National Institute for Health and Care Excellence

Final

Spinal metastases and metastatic spinal cord compression

[J] Evidence reviews for corticosteroids

NICE guideline number NG234

Evidence reviews underpinning recommendations 1.8.1 to 1.8.7 in the NICE guideline

September 2023

Final

This evidence review was developed by NICE

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Corticosteroids

Review question

How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

Introduction

Corticosteroids (typically dexamethasone) are routinely given to patients with MSCC with the intent to reduce tumour bulk or spinal cord swelling, relieve spinal cord pressure and improve treatment outcomes. They may result in a rapid improvement of neurological function but there is limited evidence about their longer-term benefits and harms. High-dose, long-duration treatment with corticosteroids can cause significant adverse effects. This evidence review aimed to summarise the balance of benefits and harms of corticosteroids in people with spinal cord or nerve root compression due to metastases or malignancy.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults with spinal cord or nerve root compression because of: • metastatic spinal disease or • direct malignant infiltration
Intervention	• Dexamethasone (oral or intravenous)
Comparison	• No dexamethasone • Different regimens (for example different dosage or duration)

Outcome	**Critical**
	• Neurological and functional status including:
	  ○ Bowel and bladder function
	  ○ Mobility or ambulatory status
	• Pain
	
	Important
	• Treatment related toxicity including:
	  ○ Steroid adverse effects
	  ○ Tumour lysis syndrome (in haematological cancers)

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Three randomised controlled trials were included in this review (Graham 2006, Sorensen 1993, Vecht 1989).

The included studies are summarised in Table 2.

One trial compared high dose dexamethasone to no treatment (Sorensen 1993) and 2 trials compared high dose dexamethasone to low dose dexamethasone (Graham 2006 and Vecht 1989).

One study was from Australia (Graham 2006) and the others from Denmark (Sorensen 1994) and the Netherlands (Vecht 1989).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Graham 2006 RCT Australia	N=20 Age, mean, years (range): 66 (41 – 81). SD not reported. Sex: female n=20, male n=14.	High dose dexamethasone 96 mg intravenous daily dexamethasone - days 0 - 2, then tapered to 0 mg by day 15.	Low dose dexamethasone 16 mg intravenous daily dexamethasone - days 0 - 2, then weaned to 0 mg by day 15.	Functional status Treatment related toxicity
Sorensen 1994 RCT Denmark	N=57 Age, years, median (range): High dose 60 (25-81); no treatment 64 (41-82). Sex: female n=39, male n=18.	High dose dexamethasone Intravenous bolus of 96 mg dexamethasone given immediately after myelography or MRI, then maintained on a 96 mg dose of dexamethasone for 3 days (given orally when possible in four divided doses). Treatment was then then tapered over 10 days.	No treatment No details reported.	Functional status Treatment related toxicity
Vecht 1989	N=37	High dose dexamethasone	Low dose dexamethasone	Functional status

Study	Population	Intervention	Comparison	Outcomes
RCT Netherlands	Age, years, mean (SD): 61 (range 22 -87). SD not re-ported. Sex: female n=11; male n=26.	100 mg. No further details reported.	10 mg. No further details reported.	Pain

mg: milligram; MRI: Magnetic Resonance Imaging; RCT: randomised controlled trial.

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

Dexamethasone verses no treatment

Evidence comparing high dose dexamethasone to no treatment came from a single small RCT and ranged from low to moderate quality. For most outcomes there was no clinically important difference. There was a possible important benefit with dexamethasone at 6 months (the 90% confidence intervals showed an important benefit, but the 95% confidence intervals included no effect): people in this arm were more likely to be alive and ambulant at 6 months but by 1 year there was no difference. 11% of people taking high dose dexamethasone experienced significant side effects compared to none in the no treatment arm.

High verse low dose dexamethasone

Evidence comparing low to high dose dexamethasone came from 2 small RCTs and ranged from low to high quality. There was no clinically important difference in any of the outcomes.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See supplement 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in supplement 2.

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Neurological status, functional status and pain were prioritised as critical outcomes by the committee. This is because spinal cord or nerve root compression is often accompanied by neurological and functional impairment and pain. Corticosteroids are typically used with the aim to alleviate these in the acute setting. The committee agreed that treatment related toxicity was an important outcome because although corticosteroid related toxicity is a well known long term adverse effect, the medication would not usually be a long term treatment for this indication.

The quality of the evidence

The quality of the evidence was assessed using GRADE and ranged from low to high, with most of the evidence being of a low quality. This was predominately due to imprecision around the effect estimates: the evidence originated from 3 small studies.

Evidence was lacking for the adverse outcome of tumour lysis syndrome in people with haematological cancers.

For this reason, the committee used their expertise and experience to make the recommendations, while also taking into account the recommendations from the previous version of the guideline and their relevance to current practice.

Benefits and harms

There was some evidence that functional status was improved with dexamethasone, but the studies were too small to draw clear conclusions: the 90% confidence intervals showed an important benefit in terms of ambulation and survival at 6 months, but the 95% confidence intervals included no effect. The committee noted that this was supported by their expertise and experience. They agreed that for people with MSCC with clinical symptoms or signs which are commonly neurological, steroids can reduce inflammation and promote stabilisation of blood vessel membranes at the compression site, consequently reducing back pain and neurologic deficits. The evidence also showed an increase in treatment-related significant toxicity but numbers in the trial were small so there was some uncertainty in these findings. The committee acknowledged that toxicity is a known adverse event of corticosteroids, and that they should be stopped once other treatment options, such as surgery or radiotherapy, are available and have been initiated. Corticosteroids would need to be reduced because a sudden withdrawal may cause adverse events, such as a sharp fall in blood pressure, and affect blood glucose levels. They also decided that dexamethasone should be discontinued if spinal metastases, DMI of the spine or MSCC are ruled out and corticosteroids should not be given to people with MSCC without neurological symptoms unless it is part of radiotherapy regimen or the person has severe pain or the person has a haematological malignancy.

