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Metamizole/dipyrone for the relief of cancer pain: A systematic review and evidence-based recommendations for clinical practice

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Abstract

Background: Dipyrone (metamizole) is one of the most widely used non-opioid analgesics for the treatment of cancer pain.

Aim: Because evidence-based recommendations are not yet available, a systematic review was conducted for the German Guideline Program in Oncology to provide recommendations for the use of dipyrone in cancer pain.

Design: First, a systematic review for clinical trials assessing dipyrone in adult patients with cancer pain was conducted. Endpoints were pain intensity, opioid-sparing effects, safety, and quality of life.

Data sources: The search was performed in MedLine, Embase (via Ovid), and the Cochrane Library (1948–2013) and additional hand search was conducted. Finally, recommendations were developed and agreed in a formal structured consensus process by 53 representatives of scientific medical societies and 49 experts.

Results: Of 177 retrieved studies, 4 could be included (3 randomized controlled trials and 1 cohort study, $n = 252$ patients): dipyrone significantly decreased pain intensity compared to placebo, even if low doses (1.5–2 g/day) were used. Higher doses (3×2 g/day) were more effective than low doses (3×1 g/day), but equally effective as 60 mg oral morphine/day. Pain reduction of dipyrone and non-steroidal anti-inflammatory drugs did not differ significantly. Compared to placebo, non-steroidal anti-inflammatory drugs, and morphine, the incidence of adverse effects was not increased.

Conclusion: Dipyrone can be recommended for the treatment of cancer pain as an alternative to other non-opioids either alone or in combination with opioids. It can be preferred over non-steroidal anti-inflammatory drugs due to the presumably favorable side effect profile in long-term use, but comparative studies are not available for long-term use.

Keywords

Dipyrone, palliative care, neoplasms, pain management, review, non-steroidal anti-inflammatory agents

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What is already known about the topic?

- Dipyrone and other non-opioid analgesics (NOAs) are frequently used to treat cancer pain.
- Dipyrone is one of the most widely used NOAs worldwide.
- Use of NOAs is associated with significant safety concerns.

What this paper adds?

- A systematic review on dipyrone for cancer pain was conducted.
- The findings of this systematic review were discussed in a formal, standardized consensus process by delegates and experts of German Medical Scientific Associations.
- Evidence-based recommendations on a national level are now available for the treatment of cancer pain with dipyrone.

Implications for practice, theory, or policy?

- Experts agreed that dipyrone and other non-opioids can be used alone or in combination with opioids to treat cancer pain.
- Clinicians should critically outweigh safety concerns of the particular non-opioid before initiating long-term therapy.
- In the light of scarce evidence despite high relevance of the questions concerning efficacy and safety of non-opioid therapy for cancer pain, high-quality randomized controlled trials (RCTs) are urgently needed.

Introduction

Dipyrone (metamizole, novaminsulfone) is a widely used non-opioid analgesic (NOA) in parts of Europe, the Middle East, Asia, South Africa, and Latin America, although it is not available in other European regions, Japan, India, the United States, and the United Kingdom.[1,2] It was first synthesized in 1920, and the first mass production started already in 1922.[1] Meanwhile, it is the main representative of this group.[3,4] Dipyrone is a non-acidic, antipyretic analgesic just as paracetamol/acetaminophen but belongs to the group of phenazones (phenylpyrazolones).[3] In contrast to non-steroidal anti-inflammatory drugs (NSAIDs), it exerts minor antiphlogistic and anti-inflammatory properties, but strong hypothermic actions.[1,5,6] Additionally, clinicians welcome its spasmolytic properties, although the scientific evidence for this mechanism is sparse.[1]

Dipyrone is a prodrug, but the pharmacological mechanism of action of its multiple active metabolites is not precisely known. Similar to paracetamol/acetaminophen, its effects may result from the interference with prostaglandin synthesis through the inhibitory potential on different cyclo-oxygenase (COX) isoenzymes.[7] Yet, interactions with the endogenous opioid, peroxidase, cannabinoid, and glutamate systems are also discussed.[6,8,9]

