REVIEW

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Non-steroidal anti-inflammatory drugs for treatment of cancer cachexia: A systematic review

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Abstract

Cancer cachexia (CC) is a multifactorial syndrome driven by inflammation, defined by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support. CC leads to progressive functional impairment, with its clinical management complicated and limited therapeutic options available. The objective of this review was to assess the efficacy and safety of non-steroidal anti-inflammatory drugs (NSAIDs) on patient-centred outcomes in patients with CC. In 2013, two systematic reviews concluded that there was insufficient evidence to recommend NSAIDs for clinical management of CC outside of clinical trials. However, clinical trials of multi-component CC interventions have included NSAIDs as an intervention component, so an up-to-date assessment of the evidence for NSAIDs in the treatment of CC is warranted. Four databases (MEDLINE, EMBASE, CENTRAL and CINAHL) and three trial registers (clinicaltrials.gov, WHO ICTRP and ISRCTN) were searched on 16 December 2022. Randomized controlled trials (RCTs) comparing any NSAID (any dose or duration) with a control arm, in adult patients with CC, reporting measures of body weight, body composition, nutrition impact symptoms, inflammation, physical function or fatigue, were eligible for inclusion. Primary outcomes (determined with patient involvement) were survival, changes in muscle strength, body composition, body weight and quality of life. Included studies were assessed for risk of bias using the Revised Cochrane risk-of-bias tool for randomized trials. Five studies were included, which investigated Indomethacin ($n = 1$), Ibuprofen ($n = 1$) and Celecoxib ($n = 3$). Four studies were judged to be at high risk of bias for all outcomes, with one study raising concerns for most outcomes. Considerable clinical and methodological heterogeneity amongst the studies meant that meta-analysis was not appropriate. There was insufficient evidence to determine whether Indomethacin or Ibuprofen is effective or safe for use in patients with CC; RCTs with lower risk of bias are needed. Celecoxib studies indicated it was safe for use in this population at the doses tested (200–400 mg/day) but found contrasting results regarding efficacy, potentially reflecting heterogeneity amongst the studies. There is inadequate evidence to recommend any NSAID for CC. While current clinical trials for CC treatments are shifting towards multi-component interventions, further research to determine the efficacy and safety of NSAIDs alone is necessary if they are to be included in such multi-component interventions. Furthermore, the lack of data on patient-determined primary outcomes in this review highlights the need for patient involvement in clinical trials for CC.

Keywords anti-inflammatory; cachexia; cancer; NSAID; palliative care; wasting

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Background

Description of the condition

An international consensus has defined cancer cachexia (CC) as 'a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment'.[1] Key pathophysiological features include a negative protein and energy balance, resulting from reduced nutritional intake in combination with abnormal metabolism.[1,2] CC is a progressive syndrome, with stages including pre-cachexia, followed by cachexia and finally refractory cachexia.[1] It has a significant negative impact on quality of life (QoL) and functional performance and is associated with increased morbidity and mortality.[3] CC is estimated to occur in up to 80% of people with advanced cancer and directly cause at least 20% of cancer-related deaths.[2,4,5]

Description of the intervention

Given the complex pathophysiology of CC, clinical management is complicated and there are no established treatments at present. Corticosteroids or progestins are often prescribed, but significant adverse reactions limit their use.[6,7] Non-steroidal anti-inflammatory drugs (NSAIDs) represent one class of drugs under investigation for CC.[8] Therapeutic effects include both analgesic and anti-inflammatory activity, with approximately 60% of patients responding to any NSAID, as per the British National Formulary (BNF).[9] NSAIDs are blockers of the cyclooxygenase (COX)/prostaglandin pathway, involved in regulation of the inflammatory response. Non-selective NSAIDs (e.g., Ibuprofen) inhibit both COX1 and COX2, while selective NSAIDs (e.g., Celecoxib) inhibit only COX2.[10] With inflammation recognized as a key driver in the development of CC,[1] in addition to their overall safety in the general population, NSAIDs have therefore been proposed as treatment candidates for CC.

How the intervention might work

Several inflammatory cytokines, including interleukin (IL)-1, IL-6, interferon (IFN)-γ and tumour necrosis factor (TNF)-α, have been postulated to play a role on the aetiology of CC. For example, they have been associated with anorexia and hypermetabolism and have been implicated in skeletal muscle atrophy induction, mediated via the ubiquitin proteosome pathway.[11–14]

Why it is important to do this review

Two systematic reviews published in 2013 evaluated the efficacy and safety of NSAIDs for CC.[15,16] At the time of writing and to the best of our knowledge, no further systematic review on this topic has been published or registered on PROSPERO. While the search strategies and eligibility criteria differed between these reviews, both concluded that, while there was some evidence of beneficial effects, it was not sufficient to recommend the use of NSAIDs for clinical management of CC outside of clinical trials. However, many recent clinical trials of multi-component CC interventions have included NSAIDs as a core component.[17–20] Thus, an up-to-date assessment of the evidence for NSAIDs in the treatment of CC is required. This review provides this, as well as a broader range of patient-centred outcomes, and a risk of bias assessment amongst included studies, which was not produced in the previous reviews.

Objectives of this review

This review aimed to assess the efficacy and safety of NSAIDs on patient-centred outcomes in adults with CC.

Methods

A systematic review of the literature was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. The review was registered on PROSPERO (CRD42022342059); the full protocol, completed prior to initiation of this review, can be found in Supporting Information S1.

Criteria for considering studies for this review

Types of studies

Only interventional randomized controlled trials (RCTs) were eligible for inclusion in this review. Cross-over studies were not considered, due to the potential long-term effects of the intervention. Included RCTs could be blinded or unblinded, and the control could involve placebo or no treatment.

Types of participants

Inclusion criteria for participants were as follows: aged ≥18 on enrolment, clinical diagnosis of any cancer and evidence of cachexia (as shown by recent unintentional weight loss, irrespective of the terminology or definition used). Studies were excluded if participants did not meet these criteria, or if they included participants with a clinical diagnosis of any eating disorder, or who were pregnant or lactating.

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Types of interventions and comparisons

Studies were eligible if the intervention involved any NSAID, at any dose, and for any duration, as long as the comparison allowed for determination of the effect of the NSAID (NSAID vs. placebo; NSAID vs. no treatment; NSAID plus intervention X vs. intervention X). Studies were excluded if they did not meet these criteria, or if the comparison was with healthy controls.

Types of outcome measures

Outcomes were classified as primary or secondary based on the results of surveys (Supporting Information S2) given to patients (n = 6) with cancer at University College London Hospital (UCLH). This patient involvement in refining outcome measures is increasingly recognized as important to ensure research is patient focused.[21] Participants were asked to score each outcome out of 10 (0 = *not at all important*, 10 = *very important*), with free text available to identify other outcomes of importance to the individual. Outcomes with a mean score of 9 or more were classified as primary outcomes, with the remaining classified as secondary. Primary outcomes were survival and changes in muscle strength, body composition, total body weight (TBW) and QoL. Secondary outcomes were changes in nutrition impact symptoms (NIS), fatigue, physical function (performance status [PS]), inflammation, length of hospital stay (LoS) and adverse events (AEs). Two participants also noted the ability to return to work as an important outcome. Subsequently, metabolic rate and food/energy intake were included as additional secondary outcome measures due to their relevance with CC.[1–3,5,11–14]

Search methods for identification of studies

Electronic searches

The following electronic databases were searched from their start date until 16 December 2022:

- MEDLINE via Ovid
- EMBASE via Ovid
- Cochrane Register of Controlled Trials (CENTRAL)
- CINAHL via EBSCO

No language or other limitations were set. Search filters developed by Scottish Intercollegiate Guidelines Network (SIGN) to retrieve RCTs were combined with strategies to retrieve trials of NSAIDs for CC (see Supporting Information S3 for search strategies). Search alerts were established for notification of additional studies.

Searching other resources

The following trial registers were searched on 16 December 2022:

- Clinicaltrials.gov
- ISRCTN Registry
- WHO ICTRP

Where possible, a limitation was set to only retrieve trials with results. No further limitations were set.

MedRxiv was also used to search for grey literature.

Reference lists from both previous systematic reviews (references[5,6] and references[1,2]) were examined for additional studies.

Finally, reference lists from included studies were examined for additional studies.

Data collection and analysis

Selection of studies

Rayyan systematic review software was used to collate records from different electronic database searches and remove duplicates. Records were screened based on titles and abstracts by two independent reviewers (M. B. and A. S.) using the eligibility criteria detailed above. Subsequently, full texts for all records considered eligible were sought for screening by two independent reviewers (M. B. and A. S.).

Data extraction and management

Data from included studies were extracted using a data extraction form completed prior to initiation of review.

Assessment of risk bias in included studies

Studies were assessed for risk of bias by two independent reviewers (M. B. and B. C.), using the Revised Cochrane risk-of-bias tool for randomized trials (RoB-2). This review was interested in the effect of adhering to the intervention as specified in the trial protocol (per-protocol effect), as this effect is appropriate for informing care decisions for an individual patient—that is, whether to use NSAIDs to treat CC.

Measures of treatment effect

Dichotomous variables were recorded as total number of participants in each study arm. Calculation of risk ratio or odds ratios were planned, to be followed by pooling in a meta-analysis. Continuous variables were recorded preferentially as mean and standard deviation (SD); where this was not possible, variables were recorded as reported by the study. Where possible and appropriate, treatment effect size was calculated for each outcome measurement by raw mean difference or standardized mean difference if required. Pooling of these treatment effect sizes in a meta-analysis was planned, using a fixed-effects model to estimate the overall direction, size and consistency of an effect using *RevMan*.

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Data synthesis

Meta-analyses were planned for each NSAID investigated, but this was not possible due to the small number of studies and high level of heterogeneity. Pooling of treatment effect sizes was therefore inappropriate,[22] and a qualitative description of studies was provided with supporting tables.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to consider differences in effect between subgroups according to cancer site and stage; however, due to the small number of studies, this was not possible.[22]

Sensitivity analysis

Sensitivity analysis was planned, to consider differences in effect when studies at high risk of bias were omitted from analyses; however, due to the small number of included studies, this was not possible.[22]

Results

Description of studies

Results of the search

The PRISMA flow diagram detailing the selection process is shown in *Figure 1*. The four electronic databases and three clinical registers retrieved a total of 918 records; after duplicate removal, 810 remained. These were screened based on titles and abstracts; 751 were excluded, and 38 were retrieved and assessed for eligibility. Of these, 29 were excluded (*Table 2*) based on ineligible study design (not controlled $n = 9$; retrospective analysis of observational data $n = 1$), ineligible population (nil cachexia reference $n = 8$), ineligible comparison (NSAID given to all study arms $n = 5$, NSAID given as part of multi-component intervention $n = 6$) or ineligible outcomes (no outcomes of interest were evaluable $n = 3$). Six reports of five studies were identified for inclusion.

