<table>
<tr><th colspan="3">Evidence-to-Decision table 5.1.1</th></tr>
<tr><td colspan="3">In adults (including older persons) and adolescents with cancer-related pain are adjuvant steroids more effective than no steroids or placebo to achieve pain control?</td></tr>
<tr><td>POPULATION:</td><td>Adults (including older persons) and adolescents with cancer-related pain</td><td rowspan="8">Background:

Steroids are among the most commonly used medications in palliative care, and are commonly used to relieve cancer pain[76]. There use as adjuvant medications has been indicated for management of metastatic bone pain, neuropathic pain, and visceral pain[77].

Current WHO recommendation:

• Corticosteroids are indicated in the following general cases:
○ To improve appetite
○ To enhance sense of well-being
○ To improve strength
○ Hormone therapy
▪ Replacement
▪ Anticancer
○ To relieve pain caused by
▪ Raised intracranial pressure
▪ Nerve compression
▪ Spinal cord compression
▪ Metastatic arthralgia
▪ Bone metastasis
• Corticosteroids are indicated in the following specific cases:
○ Spinal cord compression
○ Nerve compression
○ Dyspnoea:
▪ Pneumonitis (after radiotherapy)
▪ Carcinomatous lymphangitis
▪ Tracheal compression/stridor
○ Superior vena caval obstruction
○ Pericardial effusion</td></tr>
<tr><td>INTERVENTION:</td><td>Steroids (adjuvant)</td></tr>
<tr><td>COMPARISON:</td><td>Placebo (no treatment)</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>• Pain relief
• Pain relief speed
• Pain relief maintenance
• Quality of life (QoL)
• Functional outcomes
• Gastrointestinal bleed (adverse event)
• Psychiatric effects (adverse event)</td></tr>
<tr><td>STRATIFICATIONS:</td><td>• Age (adults, older persons, adolescents, children)
• History of substance abuse
• Refractory pain</td></tr>
<tr><td>SETTING:</td><td>All</td></tr>
<tr><td>PERSPECTIVE:</td><td>Population</td></tr>
</table>

		○ Haemoptysis ○ Obstruction of hollow viscus ▪ Bronchus ▪ Ureter ▪ Intestine ○ Hypercalcaemia (in lymphoma, myeloma) ○ Radiation-induced inflammation ○ Leukoerythroblastic anaemia ○ Rectal discharge (give per rectum) ○ Sweating • Either prednisolone or dexamethasone are recommended, the dose depending on clinical situation. 7mg of prednisolone is equivalent to 1mg of dexamethasone. • For nerve compression pain, prescribe 20-40mg prednisolone/4-6mg of dexamethasone per day. Reduce dose step by step to a maintenance dose after one week. The maintenance dose will depend on the amount necessary to relieve pain, but could be as low as 15mg prednisolone or 2mg dexamethasone. Occasionally, a higher dose may be necessary to achieve significant benefit. • In patients with raised intracranial pressure, an initial daily dose of 8-16mg dexamethasone is appropriate. It may be possible to begin to reduce this to a maintenance dose after one week. With spinal cord compression, even higher doses have been used in some centres – up to 100mg per day initially, reducing to 16mg during radiation therapy. • Adverse events include oedema, dyspeptic symptoms, and occasionally gastrointestinal bleeding. Proximal myopathy, agitation, hypomania, and opportunistic infections may also occur. The incidence of adverse gastrointestinal effects is increased if corticosteroids are used in conjunction with NSAIDs.

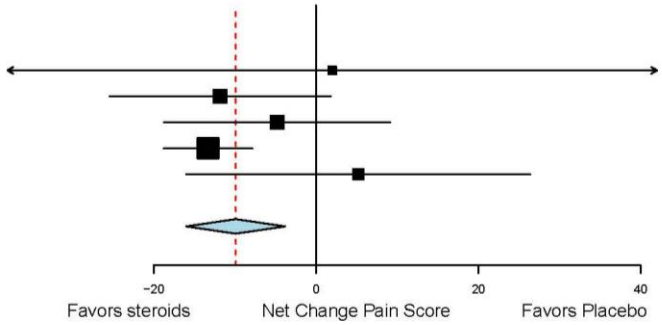
	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	**Research Evidence** Steroids are among the most commonly used medications in palliative care, and are commonly used to relieve cancer pain[76]. **Additional considerations** The 1996 WHO cancer pain guidelines made recommendations on their use – so too should updated guidelines, which can make use of any evidence developed since the formulation of the previous guidelines.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes No Uncertain Yes	• **Seven randomized controlled trials** compared steroids to placebo in patients with a variety of cancers; although most studies did not report the cancer types. The studies evaluated methylprednisolone (4 trials), dexamethasone (2 trials), and prednisolone (1 trial). Trials were mostly conducted in adults with a wide age range; one was conducted in older adults. The GDG was of the view that none of the trials were of high enough power to accurately capture rates of adverse events from the therapy. **BENEFITS and HARMS** • **Five trials** provided **moderate strength of evidence** that **pain relief was greater in patients taking steroids than placebo**. The summary net difference in pain scores between arms was -9.9 (on a 0 to 100 [worst] scale), 95% CI -16.0 to -3.8, favoring steroids. • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **Three trials** provided **low strength of evidence** that **patients taking steroids had improved QoL compared to placebo**, with a summary net difference (on a 0 to 100 [best] scale) of 12.6 (95% CI 6.2, 19.0). • **Two trials** provided **low strength of evidence** regarding functional outcomes, using FACT and FACIT, suggesting **no difference in functional score** (net difference -0.2; 95% CI -2.0, 1.6) or **social function** (net difference -0.2; 95% CI -2.4, 1.9), both on 0 to 100 scales. The two studies had **conflicting findings regarding physical function**, with one study finding significant benefit with steroids on the FACIT scale, but the other presenting data that suggested statistically significant worse physical function with steroids on the FACT scale (however, the study implied that they found no significant difference). • **One trial** provided **very low strength of evidence** regarding gastrointestinal bleeds, being the only study to explicitly report this adverse event. **No gastrointestinal bleeds occurred** among 31 patients in this crossover study. • **Two trials** reported on psychiatric adverse events. **One provided very low strength of evidence regarding depression**, failing to provide a precise estimate (RR = 1.00; 95% CI 0.06, 15.2). **One provided very low strength of evidence regarding both anxiety and "psychic change"** (undefined), also failing to provide precise estimates (both RR = 0.59; 95% CI 0.11, 3.20). No study reported on delirium or psychosis. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY**