The committee decided that it was important to make separate recommendations for people with haematological malignancy. For those with confirmed haematological malignancy with spinal metastases or direct malignant infiltration (DMI) of the spine, the committee agreed based on expertise that dexamethasone was indicated regardless of whether or not people have neurological symptoms (which is what corticosteroid treatment is usually aimed at alleviating in the context of spinal cord compression). This is because corticosteroids in combination with anticancer treatments such as bortezomib or thalidomide are commonly used for treating myeloma once a haematological malignancy is confirmed (see first-line treatment and subsequent therapy recommendations in NICE guideline myeloma: diagnosis and management).

The committee agreed that a 16 mg dose of dexamethasone oral (or equivalent parenteral dose) to start with was current practice but were aware that in some cases a different corticosteroid or a different dose may be used so they recommended that ongoing treatment should be discussed with the specialist team to allow for dose adjustments.

The committee discussed that corticosteroids ought to be avoided if a haematological malignancy is suspected but has not been confirmed, because their administration may have a direct anti-tumour effect on B-cell lymphoma and cause reduction in MRI abnormalities, making biopsy and histologic confirmation more difficult. Therefore, the committee based on experience and expertise agreed that in these cases specialist haematological advice would be needed before corticosteroid treatment is started.

In situations where there are no other treatment options (because they have been tried and were not effective, the person is too unwell to tolerate other treatment, or giving another treatment is too risky) and symptoms return or worsen as dexamethasone is reduced, the committee agreed that it could be considered for longer.

One of the side effects of corticosteroid treatment is to increase blood glucose since these drugs promote glucose production in the liver and reduce the sensitivity of the cells to insulin so the committee recommended to monitor blood glucose. They also recommended to co-prescribe proton pump inhibitor (PPI) acid suppression to reduce the potential risk of peptic ulcer associated with corticosteroid therapy. They acknowledged that glucose monitoring and giving adjunct PPI treatment is common practice.

The committee acknowledged that the evidence was limited they noted that the use and mechanisms of action of corticosteroids treatments can be extrapolated from their use in other conditions that the committee could draw on from their expertise and they therefore did not prioritise this topic for a research recommendation.

Cost effectiveness and resource use

The committee agreed that the recommendations reflect current practice and that there will be no change in resource use as a result of these recommendations.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.1 to 1.8.7 of the guideline.

References – included studies

Effectiveness

Graham 2006

Graham P, Capp A, Delaney G et al. A pilot randomised comparison of dexamethasone 96 mg vs 16 mg per day for malignant spinal-cord compression treated by radiotherapy: TROG 01.05 Superdex study. Clinical Oncology, 18, 70-6, 2006

Sorensen 1994

Sorensen P, Helweg-Larsen S, Mouridsen H, et al. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: A randomised trial. European Journal of Cancer, 30, 22-27, 1994

Vecht 1989

Vecht C, Haaxma-Reiche H, van Putten W, et al. Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. Neurology, 39, 1255-7, 1989

Appendices

Appendix A Review protocols

Review protocol for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022303508
1.	Review title	Corticosteroid therapy in the management of neurological consequences of metastatic spinal cord compression
2.	Review question	How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?
3.	Objective	To establish the effectiveness of corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Cumulative Index to Nursing and Allied Health Literature (CINAHL) • Database of Abstracts of Reviews of Effects (DARE) • Embase • Epistemonikos • International Health Technology Assessment (IHTA) database • MEDLINE & MEDLINE In-Process Searches will be restricted by:

ID	Field	Content
		• English language studies • Human studies Other searches: Inclusion lists of systematic reviews With the agreement of the guideline committee the searches will be re-run between 6-8 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression
6.	Population	Inclusion: Adults with spinal cord or nerve root compression because of: • metastatic spinal disease or • direct malignant infiltration Exclusion: • Adults with spinal cord compression because of primary tumours of the spinal cord, meninges or nerve roots. • Adults with spinal cord compression because of non-malignant causes. • Adults with primary bone tumours of the spinal column. • Children and young people under the age of 18.
7.	Intervention	Dexamethasone (oral or intravenous)
8.	Comparator	• No dexamethasone • Different regimens (dosage and duration)
9.	Types of study to be	Experimental studies (where the investigator assigned intervention or control) including:

ID	Field	Content
	included	• Randomised controlled trials • Non-randomised controlled trials • Comparative observational studies (in the absence of RCTs) • Systematic reviews/meta-analyses of controlled trials.
10.	Other exclusion criteria	Inclusion: Full text papers Observational studies should adjust for baseline differences between patients in different intervention groups in their analyses Exclusion: • Conference abstracts • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/study quality. • Non-English language articles For NMA: Active interventions that are not part of the decision problem will not be considered in the analysis, unless they act as the sole connectors of the interventions of interest in the network.
11.	Context	Metastatic spinal cord compression in adults: risk assessment, diagnosis and management (2008) NICE guideline will be updated by this review question

12.	Primary outcomes (critical outcomes)	• Neurological & functional status including:
		  ○ Bowel & bladder function
		  ○ Mobility or ambulatory status
		• Pain

13.	Secondary outcomes (important outcomes)	• Treatment related toxicity including:
		  ○ Steroid adverse effects
		  ○ Tumour lysis syndrome (in haematological cancers)

ID	Field	Content
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. Draft excluded studies will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual. ROBIS tool for systematic reviews Cochrane RoB tool v.2 for RCTs and quasi-RCTs The non-randomised study design appropriate checklist. For example Cochrane ROBINS-I tool for non-randomised controlled trials and cohort studies; the EPOC RoB tool for controlled before and after studies. The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.

