Review Title

Impact of regulatory risk communications in the United Kingdom on prescribing and clinical outcomes

Review Question(s)

1. What impact do regulatory risk communications (such as from the Medicines and Healthcare Products Regulatory Agency or the Committee on Safety of Medicines) have on prescribing and clinical outcomes in the United Kingdom?
2. To which extent does the impact of different regulatory risk communications vary?
3. Which characteristics of risk communications are associated with variation in impact?

Objective

To perform a systematic review of literature on the impact of MHRA risk communications on prescribing and clinical outcomes and to examine factors that cause variation in impact.

Primary Outcome

Change in rates of prescription or monitoring of medicines which were the subject of risk communication in primary and secondary care populations

Secondary Outcomes

Intended consequences of the communication, measured as

a) Use of the target drug in the population targeted by the communication
b) Monitoring implemented as recommended by risk communication

Unintended consequences of the communication measured as

a) Use of the target drug in populations not targeted by the communication but potentially affected by the intervention because of a 'spill over' effect or
b) Use of drugs and monitoring not directly targeted by the intervention, but potentially used as substitute drugs

Data on other relevant clinical outcome such as hospital admissions, accident & emergency attendance, measures of workload, mortality and clinical consequences if reported will be assessed. This example list is not inclusive.

Background

The European Medicines Agency (EMA) [1] supervises the monitoring and regulation of medications in Europe and works closely with the Medicines and Healthcare products (MHRA) in the United Kingdom. The safety of medications are monitored in the United Kingdom by methods including the Yellow Card scheme in and particular new medications are flagged for more intensive monitoring. If new information is found about medicine harm that is significant then the MHRA can issue risk communications to prescribers including noting them in circulated bulletins such as Drug Safety Update or sending specific warnings about particular drugs to prescribers through Direct Healthcare Professional Communications

which are intended to rapidly disseminate information to healthcare professionals to inform practice and minimize potentially avoidable patient harm [2]. These different type of risk communication vary in how they are constructed, the advice they provide, ways in which they are handled at regional, health board and practice levels and have the ability to cause unintended consequences.

It is important to understand this process as adverse drug events are known to be common and are often preventable [3]. The incidence of serious and fatal adverse drug reactions in hospital are high and have been shown to account for 6.5% of hospital admissions and most of these reactions are definitely or possibly avoidable [4, 5]. This is becoming increasingly important as there is an escalating use of prescribed drugs - the number of patients' dispensed more than 10 medications has tripled and we have seen a more than doubling of serious drug-drug interaction between 1995 and 2010. The use of 10 of more medications is strongly associated with increasing age [6]. Each further medication adds increasing complexity to care, meaning that with an ageing population and with multimorbid conditions becoming the norm the risk communication process needs to be the best possible to prevent avoidable harm [7-9]. This systematic review will establish the current risk communication impact and assess if there are known ways that the risk communications can be improved to achieve maximal intended impact.

Methods

We will search MEDLINE, Scopus, EMBASE, and Cochrane Library.

Proposed MEDLINE search:

1. United Kingdom [MeSH Terms]
2. medicines and healthcare products regulatory agency [Title/Abstract]
3. mhra [Title/Abstract]
4. European Agency for the Evaluation of Medicinal Products [Title/Abstract]
5. European Medicines Agency [Title/Abstract]
6. EMA [Title/Abstract]
7. EMEA [Title/Abstract])
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. Regulatory risk [Title/Abstract]
10. advisory [Title/Abstract]
11. advisories [Title/Abstract]
12. alert [Title/Abstract]
13. alerts [Title/Abstract]
14. Risk communication [Title/Abstract]

15. Regulatory reports [Title/Abstract]
16. Risk alerts [Title/Abstract]
17. Warning [Title/Abstract]
18. Warnings[Title/Abstract]
19. CAB[Title/Abstract]
20. Current Awareness Bulletins [Title/Abstract]
21. Update[Title/Abstract]
22. Central Alerting System [Title/Abstract]
23. CAS [Title/Abstract]
24. Adverse Drug Reaction Reporting Systems [Title/Abstract]
25. Drug Prescriptions [mesh]))
26. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25

