ABSTRACT

OBJECTIVE: To qualitatively describe differences between a series of preventable drug-related morbidity (PDRM) indicators in the United States (U.S.) and the United Kingdom (U.K.), after transfer from the U.S. to the U.K. health care setting.

METHODS: A preliminary validation was undertaken of the U.S.-derived indicators within the University of Manchester School of Pharmacy, followed by a 2-round Delphi questionnaire of a sample of general practitioners (n=6) and primary care pharmacists (n=10). The main outcome measures were (1) relevance of the U.S. indicators to U.K. primary care prescribing as determined by preliminary validation and (2) the establishment of consensus among the Delphi participants that an indicator represented PDRM.

RESULTS: After preliminary validation, 7 of the U.S. indicators and a part of 2 indicators were considered of insufficient relevance to take any further part in the validation process. A further 18 of the U.S.-derived indicators failed to achieve consensus as PDRMs by the U.K. Delphi panel. At the end of the validation process, 19 indicators remained.

CONCLUSIONS: Many of the U.S.-derived indicators lacked relevance in the U.K. due to differences in transatlantic clinical practice. In addition, there may be differences in the philosophical viewpoints of health professionals practising in the U.S. and the U.K. In practice, it is therefore inappropriate to transfer quality indicators of this nature directly from the U.S. to the U.K. However, if some form of validation process is undertaken, indicators derived in one health care setting appear to provide a very useful starting point for those developed in another.

KEYWORDS: Preventable drug-related morbidity, PDRM, Quality indicators

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Preventable Drug-related Morbidity Indicators in the U.S. and U.K.

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The process undertaken to determine the applicability of the U.S.-derived PDRM indicators to the U.K. setting involved 2 distinct phases. The approach, briefly described here, has been previously reported in full.\textsuperscript{17} The face validity of each U.S. indicator was initially assessed by 3 experienced clinical pharmacists from the University of Manchester (U.K.), School of Pharmacy. These pharmacists each had a minimum of 10 years experience practicing as clinical pharmacists in a secondary care setting, and all possessed a formal postgraduate clinical pharmacy qualification. The PDRM indicators considered to display insufficient relevance to U.K. primary care prescribing were immediately deleted, thus taking no further part in the validation process.

For the next stage of validation, we used the Delphi technique, a consensus-building method that utilises postal questionnaires.\textsuperscript{18,19} A 2-round Delphi survey was then conducted with a sample of 16, comprising general practitioners (GPs, $n=6$) and primary care pharmacists ($n=10$). To be eligible for inclusion as a Delphi panelist, each GP had to be the “prescribing lead” in their clinic practice (i.e., the GP responsible for prescribing-related issues within the practice), and each pharmacist had to be currently involved in patient medication review within a GP practice. The Delphi process was used to formally assess the face and content validity of the remaining indicators and establish consensus as to whether they represented PDRM in elderly patients in primary care in the U.K.

Although the content of the U.S.-derived indicators was retained, the format was altered and, where necessary, terminology changed (e.g. “gastritis” replaced by “dyspepsia”; “ER visit” replaced by “hospital contact”) and spelling Anglicised (e.g. “anemia” changed to “anaemia”; “hyperkalaemia” changed to “hyperkalaemia”) prior to their incorporation into the Delphi questionnaire.

### Method

### Results and Discussion

#### Initial Assessment of Face Validity

Seven of the U.S.-derived indicators, and a part of 2 indicators (indicators 8 and 9), were considered to display insufficient relevance to U.K. primary care prescribing to take any part in the further validation (Table 1).

On reviewing these indicators, it was apparent that this often reflected a difference in transatlantic clinical practice. Drug therapies were represented in the U.S. PDRM indicators that are not, or seldom, used in the U.K. Troglitazone (indicator 1) was voluntarily withdrawn in the U.K. by the marketing drug company in 1997, more than 2 years earlier than in the U.S.,\textsuperscript{20} as a result of serious hepatic reactions,\textsuperscript{21} and, hence, is not available for prescribing. The use of barbiturates (indicator 2) and the traditional centrally acting antihypertensives (indicator 3) is very rare in the U.K.,\textsuperscript{22} whilst tetracycline (indicator 4) has limited use. The use of trimethoprim/sulfamethoxazole combinations [co-trimoxazole] (indicator 5) has substantially reduced since 1995 when the Committee on Safety of Medicines severely limited its indications.\textsuperscript{23} It is now used almost exclusively for

