The Utility of "Single Exposure" versus Causal Architecture Approaches in Real-World Research

Andy Osterland, PharmD, MS; Joseph T. Dye, PhD; Srinivas Annavarapu, MBBS; Amy K. O'Sullivan, PhD, E. Susan Amirian, PhD
Ontada, Irving, TX, USA

Introduction

- Over recent decades, epidemiologic methodology has evolved substantially to encompass a gamut of techniques for focalizing on the most unbiased effect estimate of a single exposure (e.g., a treatment effect).
- By contrast, less attention has been paid to the refinement of study designs and analytic techniques intended to encompass the underlying milieu of clinical, environmental, and social determinants that interactively influence disease risk or outcomes.
- Single exposure approaches have been criticized as being reductionist and have long been debated in the broader epidemiologic community, despite the utility of this approach in optimizing internal validity.[1-2]
- Further, the gap between clinical trial efficacy and real-world (RW) effectiveness remains a concern for both regulatory entities and payers, though this gap may be partly attributable to varying prevalences of important effect modifiers between trial and RW patient populations.
- The objectives of this study are to (1) define single exposure and causal architecture approaches, and (2) delineate key considerations for using each approach based on the overarching research question.

Study Criteria
Greater variability in:
- Severity of underlying condition
- Use of concomitant medications
- Presence of comorbidities

Variables
Enhanced data capture:
- Social determinants of health
- Access and cost of care

Analysis
Causal relationships explored using:
- Directed acyclic graphs
- Mediation analysis

Study Approaches, Case Studies, and Considerations

Single Exposure Approach in Real-World Research

✓"Is an exposure (e.g., treatment, risk factor) associated with outcomes with/without controlling for confounders?"
✓"Does the exposure interact with other factors to impact outcomes?"
✓"What are the mechanisms through which an exposure works?" *[adapted from Keyes and Galea, 2017[1]]*

Case Study 1[3]	**Case Study 2**[4]	**Case Study 3**[5]
Tumor Type, Outcome(s) and Exposure(s)		
• Merkel cell carcinoma (MCC) • ORR, DOR, OS, PFS • SOC, external control arm	• Multiple myeloma • Infusion reactions • Daratumumab, split/single dose	• HER2+ metastatic breast cancer • PFS, safety • Pertuzumab, addition to SOC
Key Findings & Implications		
• Outcomes in this historical, observational cohort were poor. vs. single-arm RCT of avelumab • Helped establish FDA approval of avelumab in 1L MCC.	• Outcomes were similar from single 8-hour infusion vs. two 4-hour infusions over 2 days. • Supported label expansion for split-dosing of daratumumab.	• Outcomes were consistent with those observed in clinical trial. • Expanded understanding of safety and effectiveness of approved treatment option.

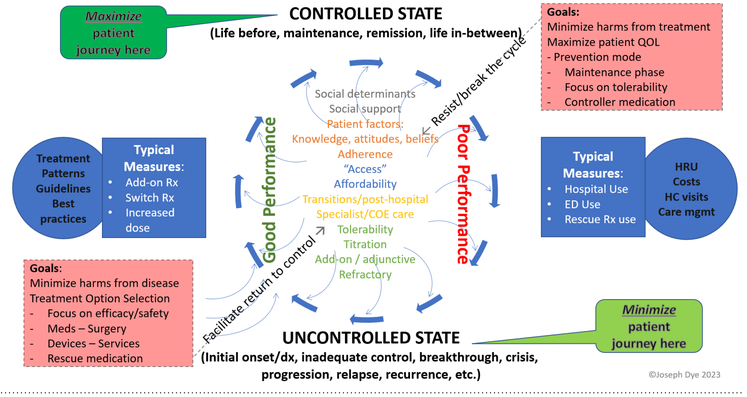
Causal Architecture Approach in Real-World Research

✓"What is the structure of underlying causes of a particular state of health or disease?"
✓"Do these causes work together or separately?"
✓"Which causes are the most prevalent in the population?" *[adapted from Keyes and Galea, 2017[1]]*

Case Study 1[6]	**Case Study 2**[7]	**Case Study 3**[8]
Tumor Type, Outcome(s) and Exposure(s)		
• Triple-neg. breast cancer (TNBC) • Prevalence of TNBC • Census-tract ICE-Race/Income	• Breast cancer (BC) • Rates of mammography • Scope of practice, other factors	• Oropharyngeal cancer (OPC) • OS, OPC-specific survival • Smoking, SES
Key Findings & Implications		
• TNBC was more prevalent in predominantly Black vs. White neighborhoods, driven by modifiable metabolic exposures. • Can inform local cancer control and prevention efforts.	• Racial and ethnic disparities in mammography were identified among Medicaid patients. • Relaxed NP scope of practice laws were associated with improved BC screening rates.	• Lower SES, smoking, and living in high smoking areas were associated with poorer survival. • Supports targeting individual and contextual factors for future smoking cessation interventions.

BC=breast cancer; DOR=duration of response; ICE=index of concentration at extremes; MCC=Merkel cell carcinoma; NP=nurse practitioner; OPC=oropharyngeal cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RCT=randomized controlled trial; SES=socioeconomic status; TNBC=triple-negative breast cancer

Conceptual model for chronic illness



Conclusions

A **single exposure** approach **enables hypothesis testing in specific populations;** however, results may **not be generalizable** and **lack identification of subpopulations receiving the most or least benefit.**

A **causal architecture** approach can **identify multi-level, multi-factorial relationships to inform risk stratification approaches**; however, this approach **does not preclude the study of individual risk factors** and **dynamic causes may be difficult to measure.**

While causal architecture approaches are seldom used in RW research settings, a **careful examination of when each approach is fit-for-purpose** can lead to the application of innovative strategies to the design and conduct of RW studies.

References & Acknowledgments

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Questions?
Andy.Osterland@McKesson.com