    INCLUDE 8 AND 26

Proposed Scopus search:

1. medicines and healthcare products regulatory agency [Title/Abstract/Keywords]
2. mhra [Title/Abstract/Keywords]
3. European Agency for the Evaluation of Medicinal Products [Title/Abstract/Keywords]
4. European Medicines Agency [Title/Abstract/Keywords]
5. EMEA [Title/Abstract/Keywords]
6. 1 OR 2 OR 3 OR 4 OR 5
7. advisory [Title/Abstract/Keywords]
8. advisories [Title/Abstract/Keywords]
9. 7 OR 8
10. United Kingdom [Title/Abstract/Keywords]
11. 9 AND 10
12. 6 OR 11

13. Regulatory risk [Title/Abstract/Keywords]
14. alert [Title/Abstract/Keywords]
15. alerts [Title/Abstract/Keywords]
16. Risk communication [Title/Abstract/Keywords]
17. Regulatory reports [Title/Abstract/Keywords]
18. Risk alerts [Title/Abstract/Keywords]
19. Warning [Title/Abstract/Keywords]
20. Warnings [Title/Abstract/Keywords]
21. Current Awareness Bulletins [Title/Abstract/Keywords]
22. Update [Title/Abstract/Keywords]
23. Central Alerting System [Title/Abstract/Keywords]
24. Adverse Drug Reaction Reporting Systems [Title/Abstract/Keywords]
25. Drug Prescriptions [Title/Abstract/Keywords]
26. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25

    INCLUDE 12 AND 26

Proposed Embase search:

1. medicines and healthcare products regulatory agency [Title/Abstract]
2. mhra [Title/Abstract]
3. European Agency for the Evaluation of Medicinal Products [Title/Abstract]
4. European Medicines Agency [Title/Abstract]
5. EMA [Title/Abstract]
6. EMEA [Title/Abstract]
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. advisory [Title/Abstract]
9. advisories [Title/Abstract]
10. 8 OR 9
11. United Kingdom [Title/Abstract]

12. 10 AND 11
13. 7 OR 12
14. Regulatory risk [Title/Abstract]
15. alert [Title/Abstract]
16. alerts [Title/Abstract]
17. Risk communication [Title/Abstract]
18. Regulatory reports [Title/Abstract]
19. Risk alerts [Title/Abstract]
20. Warning [Title/Abstract]
21. Warnings [Title/Abstract]
22. CAB [Title/Abstract]
23. Current Awareness Bulletins [Title/Abstract]
24. Update [Title/Abstract]
25. Central Alerting System [Title/Abstract]
26. CAS [Title/Abstract]
27. Adverse Drug Reaction Reporting Systems [Title/Abstract]
28. Drug Prescriptions [Title/Abstract]
29. 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28

    INCLUDE 13 AND 29

Proposed Cochrane Library search:

1. United Kingdom [Mesh]
2. medicines and healthcare products regulatory agency
3. mhra
4. European Agency for the Evaluation of Medicinal Products
5. European Medicines Agency
6. EMA
7. EMEA

8. 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. 1 OR 8
10. Regulatory risk
11. advisory
12. advisories
13. alert
14. alerts
15. Risk communication
16. Regulatory reports
17. Risk alerts
18. Warning
19. Warnings
20. CAB
21. Current Awareness Bulletins
22. Update
23. Central Alerting System
24. CAS
25. Adverse Drug Reaction Reporting Systems
26. 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25
27. Drug Prescriptions [Mesh]
28. 26 OR 27

INCLUDE 9 AND 28

Eligibility criteria

Studies must feature a medication risk communication where UK prescribers are one of the intended audiences, with data from the UK present both before and after the risk communication. Prescribing data or a relevant clinical outcome must be reported.

