRATION----------

Indication	Starting Dose	Target Dose	Maximum Dose
MDD (2.1)	37.5 -75 mg/day	75 mg/day	225 mg/day
GAD (2.2)	37.5 -75 mg/day	75 mg/day	225 mg/day
SAD (2.3)	75 mg/day	75 mg/day	75 mg/day
PD (2.4)	37.5 mg/day	75 mg/day	225 mg/day

- Take once daily with food (2). Capsules should be taken whole; do not divide, crush, chew, or dissolve (2).
- When discontinuing treatment, reduce the dose gradually (2.8, 5.7).
- Renal impairment: reduce the total daily dose by 25% to 50% in patients with renal impairment. Reduce the total daily dose by 50% or more in patients undergoing dialysis or with severe renal impairment (2.6).
- Hepatic impairment: reduce the daily dose by 50% in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment or hepatic cirrhosis, it may be necessary to reduce the dose by more than 50% (2.6).

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020699s107lbl.pdf

Informing the Drug Label: Special Populations



Abbreviations: ODV, O-desmethylvenlafaxine; AUC, area under the curve; Cmax, peak plasma concentrations;
*Similar effect is expected with strong CYP2D6 inhibitors

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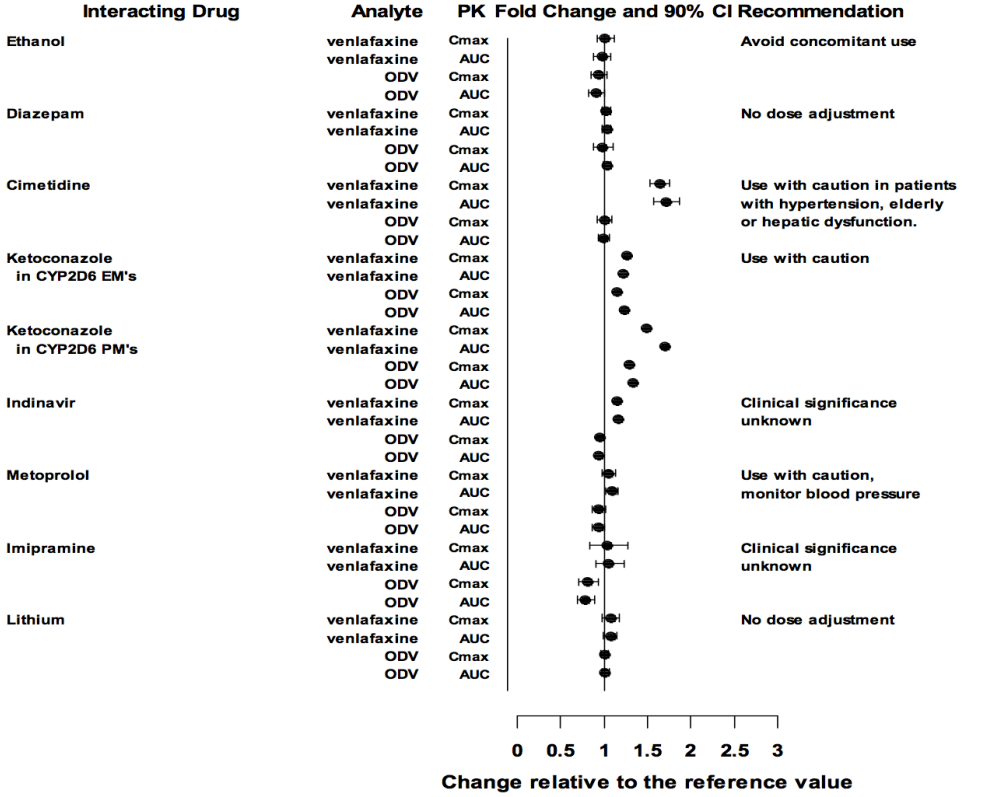
Informing the Drug Label: Drug Interactions

