Measuring Medication Burden

Andrew Zullo, PharmD, PhD
Assistant Professor, Departments of Health Services, Policy, and Practice and Epidemiology

USDeN/AGING Webinar, July 14, 2021

BROWN
School of Public Health

Disclosures

I have the following relevant disclosures to report:

- Grant funding from Sanofi Pasteur to Brown University for research on the epidemiology of infections and vaccine use among older adults in long-term care facilities
- Grant funding from Sanofi Pasteur to Brown University for research on respiratory syncytial virus in infants

My additional disclosures include:

- National Institute on Aging grants R21AG061632, R01AG065722, P01AG027296, P01AG066605, U54AG063546, R01AG062492, and RF1AG061221
- USDeN support for participation in the Investigator Development Core

Agenda

- Background (5 mins)
- Objective (1 min)
- Biologically Burdensome Polypharmacy (10 mins)
- A Successful Example (2 mins)
- Summary (2 mins)

Background

Background

- What exactly is medication burden?

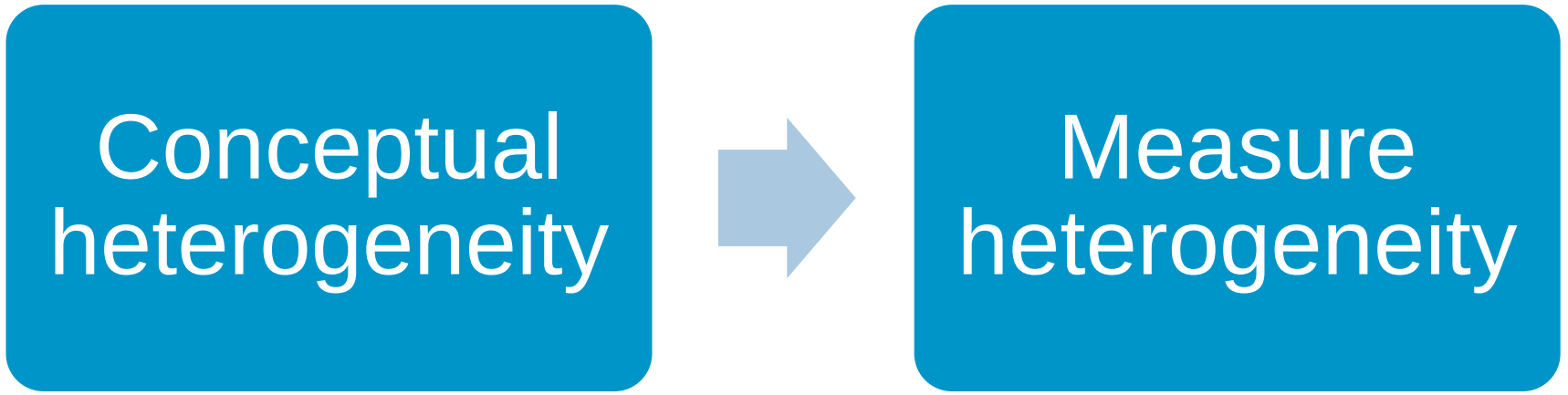
Background

- Burdensome in what way(s)?
  - Adherence
  - Lifestyle
  - Cost
  - Achieving goals of care
  - Physically
  - Others

Background

- Burdensome to whom?
  - Patient
  - Caregiver(s)
  - Staff
  - Clinicians
  - Healthcare system

