RELIABILITY OF A MODIFIED MEDICATION APPROPRIATENESS INDEX IN AMBULATORY OLDER PERSONS

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OBJECTIVE: To evaluate the reliability of a medication appropriateness index (MAI) modified for elderly outpatients in a non-Veterans Affairs setting.

DESIGN: Reliability study.

SETTING: General community.

PARTICIPANTS: Ten community-dwelling elderly (> 65 y) taking five or more regularly scheduled medications and participating in a university-based health service intervention study.

MAIN OUTCOME MEASURES: Interrater reliability of MAI ratings of 65 medications made by two clinical pharmacists for individual items and for an overall summed score was calculated by use of κ statistics and intraclass correlation coefficient.

RESULTS: The interrater agreement for each of the individual MAI items was high for both appropriate and inappropriate ratings and ranged from 80% to 100% (overall $\kappa = 0.64$). Overall agreement for the summed score was good (intraclass correlation = 0.80).

CONCLUSIONS: The modified MAI is a reliable instrument for evaluation of medication appropriateness in a non-Veterans Affairs, ambulatory, elderly population and may provide pharmacists with a practical and standard method to evaluate patients' drug regimens and identify some potential drug-related problems.

KEY WORDS: geriatrics, medication appropriateness index.

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AMBULATORY CARE PHARMACISTS, in part because of mandates such as the Omnibus Budget Reconciliation Act of 1990, are becoming increasingly involved in the provision of pharmaceutical care. Pharmaceutical care is defined as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve the quality of life," and it involves "identifying, resolving and preventing drug-related problems."[1] In part, drug-related problems include therapeutic failure, intentional noncompliance, medication error, drug overdose, drug withdrawal, and adverse drug reaction,[2] many of which are a result of inappropriate prescribing.

Prescribing inappropriateness is measurable by using either explicit or implicit review methods.[3-7] Explicit review methods are standardized guidelines that require little or no clinical judgment to apply. Drug use evaluation is an example of explicit review, and its reliability has been questioned recently.[8,9] Implicit methods to evaluate medication appropriateness at the patient level are typically used by pharmacists who provide pharmaceutical care for ambulatory patients.[1] These implicit reviews focus on the appropriateness of a patient's entire medication regimen rather than focusing on a single drug or drug class, and combine the patient's medical history and the clinician's judgment and knowledge. The results can be used to measure pre-

scribing quality and, more importantly, to develop measures to correct prescribing problems.[10,11]

The limitations of implicit review include the high degree of individualization and lack of systematic approach that may make findings nonvalid or not generalizable. Several investigators using implicit criteria have examined certain aspects of medication appropriateness (e.g., drug interactions, adverse drug reactions).[12,13] However, few have considered comprehensively the area of inappropriate prescribing.[10,11,14-17] Only the instrument by Lipton et al.[17] has been tested for reliability and none has reported validity.

A new approach that may be useful to ambulatory care pharmacists is known as the medication appropriateness index (MAI).[18-20] The MAI is designed to measure 10 components of medication prescribing with support from explicit definitions and instructions for use. It has demonstrated both reliability and content validity in a select Veterans Affairs (VA) outpatient, male, elderly population.[18-20] Its reliability and generalizability to other ambulatory populations, however, have not yet been evaluated. The purpose of our study was to evaluate the reliability of the MAI for elderly outpatients in a non-VA setting by replicating a previously published approach.

Methods

MEDICATION APPROPRIATENESS INDEX INSTRUMENT AND MODIFICATIONS

A description of the MAI is provided in Appendix I and in prior publications.[18,19] Briefly, the original scale consisted of 10 items regarding medication indication, effectiveness, dosage, directions, drug–drug interactions, drug–disease interactions, direction practicality, duplication, duration, and medication expense. For each criterion, the index has operational definitions, explicit instructions, and examples; the evaluator rates whether the particular medication is "appropriate," "marginally appropriate," or "inappropriate." The instrument was designed for use in elderly patients of a VA ambulatory care clinic that uses a closed formulary system.

The instrument was modified for broader use by ambulatory care pharmacists for an elderly population with no formulary restrictions and less comprehensive clinical information. Four components of the MAI were modified and pilot-tested prior to study initiation.

