ORIGINAL ARTICLE

Guidelines for Neuropathic Pain Management in Patients with Cancer: A European Survey and Comparison

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■ **Abstract:** Between 19% and 39% of patients with cancer pain suffer from neuropathic pain. Its diagnosis and treatment is still challenging. Yet, national clinical practice guidelines (CPGs) have been developed in several European countries to assist practitioners in managing these patients safely and legally. The aim of this study was to assess the quality of the development and reporting of these CPGs.

Methods: In collaboration with the European Federation of IASP Chapters, a European inventory of CPGs was conducted. Inclusion criteria were at least one paragraph dedicated to the treatment of neuropathic pain in cancer. Using the Appraisal of Guidelines, Research and Evaluation II instrument, 2 appraisers independently assessed the quality of the development process of the included CPGs in 6 quality domains. Besides, CPGs developed by governmental organization were compared with those developed by professional societies using *t*-tests.

Results: Mean scores of the domains "scope and purpose" (80%) and "clarity of presentation" (61%) were satisfactory, "stakeholder involvement" (58%), "rigor of development" (57%), and "editorial independence" (53%) were acceptable, and "applicability" was insufficient (39%). Governmental guidelines had higher quality scores than professional society guidelines for domain "stakeholder involvement" and "editorial independence" ($P < 0.01$).

Conclusions: The quality of the development process of the 9 included CPGs varied widely. CPGs should be developed within a structured guideline program, including methodological support. As developing a CPG is expensive and time-consuming, we recommend more international cooperation to increase quality and lower the development costs. ■

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Disclosure: The appraisers were French and Dutch, and CPGs were assessed from both countries. By analyzing independently, we tried to overcome the potential problem of not being neutral toward a national CPG. Moreover, the appraisers were not members of the guideline development group of one of the CPGs.

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INTRODUCTION

Pain is a common symptom in cancer patients. In Europe, 56% of cancer patients suffer from moderate-to-severe pain and consequently report difficulties in their daily activities and high impairment of their quality of life.[1] For adequate treatment of pain, it is important that both nociceptive and neuropathic pain is diagnosed, as they need different treatments.

In 1986, the World Health Organization (WHO) published the "WHO analgesic ladder", a tool for a stepwise pharmacological approach for the treatment of nociceptive pain in cancer patients.[2] This 3-step approach can be effective in approximately 80% of cancer patients.[3] Despite the introduction of this pain ladder and new analgesic pain therapies, the prevalence of pain in cancer patients remained around 50% during the past 40 years.[4] One of the possible reasons for incomplete pain relief may be the presence of neuropathic pain, because 40% of patients with cancer on opioid therapy referred to a specialized pain clinic appeared to have neuropathic pain alone or in combination with nociceptive or visceral pain.[5] No evidence-based algorithm for the treatment of neuropathic pain in cancer exists. In clinical practice, neuropathic pain is often treated with adjuvants like tricyclic antidepressants (amitriptyline or nortriptyline) or anticonvulsants (gabapentin or pregabalin).[6] The evidence for these types of drugs, based on number needed to treat (NNT 1.2–3.6) and number needed to harm (NNH 6–28), is mainly derived from research performed in patients with painful diabetic neuropathy or postherpetic neuralgia (PHN).[7–9] Little scientifically sound data are available to determine these figures for cancer patients with neuropathic pain.[10] Hence, the benefit vs. risk ratio for cancer patients might be worse for these antineuropathic drugs. Additionally, adjuvant drugs for the treatment of neuropathic pain are frequently prescribed in combination with opioids, which can increase side effects.[6] Lastly, the mechanisms of neuropathic pain in patients with DPN or PHN are most likely more localized than in patients with cancer, which also may decrease the chance that these patients will benefit from the same symptomatic approach.[11] Clinical practice guidelines (CPGs) can contribute to effective and safe prescription.[12] Systematically developed guidelines can support the practitioner in making appropriate decisions.[13] Therefore, in this study, we assessed the quality of the development process of national CPGs, developed in European countries, which contain at least one section about neuropathic pain treatment in patients with cancer. While professional societies of medical specialists should be better informed about clinical aspects, organizations specialized in guideline development should be better equipped to guide the process of guideline development. We also studied whether such differences have consequences for the guideline development quality.

