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PHARMACOEPIDEMIOLOGY REPORT

# The Assessment of Refill Compliance Using Pharmacy Records: Methods, Validity, and Applications

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**ABSTRACT.** The refill records of computerized pharmacy systems are used increasingly as a source of compliance information. We reviewed the English-language literature to develop a typology of methods for assessing refill compliance (RC), to describe the epidemiology of compliance in obtaining medications, to identify studies that attempted to validate RC measures, to describe clinical features that predicted RC, and to describe the uses of RC measures in epidemiologic and health services research. In most of the 41 studies reviewed, patients obtained less medication than prescribed; gaps in treatment were common. Of the studies that assessed the validity of RC measures, most found significant associations between RC and other compliance measures, as well as measures of drug presence (e.g., serum drug levels) or physiologic drug effects. Refill compliance was generally not correlated with demographic characteristics of study populations, was higher among drugs with fewer daily doses, and was inconsistently associated with the total number of drugs prescribed. We conclude that, though some methodologic problems require further study, RC measures can be a useful source of compliance information in population-based studies when direct measurement of medication consumption is not feasible. *Copyright © 1997 Elsevier Science Inc.* J CLIN EPIDEMIOL 50;1:105–116, 1997.

**KEY WORDS.** Patient compliance, drug prescriptions, drug utilization, community pharmacy

## INTRODUCTION

The process of medication compliance begins with appointment-keeping, followed by submission of a prescription to a pharmacy, acquisition of medications from the pharmacy, and medication consumption [1]. Researchers have developed compliance measures for all of the steps in this process, because accurate assessment of drug effects requires evidence that the medication was obtained and taken [2]. Most compliance studies have assessed medication consumption, and some have evaluated appointment-keeping or lapses in obtaining initial drug prescriptions [3,4]. Though numerous measures of medication acquisition have been proposed, the validity and utility of these measures have not been assessed systematically.

Pill counts and pharmacologic tracers have been the customary measures of drug consumption in randomized clinical trials [5]. Electronic compliance monitors, which record the actual time at which pill bottles are opened and medications are presumably taken, have shown that pill counts typically overestimate medication consumption and cannot evaluate the timing of doses, which may critically influence the efficacy and adverse effects of treatment. Such electronic compliance monitoring has become the new "gold standard" for pharmacologic treatment studies [5–7]. These methods are difficult to use clinically because of the expense, effort, and time necessary to obtain measurements. Other measures, such as serum drug levels, assessment of physiologic drug effects, patient self-report, and clinician assessment have also been evaluated in clinical settings [5,8]. Even these measures may be of little use in studies of large populations, such as pharmacoepidemiology or health services research. In such studies, pharmacy refill records can provide otherwise unobtainable information about the pattern and timing of drug exposure, and the determinants and consequences of adherence. In this paper, we will (1) review the methods developed to assess medication refill compliance from pharmacy records and propose a taxonomy for classification of these measures; (2) describe the patterns of refill compliance observed in these studies; (3) summarize the evidence for the validity of these techniques; and (4) evaluate the uses and problems of refill compliance measures.

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## METHODS OF LITERATURE REVIEW

To identify studies that employed measures of refill compli-

January, 1969 to June, 1994. MEDLINE searches were performed using the key words: patient compliance, cooperative behavior, patient acceptance of health care, patient dropouts, treatment refusal, drug prescription, drug utilization, community pharmacy services, and hospital pharmacy services. Additional papers were identified from the reference lists of these articles and from searches of the Scientific Citation Index for important references.

All studies that described measures of refill compliance were reviewed independently by the two study investigators for information in four categories: the epidemiology of refill compliance; comparison with other compliance measures; validation through association with measures of drug presence (such as serum drug levels) or physiologic drug effects (such as blood pressure control for patients prescribed antihypertensive drugs); and identification of clinical features associated with variations in refill compliance. In some instances, data presented in the original papers could be reanalyzed to facilitate comparisons. To estimate compliance for an entire study population when refill compliance was reported only for subgroups, we calculated a "weighted" measure by multiplying the refill compliance for each subgroup by the number of patients in that group, and dividing the sum of these products by the total number of patients in the study. We also conducted additional analyses of our own published studies using these measures to allow better comparison with the work of other researchers [9–12]. After the independent abstraction of all papers, the reviews were compared to attain a consensus. Meta-analytic methods were not used to aggregate study findings because of the diversity of refill compliance measures, clinical settings, and validation strategies.

