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A METHOD FOR ASSESSING DRUG THERAPY APPROPRIATENESS*

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Abstract—This study evaluated the reliability of a new medication appropriateness index. Using the index, independent assessments were made of chronic medications taken by 10 ambulatory, elderly male patients by a clinical pharmacist and an internist-geriatrician. Their overall inter-rater agreement for medication appropriateness (ppos) was 0.88, and for medication inappropriateness (pneg) was 0.95; the overall kappa was 0.83. Their intra-rater agreement for ppos was 0.94 overall, for pneg was 0.98 overall while the overall kappa was 0.92. The chronic medications taken by 10 different ambulatory elderly male patients were independently evaluated by two different clinical pharmacists. Their overall inter-rater agreement for ppos was 0.76, and for pneg was 0.93, while the overall kappa was 0.59. This new index provides a reliable method to assess drug therapy appropriateness. Its use may be applicable as a quality of care outcome measure in health services research and in institutional quality assurance programs.

Drug therapy Elderly Physicians Quality of Health Care Drug evaluation Reliability

INTRODUCTION

Clinicians face a demanding task when prescribing medications. Rational prescribing requires the practitioner to make an accurate diagnosis, understand the pathophysiology of the disease or condition, know the pharmacology of the drug prescribed, and consider the many other elements of appropriate medication use [1]. Although medications may cure or palliate, they also may be unnecessary, ineffective, impractical, harmful and costly. These undesirable aspects of medication have been reported to be important causes of morbidity, institutionalization and cost, particularly among elderly populations [2]. Thus, the appropriate use and the misuse of medications are active areas of research, and primary targets for quality assurance activities by health care institutions, the Joint Commission on Accreditation of Health Care Organizations and federal regulatory agencies. Consequently, the accurate assessment of appropriate medication use is important for

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patient care, research and quality assurance programs.

To date, most research on medication appropriateness has focused on adverse drug reactions [3, 4]. Two well-known adverse drug reaction scales with good psychometric properties include a 56-item scale developed by Kramer *et al.* [5], and a 10-item scale developed by Naranjo *et al.* [6]. There is little published work regarding standardized methods that consider other potential drug-related problems. Institutional drug use reviews and medication evaluation scales derived from research studies [7–11] have been reported, but these strategies are limited since they often apply only to a particular institution, a specific drug or drug class, or a particular patient group.

Accordingly, as part of a randomized controlled health services research trial we are currently conducting, we sought to develop a reliable, standardized method to address multiple elements of drug therapy prescribing, applicable to a variety of medications, clinical conditions and settings. This report describes the development of the Medication Appropriateness Index (MAI), and the results of its reliability testing.

METHODS

Index development

To identify articles regarding medication assessment measures or evaluation scales, we conducted a Medline search and a manual search of several pharmacy specialty journals. Several articles were identified that discussed drug-related problems [9–15]. Based on clinical experience and this background literature, a clinical pharmacist (JTH) and an internist-geriatrician (KES) independently identified key elements of desirable medication use. From these elements, the two investigators created the Medication Appropriateness Index (MAI) (Table 1) consisting of 10 criteria worded as questions. For example, criterion 1 asks, is there an indication for the drug? General instructions for the use of the index, specific instructions regarding how to answer each of the 10

Table 1. Medication Appropriateness Index*

To assess the appropriateness of the drug, please answer the following questions and circle the applicable score:				
1. Is there an indication for the drug? Comments:	1 Indicated	2	3 Not Indicated	9 DK†
2. Is the medication effective for the condition? Comments:	1 Effective	2	3 Ineffective	9 DK
3. Is the dosage correct? Comments:	1 Correct	2	3 Incorrect	9 DK
4. Are the directions correct? Comments:	1 Correct	2	3 Incorrect	9 DK
5. Are the directions practical? Comments:	1 Practical	2	3 Impractical	9 DK
6. Are there clinically significant drug–drug interactions? Comments:	1 Insignificant	2	3 Significant	9 DK
7. Are there clinically significant drug–disease/condition interactions? Comments:	1 Insignificant	2	3 Significant	9 DK
8. Is there unnecessary duplication with other drug(s)? Comments:	1 Necessary	2	3 Unnecessary	9 DK
9. Is the duration of therapy acceptable? Comments:	1 Acceptable	2	3 Unacceptable	9 DK
10. Is this drug the least expensive alternative compared to others of equal utility? Comments:	1 Least expensive	2	3 Most expensive	9 DK