First, the definition for "ineffective" (criterion 2) was expanded to include any drug considered by the Food and Drug Administration (FDA) to be "less than effective" and appearing on the Drug Efficacy Study Implementation list.[21]

Directions for instructions regarding food or liquid and scheduling of drug administration, including time of day, constituted the second modification. Drugs approved for marketing by the FDA between 1989 and 1993 were reviewed and appropriate instructions were added to the instrument directions.

The third modification was the procedure used to assess drug interactions. In the original design, clinical evidence that a harmful drug–drug interaction had occurred was required for the interaction to be considered significant. Since practicing pharmacists often have knowledge-based systems available, the computer software program RxTriage[22] was used as the reference for interactions to supplement clinical evidence. A drug–drug interaction was defined as a significant rating if RxTriage noted a "most significant" interaction or a "significant" interaction in the presence of a preexisting medical condition. A drug interaction was also considered significant on the basis of the pharmacist's clinical knowledge or if the medical record contained a documented interaction.

Finally, the method for determining medication expense was altered. The cost of each medication was assessed by taking the average wholesale price[23] for the smallest package size available (excluding unit dose) and calculating the cost for a 30-day supply. A drug was considered more expensive if its cost exceeded the average prescription price in the US ($22.44)[24] and a less expensive alternative within the same therapeutic class (VA Medication Classification System[25]) was available.

DATA COLLECTION

As part of a university-based health services intervention study, community-dwelling elderly subjects were interviewed via telephone by a trained research assistant to obtain information on prescription and over-the-counter medication use (i.e., drug name, dose, schedule, directions, purpose, duration of therapy), medical history, and sociodemographic data using a semistructured questionnaire. The patient's medical record was available to the research assistant during the phone interview so that any documented medical conditions or medications were prompted from the patient if they did not volunteer the information. The reliability of obtaining a medication history via telephone by a trained research assistant is comparable with that of a drug history taken during a face-to-face clinic interview.[26]

The research assistant randomly selected 10 enrolled subjects for evaluation of medication appropriateness with a modified MAI. A clinical pharmacist prepared a patient profile that included problem and medication lists based on the telephone interview and medical record.

ASSESSMENT OF PRESCRIBING APPROPRIATENESS

Two clinical pharmacists were trained in the use of the MAI and performed a pilot study using other subjects. After the pilot study, the clinical pharmacists used the modified MAI and patient profiles to independently assess drug therapy appropriateness for all self-reported prescription and over-the-counter medications taken daily (excluding vitamins, laxatives, dermatologic preparations). The patient profile was supplemented with information from the subjects' university system medical record. Selected data elements included in the profile were vital signs and laboratory values within the previous 6 months and drug concentrations, procedures, and test results within the last 12 months. Responses to all 10 MAI items were coded as being "clearly appropriate," "marginally appropriate," or "clearly inappropriate." Medications were categorized into major therapeutic classes according to the VA Medication Classification System.[25] Classes with less than 3% prevalence were combined into a miscellaneous category.

STATISTICAL ANALYSIS

Descriptive statistics for all continuous variables were presented as mean ± SD.[21] The units of analysis were at the rating and the medication levels. Ratings for individual items were dichotomized into appropriate (i.e., clearly appropriate or marginally appropriate) versus inappropriate (i.e., clearly inappropriate). The proportion of appropriate (P_{pos}) and inappropriate (P_{neg}) ratings for which the two raters were in agreement was calculated for individual items.[27] Items with no inappropriate agreements were noted and excluded in the calculation of within-item P_{neg} due to inadequate variability among the ratings.

To evaluate a drug's overall appropriateness, the 10 ratings were combined. Overall, a drug was rated inappropriate if one or more items received a rating of clearly inappropriate; otherwise, the drug was rated appropriate. The P_{pos} and P_{neg} ratings overall for which the two raters were in agreement were computed with κ statistics calculated to assess overall interrater agreement.[28] A κ value of 0.4–0.75, inclusive, denotes good reproducibility and a κ value greater than 0.75 denotes excellent reproducibility.[27,28]

A summed MAI score, derived by a survey of clinicians, was also calculated to serve as a summary measure of inappropriateness as described previously.[19] Weights of 3 were applied to inappropriate ratings for indication and effectiveness; 2 to dosage, correct directions, drug–drug interactions, and drug–disease interactions; and 1 to practical directions, therapeutic duplication, duration, and cost. The possible range for weighted MAI scores per drug was 0 (no prescribing problems) to 18 (the most prescribing problems).[19]