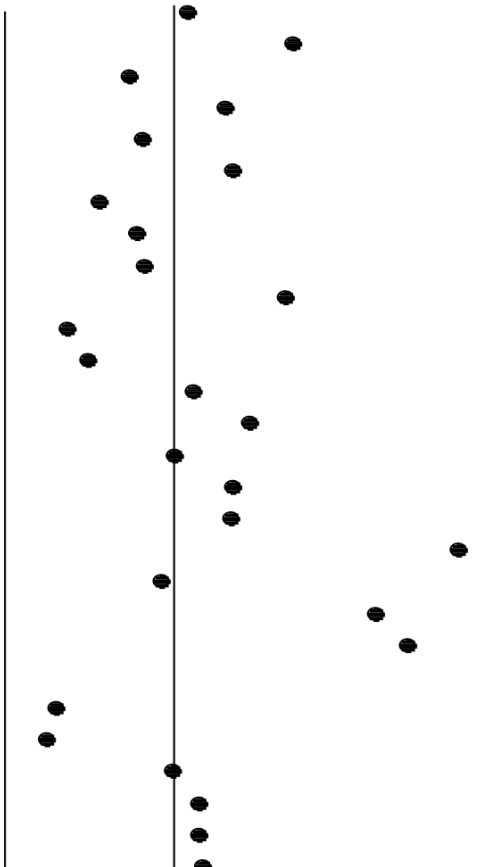


Abbreviations: ODV, O-desmethylvenlafaxine; AUC, area under the curve; Cmax, peak plasma concentrations; EM's, extensive metabolizers; PM's, poor metabolizers

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020699s107lbl.pdf

Informing the Drug Label: Special Populations (zoom-in)

Special Population	Analyte	PK	Fold Change and 90% CI	Recommendation
Hepatic (cirrhosis)	venlafaxine	Cmax		Reduce dose by 50% or greater
	venlafaxine	AUC		Individualization of dosing
	ODV	Cmax		may be necessary
	ODV	AUC		
Hepatic (mild impairment)	venlafaxine	Cmax		Reduce dose by 50%
	venlafaxine	AUC		
	ODV	Cmax		
	ODV	AUC		
Hepatic (moderate impairment)	venlafaxine	Cmax		Reduce dose by 50%
	venlafaxine	AUC		
	ODV	Cmax		
	ODV	AUC		
Renal (mild/moderate impairment)	venlafaxine	Cmax		Reduce dose by 25% to 50%.
	venlafaxine	AUC		Individualization of dosing
	ODV	Cmax		may be necessary
	ODV	AUC		
Renal (hemodialysis)	venlafaxine	Cmax		Reduce dose by 50% or greater
	venlafaxine	AUC		Individualization of dosing
	ODV	Cmax		may be necessary
	ODV	AUC		
CYP2D6 polymorphism* poor / extensive metabolizer	venlafaxine	Cmax		No dose adjustment
	venlafaxine	AUC		
	ODV	Cmax		
	ODV	AUC		
Age (> 60 years)	venlafaxine	Cmax		No dose adjustment
	venlafaxine	AUC		
	ODV	Cmax		
	ODV	AUC		



https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020699s107lbl.pdf

Informing the Drug Label: Study Design and Analysis

- Dedicated Clinical Pharmacology Studies
  - Single clinical trial with primary goal of assessing covariate effect
  - Randomization, Stratification, Test and Reference Control
  - Sample size justification based on expected power
  - Typically, otherwise healthy volunteers
  - Extensive PK sampling and simple data analysis (NCA)

Informing the Drug Label: Age and Gender (Model-Based)

