Objective: Medication Therapy Management service (MTMs) has been introduced to improve cooperation among pharmacists and other healthcare professionals in the management of chronic diseases, drug therapy, and patients on polypharmacy. One part of MTMs is detection and resolution of possible drug-related problems (DRPs). Nowadays, numerous DRPs classification systems are available, but due to some defects none of them are currently accepted and implemented universally. The purpose of this study is to design and validate a comprehensive system for classification and documentation of possible DRPs for the Iranian patients.

Methods: In this methodological study, four classification systems were studied, and their differences were reviewed, compared. Ultimately, a comprehensive documentation system was developed and tested for validity using experts’ opinions.

Findings: A comprehensive list of 53 DRPs under eight categories was developed and examined for validity. After collecting the data and validity assessment, questions with content validity ratio of <0.4 and content validity index of <70% were excluded and modified. Finally, with the exclusion and modification of eight DRPs, a modified DRPs list was created.

Conclusion: According to the universality and validity assessment and based on consensus of 20 experts, this DRPs list can be used to regulate the standard operation procedure of outpatient clinics in Iran, and could act toward standardization of this service.

Keywords: Drug-related problems, medication therapy management, pharmaceutical care, validation
the severity of illness, assessing the risk of mortality, quality management, risk management, clinical outcomes, regulatory compliance, joint commission accreditation, managed care, and reimbursement.[8] Good documentation minimizes coding errors, reduces claim denials, and optimizes reimbursement, and in the long run, it can improve the service and operation of MTM clinics. Implementing quality improvement strategies that make documentation and coding an organizational priority can positively influence operations, services, and revenue.[8] A classification system appears to be essential to cover and classify all the possible DRPs in this setting method for interprofessional communication, follow-up monitoring, prevention of potential and actual DRPs, development of pharmaceutical care practice, and pharmaceutical care research.[10,11]

Nowadays, more than 20 DRPs classification systems are available. The most important and most implemented DRPs classification systems currently used in Iran are: Cipolle et al.,[3] DOCUMENT,[11] Westerlund et al.,[12] and pharmaceutical care network Europe classification system.[13] Each of these classification systems has some defects, and none of them is absolutely comprehensive and universally valid and accepted.[14] Table 1 provides a comparison of information on these classification systems.[15]

Today in Iran, there are four university-affiliated MTM clinics currently operating with different documentation systems. However, since each DRPs classification system mentioned above has some defects and none of them is absolutely comprehensive, universally valid and accepted,[15] and they differ in the classification of possible DRPs, these centers cannot share data with each other. The purpose of this study is to develop and validate a comprehensive classification system for DRPs documentation for the Iranian patients.

**METHODS**

A preliminary study was conducted between December 2016 and May 2017 in Ahvaz Jundishapur University of Medical Sciences (AJUMS). In this study, a group of experts was formed in MTMS including clinical pharmacy specialists who were practicing in MTM clinics (faculty members of the clinical pharmacy department at AJUMS and MTM consultants in 13-Aban pharmacotherapy clinic in Tehran). This group evaluated different DRPs classification systems from several aspects such as the adaptation of their process to the Iranian pharmacy practice, ability to implement them in MTM clinics, collection of these classification systems to include all potential DRPs based on various coding systems and the legal aspects of the health system. Ultimately, a comprehensive list of all possible DRPs consisting of 8 groups and 53 subgroups was created [Table 2], underwent validity test using experts' evaluation.

For the content validity test, we used the content validity ratio (CVR) and the content validity index (CVI). CVR is a linear transformation of a symmetrical level of concurrence on how many “experts” within a penal rate an item as essential, this formula yields values ranging from +1 to −1; positive values demonstrate that at least half of the experts rated the item as essential. The mean CVR across items may be used as an indicator of overall test content validity.[16] CVI is the most widely used method of quantifying content validity for multi-item scales which is based on expert ratings of relevance.[17] Accordingly, a questionnaire containing a list of the proposed 53 DRPs was presented to 20 clinical pharmacy specialists and residents of clinical pharmacy who had experience in MTMs setting. Each DRP was evaluated as necessary, useful but unnecessary and unnecessary. The collected data were then tested for validity using CVR and CVI. The minimum number of experts required to approve a DRP as essential was calculated as 14 by CRITBINOM function.[18] This test is usually used for measuring content validity.