A total of 262 records were retrieved from MedRxiv, reference lists of the two previous systematic reviews and

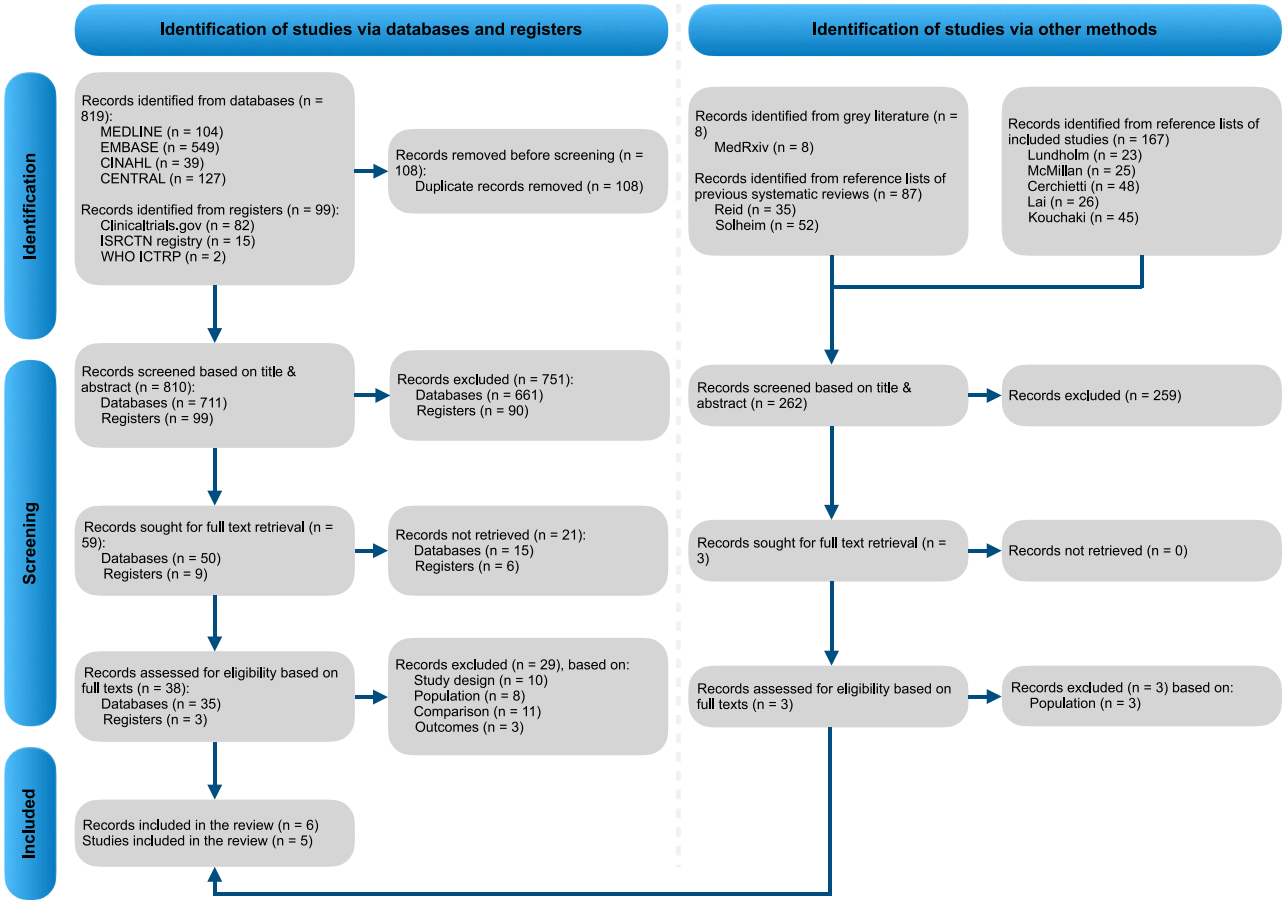

Figure 1 PRISMA flow diagram showing the selection process for identification, screening and inclusion of studies.

reference lists from the five included studies. These were screened based on titles and abstracts; 259 were excluded, and 3 were retrieved and assessed for eligibility. All three were excluded based on ineligible population (nil cachexia reference n = 3).

Search alerts did not identify any further eligible studies from databases between 16 December 2022 and 19 May 2023.

Included studies

Five studies[23–27] were included in this review, published between 1994 and 2018. All were published in English. All studies were parallel RCTs. *Table 1* shows characteristics of included studies; *Table 2* shows excluded studies with justifications. The study sample sizes ranged from 11 to 135. Details on patient flow are provided in *Table 3*. Three studies enrolled participants from a single centre,[23,26,27] one study was two-centred[24] and one was unspecified.[25] The studies were from Sweden,[23] the United Kingdom,[24] Argentina,[25] the United States[26] and Iran.[27]

All participants were adult cancer patients, with mean/median age ranging from 55.3 to 72 years. Four studies enrolled men and women,[23–25,27] with men making up the majority in all; one study only enrolled men.[26] Primary cancer sites were gastrointestinal tract,[23,24,26,27] head and neck,[23,26] lung,[25] breast,[23] skin[23] and miscellaneous.[23] Three studies required weight loss of ≥5%[24,26,27] (in the 6 months prior to enrolment in two studies,[26,27] time unspecified in one study[24]); one study required ≥10% weight loss (time unspecified),[25] and one study required 'insidious or ongoing weight loss' (time and extent unspecified).[23]

Four studies randomized participants into two arms[24–27]; one study included a third arm.[23] All studies included a control arm that received placebo. None included healthy controls. Duration of treatments were 12 weeks,[24] 6 weeks,[25] 3 weeks[26] and 2 months.[27] Of note, the anti-inflammatory effect of NSAIDs can take up to 3 weeks to be achieved; all studies therefore administered the NSAIDs for a sufficient length of time.[9] In one study, duration of treatment was unclear[23]—direct correspondence with the author indicated it was not unified; 'duration of treatment continued as long as the patient was able or willing to continue', 'there was no unified follow-up time according to the protocol'.

Three different NSAIDs were investigated: Indomethacin in one study,[23] Ibuprofen in one study[24] and Celecoxib in three studies.[25–27] In the Indomethacin study,[23] the intervention arm received 50 mg of Indomethacin twice daily (BID) (daily total 100 mg), while the control arm received placebo. A third arm received Prednisolone; however, this arm was not analysed in this review. In the Ibuprofen study,[24] both arms received 160 mg of megestrol acetate (MA). The intervention arm also received 400 mg of Ibuprofen three times daily (TID) (daily total 1200 mg), while the control arm received placebo TID. In the first Celecoxib study,[25] both arms received 2 × 1 g of fish oil capsules TID, 7 mg of Aspirin and oral food supplementation. The intervention arm also received 200-mg capsules of Celecoxib BID (daily total 400 mg), while the control arm received 200-mg capsules of placebo BID. Of note, both Aspirin and omega-3-acid ethyl esters are listed as having interactions with Celecoxib.[28] In the second Celecoxib study,[26] the intervention arm received 200-mg capsules of Celecoxib BID (daily total 400 mg), while the control arm received placebo capsules BID. In the third Celecoxib study,[27] both arms received 160 mg of MA BID. The intervention arm also received 100 mg of Celecoxib BID (daily total 200 mg), while the control arm received placebo.

Two studies measured survival[23,27]; however, neither reported evaluable data values (one included survival curves only,[23] and the second did not present any findings[27]). Three studies measured muscle strength,[23,25,27] all using hand grip strength (HG). Four studies measured body composition,[24–27] using anthropometry, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA) and/or total body potassium (TBK). All five studies measured body weight in kilograms (BW-kg), and three studies also measured body mass index (BMI).[24,26,27] Three studies measured QoL,[24,26,27] using the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30), EuroQoL-EQ-5D and/or Functional Assessment of Anorexia Cachexia Therapy (FAACT). Three studies reported NIS,[24,25,27] including appetite, nausea, taste change, early satiety and/or vomiting, which were measured using visual analogue scale (VAS) and/or subscales of the EORTC QLQ-C30. Three studies measured fatigue,[23–25] using VAS and/or EORTC QLQ-C30 subscale. Four studies measured AEs.[24–27] All five studies measured PS, with either Karnofsky (KPS) or European Cooperative Oncology Group (ECOG-PS). All five studies measured inflammation, including C-reactive protein (CRP), albumin, Glasgow Prognostic Score (GPS) and/or various cytokines (IL-1b, IL-2, IL-6, IL-8, IL-10, TNF-α and IFN-γ). No study measured LoS. Two studies measured metabolic rate,[23,26] as resting energy expenditure (REE) through indirect calorimetry. One study measured food/energy intake.[25] No study measured return to work.

Risk of bias in included studies

Included studies were assessed for risk of bias using the RoB-2 tool. *Table 4* provides a summary with domain-level judgements; full assessments can be found in Supporting Information S4. Overall, risk of bias in all studies was high; four studies were judged to be at high risk of bias for all outcomes,[23,24,26,27] with one study at high risk of bias for some outcomes, raising some concerns for all others.[25]

Bias arising from the randomization process

Only one study was judged to be at low risk of bias in this domain,[27] while four studies raised some concerns.[23–26]

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Table 1 Characteristics of included studies

	Lundholm et al., 1994	McMillan et al., 1999	Cerchietti et al., 2007	Lai et al., 2008	Kouchaki et al., 2018
			Study design		
Prospective	Yes	Yes	Yes	Yes	Yes
Randomized	Yes	Yes	Yes	Yes	Yes
Blinded	Single-blinded (participants blinded)	Not reported	Not reported	Not reported	Double-blinded
Controlled	Yes (placebo-controlled)	Yes (placebo-controlled)	Yes (placebo-controlled)	Yes (placebo-controlled)	Yes (placebo-controlled)
Centres	Single-centred	Two-centred	Not stated	Single-centred	Single-centred
Country(ies)	Sweden	United Kingdom	Argentina	United States	Iran
Institution(s)	University of Göteborg, Sahlgrenska Hospital	Royal Infirmary Edinburgh and Royal Infirmary Glasgow	Universidad de Buenos Aires	University of North Carolina School of Medicine	Mazandaran University of Medical Sciences
Declared conflicts of interest	None	None	None	None	None