*Complete instructions in the use of the scale are available upon request.
†Don't know.

questions, and operational definitions for each criterion were developed. The operational definitions are:

Indication: the sign, symptom, disease, or condition for which the medication is prescribed;
Effectiveness: producing a beneficial result;
Dosage: total amount of medication taken per 24 hour period;
Directions: instructions to the patient for the proper use of a medication;
Practicality: capability of being used or being put into practice;
Drug–drug interaction: the effect that the administration of one medication has on another drug; clinical significance connotes a harmful interaction;
Drug–disease interaction: the effect that the drug has on a pre-existing disease or condition; clinical significance connotes a harmful interaction;
Unnecessary duplication: non-beneficial or risky prescribing of two or more drugs from the same chemical or pharmacological class;
Duration: length of therapy;
Expensiveness: cost of the drug in comparison to other agents of equal efficacy and safety.

For each criterion, examples of appropriate and inappropriate ratings were provided. Instructions for criterion two, effectiveness, is presented in the Appendix. Full instructions for using the scale are available upon request.

The index was originally developed with a 5-point modified Likert scale for each criterion. The index was pilot-tested and subsequently revised to utilize a 3-point scale. For each criterion a rating of 1 represented appropriate medication use; a rating of 2 represented marginally appropriate medication use; and a rating of 3 represented inappropriate use.

Index evaluation

After the pilot-testing, a formal evaluation was conducted of the MAI's reliability. A research assistant selected a random sample of 10 elderly patients who regularly attended a Veterans Affairs (VA) General Internal Medicine Clinic and who took five or more regularly scheduled drugs ($n = 60$ drugs). The research assistant then abstracted from each patient's medical chart a problem list, the previous 2 years of medication use, outpatient and inpatient physician notes, and laboratory and diagnostic test results. A separate pilot study had determined that these abstracted materials could be collected in a reproducible manner. Utilizing these chart abstracts and the MAI, the index originators (JTH and KES) performed independent assessments of the patients' medication use at baseline and 2–4 months later. Both evaluators were blinded to patient and physician identities.

To determine the generalizability of the index, two different clinical pharmacists with specialty training in geriatrics (KMU, IKL) were instructed in the proper use of the index. The research assistant selected for them a second random sample of 10 elderly patients who regularly attended a VA General Internal Medicine Clinic and who took five or more regularly scheduled drugs ($n = 105$ drugs). The purpose of selecting a second sample was to further test the MAI's performance in different patients who took different medications. Utilizing chart abstracts and the MAI, the two clinical pharmacists performed independent blinded assessments of drug therapy appropriateness.

Information was also collected about practical considerations, such as the average time to prepare the abstract, to review the materials and to evaluate the appropriateness of each drug.

Statistical analyses

Agreement was assessed both for inter-rater and intra-rater reliability. For purposes of presentation, the data are pooled over occasion and/or observer. For example, the intra-rater analyses are not disaggregated according to rater, but are based upon a 2×2 table which includes data from both raters.

For the primary analyses, ratings for individual items were dichotomized into appropriate (i.e. "1" or "2") vs inappropriate (i.e. "3"). Additionally, drugs rated as being "not indicated" (criterion 1) were also rated as having inappropriate duration and expense (criteria 9 and 10). To consider a specific drug's overall appropriateness, we also combined the 10 ratings. Thus, a drug was rated inappropriate overall if one or more items received a rating of "3"; otherwise, the drug overall was rated appropriate. Both agreement and chance-adjusted agreement were determined, the latter being quantified using kappa statistics [16]. In addition, weighted kappa statistics were computed with the difference between a "1" and "2" rating weighted 0.25, the difference between a "2" and "3" rating weighted 0.75, and the difference between a "1" and "3" rating weighted 1.00. This weighting reflected the index originators'

judgment that the difference between a "1" or a "2" and a "3" rating was clinically more important than the difference between a "1" and "2" rating. These weighted results were similar to the unweighted results and thus are not reported. Kappa statistics were supplemented with the proportion of appropriate (ppos) and inappropriate (pneg) ratings for which the two evaluators were in agreement [17]. Items with fewer than 10 inappropriate ratings were noted. These items were not included in the calculation of median within-item pneg, or kappa.