Background

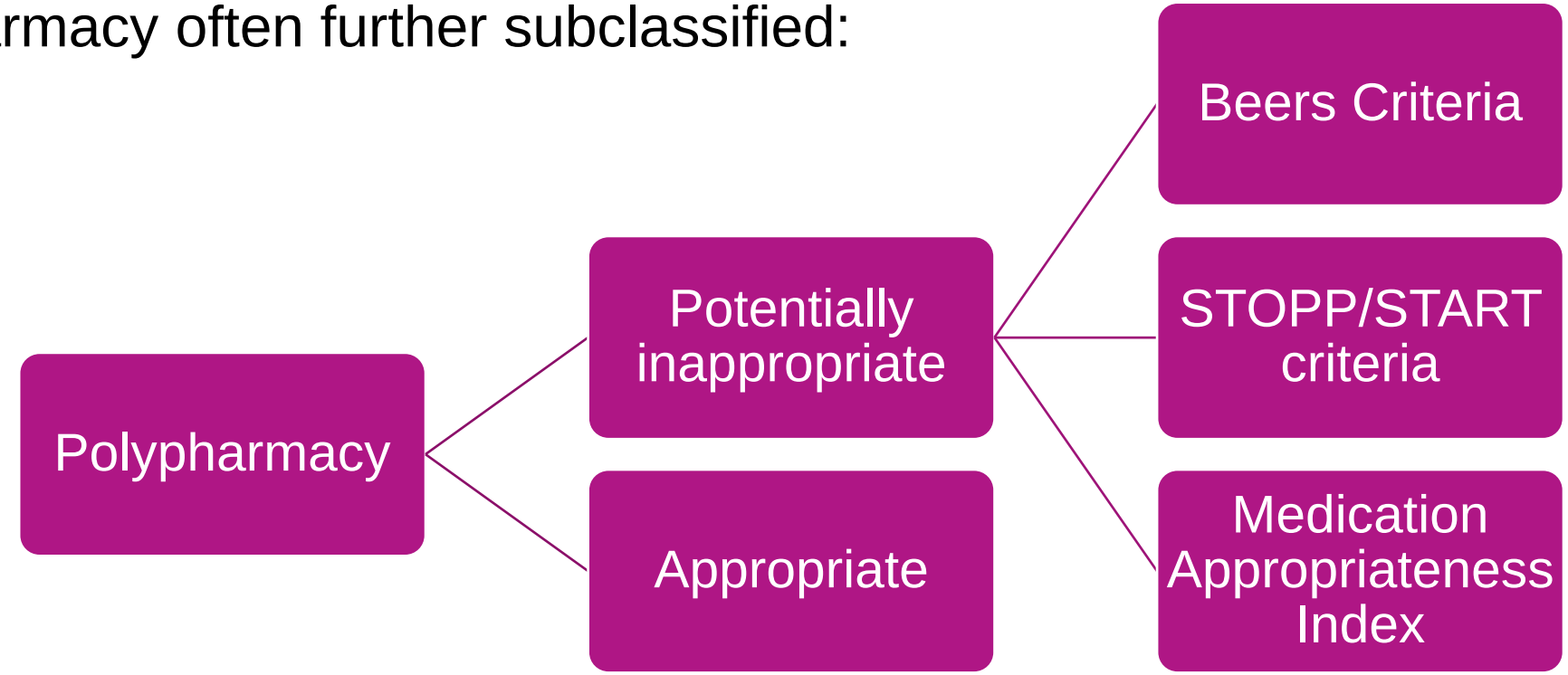


Background

- **Polypharmacy** is the most common measure of medication burden
- Polypharmacy = total number of medications
- Often dichotomized with a threshold
  - ≥ 5 concurrent medications = polypharmacy
  - ≥10 concurrent medications = hyperpolypharmacy

Background

- Polypharmacy often further subclassified:



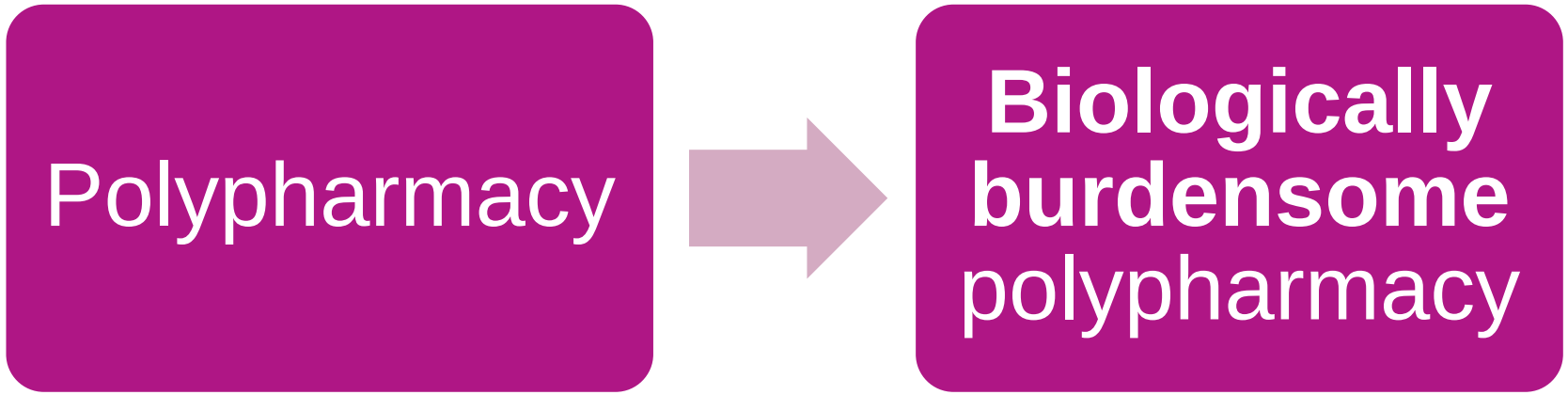
Background

- For questions about quality of care, perhaps a count of medications and a subclassification of appropriateness thereof is sufficient?
- What about if you want to understand the biological burden exacted on the body through the use of multiple medications?
  - Is total count of medications ideal?
  - Is it possible to create better measures?

Objective

Objective

- To stimulate discussion about how we might continue to progress from a count of medications (polypharmacy) toward measures that capture the biological burden of multiple medication use

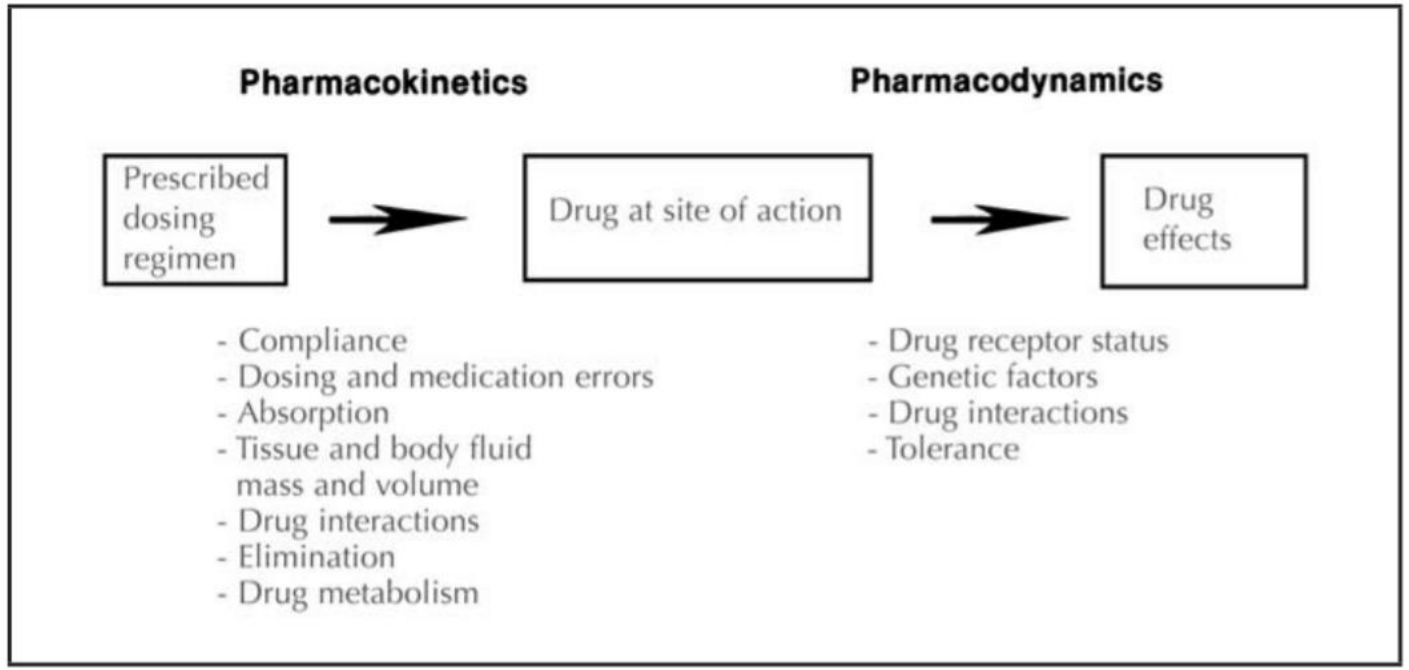


Biologically Burdensome Polypharmacy

Developing Biologically Burdensome Polypharmacy Measures

- One way to develop measures of biologically burdensome polypharmacy is to incorporate **clinical pharmacology** knowledge into measure development

