Unlicensed medicines use in the UK: A systematic review and quality assessment of published guidelines

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Background

An unlicensed medicine is defined as a medicinal product for which there is no marketing authorisation granted by the Medicines Healthcare and Regulatory Agency (MHRA)[1]. Unlicensed medicines are widely used within the UK and there are many guidance documents which exist to support their use. However, each guidance document is published for individual organisations and there has never been an analysis of the different approaches these documents take nor an evaluation of their quality.

Aim: To analyse the content and quality of unlicensed medicines guidance documentation in use in the UK.

Methods

A systematic search of the published and unpublished literature between 2000 and June 2015. This included:

- A database search including Medline, Embase, ISI Web of Knowledge, Google Scholar, PubMed and International Pharmaceutical Abstracts. Search terms included 'unlicensed medicine' or 'specials' combined with; guideline, policy, framework, standardized operating procedure, standard operating procedure or recommendation.
- A 'call for guidance' which was distributed to encourage organisations to submit their guidance documentation for the review. This was distributed to secondary care, primary care, community pharmacy and pharmaceutical industry networks both locally and nationally.
- Website searches for organisations within the North East and North Cumbria Local Clinical Research Network.

Identified documentation included guidance designed to aid professionals within the UK on the use of unlicensed medicines, covering areas such as prescribing, procurement, dispensing or administration. Excluded documents consisted of those providing specific guidance on homeopathic medicines, food or dietary supplements, herbal medicines, radiopharmaceuticals, orphan drugs and investigational medicinal products.

The quality of the guidelines was assessed using the AGREE II tool[2]. Content was evaluated by conducting a thematic analysis. The AGREE II tool rates the quality of the documentation across six domains and provides a score from 0% for very poor quality to 100% for excellent quality. Each guideline was independently assessed by two researchers.

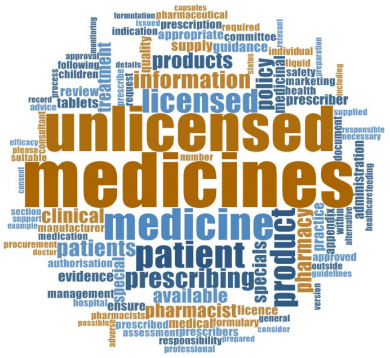

Figure 1: A word frequency cloud of the 1000 most commonly used words included in the guidelines

Results

A total of 24,025 documents were screened from a combination of database searching (n=24,025), website searches (n=19) and submissions (n=87). Following application of exclusion criteria and removal of duplicates, a total of 52 guidance documents were included in the analysis. This included those from NHS secondary and tertiary care trusts (n=29), professional bodies and regulators (n=12), community pharmacy and primary care (n=11). Documents included within the analysis ranged from guidelines (n=28), policies (n=10), standard operating procedures (n=9) and frameworks (n=5).

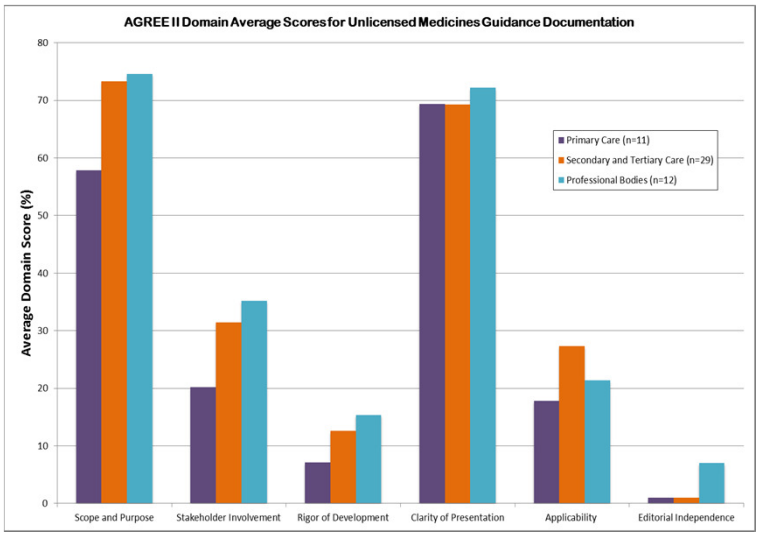

Figure 2: AGREE II Average Domain Scores for Unlicensed Medicines Guidance Documentation

AGREE Scores

Average domain scores for each documentation setting can be seen in Figure 2.

Overall the best performing domains were:

- 'Scope and Purpose' (70.6%)
- 'Clarity of Presentation' (70.4%)

Most documents had specific objectives that were well described. The presentation of information was good, enabling key recommendations to be easily identified.

The least well performing domains overall were:

- 'Rigour of Development' (12.1%)
- 'Editorial Independence' (2.6%)

There was a lack of documented references to a clear evidence base. It was not clear in the majority of cases if there were any funding bodies or competing interests in the development of the unlicensed guidance documentation.

There was a variation within some of the domains:

- 'Applicability' (23.9%)
- 'Stakeholder Involvement' (30%)

Whilst some documents provided advice and tools in implementation of the recommendations, many did not and there was a deficit in the acknowledgement of the potential barriers and facilitators to implementation of recommendations. For 'Stakeholder development' it wasn't always apparent if there was a diverse mix of professionals involved in the development of the guidance documentation and there was little to no involvement of patients.

Thematic analysis

Thematic analysis of the guidance documents revealed four parent themes across the documentation (see Table 1).

Table 1: Themes from analysis of guidance documentation

Parent theme	Sub-themes
Responsibility around the use of unlicensed medicines	Understanding the definitions around unlicensed medicines Awareness of patients and professionals when using an unlicensed medicine Responsibilities of individuals and organisations involved in using unlicensed medicines References to the guidance and legislation which informed guidance documentation
Operational issues with using unlicensed medicines	Selecting the pharmaceutical formulation Role of the pharmacist and the wider pharmacy team in managing the use of unlicensed medicines Patient involvement Stages of using an unlicensed medicine Continuing treatment
Risk versus benefit	Evidence to support use of unlicensed medicines Place of unlicensed medicines in the treatment of a patient and potential alternatives Describing and assessing risk Reporting of errors and adverse effects associated with unlicensed medicines
Controlling the use of unlicensed medicines	Costs associated with unlicensed medicines Audit of unlicensed medicines use Restricting use of unlicensed medicines Organisational decision making surrounding unlicensed medicines

Discussion and conclusion

- Both forms of analysis demonstrated a lack of consistency of content and quality across guidance documentation used for unlicensed medicines.
- The AGREE II scores also exhibit a lack of transparency around who writes and updates guidance on unlicensed medicines
- The lack of evidence base for recommendations is likely to reflect a wider issue around lack of evidence for unlicensed medicines use.
- There is a deficit in patient involvement in guidance
- There was a lack of documentation from community pharmacy and primary care. It is not clear if this is due to a lack of guidance or a lack of submission to the project.
- Healthcare organisations would benefit from agreeing a 'core content' for unlicensed medicines documentation

References

1. MHRA. Guidance note 14: The supply of unlicensed medicinal products ("specials"). 2014. http://www.mhra.gov.uk/home/groups/is-lic/documents/publication/con413520.pdf (Accessed 27 August 2015)
2. Brouwers M, Kho ME, Browman GP, Cluzeau F, Feder G, Fervers B, Hanna S, Makarski J. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. Can Med Assoc J. 2010; 182: E839-842

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http://wp.sunderland.ac.uk/emulsionstudy