RESULTS

Inter-rater reliability

To determine the initial inter-rater reliability of the MAI, responses of the clinical pharmacist and the internist-geriatrician were cross-classified (Table 2). For example, in 120 paired drug ratings for the criterion, indication, 105 were assessed as appropriate by both raters (column A). There were few inappropriate ratings (columns B, C and D) for the effectiveness, drug–drug interactions, drug–disease interactions, and therapeutic duplication questions. The most inappropriate ratings were found for correct directions, expense and dosage questions. Overall, 91 of the 120 (74.8%) ratings had one or more questions rated as inappropriate. Inter-rater agreement for individual items varied from 92 to 100%; when all rated drugs were considered, inter-rater agreement was 93%.

The chance adjusted agreement reflected by the kappa statistic was excellent, and ranged from 0.71–0.96 (median, 0.88) for individual questions and 0.83 for drugs overall [16]. The ppos for individual questions ranged from 0.94–1.0 (median, 0.99) and was 0.88 overall. The pneg for individual questions ranged from 0.75 to 0.97 (median, 0.92) and was 0.95 overall.

To determine the inter-rater reliability of the index by evaluators other than the index originators, assessments made by two different clinical pharmacists (KMU, IKL) were compared (Table 3). The responses for individual items followed the same patterns as those by the index originators. When all drugs were considered, the overall inter-rater agreement was high (89%). The kappa statistic of 0.59 for drugs overall was good [16] with ppos and pneg overall being 0.76 and 0.93, respectively.

Intra-rater reliability

To determine the intra-rater reliability of the index, the baseline ratings of the clinical pharmacist and the internist-geriatrician were compared to ratings made approximately two to four months later (Table 4). Again, the patterns of responses for individual questions were similar to prior comparisons. The intra-rater agreement for drugs overall was 97%; the kappa statistic was 0.92, with ppos of 0.94 and pneg of 0.98.

Practical considerations

The research assistant required approximately 45 minutes to prepare each medical information abstract utilized by the raters. The raters spent approximately 10 minutes evaluating the appropriateness of each drug.

Table 2. Pooled inter-rater agreement between a clinical pharmacist and an internist-geriatrician (n = 120 paired ratings)

Question	A	B	C	D	ppos	pneg	Kappa
1. Indication	105	0	1	14	0.99	0.97	0.96
2. Effectiveness	112	0	0	8	1.00	1.00*	1.00*
3. Dosage	89	2	8	21	0.95	0.81	0.76
4. Correct directions	62	6	2	50	0.94	0.93	0.87
5. Practical directions	100	1	7	12	0.96	0.75	0.71
6. Drug–drug interaction	118	0	2	0	0.99	0.00*	0.00*
7. Drug–disease interaction	118	2	0	0	0.99	0.00*	0.00*
8. Duplication	120	0	0	0	1.00	—*	1.00*
9. Duration	102	1	2	15	0.99	0.91	0.89
10. Expense	76	5	1	38	0.96	0.93	0.89
Overall	29	2	6	83	0.88	0.95	0.83

A: Both raters scored item as appropriate.
B: Rater 1 scored item as appropriate, Rater 2 scored item as inappropriate.
C: Rater 1 scored item as inappropriate, Rater 2 scored item as appropriate.
D: Both raters scored item as inappropriate.
*Inadequate variability in ratings.

