



MEASURING MULTIPLE MEDICATION ADHERENCE – WHICH MEASURE WHEN?



An ISPOR Workshop by the
Multiple Medication Adherence Measurement Working
Group of the ISPOR Medication Adherence and Persistence
Special Interest Group
Wednesday, November 2, 2016

MEASURING MULTIPLE MEDICATION ADHERENCE – WHICH MEASURE WHEN?



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Multiple Medication Adherence Measurement Working Group



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Multiple Medication Adherence Measurement Working Group



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Special Interest Group

- Conduct a systematic literature search of methods used calculating medication adherence for multiple drugs
- Summarizing the methods including disease area usage
- Using statistical methods investigate the accuracy of the measurements using simulation or patient data
- Conduct a GAP analysis of existing methods

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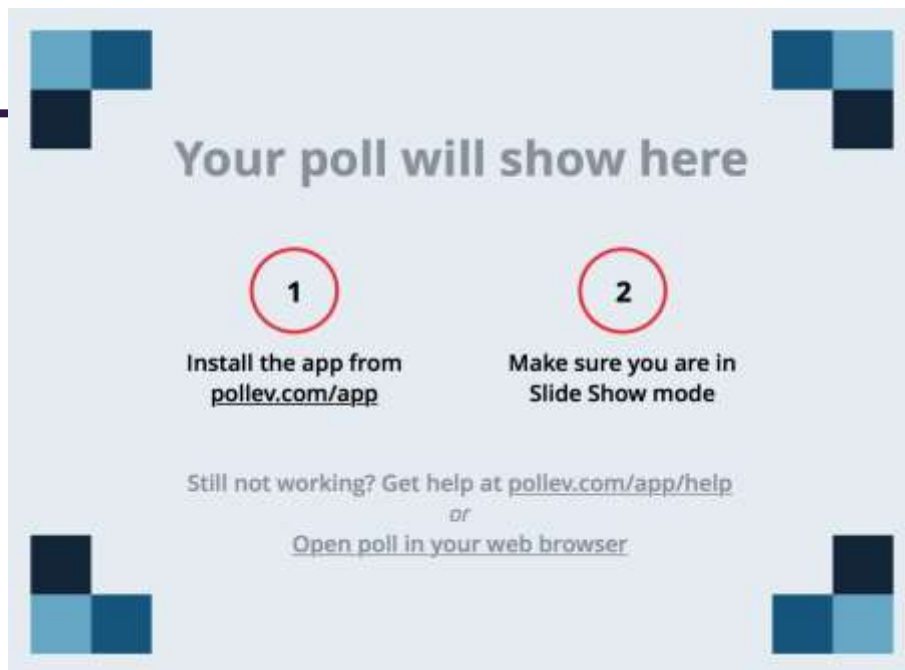
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MEASURING MULTIPLE MEDICATION ADHERENCE – WHICH MEASURE WHEN?



Priti Pednekar, MPharm, Graduate Student, Mayes College of Healthcare Business and Policy, University of the Sciences, Philadelphia, PA, USA



Search Strategy - Databases Searched

- PubMed® (PubMed.gov)
 - PsycINFO®
 - IPA
 - CINAHL
 - The COCHRANE library®
-
- Literature/data providing information about medication adherence methods using multiple drugs
 - Literature/data written in English
 - Published between January 1973 - May 2015
 - Limitations – Human subjects

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Search Strategy - Search Terms Used

- MeSH and non-MeSH terms
- Boolean operators

Search terms used

| Category | Keywords |
|-----------------------------|---|
| Adherence | Medication Adherence, patient compliance, persistence |
| Polypharmacy | Multiple therapies, polypharmacy, overlapping prescriptions |
| Measurement methods | Self-reported, proportion of days covered, Morisky scale, electronic health records, concurrent |
| Multiple disease conditions | Comorbidity, multi-comorbidity, multi-morbidity |

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Search Strategy- Eligibility Criteria

■ Inclusion Criteria

- Studies including method for calculating medication adherence
- Any disease area
- Randomized Controlled Trials (RCTs) and Observational studies were included

■ Exclusion Criteria

- Not original research (Only peer-reviewed publications were included)
- No measurement method for medication adherence discussed
- Studies not assessing multiple medication adherence
- Studies assessing adherence to guidelines but not medications
- Studies assessing adherence to diet

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Article Selection Process

1. Initial electronic search
2. Addition of manual searched publications
3. Duplicates removal – EndNote and manually
4. First Pass Screening
 - Based on **title and abstract**
 - Include **double independent reviews** by seven pairs of SIG members
5. Second Pass Criteria and # of articles
 - Based on **full texts**
 - Include **double independent reviews** by seven pairs of SIG members
6. Resolution of discrepancies
 - Consensus between each pair of reviewers
 - Group discussions

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Data Extraction

- Study design
- Characteristics of participants of the study
- Disease studied
- Study period and duration of the study
- Number and type of medications studied
- Type of medication adherence measure studied
- Measurement method/s of medication adherence used

