FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Clinical Pharmacology Strategies for New Drug Evaluation in Older Adults

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Outline

- Clinical pharmacology considerations in older adults
- Limitations of current paradigm in drug development
- Strategies for advancing new drug evaluation in older adults

Impact of Aging on Pharmacokinetics

ABSORPTION

- ↑gastrointestinal transit time
- ↑gastric pH
- ↓ splanchnic blood flow

METABOLISM

- ↓ hepatic blood flow
- ↓ production and flow of bile
- ↓ capacity of phase I enzymes *(frailty)*
- ↓capacity of phase II enzymes?

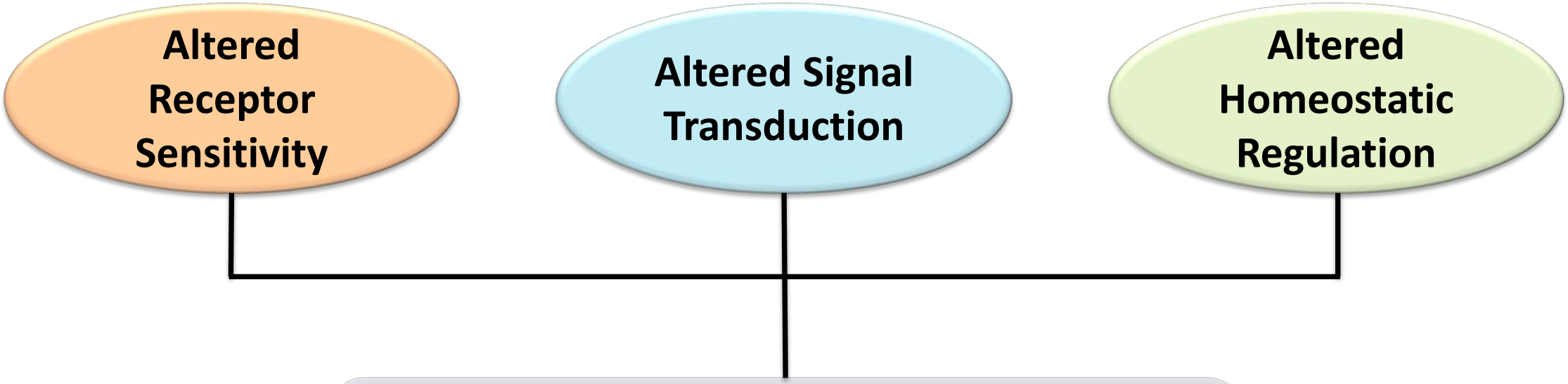
DISTRIBUTION

- ↓muscle mass
- ↓ total body water
- ↑overall adiposity
- ↓ Pgp function at the blood-brain-barrier

ELIMINATION

- ↓ renal blood perfusion
- ↓ glomerular filtration
- ↓ tubular secretion and reabsorption

Impact of Aging on Pharmacodynamics



- ↓ sensitivity and uncertain effect
- ↑sensitivity and exaggerated response
- ↑ risk of adverse drug reactions

