Disclosures

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I will present examples that evaluate off label dosing of approved medications.
Objectives

• Discuss the need to evaluate the gap between the phase III study sample and real-world patient population

• Review the pharmacometric considerations to developing precision dosing strategies

• Discuss advances in the electronic patient care environment that can facilitate precision dosing
Current Basis for Drug Dosing

1. Clinical trial evidence for approval

2. Bridging
   a. **Pharmacokinetic/pharmacodynamic modeled link to outcome** [e.g., 1st dose & adjustment to a biomarker associated with outcome]
   b. **Pharmacokinetic bridging.** Determine dosing to match exposure for patients outside the pivotal trial experience (e.g., renal failure, pediatrics) to a reference PK drug profile associated with favorable efficacy/safety
What’s the Problem with this Approach?

1. A large fraction of the real-world patient population excluded
   a. Patients at the extremes of age, size, and organ function may not be studied, and the data needed to inform dosing for these patients may not be collected
   b. Results in a delay (or a lack of) dosing recommendations for special populations (e.g., pediatric patients, pregnant women)

2. The drug label usually has univariate dosing recommendations (e.g., based on renal function), whereas dosing may be dependent on multiple factors observed together in the same patient (e.g., renal failure, drug interactions, genetic variation)

3. The above issues may not be improved over the drug product cycle, and there may not be an update to reflect the real-world patient population experience once generics are approved
As many as 58% of Real-World Patients may be Excluded from Clinical Research

Phase III – Real-World Patient Gap

Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals
A Systematic Sampling Review

- Potential participants were excluded from trial participation due to medical comorbidities in 81.3% of the RCTs
- Patients <16 and >65 years of age were excluded from 60.1% and 38.5% of RCTs, respectively
- Participants receiving commonly prescribed medications were excluded in 54.1% of trials

Phase III – Real-World Patient Gap

• Why characterize the gap?
  • There may be differences in dose-exposure and exposure-response relationships between phase III and real-world patients

• Which patient characteristics are likely to exist for real world patients for many drugs?
  • Age extremes (neonate-110 years)
  • Size extremes (adult 30-250 kg)
  • Pregnancy & immediately post-pregnancy
  • Varying renal and liver function
  • Relevant genotypes
  • Drug-drug interactions

• When to characterize the gap?
  • Phase I-II

• How to evaluate the gap?
  • Best practice recommendations are needed (e.g., data source, methodology)

• How to communicate the gap?
  • To FDA: End of phase II meeting and assessment made public
  • To public: product label
Applications of Pharmacometrics in Drug Development, Regulatory Review, and Post-Approval

Target Knowledge Integration → Learning

- Preclinical Development
- Clinical Development
- Regulatory approval
- Therapeutic Use in Patients

Likely Impact:
- **Patients**: Better drugs for more patients
- **Sponsor**: Greater trial & market predictability
- **Payers**: Improved health care quality and reduced costs
- **FDA**: More effective regulatory reviews
Predicted Rivaroxaban AUC for Labeled Dosing in Varying CrCl

Proposed CrCl-Based Dosing Strategy


Unpublished Data Removed
Unpublished Data Removed
Simulations Suggest Benefit of Model-Based Dosing for Infliximab

Circles and error bars represent median and interquartile range for each covariate subpopulation, respectively. Target trough concentration: 3 mg/L.


Numbers above error bars: Proportion of individuals developing anti-drug antibodies.
Morphine Precision Dosing in Neonates

Potential target range (10-30 ng/mL)

Bayesian estimation and dose adjustments

Example case: PMA=40 weeks, PNA=2 days, BW=3.5 kg ↓ Timed PK sample collection

Scientific Challenges Related to Model-Informed Precision Dosing

1. Model selection
   • Some times many models may be available -> which one do you select?
   • Predictive performance of the model -> does it work well in my patient population?
   • There is a model published, but patients at the extremes are not represented -> can we access the raw data to merge it with new data and update the model?

2. Model qualification
   • Covariate-based *a priori* dosing and TDM-based *a posteriori* dosing -> does the model perform as expected?

3. Model bias
   • Bias resulting from differences in patient characteristics, parameters estimates, missing or erroneous data, and selection bias -> how to handle it?

4. Interoccasion variability
   • Time varying changes in pharmacokinetics/pharmacodynamics-> how to handle it?

Future Directions to Facilitate Precision Dosing

• Quantitate the phase III-real-world patient gap
• PK sampling in phase III trial to relate exposure to outcome
• Availability of clinical data to evaluate dose-exposure and exposure-response relationships across real-world patient populations (e.g., obese, geriatrics, pediatrics)
• Clinical decision support tools to deliver dosing recommendations to prescribers and patients
• Multistakeholder collaborations will be important to validate, implement, and demonstrate the value of precision dosing tools
• Regulatory incentive or requirement
EHR Environment and Precision Dosing

- In 2015, >8 in 10 non-federal acute care hospitals in the U.S. had adopted a basic electronic health record (EHR) system, which will facilitate precision dosing

- Availability of machine learning and artificial intelligence

- Advances in digital health technologies (e.g., mobile applications, wearable devices)

https://dashboard.healthit.gov/

CPOE: computer provider order entry
CDS: clinical decision support
Application of AI to Optimize Drug Dosing

MIMIC-III: Medical Information Mart for Intensive Care version III
eRI: eICU Research Institute Database

Patients that Received Doses Similar to the AI Recommended Dose had a Better Outcome

- Excess dose refers difference between the given and suggested dose averaged over all time points per patient.

- Dose-dependent changes in mortality were observed when administering more or less than the AI recommended vasopressor dose.
Precision Dosing – Why Now?

• The need to study drugs in more diverse patient populations is now more widely recognized

• Pharmacometrics can be applied to characterize differences in drug exposure and response at the extremes of age, and allow for model-informed precision dosing

• Widespread adoption of electronic health record systems will facilitate precision dosing

• Application of machine learning and artificial intelligence to improve drug treatment strategies
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