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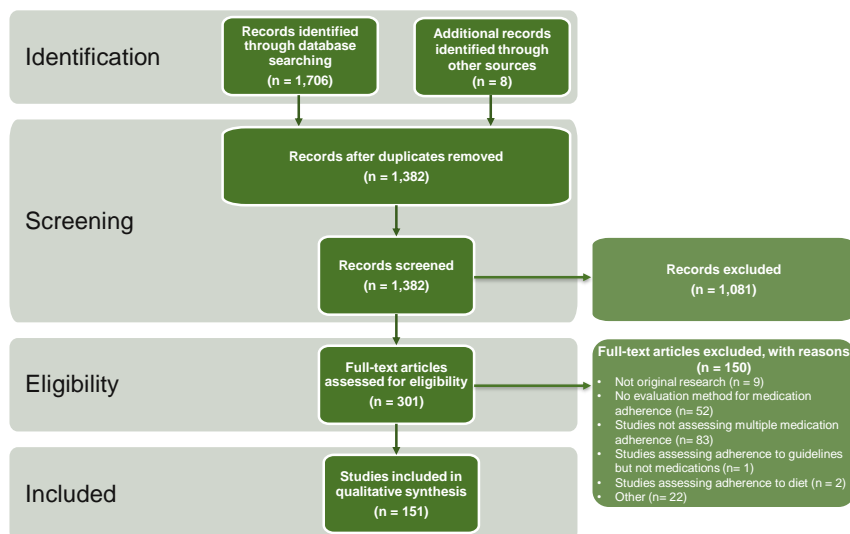
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Tamas Agh, MD, MSc, PhD, Principal Researcher, Syreon Research Institute, Budapest, Hungary



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The flow diagram of the systematic literature review process



Based on the PRISMA template: Panic, N., et al., PLoS One, 2013. 8(12): e83138.



General characteristics of the included studies



Study design

| | N | % |
|-----------------------------|-----|-------|
| Observational studies | 130 | 86% |
| Retrospective cohort | 58 | 38.4% |
| Prospective cohort | 47 | 31.1% |
| Cross-sectional | 25 | 16.6% |
| Randomized controlled trial | 20 | 13.2% |
| Validation study | 1 | 0.7% |

Sample size

| | N | % |
|----------------|----|-------|
| <100 | 20 | 13.2% |
| 100 to 999 | 63 | 41.7% |
| 1,000 to 4,999 | 30 | 19.9% |
| >5,000 | 38 | 25.2% |

Age groups

| | N | % |
|--------------|----|-------|
| Mean age <65 | 90 | 59.6% |
| Mean age ≥65 | 35 | 23.2% |
| Not reported | 26 | 17.2% |



General characteristics of the included studies

■ Countries

- Studies originated from 32 countries, 57.6% (n=87) from the US

■ Disease areas

- 13 disease areas

| Disease areas investigated in >10 studies | N | % |
|---|----|-------|
| Cardiovascular | 46 | 30.5% |
| Sexually transmitted (HIV/AIDS) | 45 | 29.8% |
| Metabolic | 18 | 11.9% |
| Mental | 15 | 9.9% |

■ Number of medications investigated

| | N | % |
|------------------------------|----|-------|
| >1 to 5 medications | 44 | 29.1% |
| >5 to 10 medications | 14 | 9.3% |
| >10 medications | 6 | 4% |
| Not reported (>1 medication) | 87 | 57.6% |

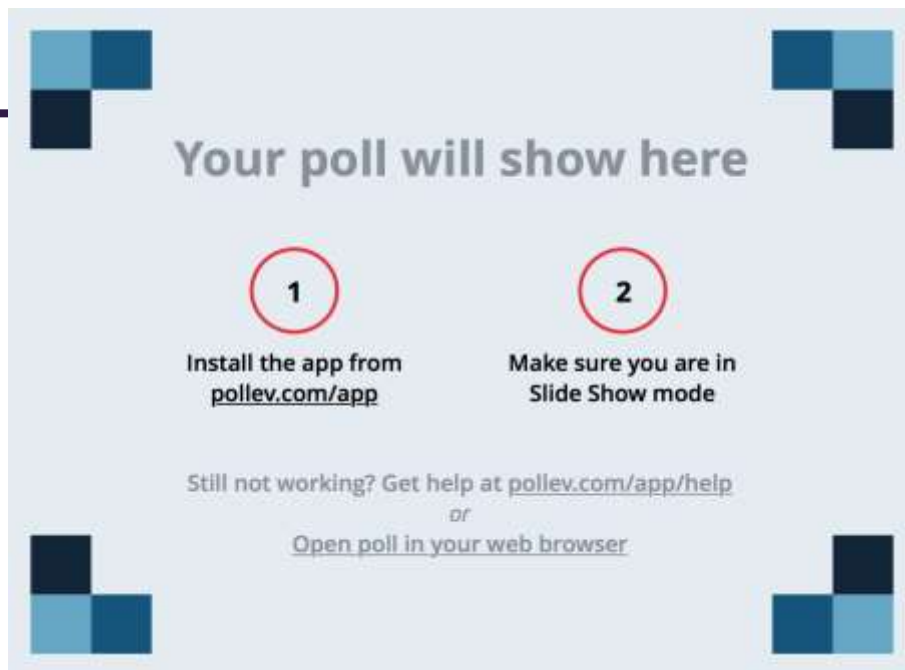
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AUDIENCE INTERACTION

- What would you think is the **BEST METHOD** of measuring multiple medication adherence?