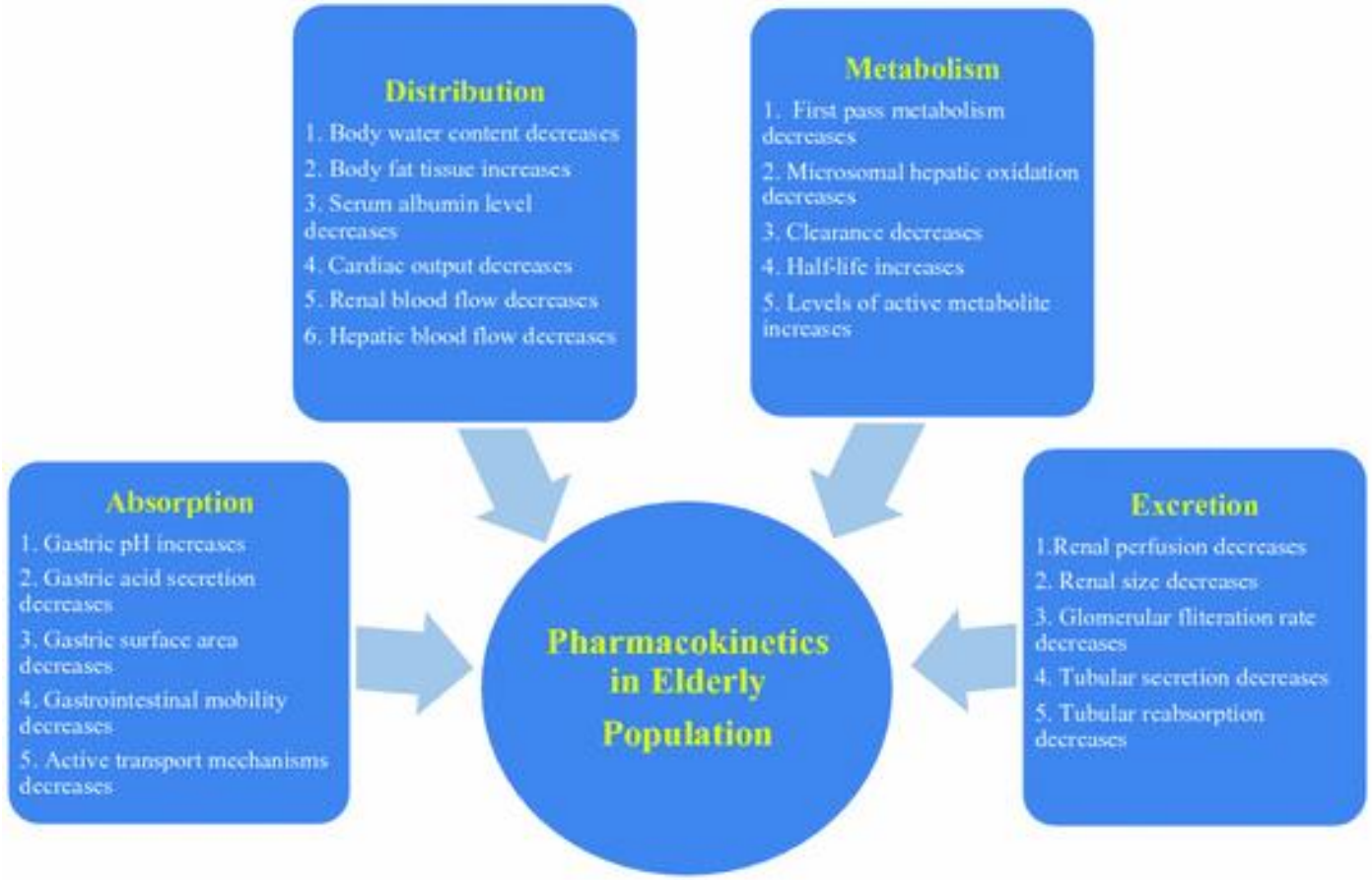
- Specifically, both pharmacokinetic and pharmacodynamic knowledge



