Observatory
29th July 2015

Observatory of recent safe medication practice research, reports, and publications

Presented by Varinder Rai
varinder.rai@nhs.net
Recent regulator and statutory body activity

NHS England

MHRA
Regulating Medicines and Medical Devices

European Medicines Agency
Science Medicines Health

FDA
U.S. Food and Drug Administration

UKMi
UK Medicines Information
Recent regulator and statutory body activity

Class 4 drug alert July 15: Propofol 10mg/ml (1%) Emulsion for Injection/Infusion 50ml presentation - incorrect colour identifying volume on package

- Peckforton Pharmaceuticals Limited: 50ml carton - the coloured band on the package should be purple not pink although text is correct.
- Distribution of affected stock will continue and it will be necessary to release further batches.
Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk
• Product information is being updated and reminder cards being introduced

Osteonecrosis of the jaw
• The risk of ONJ is small with patients treated for osteoporosis vs. higher doses used for cancer-related conditions (regardless of route of administration).
• Drug-specific risk factors: drug potency, route of administration and cumulative dose.
• Oral bisphosphonates: reminder of precautions to take e.g. tell patients to maintain good oral hygiene, attend dental check-ups and report any oral symptoms to a doctor/dentist.

Denosumab – new contraindication
• Recommended that denosumab 120 mg contra-indicated in patients with unhealed lesions from dental or oral surgery.

*UKMi comment: Reminder cards available on the Electronic Medicines Compendium Practical implementation may include local strategies to minimise risk such as education of prescribers and pharmacists, counselling patients and distribution of cards*
EU review confirms that CV risk of high-dose ibuprofen (≥2400mg/day) is similar to COX 2 inhibitors and diclofenac.

- Naproxen and low-dose ibuprofen (≤1200mg per day) are considered to have most favourable thrombotic CV safety profiles of all NSAIDs.
- <1% of all Rx for ibuprofen in primary care in the UK were for 2400 mg per day or more.
- When prescribing any NSAID, base the decision on an assessment of a patient’s individual risk factors e.g. history of CV and GI illness
- Use lowest effective dose for the shortest duration necessary to control symptoms and re-evaluate the patient’s need for symptomatic relief and response to treatment periodical

**UKMi comment:**

Practical implementation to support safe prescribing may include identifying, reviewing and managing patients on regular NSAIDs including those on regular and/or high dose ibuprofen
EMA has started a safety review of canagliflozin, dapagliflozin and empagliflozin (SGLT2 inhibitors) to evaluate the risk of diabetic ketoacidosis.

**MHRA:**

- Test for raised ketones in patients with symptoms of diabetic ketoacidosis (DKA); omitting this test could delay diagnosis of DKA.
- If DKA suspected, stop SGLT2 inhibitor treatment.
- If DKA confirmed, take appropriate measures to correct the DKA and to monitor glucose levels.
- Inform patients of the symptoms and signs of DKA and get immediate medical help if these occur.
- SGLT2 inhibitors are not approved for treatment of type 1 diabetes.
- Report suspected side effects to SGLT2 inhibitors on a yellow card.

**UKMi comment:** To support safe prescribing introduce local strategies which may include education of prescribers and pharmacists, in addition to identifying, reviewing and counselling patients prescribed SGLT2 inhibitor treatment.
Latanoprost (Xalatan): increased reporting of eye irritation since reformulation

- In 2013, the Xalatan pH reduced from 6.7 to 6.0 to allow for storage at room temperature. Increase in the number of reports of eye irritation from across the EU (MHRA: 22 reports vs. 0).
- It is important that patients continue their treatment.
- When prescribing or dispensing the Xalatan advise patients to tell their health professional if they experience severe eye irritation
- Review treatment if patients mention severe eye irritation e.g. excessive watering
- Continue to report suspected side effects to latanoprost on a yellow card
A Yellow Card smartphone app has been launched

- The only app that allows direct reporting to the Yellow Card Scheme
- Free to use for everyone on iOS and Android
- See immediate response that shows Yellow Card has been accepted
- Submit updates to Yellow Cards already submitted
- View previous Yellow Cards submitted through the app
- Create a ‘watch list’ of medications to receive official news and alerts
Lixiana®▼ (Edoxaban): risk minimisation resources

Educational materials contain important safety information on potential risk of bleeding during treatment and provide guidance on how to manage that risk.