Table 3. Inter-rater agreement between two clinical pharmacists (n = 105 ratings)

Question	A	B	C	D	ppos	pneg	Kappa
1. Indication	84	5	4	12	0.95	0.73	0.68
2. Effectiveness	99	3	1	2	0.98	0.50*	0.48*
3. Dosage	76	4	12	13	0.90	0.62	0.53
4. Correct directions	63	2	7	33	0.93	0.88	0.81
5. Practical directions	72	3	7	23	0.94	0.82	0.76
6. Drug–drug interaction	104	0	1	0	0.99	0.00*	0.00*
7. Drug–disease interaction	102	0	3	0	0.99	0.00*	0.00*
8. Duplication	99	1	0	5	0.99	0.91*	0.90*
9. Duration	77	7	9	12	0.91	0.60	0.51
10. Expense	69	6	6	24	0.92	0.80	0.72
Overall	17	3	8	77	0.76	0.93	0.59

A: Both raters scored item as appropriate.
B: Rater 1 scored item as appropriate, Rater 2 scored item as inappropriate.
C: Rater 1 scored item as inappropriate, Rater 2 scored item as appropriate.
D: Both raters scored item as inappropriate.
*Inadequate variability in ratings.

DISCUSSION

While the potential benefits of medications are great, so are their potential risks. In order to identify these negative effects of medications, clinicians and researchers require standardized, reliable methods to assess the appropriateness of drug therapy. The results of these preliminary analyses demonstrate that the MAI may have the capacity to fill this requirement.

The MAI appears to be sensible [18, 19]. It contains 10 elements of medication prescribing that are essential to the evaluation of potential drug-related problems [9–15, 20] and thus appears to meet both face and content validity criteria. However, several important areas of medication use are not addressed by the MAI. Although adverse drug reactions due to drug–drug or drug–disease interactions are considered, the full scope of adverse drug reactions is not included, both because the topic is large and difficult and because excellent scales already exist to assess adverse drug reaction causality [3–6]. Patient medication compliance is also not incorporated, since all items deal with decisions or outcomes primarily related to the prescriber. Finally, the MAI is easy to use due to its explicit instructions, but the amount of time required to apply the index (10 minutes/drug) may preclude its use in busy clinical practice settings. However, this time requirement is consistent with the time necessary to assess adverse drug reaction causality [5, 6].

This clinical index also appears to be reliable as quantitatively assessed by testing inter-rater reliability both for the index originators and the two clinical pharmacists [18, 19]. The differences between the two pairs of evaluators may be related to the fact that the results of the index originators likely represent the upper bound of agreement to be expected, whereas the results of the two pharmacists may represent the agreement to be expected in actual practice. This level

Table 4. Pooled intra-rater agreement between a clinical pharmacist and an internist-geriatrician (n = 120 paired ratings)

Question	A	B	C	D	ppos	pneg	Kappa
1. Indication	105	0	1	14	0.99	0.97	0.96
2. Effectiveness	112	0	0	8	1.00	1.00*	1.00*
3. Dosage	91	1	5	23	0.97	0.88	0.85
4. Correct directions	64	2	2	52	0.97	0.96	0.93
5. Practical directions	100	4	4	12	0.96	0.75	0.71
6. Drug–drug interaction	119	0	0	1	1.00	1.00*	1.00*
7. Drug–disease interaction	118	0	2	0	0.99	0.00*	0.00*
8. Duplication	120	0	0	0	1.00	—*	1.00*
9. Duration	102	1	2	15	0.99	0.91	0.89
10. Expense	77	2	2	39	0.97	0.95	0.93
Overall	31	1	3	85	0.94	0.98	0.92

A: Both raters scored item as appropriate.
B: Rater 1 scored item as appropriate, Rater 2 scored item as inappropriate.
C: Rater 1 scored item as inappropriate, Rater 2 scored item as appropriate.
D: Both raters scored item as inappropriate.
*Inadequate variability in ratings.

of agreement and kappa statistics are similar to those reported for adverse drug reaction scales [5, 6]. The tests of intra-rater variability further demonstrate the reliability of the MAI.