Source: Concepts in Clinical Pharmacokinetics, 6th Edition, Lesson 1

Pharmacokinetics

- Pharmacokinetics (PK) is often described as “what the body does to a drug” and is the phases of how a drug moves through the body



Source: Mukker et al. (2016) Pharmacokinetic and Pharmacodynamic Considerations in Elderly Population. In: Stegemann S. (eds) Developing Drug Products in an Aging Society.

Pharmacokinetics

- Metabolism is frequently the most important phase of PK for determining the effects of drugs and occurs through phase 1 and phase 2 pathways.
- Phase 1 pathways activate and inactivate drugs, and include hydroxylation, oxidation, dealkylation, and reduction by cytochrome P450 (CYP) enzymes.
- Phase 2 pathways change the substances produced in phase 1 into compounds that can be excreted in urine, and include glucuronidation, conjugation, and acetylation.
- Most drugs undergo phase 1 followed by phase 2 metabolism

Pharmacokinetics

- As age increases, impairment in phase 1 pathways increases, resulting in reduced CYP metabolism, greater than expected serum concentrations of medications, and a higher risk of serious PK drug interactions.

- PK interactions frequently occur because of modified transport or metabolism of an object drug, most commonly mediated by the CYP isoenzyme system, solute carrier uptake transporters, and/or adenosine triphosphate (ATP)-binding cassette efflux pumps.

Pharmacodynamics

- Pharmacodynamics (PD) is often informally described as “what the drug does to the body”
- Involves drug-receptor interaction, post-receptor events, adaptive homeostatic responses and, pathologic changes in organs
- Is why in older adults, the effects of similar drug concentrations at the site of action (sensitivity) may be greater or smaller than those in younger people

What to incorporate from PK/PD into our measures of multiple medication use?

- How many of the drugs act on the same receptors?
- How many of the drugs are metabolized through the same CYP enzymes?
- What are the doses of the drugs?
- What is known about the dose responses of the drugs?
- What are the maximal effects of the drugs?
- What are the half-lives of the drugs?

Biologically Burdensome Polypharmacy

- Consider:
  - Do you believe that all possible combinations of the same number of drugs exert the same effect in an older adult, or do you believe that some combinations of five drugs are worse than other combinations?
  - Do you believe that five drugs that are all processed through the same CYP enzyme might be more biologically burdensome than five drugs that are each processed through a different enzyme?

A Successful Example

The Drug Burden Index (DBI)
(patented by Drs. Sarah Hilmer, Donald Mager, & Darrell Abernethy)

Example: The Drug Burden Index

- The drug burden index is
  - "…an integrated model of exposure to the medications that have been most consistently associated with functional impairment: those with anticholinergic and sedative effects" *[Source: Hilmer SN et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med. 2007 Apr 23;167(8):781-7. doi: 10.1001/archinte.167.8.781. PMID: 17452540.]*
  - "…essentially a linear additive model of pharmacological effect. It incorporates principles of pharmacokinetics (dose) and pharmacodynamics (dose response, maximal effect) to measure cumulative exposure to anticholinergic and sedative medications." *[Source: Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. Clin Pharmacol Ther. 2009 Jan;85(1):86-8. doi: 10.1038/clpt.2008.224. Epub 2008 Nov 26. PMID: 19037203.]*