METHODS

Collection and Selection of Guidelines

Guideline collection was conducted in 2 steps: (1) a review of the literature and (2) an email with a questionnaire to European pain experts. This second step was needed, as most of the guidelines are non-English and not published in scientific papers, and thus, a review in usual databases would not be sufficient to obtain all guidelines.

For the review, we searched CPGs in MEDLINE in Europe containing at least one chapter on the management of neuropathic pain in patients with cancer. A literature search of the English and non-English literature indexed in Ovid-Medline, Pubmed, Embase, Cinahl, and the National Guideline Clearinghouse database in April 2010 was conducted using the following search strategy: "Practice Guideline" [Publication Type] or "Guideline" [Publication Type] or "Guidelines as Topic" [Mesh], "Neuralgia" [Mesh], or "neuropathic pain" [All Fields] and "Neoplasms" [Mesh] or "cancer" [All Fields]. Exclusion criteria were studies on guidelines about children or the elderly, guidelines from non-European countries, and international guidelines (when at least 2 countries are represented in the development of the guideline).

All articles about clinical practice guideline (CPG) on cancer pain or neuropathic cancer pain were included. Selection was carried out by titles, then by abstracts and finally by reading full text.

For step 2, an invitation for collaboration with the European Federation of IASP Chapters (EFIC) was accepted by as well the past and the current president. The official EFIC ($n = 34$), and representatives of the NeuPSIG (Neuropathic Pain Special Interest Group of the IASP), all pain specialists ($n = 32$), were invited by email in March 2010 to mention and send current guidelines in their country that contain information

about neuropathic pain treatment in cancer patients. In a second mail, they were invited to validate the collected documents.

Inclusion and Exclusion Criteria

Inclusion criteria for further analyses of the collected guidelines were (1) fulfillment of the definition of the Institute of Medicine for practice clinical guidelines[14] and (2) having at least one paragraph dedicated to the treatment of neuropathic pain in cancer. The search period was from January 2007 to March 2010. A CPG was excluded if (1) it was restricted to specific groups, for example, children or frail elderly; (2) it did not include systematically collected literature to support the recommendations; or (3) if it was published after our inclusion time (March 2010). Each collected CPG was sent to the participant to check and validate our collection.

Translation Process

Each non-English included CPG was translated with the help of a translator toolkit and checked by the authors. All authors were fluent in English. VP, MLM, and KV are French-speaking and able to translate the French guidelines; AS, SV, JB, YE, YH are Dutch, YH is also fluent in Norwegian, and HK, fluent in German. Additional native speakers were contacted for CPGs in other languages.

Assessment Tool: The AGREE II Instrument

At least 2 authors independently scored included CPGs according to the Appraisal of Guidelines, Research and Evaluation II (AGREE II) instrument.[15,16] The AGREE II instrument is widely used to assess the quality of development and reporting of CPGs. It provides an appraisal of the predicted validity of a CPG, that is, the likelihood of a CPG to achieve its intended outcome. This internationally validated 23-item instrument consists of 6 domains divided in items: (1) scope and purpose, which covers the overall aim of the guideline and target groups for whom the guideline is intended (3 items); (2) stakeholder involvement, which evaluates the appropriate stakeholders involved in guideline development and the views of its intended users (3 items); (3) rigor of development, which assesses the selection of the evidence and the method to create recommendations (8 items); (4) clarity and presentation, which evaluates the structure and the format of the guideline (3 items); (5) applicability, which assesses facilitators and potential barriers for guideline implementation (4 items); and (6) editorial independence, which covers biases concerning conflicts of interest (2 items) and one overall assessment item, judging whether the guideline ought to be recommended for its use in clinical practice. Each item was rated by using a 7-point Likert scale (from 1 "strongly disagree" to 7 "strongly agree"). All CPGs were integrally assessed.

Appraisers

According to the AGREE protocol, 2 appraisers (VP and AS) independently assessed each guideline with AGREE II. They were trained in using the AGREE II instrument. Each item score needed to be explained by specific comments. Differences on items scores of more than 1 point on the Likert scale were discussed until consensus was obtained. If no consensus was reached on a specific item, a third appraiser (YE) assessed it independently, and the same procedure of consensus with 3 appraisers was carried out.