After data collection and validity assessment, questions with CVR of <0.4 and CVI of <70% were excluded from the study.

For assessment of construct validity of the DRPs classification systems, three methods including convergence (the correlation coefficient of these two classification systems [our system and DOCUMENT] with the patient data), the comparison method between our classification system and DOCUMENT system, and factorial validity were used.[19]

To evaluate the criterion validity, we used Receiver Operating Characteristic (ROC) curve. For this purpose, the area under the ROC curve should be considered, where the values closer to 1 possess a greater criterion validity.[20]

For the face validity, we could use quantitative and qualitative parameters, because the quantitative face

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**Table 1: Drug-related problems classification systems**

| DRP classification system | Health care setting | Number of category |
|---------------------------|---------------------|--------------------|
| Cipolle[3]                | Multiple            | 7 categories       |
| DOCUMENT[11]              | Community Pharmacy  | 8 categories and 30 subcategories |
| PCNE[13]                  | Multiple            | 4 categories and 11 subcategories |
| Westerlund[12]            | Community Pharmacy  | 11 categories      |

PCNE=Pharmaceutical Care Network Europe

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validity is only for questionnaires and needs participant’s comments. Furthermore, regarding the specialty of items and their unfamiliarity to patients, we used qualitative face validity. For this purpose, experts’ comments were asked about each of DRPs, and they were used to find the level of difficulty, the degree of mismatch, and ambiguity of phrases.[21]

RESULTS
The proposed DRPs classification system and the results of the panel rating of DRPs are presented in Table 2.

For face validity, the expert’s comments were utilized to modify and optimize the DRPs classification system.

The correlation coefficient of our DRPs classification system and DOCUMENT was 0.621 and 0.897, respectively [Table 3].

The statistical significance of our system’s score was less than that of the DOCUMENT system in construct validity. Our system with one factor had 87% variance. DOCUMENT system with four factors, factors one and two accounted for 58% and 69% variance, respectively. In the construct validity analysis of our system and DOCUMENT system, one factor was obtained. According to the results in Table 4, the construct validity of the system was confirmed.

For criterion validity, the area under the ROC curve for our system and DOCUMENT was 0.78 and 0.96, respectively. The obtained levels of the curves for our system were acceptable and well evaluated.

The excluded and the modified DRPs are as follows: precaution apparent (CVI = 55%),

Table 2: The proposed drug-related problems classification system and the results of the panel rating of drug-related problems

| Category          | DRPs                  | Necessary | Useful but unnecessary | Unnecessary | CVI (%) | CVR |
|-------------------|-----------------------|-----------|------------------------|------------|---------|-----|
| Drug Selection    | Duplication           | 18        | 1                      | 1          | 90      | 0.8 |
|                   | Drug interaction      | 19        | 1                      | 0          | 95      | 0.9 |
|                   | Wrong drug            | 18        | 1                      | 1          | 90      | 0.8 |
|                   | Incorrect strength    | 15        | 2                      | 3          | 75      | 0.5 |
|                   | Inappropriate dosage form | 18   | 1                      | 1          | 90      | 0.8 |
|                   | Precaution apparent   | 11        | 5                      | 4          | 55      | 0.1 |
|                   | Contraindication      | 15        | 4                      | 1          | 75      | 0.5 |
|                   | No indication apparent| 14        | 5                      | 1          | 70      | 0.4 |
|                   | Using expired drugs   | 14        | 4                      | 2          | 70      | 0.4 |
|                   | Lack of efficacy      | 15        | 2                      | 3          | 75      | 0.5 |
|                   | More effective drugs  | 13        | 5                      | 2          | 65      | 0.3 |
|                   | Lack of proper medication storage | 19 | 1 | 0 | 95 | 0.9 |
|                   | Inappropriate medical treatment period | 18 | 0 | 2 | 90 | 0.8 |
|                   | Other drug selection problem | 14 | 4 | 2 | 70 | 0.4 |
| Over or Under use | Prescribed dose too high | 19 | 0 | 1 | 95 | 0.9 |
|                   | Prescribed dose too low | 18 | 0 | 2 | 90 | 0.8 |
|                   | Unclear dose instruction | 19 | 1 | 0 | 95 | 0.9 |
|                   | Dose adjustment       | 18        | 1                      | 1          | 90      | 0.8 |
|                   | Wrong time medication administration | 16 | 3 | 1 | 80 | 0.6 |
|                   | Other dose problem    | 13        | 1                      | 6          | 65      | 0.3 |
| Compliance        | Under use by consumer | 15        | 4                      | 1          | 75      | 0.5 |
|                   | Over use by consumer  | 17        | 3                      | 0          | 85      | 0.7 |
|                   | Erratic use of medication | 16 | 4 | 0 | 80 | 0.6 |
|                   | Drug misuse           | 14        | 4                      | 2          | 70      | 0.4 |
|                   | Difficulty using dosage form | 15 | 3 | 2 | 75 | 0.5 |
|                   | Noncompliance due to not believing in medication efficacy | 12 | 5 | 3 | 60 | 0.2 |
|                   | Noncompliance due to ADR and toxicity concern | 14 | 3 | 3 | 70 | 0.4 |
|                   | Failure to learn drug Administration | 16 | 0 | 4 | 80 | 0.6 |
|                   | Forgetting to take medication | 14 | 3 | 3 | 70 | 0.4 |
|                   | Other compliance problem | 12 | 4 | 4 | 60 | 0.2 |