## RESULTS

### *Study Settings and Data Requirements*

In all, 41 studies that employed refill compliance measures were identified from the United States, the United Kingdom, Australia, and Finland. [9–49]. These studies were generally conducted in health care systems that provided a financial incentive to obtain all medications from pharmacies with centralized records. Study sites included United States Department of Veterans Affairs (VA) Medical Centers [9–12,17,21,22,26,27,29,32,49], health maintenance organizations (HMOs) [31,33,36,38,43,47], the administrative data bases of Medicaid programs [34,35,39,44,46,48], medical practices [13,16,18,28], single pharmacies [15,25, 40–42], and insurance plans [37,45]. Three studies assessed the completeness of medication acquisition within the system. One study in the Group Health Cooperative of Puget Sound reported that more than 90% of prescriptions were filled within the HMO [31]. In two VA studies, 98–100% of patients reported obtaining all medications at that facility [9,32].

of medications dispensed at each pharmacy fill, and the dates of prescription fills. Though dosage instructions (pills per dose and total doses per day) were available in most pharmacy systems, studies in Medicaid programs imputed dosage instructions from pharmacy policies restricting prescription size to a defined "days' supply" [48].

### *Typology of Measures of Refill Compliance*

The measures of refill compliance in these studies could be characterized by three attributes: (1) the distribution of the compliance variable [continuous (C) versus dichotomous (D)]; (2) the number of refill intervals evaluated [either single (S) or multiple (M) intervals]; and (3) the use of the measure to assess either the time period over which medications were available (A) to the patient or the time intervals during which gaps (G) in therapy occurred. A simple notation consisting of a combination of three letters (e.g., CMA) thus defines a typology of refill compliance measures. Calculation of each type of measure is demonstrated using hypothetical refill data (Table 1), beginning with an initial fill on day 0 and ending on day 450 after a total of six medication fills. Figure 1 demonstrates the time span of each prescription for these hypothetical data, periods of overlap, treatment gaps, and fluctuations in two typical compliance indices. In the sample data, the initial three prescriptions are for a 30-day supply, while the subsequent three prescriptions are for 90-day supplies. If the final day of the measurement period is defined by the date of the last medication fill in the series (Day 250 in Table 1), the calculated compliance indices can be defined as "embedded" in the series of refills. If the end of the period of observation is identified by an arbitrary date (Day 450 in Table 1), the compliance measures include a "terminal gap" after the final prescription fill.

(1) CONTINUOUS, SINGLE-INTERVAL MEASURES OF MEDICATION AVAILABILITY (CSA). Using the hypothetical data in Table 1, a CSA measure for each of the six refill intervals is calculated by dividing the days' supply obtained during each interval by the total days in the interval. For example, in interval 3 of the hypothetical data, 30 days of medications are obtained over a period of 90 days, for a CSA of 0.33.

(2) CONTINUOUS, SINGLE-INTERVAL MEASURES OF MEDICATION GAPS (CSG). Such measures identify time periods during which medication exposure is unlikely by assuming that the medication is taken exactly as prescribed until the supply is exhausted, though patients may in fact be partially compliant with their drugs throughout such an interval. In interval 3 of Table 1, the 30-day supply is presumed to have been depleted by day 90, leaving a 60-day medication gap until the next fill on day 150, so that CSG = 60/90 = 0.67. When no gap occurs, as in intervals 1, 2, 4, and 5 of Table

**TABLE 1. Hypothetical refill compliance data and calculation of continuous compliance indices**

| Prescription interval | Day of fill | Days' supply obtained | Days in interval[a] | Single interval compliance (CSA) | Cumulative days' supply obtained | Continuous measure of medication acquisition (CMA) | Days with treatment gap in interval | Single interval gap (CSG) | Total days of treatment gap[b] | Continuous measure of medication gaps (CMG) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 30 | 30 | 1.00 | 30 | 1.00 | 0 | 0.00 | 0 | 0.00 |
| 2 | 30 | 30 | 30 | 1.00 | 60 | 1.00 | 0 | 0.00 | 0 | 0.00 |
| 3 | 60 | 30 | 90 | 0.33 | 90 | 0.60 | 60 | 0.67 | 60 | 0.40 |
| 4 | 150 | 90 | 50 | 1.80 | 180 | 0.90 | 0 | 0.00 | 60 | 0.30 |
| 5 | 200 | 90 | 50 | 1.80 | 270 | 1.08 | 0 | 0.00 | 60 | 0.24 |
| 6 | 250 | 90 | 200 | 0.45 | 360 | 0.80 | 110 | 0.55 | 90 | 0.20 |
| — | 450[c] | — | — | | | | | | | |

Calculation of continuous refill compliance indices (abbreviations): CSA = Days' supply obtained at beginning of interval/Days in interval; CMA = Cumulative days' supply obtained/Total days to next fill or end of observation period; CSG = (Days in interval − days' supply obtained at beginning of interval)/Days in interval, CSG = 0.00 if days in interval ≤ days' supply obtained; CMG = Total days of treatment gaps/Total days to next fill or end of observation period.

