Can clinical practice guidelines lead astray?

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Clinical practice guidelines (CPGs) are "systematically developed statements to assist practitioner and patient decisions for specific clinical circumstances" [1]. They are collections of statements (recommendations) to be used in order to change or support current clinical practice [2]. CPGs, as well as systematic reviews and economic or decision analyses, constitute so-called secondary publications, which synthesize data from primary research on a particular, defined clinical problem. The main difference between CPGs and other publications, both primary and secondary, is that CPGs include formal recommendations on practical application of the available information. To be evidence based, CPG should rely on on valid systematic reviews of current evidence.

The number of such publications is rising constantly. In 2006, almost 700 new or updated CPGs were registered in MEDLINE database. Their significance for clinical care is also rising as clinicians increasingly use them to guide their decisions concerning patient management, being convinced (or at least hoping) that they will not err, will help their patients, or that at least they will do no harm.

One may ask, however, if there is a risk that relying on currently available CPGs will not result in optimal patient care? We believe that such a risk exists and that all clinicians using CPGs should be aware of it. The danger of error exists at each stage of the guidelines development process: from choosing the scope of a guideline, through selection of authors, deciding what type of evidence and outcomes to consider, interpreting the balance between benefits and downsides of alternative management strategies, to the formulation of recommendations. Furthermore, guidelines may be incorrectly interpreted or inappropriately used.

How to assess the quality of clinical practice guidelines?

Let us start with the methodology of CPG development. Although the number of guidelines is constantly increasing, their quality and resulting validity may still be far from optimal. CPGs must fulfill certain criteria of quality. An international group of methodologists and CPG developers have proposed such criteria in an AGREE instrument [3,4]. Each of the twenty three criteria, grouped in six domains (tab. 1) is assessed on a four point scale. A summary score suggests to what degree a guideline is valid, reliable, and worth applying in clinical practice.

The first domain deals with a scope of the guideline, precision of clinical questions addressed, and description of the target population of patients. The second domain evaluates how well the given guideline reflects views and preferences of prospective users. This is because different management decisions may be made on the basis of the same objective evidence, depending on cultural, religious, and legal determinants, or personal values and preferences. Hence, guideline panels should include representatives of all stakeholders, including patients. The third domain assesses the process of selection and summarising of the evidence (this part of CPG development is relatively objective, verifiable, and reproducible) and the process of formulating and updating recommendations (which is relatively subjective). This is a critical issue in the evaluation of CPG validity. A full review of this process exceeds the scope of this article. However, we would like to point out the growing worldwide acceptance of the GRADE system [5–10], which was created to make the process of CPG development and formulating recommendations more systematic and uniform. The fourth domain of the AGREE instrument evaluates user-friendliness of the guidelines. The greatest importance is attached to specificity and unequivocality of the recommendations. The fifth domain comprises criteria that allow to assess if the CPG could be used in daily clinical practice, if its economic consequences have been considered, and if criteria for monitoring and audit are included. The sixth domain evaluates the probability that the authors' conflict of interest may have influenced the recommendations. This is possible at the level of the organization financially supporting the development of the CPG or through financial relationships between authors and the medical industry. One of the limitations of the AGREE Instrument is the lack of formal rules for interpretation of the derived scores. Nevertheless, the instrument helps to identify limitations of the CPGs.

The development of new practice guidelines is extremely time and effort-consuming, costly, organizationally difficult and requires specific knowledge (not only in clinical aspects but also in the methodology of the CPG development). It also

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Table. The AGREE Instrument

Scope and purpose
1. The overall objective(s) of the guideline is (are) specifically described.
2. The clinical question(s) covered by the guideline is (are) specifically described
3. The patients to whom the guideline is meant to apply are specifically described
Stakeholder involvement
4. The guideline development group includes individuals from all the relevant professional groups
5. The patients' views and preferences have been sought
6. The target users of the guideline are clearly defined
7. The guideline has been piloted among target users
Rigour of development
8. Systematic methods were used to search for evidence
9. The criteria for selecting the evidence are clearly described
10. The methods for formulating the recommendations are clearly described
11. The health benefits, side effects and risks have been considered in formulating the recommendations
12. There is an explicit link between the recommendations and the supporting evidence
13. The guideline has been external reviewed by experts prior to its publication
14. A procedure for updating the guideline is provided
Clarity and presentation
15. The recommendations are specific and unambiguous
16. The different options for management of the condition are clearly presented
17. Key recommendations are easily identifiable
18. The guideline is supported with tools for application
Applicability
19. The potential organisational barriers in applying the recommendations have been discussed
20. The potential cost implications of applying the recommendations have been considered
21. The guidelines presents key review criteria for monitoring and/or audit purposes
Editorial independence
22. The guideline is editorially independent from the funding body
23. Conflicts of interest of guideline development members have been recorded

requires that the authors remain neutral as much as possible. If these conditions are not fulfilled, it is suggested that existing valid CPGs should be adapted. Such approach is recommended e.g. by the Council of Europe [11]. As an example we point out Polish guidelines on prophylaxis and treatment of venous thromboembolic disease, developed in 2002 [12] and updated in 2005 [13] through a rigorous process of adaptation of original CPGs issued by the American College of Chest Physicians [14], while taking into account local factors. These adapted guidelines have been endorsed by many professional and scientific societies in Poland.

Do we get the guidelines right?