						Participants					
Study arm	**Intervention**	**Control**	**Other drug**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Age at baseline, mean ± SD or median (range) in years	69 ± 1.5	66 ± 1.5	66 ± 1.5	69 (52–88)	72 (50–90)	64 (44–90)	61 (44–83)	55.3 ± 8.5	61.3 ± 10.5	61.84 ± 12.61	60.60 ± 13.40
Sex at baseline (sex ratio M:F)	29:16	28:17	29:16	22:13	21:17	8:2	9:3	4:0	7:0	28:17	28:17
Cancer site (*n*)	Liver, pancreas: 44 Colon, rectum: 30 Gastric: 18 Oesophagus: 15 Melanoma: 7 Breast: 3 Head and neck: 3 Miscellaneous: 15 Inclusion criteria: ‘Solid tumour type’			Colorectal: 7 Oesophageal: 4 Gastric: 11 Pancreatic: 49 Cholangiocarcinoma: 1 Inclusion criteria: ‘Gastrointestinal cancer’		NSCLC: All Inclusion criteria: ‘Advanced NSCLC’		Head and neck: 3 Gastrointestinal: 8 Inclusion criteria: ‘Carcinoma of the head and neck or gastrointestinal tract (oesophagus, stomach, pancreas)’		Oesophageal: 14 Gastric: 47 Colorectal: 26 Pancreatic: 3 Inclusion criteria: ‘GI cancer at any site’	
Cancer stage (*n*)	Local spread: 39 Liver metastasis: 41 Pulmonary metastasis: 9 Peritoneal metastasis: 7 Skeletal metastasis: 1 Not stated in inclusion criteria			Not reported Inclusion criteria: ‘Locally advanced or metastatic’		Not reported Inclusion criteria: ‘Stage IV from presentation or systemically progressed disease from stage IIIb’		Stage I: 0 Stage II: 0 Stage III: 2 Stage IV: 9 ‘None of the patients had incurable or known metastatic disease at the time of this trial’		Number of participants with metastasis: 30 Not stated in inclusion criteria	
Cancer treatment (*n*)	Prior to enrolment in this trial: Operation only: 79 Radiotherapy: 1 Chemotherapy: 1 Immune therapy: 1 More than one of the above: 14			Not reported Inclusion criteria: ‘No tumour therapy in the 6 weeks prior’, ‘receiving supportive care only’		Not reported Not stated in inclusion criteria		All the patients had newly diagnosed cancer and began anticancer therapy after this clinical trial Exclusion criteria: ‘Active cancer treatment within		Palliative treatments or antineoplastic chemotherapy was allowed in our patients Prior surgery: 51 Concomitant chemotherapy: 87	

(*Continues*)

Table 1 (continued)

Study arm	Participants										
	Intervention	Control	Other drug	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
		No earlier treatment: 38 Inclusion criteria: 'Most recent tumour therapy completed beyond 6 months prior to starting this treatment'						4 weeks of entering the study'			
Expected survival (*n*)			6 months: 84 6–12 months: 42 >12 months: 9 Inclusion criteria: 'Expected survival more than 6 months'			Not reported Inclusion criteria: 'Life expectancy of at least 2 months'		Not reported Not stated in inclusion criteria		Not reported Not stated in inclusion criteria	Not reported Inclusion criteria: 'Life expectance of at least 2 months'
Weight loss at baseline, mean ± SD or median (range) as a %	9.30 ± 1.20	10.40 ± 1.30 Inclusion criteria: 'Insidious or ongoing weight loss' Time period not reported	9.70 ± 1.30	18 (5–34) Inclusion criteria: 'More than 5% weight loss' Time period not r eported	18 (5–33)	Not reported Inclusion criteria: 'More than 10% weight loss' Time period not reported		Not reported Inclusion criteria: 'Unintentional loss of greater than 5% body weight in the past 6 months'		15.89 ± 7.14 (In the past 6 months) Inclusion criteria: 'At least 5% unintentional weight loss in the past 6 months'	19.08 ± 7.54

Study arm	Intervention and comparison										
	Intervention	Control	Other drug	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
NSAID	Indomethacin 50 mg BID (total daily intake 100 mg)			Ibuprofen 400 mg TID (total daily intake 1200 mg)		Celecoxib 200 mg BID (total daily intake 400 mg)		Celecoxib 200 BID (total daily intake 400 mg)		Celecoxib 100 mg BID (total daily intake 200 mg)	
Placebo		Placebo			Placebo TID		Placebo 200 mg BID		Placebo BID		Placebo
Other			Prednisolone 10 mg BID	MA 160 mg TID	MA 160 mg TID	Fish oil 2 g TID Aspirin 75 mg Oral food supplementation	Fish oil 2 g TID Aspirin 75 mg Oral food supplementation			MA 160 mg BID	MA 160 mg BID

Primary outcomes	Outcomes of interest in this review										
Survival		X								X	
Muscle strength		//				X				X	
Body composition		X		X		X		X			
Body weight		X		X		X		X		X	
Quality of life				X				X		X	
Secondary outcomes											
Nutritional impact symptoms				X		X				X	
Fatigue		//		//		X					
Adverse events				X		X		X		X	

(*Continues*)

Primary outcomes	Outcomes of interest in this review													
Physical function	X			//				//			X			X
Inflammation	X			X				X			X			X
Length of hospital stay														
Extra outcomes														
Metabolic rate	//										X			
Food/energy intake								//						
Return to work														

Note: X indicates at least one outcome measurement was reported on in this domain and was evaluable. // indicates at least one outcome measure was reported on in this domain but none were evaluable (e.g., due to measure being reported at only one timepoint). Abbreviations: BID, two times daily; GI, gastrointestinal; MA, megestrol acetate; NSAID, non-steroidal anti-inflammatory drug; NSCLC, non-small-cell lung cancer; SD, standard deviation; TID, three times daily.

These concerns primarily arose from lack of information regarding concealment of the allocation sequence. However, baseline differences between study arms did not suggest problems with randomization in any study.

Bias due to deviations from intended interventions

Two studies were judged to be at low risk of bias in this domain,[25,27] one raised some concerns[26] and two were at high risk of bias.[23,24] One study[27] explicitly stated it was double-blinded, one study was single-blinded[23] and in three studies, the blinding status was not explicitly stated—the use of placebo pills indicated participants were likely blinded, but it was unclear whether those delivering the interventions were blinded.[24–26] No study included explicit information regarding non-protocol interventions or failures in implementation. Two studies did not report adequate information regarding adherence, or analysis of treatment effect.[23,24]

Bias due to missing outcome data

Three studies were judged to be at low risk of bias in this domain[23,25,26]; however, two studies[24,27] were at high risk of bias. For the latter studies, concerns arose from significant attrition that was attributable to the health status of participants (*Table 3*).

Bias in measurement of the outcome

One study was judged to be at low risk of bias in this domain for all outcomes,[27] while four studies had judgements that varied amongst outcomes.[23–26] In two studies, measurement instruments were not appropriate for some outcome measures.[23,25] In one study, outcome assessors were likely aware of the intervention received,[23] with no detail provided in three studies.[24–26] Therefore, assessment of non-patient-reported, subjective measures could have been influenced by this knowledge; these outcomes either raised some concerns or were judged to be at high risk of bias.

Bias in selection of the reported result

Three studies were judged to be at high risk of bias in this domain for all outcomes,[23,24,26] while two studies had judgements that varied amongst outcomes.[25,27] For one study, a protocol published separately was found and compared.[27] One study was closed early based on preferable interim results.[23] In all studies, reporting of various outcomes did not match the intent to measure stated in their methods. Concerns also arose due to the potential for selective reporting of results from multiple eligible timepoints in one study[23] and from multiple eligible measures within an outcome domain in three studies.[24–26] In three studies, statistical analysis plans lacked specificity with multiple options for analysis.[23,24,26]

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Table 2 Excluded studies with reasons for exclusion

First author, year	Source	Title	NSAID	Reason for exclusion
Lundholm, 2004	Database search	Evidence that long-term COX-treatment improves energy homeostasis and body composition in cancer patients with progressive cachexia	Indomethacin	Study design does not fit the criteria for this review—a secondary analysis was performed whereby cancer patients who had been treated with indomethacin were compared with those who had not been treated with indomethacin and so the design is nonrandomized and observational.
Cerchietti, 2004	Database search	Effects of celecoxib, medroxyprogesterone, and dietary intervention on systemic syndromes in patients with advanced lung adenocarcinoma: a pilot study	Celecoxib	Study design does not fit the criteria for this review—this was a single-armed uncontrolled pilot study.
Gore, 2011	Database search	Phase I/II trial of a COX-2 inhibitor with limited field radiation for intermediate prognosis patients who have locally advanced non-small-cell lung cancer: radiation therapy oncology group 0213	Celecoxib	Study design does not fit the criteria for this review—this was a single-armed uncontrolled study.
Liu, 2008	Database search	A randomised pilot study of atractylenolide I on gastric cancer cachexia patients	None	Study design does not fit the criteria for this review—this study was randomized but did not include a control: Arm 1 received a fish-oil-enriched nutritional supplement and arm 2 received atractylenolide I.
McMillan, 1997	Database search	A pilot study of megestrol acetate and ibuprofen in the treatment of cachexia in gastrointestinal cancer patients	Ibuprofen	Study design does not fit the criteria for this review—this was a single-armed uncontrolled pilot study.
Dy, 2005	Database search	A phase I trial of celecoxib in combination with docetaxel and irinotecan in patients with advanced cancer	Celecoxib	Study design does not fit the criteria for this review—this was an uncontrolled dose escalation study.
Xue, 2011	Database search	Phase I clinical trial of nasopharyngeal radiotherapy and concurrent celecoxib for patients with locoregionally advanced nasopharyngeal carcinoma	Celecoxib	Study design does not fit the criteria for this review—this was an uncontrolled dose escalation study.
Mantovani, 2004	Database search	Cancer-related anorexia/cachexia syndrome and oxidative stress: an innovative approach beyond current treatment	Celecoxib	Study design does not fit the criteria for this review—this was a single-armed, nonrandomized, uncontrolled study.
Mantovani, 2006	Database search	A phase II study with antioxidants, both in the diet and supplemented, pharmaconutritional support, progestogen, and anti-cyclooxygenase-2 showing efficacy and safety in patients with cancer-related anorexia/cachexia and oxidative stress	Celecoxib	Study design does not fit the criteria for this review—this was a single-armed uncontrolled study.
Mantovani, 2009	Database search	Phase II nonrandomised study of the efficacy and safety of COX-2 inhibitor celecoxib on patients with cachexia	Celecoxib	Study design does not fit the criteria for this review—this was a single-armed, nonrandomized, uncontrolled study.
Reckamp, 2016	Database search	Randomised phase II trial of erlotinib in combination with high dose-celecoxib or placebo in patients with advanced non-small cell lung cancer	Celecoxib	Population does not fit the criteria for this review—participants were cancer patients but there is no mention of cachexia, anorexia or weight loss in inclusion criteria for enrolment. In fact, included participants had ECOG score of 0 or 1.
Guzman-Esquivel	Database search	Decreased biochemical progression in patients with castration-resistant prostate cancer using a novel mefenamic acid anti-inflammatory therapy: a randomised controlled trial	Mefenamic acid	Population does not fit the criteria for this review—participants were cancer patients but there is no mention of cachexia, anorexia or weight loss in inclusion criteria for enrolment. In fact, included participants had ECOG score of 0–2.
Gross, 2014	Database search	Erlotinib, erlotinib-sulindac vs. placebo: a randomised, double-blind, placebo-controlled window trial in operable head and neck cancer	Sulindac	Population does not fit the criteria for this review—participants were cancer patients but there is no mention of cachexia, anorexia or weight loss in inclusion criteria for enrolment. In fact, included participants had ECOG score of 0–1.
Debucquoy, 2009	Database search	Double blind randomised phase II study with radiation + 5-fluorouracil ± celecoxib for resectable rectal cancer	Celecoxib	Population does not fit the criteria for this review—participants were cancer patients but there is no mention of cachexia, anorexia or weight loss in inclusion criteria for enrolment. In fact, included participants had a Karnofsky performance status higher than 60%.