To analyze overall interrater agreement of the summed MAI score per drug, an intraclass correlation coefficient (ICC) was calculated.[29,30] The ICC was derived from a two-way ANOVA model. Large intraclass

correlation coefficients (e.g., >0.5) reflect good reliability.[29] Finally, a comparison of the difference in mean summed MAI scores between raters was made using a one-sample *t*-test. All analyses were conducted using SAS (Cary, NC).[31]

Results

The 10 enrolled subjects were older than 70 years (mean ± SD age 72.1 ± 5.0 y), were primarily male (60%), white (90%), and taking 6.5 ± 2.3 drugs. The largest proportion were cardiovascular drugs (41.5%), followed by central nervous system (CNS) (15.4%), musculoskeletal (9.2%), nutrients/electrolytes (9.2%), gastrointestinal (4.6%), ophthalmic (4.6%), and endocrine (3.1%) drugs. Miscellaneous drugs accounted for the remaining 12.4% of medications.

INTERRATER RELIABILITY

The cross-classified ratings of the two clinical pharmacists for 65 drugs are presented in Table 1. For example, in 65 drug ratings for criterion 2 (effectiveness), 57 were assessed as appropriate by both raters (column A, Table 1), 4 were assessed as inappropriate by both raters (column D), and the raters disagreed on 4 effectiveness ratings (columns B and C). Overall, 46 of the 130 (35.4%) ratings were deemed inappropriate. There were few inappropriate ratings (columns B, C, and D) for indication, drug–drug interactions, drug–disease interactions and duplication. The most inappropriate ratings found were for correct directions, dosage, and duration of therapy.

The interrater agreement for each of the 10 individual MAI items ranged from 87% to 100% for appropriate ratings and from 47% to 100% for inappropriate ratings. The overall appropriate and inappropriate ratings were 0.78 and 0.86, respectively. Chance-adjusted agreement overall, as reflected by the κ statistic, was good (κ = 0.64).[28]

Table 1. Interrater Agreement Between Two Clinical Pharmacists Using a Modified Medication Appropriateness Index (n = 65 ratings)

QUESTION	A	B	C	D	P_{pos}	P_{neg}
Indication	63	0	0	2	1.00	1.00
Effectiveness	57	1	3	4	0.97	0.67
Dosage	45	6	7	7	0.87	0.47
Correct directions	36	4	4	21	0.90	0.84
Practical directions	57	5	1	2	0.94	0.40
Drug–drug interaction	61	2	0	2	0.98	0.67
Drug–disease interaction	62	2	1	0	0.97	[a]
Duplication	61	0	1	3	0.99	0.86
Duration	48	4	7	6	0.90	0.52
Expense	60	0	0	5	1.00	1.00
Overall	19	5	6	35	0.78	0.86

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; P_{neg} = the proportion of inappropriate ratings for which the two raters were in agreement; P_{pos} = the proportion of appropriate ratings for which the two raters were in agreement.
[a]Inadequate variability in ratings.

The mean ± SD weighted modified MAI scores per medication for the two clinical pharmacists were 2.1 ± 2.1 and 2.1 ± 2.2. Figure 1 depicts the interobserver differences in summed MAI scores between the two clinical pharmacists. There was no statistical difference in the summed MAI scores (*t*-test, p = 0.86). High interrater agreement in summed MAI scores, as reflected by the intraclass correlation coefficient (0.80), was demonstrated.[29]

Discussion

The modified MAI is reliable as quantitatively assessed by testing interrater reliability for two clinical pharmacists. Our interrater agreement on the item level is consistent with previous work[18] and the overall ICC per medication was similar to that found in a previous reliability study (0.80 vs. 0.74).[19] This evaluation differed from the original assessment in that the patients were from a non-VA, university-based population and the testing was performed by two other clinical pharmacists with specialty training in geriatrics. Moreover, the current assessment was performed on both prescribed and over-the-counter medications taken daily.