ID	Field	Content
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Data Synthesis Where possible, pairwise meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events. Mean differences or standardised mean differences will be calculated for continuous outcomes. If sufficient RCTs are available forming a network of relevant interventions, network meta-analysis will be done using MetaInsight V3 (Owen, RK, Bradbury, N, Xin, Y, Cooper, N, Sutton, A. MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. Res Syn Meth. 2019; 10: 569-581) Heterogeneity Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. In the case of serious or very serious unexplained heterogeneity (remaining after pre-specified subgroup and stratified analyses) meta-analysis will be done using a random effects model. Minimal important differences (MIDs) Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes For risk ratios: 0.8 and 1.25. For continuous outcomes: MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD. For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries. Validity

ID	Field	Content	
		The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/	
17.	Analysis of sub-groups	Evidence will be stratified by: • No pre-stratified analysis Evidence will be sub grouped by the following only in the event that there is significant heterogeneity in outcomes: • Subgroups listed in the equality impact assessment form: age, race, sex & socioeconomic status • Primary cancer type Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	04 January 2022	
22.	Anticipated completion date	23 August 2023	

ID	Field	Content		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Alliance 5b Named contact e-mail metastaticspinal@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
25.	Review team members	NGA Technical Team		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests		

ID	Field	Content	
		will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website:.	
29.	Other registration details		
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=303508	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Corticosteroid therapy; MSCC; neurological consequences	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Search strategies (clinical / economic)

Literature search strategies for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

Database: Medline – OVID interface

#	Searches
1	exp spinal cord neoplasms/ or Spinal Neoplasms/
2	((spine or spinal or vertebr*) adj2 (adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or neoplas* or tumo?r*)).tw.
3	((spine or spinal or vertebr*) and (metast* or oligometast*)).tw.
4	or/1-3
5	spinal cord compression/
6	((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) and (collaps* or compress* or pinch* or press*) and (adeno* or cancer* or carcinoma* or chordoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or oligometast* or tumo?r*)).tw.
7	(myelopath* or myeloradiculopath* or radiculopath*).tw,hw. or (radicular adj2 (disorder* or syndrome*)).tw.
8	(mescc or mscc).tw.
9	or/5-8
10	((adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or metast* or oligometast* or neoplas* or tumo?r*) adj3 (escap* or infiltrat* or invasiv* or metast* or spread*) adj5 (cauda equina or cervical* or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac*or lumbo sac* or medulla* or orthorthoacic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr*)).tw.
11	4 or 9 or 10
12	Adrenal Cortex Hormones/
13	(((adrenal or adreno*) adj2 (hormone* or steroid*)) or adrenocorticosteroid* or corticoid* or corticosteroid* or cortico steroid* or cortical steroid* or dermocorticosteroid*).tw.
14	exp dexamethasone/
15	(Adrecort or adrenocot or aeroseb* or aflucoson* or alfalyl or anaflogistico or aphtasolon or Arcodexan or arcodexan* or artrosone or auxiron or azium or bidexol or bisu ds or calonat or cebedex or cetadexon or colofoam or corson? or cortastat or cortidex or cortidexason or cortidrona or cortidrone or cortisumman or dacortina or dalalone or dalalone or danasone or decacortin or decadeltoson* or decaderm or decadion or decadran or decadron or decadron or decadronal or decadrone or decaesadril or decagel or decaject or decaject or decalix or decameth or decamethasone or decasone or decaspray or decaspray or decasterolone or decdan or decilone or decofluor or dectancyl or dekacort or delladec or deltafluoren or deltafluorene or dergramin or deronil or desacort or desacortone or desadrene or desalark or desameton* or desigdron or de sone la or dexa cortisyl or dexa dabrosan or dexa korti or dexa scheros?n* or dexacen 4 or dexacen 4 or dexachel or dexacort or dexacortal or dexacorten or dexacortin or dexacortisyl or dexadabroson or dexadecadrol or dexadrol or dexagel or dexagen or dexahelvacort or dexakorti or dexalien or dexalocal or dexame or dexamecortin or dexameson or dexamesone or dexametason* or dexameth or dexamethasone* or dexamethazon* or dexamethonium or dexamonozon or dexan or dexane or dexano or dexa p or dexapot or dexascheroson or dexascherozon* or dexason or dexasone or dexasone or dexinoral or dexionil or dexmethsone or dexona or dexone or dexone or dexpak or dexpak taperpak or dextelan or dextenza or dextrasone or dexycu or dezone or dibasona or esacortene or exadion or exadione or firmalone or fluormethyl?prednisolone* or fluormone or fluorocort or fluorodelta or fluoromethylprednisolone or fortecortin or gammacorten* or grosodexon* or hemady or hexad?ol or hexadecad?ol or hexadecadrol or hexad?ol or isnacort or isopto dex or isopto?maxidex or isoptodex or lokalison f or loverine or luxazone or marvidione or maxidex or maxidex or mediamethasone or megacortin or mephameson* or metasolon or metasolone or methazon ion or methazone ion or methazonion* or methylfluorprednisolone or metisone lafi or mexasone or millicorten or millicorten* or mk?125 or mymethasone or neoforderx or neofordex or nisomethasona or novocort or oftan dexa or opticorten or opticortinol or oradex?n * or oradexon or orgadrone or ozurdex or pidexon or policort or posurdex or predni f tablinen or predni f or prednisolone or prodexona or prodexone or sanamethasone or santenson or santeson or sawasone or solurex or spoloven or sterasone or thilodexine or triamcimetil or vexamet or visumetazone or visumethazone).tw.
16	Or/12-15
17	11 and 16
18	(animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
19	17 not 18
20	limit 19 to english language

