Measuring Multiple Medication Adherence–Which Measure When?

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KEY POINTS . . .

Self-reported and quasi-objective (e.g., proportion of days covered, medication possession ratio) methods are the most popular measurements to evaluate multiple medication adherence; however, several variations of these methods have been used.

Today's existing measurement methods are likely to over- or underestimate medication adherence when multiple medications are involved.

The goal of the ISPOR Medication Adherence and Persistence Special Interest Group (MAP-SIG) is to stimulate research and evaluation on issues related to medication adherence, treatment persistence, and implications for health outcomes. Within the MAP-SIG, the aim of the Multiple Medication Adherence Measurement Working Group is to summarize, compare, and evaluate the existing measurement methods used for calculating medication adherence, regardless of disease area, in patients using poly-pharmacotherapy. Working toward these goals, a systematic review of the literature as well as an assessment of the measurements was conducted.

The aim of this article is to share preliminary results from this work, to summarize different methods used to calculate multiple medication adherence (MMA), and to assess whether there were any superior measurement methods among the existing ones using the simulation modeling.

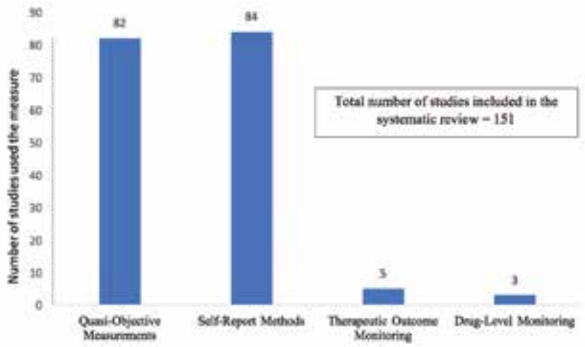
Systematic Literature Review: Existing Methods for Measurement of MMA

The working group conducted a systematic literature review using electronic bibliographic databases to identify current measurement methods used to calculate adherence rates for patients using more than one drug to treat any disease. In this review, literature published in English during the period of 1973 to 2015 was examined. Although the review was not comprehensive because gray literature was excluded, it included 151 articles and covered observational studies (retrospective cohort, prospective cohort, and cross-sectional studies); randomized controlled trials; and a validation study.

Several different methods using varying measures to calculate MMA were identified. Some studies used more than one method to calculate MMA; however, the comparisons between methods were rarely observed. Although the working group found that there was no method that could be considered as a gold standard for calculating MMA, two broad methods were identified: self-reported assessment and quasi-objective measurements (Figure 1). While therapeutic outcome and drug-level monitoring methods were also used to calculate MMA, these were used only in five and three studies, respectively.

Of the 151 studies analyzed, 55.6% (N= 84) used self-report methods to measure medication adherence to multiple drugs (Table 1). We found that the Morisky Medication Adherence Scale was the most common self-reported measurement method. Although self-reported methods are the preferred choice for most researchers because of ease of administration, they have the potential of over-reporting adherence or failing to disclose non-adherence due to recall bias, missing data, social desirability concerns, and faults in self-observation [1,2]. In different types of adherence questionnaires and patient interviews, the phrasing of questions, the way a question is asked, the >

Figure 1: Measurement methods used for multiple medication adherence.



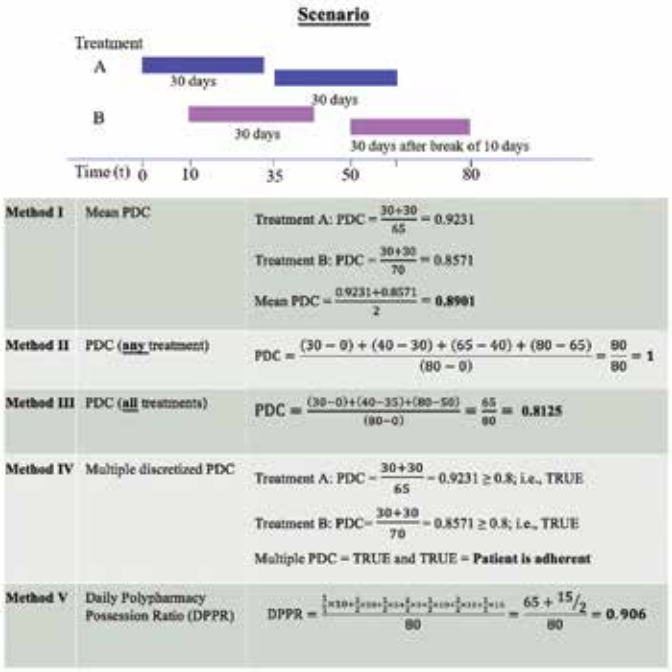
Note: Some studies used more than one measure to calculate multiple medication adherence.