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### TABLE 1  U.S.-Derived Indicators Considered Irrelevant to U.K. Primary Care Prescribing After Preliminary Validation

<table>
<thead>
<tr>
<th>Indicator Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome:</strong> ER visit/hospitalization due to liver toxicity.</td>
</tr>
<tr>
<td>1. Use of troglitazone (Rezulin).</td>
</tr>
<tr>
<td>2. Liver function tests not done at baseline and at least monthly for the first 8 months of therapy and at least every 2 months for the remainder of the first year.</td>
</tr>
<tr>
<td><strong>Outcome:</strong> ER visit/hospitalization due to depression and/or increase in dosage of antidepressant.</td>
</tr>
<tr>
<td>2. Use of a barbiturate (e.g., butalbital).</td>
</tr>
<tr>
<td><strong>Outcome:</strong> ER visit/hospitalization due to worsening renal impairment and/or acute renal failure and/or renal insufficiency.</td>
</tr>
<tr>
<td>1. Diagnosis history of moderate to severe renal impairment and/or history of kidney disease.</td>
</tr>
<tr>
<td>2. Use of tetracycline.</td>
</tr>
<tr>
<td>3. BUN/serum creatinine not done within 30 days of initiation of therapy and at least every 6 months.</td>
</tr>
<tr>
<td><strong>Outcome:</strong> Blood dyscrasias.</td>
</tr>
<tr>
<td>1. Concurrent use of trimethoprim/sulfamethoxazole (Bactrim, Septra) and methotrexate.</td>
</tr>
<tr>
<td>2. WBC/platelets/CBC not done at least every 4 weeks.</td>
</tr>
<tr>
<td><strong>Outcome:</strong> Major and/or minor hemorrhagic event.</td>
</tr>
<tr>
<td>1. Use of IV heparin.</td>
</tr>
<tr>
<td>2. PTT not done at least every day.</td>
</tr>
<tr>
<td><strong>Outcome:</strong> Status epilepticus and/or ER visit/hospitalization due to seizure activity.</td>
</tr>
<tr>
<td><strong>Pattern of care:</strong></td>
</tr>
<tr>
<td>1. Use of a sympatholytic antihypertensive (e.g., reserpine, methyldopa, clonidine, etc.).</td>
</tr>
<tr>
<td><strong>Outcome:</strong> Anticonvulsant drug toxicity.</td>
</tr>
<tr>
<td>1. Use of an anticonvulsant requiring drug level monitoring (e.g., phenytoin, carbamazepine, valproic acid).</td>
</tr>
<tr>
<td>2. Drug level not done at least every 6 months.</td>
</tr>
</tbody>
</table>

*The valproic acid part of these indicators was considered irrelevant.
Preventable Drug-related Morbidity Indicators in the U.S. and U.K.