Agreement for appropriate ratings was greater than 86% for each individual criteria and was 78% overall. The fact that overall agreement was lower than agreement for any of the individual criteria is explained by the fact that overall appropriateness agreement only occurred when both reviewers concluded that all 10 criteria were appropriate, a less common finding. Agreement for inappropriate ratings for individual items was greater than 50% for all items, with exceptions being dosage and correct directions. These findings of lower but acceptable agreement for these two items is similar to that found in other applications of the MAI.[18] It may be informative to provide some examples of disagreement with these items. An example of disagreement with dosage occurred with a patient whose phenytoin dosage was being tapered. One rater evaluated the dosage as inappropriate because the blood concentration was low, while the second rated it as appropriate since the drug was being discontinued correctly. Future MAI instructions will provide more explicit directions for evaluating the tapering of medication dosages. An example of a problem with correct directions occurred in evaluation of daily subject-initiated as-needed drugs. Criterion 4 (correct directions) for

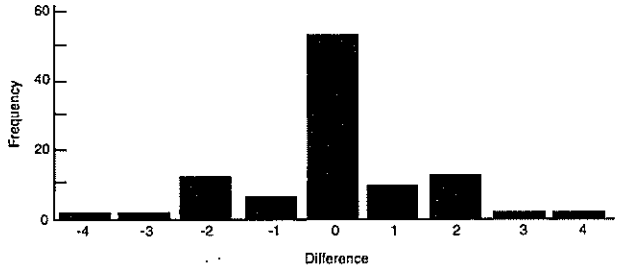

Figure 1. Interobserver differences in medication appropriateness index (MAI) scores between two clinical pharmacists. The x-axis denotes the interobserver differences in mean weighted modified MAI scores between the two clinical pharmacists; the y-axis denotes the frequency (%) with which the two clinical pharmacists differed in the per-medication MAI score.

the MAI was originally designed for evaluation of regularly scheduled chronic medications; thus, a drug taken as needed but recommended in textbooks to be administered chronically could be considered inappropriate. However, since the regimen may produce the desired outcome for an individual patient, it could also be considered marginally appropriate. Future applications of the MAI may need to consider a single criterion that combines dosage and direction, as recently reported.[32]

The modified MAI appears to be a tool that could be used for assessing medication prescribing as part of providing pharmaceutical care. It addresses 10 important elements of prescribing in an attempt to identify drug-related problems. However, several areas of medication use are not addressed by the modified MAI, including undertreatment, drug allergy, and suboptimal choice. Allergy could be considered a preexisting condition and evaluated by MAI criterion 7, drug–disease interaction. Suboptimal choice is highly subjective unless defined by published explicit criteria developed by consensus of medical experts. Such criteria were recently published for 20 drugs whose use should be avoided in the elderly.[6] Perhaps the evaluation of prescribing could be expanded by applying the MAI instrument in concert with such published explicit criteria.[6,33]

Several potential study limitations exist. The first is the small sample size (n = 10). While evaluation of a larger sample size may have been desirable, this approach was chosen to replicate and allow direct comparisons with our previous published reliability study using the MAI.[18] A second potential limitation was the use of two pharmacist raters. Generalizability could be enhanced if multiple pairs of reviewers were used, since any potential random measurement error would be reduced. However, we felt the use of multiple pairs of reviewers was not critical for our study, as it replicates two previous studies that demonstrated similar agreement between a pair of raters consisting of a clinical pharmacist, a physician, and two separate pairs of clinical pharmacists.[18,32] Moreover, generalizability may be enhanced by knowledge of the findings from a recent report of a randomized controlled trial (n = 208 ambulatory elderly taking >1600 medications at baseline) that used the MAI as both a process and outcome measure to help demonstrate that a sustained ambulatory care clinical pharmacist intervention based on the principles of pharmaceutical care is effective.[34] Another limitation was that intrarater reliability was not assessed. However, intrarater reliability with the MAI was previously tested and found to be reliable.[18] Moreover, since one would expect the agreement to be higher within a rater than among raters and because our study replicates previous work, we felt the assessment was not necessary.[27,28]

Despite these potential limitations, the modified MAI is a reliable instrument for evaluation of medication appropriateness in a non-VA, ambulatory, elderly population. The instrument may provide ambulatory care pharmacists with a practical and standard method to evaluate patients' drug regimens and identify potential prescribing problems. Future studies are necessary to assess the usefulness of the MAI in other settings and its relationship with health outcomes. ≏

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Appendix I. Medication Appropriateness Index[a]