Table 1. Most commonly used measures to assess multiple medication adherence

Type of Measure	Name of Measure Used	Number of Studies identified using the Measure
Self-Reported Measures	Single or Multi-item Questionnaire (Including MMAS)	72
	Interviews (Telephone/face-to-face)	9
	Informant Rating	5
	Other	6
Quasi-Objective Measures	Proportion of Days Covered (PDC)	29
	Medication Possession Ratio (MPR)	25
	Time to Discontinuation	18
	Persistence Rate	14
	Medication Gaps	6
	Other	20

Note: Some studies used more than one measure to calculate multiple medication adherence.

Table 2: Illustration of different measures used to calculate multiple medication adherence



mode of communication (face-to-face, paper and pen, or telephone interview), the skills of the interviewer, and the aptitude of the respondent to understand the question and willingness to provide information can influence the accuracy of responses [3]. These differences play an important role and further question the validity of self-report methods used to estimate MMA.

In this systematic review, 54.3% (N= 82) of the studies identified several quasi-objective measures deriving MMA using prescription refill data, pharmacy claims data, medical records, administrative claims data, pill counting, and electronic adherence monitoring data (Table 1). Few studies used multiple quasi-objective measures. The working group found that where these quasi-objective methods were employed to measure MMA, Proportion of Days Covered (PDC) followed by Medication Possession Ratio (MPR) was most widely used by included studies. Both PDC and MPR are generally reported as percentage of the time when a patient has medication available [4,5]. However, MPR as commonly calculated has been reported to overestimate adherence by considering overlapping days of supply even for mono-pharmacotherapy [6]. Even though PDC includes an adjustment for overlapping days' supply of medication, it ignores the situations of early filling of prescriptions and stockpiling [6,7]. The review found that few studies (n=6) included "medication gaps" as a MMA measurement which derives the mean number of days for which medication was not available over the time (Table 1).

Our systematic review also revealed that while calculating MMA, measurements used for single treatment were implemented, however these studies reported including corrections to consider multiple treatments. For example, while deriving MPR or PDC for multiple treatments, following types of adherence measurement methods were observed:

- MPR/PDC was calculated for each treatment and then averaged to calculate mean MPR/PDC for polytherapy (Method I)
- MPR/PDC was calculated for any of the medications available (Method II)
- MPR/PDC for all medications (Method III) was calculated using only days when all the prescribed medications were available
- Multiple discretized MPR/PDC was calculated using a dichotomized adherence rate (≥80% yes/no) (Method IV) where all treatments needed to have an adherence above ≥80% to be adherent
- "Daily Polypharmacy Possession Ratio" (Method V) which summarizes the proportion of medications available for each day in the observation period.

Table 2 illustrates how MMA was derived using these five measurement methods based on the scenario. It was also observed that the last refill was either included or excluded while calculating MMA using the five measurement methods. Different measurement methods resulted in different values for adherence; however, it was difficult to identify which measurement method gave the correct estimate. Hence, we decided to run simulations that would help to recommend the best measurement method to calculate MMA.

Simulation for MMA

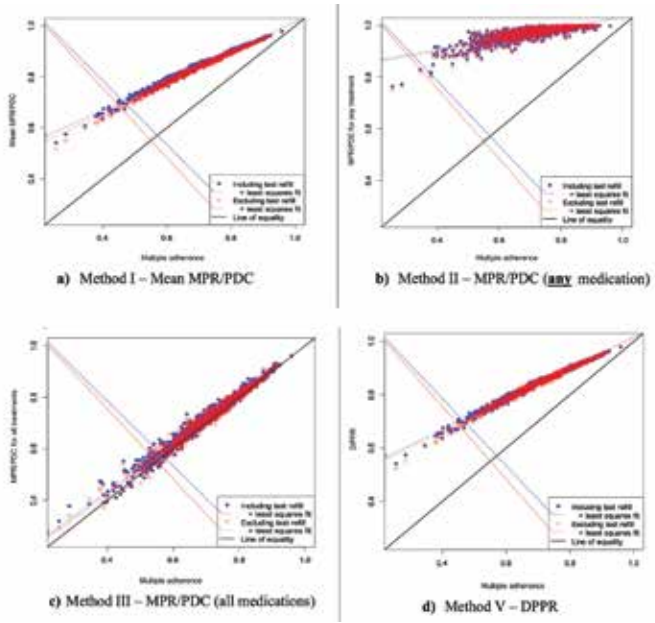
We carried out a simulation including data on 1000 patients to examine which measurement method was more exact. Using a random effect for subject and fixed effect for treatment, all patients were prescribed two treatments (A and B) throughout a 365-day period. Each dose was given for 30 days, although it was unknown whether a refill after 365 days existed or not. The first prescription started on the first day and a new prescription was refilled as soon as the previous prescription ran out and not before. Based on the simulated observable data, five measurement methods (Methods I, II, III, IV, and V) were derived. For each measure, metrics were calculated considering both approaches, one that included the final prescription and another that excluded the final prescription. Patients were classified as "adherent" if adherence value was

Table 3. Comparison of different measures used to calculate multiple medication adherence based on the simulation modeling