| Indicator Details | 10. Management: Use of phenytoin without drug level monitoring at least every 6 months. | Outcome: Loss of seizure control. |
|                  | 11. Management: Use of phenytoin without drug level monitoring at least every 6 months. | Outcome: Phenytoin toxicity. |
|                  | 12. Management: Use of carbamazepine without drug level monitoring at least every 6 months. | Outcome: Loss of seizure control. |
|                  | 13. Management: Use of carbamazepine without drug level monitoring at least every 6 months. | Outcome: Carbamazepine toxicity. |
|                  | 14. Management: Use of theophylline without drug level monitoring at least every 6 months. | Outcome: Theophylline toxicity. |
|                  | 15. Management: Use of an oral hypoglycaemic agent without monitoring the haemoglobin A1c level at least every 6 months. | Outcome: Hypoglycaemia or hyperglycaemia. |
|                  | 16. Management: Use of insulin without monitoring the haemoglobin A1c level at least every 6 months. | Outcome: Hypoglycaemia or hyperglycaemia. |
|                  | 19. Management: Use of a long-acting benzodiazepine in a patient with a past medical history (PMH) or current diagnosis of depression. | Outcome: GP practice or hospital contact due to depression and/or an increase in the dosage of an antidepressant. |
|                  | 20. Management: Use of a tricyclic antidepressant. | Outcome: Fall or broken bone. |
|                  | 21. Management: Use of a medium to long-acting benzodiazepine in a patient with chronic obstructive pulmonary disease (COPD). | Outcome: GP or hospital contact due to an exacerbation of COPD. |
|                  | 22. Management: Use of an antipsychotic. | Outcome: Fall or broken bone. |
|                  | 23. Management: Use of a beta-blocker in a diabetic patient. | Outcome: GP or hospital contact due to hypoglycemia. |
|                  | 24. Management: Use of an oral/topical nonsteroidal anti-inflammatory drug (NSAID) for more than 3 months without monitoring serum creatinine at least every 3 months. | Outcome: Raised serum creatinine. |
|                  | 25. Management: In the absence of any contraindication, failing to prescribe aspirin in a patient with a PMH of a myocardial infarction (MI). | Outcome: A second MI. |
|                  | 26. Management: In the absence of any contraindication, failing to prescribe a beta-blocker in a patient with a PMH of an MI. | Outcome: A second MI. |
|                  | 27. Management: In the absence of any contraindication, failing to prescribe an ACE inhibitor in a patient with congestive heart failure. | Outcome: GP practice or hospital contact due to congestive heart failure. |

Note: The format of the indicators is different in Tables 1 and 2. Table 1 shows the original U.S. format. Table 2 shows the altered U.K. format used after the preliminary validation phase.

However, although few would argue with the rationale behind the routine monitoring of haemoglobin A1c in diabetic patients in order to help prevent long-term complications, consensus was not achieved for indicators 15 and 16. This appeared to be related to the monitoring of carbamazepine concentration “may be useful.”

Delphi Questionnaire Survey

Despite displaying adequate face validity on preliminary validation, it is notable that 18 of the U.S.-derived indicators did not ultimately achieve consensus as PDRMs in the U.K. (Table 2).

It can be seen from Table 2 that this included indicators related to the monitoring of antiepileptic and theophylline therapies (indicators 10 to 14). Whilst the existence of a relationship between plasma concentration and dose for phenytoin, carbamazepine, and theophylline is well accepted, routine monitoring in the absence of any adverse clinical signs or symptoms, the introduction of an interacting drug, or concerns over noncompliance, is not. This view is supported by a comment made by one of the Delphi panelists who deemed one indicator not to represent PDRM:

“Assuming previously stable and no enzyme inducers/inhibitors prescribed.” (Indicator 13)

Indeed, it would appear unlikely, on logical grounds, that a routine assessment of plasma concentration would prevent these drug-related morbidities from occurring.
the acute nature of the morbidity (outcome) specified in these indicators. Furthermore, a number of panelists suggested an alternative patient management option that they considered to be more likely to prevent the specified morbidity:

"Regular blood glucose testing more important for day-to-day control." (Indicator 16)

Comments made by the panelists suggested that a further 2 indicators did not achieve consensus as PDRMs because they lacked specificity:

"Effect on CCF (congestive cardiac failure) minor for some calcium channel blockers." (Indicator 17)

"Specify which beta-blocker. New ones have licences for heart failure." (Indicator 18)

Indeed, the comment made about indicator 18 also raises the issue of changes that may occur over time. Would this indicator lack specificity:

"Effect on CCF (congestive cardiac failure) minor for some calcium channel blockers." (Indicator 17)

"Specify which beta-blocker. New ones have licences for heart failure." (Indicator 18)
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Although it was not explicitly stated, it is possible that doubts existed about whether potentially a further 4 indicators (indicators 19 to 22) represented PDRMs on the grounds that a causal relationship between the patient management and the adverse outcome has not been clearly established.

There were few clues as to why indicators 23 and 24 did not achieve consensus. However, one panellist clearly felt indicator 23 to be clinically insignificant, whilst another questioned the frequency of monitoring serum creatinine in patients prescribed nonsteroidal anti-inflammatory drugs:

“More theoretical than practical.” (Indicator 23)

“Monitor every 6 to 12 months.” (Indicator 24)

It may be for some indicators, for example, indicator 23, that it might be more appropriate to apply them at the patient, rather than a population, level, thus taking into account individual patient factors such as whether the patient has previously had a myocardial infarction.