(*Continues*)

Table 2 (continued)

First author, year	Source	Title	NSAID	Reason for exclusion
Gupta, 2019	Database search	Randomised trial of oral cyclophosphamide versus oral cyclophosphamide with celecoxib for recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer	Celecoxib	Population does not fit the criteria for this review—participants were cancer patients but there is no mention of cachexia, anorexia or weight loss in inclusion criteria for enrolment. In fact, included participants had a Karnofsky performance status of 60–100.
Groen, 2011	Reference list of previous systematic review	Randomised, placebo-controlled phase III study of docetaxel plus carboplatin with celecoxib and cyclooxygenase-2 expression as a biomarker for patients with advanced non-small-cell lung cancer: the NVALT-4 study	Celecoxib	Population does not fit the criteria for this review—participants were cancer patients but there is no mention of cachexia, anorexia or weight loss in inclusion criteria for enrolment. In fact, included participants had ECOG score of 0–2.
Jackson, 2009	Reference list of previous systematic review	Comparing safety and efficacy of first-line irinotecan/fluoropyrimidine combinations in elderly versus non elderly patients with metastatic colorectal cancer	Aspirin	Population does not fit the criteria for this review—participants were cancer patients but there is no mention of cachexia, anorexia or weight loss in inclusion criteria for enrolment. In fact, included participants had ECOG score of 0–1.
Guo, 2017	Database search	Comprehensive evaluation of clinical efficacy and safety of celecoxib combined with chemotherapy in management of gastric cancer	Celecoxib	Population does not fit the criteria for this review—participants were cancer patients but there is no mention of cachexia, anorexia or weight loss in inclusion criteria for enrolment. In fact, included participants had ECOG score of 0–2.
Guo, 2019	Database search	A comprehensive evaluation of clinical efficacy and safety of celecoxib in combination with chemotherapy in metastatic or postoperative recurrent gastric cancer patients	Celecoxib	Population does not fit the criteria for this review—participants were cancer patients but there is no mention of cachexia, anorexia or weight loss in inclusion criteria for enrolment. In fact, included participants had ECOG score of 0–2.
Creagan, 1988	Reference list of previous systematic review	An evaluation of recombinant leukocyte A interferon with aspirin in patients with metastatic renal cell cancer	Aspirin	Population does not fit the criteria for this review—participants were cancer patients but there is no mention of cachexia, anorexia or weight loss in inclusion criteria for enrolment. In fact, included participants had ECOG score of 3 or better.
Gridelli, 2007	Database search	Factorial phase III randomised trial of rofecoxib and prolonged constant infusion of gemcitabine in advanced non-small-cell lung cancer: the GEmcitabine-COxic in NSCLC (GECO) study	Rofecoxib	Population does not fit the criteria for this review—participants were cancer patients but there is no mention of cachexia, anorexia or weight loss in inclusion criteria for enrolment. In fact, included participants had ECOG score of 0 or 1.
Madeddu, 2011	Database search	Randomised phase III clinical trial of a combined treatment with carnitine + celecoxib ± megestrol acetate for patients with cancer-related anorexia/cachexia syndrome	Celecoxib	Comparison does not fit the criteria for this review—the NSAID was given to both study arms and so its effects cannot be determined.
Macciò, 2012	Database search	A randomised phase III clinical trial of a combined treatment for cachexia in patients with gynaecological cancers: evaluating the impact on metabolic and inflammatory profiles and quality of life	Celecoxib	Comparison does not fit the criteria for this review—the NSAID was given as part of a multi-component intervention with L-carnitine and antioxidants and so its effects cannot be determined.
Kanat, 2013	Database search	Comparison of three different treatment modalities in the management of cancer cachexia	Meloxicam	Comparison does not fit the criteria for this review—the NSAID was given to all three study arms and so its effects cannot be determined.

(*Continues*)

Table 2 (continued)

First author, year	Source	Title	NSAID	Reason for exclusion
Lundholm, 2004	Database search	Palliative nutritional intervention in addition to cyclooxyrgenase and erythropoietin treatment for patients with malignant disease: effects on survival, metabolism, and function	Indomethacin	Comparison does not fit the criteria for this review—the NSAID was given to both study arms and so its effects cannot be determined.
Solheim, 2017	Database search	A randomised phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer	Celecoxib	Comparison does not fit the criteria for this review—the NSAID was given as part of a multimodal intervention with ONS, nutritional counselling and an exercise programme and so its effects cannot be determined.
Maeng, 2022	Database search	Effect of multimodal intervention care on cachexia in patients with advanced cancer compared to conventional management (MIRACLE): an open-label, parallel, randomised, phase 2 trial	Ibuprofen	Comparison does not fit the criteria for this review—the NSAID was given as part of a multimodal intervention with omega-3 FA, psychotherapy, exercise and so forth and so its effects cannot be determined.
	Database search	The MENAC trial—a randomised, open-label trial of a multimodal intervention (exercise, nutrition and anti-inflammatory medication) plus standard care versus standard care alone to prevent/attenuate cachexia in advanced cancer patients undergoing chemotherapy	Ibuprofen	Comparison does not fit the criteria for this review—the NSAID was given as part of a multimodal intervention with EPA, exercise and so forth and so its effects cannot be determined.
Rogers, 2011	Database search	A randomised feasibility study of EPA and Cox-2 inhibitor (Celebrex) versus EPA, Cox-2 inhibitor (Celebrex), Resistance Training followed by ingestion of essential amino acids high in leucine in NSCLC cachectic patients—ACCeRT study	Celecoxib	Comparison does not fit the criteria for this review—the NSAID was given to both study arms and so its effects cannot be determined.
Hyltander, 1993	Database search	Evaluation of mechanisms behind elevated energy expenditure in cancer patients with solid tumours	Indomethacin	Outcomes do not fit the criteria for this review—CRP was measured but the data were not reported. Author (Lundholm) was contacted but was not able to provide the data.
Preston, 1995	Database search	Effect of ibuprofen on the acute-phase response and protein metabolism in patients with cancer and weight loss	Ibuprofen	Outcomes do not fit the criteria for this review—CRP and cytokine data at follow-up were only provided for the intervention arm and not for the control arm. Author (Preston) was contacted, but no response was received.
Wigmore, 1995	Database search	Ibuprofen reduces energy expenditure and acute-phase protein production compared with placebo in pancreatic cancer patients	Ibuprofen	Outcomes do not fit the criteria for this review—CRP data were only provided for the intervention arm (in a graph, with no values) and not for the control arm. Author (Wigmore) was contacted but was not able to provide the data.

Abbreviations: COX, cyclooxygenase; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; EPA, eicosapentaenoic acid; FA, fatty acid; NSAID, non-steroidal anti-inflammatory drug; NSCLC, non-small-cell lung cancer; ONS, oral nutritional supplement.

Table 3 Patient flow through each of the included studies

	Lundholm, 1994			McMillan, 1999		Cerchietti, 2007		Lai, 2008		Kouchaki, 2018	
Eligibility											
Patients assessed for eligibility	Not reported			Not reported		24		Not reported		190	
Excluded (ineligible)	Not reported			Not reported		2		Not reported		75	
Refused participation	0			Not reported		0		Not reported		25	
Randomization											
Total number of patients randomized	135			73		22		11		90	
Study arm	**Intervention**	**Control**	**Other drug**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Patient numbers	45	45	45	35	38	10	12	4	7	45	45
Follow-up											
Timepoint 1	**Not unified**[a]			**4–6 weeks**		**6 weeks**		**3 weeks**		**1 month**	
Patients remaining	45	45	45	22	19	10	12	4	7	27	33
Reasons for loss	NA			'Mainly because of disease progression requiring hospital admission'		NA		'All patients but one completed the trial'		Death (n = 5), adverse effects (n = 5), disease progression (n = 5), non-adherence (n = 3)	Death (n = 3), adverse effects (n = 3), disease progression (n = 5), non-adherence (n = 1)
Timepoint 2	NA			**12 weeks**		NA		NA		**2 months**	
Patients remaining				16	11					16	17
Reasons for loss				Venous thrombosis (n = 2), upper gastrointestinal bleeding (n = 2), ascites (n = 3), disease progression (n =?)	Venous thrombosis (n = 1), fatal upper gastrointestinal bleeding (n = 1), ascites (n = 2), disease progression (n =?)					Adverse effects (n = 1), disease progression (n = 3), non-adherence (n = 7)	Death (n = 5), adverse effects (n = 3), disease progression (n = 2), non-adherence (n = 6)

[a]Information from direct correspondence with author.