Data Collection

An item rating < 4 was considered low, ≥ 4 acceptable, and ≥ 6 high. Domain scores per CPG were calculated by summing up the AGREE II item scores and standardizing them as a percentage of the maximum possible domain score, according to the instructions within the instrument with this formula: [(score obtained−minimum score possible)/(maximum score possible−minimum score possible)] $\times$ 100. A domain score $< 60\%$ was considered as low, $\geq 60\%$ as acceptable, and $\geq 80\%$ as high.

Statistical Analysis

All data were collected and analyzed with SPSS 16.0 (NY, USA) using descriptive statistics. Median item and domain scores were calculated. Finally, median domain scores of CPGs developed by organizations specialized in guideline development and CPGs developed by professional bodies were calculated and compared using *t*-test.

RESULTS

Literature Review

Selection on Title. The Embase search yielded 177 articles, of which 8 were selected (Figure 1). Of the

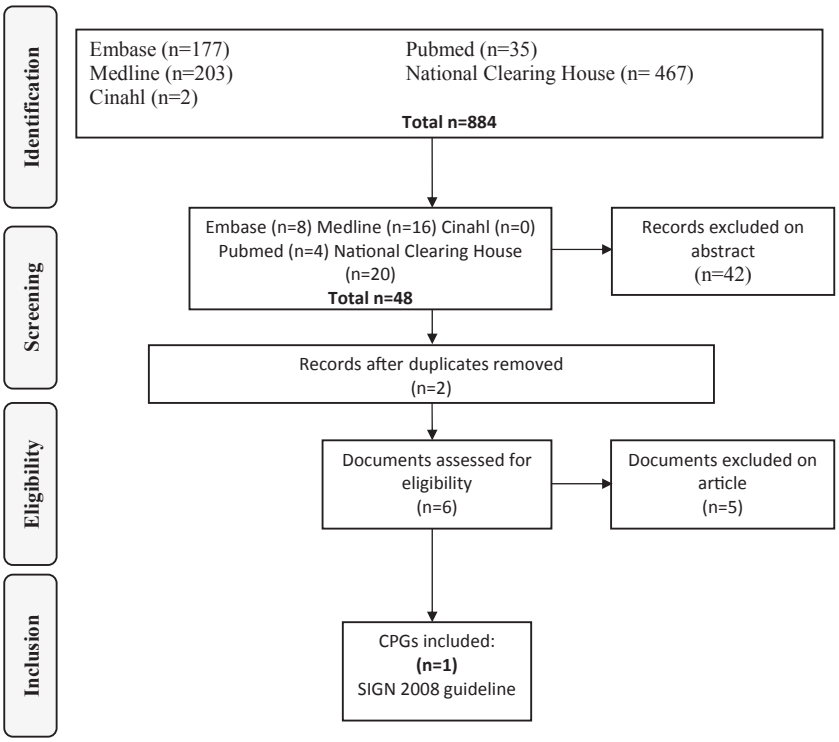

Figure 1. Review of clinical practice guidelines (CPGs) concerning the treatment of neuropathic pain in cancer patients in Europe.

Medline search, another 16 of 203 retrieved articles were selected. The Cinahl database contained 2 articles, none being selected. A Pubmed search found 35 articles, of which 4 were selected. The National Clearing House search yielded 467 articles, of which 20 were selected.

Selection of Abstract. Of the 48 articles selected by titles, 6 were selected by the abstract, and 2 were duplicates. On this selection, only 1 was included: the SIGN 2008 guideline from the National Clearing House database.[17]

CPG Collection via EFIC

Sixty-two percent of the EFIC and NeuPSIG members responded. Fifty-four documents about pain (including pain in children and pain in elderly), neuropathic pain, and cancer pain were collected. Of these, 17 contained at least one section about neuropathic pain treatment in patients with cancer and were validated by the participants. Nine of these fulfilled the definition of a clinical practice guideline (CPG) and thus met all inclusion criteria (Figure 2).[17–25]

Only one included guideline was in English. The other included guidelines were translated into English by the authors for the French and the Dutch guidelines. The Norwegian guidelines were translated into English with the help of the translator toolkit and checked by YH. The Italian and Spanish guideline translations were checked by native speakers who are also fluent in English.