It was of particular note that the 3 U.S. indicators that related to “failing to prescribe” a medicine also did not achieve consensus by the U.K. panel (indicators 25 to 27). Indeed, from comments made, it appeared obvious that some panellists had clearly agonised over the philosophical difference between doing something that is widely regarded as bad practice (definitely PDRM) as opposed to failing to do something where there is evidence to suggest it is (or is widely regarded as) good practice.

“They reduce the risk, but is failure to prescribe a drug-related problem?” (Indicator 26)

Clearly this is an area that will need to be considered further in future work.

At the end of the validation process, the U.K. PDRM indicator set contained 19 indicators. These are shown in Table 3.

The starting point for this U.K. work was PDRM indicators developed in the U.S.14 Other European workers25,26 have identified that there may be country-specific factors, such as differences in clinical practice, that preclude the direct transfer of quality indicators from the U.S. to the U.K.. Indeed, our work supports their view. We have identified that direct transcription of U.S. PDRM indicators cannot be automatically assumed for a similar reason and, unquestionably, the converse also holds true. PDRM indicators derived in the U.K. should not automatically be applied in the U.S. health care system without firstly undergoing some form of validation process. However, in addition, we have also identified that there may be differences in philosophical viewpoints between some health care professionals practising in these very different health care systems (a managed care system in the U.S.; the NHS or private sector in the U.K.). Although the direct transfer of quality indicators would not appear to be appropriate, it is undoubtedly a very useful starting point to use tools developed by others even if they were developed in a different country or health care setting. Whilst some form of modification process is necessary, it also needs to be borne in mind that there may well be indicators that are highly relevant to the transferring country, yet of no relevance in the originating country. This is an issue that we considered, and addressed, when undertaking the transfer of the U.S. PDRM indicators to the U.K. setting.17 As part of the Delphi process, participants were asked to give examples of any additional indicators they felt were missing from the set provided but were relevant to the health care environment in which they practiced.

The focus of the next stage of this work is on retrospectively operationalising these indicators in both the primary and secondary care settings. These data will form a key part of the ongoing refining, modification, and, hence, further validation, of the indicators. Furthermore, the secondary care work will also aid in the development of further new indicators, all of which will ultimately be fed back to our transatlantic colleagues.

We believe that the indicators are likely to prove of greatest value if they are applied in a sequential fashion at, firstly, the population and, then, an individual patient level. As these indicators are evidence-based, once differences in clinical practice are put to one side, they should be equally applicable in an NHS or managed care environment or, indeed, any health care system in the developed world. The U.K.-validated PDRM indicators have already been applied in primary care at a subpopulation level to all the patients (~6,000) in one GP practice. (In the U.K. NHS, all patients are registered with a GP within a GP practice. Each GP in England has a list size of approximately 1,800 patients. The GP is responsible for all their health-related needs and is the gatekeeper to secondary care services.) A pharmacist is now currently reviewing the subgroup of patients identified as having experienced a PDRM event at an individual patient level. This is to determine what action, if any, is appropriate.

Conclusion

This work has attempted to identify process-of-care steps that can contribute to PDRM in the U.K. setting using quality indicators designed to represent PDRM. However, many of the U.S.-derived indicators lacked relevance in the U.K. because of differences in transatlantic clinical practice. Because of the difference in quality standards between countries, it is therefore inappropriate, in practice, to transfer quality indicators of this nature directly from the U.S. to the U.K. However, if some form of validation process is undertaken, indicators derived in one health care setting appear to provide a very useful starting point for those developed in another.
DISCLOSURES

Funding for this research was contributed by the School of Pharmacy and Pharmaceutical Services, University of Manchester, U.K., and was obtained by author Caroline Morris. Both Morris and author Judy Cantrill are employed by the university. Morris served as principal author of the study and was primarily responsible for drafting the manuscript. Study concept and design and critical revision of the manuscript were contributed by Morris and Cantrill. Statistical analysis of data was contributed by Morris, interpretation of data was contributed by both authors.

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