Dipyrone is available in formulations for oral and rectal drug administration. Intravenous administration is possible, but sudden and profound arterial hypotension has been reported in case of rapid infusion. Especially in palliative care and hospice settings, the subcutaneous route is also used (unlicensed use) but has been associated with local granuloma and skin lesions.[10] Agranulocytosis is one of the most threatening toxicities of dipyrone.[11] This has been repeatedly reported since the 1950s, foremost outside the field of cancer pain management.[11] Resulting safety concerns eventually lead to the withdrawal of the drug in several countries, such as the Anglo-American and Scandinavian countries. In other countries, where dipyrone is available, the prescription is steadily increasing.[12] For example, in Germany and other countries, up to fourfold increase in dipyrone prescriptions has been reported over a 12-year period (2000–2012)[13] and dipyrone is among the most extensively used analgesics.[14,15] Also, in vulnerable patients such as elderly patients in nursing homes, dipyrone is one of the most frequently used analgesics,[12,15,16] although the approval of the drug is strictly limited to specific indications.

For Germany, these indications are as follows:[17,18]

1. Fever that is unresponsive to other measures;
2. Postoperative pain;
3. Pain due to trauma;
4. Pain due to intestinal colic;
5. Cancer pain;
6. Other cases of severe pain, if other therapeutic measures are not indicated.

Despite its widespread and increasing use, little is known about the overall effectiveness of the drug. For the National Guideline "Palliative Care for patients with incurable cancer" in the context of the German Guideline Program in Oncology http://leitlinienprogramm-onkologie.de/Palliativmedizin.80.0.html we aimed to identify, critically appraise, and summarize the efficacy and effectiveness of dipyrone in order to provide evidence-based recommendations for its use in the treatment of cancer pain.

Methods

We conducted a systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations[19] and searched three databases: MedLine, Embase (via Ovid), and the Cochrane Library of Controlled Trials. The search was initially performed for the time from 1948 to 27 September 2012. An update was carried out on 12 September 2013 to identify studies that were published in the meantime. We included studies with the following design: randomized controlled trials (RCTs) and observational studies (including cohort, case–control, cross-sectional, and before–after studies, interrupted time series, and case reports). Studies were eligible if they were assessing the effect of dipyrone in the treatment of adult cancer pain by examining at least one of the following outcomes: pain intensity (or reduction of pain intensity), opioid-sparing effects, safety (adverse effects (AEs) including mortality), or quality of life. We aimed to identify additional publications via hand searching of the reference lists of the included studies, "citation tracking" via the PubMed feature "related articles" of the included studies and interviews with expert members of the guideline panel. For MedLine (via Ovid), the search strategy is presented in Table 1. Inclusion and exclusion criteria are summarized in Box 1. The search was performed without language restrictions as the selected databases always provide an English title and abstract for each document.

Box 1. Inclusion and exclusion criteria.

Inclusion criteria (IC):
IC1. Population: Adults with cancer pain
IC2. Intervention: Dipyrone for cancer pain
IC3. Outcome: Pain intensity or pain reduction, opioid-sparing effect, quality of life, adverse effects
IC4. Study type: Meta-analyses, randomized controlled trials (RCTs), case-controlled trials, observational studies (including cohort studies, case–control studies, cross-sectional studies, and before–after studies; interrupted time series; and case reports)

Study selection was performed stepwise. One reviewer (A.P.) removed duplicates and non-relevant studies after reading the titles. One reviewer (A.P.) removed all irrelevant studies after consulting title and abstract. Another reviewer (S.T.S.) checked all included studies for eligibility and checked a random sample of the excluded studies. Two reviewers (A.P. and W.M.) independently included all relevant studies after assessing the full-text version. Disagreement was resolved by the consultation of a third reviewer (S.T.S.).