If we want to use the guidelines in everyday practice, we must be able to interpret the recommendations correctly. First of all, we must know if a specific recommendation applies to our patient (or a specific group of patients) as their liberal extrapolation may not be appropriate. Another limitation of most CPGs is that they apply to "average" patients and frequently do not take into account existing comorbidities although they are common in clinical practice. It is also crucial to understand the authors' confidence in their recommendations. The present-day variety of different systems of grading strength of recommendations makes this judgment even more difficult. If we are not sure as to the strength of recommendations and quality of evidence on which recommendations are based, we risk making wrong decisions. It is noteworthy that less rigorously developed guidelines usually comprise stronger recommendations.

Are clinical practice guidelines appropriately used?

CPGs may be intentionally or unintentionally used for a purpose that they are not intended for.

One of the aforementioned guideline validity criteria is the inclusion of specific means to monitor adherence to guidelines and the effects of following the recommendations. These evaluate mainly clinicians' adherence to the guideline, since the impact of guideline implementation on patient outcomes is much more difficult to assess. Thus, one may monitor effects of CPG implementation measuring the change in behaviour (e.g. one may check the percentage of patients with diabetic nephropathy who received a renin-angiotension system blocker). This system of quality control however is occasionally used to assess the performance of individual physicians [15] and – depending on the results – determine their salary. Such an approach may lead to the neglect of patient preferences while making decisions to use a diagnostic or therapeutic strategy recommended in the guideline, when the patient either cannot or does not want to take the recommended medication or agree to an invasive diagnostic procedure.

There is also a risk of indiscriminate implementation of all recommended interventions, which may create significant

problems for patients suffering from several coexisting diseases, especially for the elderly. This was well illustrated by Boyd and colleagues, who considered a hypothetical situation of having to manage according to current guidelines a 79-year-old woman with chronic obstructive pulmonary disease, type 2 diabetes, osteoporosis, hypertension, and osteoarthritis [16]. It turned out that such a patient should be taking twelve different medications and on top of this follow an appropriate diet. One can easily imagine the burden associated with such a management, not to mention its cost, and the risk of harmful drug interactions.

It is also quite likely that an elderly patient will not necessarily gain expected benefits from all prescribed medications and that the quality of her life may actually worsen due to a complex medication scheme. It is also quite probable that given a large number of pills the patient will simply not follow the physician's recommendations.

Clinical practice guidelines are sometimes also used for marketing of medical products. It has to be stressed that it is not only important if authors of CPGs actually did recommend certain option based on a biased judgement but also if a rational person could get an impression that it may have happened. We will illustrate this problem with a promotional strategy of a new drug used to treat severe sepsis and septic shock – a recombinant human activated protein C (rhAPC) [17]. This example shows several problems occurring at the junction of guideline development and marketing efforts of the pharmaceutical industry. In the United States, rhAPC was introduced in 2001 to treat sepsis and septic shock on the basis of one phase III trial, even though half of the FDA panel that assessed the application for drug voted for a requirement of one more randomized trial to confirm benefits. In 2002, in order to increase administration of rhAPC, the manufacturer hired a public relation company. Its task was to develop and help to implement a multi-stage marketing strategy. One of the main instruments of this strategy became the CPG developed by an international group of experts that strongly recommended the use of rhAPC [18]. The authors of a recent editorial in the New England Journal of Medicine describing the above story pointed out that the development of these clinical practice guidelines was sponsored in over 90% by the manufacturer of rhAPC and that several of the panel members were financially connected with this company, receiving research or conference grants, lecture honoraria, etc [17]. This obviously does not imply that authors were not objective and that recommendations were consciously biased, nevertheless it calls for more cautious approach to these recommendations and provides argument for those who disagree with them. In subsequent studies, although in slightly different populations, the efficacy of rhAPC was not confirmed and an increased risk of bleeding was observed. Those findings have not yet been reflected in CPGs (although an update is expected soon).

Another aspect of the rhAPC promotion strategy was to introduce its use (or at least consideration of it) to sepsis and septic shock management algorithms in hospitals. Again, the financial contributions of the drug manufacturer to the development and implementation of these algorithms might have led to an impression of restricting physicians' freedom of independent judgment about the available data and of drug promotion.

The story described above is not unique as regards the interactions between industry and clinical medicine. The particular attention it received was due to the concerns elicited by a single sponsor and one very expensive drug.

It is possible that a planned repetition of the first trial, which showed significant benefit, may satisfy those who believe that rhAPC is a life-saving drug the cost of which is similar or even smaller than that of other widely accepted interventions. Time will show. In the meantime, it is worth to remember that even an impression of the conflict of interests may determine the fate of guidelines, i.e. their uptake and implementation in everyday practice.

How to use practice guidelines?

What are the prerequisites for CPGs to bring the expected clinical benefits? First, CPGs must address clinically important questions. Second, all recommendations should be supported by systematically collected and appraised evidence, and clearly connected to this evidence, even though they are always to a degree subjective. The strength of recommendations should be stated, reflecting the confidence of the guideline panel that adherence to these recommendations will do more good than harm. Third, users of CPGs must be able to assess their validity and properly interpret recommendations. Fourth, and the most important, CPGs should not replace clinical judgement and should not be used as rigid rules [19,20]. Let us remember that CPGs constitute just one, even though important and useful, of the elements to be considered in clinical decision making. Ignoring other elements, especially specific clinical circumstances or values and preferences of a patient may lead to loss of expected benefits from using CPGs.

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