[a]Defined as days until next fill or end of observation period.

[b]After correction for any oversupplies obtained in previous intervals.

[c]Arbitrary day ending observation period.

(3) CONTINUOUS, MULTIPLE-INTERVAL MEASURES OF MEDICATION AVAILABILITY (CMA). This measure is generally calculated as the sum of the days' supply obtained over a series of intervals, divided by the total days from the beginning to end of the time period. The hypothetical compliance data in Table 1 demonstrate a common discrepancy between the "embedded" CMA measure (270 days worth of medications obtained over 250 days, CMA = 1.08) which can be calculated between prescription 1 and prescription 6, and the much lower estimate of CMA (360 days worth of medications obtained by the end of observation on day 450, CMA = 0.8) if the terminal gap after interval 6 is included in the calculation. In some studies, the number of refills obtained (rather than the days' supply obtained)

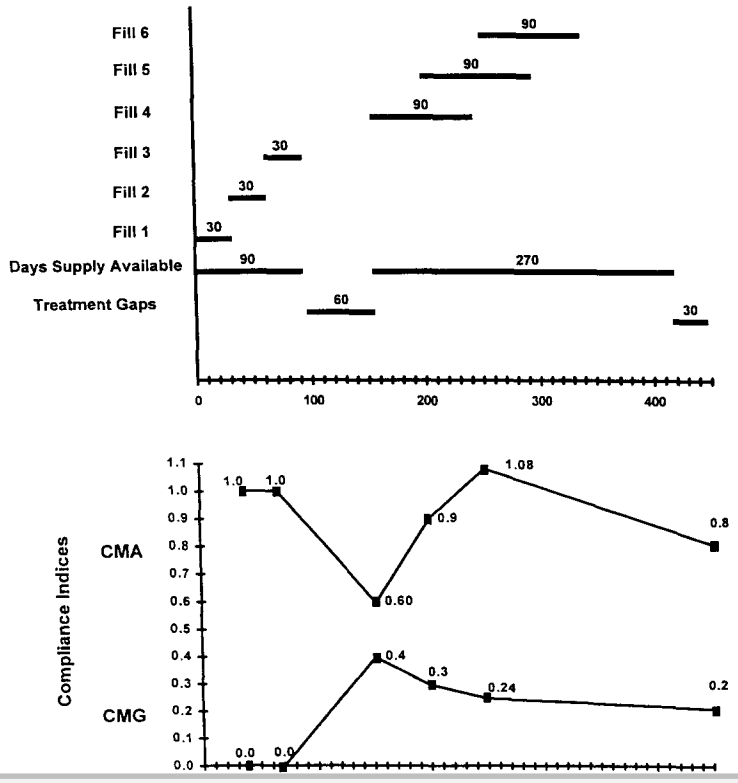


**FIGURE 1. The upper panel depicts the time span of six prescription fills from Table 1, periods of drug availability and treatment gaps. The lower panel portrays fluctuations in compliance indices CMA (a continuous, multiple-interval measure of medication availability) and CMG (a continuous multiple-interval measure of treatment gaps) over the same time period.**

divided by the expected number of refills in a given time span was calculated as an ordinal CMA measure [17,22,27,32].

CMA measures described medication oversupplies in different ways. For example, in Table 1, the patient accumulates an 80-day oversupply of medications during prescription intervals 4 and 5. Such an oversupply can be subtracted from 1.0 to reflect variance from perfect compliance [23], or the proportion of medications obtained can be greater than 1.0 as exemplified in Table 1, where CMA = 1.08 at the end of interval 5 [9,16].

(4) CONTINUOUS, MULTIPLE-INTERVAL MEASURES OF MEDICATION GAPS (CMG). This measure divides the total number of days in treatment gaps by the duration of the time period of interest. In Table 1, 90 days without medication occurred over 450 days of observation, so that CMG = 0.20. Some CMG measures adjust for oversupplies obtained during previous prescription intervals which reduces the duration of treatment gaps [9]. In Table 1, the 90-day supply obtained on Day 250 and the 80-day surplus already available are presumed to be depleted by Day 450, the end of the observation period, resulting in 200 − (90 + 80) = 30 days of treatment gap during interval 6, rather than the 110-day gap if only data from interval 6 were used.