For each item, consensus in rating was reached between the 2 appraisers. Domain scores for the 9 CPGs are presented in Table 1. The overall median scores were 81% for "scope and purpose", 58% for "stakeholder involvement", 57% for "rigor of development", 61% for "clarity and prescription", 39% for "applicability", and 53% for "editorial independence".

The 4 CPGs developed by a guideline development organization[17,20,22,23] had higher domain scores than the 5 CPGs developed by a medical society.[18,19,21,24,25] The difference was significant ($P < 0.05$) for the domains "stakeholder involvement" and "editorial independence" (Table 2).

All items in the domain "scope and purpose" as well as in the domain "clarity and presentation" had a median score of 6 or higher (Table 3). In the domain "stakeholder involvement", all CPGs included a clear definition of the target users (item 6); other items within this domain received lower median scores. In the domain

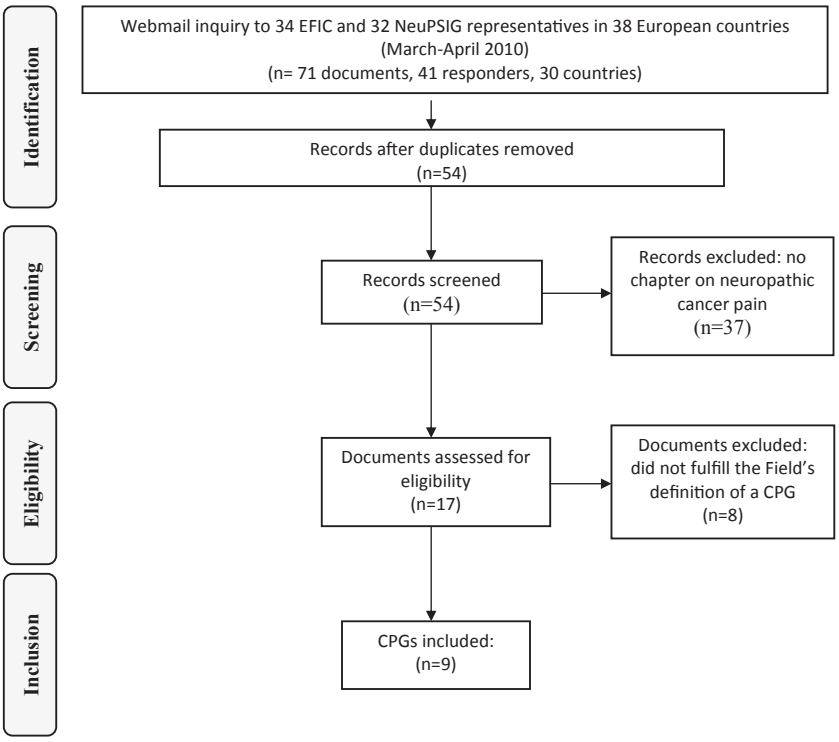

Figure 2. Flow chart: collection of European national Clinical Practice Guidelines (CPGs) from March to April 2010.

Table 1. Assessment of the Quality of the 9 Clinical Practice Guidelines About Neuropathic Cancer Pain Treatment with AGREE II Instrument Between 2005 and 2010

	Guidelines	Scope and Purpose	Stakeholder Involvement	Rigor of Development	Clarity and Presentation	Applicability	Editorial Independence
	All guidelines	**81**	58	57	61	39	53
Netherlands 2008-I	Diagnosis and treatment of pain in patients with cancer*	**95**	**95**	**96**	75	43	**100**
Norway 2009	Pain treatment	**86**	**86**	61	61	79	79
United Kingdom 2008	Control of pain in adults with cancer *	**91**	**81**	70	64	48	79
France 2010	Chronic neuropathic pain	**86**	48	**80**	71	29	64
Spain 2008	Palliative care *	**86**	67	52	64	25	79
Netherlands 2008-II	Pain in palliative care	**95**	57	32	64	39	29
Italy 2008	Pain management in cancer	**81**	24	52	54	21	14
Norway 2007	Palliative care *	67	33	41	29	29	21
Italy 2006	Control of cancer pain †	41	29	32	64	39	14

*Guideline development group.
†Local initiative of guideline development; A domain score < 60% was considered as low, ≥ 60% as acceptable, and ≥ 80% as high (in bold). AGREE, Appraisal of Guidelines, Research and Evaluation II instrument.