Table 4 Risk of bias assessment summary

		Lundholm, 1994	McMillan, 1999	Cerchietti, 2007	Lai, 2008	Kouchaki, 2018
Outcome domains assessed for risk of bias:		Survival, muscle strength, body composition, weight, fatigue, PS, inflammation, metabolic rate	Body composition, weight, QoL, NIS, fatigue, adverse events, PS, inflammation	Muscle strength, body composition, weight, NIS, fatigue, adverse events, PS, inflammation, food/energy intake	Body composition, weight, QoL, adverse events, PS, inflammation, metabolic rate	Survival, muscle strength, weight, NIS, adverse events, PS, inflammation
Risk of bias arising from the randomization process	**Author's judgement**	**Some concerns for all outcomes**	**Some concerns for all outcomes**	**Some concerns for all outcomes**	**Some concerns for all outcomes**	**Low risk of bias for all outcomes**
	Justification	Participants were randomized 'by a computer-based algorithm' stratified for numerous factors. No information is given regarding whether the allocation sequence was concealed until participants were enrolled and assigned to interventions. Baseline differences between study arms did not suggest a problem with the randomization process.	The authors report randomizing participants, but no information is given regarding the process. No information is given regarding whether the allocation sequence was concealed until participants were enrolled and assigned to interventions. Baseline differences between study arms did not suggest a problem with the randomization process.	Participants were randomized 'according to a random number generator'. No information is given regarding whether the allocation sequence was concealed until participants were enrolled and assigned to interventions. Baseline differences between study arms did not suggest a problem with the randomization process.	Participants were randomized 'by an independent Biostatistician'. No information is given regarding whether the allocation sequence was concealed until participants were enrolled and assigned to interventions. Baseline differences between study arms did not suggest a problem with the randomization process.	Participants were randomized by 'a computer-based random number producer'. This study was double-blinded, which implies the allocation sequence was concealed. Baseline differences between study arms did not suggest a problem with the randomization process.
Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	**Author's judgement**	**High risk of bias for all outcomes**	**High risk of bias for all outcomes**	**Low risk of bias for all outcomes**	**Some concerns for all outcomes**	**Low risk of bias for all outcomes**
	Justification	Participants 'were blinded for their treatment', but the clinician 'in charge of principally all patients (…) knew the treatment code (…) the study was thus single-blinded'. No information is given regarding non-protocol interventions, failures in implementation or adherence to the assigned interventions.	The authors do not explicitly state the blinding status of the study, but placebo pills were used. It is unclear whether people delivering the interventions were aware of the assigned interventions during the trial. It is implied, but not explicit, that there were no non-protocol interventions or failures in implementation. No information is given regarding failures in implementation, or	The authors do not explicitly state the blinding status of the study, but placebo pills were used. It is unclear whether people delivering the interventions were aware of the assigned interventions during the trial. It is implied, but not explicit, that there were no non-protocol interventions or failures in implementation. Compliance was reported to be almost 100% in both arms.	The authors do not explicitly state the blinding status of the study, but placebo pills were used. It is unclear whether people delivering the interventions were aware of the assigned interventions during the trial. It is implied, but not explicit, that there were no non-protocol interventions or failures in implementation. Compliance was 74% in the Celecoxib arm and 88% in the placebo arm.	This study was double-blinded, and placebo pills were used. It is implied, but not explicit, that there were no non-protocol interventions or failures in implementation.

(*Continues*)

Table 4 (continued)

		Lundholm, 1994	McMillan, 1999	Cerchietti, 2007	Lai, 2008	Kouchaki, 2018
			adherence to the assigned intervention.			
		'All 135 patients are including in the final analyses.' No information is given on adherence. Thus, it is assumed that data were analysed on an intention-to-treat basis, which is not appropriate for assessing the effect of adhering to the intervention.	Some outcomes were analysed 'on an intention-to-treat basis', which is not appropriate for assessing the effect of adhering to the intervention. It is unclear whether participants who did not adhere to the intervention were included in any analyses.	All participants adhered to the intervention and so were included in the analysis. This is therefore appropriate for assessing the effect of adhering to the intervention.	'All data were analysed with per protocol analysis', which is appropriate for assessing the effect of adhering to the intervention.	Participants with non-adherence were not included in the final analysis, which is appropriate for assessing the effect of adhering to the intervention.
Risk of bias due to missing outcome data	**Author's judgement** **Justification**	**Low risk of bias for all outcomes** 'All 135 patients are including in the final analyses.'	**High risk of bias for all outcomes** The authors report randomizing 73 patients, but 32 'failed to reach the 4–6 weeks assessment' and only 3 'were available for assessment at 12 weeks'. Reasons for this included adverse events and disease progression, which are related to the health of the participants.	**Low risk of bias for all outcomes** The authors report randomizing 22 patients, and all were included in the analysis.	**Low risk of bias for all outcomes** 'All patients but one completed the trial.'	**High risk of bias for all outcomes** The authors report randomizing 45 participants into each study arm, but only 33 and 27 were evaluable at 1 month, and 17 and 16 at 2 months. Reasons for this included death, adverse events, disease progression and non-adherence, which are related to the health of the participants.
Risk of bias in measurement of the outcome	**Author's judgement**	**Low risk of bias for all outcomes, except: Some concerns for PS High risk of bias for fatigue**	**Low risk of bias for all outcomes, except: Some concerns for PS and adverse events**	**Low risk of bias for all outcomes, except: Some concerns for PS High risk of bias for NIS**	**Low risk of bias for all outcomes, except: Some concerns for PS and adverse events**	**Low risk of bias for all outcomes**
	Justification	Measurement instrument was not appropriate for fatigue (VAS estimated by practitioner instead of patient), and instruments were not described for HG or TBK. Measurement instruments were	Measurement method was not described for adverse events. Measurement instruments were appropriate for all other outcome measures.	Measurement instruments were not appropriate for some NIS (taste change and early satiety as number of participants instead of scores), and instrument was not described for food/energy intake. Measurement instruments were	Measurement instruments were appropriate for all outcome measures.	Measurement instruments were appropriate for all outcome measures.

(*Continues*)

Table 4 (continued)

		Lundholm, 1994	McMillan, 1999	Cerchietti, 2007	Lai, 2008	Kouchaki, 2018
		appropriate for all other outcome measures.		appropriate for all other outcome measures.		
		Ascertainment of outcome measurements 'were determined at 3-month intervals until the patient died or the study was closed' and so are unlikely to have differed between study arms.	Ascertainment of outcome measurements 'were repeated at 4–6 and 12 weeks' and so are unlikely to have differed between study arms.	Ascertainment of outcome measurements were 'baseline and weekly measurements' and so are unlikely to have differed between study arms.	Ascertainment of outcome measurements were 'on Day 1' and 'at the end of the pharmacologic intervention (Day 21)' and so are unlikely to have differed between study arms.	Ascertainment of outcome measurements were 'at baseline and 2 months later' for inflammation, and 'just before starting interventions, then 1 and 2 months later' for all other outcomes, and so are unlikely to have differed between study arms.
		Outcome assessors were probably aware of the intervention received (single-blinded study). Therefore, assessment of subjective measures (PS and fatigue) could have been influenced by this knowledge.	It is unclear whether outcome assessors were aware of the intervention received. If they were, assessment of non-patient-reported, subjective measures (PS and adverse events) could have been influenced by this knowledge.	It is unclear whether outcome assessors were aware of the intervention received. If they were, assessment of non-patient-reported, subjective measures (some NIS, adverse events and PS) could have been influenced by this knowledge.	It is unclear whether outcome assessors were aware of the intervention received. If they were, assessment of non-patient-reported, subjective measures (adverse events and PS) could have been influenced by this knowledge.	The study was double-blinded, which implies outcome assessors of patient-reported and non-patient-reported outcomes were unaware of the intervention received.
Risk of bias in selection of the reported result	**Author's judgement**	**High risk of bias for all outcomes**	**High risk of bias for all outcomes**	**Low risk of bias for all outcomes, except: Some concerns for PS and food/energy intake High risk of bias for NIS and inflammation**	**High risk of bias for all outcomes**	**Low risk of bias for all outcomes, except: Some concerns for survival, weight and inflammation**
	Justification	The study was closed early on the basis of the interim results. Reporting matched intent to measure in methods for muscle strength, some body composition measures, weight, fatigue, PS and inflammation. For survival, some body composition measures	Reporting matched intent to measure in methods for most body composition measures, some weight measures, NIS and some inflammation measures. For QoL, PS, adverse events, some body composition, some inflammation and some weight	Reporting matched intent to measure in methods for body composition, some NIS, fatigue, adverse events and some inflammation measures. For some NIS, some inflammation, PS and food/energy intake, reporting did not match intent to measure stated in methods.	Reporting matched intent to measure in methods for body composition, some weight, QoL, metabolic rate and most inflammation measures. For some inflammation, some weight and adverse events, reporting did not match intent to measure stated in methods.	There were some differences in measurement intent between the protocol and methods section in the paper. Reporting matched intent to measure in both protocol and methods for NIS, some inflammation measures, QoL and some weight

(*Continues*)

Table 4 (continued)

		Lundholm, 1994	McMillan, 1999	Cerchietti, 2007	Lai, 2008	Kouchaki, 2018
		and metabolic rate, reporting did not match intent to measure stated in methods.	measures, reporting did not match intent to measure stated in methods.			measures. For muscle strength, adverse events, PS, some inflammation measures, survival and some weight measures, reporting did not match intent to measure stated at least one (protocol or methods).
		Statistical analysis plans provided in methods section of paper lacks specificity with multiple options for analysis.	Statistical analysis plans provided in methods section of paper lacks specificity with multiple options for analysis.	Clear statistical analysis plans provided in methods section of paper without multiple options for analysis.	Statistical analysis plans provided in methods section of paper lacks specificity with multiple options for analysis.	Clear statistical analysis plans provided in methods section of paper (not mentioned in protocol) without multiple options for analysis.
		For all outcomes, there were multiple eligible timepoints but it is unclear which were used for analysis or whether this differed amongst participants.	For QoL and NIS, multiple eligible measures were used but not all were reported on.	For NIS and inflammation, multiple eligible measures were used but not all were reported on.	For body composition, two measurement instruments were used but it is unclear which was reported on. For inflammation, multiple eligible measures were used but not all were reported on.	For all outcomes, there were no omissions in timepoint reporting, or of any alternate outcome domain measures.
Overall risk of bias	**Author's judgement**	**High risk of bias for all outcomes**	**High risk of bias for all outcomes**	**Some concerns for all outcomes, except: High risk of bias for NIS and inflammation**	**High risk of bias for all outcomes**	**High risk of bias for all outcomes**
	Justification	The study is judged to be at high risk of bias in at least 2 domains for all outcomes.	The study is judged to be at high risk of bias in at least 3 domains for all outcomes.	The study is judged to raise some concerns for all outcomes in at least 1 domain and to be at high risk of bias for NIS and inflammation in at least 1 domain.	The study is judged to be at high risk of bias in 1 domain for all outcomes.	The study is judged to be at high risk of bias in 1 domain for all outcomes.

Abbreviations: HG, hand grip strength; NIS, nutrition impact symptoms; PS, performance status; QoL, quality of life; TBK, total body potassium; VAS, visual analogue scale.

Effects of interventions

This review focused on 14 patient-centred outcome domains; results are presented in order of importance as specified through patient involvement activities.