The MAI is a scale for evaluating 10 key elements of medication prescribing. Those elements and their operational definitions follow: Indication — the sign, symptom, disease, or condition for which 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 — capable of being used or put into practice. Drug–drug interaction — the effect the administration of one medication has on another; clinical significance connotes a harmful interaction. Drug–disease interaction — the effect the drug has on a preexisting disease or condition. Duration — length of therapy. Expensiveness — cost of the drug in comparison with other drugs of equal efficacy and safety. Each criterion is worded as a question. Using clinical data, the clinician rates each drug on a three-point scale (A = appropriate, C = inappropriate). For each criterion, the index has instructions, the operational definitions above, and examples. An example is provided for indication:

Definition: Indication is defined as the sign, symptom, disease, or condition for which the medication is prescribed. The question assesses whether there is sufficient reason to use the drug. Sufficient reason includes not only curative and palliative therapy, but also preventive therapy for a disease, condition, or drug effect.

Instructions: A drug is indicated only if a condition exists for its use. Answer the question with the conditions found in the problem list. If score = C, then questions 9 and 10 are scored C.

Examples: Hydrochlorothiazide is prescribed and hypertension is recorded on the problem list = A (indicated). Haldol is prescribed and a condition such as psychosis or schizophrenia is not documented = C (not indicated). Dipyridamole and stroke prevention = B.

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?	A	B	C	Z
Comments:	Indicated		Not indicated	DK
2. Is the medication effective for the condition?	A	B	C	Z
Comments:	Effective		Incorrect	DK
3. Is the dosage correct?	A	B	C	Z
Comments:	Correct		Incorrect	DK
4. Are the directions correct?	A	B	C	Z
Comments:	Correct		Incorrect	DK
5. Are the directions practical?	A	B	C	Z
Comments:	Practical		Impractical	DK
6. Are there clinically significant drug–drug interactions?	A	B	C	Z
Comments:	Insignificant		Significant	DK
7. Are there clinically significant drug–disease/condition interactions?	A	B	C	Z
Comments:	Insignificant		Significant	DK
8. Is there unnecessary duplication with other drug(s)?	A	B	C	Z
Comments:	Necessary		Unnecessary	DK
9. Is the duration of therapy acceptable?	A	B	C	Z
Comments:	Acceptable		Not acceptable	DK
10. Is this drug the least expensive alternative compared with others of equal utility?	A	B	C	Z
Comments:	Least expensive		Most expensive	DK

DK = don't know; MAI = medication appropriateness index; Z = don't know.
[a]Complete instructions for use are available upon written request.

EXTRACTO

OBJETIVO: Evaluar la confiabilidad del Indice de Adecuación de Medicamentos (IAM) modificado para personas de edad avanzada en un escenario ambulatorio diferente al de la Administración de Veteranos (VA).

DISEÑO: Estudio de confiabilidad.

ESCENARIO: La comunidad general.

PARTICIPANTES: Diez personas de edad avanzada (>65 años) que viven en la comunidad y toman cinco o más medicamentos regularmente participaron en un estudio de intervención de servicios de salud.

MEDICIÓN DE RESULTADOS: Se calculó la confiabilidad entre evaluaciones de las puntuaciones de IAM de 65 medicamentos hechas por 2 farmacéuticos clínicos para cada item y para la puntuación global. Se utilizó la estadística κ y el coeficiente de correlación intraclases.

RESULTADOS: El acuerdo entre evaluaciones para cada uno de los items de IAM fue alto para evaluaciones de adecuación y de inadecuación y fluctuó entre 80% et 100% (κ global = 0.64). El acuerdo general para la punctuación global fue bueno (correlación intraclase = 0.80).

CONCLUSIONES: El IAM modificado es un instrumento confiable para evaluar la adecuación de los medicamentos en una población de personas de edad avanzada que viven en la comunidad y no son veteranos. Este puede proveerle a los farmacéuticos un método práctico y estandarizado para evaluar el régimen de medicamentos de los pacientes e identificar algunos problemas potenciales relacionados con los medicamentos.

LYDIA GONZÁLEZ

RÉSUMÉ

OBJECTIF: Évaluer la précision de l'index de la appropriée médicamenteuse (IAM) modifiée chez des personnes âgées demeurant à la maison.

DEVIS DE L'ÉTUDE: Étude de validation.

MILIEU DE L'ÉTUDE: Population gériatrique demeurant à domicile.