"rigor of development", the "formulation of health benefits and safety" (item 11) was the only item with no scores < 4. The domain "applicability" received the lowest median scores, with 3 of 4 items lower than 3 for all CPGs except Norway 2009.

In total, for all guidelines, all items of the domain "scope and purpose" and "clarity and presentation" had high median scores. Three of the 4 items included in the domain "applicability" had median scores < 4.

DISCUSSION

Main Findings

This is the first study that systematically assessed the quality of CPGs developed in European countries about the treatment of neuropathic pain in cancer patients. There was much variation in quality between the CPGs. High-scoring domains were "scope and purpose" and "clarity of presentation", which is consistent with

Table 2. Comparison of CPGs developed by professional societies with CPGs developed by guideline development organizations

Origin	Professional Society	Guideline Development Organization	*P* Value
Scope and purpose	74	89	0.20
Stakeholder involvement	38	82	**< 0.01**
Rigor of development	48	70	0.14
Clarity and presentation	56	66	0.32
Applicability	31	49	0.15
Editorial independence	29	84	**< 0.01**

CPG, clinical practice guidelines. Professional guidelines were developed by professional societies (pain, palliative care, or oncology societies), developed by national organization mainly financed by the government.

findings from other studies.[26–28] Applicability of the guideline was low in 8 CPGs, implying that anticipating on implementation needs more emphasis in CPGs to increase practitioners' use. This confirms the findings from a recent qualitative study among general practitioners about barriers to use guidelines.[29]

One of the factors that could explain differences between CPGs may be the organization responsible for the CPG. In our study, 2 of the CPGs with the highest AGREE II scores were developed by institutes specialized in guideline development. Both the Scottish Intercollegiate Guidelines Network and the Dutch Institute for Healthcare Improvement (CBO, the Netherlands) used a development process that was based on the original AGREE instrument.[17,23] Burgers et al., who assessed the quality of 86 European and Canadian guidelines with the AGREE instrument, concluded that the quality of the development process of CPGs developed in a guideline program and by government agencies was higher than that of CPGs from other organizations.[12] A recent systematic review of Alonso-Coello et al.[26] analyzed studies assessing guidelines

Table 3. Median AGREE II item scores of included 9 CPGs

Item	Median	Range		Confidence Interval (95%)
Scope and purpose				
Overall objective(s) of the guideline is (are) specifically described	6	3	7	4.9 to 6.74
Health question(s) covered by the guideline is (are) specifically described	7	3	7	4.7 to 7.1
The population to whom the guideline is meant to apply is specifically described	6	2	7	4.1 to 6.4
Stakeholder involvement				
Guideline development group included individuals from all the relevant professional groups	5	2	7	3.4 to 6.4
Views and preferences of the target population have been sought	**1**	**1**	**7**	**0.7** to **4.2**
Target users of the guideline are clearly defined	6	2	7	3.2 to 6.4
Rigor of development				
Systematic methods were used to search for evidence	**2**	**1**	**7**	**1.4** to **5.5**
Criteria for selecting the evidence are clearly described	4	1	7	1.9 to 5.2
Strengths and limitations of the body of evidence are clearly described	5	1	7	2.9 to 6.1
Methods used for formulating the recommendations are clearly described	5	2	6	3.1 to 5.6
Health benefits, side effects, and risks have been considered in formulating the recommendations	6	4	7	4.9 to 6.2
Explicit link between recommendations and supporting evidence	3.5	1	7	2.0 to 5.2
Guideline has been externally reviewed by experts prior to its publication	**2**	**1**	**7**	**1.2** to **4.6**
Procedure for updating is provided	5	1	7	2.2 to 6.2
Clarity and presentation				
Recommendations are specific and unambiguous	6	2	7	4.6 to 7.0
Different options for management of the condition are clearly presented	6	4	7	5.1 to 6.7
Key recommendations are easily identifiable	6	2	7	4.1 to 6.6
Applicability				
Guideline described facilitators and barriers to its application	**2**	**1**	**5**	**1.1** to **3.4**
Guideline provides advice and/or tools on how the recommendations can be put into practice	4	3	7	3.6 to 5.8
Potential cost implications of applying the recommendations have been considered	**1**	**1**	**5**	**0.7** to **2.9**
Guideline presents monitoring and/or auditing criteria	**2**	**1**	**5**	**1.1** to **3.4**
Editorial independence				
The views of the funding body have not influenced the content of the guideline	5	1	7	2.2 to 5.6
Competing interests of guideline development group members have been recorded and addressed	4	1	7	1.6 to 5.5