Contd...
more effective drugs (CVI = 65%), other dose problems (CVI = 65%), noncompliance due to not believing in medication efficacy (CVI = 60%), other compliance problems (CVI = 60%), other untreated indication problems (CVI = 65%), other monitoring problems (CVI = 60%), and not classifiable under another category (CVI = 60%). Finally, with the exclusion and modification of eight DRPs, a new DRPs list with 7 categories and 45 subcategories was created [Table 5]. Given that the deleted items were mostly miscellaneous and the CVI average was more than 70% (S-CVI/Ave = 78.2%), the validity of the system was confirmed.

**DISCUSSION**

DRPs is one of the major health problems which can cause mortality, morbidity, and cost. According to other studies, the incidence of DRPs in outpatient setting is high and comparable with that of inpatient setting. Documentation and classification of DRPs are one of the most important parts of MTMs and pharmaceutical care processes. Since the existing documentation system is neither universal nor comprehensive, developing a comprehensive system of classification to cover all possible DRPs across Iranian patients seems necessary. In this study, a number of the most widely used DRPs classification systems have been studied, and differences were compared and reviewed by a group of experts in MTMs independently. Ultimately, a comprehensive system was designed for classification and documentation of possible DRPs in Iranian patients,
and the validity of this DRPs classification was evaluated through questionnaires.

Compared to others DRPs classification systems such as Westerlund et al. system,\cite{12} Cipolle et al. classification system,\cite{3} and Hepler–Strand classification system,\cite{1} our system had a greater emphasis on laboratory and nonlaboratory monitoring. Meanwhile, Cipolle et al. system does not classify drug interactions. Our list covers more DRPs than the other classification systems. For example, our classification system has separated patient compliance issues from education and information, which is not observed in any other classification system.

As shown in Table 5, in addition by including medical device training (CVI = 85%), most of these DRPs were related to toxicity and side effects, which are less addressed in other systems. Our classification system was similar to that of the DOCUMENT system, except that our system covered more problems. Given the fact that many patients have difficulty in educational and information issues, and these problems increase the likelihood of occurrence of DRPs, it is necessary to pay attention to this issue, which has been adequately discussed in our system.

According to the universality and validity assessment, and based on consensus of 20 experts, this DRPs list can be used to regulate the standard operation procedure of outpatient pharmacotherapy clinics in Iran, and could act toward standardization of this service. Definitely, the reliability of this system should also be examined in another study.

**Authors' Contribution**

Soheil Roshanzamiri participated in literature search, data analysis, statistical analysis, and manuscript preparation; Kaveh Eslami, Farhad Najmeddin, and Elham Hadidi participated in concepts design, manuscript editing and review; Mandana Izadpanah participated in the definition of intellectual content, data acquisition and manuscript preparation and Reza Ganji participated in manuscript editing and review. All authors read and approved the final manuscript.

**Acknowledgments**

The authors are thankful to the Masoud Mahdavinia the head of the Tutorial Pharmacy at AJUMS. The results described in this paper are part of a Pharm. D thesis.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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