Data were extracted into extraction tables by one reviewer (U.M.S.) and double-checked by another (A.P.). The level of evidence (LoE) was graded according to *Scottish Intercollegiate Guidelines Network* (SIGN)[20] by two independent reviewers (U.M.S. and A.P.). Disagreements were resolved through discussions between both reviewers and, in case of persisting disagreement, a third reviewer (S.T.S.) was contacted to do the final grading.

Table 1. Search strategies (MedLine via Ovid).

1	exp Pain/
2	pain$.mp.
3	1 or 2
4	exp dipyrone/
5	(metamizol$ or dipyron$ or novaminsulfon$ or noramidopyrin$ or methylmelubrin$).mp.
6	4 or 5
7	exp Neoplasms/
8	(cancer$ or malignan$ or carcino$ or neoplasm$ or tumor$ or tumour$ or oncolog$).mp.
9	7 or 8
10	3 and 6 and 9
11	exp animals/ not humans.sh.
12	10 not 11
13	exp child/ not adult.sh.
14	12 not 13
15	(editorial or erratum).pt.
16	14 not 15

Recommendations were developed by an interprofessional and multidisciplinary guideline group of elected representatives from 53 scientific medical societies and other relevant organizations, including patient advocates and additional experts. This development process complies with the highest international standards for medical guideline development.[21,22] Recommendations are developed and agreed upon in a formal structured consensus process. This process follows a standardized algorithm for medical guideline development as provided by the Association of the Scientific Medical Societies in Germany (AWMF).[21,22] It includes systematic search of evidence, representative setup of guideline groups, and formal consensus methods to integrate evidence into practice by accounting for expert clinical experience.[21,22] Concerning the recommendations, consensus is deemed if more than 75% of the representatives agree with the presented recommendation.[21,22] These votes are obtained anonymously via an electronic voting system in a final consensus conference.[21,22] The recommendations presented in this article were also approved by all scientific medical societies that participated in the guideline program.

Results

A total of 186 hits were initially obtained in the databases (Medline 48, Embase 121, and Cochrane Library 17). Of these, 18 duplicates were removed. From the remaining