It is instructive to examine the frequency of inappropriate ratings and provide some examples. Inappropriate ratings were most numerous for a less critical criterion, correct directions (e.g. no directions to take ibuprofen (Motrin®) with food or milk). Some clinicians did not prescribe the least costly medication, as exemplified by ranitidine (Zantac®) use instead of the less expensive option of cimetidine (Tagamet®) in a patient where concern for potential drug interactions was not relevant. A fair number of inappropriate ratings were found for daily dosage, an outcome measure that utilizes patient-specific data, such as vital signs and laboratory findings. For example, the dosage of 6 mg/kg/day of theophylline SR (Theodur®) in divided doses resulted in a subtherapeutic trough level of 4.1 μg/ml in a smoking patient with chronic obstructive pulmonary disease. Some problems were uncovered with impractical directions; e.g. the prescribing of cimetidine (Tagamet®) for peptic ulcer disease twice a day when once daily at bedtime would have been sufficient. Fewer problems with unacceptable duration of use were found perhaps because prescribing texts rarely specify this dimension. For two of the more important criteria, indication and effectiveness, it was reassuring to find few instances of inappropriate ratings. An example of ineffectiveness was the prescribing of dipyridamole (Persantine®) for stroke prophylaxis, which is not supported by evidence from clinical trials [21]. There were also few examples of clinically significant drug–drug or drug–disease interactions, and therapeutic duplication [i.e. simultaneous prescribing of skeletal muscle relaxants methocarbamol (Robaxin®) and cyclobenzaprine (Flexeril®)].

Although the overall sensibility and reliability of the MAI were good, several potential limitations should be noted. First, rater agreement may have been enhanced because raters reviewed the same abstracted material. While of potential concern, our pilot study showed that each of the raters prepared the abstract in a qualitatively similar way as did the research assistant. Abstracting saved raters' time and prevented the introduction of bias that could occur if the rater recognized a particular physician's note while reviewing the patient's medical record. Second, limited variability was found for drug–drug interactions, drug–disease interactions, and therapeutic duplication since the evaluators agreed that the majority of drugs were prescribed appropriately for these items. The low prevalence of these items precluded a complete analysis of their clinimetric properties, although these rare events are important to target. Third, despite the availability of explicit instructions, disagreement was higher for dosage and practical directions, because these items require more judgment on the part of the evaluators. Disagreements by raters on judgmental questions have been noted with other standardized methods [22]. Fourth, it is important to stress that not all of the 10 criteria are of equal importance. Some clinicians may argue that the most important aspects of medication appropriateness are indication and effectiveness. Because we were interested in all aspects of medication utilization, we chose not to limit the definition of appropriateness to these items and not to weigh the index accordingly. Furthermore, a clinician may have had sufficient reason to prescribe a medication but did not record the indication in the medical record. Nevertheless, we did place greater emphasis on drugs rated as being "not indicated" by also considering them to be unacceptable duration and expense. Fifth, weighting the overall scale to devise a summary score was unnecessary for the index's use as a process measure in our health services research study, although this may be useful for other applications. Finally, the generalizability of the index is currently unknown, since it has been tested only in elderly ambulatory veterans with polypharmacy, in whom full information about hospitalization, clinic visits, test results, and medications were readily available. Further research will determine its use and reliability with other types of evaluators, patient populations and clinical settings. Further testing of the index's validity is also necessary, but may be limited by the lack of an accepted "gold standard" [19].

Despite these potential limitations, the MAI shows promise, since it is both sensible and reliable. In contrast to previous scales, it can be used with a variety of medications. Therefore, this index may be valuable for use as a process or outcome measure in health services research studies and quality assurance programs in institutional settings.

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APPENDIX

Specific Instructions for Index Criterion, Effectiveness

Question 2: Is the medication effective for the condition?

1	2	3	9
effective	marginally effective	ineffective	do not know

Definition

"Effective" is defined as producing a beneficial result. The question assesses whether the drug prescribed is efficacious for the indication in a population of patients.

Instructions

Indication and efficacy are tightly but not perfectly linked items. Physicians may prescribe a drug for a given condition because of theoretical and standard practice reasons (indication) but investigators may demonstrate in clinical trials that the drug is ineffective [dipyridamole (Persantine®) prescribed for stroke prophylaxis; ergoloid mesylates (Hydergine®) prescribed for memory enhancement]. Conversely, an indication may not be documented for a drug yet the drug may work well for the intended effect [potassium chloride and diuretic-induced hypokalemia]. In those cases, the reviewer must note the assumed indication in the comments.

Examples

Hydrochlorothiazide and hypertension = 1. H_2 antagonist prophylaxis of gastritis induced by a non-steroidal anti-inflammatory drug = 3.