- Subjective measures: self-report (e.g. patient-reported outcome, observer-reported outcome)
- Objective measures: Pharmacy dispensing data records / medical records / pill counting / electronic adherence monitoring
- Therapeutic outcome monitoring
- Drug level monitoring

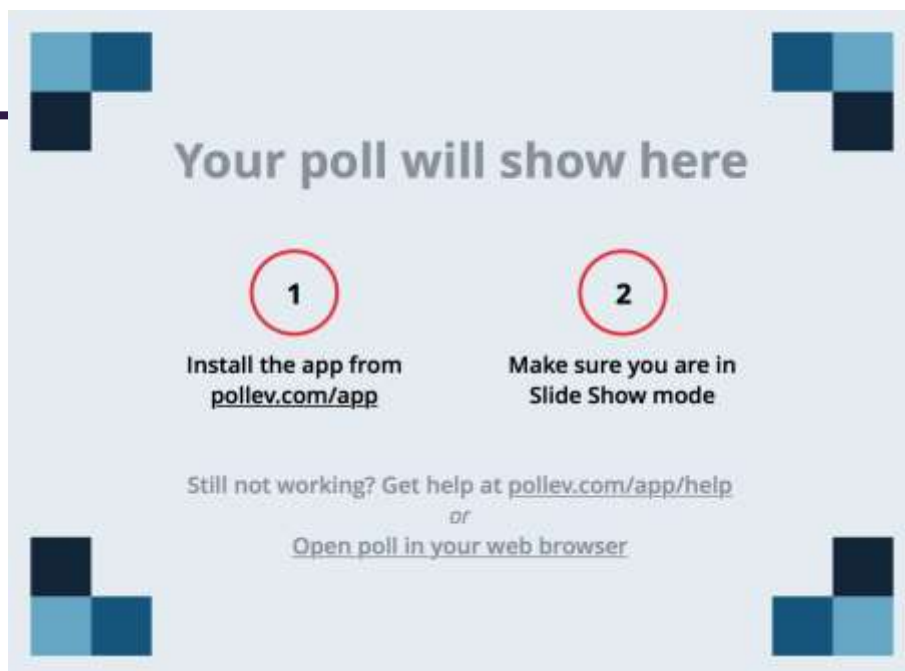
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AUDIENCE INTERACTION



- Which method do you think is the **MOST COMMONLY USED** method of measuring multiple medication adherence?
 - A. Subjective measures: self-report (e.g. patient-reported outcome, observer-reported outcome)
 - B. Objective measures: Pharmacy dispensing data records / medical records / pill counting / electronic adherence monitoring
 - C. Therapeutic outcome monitoring
 - D. Drug level monitoring



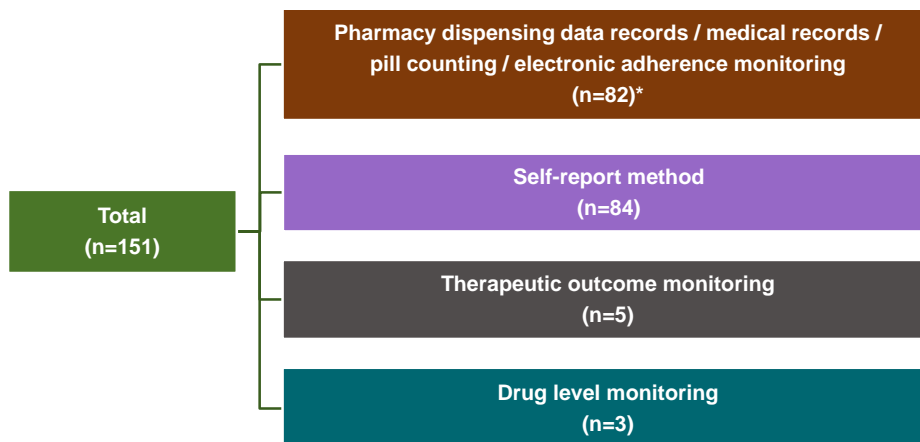
MEASURING MULTIPLE MEDICATION ADHERENCE – WHICH MEASURE WHEN?



Bryan Bennett, Director, Patient Centered Outcomes, Adelphi Values, Adelphi Mill, UK



Measures of adherence to multiple medications in the included studies



*: Adherence was measured in 75 studies, persistence was measured in 18 studies.
Please note that some articles included more than one method for measuring adherence to multiple medications.
MPR: Medication Possession Ratio, PDC: Proportion of Days Covered

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Self-report methods for measuring adherence to multiple medications



- **30 different self-report measures/methods were used in the studies**
- **Multi- / single-item questionnaire (n=84)**
 - The Morisky Medication Adherence Scale (MMAS) was the most commonly used PRO instrument (n=21)
 - MMAS 4-item (n=15)
 - MMAS 8-item (n=6)
 - MMAS 9-item (n=1)
- **Telephone / face-to-face interview (n=9)**
- **Informant rating - family member, nurse, doctor (n=5)**
- **Undefined - no further information given except self-report (n=3)**

Please note that some articles included more than one self-report method for measuring adherence to multiple medications.