As stated previously, a meta-analysis was not possible in this review. Only one study[23] investigated Indomethacin, or Ibuprofen.[24] Three studies investigated Celecoxib[25–27] but were not comparable due to the methodological heterogeneity. This included differing daily intake of Celecoxib (400 vs. 200 mg) and treatment duration (6 weeks vs. 3 weeks vs. 2 months). Two of these studies gave additional interventional treatments to both study arms (*Table 1*),[25,27] some of which are listed as possible interactions with Celecoxib.[28] Furthermore, there was considerable clinical heterogeneity between the studies; subgroup analysis was planned, but due to the small number of studies, this was not conducted.[22] This highlights the variability in the participants and methods used in studies investigating NSAIDs for treatment of CC and demonstrates the inherent difficulties with pooling studies for meta-analysis.

Table 5 shows all continuous outcome measures for which there was at least one study with evaluable data. Some studies reported change from baseline and, where these data were available, they were directly included in this review. However, some studies reported only baseline and endpoint data; where this is the case, change from baseline was calculated for the purposes of this review. Treatment effect size, as raw mean difference, was calculated for each outcome measurement where a statistically significant difference was reported between study arms.

Indomethacin

One study investigated Indomethacin.[23] Data were presented as mean and standard error of mean (SEM) at baseline and one follow-up (not unified). Statistical significance was tested between study arms with one-way analysis of variance (ANOVA) followed by Fisher's least significant difference (LSD) post hoc test, with significance set at 0.05. Statistical significance within study arms was not tested. This study was judged to be at high risk of bias for all outcomes (*Table 4*), so caution should be taken when considering the results presented. Thirteen outcome measures in eight outcome domains of interest to this review were reported; however, only seven measures in five domains had evaluable data.

Survival: The authors reported that participants given Indomethacin had significantly prolonged survival compared with those given placebo ($P < 0.05$); however, data were only provided through survival curves without data values.

Body composition: There was no significant difference in mid-upper arm circumference (MUAC), arm muscle circumference (AMC) or triceps skinfold (TSF) between arms at baseline. At follow-up, there remained no significant difference in AMC or TSF, but MUAC was significantly higher in the placebo arm (26.0 ± 0.4 cm) compared with the Indomethacin arm (25.4 ± 0.3 cm; $P < 0.05$). However, mean change from baseline calculated for this review was equal in both arms (−0.7 cm).

Body weight: There was no significant difference in BW-kg between arms at baseline or at follow-up. However, calculated mean change from baseline indicated a possible negative effect of Indomethacin on BW-kg (Indomethacin −3.5 kg; placebo −0.9 kg; effect size −2.6 kg).

PS: There was no significant difference in KPS between arms at baseline. At follow-up, scores were significantly higher in the Indomethacin arm (75.0 ± 2.0) compared with the placebo arm (66.0 ± 3.0; $P < 0.05$). Furthermore, calculated mean change from baseline calculated indicated a beneficial effect of Indomethacin on PS (Indomethacin 1; Placebo −10; effect size 11).

Inflammation: There was no significant difference in serum albumin between arms at baseline or at follow-up. Calculated mean change from baseline found a relatively small effect size (0.5 g/dL).

Ibuprofen

One study investigated Ibuprofen.[24] Data were presented as median and range, as change from baseline at 4–6 and 12 weeks. Statistical significance was tested between study arms with the Mann–Whitney *U*-test and Fisher's exact test; significance level was not reported. This study was judged to be at high risk of bias for all outcomes (*Table 4*), so caution should be taken when considering the results presented.

Seventeen outcome measures in eight outcome domains of interest to this review were reported; however, only 11 measures in six domains had evaluable data.

Body composition: There was no significant difference in TSF or biceps skinfold (BSF) change between study arms ($P > 0.05$). However, at both timepoints, the Ibuprofen arm experienced a significantly greater increase in MUAC than the placebo arm at 4–6 weeks (Ibuprofen 0.1 cm [−2.5 to 3.1]; placebo −0.6 cm [−5.7 to 0.6]; effect size 0.7 cm; $P < 0.01$) and at 12 weeks (Ibuprofen 0.0 cm [−5.4 to 3.0]; placebo −1.0 cm [−5.7 to 0.4]; effect size 1.0 cm; $P < 0.05$). The authors reported no significant difference in TBW change between study arms after 4–6 weeks; however, data were not provided for both arms, and the sample size was too small for analysis at 12 weeks.

Body weight: There was a significant difference in BW-kg change between study arms (4–6 weeks $P < 0.01$; 12 weeks $P < 0.001$). After 4–6 weeks, the Ibuprofen group experienced a median increase of 1.0 kg (−3.7 to 6.5) while the placebo group experienced a decrease of −1.5 kg (−6.0 to 4.5); this widened by 12 weeks (Ibuprofen 2.3 kg [−2.0 to 12.4]; placebo −2.8 kg [−7.0 to 2.2]).

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Table 5 Continuous outcome measures reported in the included studies

Study	Outcome measure	Measurement instrument	Statistic reported	Endpoint	Study arm	*N*	Change from baseline	Sig between arms	Effect size
Outcome domain: Muscle strength									
Cerchietti, 2007	HG (kg)	Not reported	Mean ± SEM[a]	6 weeks	Celecoxib	10	3.12 ± 0.98	$P = 0.002$	1.96 kg
					Placebo	12	1.16 ± 0.3		
Kouchaki, 2018		Jamar hydraulic hand dynamometer	Mean ± SD[c]	1 month	Celecoxib	27	2.0	NS	NA
					Placebo	33	1.9		
				2 months	Celecoxib	16	3.9	NS	NA
					Placebo	17	6.8		
Outcome domain: Body composition									
Cerchietti, 2007	LBM (kg)	BIA	Mean ± SEM[a]	6 weeks	Celecoxib	10	0.4 ± 0.6	NS	NA
					Placebo	12	−0.6 ± 0.67		
Lai, 2008		DEXA and BIA[d]	Mean ± SD[b]	3 weeks	Celecoxib	4	0.3 ± 2.8	NS	NA
					Placebo	7	0 ± 1.6		
Cerchietti, 2007	FM (kg)	BIA	Mean ± SEM[a]	6 weeks	Celecoxib	10	1.2 ± 0.64	NS	NA
					Placebo	12	−0.6 ± 0.8		
Lai, 2008		DEXA and BIA[d]	Mean ± SD[b]	3 weeks	Celecoxib	4	−0.2 ± 1.0	NS	NA
					Placebo	7	−0.5 ± 1.2		
McMillan, 1999	TBW (L)	BIA	Median[a]	4–6 weeks	Ibuprofen	22	1.31	NS	NA
					Placebo	19	Not reported		
Cerchietti, 2007		BIA	Mean ± SEM[a]	6 weeks	Celecoxib	10	0.3 ± 0.9	NS	NA
					Placebo	12	0.4 ± 0.85		
Lai, 2008		DEXA and BIA[d]	Mean ± SD[b]	3 weeks	Celecoxib	4	1.1 ± 1.4	NS	NA
					Placebo	7	1.2 ± 3.2		
Lundholm, 1994	MUAC (cm)	Not reported	Mean ± SEM[c]	Not unified[d]	Indomethacin	45	−0.7	Unknown	0.0 cm
					Placebo	45	−0.7		
McMillan, 1999		Stretch-resistant tape	Median (range)[a]	4–6 weeks	Ibuprofen	22	0.1 (−2.5 to 3.1)	$P < 0.01$	0.7 cm
					Placebo	19	−0.6 (−5.7 to 0.6)		
				12 weeks	Ibuprofen	16	0.0 (−5.4 to 3.0)	$P < 0.05$	1.0 cm
					Placebo	11	−1.0 (−5.7 to 0.4)		
Lundholm, 1994	AMC (cm)	NA (calculated from MUAC and TSF)	Mean ± SEM[c]	Not unified[d]	Indomethacin	45	−0.3	Unknown	0.4 cm
					Placebo	45	−0.7		
Lundholm, 1994	TSF (mm)	Not reported	Mean ± SEM[c]	Not unified[d]	Indomethacin	45	−1.4	Unknown	−1.6 mm
					Placebo	45	0.2		
McMillan, 1999		Harpenden skinfold callipers	Median (range)[a]	4–6 weeks	Ibuprofen	22	0.0 (−2.8 to 1.7)	NS	NA
					Placebo	19	−0.1 (−5.0 to 2.6)		
				12 weeks	Ibuprofen	16	0.1 (−0.6 to 6.0)	NS	NA
					Placebo	11	0.0 (−4.8 to 1.8)		
McMillan, 1999	BSF (mm)	Harpenden skinfold callipers	Median (range)[a]	4–6 weeks	Ibuprofen	22	0.0 (−3.7 to 0.9)	NS	NA
					Placebo	19	0.0 (−2.4 to 2.0)		
				12 weeks	Ibuprofen	16	−0.2 (−4.4 to 3.0)	NS	NA
					Placebo	11	−0.5 (−3.3 to 0.0)		
Outcome domain: Body weight									
Lundholm, 1994	BW (kg)	Not reported	Mean ± SEM[c]	Not unified[d]	Indomethacin	45	−3.5	Unknown	−2.6 kg

(*Continues*)

Table 5 (continued)