Health economics search

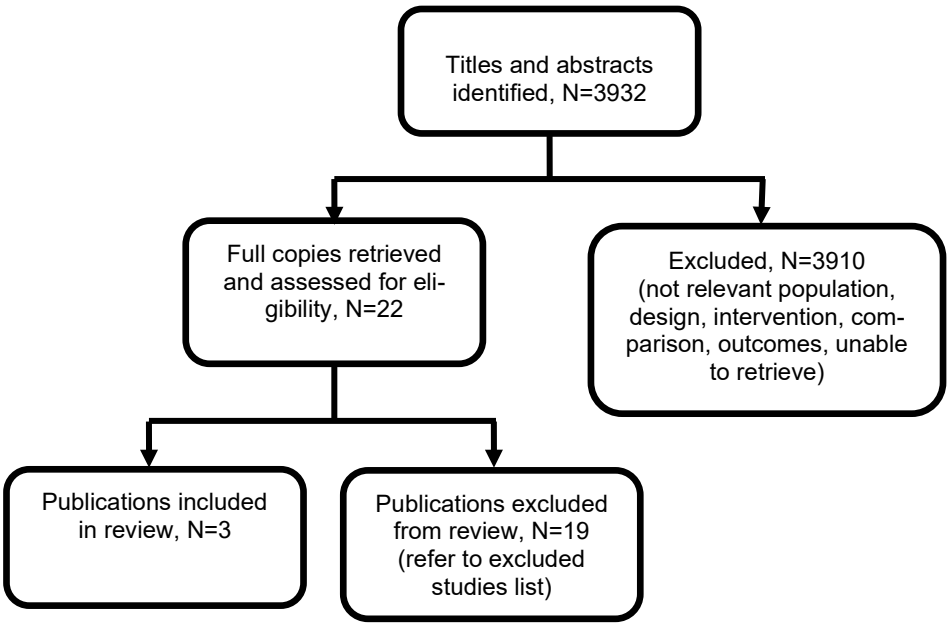
Database: Medline – OVID interface

#	Searches
1	exp Spinal Cord Neoplasms/ or Spinal Neoplasms/
2	((spine or spinal or vertebr*) adj2 (adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or neoplas* or tumo?r*)).tw.
3	((spine or spinal or vertebr*) and (metast* or oligometast*)).tw.
4	or/1-3
5	Spinal Cord Compression/
6	((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) and (collaps* or compress* or pinch* or press*) and (adeno* or cancer* or carcinoma* or chordoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or oligometast* or tumo?r*)).tw.
7	(myelopath* or myeloradiculopath* or radiculopath*).tw,hw. or (radicular adj2 (disorder* or syndrome*)).tw.
8	(mescc or mscc).tw.
9	or/5-8
10	((adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or tumo?r*) adj3 (escap* or infiltrat* or invasiv* or metast* or spread*) adj5 (cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root))).tw.
11	or/4,9-10
12	Economics/ or Value of life/ or exp "Costs and Cost Analysis"/ or exp Economics, Hospital/ or exp Economics, Medical/ or Economics, Nursing/ or Economics, Pharmaceutical/ or exp "Fees and Charges"/ or exp Budgets/
13	(cost* or economic* or pharmacoeconomic*).ti.
14	(budget* or financ* or fee or fees or price* or pricing* or (value adj2 (money or monetary))).ti,ab.
15	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
16	or/12-15
17	11 and 16
18	limit 17 to english language
19	limit 18 to yr="2005 -Current"

Appendix C Effectiveness evidence study selection

Study selection for: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

Table 4: Evidence tables

Graham, 2006
Graham P, Capp A, Delaney G et al., A pilot randomised comparison of dexamethasone 96 mg vs 16 mg per day for malignant spinal-cord compression treated by radiotherapy: TROG 01.05 Superdex study. Clinical oncology, 18, 70-6, 2006

Study details

Country/ies where study was carried out	Australia
Study type	Randomised controlled trial (RCT) 8 recruiting hospitals.
Study dates	September 2001 - November 2003.
Inclusion criteria	• MRI evidence of MSCC and at least one of pain, weakness, sensory symptoms or sphincter disturbance symptoms. • Prior histological proof of malignancy. • Age > 16 years • Eastern Co-operative Oncology Group (ECOG) performance status less than 4 before MSCC event. • Minimum power 1 out of 5. • Estimated minimum survival of 2 months. • Written informed consent.
Exclusion criteria	• Prior radiotherapy (defined as being within one vertebral level). • Prior treatment for MSCC. • Multi-level MSCC or other central nervous system disease. • Lymphoma or myeloma histology. • Definite history of peptic ulceration or cardiac failure. • Pregnancy. • Ongoing nonsteroidal medication. • Patients undergoing surgery.