- Prescriber Guide – for healthcare professionals
- Patient Alert Card – for patients (inserted into the packs)
- Summary of Product Characteristics – for healthcare professionals

Ensure all patients familiarise themselves with the Patient Alert Card found in their pack before starting treatment. Advise them on:

- signs or symptoms of bleeding and when to seek attention from a healthcare professional
- importance of treatment compliance
- to carry the Patient Alert Card with them at all times
- inform healthcare professionals that they are taking edoxaban if they are due for surgery or invasive procedure
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC has started two safety review:

1. **Canagliflozin, dapagliflozin and empagliflozin (the SGLT2 inhibitors).**
   Aim of evaluating their risk of diabetic ketoacidosis. It is estimated that the review will complete in October 2015. Follow MHRA advice meanwhile.

2. **To clarify safety profile of human papillomavirus (HPV) vaccines.**
   The review will focus on rare reports of two conditions complex regional pain syndrome and postural orthostatic tachycardia syndrome. While the review is ongoing there is no change in recommendations for the use of the vaccine.
Report from Asthma UK

• Published one year on from the National Review of Asthma Deaths: avoidable harm and preventable asthma deaths
• 127,617 people with asthma in the UK at risk of a potentially life-threatening asthma attack due to unsafe prescribing.
• Asthma UK: 500 UK GP practices - prescribing errors were just the tip of the iceberg.
• Estimated 100,000 people with asthma have been prescribed too many short-acting reliever inhalers (more than 12 in a year)
• Prescribing data suggests 80% are under prescribed preventer inhalers
• Recommendations include identifying and recalling patients for review, audits, use of electronic systems…..

http://www.asthma.org.uk/patient-safety
Drug shortages/discontinuations

• Discontinuation of supply of De-Noltab (tri-potassium di-citrato bismuthate 120mg) from the UK market at the end of December 2015 for commercial reasons.
• Main use (off label) is as part of a *Helicobacter pylori* (HP) eradication regimen (e.g. De-Noltab 120mg QDS, proton pump inhibitor, tetracycline and metronidazole) following failure of standard regimens.
• Refer to the memo for alternative agents and management options

The EMA (Oct 2014) completed a review of colistimethate sodium subsequent to concerns raised in relation to product information

- Significant gaps exist in the literature in relation to dosing in special populations
- Differences in expression of strength in the EU compared to other regions, USA and Australia, have led to errors in international medical literature.
- **UKMi assessment reviews** UK licensed colistimethate sodium products given via the nebulised or parenteral route and summarises considerations associated with their in-use safety in NHS practice.

This months’ papers


This months’ papers

- Published costs of medication errors leading to preventable adverse drug events in us hospitals. Value in Health May 2015: 18/3(A83), 1098-3015. http://www.ispor.org/research_pdfs/49/pdffiles/PHP73.pdf
Quality Indicators for Safe Medication Preparation and Administration: A Systematic Review.
PLoS ONE, April 2015, vol./is. 10/4, 1932-6203 (17 Apr 2015)

• Systematic review to identify evidence-based quality indicators (QI) for safe in-hospital medication preparation and administration.

• Safe medication preparation related to the “7 rights” of medication: right patient, right drug, right dose, right time, right route, right reason and right documentation

• Aimed to identify evidence-based QI for the 7 rights of safe in-hospital medication preparation and administration.
Quality Indicators for Safe Medication Preparation and Administration: A Systematic Review.

- Literature review: start - January 2015
- Eligible studies were those:
  1. the method for QI development combined a literature search with expert panel opinion
  2. the study contained QI on medication safety
  3. any of the QI were applicable to hospital medication preparation and administration.
- A multidisciplinary team appraised studies independently: AIRE instrument; aim and the context of the QI clearly described and evidence based
- 1683 studies → 64 reviewed in detail → 5 met inclusion criteria

Results: 21 evidence based quality indicators identified for the nursing process of safe in-hospital medication and preparation according to the 7 rights
Quality Indicators for Safe Medication Preparation and Administration: A Systematic Review.

QI categorised according to the structure, process and outcome framework.