Study	Outcome measure	Measurement instrument	Statistic reported	Endpoint	Study arm	*N*	Change from baseline	Sig between arms	Effect size
					Placebo	45	−0.9		
McMillan, 1999		Not reported	Median (range)[a]	4–6 weeks	Ibuprofen	22	1.0 (−3.7 to 6.5)	$P < 0.01$	2.5 kg
					Placebo	19	−1.5 (−6.0 to 4.5)		
				12 weeks	Ibuprofen	16	2.3 (−2.0 to 12.4)	$P < 0.001$	1.8 kg
					Placebo	11	−2.8 (−7.0 to 2.2)		
Cerchietti, 2007		Not reported	Mean ± SEM[a]	6 weeks	Celecoxib	10	1.5 ± 1.2	$P = 0.05$	2.9 kg
					Placebo	12	−1.4 ± 0.84		
Lai, 2008		Digital electronic scale	Mean ± SD[a]	3 weeks	Celecoxib	4	1 ± 1.3	$P = 0.05$	2.3 kg
					Placebo	7	−1.3 ± 1.7		
Kouchaki, 2018		Standard scale	Mean ± SD[a]	1 month	Celecoxib	27	0.8 ± 1.7	NS	NA
					Placebo	33	1.3 ± 2.4		
				2 months	Celecoxib	16	2.2 ± 3.6	NS	NA
					Placebo	17	4 ± 3.4		
Lai, 2008	BMI (kg/m^2)	NA (calculated from BW and height)	Mean ± SD[a]	3 weeks	Celecoxib	4	0.3 ± 0.5	$P = 0.05$	0.9 kg/m^2
					Placebo	7	−0.6 ± 0.7		
Kouchaki, 2018		NA (calculated from BW and height)	Mean ± SD[c]	1 month	Celecoxib	27	1.2	NS	NA
					Placebo	33	0.6		
				2 months	Celecoxib	16	1.3	NS	NA
					Placebo	17	2.2		
			Outcome domain: Quality of life						
Lai, 2008	FAACT V4 score (0–100)	Patient-reported questionnaire	Mean[c] (on a graph only)	3 weeks	Celecoxib	4	Not provided	$P = 0.05$	Unknown
					Placebo	7	Not provided		
McMillan, 1999	EuroQoL-EQ-5D	Patient-reported questionnaire	None	12 weeks	Ibuprofen	16	Not provided	$P < 0.05$	Unknown
					Placebo	11	Not provided		
McMillan, 1999	EORTC QLQ-C30 scale (0–100)	Patient-reported questionnaire	None	4–6 weeks	Ibuprofen	22	Not provided	NS	NA
					Placebo	19	Not provided		
Kouchaki, 2018		Not reported	Mean ± SD[c]	1 month	Celecoxib	27	7.9	NS	NA
					Placebo	33	8.9		
				2 months	Celecoxib	16	15.7	NS	NA
					Placebo	17	19.8		
			Outcome domain: Nutrition impact symptoms						
McMillan, 1999	Appetite	10-cm linear analogue scale (patients)	Median (range)[a]	4–6 weeks	Ibuprofen	22	2.0 (−5.0 to 8.9)	NS	NA
					Placebo	19	3.0 (−2.0 to 9.0)		
				12 weeks	Ibuprofen	16	1.0 (−5.0 to 8.1)	NS	NA
					Placebo	11	1.0 (−3.0 to 9.0)		
McMillan, 1999		EORTC QLQ-C30 appetite loss subscale	None	4–6 weeks	Ibuprofen	22	Not provided	NS	NA
					Placebo	19	Not provided		
Cerchietti, 2007	Appetite	Numerical rating scale (0–10)	Mean ± SEM[a]	6 weeks	Celecoxib	10	3.1 ± 1.2	NS	NA
					Placebo	12	3.8 ± 0.8		
Kouchaki, 2018		10-point VAS	Mean ± SD[c]	1 month	Celecoxib	27	1.7	NS	NA
					Placebo	33	1.8		
				2 months	Celecoxib	16	2.5	NS	NA
					Placebo	17	3.1		
			Outcome domain: Fatigue						
	Fatigue (0–10)	Numerical rating scale (0–10)	Mean ± SEM[a]	6 weeks	Celecoxib	10	−3.0 ± 0.9	NS	NA

(*Continues*)

Table 5 (continued)

Study	Outcome measure	Measurement instrument	Statistic reported	Endpoint	Study arm	*N*	Change from baseline	Sig between arms	Effect size
Cerchietti, 2007					Placebo	12	−3.5 ± 0.9		
			Outcome domain: Physical function						
Lundholm, 1994	KPS scale (0–100)	KPS (classified by a nurse)	Mean ± SEM[c]	Not unified[d]	Indomethacin	45	1	Unknown	11
					Placebo	45	−10		
Lai, 2008		KPS (physician-based score)	None	3 weeks	Celecoxib	4	Not provided	NS	NA
					Placebo	7	Not provided		
Kouchaki, 2018	ECOG-PS scale (0–5)	ECOG-PS	Mean ± SD[c]	1 month	Celecoxib	27	−0.2	NS	NA
					Placebo	33	−0.1		
				2 months	Celecoxib	16	−0.6	NS	NA
					Placebo	17	−0.8		
			Outcome domain: Inflammation						
Lundholm, 1994	Albumin (g/L or g/dL)	Not reported	Mean ± SEM[c]	Not unified[d]	Indomethacin	45	0.4	Unknown	0.5 g/L
					Placebo	45	−0.1		
McMillan, 1999			Median (range)[a]	4–6 weeks	Ibuprofen	22	1 (−6 to 6)	NS	NA
					Placebo	19	1 (−6 to 6)		
				12 weeks	Ibuprofen	16	−2 (−5 to 1)	NS	NA
					Placebo	11	0 (−8 to 3)		
Kouchaki, 2018			Mean ± SD[a]	2 months	Celecoxib	16	0.23	NS	NA
					Placebo	17	0.24		
Cerchietti, 2007	CRP (μg/mL)	Not reported	Mean ± SEM[a]	6 weeks	Celecoxib	10	−21.3 ± 7.0	$P = 0.005$	−14.6 μg/mL
					Placebo	12	−6.7 ± 4.5		
Lai, 2008		BN-II nephelometer	Mean ± SD[a]	3 weeks	Celecoxib	4	0.8 ± 2.7	NS	NA
					Placebo	7	1.6 ± 6.0		
Kouchaki, 2018		Not reported	Mean ± SD[a]	2 months	Celecoxib	16	1.1	NS	NA
					Placebo	17	−4.3		
Kouchaki, 2018	GPS	NA (calculated from albumin and CRP)	Mean ± SD[a]	2 months	Celecoxib	16	−0.23	NS	NA
					Placebo	17	−0.51		
Lai, 2008	IL-6 (pg/mL)	Luminex 100 analyser	Mean ± SD[a]	3 weeks	Celecoxib	4	−3.2 ± 5.3	NS	NA
					Placebo	7	0.1 ± 1.4		
Kouchaki, 2018		ELISA	Mean ± SD[a]	2 months	Celecoxib	16	−0.036	NS	NA
					Placebo	17	−0.826		
Lai, 2008	IL-6HS (pg/mL)	ELISA	Mean ± SD[a]	3 weeks	Celecoxib	4	−8.8	NS	NA
					Placebo	7	−0.3		
Lai, 2008	IL-1b (pg/mL)	Luminex 100 analyser	Mean ± SD[a]	3 weeks	Celecoxib	4	0.0 ± 0.0	NS	NA
					Placebo	7	0.0 ± 0.1		
Lai, 2008	IL-2 (pg/mL)	Luminex 100 analyser	Mean ± SD[a]	3 weeks	Celecoxib	4	−0.1 ± 0.2	NS	NA
					Placebo	7	0.0 ± 0.3		
Lai, 2008	IL-8 (pg/mL)	Luminex 100 analyser	Mean ± SD[a]	3 weeks	Celecoxib	4	−11.0 ± 12.0	NS	NA
					Placebo	7	14.6 ± 33.5		
Lai, 2008	TNF-α (pg/mL)	Luminex 100 analyser	Mean ± SD[a]	3 weeks	Celecoxib	4	0.0 ± 1.9	NS	NA
					Placebo	7	0.6 ± 2.1		

(*Continues*)

Table 5 (continued)

Study	Outcome measure	Measurement instrument	Statistic reported	Endpoint	Study arm	*N*	Change from baseline	Sig between arms	Effect size
Lai, 2008	IFN-γ (pg/mL)	Luminex 100 analyser	Mean ± SD[a]	3 weeks	Celecoxib	4	0.1 ± 0.2	NS	NA
					Placebo	7	0.0 ± 0.1		
			Outcome domain: Metabolic rate						
Lai, 2008	REE (kcal/day)	Indirect calorimeter	Mean ± SD[a]	3 weeks	Celecoxib	4	6.3 ± 18.6	$P = 0.04$	25.6 kcal/day
					Placebo	7	−19.3 ± 24.6		

Note: Grey boxes indicate that value was calculated for the purposes of this review; white boxes indicate that value was taken directly from the study. Abbreviations: AMC, arm muscle circumference; BIA, bioelectrical impedance assay; BMI, body mass index; BSF, biceps skinfold; BW, body weight; CRP, C-reactive protein; DEXA, dual-energy X-ray absorptiometry; ECOG-PS, European Cooperative Oncology Group Performance Status; ELISA, enzyme linked immunosorbent assay; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life; FAACT, Functional Assessment of Anorexia Cachexia Therapy; FM, fat mass; HG, handgrip strength; IFN, interferon; IL, interleukin; KPS, Karnofsky performance status; LBM, lean body mass; MUAC, mid-upper arm circumference; NA, not applicable; NS, non-significant; SD, standard deviation; SEM, standard error of mean; TBW, total body weight; TNF, tumour necrosis factor; TSF, triceps skinfold; VAS, visual analogue scale.

[a]Data reported as change from baseline.

[b]Data reported as % change from baseline.

[c]Data reported at baseline and follow-up (change from baseline not reported).

[d]Both BIA and DEXA were used, but it was unclear which was reported.

QoL: The authors reported no significant difference in EORTC QLQ-C30 score change between study arms after 4–6 weeks; however, at 12 weeks, the Ibuprofen arm experienced a significantly greater increase in EuroQoL-EQ-5D scores than the placebo arm after 12 weeks ($P < 0.05$). Data were not provided for either measure at either timepoint.

NIS: There was no significant difference in appetite VAS or EORTC QLQ-C30 appetite subscale score change between study arms at either timepoint.

AEs: 11 AEs were reported: venous thrombosis (Ibuprofen $n = 2$; placebo $n = 1$), upper gastrointestinal bleeding (Ibuprofen $n = 2$; placebo $n = 1$) and ascites (Ibuprofen $n = 3$; placebo $n = 2$).

Inflammation: There was no significant difference in serum albumin change between study arms at either timepoint.

Celecoxib

Three studies investigated Celecoxib.[25–27] In the first,[25] data were presented as mean and SEM as change from baseline at 6 weeks. Statistical significance was tested between the two arms using the Mann–Whitney *U*-test or *t*-test, with significance set at 0.05. However, analysis may have been underpowered due to the small sample size ($n = 22$), although this is not stated in the paper. This study was judged to be at high risk of bias for NIS and raised some concerns for all other outcomes (*Table 4*), so caution should be taken when considering the results presented. Fifteen outcome measures in nine outcome domains of interest to this review were reported; however, only nine measures in seven domains had evaluable data.

Muscle strength: The Celecoxib arm experienced a significantly greater increase in HG than the placebo arm (Celecoxib 3.12 ± 0.98 kg; placebo 1.16 ± 0.3 kg; $P < 0.05$; effect size 1.96 kg).

Body composition: There was no significant difference in lean body mass (LBM), fat mass (FM) or TBW change between study arms ($P > 0.05$).

Body weight: There was a significant difference in BW-kg change between study arms ($P < 0.05$). The Celecoxib arm saw a mean increase of 1.5 ± 1.2 kg, while the placebo group saw a decrease of −1.4 ± 0.84 kg (effect size 2.9 kg).

NIS: There was no significant difference in appetite VAS change between study arms ($P > 0.05$).