8.6 Age and Gender

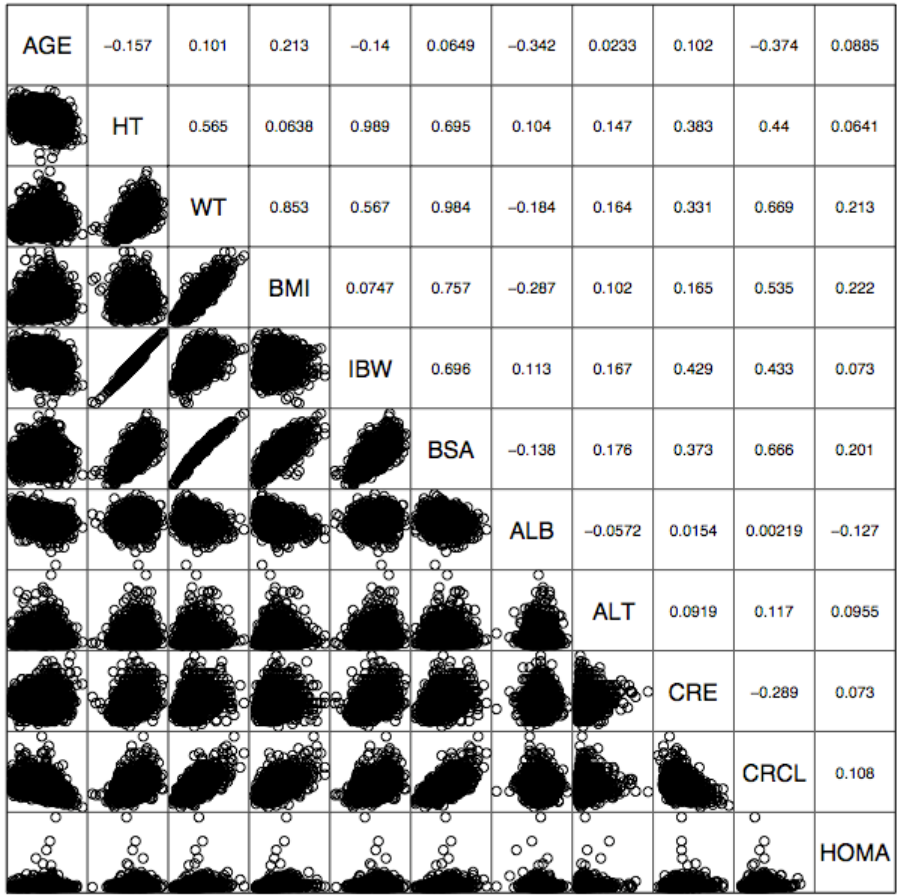
A population pharmacokinetic analysis of 404 Effexor-treated patients from two studies involving both twice daily and three times daily regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary [*see Dosage and Administration (2.6)*] (see Table 15).

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020699s107lbl.pdf

Informing the Drug Label: Study Design and Analysis

- Population PK(PD) Studies
  - Often pooled data – cross-study comparisons
  - Covariate effect assessment is not primary goal
  - Typically no randomization, stratification, or control for covariates
  - Target patient population
  - Model-based analysis

Correlation and Collinearity



Covariate effects to be included in model should be independent, e.g. they carry unique information.

Rule of thumb:
Be cautious when |corr. coef.| > 0.3

See:

Pharmaceutical Research, Vol. 16, No. 5, 1999

The Effect of Collinearity on Parameter Estimates in Nonlinear Mixed Effect Models

Peter L. Bonate[1,2]

Appropriate Inference About Covariates?

Table III (continued)

Model	Question	Equation	Objective Function	Conclusion (Significance = Yes)
Model 15	Does condition (Healthy/asthmatic) affect the volume of distribution (V2) (LINEAR MODEL)?	TVKA = θ (1) TVCL = θ (2) TVV2 = θ (3)*COND + θ (4)*(1 – COND) θ (1) = 4.42 h^{-1} ω1 = 20% θ (2) = 392 L/h ω2 = 64.18% θ (3) = 1170 L ω3 = 40.74% θ (4) = 1510 L	–9603	No
Model 16	Does condition (Healthy/asthmatic) affect the clearance (POWER MODEL)?	TVKA = θ (1) TVCL = θ (2)* θ (3)**COND TVV2 = θ (4) θ (1) = 4.42 h^{-1} ω1 = 20% θ (2) = 363 L/h ω2 = 7.07E–4% θ (3) = 468 ω3 = 38.72% θ (4) = 1720 L	–240	No
Model 17	Does condition (Healthy/asthmatic) affect the clearance (LINEAR MODEL)?	TVKA = θ (1) TVCL = θ (2)*COND + θ (3)*(1 – COND) (TVV2 = θ (4) θ (1) = 4.42 h^{-1} ω1 = 20% θ (2) = 384 L/h ω2 = 61.6% θ (3) = 438 L/h ω3 = 41.47% θ (4) = 1180 L	–9598	No
Model 18	Does weight affect clearance and volume of distribution (POWER MODEL)?	TVCL = θ (2)*(WT/75)** θ (3) TVV2 = θ (4)*(WT/75)** θ (5) θ (2) = 393 L/h ω2 = 60.8% θ (3) = 0.56 ω3 = 40% θ (4) = 1220 L θ (5) = 1.28	–9738	Yes

Appropriate Inference About Covariates?