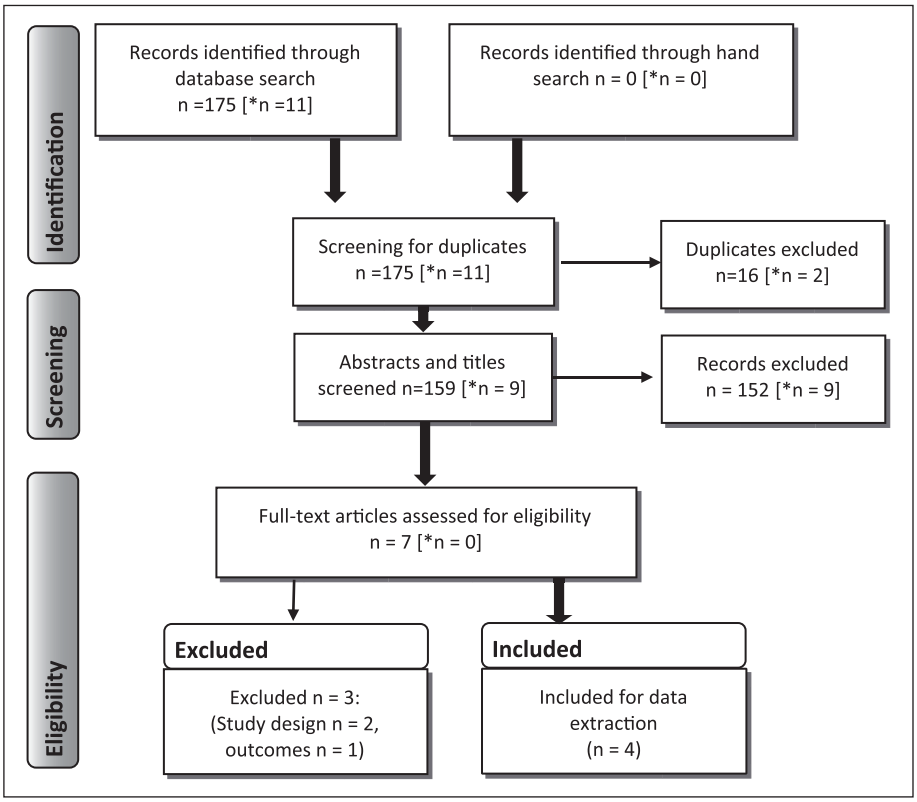

Figure 1. Screening and selection of studies (27 September 2012 (*updated 12 September 2013)).

168 hits, another 161 studies were excluded after the screening of title and abstracts. Of the remaining seven studies, three had to be removed after checking the full-text version of the article (failed inclusion criteria: outcome (one study), study type (two studies)) (Figure 1). The four included studies (three RCTs[23–25] and one cohort study[26]) analyzed a total of 252 patients (Table 2). All studies evaluated adult patients suffering from moderate to severe cancer pain. The LoE of the RCTs was 1 for each RCT, while the cohort study was rated 2. Shortcomings of the four studies are presented in Table 3. Due to the profound heterogeneity of the trials (i.e. different dipyrone doses, comparators, and measured endpoints), a meta-analysis of the studies was not feasible.

Three studies[23,25,26] used low doses of dipyrone (maximum of 2 g/day) and only one study[24] used dipyrone combined with a strong opioid (morphine). Dipyrone was compared to placebo,[23] morphine,[24] or one of two NSAIDs (diflunisal[25] and ketorolac[26]). One study compared two different daily doses of dipyrone (3 g vs 6 g/day) (Table 2).[24]

Pain reduction

Low doses of dipyrone[23,25,26] and the two NSAIDs[25,26] significantly reduced pain intensity by more than three points on an 11-point verbal analogue scale (VAS 10), and no significant differences between trial arms were observed (Table 3). For example, in the study of Yalçin et al.,[25] pain reduction on the VAS 10 was 4.65 (±3.10) for diflunisal 1 g/day p.o. (per os) and 3.25 (± 2.85) for 1.5 g dipyrone p.o. ($p < 0.001$). For the only trial assessing dipyrone as an add-on to opioid therapy (here: morphine),[23] significant improvements in pain control for the combination of morphine (60 mg/day p.o.) and dipyrone (2 g/day p.o.) compared to morphine (60 mg/day p.o.) and placebo were found. Specifically, Duarte Souza et al.[23] reported that on a VAS 10, the addition of dipyrone to morphine therapy reduced pain intensity from 7.06 (±0.32) to 3.18 (±0.39; $p = 0.03$). The group of Rodríguez et al.[24] compared two different doses of dipyrone (3 g or 6 g/day p.o.) to morphine (60 mg/day p.o.) (Tables 2 and 3). In their trial, higher doses of dipyrone were more effective than lower doses and equally effective as morphine 60 mg/day p.o.[24] Specifically, on a VAS 100, dipyrone reduced pain intensity from 82.9 (±8.5) to 51.3 (±31.5; $p < 0.05$) in the 3 g/day group and from 81.8 (±0.6) to 34.9 (±25.8; $p < 0.05$) in the 6 g/day group, while 60 mg morphine reduced pain intensity from 83.5 (±9) to 39.9 (±31.1; $p < 0.01$) after 1 week.

Side effects and patient preference

When low-dose dipyrone was compared to diflunisal, both drugs were equally well tolerated. Specifically, 2 of 25

Table 2. Included studies: characteristics.