Example: The Drug Burden Index

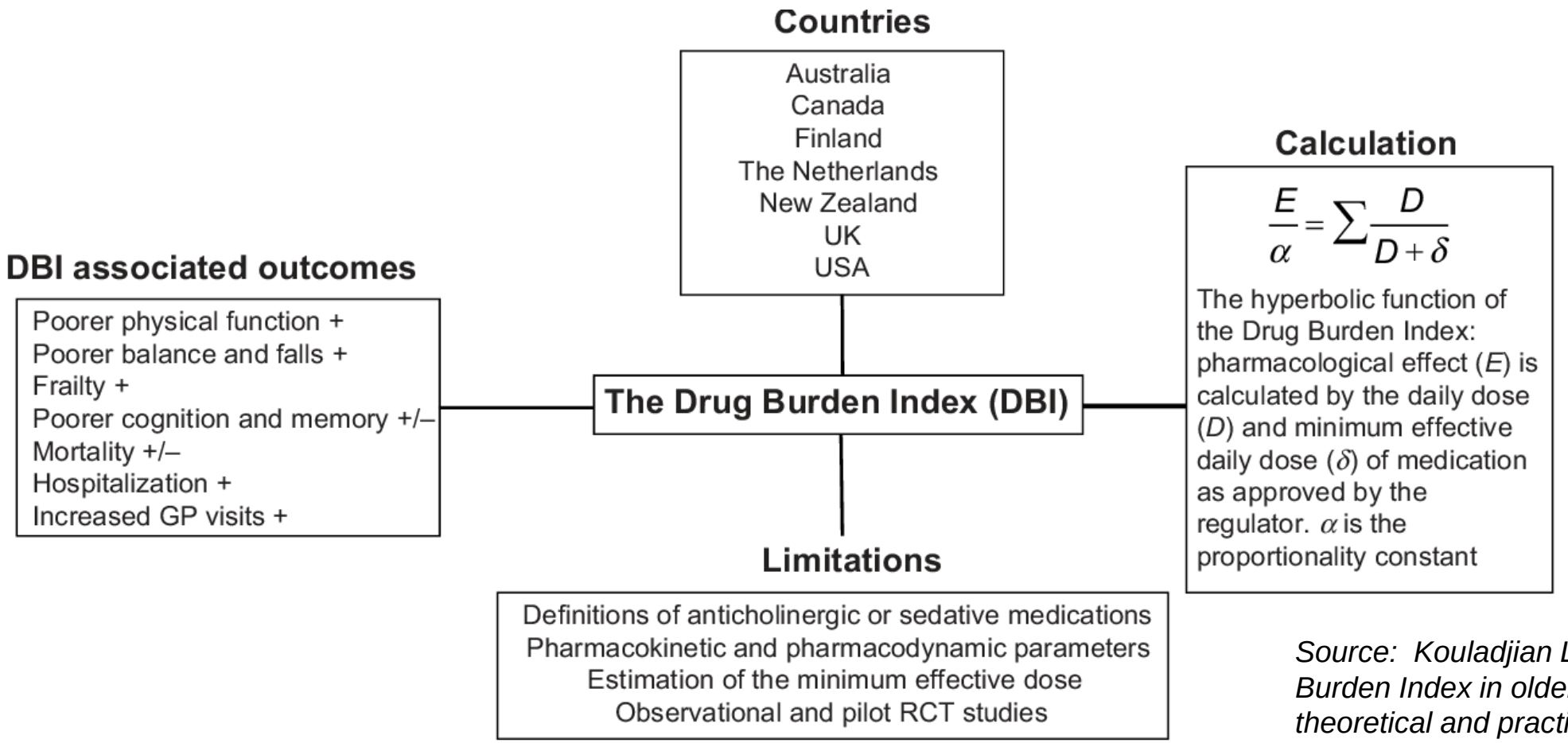


Figure 1 Summary of aspects of the DBI.
Notes: +, positive association; +/–, inconsistent association.

Source: Kouladjian L et al. Drug Burden Index in older adults: theoretical and practical issues. Clin Interv Aging. 2014 Sep 9;9:1503-15. doi: 10.2147/CIA.S66660. PMID: 25246778.

Summary

Summary

- For many research questions, we may need to move beyond a simple count of the number of medications someone is taking, or even the number of potentially inappropriate medications

- Incorporating pharmacological principles into our measures of multiple medication use to derive “biologically burdensome” polypharmacy measures is one potential and likely important important path forward

- The DBI is an excellent example that could be emulated to develop biologically burdensome polypharmacy measures that expand beyond sedative and anticholinergic drug use

Thank You

Andrew Zullo, PharmD, PhD
andrew_zullo@brown.edu