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Methods for calculating adherence to multiple medications



- **MPR for multiple medications (n=25)**
 - 10 different variations of MPR
 - Method of MPR was not reported/unclear in 8 studies
- **PDC for multiple medications (n=29)**
 - 9 different variations of PDC
 - Method of PDC was not reported/unclear in 2 studies
- **Medication gaps for multiple medications (n=6)**
 - 4 different methods
- **Other methods for multiple medications (n=20)**
 - 7 different methods
 - Method was not reported/unclear in 11 studies

MPR: Medication Possession Ratio, PDC: Proportion of Days Covered

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AUDIENCE INTERACTION



- Does the disease condition have an impact on how adherence to multiple medications should be measured?
 - A. Yes
 - B. Maybe, but it is situation specific
 - C. No
 - D. I don't know

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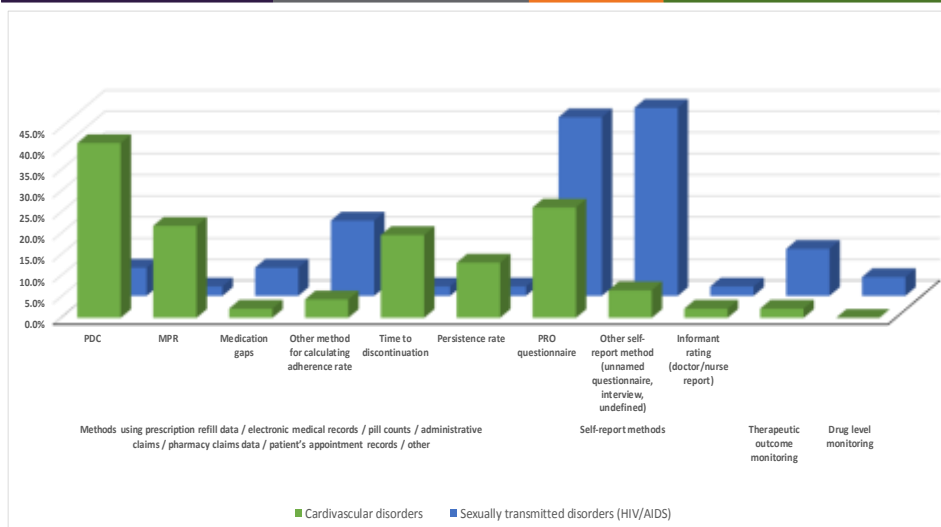
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Multiple Medication Adherence Measures: STDs and CV Disease



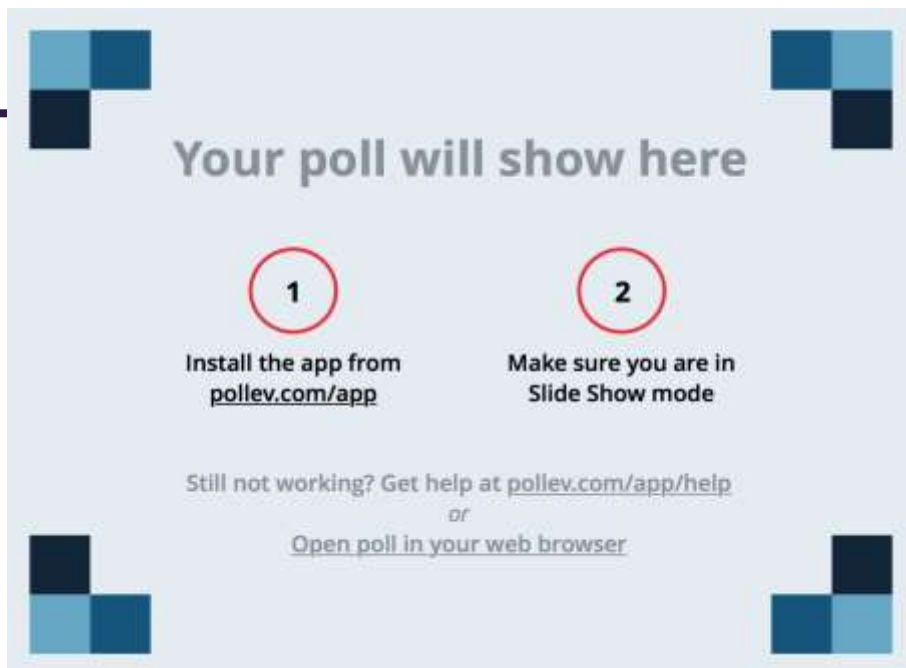
Please note that some articles included more than one method for measuring adherence to multiple medications.