Author	Study type	Number of patients	Patients characteristics	Intervention and control	Outcome and outcome measure
Duarte Souza et al.[23]	RCT Double-blinded Cross-over Placebo controlled	34 Intention to treat Note: 1 patient taking paracetamol + codeine not excluded	Cancer pain treated with morphine Exclusion criteria: neuropathic pain, renal, hepatic failure, jaundice, additional analgesic co-medication	1. Morphine 6 × 10 mg p.o. + placebo 2. Morphine 6 × 10 mg p.o. + **dipyrone 4 × 500 mg** Cross-over after 48 h	Primary: pain intensity (VAS, 0–10) at baseline and 48 and 96 h Secondary: preference of dipyrone versus placebo versus indifferent Toxicities (not mentioned in methods)
Rodríguez et al.[24]	RCT Double-blinded Parallel Multi-center	149 eligible 121 analyzed Note: dropouts not mentioned	Cancer pain VAS ⩾70 mm KPS > 30% Exclusion criteria: brain, liver metastasis, gastric disorders, insufficient mental status, etc.	1. **Dipyrone 3 × 1 g** p.o. + 3× placebo 2. **Dipyrone 3 × 2 g** p.o. + 3 × placebo 3. Morphine 6 × 10 mg p.o. for 7 days Dose escalation possible on day 4 Rescue medication paracetamol + codeine	Primary: pain reduction on VAS 0–100 Secondary: number of patients who decided to increase the dose on day 7 Grading of "tolerance" as excellent/good on day 7 by patients and observers Side effects not mentioned in the methods but described in results
Yalçin et al.[26]	Cohort study Not randomized Not blinded Not controlled	50 25 per group No dropouts	Severe cancer pain No regular analgesic treatment before enrolling Exclusion criteria: significant impairment of brain, liver, kidney, or lung	1. 4 × 10 mg ketorolac p.o. 2. **3 × 500 mg dipyrone** p.o.	Not explicitly mentioned (assumed) Primary: decrease in pain scores after 2 days compared to worst pain score for 24 h before start of the study Secondary: number of patients with complete pain relief, incomplete relief, and no benefit
Yalçin et al.[25]	RCT Not blinded Cross-over	50 25 per group 3 dropouts (1 died, 2 lost to follow-up)	14 cancer entities, e.g., breast, lung, colorectal, gastric VAS > 5 ECOG 0, 1, or 2 Exclusion criteria: history of long-term analgesic use, renal or liver impairment, active peptic ulcer, hemorrhagic diathesis, intracranial metastasis, etc.	1. **Dipyrone 3 × 500 mg** p.o. 2. Diflunisal 2 × 500 mg p.o. Both for 1 week followed by 1 day washout, then cross-over to the other drug for 1 week	Not explicitly mentioned Primary: decrease in pain scores after 7 days of treatment in the whole group and in subgroups with no metastasis, metastasis, and bone metastasis Secondary: side effects

ECOG: Eastern Cooperative Oncology Group Score; GI: gastrointestinal; KPS: Karnofsky Performance Scale Index; p.o.: per os; RCT: randomized controlled trial; VAS: visual analogue scale.

Table 3. Included studies: main findings, comments, and level of evidence.