Patient characteristics	Age, mean, years (range): 66 (41 – 81). Sex: female n=20, male n=14. Primary site, n: Breast/prostate – high dose 5; low dose 6; total 11. Other (lung, gastrointestinal tract, renal, other) – high dose 4; low dose 5; all patients 9. Level, n: Cervical – high dose 0; low dose 1, all patients 1. Thoracic - high dose 8; low dose 7; all patients 15. Lumbar – high dose 1; low dose 3, all patients 4. Hours of dexamethasone pre-randomisation, n: 0 hours – high dose 7; low dose 6; all patients. 0 – 10 hours – high dose 2; low dose 3; all patients 5. > 10 hours – high dose 0; low dose 2; all patients 2. > 6 months from cancer diagnosis, n: high dose 3; low dose 6; all patients 9. Ambulant, n: high dose 6; low dose 9; all patients 15.
Intervention(s)/control	High dose dexamethasone = 96 mg intravenous daily dexamethasone - days 0 - 2, then weaned to 0 mg by day 15. *versus* Low dose dexamethasone = 16 mg intravenous daily dexamethasone - days 0 - 2, then weaned to 0 mg by day 15. More rapid reduction was permitted if steroid toxicity was diagnosed, and reductions could be ceased or reversed if neurological deterioration occurred with reducing dexamethasone dose. An increase above the day 0 dose was not permitted. Peptic ulcer prophylaxis consisted of cessation of any non-steroidal medication and commencement of omeprazole 40 mg daily reduced to 20 mg when the dexamethasone dose was less than 16 mg. Daily glucometer finger prick assays were undertaken. Patients with indwelling urinary catheters were prescribed trimethoprim 300 mg daily prophylactically, and nystatin drops were given orally to all patients. An appropriate laxative schedule was given. Radiation was given on megavoltage linear accelerators after simulation, using a minimum field width of 8 cm. The minimum supero-inferior tumour margin to field edge was 3 cm, typically one vertebral body. The dose was 30 Gy in 10 fractions prescribed at a depth of 5 cm. The first two fractions were to be given on consecutive days, including weekends.
Duration of follow-up	12 months.
Sources of funding	Trans-Tasman Radiation Oncology Group (TROG); Cancer Council New South Wales.
Sample size	N=20. (96 mg group n=9; 16 mg group n=11).
Other information	Patients had to be randomised within 12 hours of receiving more than 4 mg/24 h of dexamethasone or equivalent steroid.

	Serious adverse events defined as events that require hospitalisation or prolongation of an existing admission, life-threatening events or death within 30 days of study treatment. For the first 10 days, mean doses received were within 20% of scheduled doses. Beyond this time, a patient randomised to the low-dose arm remained on 12 mg because of neurological decline, thus influencing the mean upwards. Although compliance was satisfactory, there seemed to be a tendency to reduce steroid doses faster than the protocol specification in the high-dose group compared with the low-dose group. Two out of six patients commencing radiotherapy on a Friday did not receive radiotherapy for two consecutive days at the commencement of treatment. Two patients received less than 30 Gy because of general deterioration (n=1) or death (n=1).

Outcomes

Outcome	High dose dexamethasone (96mg), n=9	Low dose dexamethasone (16mg) n=11
Neurological and functional status - ambulation rate (patients ambulant at study entry, 1 month)	n=2/6	n=6/9
Treatment related toxicity - serious adverse effects - any	n=5/9	n=4/11
Treatment related toxicity - serious drug related adverse effects	n=1/9	n=0/11

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly appli-

Section	Question	Answer
		cable

Sorensen, 1994
Sorensen P, Helweg-Larsen S, Mouridsen H, et al. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotheraphy: A randomised trial. European Journal of Cancer, 30, 22-27, 1994

Study details

Country/ies where study was carried out	Denmark.
Study type	Randomised controlled trial (RCT)
Study dates	May 1987 and April 1989.
Inclusion criteria	Patients referred for radiotherapy with compression of the spinal cord or cauda equina by epidural metastasis from a carcinoma. Diagnosis of spinal cord compression confirmed by myelography and, in some cases, by supplementary magnetic resonance imaging, with definition of the cranial and caudal margins of the epidural block.
Exclusion criteria	• Patients with lymphoma. • Previous treatment for epidural metastasis. • Meningeal carcinomatosis. • Infectious disease • Patients with peptic ulcers in whom treatment with high-dose dexamethasone was considered inappropriate. • Patients who underwent surgery. Surgery was considered in patients without previously established diagnosis of cancer, and in a few patients with unstable vertebral lesions. In all other patients, radiotherapy was offered as the department's standard treatment.
Patient characteristics	Age, years, median (range): High dose 60 (25-81); no treatment 64 (41-82). Sex: female n=39, male n=18. Primary tumour site, n: Breast - Dexamethasone 18; no treatment 16. Gastrointestinal – Dexamethasone 3; no treatment 3. Prostrate - Dexamethasone 1; no treatment 4. Lung - Dexamethasone 2; no treatment 1. Sarcoma - Dexamethasone 1; no treatment 3. Melanoma - Dexamethasone 1; no treatment 1.