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AUDIENCE INTERACTION

- What do you think is the objective **BEST MEASURE** used to calculate multiple medication adherence?
 - A. PDC
 - B. MPR
 - C. No single measure is the best
 - D. I don't know

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Maria Malmenäs, MSc, Senior Director, Health Outcomes, PAREXEL International, Stockholm, Sweden



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Adherence – single treatment



- Medication Possession Ratio (MPR)
 - Mean days' medication supplied over period
 - May 'double-count' if refill before Rx exhausted
- Proportion Days Covered (PDC)
 - Mean number of days for which medication is held over a period
 - Doesn't double-count, but assumes that early refill will not be started until previous Rx exhausted
- Missing Days/Dose
 - Mean number of days for which medication is not held over a period
 - Typically 1-PDC

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Adherence – multiple treatments

- Measures of multiple adherence are generally based on single treatment adherence:
 - Mean of single adherence measure
 - Single adherence measure (MPR, PDC, Missing days/dose) where
 - Medication=all medications; or
 - Medication=any medications; or
 - Some other derivation – e.g. three out of four medications, or weighted by number of treatments

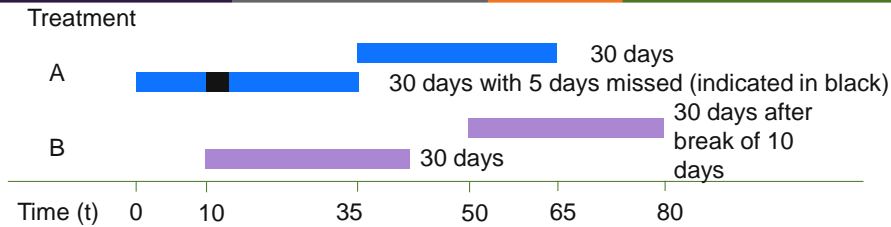
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Daily Polypharmacy Possession Ratio (DPPR)

- DPPR is defined according to the mean proportion of prescriptions available on each day
- For example:
 - E.g. prescribed one medication and hold supply then count each such day as 1/1;
 - E.g. prescribed two medications and only hold supply of one then count each such day as 1/2.
- As with PDC, any overlap of prescription for a single medication is assumed to be deferred until previous prescription is fully exhausted

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Scenario



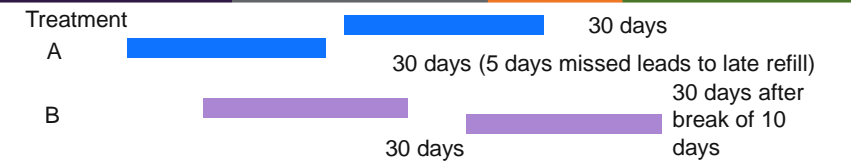
Multiple adherence

i.e. whether complied with prescription(s) on each day

$$\frac{(10 - 0) + (40 - 15) + (80 - 50)}{(80 - 0)} = 0.8125$$

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Scenario



| | |
|--|--|
| Mean PDC | Treatment A: $PDC = \frac{30+30}{65} = 0.9231$ Treatment B: $PDC = \frac{30+30}{70} = 0.8571$ Mean PDC = $\frac{0.9231 + 0.8571}{2} = 0.8901$ |
| Days with any treatment available | $PDC = \frac{(30 - 0) + (40 - 30) + (65 - 40) + (80 - 65)}{(80 - 0)} = \frac{80}{80} = 1$ |
| Days with all treatments available | $PDC = \frac{(30-0)+(40-35)+(80-50)}{(80-0)} = \frac{65}{80} = 0.8125$ |
| Multiple discretised PDC | Treatment A: $PDC = \frac{30+30}{65} = 0.9231 > 0.8$; i.e. TRUE Treatment B: $PDC = \frac{30+30}{70} = 0.8571 > 0.8$; i.e. TRUE Multiple PDC = TRUE and TRUE = TRUE |
| Daily Polypharmacy Possession Ratio (DPPR) | $DPPR = \frac{\frac{1}{1} \times 10 + \frac{2}{2} \times 20 + \frac{1}{2} \times 5 + \frac{2}{2} \times 5 + \frac{1}{2} \times 10 + \frac{2}{2} \times 15 + \frac{1}{1} \times 15}{80} = \frac{65 + 15/2}{80} = 0.906$ |

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Simulation

- Simulate data for large number of subjects ($i = 1, \dots, 1000$)
- Use two treatments ($j = 1, 2$)
- Assume both treatments prescribed throughout a 365 day period
- Simulate b_i and use specified β_j
 - E.g. $\beta_1 = \text{logit}^{-1}(0.8)$, $\beta_2 = \text{logit}^{-1}(0.9)$
- Derive p_{ij} and simulate adherence sequence for each subject (as Bernoulli random variables)

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Simulating observable data

- Assumptions
 - Each dose is for 30 days
 - A prescription is refilled as soon as previous prescription is exhausted
 - First prescription begins on Day 1
 - Two medications are prescribed throughout a 365 day period
 - Based on underlying (unobserved) adherence rates we observe a series of prescription dates within a 365 day period
 - Unknown whether there will be a refill after Day 365

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Simulating observable data

- Limitations
 - Uniform prescription length
 - No early refill (consequently PDC and MPR are equivalent)
 - No explicit grace period or treatment holidays
 - Only two treatments
 - Both treatments prescribed throughout interval

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Generating observable metrics

- Calculate following metrics, based on simulated observable data:
 - Mean MPR/PDC
 - MPR/PDC based on any treatment
 - MPR/PDC based on all treatments
 - DPPR
- For each of the above classify based on whether ≥ 0.8
- Also classify based on all single treatment MPR/PDC classifications
- For all measures calculate based on:
 - Including final prescription
 - Excluding final prescription