Multimorbidity and Polypharmacy

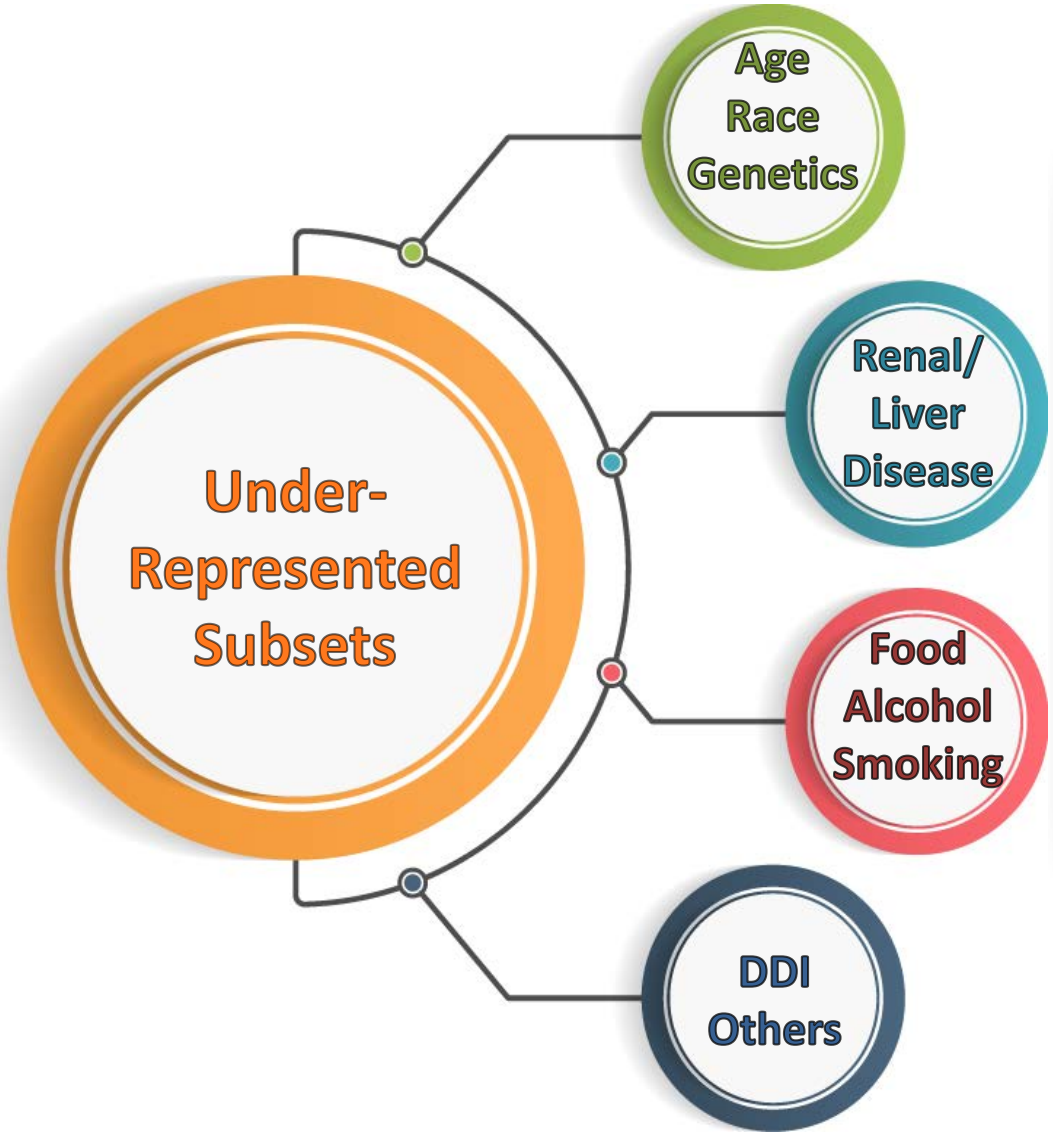
- Risk of developing chronic illness increases with aging
- Prevalence estimate of multiple chronic illness among older adults (age ≥ 65 y) is 64%

- Polypharmacy prevalent in older adults
- 40% taking 5 – 9 medications
- 18% taking 10 or more

- Increased risk for unexpected and complex drug interactions
- Increased risk of adverse drug events

http://dx.doi.org/10.5888/pcd17.200130 *DOI: 10.1056/NEJMsa1103053*

Current Paradigm:
Bridging the Gap for Under-Represented Subsets



- Any factor that affects ADME can result in altered blood levels and may lead to altered benefit-risk
- Stand-alone clinical pharmacology studies and PopPK approaches can characterize the magnitude of alteration
- Dosing derived by “exposure-matching” compared to healthy control