<table>
<thead>
<tr>
<th>Category</th>
<th>Source</th>
<th>Indicator</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety management</td>
<td>Cheng</td>
<td>Incident reporting and analysis</td>
<td>Organization has a policy and process for reporting and analyzing medication incidents (yes/no).</td>
</tr>
<tr>
<td></td>
<td>Cheng</td>
<td>Prospective medication safety analysis</td>
<td>Organization conducts at least one medication safety analysis per year (yes/no).</td>
</tr>
<tr>
<td></td>
<td>Cheng</td>
<td>Top 10 medications</td>
<td>List of top 10 medications associated with harm or death medication incidents.</td>
</tr>
<tr>
<td>Availability of high alert medication</td>
<td>NSW TAG</td>
<td>Concentrated potassium</td>
<td>Percentage of medication storage areas outside pharmacy where potassium ampules are available.</td>
</tr>
<tr>
<td></td>
<td>Cheng</td>
<td>Concentrated electolytes</td>
<td>Concentrated electrolytes (concentrated potassium chloride, potassium phosphate and sodium chloride) are removed from patient care areas (yes/no).</td>
</tr>
<tr>
<td></td>
<td>Cheng</td>
<td>Narcotic safety</td>
<td>Three criteria: 1. Removal of hydrochloride ampules or vials with concentration &gt;2 mg/0.1 ml, (except palliative care) (yes/no); 2. Removal of morphine ampules or vials with concentrations &gt;15 mg/0.1 ml (yes/no); 3. Standardization and limitation of the number of parental narcotic (yes/no).</td>
</tr>
<tr>
<td>Verification</td>
<td>Nigram</td>
<td>Monitoring and reducing adverse drug events by assigning medications on sound</td>
<td>Numerator: Number of beds with daily pharmacial participation in interdisciplinary direct patient care. Denominator: All beds.</td>
</tr>
<tr>
<td></td>
<td>Nigram</td>
<td>Verification of high alert prescription</td>
<td>Numerator: Number of prescriptions/medication orders for high-alert medications that are double-checked and documented by pharmacists before administration. Denominator: All prescriptions/medication orders for high alert medications.</td>
</tr>
<tr>
<td></td>
<td>Nigram</td>
<td>Machine readable coding systems for administration</td>
<td>Numerator: Number of doses administered with machine readable code (bar codes). Denominator: All doses administered.</td>
</tr>
<tr>
<td>Visual reminders</td>
<td>Nigram</td>
<td>Differentiation of high alert prescription medication</td>
<td>Numerator: Number of high-alert prescitations medications that are differentiated from other medications using flags, highlighting or some other system. Denominator: All high-alert prescription medications.</td>
</tr>
<tr>
<td>Protocols</td>
<td>Nigram</td>
<td>Administering protocols for high alert prescription modifications</td>
<td>Numerator: Number of prescriptions/medication orders for high-alert medications using an administering protocol. Denominator: All prescriptions/medication orders for high-alert medications.</td>
</tr>
<tr>
<td></td>
<td>NSW TAG</td>
<td>Chemotherapy protocol</td>
<td>Percentage of patients receiving cytotoxic chemotherapy whose treatment is guided by a hospital approved chemotherapy treatment protocol. Numerator: Number of patients prescribed chemotherapy whose treatment was guided by a hospital approved protocol. Denominator: Number of patients prescribed chemotherapy in sample.</td>
</tr>
<tr>
<td></td>
<td>NSW TAG</td>
<td>Antibiotic therapy for surgical patients</td>
<td>Percentage of patients undergoing specified surgical procedures that receive an appropriate prophylactic antibiotic regimen. Numerator: = Number of patients undergoing specified surgical procedures that receive an appropriate prophylactic antibiotic regimen. Denominator: = Number of patients who had a specified surgical procedure in sample.</td>
</tr>
<tr>
<td></td>
<td>Cheng</td>
<td>Antibiotic prophylaxis</td>
<td>Proportion of select surgical patients (coronary artery bypass graft, cardiac surgery, hip arthroplasty, knee arthroplasty, hysterectomy and vascular surgery) who receive prophylactic antibiotics.</td>
</tr>
<tr>
<td></td>
<td>Cheng</td>
<td>Venous thromboembolism prevention</td>
<td>Proportion of at-risk or eligible patients (undergoing major general or hip fracture surgery) who receive thromboprophylaxis.</td>
</tr>
</tbody>
</table>
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QI categorised according to the structure, process and outcome framework.