Author	Main results, *n* (%) or pain scores mean±SD	Comments	LoE
Duarte Souza et al.[23]	Pain intensity (VAS) *Baseline* Mo + placebo: 7.31 ± 0.29; Mo + dipyrone: 6.88 ± 0.28 ($p = 0.03$) *48 h* Mo + placebo: 7.06 ± 0.32; Mo + dipyrone: 5.5 ± 0.31 ($p = 0.001$) *96 h* Mo + placebo: 3.18 ± 0.39; Mo + dipyrone: 1.94 ± 0.37 ($p = 0.03$) Dipyrone significantly adds to the analgesic effect of Mo. Pain control was still improved after 96 h after switch to placebo Preference: dipyrone 28 patients (85%); placebo 4 patients. No preference: 2 patients ($p < 0.001$) Side effects: *48 h*: Mo + placebo: 9 (56.2%); Mo + dipyrone: 7 (38.9%) *96 h*: Mo + placebo: 15 (93.7%); Mo + dipyrone: 16 (88.9%)	Only study administrating Mo. Randomization: how? Power analysis? Significant results due to the low SD Evaluation by telephone interview Imbalance in baseline characteristics Mo + placebo: higher proportion of visceral pain ($p = 0.02$) Mo + dipyrone: higher proportion of bone pain ($p = 0.02$) Higher proportion of patients who had not yet received oncological treatment ($p = 0.04$) No information on funding	I
Rodríguez et al.[24]	All groups: significant improvement in pain intensity No difference between dipyrone 2 g and Mo. Less pain relieve in dipyrone 1 g versus 2 g ($p < 0.05$) and versus Mo (0.01) No difference in number of patients who decided to increase dose Dipyrone 1 g: 17/31 (55%); dipyrone 2 g: 11/27 (41%); Mo: 12/35 (35%) Excellent or good efficacy graded by patients/observers: Dipyrone 1 g: 38%/39%; Mo: 46%/47%; dipyrone 2 g 46%/47% Excellent or good "tolerance" graded by patients/observers: Dipyrone 1 g: 77%/77%, Mo: 49%/54%, dipyrone 2 g 62%/62% Side effects: Dipyrone 1 g: 52 in 27 patients; dipyrone 2 g: 63 in 25 patients; Mo: 92 in 34 More severe AEs in the Mo group (21) than in dipyrone 1 g (7) or dipyrone 2 g (14)	Participating centers not mentioned, no power analysis No information on blinding procedure/appearance of medication. No information on placebo. Physicians are not explicitly mentioned as blinded. "Observers" not specified No definition of "tolerance" In the results a lot of further comparisons between groups are preformed (e.g. grading of efficacy by patients and observers) which have not been introduced in the "Methods" section No differentiation pain at rest—movement/breakthrough pain Correction for multiple testing not mentioned No information on funding	I
Yalçin et al.[26]	Significant decrease in VAS scores in both groups (no difference between groups) Complete pain relief ketorolac $n = 13$, dipyrone $n = 4$ ($p < 0.05$) Partial relief ketorolac $n = 7$, dipyrone $n = 17$ No relief ketorolac $n = 5$, dipyrone $n = 4$	No ethics approval mentioned, no (written) informed consent mentioned No blinding, no randomization, no power analysis No statement whether it was a prospective study Ketorolac not available in Germany (due to AEs) Dipyrone dose only 1.5 g/day No differentiation pain at rest/movement; no information on funding	2
Yalçin et al.[25]	Reduction in VAS: diflunisal 4.65 ± 3.10; dipyrone 3.25 ± 2.85 ($p < 0.001$) VAS scores in subgroups Patients with or without metastases: no difference Patients with bone metastasis diflunisal: VAS after treatment 5.0 ± 3.9, dipyrone 6.2 ± 3.3; $p = 0.045$ AEs: dipyrone 14.8%, diflunisal 17.1% (not significant) no drug withdrawal	No ethics approval mentioned No (written) informed consent mentioned No information on randomization, no power analysis, no correction for multiple testing Dipyrone dose only 1.5 g/day No differentiation pain at rest—movement/breakthrough pain No information on funding	I-

LoE: level of evidence according to Scottish Intercollegiate Guidelines Network; AEs: adverse events; Mo.: morphine; VAS: visual analogue scale.

patients receiving dipyrone experienced somnolence and one patient each reported on light-headedness, loss of appetite, mild vertigo, agitation, and epigastric pain (Table 3).[25] When dipyrone and placebo were compared as an add-on to opioid therapy, AEs were rare in both groups.[23] After completing the trial, most patients ($n = 28$; 85%) favored the use of dipyrone, four (12%) preferred placebo, whereas the others remained undecided. The rate of nausea or vomiting was not increased after the administration of dipyrone. The trial comparing dipyrone to ketorolac did not report AEs.[26]

In comparison to 60 mg morphine, dipyrone did not increase the incidence of moderate to severe AEs, either in the low or in the higher dose group.[24] The most frequent moderate to severe AEs reported by the 38 patients receiving higher dipyrone dose were as follows: pyrosis (9 (24%)), constipation (5 (13%)), nausea (4 (11%)), and dizziness (4 (11%).[24] With the exception of pyrosis, incidences of each of these AEs were lower than in the morphine group.