Covariate Effects:

Creatinine clearance was the most significant covariate on [redacted] clearance. The clinical importance of this finding is unknown, since less than 2% of [redacted] dose is excreted in the urine. This may be an artifact of the data as the current analysis data set did not include patients with moderate or severe renal impairment. Weight, age and sex were not significant covariates and, therefore, require no dose adjustment.

Statement of the Problem

How to inform labeling given sparse population PK(PD) data and model-based analyses?

- Independent (marginal) inferences about each covariate
- Accurate estimation of covariate effect magnitude
- Precision of covariate effect estimate

Different Objectives of Covariate Model Development

- Understand causes of variability and apply the knowledge
  - For better clinical therapeutic use (dosing, adjustment, labeling)
  - To allow for better control in clinical trials
  - In other words, make causal inferences about covariate effects from modeling results

- Improve predictions of the dependent variable
  - For subjects in the current data set
  - For simulation of future studies
  - For future patients

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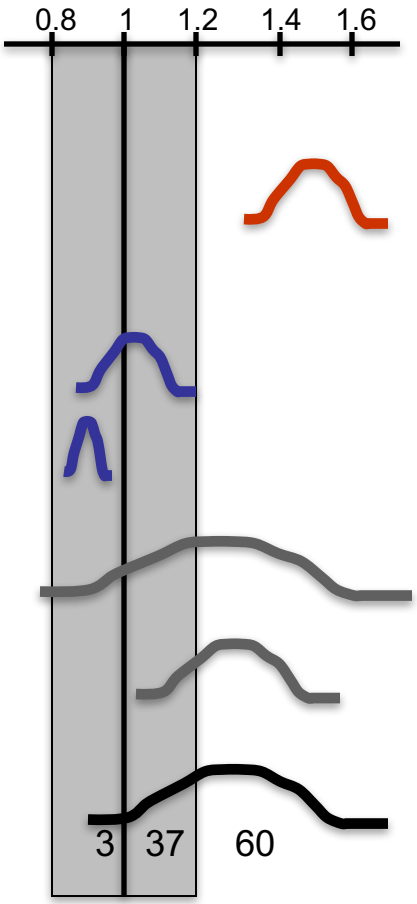
Inferences Based on Posterior Distribution of Effect



First, define effect magnitude likely to be clinically important (e.g. greater than +/- 20% of null value)