Fatigue: There was no significant difference in fatigue VAS change between study arms ($P > 0.05$).

AEs: No clinically significant side effects were detected by the authors in either arm.

Inflammation: The Celecoxib arm saw a significantly greater reduction in serum CRP than the placebo arm (Celecoxib −21.3 ± 7.9 μg/mL; placebo −6.7 ± 4.5 μg/mL; $P < 0.05$; effect size 14.6 μg/mL).

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In the second Celecoxib study,[26] data were presented as mean and SD as change from baseline to 3 weeks. Statistical significance between study arms was tested with one-way ANOVA, with significance set at 0.05. However, analysis may have been underpowered due to the small sample size (n = 11), although this is not stated in the paper. This study was judged to raise some concerns for all outcomes (*Table 4*), so caution should be taken when considering the results presented. Eighteen outcome measures in seven outcome domains of interest to this review were reported, and all but one measure had evaluable data.

Body composition: There was no significant difference in LBM, FM or TBW change between study arms ($P > 0.05$).
Body weight: There was a borderline significant difference in BW-kg change between study arms (P = 0.05). The Celecoxib arm saw a mean increase of 1.0 ± 1.3 kg, while the placebo group saw a decrease of −1.3 ± 1.7 kg (effect size 2.3 kg). A similar pattern was seen for BMI (Celecoxib 0.3 ± 0.5 kg/m^2; placebo −0.6 ± 0.7 kg/m^2; P = 0.05; effect size 0.9 kg/m^2).
QoL: The Celecoxib arm experienced a (borderline significant) greater increase in FAACT scores than the placebo arm (P = 0.05), although data were only provided in graph form.
AEs: The authors reported no AEs or toxicities.
PS: The authors reported no significant difference in KPS score change between study arms ($P > 0.05$); however, data were not provided.
Inflammation: There was no significant difference in serum CRP, IL-6, IL-6HS, IL-1b, IL-2, IL-8, TNF-α or IFN-γ change between study arms ($P > 0.05$).
Metabolic rate: There was a significant difference in REE change between study arms (P = 0.04). The Celecoxib arm saw a mean increase of 6.3 ± 18.6 kcal/day, while the placebo group saw a decrease of −19.3 ± 24.6 kcal/day (effect size 25.6 kcal/day).

In the third Celecoxib study,[27] data were presented as mean and SD at baseline and two follow-ups (1 month and 2 months). Statistical significance was tested between study arms with the Mann–Whitney U-test or independent samples t-test. Statistical significance within arms, from baseline to follow-up, was tested with Wilcoxon's signed-rank test or paired t-test. No significance level was reported. This study was judged to be at high risk of bias for all outcomes (*Table 4*), so caution should be taken when considering the results presented. Fourteen outcome measures in eight outcome domains of interest to this review were reported, 12 of which had evaluable data.

Survival: The authors reported continuing follow-up of patients after cessation of treatment. After follow-up of 10.8 ± 6.6 months, no significant difference in survival was reported between study arms; however, data were not provided.
Muscle strength: There was no significant difference in HG between study arms at any timepoint ($P > 0.05$).
Body weight: There was no significant difference in BW-kg or BMI between study arms at any timepoint ($P > 0.05$).
QoL: There was no significant difference in EORTC QLQ-C30 scores between study arms at any timepoint ($P > 0.05$).
NIS: There was no significant difference in appetite VAS scores between study arms at any timepoint ($P > 0.05$).
AEs: Six patients in each study arm discontinued treatment due to AEs: thromboembolic event (placebo n = 1; on anticoagulants), extreme fatigue (Celecoxib n = 2; placebo n = 2) and dyspepsia (Ibuprofen n = 4; placebo n = 4).
PS: There was no significant difference in ECOG-PS scores between study arms at any timepoint ($P > 0.05$).
Inflammation: There was no significant difference between study arms at any timepoint for CRP, albumin, GPS or IL-6 ($P > 0.05$).

Discussion

This review evaluated the current evidence for the use of NSAIDs in the treatment of CC in adults. With the field moving towards multi-component interventions for CC, which often include NSAIDs, it is important to understand the efficacy and safety of individual components of these interventions.

Summary of main results

Indomethacin

One RCT investigated Indomethacin for CC.[23] Results indicated that participants given Indomethacin experienced longer survival and improved PS compared with placebo, but no difference in body weight. However, the risk of bias was high for all outcomes, so these results should be considered with caution. Additionally, treatment duration was not specified. There is therefore insufficient evidence to determine whether this NSAID is effective in patients with CC, without additional RCTs with lower risk of biases. Furthermore, due to lack of safety reporting, the safety of Indomethacin in this population cannot be determined.

Ibuprofen

One RCT tested Ibuprofen for treatment of CC.[24] Results indicated that Ibuprofen may reduce muscle loss and attenuate body weight loss, but with no effect on appetite or QoL in this population. However, as the risk of bias was high for all outcomes, these results should be considered with cau-

tion. There is therefore insufficient evidence to determine whether this NSAID is effective in patients with CC, without additional RCTs with lower risk of biases. Regarding safety, this study did not indicate any significant adverse reactions; however, further studies are required for confirmation.

Celecoxib

Three RCTs investigated the effect of Celecoxib in patients with CC.[25–27] Results from the first study[25] suggested that Celecoxib could increase muscle strength and body weight and reduce inflammation (only CRP measured), but with no significant effect on body composition, appetite or fatigue. The second study[26] found that Celecoxib may increase body weight and QoL, but with no significant effect on body composition, inflammation (measured by CRP and multiple pro-inflammatory cytokines) or PS, and with an increase in metabolic rate. In contrast, the third study[27] found no significant effect of Celecoxib on survival, muscle strength, body weight, appetite, inflammation (measured by CRP, albumin, GPS and IL-6), PS or QoL.

The variation in results could reflect the considerable clinical and methodological heterogeneity amongst the three studies; further studies are required to confirm the efficacy of Celecoxib in specific patient populations, at specific doses, with specific treatment combinations and for specific durations. All three studies found no evidence of any clinically significant adverse reactions, suggesting that this NSAID, at the doses and duration used in these studies, is safe for use in patients with CC. However, two of these studies were judged to be at high risk of bias, with the other at high risk for some outcomes and raising concerns amongst all others. Therefore, these results should be considered with caution.

Overall completeness and applicability of evidence

Only five studies were identified for this review, four of which were published over a decade ago. In this review, only studies where the effect of NSAIDs could be determined were included. Studies in the field of CC treatment are shifting towards multi-component interventions, based on the principle that one intervention alone is not sufficient to combat CC[3] and that there may be cumulative or synergistic effects between components. NSAIDs have been included in many of these,[17–20] despite the lack of robust evidence for their efficacy and safety in this population.

Three out of the five studies included in this review investigated Celecoxib, but it has been noted that the use of this NSAID may exclude a large group of patients with cardiovascular disease.[19] The risk of serious upper gastrointestinal events is lower with selective NSAIDs (e.g., Celecoxib) than non-selective NSAIDs (e.g., Ibuprofen and Indomethacin).[9] However, Ibuprofen has fewer side effects than other non-selective NSAIDs, including Indomethacin.[9] Nevertheless, the anti-inflammatory properties of Ibuprofen are weaker than other non-selective NSAIDs and are considered unsuitable for conditions where inflammation is prominent.[9] Such issues are pertinent for future trials in this area.

Studies aiming to treat CC should assess key features of the syndrome, including anorexia/energy intake, catabolic drivers, muscle mass and strength, and, importantly, the effect of cachexia on the patient.[1] While all included studies had the objective of reducing cachexia symptoms, these assessments were often lacking. This review's primary outcomes were determined with patient involvement; while all five studies reported changes in body weight, only two reported on survival, which was unsurprisingly the outcome of highest importance to patients, and only three reported QoL. This highlights a lack of patient involvement and input in design of clinical trials for CC.

As well as patient-centred outcomes, the use of patient-reported outcome measures (PROMs) is becoming increasingly recognized as an important method of assessing the clinical effectiveness of treatments in oncology and palliative care.[29–31] Some PROMs were used amongst the included studies, but there was a lack of consistent tools used for the same symptoms, impacting on the ability to analyse results across studies. Furthermore, PROMs were not a large proportion of the outcome measures and often were not clearly reported.

Additionally, outcome measurements and instruments used in body composition analysis varied substantially. Imaging methods (e.g., computed tomography [CT] or magnetic resonance imaging [MRI]) are considered the most accurate methods for in vivo quantification of body composition[32]; however, no studies used these methods and instead opted for anthropometry or BIA (one study used DEXA, although it was unclear if this was reported). This highlights the need for studies to use sensitive measurement instruments, with standardization of outcome measurements allowing for better judgement of the evidence in future CC studies.

This review found considerable heterogeneity not only in the populations and methods used in studies but also in the statistical reporting of results. Amongst the five studies, measures of location included mean and median, with measures of spread including SD, SEM and 95% confidence intervals. Thus, if meta-analysis had been appropriate, only the two studies reporting mean and SD would have been suitable for inclusion. Future studies in CC should aim to report data using these measures, where possible, to allow for pooling of studies and appropriate judgement of evidence.

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Agreements and disagreements with previous reviews

This is the third systematic review of NSAIDs for CC, with two previous systematic reviews published in 2013.[15,16] Four[23–26] studies included in this review were included in both previous reviews. The most recent study included in this review[27] was published after these previous reviews. One of the previous reviews[16] included two studies that were excluded in this current review[20,33] (justification in *Table 2*).

Both previous reviews concluded that while there was some evidence of beneficial effects, it was not sufficient to recommend the use of NSAIDs for clinical practice.[15,16] Now, a decade later, only one additional eligible study was identified for this review, and there is still insufficient evidence to recommend NSAIDs for patients with CC.

Conclusions

At present, there is inadequate evidence to recommend any NSAID for CC outside of clinical trials. As studies in the field of CC are moving towards combination interventions, further research to better understand the efficacy and safety of NSAIDs in this population is recommended, as currently, the evidence is limited. Future studies of NSAIDs for treatment of CC need to be adequately powered, have low risk of bias, accurately assess the key features of cachexia and utilize patient involvement and co-design elements. Furthermore, outcomes should be measured using reference standard techniques, and reporting of data should follow standard approaches, such that an accurate judgement of evidence can be made.

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Conflict of interest statement

There are no conflicts of interest.

Differences between protocol and review

MedRxiv was searched as the source of grey literature instead of conference abstracts, due to the more substantive availability of full-text grey literature through MedRxiv.

Two additional outcome domains that were not in the protocol—metabolic rate and food/energy intake—were included in the review as they are relevant to cachexia but had not previously been considered.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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