Overall, the incidences of AEs were not increased compared to placebo, ketorolac, diflunisal, or morphine. The most frequent AEs reported were nausea, epigastric pain, dizziness, and pyrosis. Long-term toxicity was not examined. Agranulocytosis was not reported (Table 3).

Discussion

Summary of the evidence

In terms of pain reduction, dipyrone was superior to placebo and equally effective as NSAIDs and 60 mg oral morphine per day. The incidences of AEs were not increased compared to placebo, NSAIDs, or morphine. The most frequently reported AEs were pyrosis, nausea, epigastric pain, dizziness, and mild vertigo.

Efficacy. From non-cancer pain management (e.g. postoperative pain), it is well known that dipyrone is an effective analgesic when given alone or in combination with opioids.[27] For example, as single oral monotherapy, the number needed to treat (NNT) to reduce pain by at least 50% after minor surgeries, such as tooth extraction or episiotomy, is 2.1 for dipyrone 500 mg, compared to 5.3 for paracetamol/acetaminophen 1000 mg. It has to be emphasized that the effectiveness of other NOAs beside dipyrone has been studied much more intensively. For example, two systematic reviews identified seven placebo-controlled RCTs examining NSAIDs in addition to opioid therapy.[28,29] Three of these seven studies reported improved analgesia[23] and two an opioid-sparing effect[30] if NSAIDs were added to morphine. Another frequently used NOA combined with opioids in the treatment of cancer pain is paracetamol/acetaminophen. In the two reviews mentioned above, five trials which studied the use of paracetamol/acetaminophen in combination with opioids could be identified. Only in one of these studies, a marginal reduction (0.4 on a 11-point Numerical Rating Scale (NRS)) could be reported in favor for this combination when compared to placebo.[30]

Overall, experts of the guideline group agreed that in clinical practice, dipyrone (alone or in combination with opioids) is effective to relieve cancer pain.

Safety. In the review presented here, the incidence of AEs of dipyrone therapy of cancer pain reported in the literature was rather low and comparable to NSAIDs. However, these trials did not evaluate the long-term use.[2] Our findings are in accordance with a recently published systematic review of Kötter et al.[2] who assessed 79 RCTs including almost 4000 patients with short-term dipyrone treatment of different pain conditions (cancer and non-cancer pain). They reported no differences in the incidence of AEs (or severe AEs) between dipyrone, paracetamol/acetaminophen, and NSAIDs. Although the incidence of AEs did not differ in their study, the nature of the AEs was different: when compared to paracetamol/acetaminophen, dipyrone was more often associated with arterial hypotension, especially when administered intravenously. Compared to NSAIDs, dipyrone was less likely to be associated with neurological AEs such as headache, vertigo, or dizziness.

As stated in our systematic review, agranulocytosis was not reported in the work of Kötter et al.,[2] but it has to be noticed that data about the long-term use of dipyrone were not available.