AGREE, Appraisal of Guidelines, Research and Evaluation II instrument; CPG, clinical practice guidelines, Item scores below or equal to 3: insufficient quality of development (in bold).

published between 1980 and 2007 with the AGREE instrument and found a higher development quality in recently developed guidelines. In our assessment with AGREE II, we found higher median scores mainly on the purpose and clarity domains. Guideline developers became more aware of the importance and methods of a systematic development process, maybe partly by publications on this topic and the availability of the AGREE and AGREE II instrument.[30]

Most CPGs gave no information about views and preferences of the target patient population and their influence on the development of the recommendations; only 3 CPGs had patients' representatives in their workgroup (Netherlands 2008-I, U.K. 2008 and Norway 2009). Probably, more guidance is needed on how to involve patients in the guideline development process.[31] Furthermore, most CPGs gave no attention to the applicability and implementation, while this is very important for clinicians to use them.[32]

Strengths and Limitations

With the help of EFIC and NeuPSIG collaboration, we were able to obtain an extensive overview of guidelines that contain information about neuropathic pain in cancer patients, and it was possible to overcome the obstacles of gray literature. We used AGREE II, the updated version of the AGREE instrument. AGREE II, which uses a 7-point Likert scale (instead of the 4-point Likert scale in the AGREE instrument), improves the reliability of the item and domain scores.[15,16] This instrument was used recently for the assessment of guidelines for migraine and gave a good overview of the development of guidelines in pain.[33]

Although neuropathic pain in cancer patients is a worldwide problem, we only assessed European CPGs. The main reason for this restriction was the opportunity to collaborate with the EFIC and NeuPSIG, which helped us to collect information from 30 of the 38 European countries. Second, we did not find a CPG merely dedicated to the treatment of neuropathic pain in cancer patients. Third, in contrast to other studies, we also included guidelines that were not written in the native language of the researchers. With the translator toolkit, we were able to assess also these 5 CPGs after validation of the translation by native or fluent speakers. Finally, results of the AGREE II assessment should be interpreted with caution. Using information only available in the CPG may limit the validity of the scores. Besides, AGREE II focuses on the methods and reporting of the guideline, but does not assess the validity of the diagnosis, medical content, and clinical recommendations.[34] In perspective, the comparison of the content of the guidelines could be very interesting for our knowledge about neuropathic pain in patients with cancer and its management in Europe.

CONCLUSIONS AND RECOMMENDATIONS

The quality of CPGs on neuropathic cancer pain is modest. All domains and items showed room for improvement in most CPGs. Yet, 3 items need specific attention in future guideline development about this topic: incorporating the patients' views, describing the systematic review process, and giving recommendations about the implementation of the CPG.

We did not find a CPG merely dedicated to the treatment of neuropathic pain in cancer patients. Yet, this clinical problem in this specific patient group concerns an area of medical uncertainty, iatrogenic complications, and interventions carrying significant risks and costs, and therefore fits into the criteria for creating an independent CPG.[14] It implies that (1) CPG developers should emphasize that the scientific evidence is weak and should be interpreted with caution and (2) there is a need for more research on neuropathic cancer pain patients to provide evidence for more reliable CPGs. As developing guidelines is time-consuming and expensive, international cooperation in CPG development could be a solution to increase quality and reduce costs.[35]

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AUTHOR CONTRIBUTIONS

VP and AS conceived and designed the experiments and analyzed the data. They also wrote the manuscript with

YE and SV. JB contributed to the method, the interpretation of the results, and the discussion regarding the AGREE II instrument. YK contributed to the introduction and discussion. YE, SV, and MLM supervised the overall execution of the project and contributed to the experimental design with KV. HK provided support from the EFIC. All authors discussed the results and commented on the manuscript and agreed the final version.

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