Study selection

Most included studies will be interrupted time series studies. Cohort studies, cluster randomized trials, case control studies or randomized controlled trials will be included if available, but this is unlikely given that the risk communications being examined are expected to be disseminated nationally. Cross sectional studies will be excluded.

Data items and collection process

Titles and abstracts of studies identified in the literature search will be screened for full text examination by two reviewers independently with all studies identified by one or both included in full text review. Full text will be examined by two reviewers independently with disagreements resolved by mutual discussion, with involvement of a third reviewer if not resolved. Data extraction for all studies will be done by one reviewer with data for a sample of studies extracted by a second reviewer.

Risk of bias in individual studies

For publications that are reviewed in detail bias will be analysed using methods recommended by the Cochrane Effective Practice of Organised Care group [10].

Summary measures and synthesis of results

Initial data synthesis will be narrative for both research questions (impact of risk communications, and variation in impact). If there is a sufficient number of studies identified with suitably homogenous outcomes, then quantitative synthesis meta-analysis will be performed to examine impact, and meta-regression to examine variation in impact associated with the method of dissemination, and the type of advice. For the quantitative analysis assuming sufficient data a funnel plot will be used to help decide if a fixed or random effects model is the best choice for analysis. Heterogeneity of quantitative data will be assessed with both the Chi-squared and I-squared tests.

Initial coding framework

The following data will be collected:

Study ID (1st Author, Year, Journal)

Reference URL/DOI

Eligibility

MHRA / Regulatory / Risk / Alert / Update Mentioned

UK included in Analysis

Medication Regulatory Alert

Prescribing data or clinically relevant outcome

Data before and after alert

Methods

Purpose of study

Type of study

Population

Institution / group that submitted study

Country of analysis

Group restrictions on study? eg disease / gender/age

Setting(s) in which outcome has been evaluated

For all outcomes Evaluated

Type of analysis done

Data Collection (m/y to m/y)

Number of time points, before and after

Results (eg change to step / trend)

Summary of findings for outcome

Provides raw data or a usable figure(s) to extract time series data for re-analysis?

Confounding factors noted

Implementation or handling methods noted.

Other points noted

Key finding from paper

Risk of bias will be assessed using Cochrane tools [11]

Intervention (obtained from risk communication)

Date of MHRA risk communication

URL to MHRA risk communication

Nature of risk communication

Type of Dissemination

References

1. Agency., E.M., *European Medicines Agency.*
2. MHRA, *Medicines & Medical Devices Regulation: What you need to know.* 2008.
3. Gurwitz, J.H., et al., *Incidence and preventability of adverse drug events in nursing homes.* Am J Med, 2000. **109**(2): p. 87-94.
4. Lazarou, J., B.H. Pomeranz, and P.N. Corey, *Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies.* JAMA, 1998. **279**(15): p. 1200-5.
5. Pirmohamed, M., et al., *Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients.* BMJ, 2004. **329**(7456): p. 15-9.
6. Guthrie, B., et al., *The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010.* BMC Med, 2015. **13**: p. 74.

7. Barnett, K., et al., *Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study.* Lancet, 2012. **380**(9836): p. 37-43.
8. Statistics, O.f.N. *Ageing of the UK population*. 2015 [cited 2015 27 October]; Available from: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/mid-2014/sty-ageing-of-the-uk-population.html.
9. Wilson, M., et al., *Prescribing to fit the needs of older people--the NHS Scotland Polypharmacy Guidance, 2nd edition.* J R Coll Physicians Edinb, 2015. **45**(2): p. 108-13.
10. (EPOC)., E.P.a.O.o.C., *EPOC Resources for review authors. Oslo: Norwegian Knowledge Centre for the Health Services.* 2015.
11. (EPOC)., E.P.a.O.o.C., *Suggested risk of bias criteria for EPOC reviews. EPOC Resources for review authors.* 2015.