Despite the absence of such data, agranulocytosis needs to be addressed. The reason is that when safety issues were being discussed, this potentially life-threatening complication has been the center of debate for decades.[31–33] First described in the 1930s, subsequent case reports and case series indicated a possibly high incidence of this complication, and regulatory authorities withdrew dipyrone in several countries in the past.[11,34–36] A Swedish working group reported a risk of 1:3000, estimated from hospital records and sales figures.[35] However, a subsequent large-scale population trial did not support these findings.[37] In the International Agranulocytosis and Aplastic Anemia Study, a case–control trial investigating non-chemotherapy drug-induced agranulocytosis in metropolitan areas, the estimated excess risk of any exposure in a 1-week period resulting in hospital admission was 1.1 per million. Some regions even displayed much lower figures of, for example, 0.2 per million.[37–39] These findings and, especially, contrasting Swedish data referring to the period 1995–1999 with an estimated incidence of 1 case per 1439 prescriptions (95% confidence interval (CI): 1: 850/1: 4686) are a matter of debate since decades.[31–33] The most recent large-scale drug safety analysis for dipyrone-induced agranulocytosis was provided by Huber et al.[12] in 2015. The authors report findings from a prospective Case–Control Surveillance Study and found a total age- and sex-standardized incidence rate for dipyrone-induced agranulocytosis of 0.96 (95% CI, 0.95–0.97) per million per year.[12] Of these, all observed cases were "probable" or "possible" according to the criteria of the World Health Organization (WHO),[40] and no "certain" case of dipyrone-induced agranulocytosis was identified. In their analysis, the most frequent indications for dipyrone were headache and postoperative pain, respectively.

Concerning the overall risk of the long-term use of NOAs, cohort studies and meta-analyses could not identify a problematic safety profile for dipyrone, such as renal toxicity, despite few historic case reports.[2,41–44]

Instead, a meta-analysis published in 1997 reported an estimated excess mortality of 25 per 100 million for dipyrone compared to 592 per 100 million for NSAIDs.[42] The reasons for these findings are not clear, but it is known that dipyrone is relatively safe in terms of drug–drug interactions.[45] In contrast, NSAIDs interact with numerous other agents used either for active anti-cancer therapy or the treatment of co-morbidity.[45] These drug interactions also enhance the gastrointestinal, renal, cardiovascular, and cerebrovascular toxicity profiles of NSAIDs.[46]

Implications for practice: safety and efficacy

Based on the findings from the systematic review presented and on the clinical experience of the interprofessional and

multidisciplinary guideline group, two recommendations on dipyrone have been included in the German Guideline for Palliative Care (S3-Guideline Palliative Care for Patients with incurable cancer, http://leitlinienprogramm-onkologie.de/Palliativmedizin.80.0.html) as a result of the formal consensus process by mentioned experts and delegates (see "Methods" section):

1. "Dipyrone can be used as monotherapy for mild cancer pain and as an adjunct to opioids for moderate and severe cancer pain as an alternative to NSAIDs and paracetamol/acetaminophen."
2. "Dipyrone can be preferred over NSAIDs due to the favorable side effect profile, even though the effectiveness is not well documented."

Limitations

Due to the heterogeneity of endpoints, daily doses, and comparators, a meta-analysis could not be conducted. The main search included publications until 2013, but a recent search performed by one reviewer (J.G.) in October 2015 did not reveal any new relevant publications in MedLine (via PubMed).

For the development of recommendations, guideline development standards have to integrate clinical expertise of the contributing experts when judging the available evidence.[21,22] In the recommendations presented here, the question about adding dipyrone to ongoing opioid therapy was of special importance because the majority of patients in the included studies did not receive strong opioids. This should not be considered a limitation—but rather a strength—of the presented recommendations because the clinical expertise relied on a transparent, broad, and formalized consensus of various interdisciplinary experts and numerous medical/scientific associations.

Conclusion

Dipyrone can be recommended for the treatment of cancer pain as an alternative to other NOAs either alone (mild pain intensity) or in combination with opioids (moderate or severe pain intensity). It can be preferred over NSAIDs due to the presumably favorable side effect profile in long-term use. The LoE for these recommendations is low and no comparative studies are available for the long-term use. Since the drug is widely and increasingly used, it has to be noticed that in the future, high-quality RCTs assessing the efficacy and safety of dipyrone are required.

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