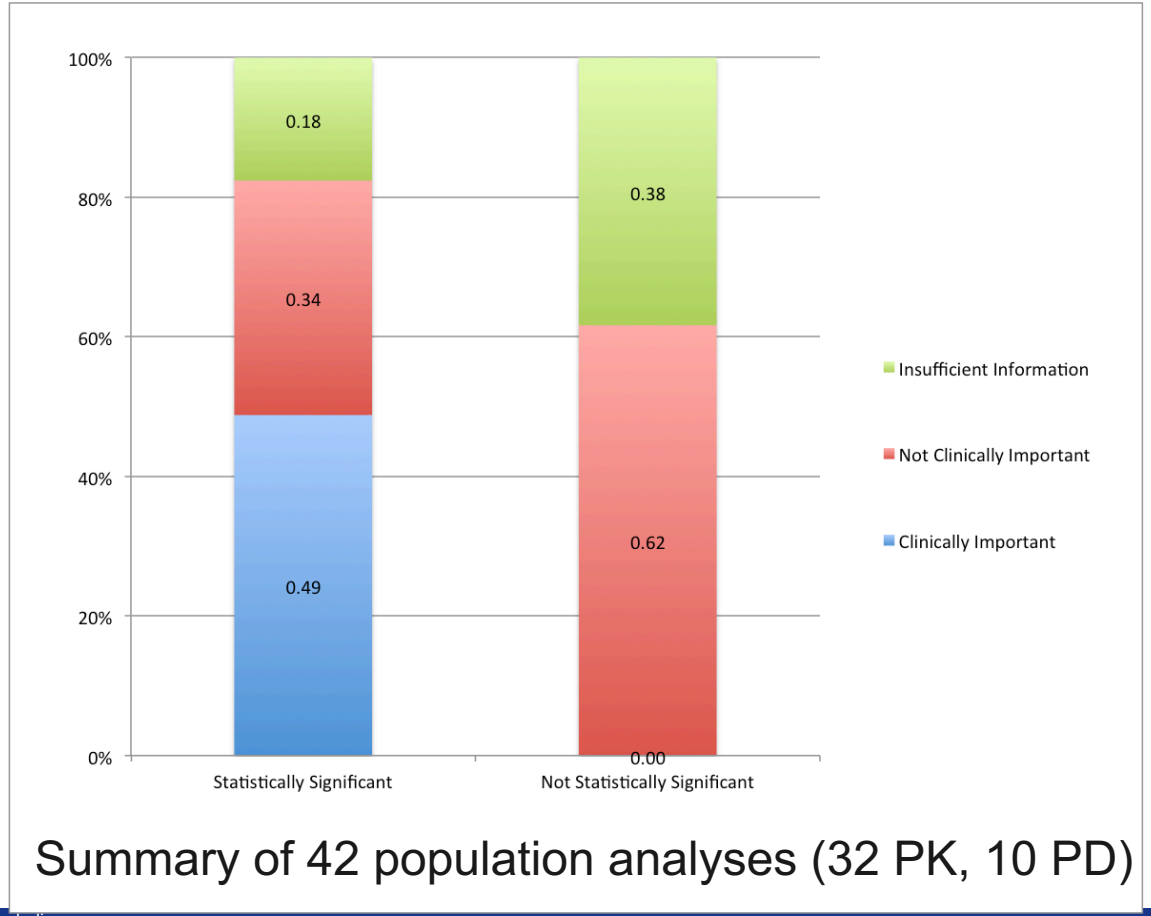
Clinically Important: Entire 95% interval of posterior distribution for covariate effect lies within clinically important region (always SS)

Not Clinically Important: Entire 95% interval of posterior distribution for covariate effect lies within clinically unimportant region. May be important in combination with other effects. (NSS or SS)

Insufficient Information: 95% interval of posterior distribution for covariate effect spans across values of covariate effect that are both clinically important and unimportant. (NSS or SS)

Or… Probabilistic Approach: Quantitatively describe probability of being clinically important using posterior distribution and reference range.

Estimation of Effect Magnitude and Precision vs. Stepwise P-Value



Summary of 42 population analyses (32 PK, 10 PD)

A Purpose-Driven Parsimony Principle

"When competing hypotheses are equal in other respects, select the hypothesis that introduces the fewest assumptions and postulates the fewest entities while still sufficiently answering the question."

-Occam's razor

- Stepwise p-value reduced models do not allow for inferences about "non-significant" covariate effects and result in biased standard errors and point estimates. They do not sufficiently answer the question about clinical importance of covariate effects.
- For the purpose of making inferences about covariate effects, a model which includes the covariates of interest is the most parsimonious model.

Pre-Specified Covariate Plan

Covariate	Model Parameters	Rationale
Weight	CL, V1, Q, V2	Clinical interest
Age	CL	Clinical interest
Race	CL, V1	Clinical interest. Bridging goal.
Disease State Type	CL	Clinical interest
Child-Pugh Score	CL	Clinical interest. Prior knowledge of hepatic elimination mechanism; CYP3A4
Drug X Interaction	CL	Clinical interest. Known CYP3A4 inhibitor and common con-med
etc…		

"The data analyst knows more than the computer… failure to use that knowledge produces inadequate data analysis".

- Henderson and Velleman. Building multiple regression models interactively. 1981, *Biometrics 37: 391–411.*

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