	Kidney - Dexamethasone 1; no treatment 0. Mesothelioma - Dexamethasone 0; no treatment 1. Thyroid - Dexamethasone 0; no treatment 1. Site of compression, n: Cervical - Dexamethasone 2; no treatment 1. Thoracic - Dexamethasone 17; no treatment 16. Lumbar - Dexamethasone 8; no treatment 13. Pre-treatment motor function, n: Ambulatory - Dexamethasone 17; no treatment 19. Paretic without gait - Dexamethasone 7; no treatment 8. Paraplegic - Dexamethasone 3; no treatment 3.
Intervention(s)/control	High dose dexamethasone = intravenous bolus of 96 mg given immediately after myelography or MRI, then maintained on a dose of 96 mg dexamethasone for 3 days (given orally where possible in four divided doses), and the treatment was then tapered over 10 days. *versus* No treatment = no details reported. Prophylactic medication against gastro-duodenal ulceration was not given routinely---only in patients with a history of peptic ulcers and in patients complaining of dyspepsia. Radiation therapy was delivered with 6 MV photon beams, administered in two parallel opposing anterior and posterior fields, encompassing one normal vertebra, cranial and caudal to the epidural block. A radiation dose of 28 Gy was given in fractions of 4 Gy on each of 7 consecutive days. The first dose of irradiation was given 1-20 h after myelography, usually within a few hours.
Duration of follow-up	Every three months for two years or until death.
Sources of funding	Danish Cancer Research Foundation; Dexamethazone provided by Merck, Sharpe and Dhome, Denmark.
Sample size	N=59 randomised (2 patients excluded after randomisation, both from dexamethasone group due to ineligibility; dexamethasone group n=27; no treatment n=30).

Outcomes

Outcome	**High dose dexamethasone (96mg), n=27**	**No treatment n=30**

Outcome	High dose dexamethasone (96mg), n=27	No treatment n=30
Neurological and functional status - ambulation (preservation or restoration of gait, 3 months, number of patients)	22/27	19/30
Neurological and functional status - survival with gait function (6 months, number of patients)	16/27	10/30
Neurological and functional status - survival with gait function (1 year, number of patients)	8/27	6/30
Treatment related toxicity – 'significant side-effects' (number of patients)	n=3/27	n=0/30
Treatment related toxicity – discontinuation of dexamethasone therapy due to adverse events (number of patients)	n=2/27	n=0/30

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Vecht, 1989

Vecht C, Haaxma-Reiche H, van Putten W, et al., Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. Neurology 39, 1255-7, 1989

Study details

Country/ies where study was carried out	Netherlands.

Study type	Randomised controlled trial (RCT)
Study dates	Not reported.
Inclusion criteria	• Histologically verified diagnosis of a primary tumour, either a carcinoma or a lymphoreticular malignancy. • Showing complete obstruction for contrast flow on myelography, which was performed on suspicion of metastatic epidural spinal cord compression.
Exclusion criteria	Not reported.
Patient characteristics	Age, years, mean (SD): 61 (range 22 -87). SD not reported. Sex: female n=11; male n=26. Pain, n: low dose 13/15; high dose 18/22; total 31/317 Paresthesis, n: low dose 4/15; high dose 6/21; total 10/36 Sensory level, n: low dose dose 13/15; high dose 12/21; total 25/36. Ambulation grade, n: I – low dose 5/15; high dose 8/22; total; 13/37 II – low dose 2/15; high dose 6/22; total; 8/37 III – low dose 2/15; high dose 4/22; total; 6/37 IV - low dose 3/15; high dose 2/22; total; 5/37 V – low dose 10/15; high dose 2/22; total; 5/37 Bladder dysfunction, n: low dose 10/15; high dose 6/19; total; 16/34 Carcinoma, n: low dose 11/15; high dose 15/22; total; 26/37 Lymphoreticular malignancy, n: conventional dose 4/15; high dose 7/22; total; 11/37
Intervention(s)/control	High dose dexamethasone = 100 mg dexamethasone *versus* Low dose dexamethasone = 10 mg dexamethasone. No further details reported.
Duration of follow-up	1 week.
Sources of funding	Not reported.

Sample size	N=37 (100 mg group n=15; 10 mg group n=22).

Outcomes

Outcome	**High dose dexamethasone (100mg), n=22**	**Low dose dexamethasone (10 mg), n=15**
Neurological and functional status - change in bladder function at 3 hours (improved or stable)	n=21/22	n=15/15
Neurological and functional status - change in bladder function at 24 hours (improved or stable)	n=19/22	n=15/15
Neurological and functional status - change in bladder function at 1 week (improved or stable)	n=20/22	n=14/15
Neurological and functional status - ambulation rate (all patients) - 24 hours	n=14/22	n=6/15
Neurological and functional status - ambulation rate (all patients) - 1 week	n=11/20	n=7/13
Neurological and functional status - ambulation rate (patients ambulant at study entry, 1 month)	n=2/6	n=6/9
Neurological and functional status - change in ambulation (improved or stable) - 3 hours	n=21/21	n=13/14
Neurological and functional status - change in ambulation (improved or stable) - 24 hours	n=20/22	n=13/15
Neurological and functional status - change in ambulation (improved or stable) - 1 week	n=14/20	n=11/13
Pain - change in pain score (improved) - 3 hours	n=9/17	n=5/12
Pain - change in pain score (improved) - 24 hours	n=10/17	n=10/13
Pain - change in pain score (improved) - 1 week	n=11/14	n=10/11
Treatment related toxicity - serious adverse effects - any	n=5/9	n=4/11