The end date of the analysis period may be either the last refill date [9] or an arbitrary date, such as the end of a calendar year [39,46,48]. In the first case, all gaps are "embedded" within a series of fills. In the second case, a "terminal gap" may be present after the last refill. Both measures assume that gaps are due to reduced compliance rather than to clinician instructions for temporary (in the case of "embedded" gaps) or permanent (in the case of "terminal" gaps) drug cessation, or to acquisition of drugs outside the pharmacy system. When a measure of embedded gaps is used, the CMG index can no longer be directly derived from the value of the CMA index (unlike the relationship between CSA and CSG), because periods of oversupply can be interspersed with periods of medication depletion, as occurs at the end of interval 5 in Table 1. When a terminal gap is sufficiently long to deplete all oversupplies, CMA = (1 − CMG), as illustrated at the end of interval 6 in Table 1.

(5–8) DICHOTOMOUS, SINGLE-, OR MULTIPLE-INTERVAL MEASURES OF MEDICATION AVAILABILITY FOR MEDICATION GAPS (DSA, DSG, DMA, DMG). These measures used dichotomous cutoffs to distinguish "compliant" from "partially compliant" individuals. In many cases, dichotomous measures were created from continuous indices, using various cutoffs with no clinical or pharmacological rationale offered for the choice of a particular threshold value. Alternatively, patients were defined as noncompliant if a gap of a specified length was identified over a period of multiple refills [20,26,29,37,41]. For example, the patient obtaining the hypothetical refill data in Table 1 would be classified as noncompliant if the presence of two prolonged treatment gaps, regardless of his CMA or CMG.

### *Epidemiology of Refill Compliance*

Table 2 presents the findings of studies that described the epidemiology of refill compliance using CMA or DMA measures, while Table 3 describes the epidemiology of multiple-interval medication gaps (CMG or DMG). Mean CMA was less than 1.0 in 17 of the 20 studies in which it was assessed. Thus, most patients obtained less of their medication than was prescribed over time periods ranging from 2 to 24 months. The wide range in refill compliance among individuals is indicated by the large standard deviation around these mean values. The compliance distributions for CMA measures generally were unimodal, bell-shaped, and skewed toward reduced refill compliance [11]. The three studies in which CMA was greater than 1.0, indicating acquisition of more medication than prescribed, were conducted in VA Medical Centers which routinely dispensed 90- to 100-day medication supplies for inexpensive, long-term drugs. One study demonstrated that distribution of such large medication supplies increased overall medication acquisition and reduced gaps in treatment [12].

Six studies in Table 2 reported CMA measures that allowed assessment of drug stockpiling, defined as acquisition of a 10% surplus or more. The prevalence of stockpiling in these studies was between 4.8% and 35.1% [9–13,16]. The characteristics of patients who stockpiled medications were not described, and no attempt was made to determine whether stockpiling led to overconsumption or simply to hoarding of drugs.

In Table 3, the four studies using CMG measures that assessed "embedded" gaps [9–12] reported gaps in treatment only about half as large as the studies that included "terminal gaps" [39,46].

### *Associations Between Refill Compliance Measures and Other Adherence Measures*

Five studies in our review reported statistical comparisons between measures of refill compliance and other compliance behaviors (Table 4). The association between refill compliance and appointment-keeping was statistically significant, but weak ($r = 0.20$), in one study [22]. Of the four studies that correlated refill compliance with measures of self-reported medication consumption, two [16,25] reported significant associations, while one [29] did not. In the fourth study [11], the overall correlation between CMA and CMG refill compliance measures and self-reported compliance, as measured by a validated four-item self-reported scale [50], was not statistically significant. However, patients providing "noncompliant" responses to all four questions had significantly lower CMA (0.89 ± 0.14) than those who gave