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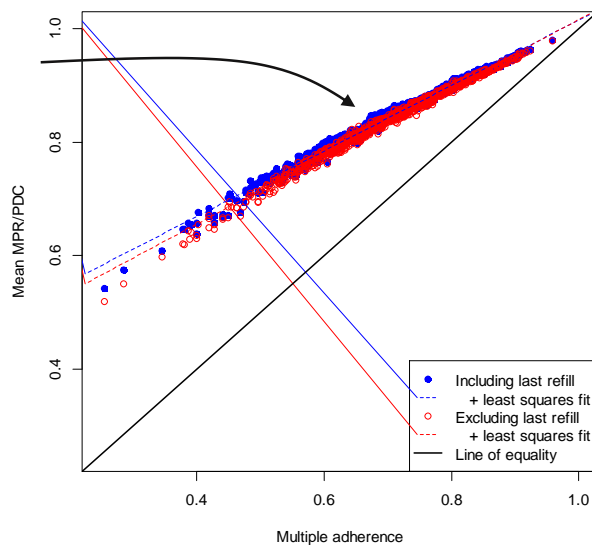
Results from simulations

| Metric | Mean | Standard deviation | Proportion adherent |
|--|-------|--------------------|---------------------|
| 'True' adherence | 0.707 | 0.108 | 0.217 |
| Mean MPR/PDC – Include last refill | 0.847 | 0.062 | 0.792 |
| Mean MPR/PDC – Exclude last refill | 0.840 | 0.065 | 0.754 |
| MPR/PDC (<u>any</u> treatment) – Include last refill | 0.971 | 0.028 | 0.998 |
| MPR/PDC (<u>any</u> treatment) – Exclude last refill | 0.969 | 0.029 | 0.998 |
| MPR/PDC (<u>all</u> treatments) – Include last refill | 0.722 | 0.103 | 0.243 |
| MPR/PDC (<u>all</u> treatments) – Exclude last refill | 0.718 | 0.104 | 0.244 |
| DPPR – Include last refill | 0.847 | 0.062 | 0.792 |
| DPPR – Exclude last refill | 0.844 | 0.064 | 0.766 |
| All adherent MPR/PDC – Include last refill | - | - | 0.562 |
| All adherent MPR/PDC – Exclude last refill | - | - | 0.488 |

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Multiple adherence vs Mean MPR/PDC

For this case –
significant bias,
overestimating
adherence

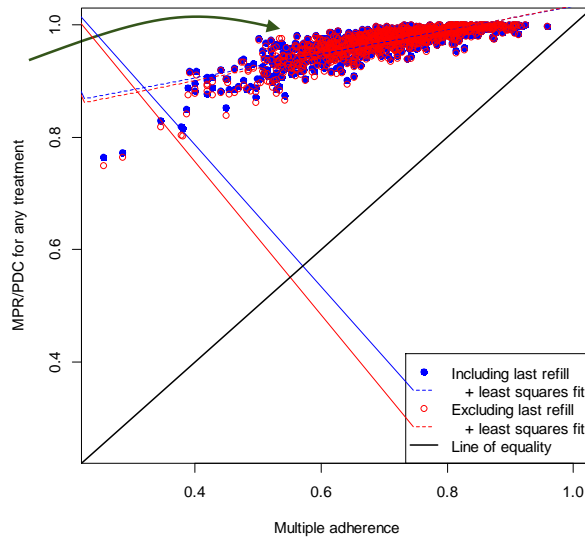


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Multiple adherence vs MPR/PDC of any medication



Again –
significant bias,
further
overestimating

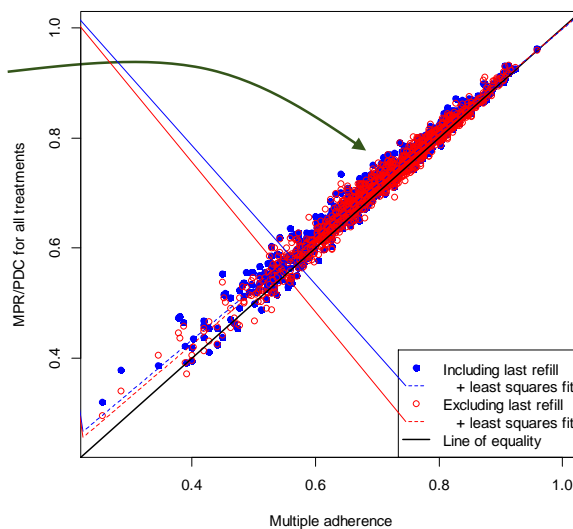


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Multiple adherence vs MPR/PDC of all medication