Method of MMA measurement	Metric		Mean	Standard deviation	Proportion of adherent patients
	'True' adherence		0.707	0.108	0.217
Method I	Mean MPR/PDC	Included last refill	0.847	0.062	0.792
		Excluded last refill	0.840	0.065	0.754
Method II	MPR/PDC (any treatment)	Included last refill	0.971	0.028	0.998
		Excluded last refill	0.969	0.029	0.998
Method III	MPR/PDC (all treatments)	Included last refill	0.722	0.103	0.243
		Excluded last refill	0.718	0.104	0.244
Method IV*	Multiple Discretized MPR/PDC	Included last refill	-	-	0.562
		Excluded last refill	-	-	0.488
Method V	DPPR	Included last refill	0.847	0.062	0.792
		Excluded last refill	0.844	0.064	0.766

**Because Method IV is a dichotomized variable, adherence ≥80% yes/no, mean and SD can't be calculated and as such it was derived using the data in the simulation.*

Figure 2: Comparison between true value and estimated value.



Note: A graph for Method IV is not shown in the figure due to the nature of the variable (dichotomized adherence ≥80% yes/no).

greater than or equal to 0.8. The different measurements were compared to the "true" adherence value (a pre-defined value in the model). The model had several limitations such as it used a uniform prescription length, included only two treatments and both treatments were prescribed throughout the interval. In addition, the model did not include any grace periods or early refills; consequently, PDC and MPR were equivalent.

The results of the simulation showed that the mean "true" adherence being 0.707 with 22% of patients adherent (Table 3). Note that for Method IV the value had to be derived using the simulated date due to it being a dichotomized variable. Method III, which calculated MPR/PDC when all medications were on hand, resulted in being closest to the true mean adherence value (0.718 when last refill was excluded and 0.722 when last refill was included) when compared to mean "true" adherence value (0.707). Method III classified 24% patients as adherent, being closest to true estimate of proportion of adherent patients. However, Method II, which calculated MPR/PDC when any treatment was available, resulted in the highest estimates (0.97) and as a result, 99.8% of the patients were adherent. Method IV provided an intermediate estimate for MMA between two extremes, still higher than values compared to true adherence.

Figure 2 depicts the extent to which each measurement method of adherence estimated true values. Method I, mean MPR/PDC, was found to overestimate MMA as the observed values lie above the line of equity (Figure 2a). This occurs when a patient is more adherent to one treatment over another and hence averaging introduces an estimation bias where the observed value appears higher than the true value. Method II further overestimates MMA (Figure 2b) as this method considers patients as adherent even if they only took one of their prescribed medications. Method II was also not sensitive to discontinuation of medications or using more than one medication. In contrast, values for Method III, which requires a patient to take all medications as prescribed, were observed to coincide with the line of equality (Figure 2c). The analyses concluded that Method III did not introduce an estimation bias and as such, more accurately estimated adherence for multiple medications. Furthermore, the Method III measure was a more accurate estimate when not including the last refill (shown by a red dotted line in Figure 2c, being closer to the line of equality). Method V, DPPR, was closer to the line of equality compared to Method I and II although still overestimating adherence (Figure 2d). These results were similar to those depicted in table 3. Based on the results of the simulation, Method III (MPR/PDC for all medications) seems to be the most accurate qualitative measurement for MMA.

The sensitivity (percentage of adherent patients correctly identified as adherent) for all methods of MMA including both scenarios (including/excluding last refill) ranged from 97% to 100% with Method III having the lowest percentage. For specificity (percentage of non-adherent patients correctly identified as non-adherent), including last refill the percentage ranging from 0 to 96 with Method II at 0% and Method III at 96%. The same pattern was seen, with Method III being closest to the true value, when excluding the last refill (Table 4).

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Table 4: Sensitivity and specificity of multiple adherence measures (vs "true")

		Mean MPR/PDC (Method I)	MPR/PDC any medication (Method II)	MPR/PDC all medications (Method III)	All MPR/PDCs ≥ 0.8 (Method V)
Include last refill	Sensitivity	100%	100%	98%	100%
	Specificity	26%	0%	96%	53%
Exclude last	Sensitivity	100%	100%	97%	100%
	Specificity	30%	0%	96%	61%

Note: Data for Method IV are not shown in the table due to being a dichotomized variable.

Conclusion

In our literature review, we identified several different ways of measuring MMA. Although self-report methods are the most commonly reported, this was probably due to convenience rather than the validity of such approaches. For studies using methods other than self-report, the accuracy of the quasi-objective methods needs further research. After conducting a simulation, we found that MPR or PDC including all prescribed medications (Method III) was the most accurate method, being closest to the true value, for measuring MMA. Following this paper, future research needs to be conducted to validate our findings.

References

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Additional information:
This article is based on a workshop presented at the 19th Annual European Congress in Vienna, Austria.

To learn more about the by the ISPOR Multiple Medication Adherence Measurement Working Group, go to https://www.ispor.org/sigs/multiple-medication-adherence-measurement.asp.