**TABLE 2. The epidemiology of refill compliance: Multi-interval measures of medication availability**

| Study | *n* | Setting | Duration (months) | Medication(s) | CMA (±SD) | Prevalence of drug stockpiling (CMA ≥ 110%) |
|---|---|---|---|---|---|---|
| [13] | 58 | British general practice | 11 | All prescribed | 0.84 ± 0.24 | 12.1% |
| | 62 | | 4 | Prenatal iron supplements | 0.67 ± 0.24 | 4.8% |
| [14] | 59 | University hospital | 12 | Atropine | 0.56 | ND |
| [16] | 71 | British general practice | 24 | All prescribed | ND | 11.9% |
| [17] | 419 | VAMC | 6 | Non-PRN drugs | 0.64 | ND |
| | | | 6 | PRN drugs | 0.40 | ND |
| [19,23] | 324 | Finnish population survey | 2 | Antihypertensives | ND | 11.5% (>100% compliance) |
| [22] | 171 | VAMC | 6 | Arthritis drugs | 0.64 ± 0.32 | 4.1% (>100% compliance) |
| [24] | 1058 | 100 private pharmacies | 12 | All prescribed | 0.54 ± 0.36 | ND |
| [42] | 276 | University hospital | 3 | Cardiovascular drugs | 0.62 | ND |
| [27] | 30 | VAMC-pharmacist consultation | 6 | Theophylline | 0.96 | ND |
| | 30 | VAMC-no consultation | 6 | Theophylline | 0.76 | ND |
| [9] | 52 | VAMC | 15 ± 4 | Phenytoin | 0.91 ± 0.21 | 15.4% |
| | 73 | VAMC | 14 ± 5 | Antihypertensives | 1.02 ± 0.23 | 33.0% |
| [32] | 93 | VAMC | ND | Lithium carbonate | 0.73 | ND |
| [10] | 85 | VAMC | 12 | All prescribed | 1.09 ± 0.47 | 27.1% |
| [11] | 118 | VAMC | 14 ± 4 | Antihypertensives | 0.96 ± 0.25 | 23.9% |
| [34] | 1135 | Medicaid | 12 | Clonidine | 0.67 | ND |
| [35] | 8894 | Medicaid | 12 | Antihypertensives | 0.62 | ND |
| [33] | 453 | 3 HMOs | 6 | Atenolol | 0.49 | ND |
| [37] | 19029 | Insurance claims | 20 | 12 selected drugs | 0.72 | ND |
| [38] | 170 | HMO | 4 | Pentoxifylline | 0.58 | ND |
| [12] | 176 | 10 VAMCs | 9 ± 5 | All prescribed | 0.92 ± 0.25 | 13.0% |
| | 114 | VAMC | 14 ± 7 | Digoxin | 1.04 ± 0.28 | 35.1% |
| [45] | 2289 | Managed care plans | 12 | Potassium supplements | 0.74 | ND |
| [44] | 78 | Medicaid | 12 | Glyburide | 0.58 ± 0.07 | ND |
| [47] | 119 | HMO | 12 | Theophylline | 0.79 ± 0.34 | ND |
| | | | | Inhaled steroids | 0.54 ± 0.43 | ND |
| | | | | Inhaled cromolyn | 0.44 ± 0.34 | ND |

Abbreviations: ND = no data, VAMC = Veterans Affairs Medical Center, HMO = health maintenance organization.

0.26, $p = 0.02$). In one small study, 23% more individuals reported compliance than were identified as compliant by a DMG measure of refill compliance [29]. A CMG measure, but not CMA calculated with the same data, correlated weakly with provider assessments of compliance in one study [11]. In the one study that correlated refill compliance with pill counts [16], CMA over a two-year period was strongly associated with pill count compliance ($r = 0.68$, $p < 0.001$). From a graph in that publication, the sensitivity of partial compliance (<80%) in obtaining refills for detecting partial compliance (<80%) in consuming them could be estimated as 53%, with a specificity of 93%. No

**TABLE 3. The epidemiology of refill compliance: Multi-interval measures of medication gaps**

| Study | *n* | Setting | Duration (months) | Medication(s) | CMG Proportion of time without medication (±SD) |
|---|---|---|---|---|---|
| [9] | 52 | VAMC | 15 ± 4 | Phenytoin | 0.16 ± 0.18 |
| | 73 | VAMC | 14 ± 5 | Antihypertensives | 0.10 ± 0.12 |
| [10] | 85 | VAMC | 12 | All prescribed | 0.14 ± 0.09 |
| [11] | 118 | VAMC | 14 ± 4 | Antihypertensives | 0.13 ± 0.14 |
| [12] | 176 | 10 VAMCs | 9 ± 5 | All prescribed | 0.15 ± 0.18 |
| | 114 | VAMC | 14 ± 7 | Digoxin | 0.10 ± 0.14 |
| [39][a] | 2440 | Medicaid | 12 | Glaucoma drugs | 0.31 ± 0.31 |
| [46][a] | 7247 | Medicaid | 12 | Heart failure drugs | 0.30 ± 0.30 |

Abbreviations: ND = no data, VAMC = Veterans Affairs Medical Center.

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