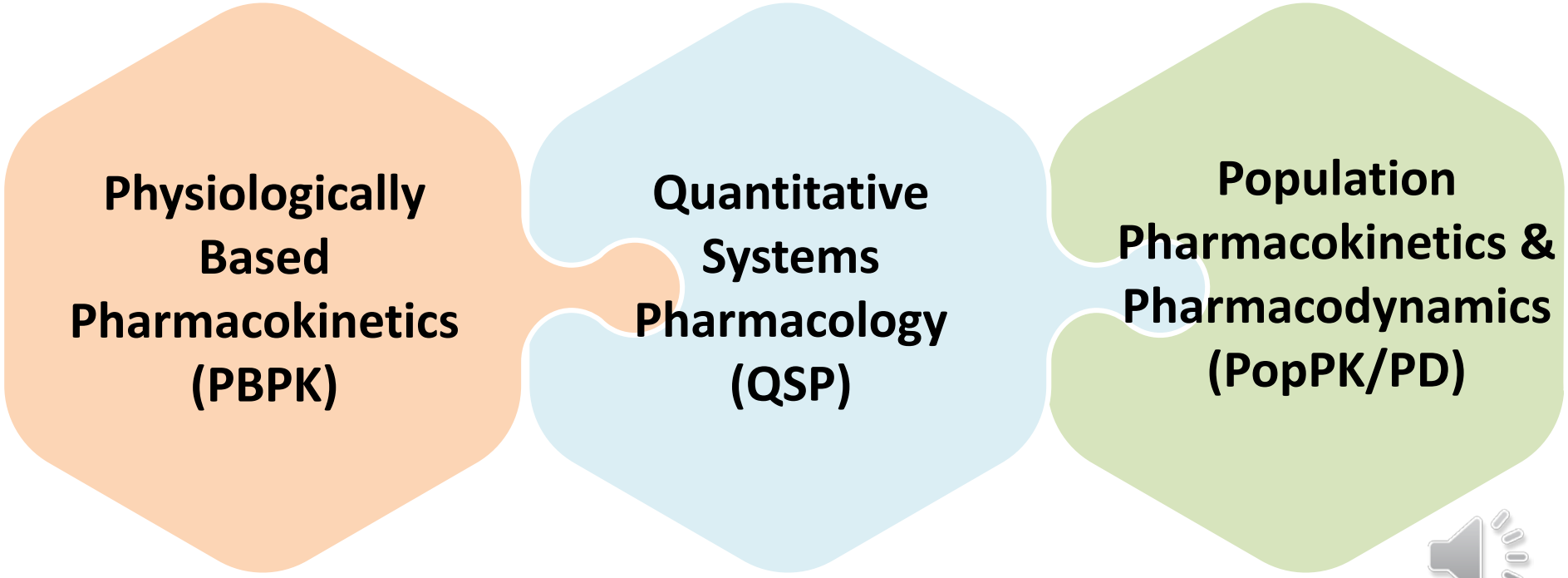
Limitations of Current Paradigm

- Univariate approach – address each factor independently
  - Aging has multifactorial impact on PK and PD
- "Exposure-matching" assumes a similar exposure-response relationship across the spectrum
  - May not be true across all indications and generally cannot be verified
- Often, such studies are conducted late in the clinical development
  - Lack of clinical experience
- PopPK approaches are limited by the availability of data in older adults

Clinical Pharmacology Strategies for Advancing New Drug Evaluation in Older Adults

- Early in the clinical development identify and characterize the impact of key factors that are likely to alter PK/PD
- Integrate early data to inform inclusion of older patients in late phase (Phase II or III) trials
  - Apply mechanistic modeling and simulation approaches to project the potential impact on PK/PD in virtual older adult population
  - Develop prospective dosing as needed
  - Incorporate precision dosing elements where possible
- Refine/Confirm the dosing in late phase trials or post-approval

Clinical Pharmacology Tools to Inform Dose Selection in Older Adults



- Can provide understanding of ADME in older adults
- Anticipate impact of polypharmacy on PK

- Integrate mechanistic understanding of biology, pharmacology, aging and comorbidities
- Anticipate PD response and clinical outcomes

- Integrate clinical data from early clinical studies
- Provide an estimate of drug variability

Proposed Approaches for Evaluation in Older Adults

Risk assessment based on preclinical and early clinical data: Low/Acceptable

SEQUENTIAL EVALUATION

- Progressively evaluate older adults
- Assess PK/PD and tolerability to inform inclusion in the next phase
- Similar to development in pediatrics

ADAPTIVE ENROLLMENT

- Dose to target a predefined PK/PD criteria in Phase II
- Use adaptive strategies to confirm/refine dosing
- Enroll older adults in Phase III
- Assessment of PK, safety and efficacy

doi:10.1002/cpt.2151

Proposed Approaches for Evaluation in Older Adults

Risk assessment based on preclinical and early clinical data: Moderate/Uncertain

SUBSTUDY APPROACH

- Opportunity to study older adults without complicating main trial
- Subset may or may not be part of primary analysis
- Allows for the assessment of PK/PD, comparative safety and potentially efficacy

OPEN LABEL EXTENSION

- Enroll older adults into a de-novo cohort
- Allows for dose adjustments during the study
- Allows for the assessment of PK/PD, tolerability and safety

doi:10.1002/cpt.2151

Additional Considerations

- In real-world, patient population and clinical contexts are likely to be more diverse compared to pre-market study population
- Increasing availability of real world data (RWD) provides an opportunity to further advance new drug evaluation in older adults
- Quantitative clinical pharmacology approaches paired with RWD will be critical in addressing dosing needs

Topics Requiring Further Discussion

- Sample size considerations
- Operationalizing the proposed approaches
  - Additional dosage strengths
  - Formulation considerations
  - Development of biomarkers
  - Managing drug interactions
  - Clinical decision support systems

Summary

- Clinical pharmacology considerations are critical for advancing new drug evaluation in older adults
- Quantitative clinical pharmacology provides a rational approach for inclusion of older adults in late phase trials
- Post-approval evaluation and refinement of dosing strategies can help bridge gaps between drug development and real world
- Operationalizing new drug evaluation for older adults requires multiple stakeholder input

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