Outcome	High dose dexamethasone (100mg), n=22	Low dose dexamethasone (10 mg), n=15
Treatment related toxicity - serious drug related adverse effects	n=1/9	n=0/11

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E Forest plots

Forest plots for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

Table 5: Evidence profile for comparison between high dose dexamethasone and no treatment

Quality assessment							No of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose dexamethasone	No treatment	Relative (95% CI)	Absolute	Quality	Importance
Neurological and functional status - ambulation (preservation or restoration of gait, 3 months)												
1 (Sorensen 1994)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	22/27	19/30	RR 1.29 (0.93 to 1.78)	184 more per 1000 (from 44 fewer to 494 more)	MODERATE	CRITICAL
Neurological and functional status - survival with gait function (6 months)												
1 (Sorensen 1994)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	16/27	10/30	RR 1.78 (0.98 to 3.22)	260 more per 1000 (from 7 fewer to 740 more)	MODERATE	CRITICAL
Neurological and functional status - survival with gait function (1 year)												
1 (Sorensen 1994)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/27	6/30	RR 1.48 (0.59 to 3.72)	96 more per 1000 (from 82 fewer to 544 more)	LOW	CRITICAL
Treatment related toxicity – 'significant' side effects												
1 (Sorensen 1994)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/27	0/30	POR 8.93 (0.89 to 89.77)	110 more per 1000 (from 20 fewer to 240 more)	LOW	IMPORTANT
Treatment related toxicity – discontinuation of dexamethasone therapy due to adverse events												

Quality assessment							No of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose dexamethasone	No treatment	Relative (95% CI)	Absolute		
1 (Sorensen 1994)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/27	0/30	POR 8.58 (0.52 to 141.22)	110 more per 1000 (from 8 fewer to 689 more)	LOW	IMPORTANT

CI: confidence interval; NA: not applicable; POR: Peto odds ratio; RD: risk difference; RR: risk ratio
1 95% CI crosses 1 MID
2 95% CI crosses 2 MIDs

Table 6: Evidence profile for comparison between high dose dexamethasone and low dose dexamethasone

Quality assessment							No of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose dexamethasone versus	Low dose dexamethasone	Relative (95% CI)	Absolute		
Neurological and functional status - change in bladder function (improved or stable) - 3 hours												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/22	15/15	RR 0.96 (0.84 to 1.11)	40 fewer per 1000 (from 160 fewer to 110 more)	HIGH	CRITICAL
Neurological and functional status - change in bladder function (improved or stable) - 24 hours												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19/22	15/15	RR 0.88 (0.72 to 1.06)	120 fewer per 1000 (from 280 fewer to 60 more)	MODERATE	CRITICAL
Neurological and functional status - change in bladder function (improved or stable) - 1 week												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/22	14/15	RR 0.97 (0.81 to 1.18)	28 fewer per 1000 (from 177 fewer to 168	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose dexamethasone versus	Low dose dexamethasone	Relative (95% CI)	Absolute	Quality	Importance
										more)		
Neurological and functional status - ambulation rate (all patients) - 24 hours												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	14/22	6/15	RR 1.59 (0.79 to 3.19)	236 more per 1000 (from 84 fewer to 876 more)	LOW	CRITICAL
Neurological and functional status - ambulation rate (all patients) - 1 week												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/20	7/13	RR 1.02 (0.54 to 1.94)	11 more per 1000 (from 248 fewer to 506 more)	LOW	CRITICAL
Neurological and functional status - ambulation rate (patients ambulant at study entry, 1 month)												
1 (Graham 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/6	6/9	RR 0.5 (0.15 to 1.7)	333 fewer per 1000 (from 567 fewer to 467 more)	LOW	CRITICAL
Neurological and functional status - change in ambulation (improved or stable) - 3 hours												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21/21	13/14	RR 1.09 (0.91 to 1.3)	84 more per 1000 (from 84 fewer to 279 more)	MODERATE	CRITICAL
Neurological and functional status - change in ambulation (improved or stable) - 24 hours												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/22	13/15	RR 1.05 (0.83 to 1.33)	43 more per 1000 (from 147 fewer to 286 more)	MODERATE	CRITICAL
Neurological and functional status - change in ambulation (improved or stable) - 1 week												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	14/20	11/13	RR 0.83 (0.57 to 1.2)	144 fewer per 1000 (from 364 fewer to 169 more)	MODERATE	CRITICAL
Pain - change in pain score (improved) - 3 hours												

Quality assessment							No of patients		Effect			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High dose dexamethasone versus**	**Low dose dexamethasone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/17	5/12	RR 1.27 (0.57 to 2.84)	113 more per 1000 (from 179 fewer to 767 more)	LOW	CRITICAL
Pain - change in pain score (improved) - 24 hours												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10/17	10/13	RR 0.76 (0.47 to 1.26)	185 fewer per 1000 (from 408 fewer to 200 more)	LOW	CRITICAL
Pain - change in pain score (improved) - 1 week												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11/14	10/11	RR 0.86 (0.62 to 1.2)	127 fewer per 1000 (from 345 fewer to 182 more)	MODERATE	CRITICAL
Treatment related toxicity - serious adverse effects - any												
1 (Graham 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/9	4/11	RR 1.53 (0.58 to 4.05)	193 more per 1000 (from 153 fewer to 1000 more)	LOW	IMPORTANT
Treatment related toxicity - serious drug related adverse effects												
1 (Graham 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/9	0/11	POR 9.23 (0.18 to 474.33)	110 more per 1000 (from 140 fewer to 360 more)	LOW	IMPORTANT

CI: confidence interval; NA: not applicable; POR: Peto odds ratio; RD: risk difference; RR: risk ratio
1 95% CI crosses 1 MID
2 95% CI crosses 2 MIDs

Appendix G Economic evidence study selection

Study selection for: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

No economic evidence was identified which was applicable to this review question.