<table>
<thead>
<tr>
<th>Category</th>
<th>Source</th>
<th>Indicator</th>
<th>Description and/or Numerator, Denominator of indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation of relevant medication related clinical information</td>
<td>NSW TAG</td>
<td>Postoperative pain management</td>
<td>Description: Percentage of postoperative patients whose pain intensity is documented using an appropriate validated assessment tool. Numerator: Number of postoperative patients whose pain intensity is documented using an appropriate validated assessment tool. Denominator: Number of postoperative patients in sample.</td>
</tr>
<tr>
<td>Adverse events</td>
<td>NSW TAG</td>
<td>Adverse drug reactions</td>
<td>Description: Percentage of patients whose known adverse drug reactions are documented on the current medication chart. Numerator: Number of patients whose known ADRs are documented on the current medication chart. Denominator: Number of patients in sample.</td>
</tr>
<tr>
<td>Outcome indicators</td>
<td>ORC Advisor</td>
<td>Medication error rate</td>
<td>Numerator and denominator: not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medication error</td>
<td>Numerator: Number of patient deaths, paralysis, coma, or other major permanent loss of function associated with a medication error. Denominator: The original developer of this indicator conceived of it as a sentinel event indicator, i.e. it would reflect events that should never happen. Consequently, the original definition has no denominator. However, if the indicator were applied to the health system level, an appropriate denominator would have to be used to be able to compare rates across countries.</td>
</tr>
<tr>
<td></td>
<td>Cheng</td>
<td>Medication incident types, harm or death incidents by type of error</td>
<td>Description: Frequency of medication incidents resulting in harm or death, categorized according to the type of incident (e.g., incorrect dose, incorrect medication, incorrect patient).</td>
</tr>
<tr>
<td></td>
<td>Cheng</td>
<td>Medication incident rates, harm/death incidents per days of patient care</td>
<td>Description: Proportion of medication incidents that result in harm or death per days of patient care.</td>
</tr>
<tr>
<td></td>
<td>Cheng</td>
<td>Deaths associated with medication incidents</td>
<td>Description: Proportion of total deaths in Ontario that are associated with medication incidents.</td>
</tr>
</tbody>
</table>
7 rights only partly covered with the current QI: mainly address “right drug” and “right dose.”

No QI were found that address “right time” and “right route”

“right time” is especially important for time-critical scheduled medications
Quality Indicators for Safe Medication Preparation and Administration: A Systematic Review.

• Evidence-based QI for medication safety with clear definitions are scarce, but the identified QI provide an excellent starting point for further development.

• Limitations: exclusion of useful indicators developed with other approaches; underestimated quality of some studies; adaptation of to the local setting (e.g. process and system variation in countries)
A systematic review of patient medication error on self-administering medication at home
Mira J.J., Lorenzo S., Guilabert M., Navarro I., Perez-Jover V.

- Systematic review to identify and describe frequency, causes, consequences and avoidance of medication errors committed involuntary by patients at home.
- Literature review: January 1990 - November 2014
- Eligible studies were those on medicines prescribed by a doctor or self-medication
- Excluded studies describing voluntary non-adherence
- Reviewed by two independent reviewers and final decision made jointly
- 250 studies → 69 reviewed in detail → 22 identified as relevant
A systematic review of patient medication error on self-administering medication at home

- The frequency of patient medication errors (PEs) were between 19 and 59%. 75% among the elderly with a complex therapeutic regimen. The preschool population constituted a higher number of mistakes than others.

- Types of PEs were: incorrect dosage, wrong medicine, forgetting, mixing up medications, failing to recall indications, taking out-of-date or inappropriately stored drugs, and misuse of inhalers.

- Consequences: majority of mistakes had no negative consequences. Prevalence of PEs causing harm has been calculated at 4/1,000.

- Causes: Intrinsic factors – patients profile and health literacy; extrinsic factors - information and communication and complexity of use of dispensing devices.

- Prevention: pill boxes, improved communication, teaching patients to use devices (e.g. inhalers) Apps and new technologies offer several opportunities for improving drug safety.