PARTICIPANTS: Dix patients âgés de plus de 65 ans demeurant à domicile et recevant cinq ou plus de médicaments prescrits ont participé à l'étude.

MESURES DES INTERVENTIONS: La précision entre les deux différents observateurs (pharmaciens cliniciens) des résultats de l'index IAM pour 65 différents médicaments a été évaluée. La somme des résultats a été calculée en utilisant les statistiques κ ainsi que le coefficient de corrélation.

RÉSULTATS: L'accord entre les différents observateurs pour chaque élément de l'index IAM était plus élevée pour la prescription appropriée et non appropriée se situait entre 80 et 100% ($\kappa = 0.64$). En général, l'accord pour le résultat total était bon (corrélation = 0.80).

CONCLUSIONS: L'index de IAM est un instrument fiable pour évaluer la pertinence médicamenteuse chez une population âgée demeurant à domicile. Cet index se veut un outil pratique qui pourrait aider le pharmacien à évaluer la thérapie des patients âgés et ainsi permettre d'identifier les problèmes reliés à la pharmacothérapie des patients.

LOUISE MALLET

Neurology

COMPARATIVE STUDY OF BIOAVAILABILITY AND CLINICAL EFFICACY OF CARBAMAZEPINE IN EPILEPTIC PATIENTS

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OBJECTIVE: To compare the bioavailability of three generic brands of carbamazepine tablets with that of a proprietary brand in adult patients with epilepsy.

DESIGN: A double-blind, randomized, three-phase crossover study.

SETTING: A psychiatric facility.

PARTICIPANTS: Eighteen patients with epilepsy who had taken carbamazepine at least 5 months before entering the study.

MAIN OUTCOME MEASURES: Ten blood specimens from each patient were collected at steady-state. Plasma concentration of carbamazepine was analyzed for pharmacokinetic parameters such as maximum plasma concentration (C_{max}), mean time to reach maximum concentration (t_{max}), and mean AUC.

RESULTS: There were no statistically significant differences in these parameters among four brands of carbamazepine. However, when comparing the 90% CI of AUC of three generic brands with that of the proprietary brand, the AUC of two generic brands lay within a range of 80% to 120%. The effects of gender and each brand of carbamazepine on these pharmacokinetic parameters were also analyzed. Breakthrough seizures occurred even though the plasma concentration of carbamazepine was therapeutic.

CONCLUSIONS: The bioavailability of two generic brands of carbamazepine tablets (Carmapine and Carzepine) and the proprietary brand (Tegretol) were equivalent in this sample of adult patients with epilepsy.

KEY WORDS: carbamazepine, bioavailability, bioequivalence.

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A FEW STUDIES[1-3] HAVE REPORTED that generic carbamazepine is not bioequivalent with the proprietary brand. For example, Koch and Allen[2] reported two cases of carbamazepine toxicity in patients taking a generic brand which resolved after switching to the proprietary brand. However, these reports were published in the first few years after carbamazepine lost patent protection in 1986, and only in some countries.[2,3] There have been many studies on the comparative bioavailability of carbamazepine, but most of these studies were carried out on healthy volunteers rather than on patients with epilepsy.[4-6] Hartley et al.[7] conducted research on children with epilepsy, and there are two clinical trials using adult patients.[8,9] These studies compared only two commercially available brands of the drug and were performed in outpatient clinics in the US. We were not aware of any studies involving patients with epilepsy in developing countries. Even though the Food and Drug Administration (FDA) regulations in Thailand for generic products follow US Pharmacopeia and British Pharmacopeia guidelines, many clinicians in Thailand find that some patients whose epilepsy is well controlled with a proprietary brand of carbamazepine develop frequent seizures after changing to a new generic formulation. For economic reasons, generic carbamazepine is widely used in Thailand, even though there are no adequate bioavailability studies of these preparations in patients with epilepsy.

This study was designed to compare the bioavailability of three brands of carbamazepine tablets commercially produced in Thailand (i.e., Carmapine, Central-Poly: lot no. C-8007; Carzepine, Condrugs: lot no. 23TC5; Panital, Pharmaland: lot no. PH 4893, as G_1–G_3, respectively) with that of the proprietary brand (Tegretol, Ciba Geigy: batch no. 162900, as O) by measuring the steady-state plasma concentration (C_{ss}) of carbamazepine in adult epileptic in-