Appendix H Economic evidence tables

Economic evidence tables for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

Excluded effectiveness studies

Table 7: Excluded studies and reasons for their exclusion –

Study	Reason for exclusion
Al-Qurainy R and Collis E (2016) Metastatic spinal cord compression: Diagnosis and management. BMJ (Online) 353: i2539	Study design does not match review protocol – expert review/narrative. Checked for relevant studies
Chamberlain, Marc C, Sloan, Andrew, Vrionis, Frank et al. (2005) Systematic review of the diagnosis and management of malignant extradural spine cord compression: The Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. Journal of clinical oncology, 23, 7750-2	Study design does not match review protocol - commentary
Climent, Miguel A., Piulats, Josep M., Sanchez-Hernandez, Alfredo et al. (2012) Recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with metastatic castration-resistant prostate cancer. Critical Reviews in Oncology/Hematology 83(3): 341-352	Other protocol criteria - systematic review, checked for relevant studies
Dy, Sydney M, Asch, Steven M, Naeim, Arash et al. (2008) Evidence-based standards for cancer pain management. Journal of clinical Oncology 26(23): 3879-85	Other protocol criteria - systematic review, checked for relevant studies
George, Reena, Jeba, J., Leng, M. et al. (2007) Interventions for the treatment of metastatic extradural spinal cord compression. Cochrane Database of Systematic Reviews: cd006716	Other protocol criteria - duplicate publication - more recent version available
George, Reena, Jeba, Jenifer, Ramkumar, Govindaraj et al. (2015) Interventions for the treatment of metastatic extradural spinal cord compression in adults. The Cochrane database of systematic reviews: cd006716	Other protocol criteria - systematic review, checked for relevant studies
George, Reena, Jeba, Jenifer, Ramkumar, Govindraj et al. (2008) Interventions for the treatment of metastatic extradural spinal cord compression in adults. The Cochrane database of systematic reviews: cd006716	Other protocol criteria - duplicate publication - more recent version available
Hardy, Janet, Haywood, Alison, Rickett, Kirsty et al. (2021) Practice review: Evidence-based quality use of corticosteroids in the palliative care of	Other protocol criteria - systematic review, checked for relevant studies

Study	Reason for exclusion
patients with advanced cancer. Palliative Medicine 35(3): 461-472	
Haywood, Alison, Good, Phillip, Khan, Sohil et al. (2015) Corticosteroids for the management of cancer-related pain in adults. The Cochrane database of systematic reviews: cd010756	Other protocol criteria - systematic review, checked for relevant studies
Janjan, Nora, Bedwinek, John M., Hartsell, William F. et al. (2009) Therapeutic guidelines for the treatment of bone metastasis: A report from the American college of radiology appropriateness criteria expert panel on radiation oncology. Journal of Palliative Medicine 12(5): 417-426	Study design does not match review protocol – expert review/narrative. Checked for relevant studies
Klimo, Paul Jr; Kestle, John R; Schmidt, Meic H (2003) Treatment of metastatic spinal epidural disease: a review of the literature. Neurosurgical focus 15(5): e1	Other protocol criteria - systematic review, checked for relevant studies
Kumar, Abhishek, Weber, Michael H, Gokaslan, Ziya et al. (2017) Metastatic Spinal Cord Compression and Steroid Treatment: A Systematic Review. Clinical spine surgery 30(4): 156-163	Other protocol criteria - systematic review, checked for relevant studies
L'esperance, S, Vincent, F, Gaudreault, M et al. (2012) Treatment of metastatic spinal cord compression: cepo review and clinical recommendations. Current oncology (Toronto, Ont.) 19(6): e478-90	Other protocol criteria - systematic review, checked for relevant studies
Loblaw, D A and Laperriere, N J (1998) Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. Journal of Clinical Oncology 16, 1613-24	Other protocol criteria - systematic review, checked for relevant studies
Loblaw A, Perry J, Chambers A et al. (2005) Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 23(9): 2028-37	Other protocol criteria - systematic review, checked for relevant studies
Loblaw, D. A. and Laperriere, N. J. (1998) Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. Journal of Clinical Oncology 16: 1613-1624	Other protocol criteria - systematic review, checked for relevant studies
Oh, Daniel Chun-Suk, Rispoli, Leia, Ghosh, Priyanka et al. (2021) Epidural Steroid Injections for the Management of Spinal Malignancy-Related Pain: A Pragmatic Review and Retrospective Study. Pain practice : the official journal of World Institute of Pain 21(3): 285-298	Other protocol criteria - systematic review, checked for relevant studies
Skeoch, Gordon D, Tobin, Matthew K, Khan, Sajeel et al. (2017) Corticosteroid Treatment for	Other protocol criteria - systematic review, checked for relevant studies

Study	Reason for exclusion
Metastatic Spinal Cord Compression: A Review. Global spine journal 7(3): 272-279	
Sorensen, S, Helweg-Larsen, S, Mouridsen, H et al. (1994) Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. European journal of cancer (Oxford, England : 1990) 30a(1): 22-7	Other protocol criteria - duplicate publication

Appendix K Research recommendations

Research recommendations for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

No research recommendations were made for this review question.