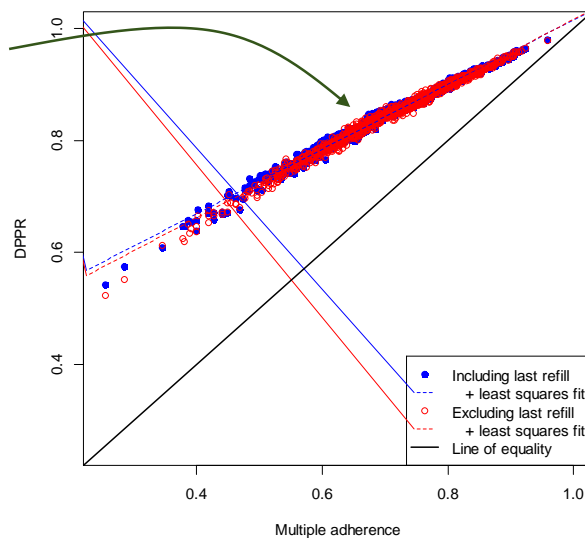
For this
scenario
these
measures had
much less
bias



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Multiple adherence vs DPPR

Levels of bias
comparable
with Mean
MPR/PDC

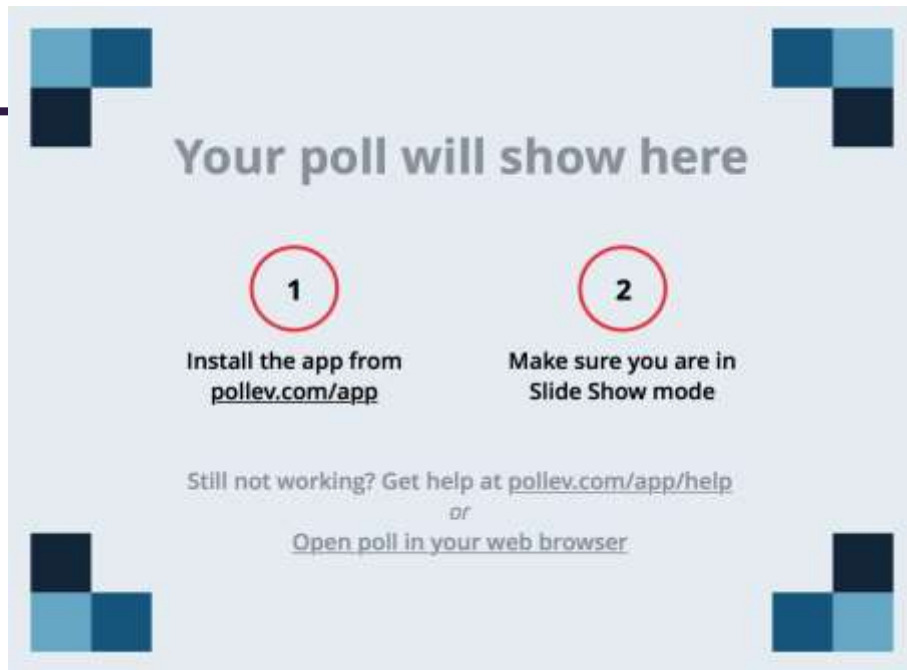


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AUDIENCE INTERACTION

- Which method do you now think is the **MOST accurate** method of measuring multiple medication adherence?
 - A. Mean MPR/PDC
 - B. MPR/PDC any treatment
 - C. MPR/PDC all treatment
 - D. DPPR
 - E. Non of the above

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Discussion



Summary



- The systematic review was conducted using PRISMA guidelines and used first-pass and second-pass screening
- 151 studies were analyzed and compared
- Self-report questionnaires and MPR/PDC were the most frequently used measures
 - Several different variations of calculation methods
- Measurement methods varied across disease areas
- The majority of derived adherence measurements seems to overestimate adherence
- MPR/PDC separately derived for all medications seems to work best

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Thank you Theresa Tesoro!



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Sign up as Review Group Member



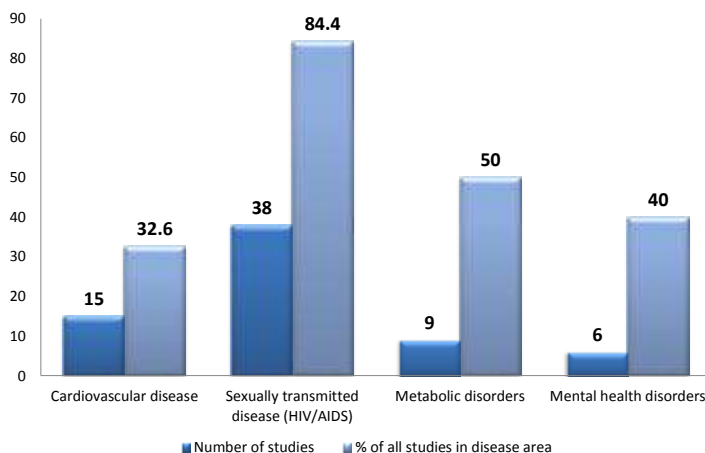
- Sign up as Review Group Member
- Join ISPOR Special Interest Groups
- Need ISPOR membership number
- Business card to Theresa or email ttesoro@ispor.org



BACKUP SLIDES

Self-report measures of adherence

■ By disease type



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MPR Studies

| Medication possession ratio (MPR) for multiple medication (N=25) | N | % |
|---|---|-----|
| Average of \sum days of supply per medications/study period | 4 | 2.6 |
| \sum days of supply for all medications/study period | 3 | 2.0 |
| \sum days with supply for any medication/study period | 2 | 1.3 |
| Average of (\sum days of supply/(days between last prescription- first prescription) per medications); supply obtained in the last fill was excluded | 2 | 1.3 |
| (\sum days of supply/(days between last prescription- first prescription) per medications) and if all were >80% then adherent; supply obtained in the last fill was excluded | 1 | 0.7 |
| (\sum days of supply/days of eligibility for that medication) per medications and if all were \geq 80% then adherent | 1 | 0.7 |
| \sum days of supply for all medications/(days between last prescription- first prescription + days of supply for last fill - number of days in hospital) | 1 | 0.7 |
| \sum days of supply for multiple medications/(days between last prescription- first prescription + days of supply for last fill) | 1 | 0.7 |
| \sum tablets dispensed/ \sum tablets recommended or prescribed | 1 | 0.7 |
| Weighted average of (\sum days for supply/days for which medication was needed) per medications | 1 | 0.7 |
| Not reported/unclear | 8 | 5.3 |

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PDC Studies

| Proportion of days covered (PDC) for multiple medication (N=29) | N | % |
|---|----|-----|
| \sum days supplied for all medications/study period | 13 | 8.6 |
| Average of \sum days supplied per medications/study period | 4 | 2.6 |
| \sum days supplied for any medication/study period | 3 | 2.0 |
| Average of (\sum days supplied/(days between last prescription- first prescription) + days supplied for the last fill)) per medications) | 2 | 1.3 |
| \sum days supplied for all medications/(study period - days of hospitalization) | 1 | 0.7 |
| \sum days supplied/study period for each medication and if all were $\geq 80\%$ then adherent | 1 | 0.7 |
| \sum days supplied/study period for each medication, adherent if at least 3 out 4 drugs were taken 50% during the study period | 1 | 0.7 |
| \sum days supplied/study period for each medication, adherent if drugs were taken 50% during the study period | 1 | 0.7 |
| \sum days for supplied per medications/(study period x number of medications) | 1 | 0.7 |
| Unclear | 2 | 1.3 |

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Other Methods Used

| Missing days/doses for multiple medication (N=6) | N | % |
|---|----|-----|
| \sum days without medications/study period | 3 | 2.0 |
| \sum days without medications/(days between last prescription- first prescription) | 1 | 0.7 |
| $(1 - \sum \text{doses of medications} / \sum \text{expected doses of medications}) \times 100$ | 1 | 0.7 |
| \sum days without medications | 1 | 0.7 |
| Other calculation method for adherence to multiple medication (N=20) | | |
| Composite Adherence Score (CAS) = a hierarchical algorithm, which combines adherence data from MEMS, pill count, and self-report | 3 | 2.0 |
| Continuous Multiple-Interval Measures of Medication Availability (CMA) = the sum of the all of the days' supply of medication / the number of days between the first fill and the last refill; the theoretical day's supply was calculated by dividing the number of units dispensed by the daily dose for the drug considered, the daily dose is the recommended dose per day for its main indication in adults | 1 | 0.7 |
| Covered minutes per day = $((1440 \text{ min} - \text{uncovered min}) / 1440 \text{ min}) \times 100$ | 1 | 0.7 |
| Daily Patient Possession Ratio (DPPR) = look at each day in the observation period separately, and determine how many medications are available, set a score between 0 (no medication available) and 1 (all medications available) weighted by the number of medications to be taken each day, resulting in daily scores indicating the proportion of medications available for each day; sum the scores and divide by the number of days in the observation period to obtain the proportion of all medications available for daily use | 1 | 0.7 |
| Medication total (MED TOT) = \sum supply of pills dispensed/number of days elapsed | 1 | 0.7 |
| Overall pill count adherence score represented the mean pill count adherence across all prescribed medications | 1 | 0.7 |
| Proportion of medications taken during the past week | 1 | 0.7 |
| Not reported/unclear | 11 | 7.3 |

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Cross-classification of multiple adherence measures (vs 'true')



| | | Mean MPR/PDC | | MPR/PDC any medication | | MPR/PDC all medications | | All MPR/PDCs ≥ 0.8 | |
|---------------------|-----|--------------|-----|------------------------|-----|-------------------------|-----|-------------------------|-----|
| | | No | Yes | No | Yes | No | Yes | No | Yes |
| Include last refill | No | 202 | 571 | 1 | 772 | 740 | 33 | 406 | 367 |
| | Yes | 0 | 227 | 0 | 227 | 4 | 223 | 0 | 227 |
| Exclude last refill | No | 231 | 542 | 0 | 773 | 745 | 28 | 470 | 303 |
| | Yes | 0 | 227 | 0 | 227 | 7 | 220 | 0 | 227 |

* Using a threshold of 0.8

Sensitivity and specificity of multiple adherence measures (vs 'true')



| | | Mean MPR/PDC | MPR/PDC any medication | MPR/PDC all medications | All MPR/PDCs ≥ 0.8 |
|---------------------|-------------|--------------|------------------------|-------------------------|-------------------------|
| Include last refill | Sensitivity | 100% | 100% | 98% | 100% |
| | Specificity | 26% | 0% | 96% | 53% |
| Exclude last refill | Sensitivity | 100% | 100% | 97% | 100% |
| | Specificity | 30% | 0% | 96% | 61% |