Steroids probably improve pain relief and may improve QoL. We are uncertain whether in this population steroids increase risks of gastrointestinal bleeds or psychiatric adverse events.

Forest Plot 5.1.1. Pain Relief (Continuous Scale) Steroids vs. Placebo

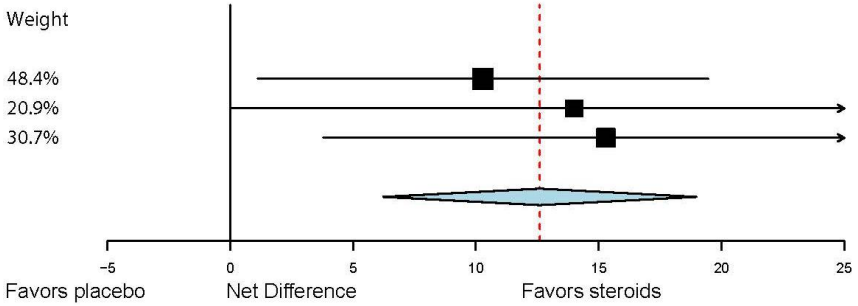
Studies	Estimate (95% C.I.)	Weight
Bruera 2004	2.00 (−38.00, 42.00)	2.28%
Yennurajalingam 2013	−11.80 (−25.44, 1.84)	16.8%
Paulsen 2014	−4.80 (−18.75, 9.15)	16.2%
Bruera 1985	−13.30 (−18.77, −7.83)	57.0%
Twycross 1985	5.20 (−16.00, 26.40)	7.69%
Overall (I^2=16.13%, P=0.39)	−9.90 (−16.01, −3.79)	



***Abbreviation**: **CI**: confidence interval.*

BENEFITS & HARMS (CONT.)

Forest Plot 5.1.1. Quality of Life (Continuous Scale) Steroids vs. Placebo



Scores from individual studies have been transformed to a uniform 0-100 scale (100 = best).

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability Yes Minor variability Uncertain **Is the option acceptable to key stakeholders?** Yes No Uncertain Yes	**Research evidence** None presented. **Additional considerations** The GDG remarked that patients, especially young patients, are sometimes reluctant to take the medications due to their common side effects. Older patients are also sometimes reluctant on account of diabetes and other comorbidities. The GDG deemed the option acceptable to clinicians, who frequently appreciate the speed of onset of steroids' beneficial effects.

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major	Minor	Uncertai
Yes		

Is the option feasible to implement?

Yes	No	Uncertain
Yes		

	Price per 1mg	Defined daily dose
Dexamethasone (Source:[78])	USD $ 0.02475	1.5mg
Prednisolone (Source:[79])	USD $ 0.00222	10mg
Methylprednisolone (Source:[80])	USD $ 0.0104	20mg

Additional considerations

The resource requirements are evidently small.

The GDG deemed the option feasible.

Would the option improve equity in health?

Yes	No	Uncertai
		Yes

Research Evidence

None

Additional considerations

The GDG did not believe the therapy would have much impact on equity.

Recommendation	**Current recommendation:**
	Corticosteroids are indicated in the following general cases:
	
	• To improve appetite
	• To enhance sense of well-being
	• To improve strength
	• Hormone therapy
	  o Replacement
	  o Anticancer
	• To relieve pain caused by
	  o Raised intracranial pressure
	  o Nerve compression
	  o Spinal cord compression
	  o Metastatic arthralgia
	  o Bone metastasis
	Corticosteroids are indicated in the following specific cases:
	
	• Spinal cord compression
	• Nerve compression
	• Dyspnoea:
	  o Pneumonitis (after radiotherapy)
	  o Carcinomatous lymphangitis
	  o Tracheal compression/stridor
	• Superior vena caval obstruction
	• Pericardial effusion
	• Haemoptysis
	• Obstruction of hollow viscus
	  o Bronchus
	  o Ureter
	  o Intestine
	• Hypercalcaemia (in lymphoma, myeloma)
	• Radiation-induced inflammation
	• Leukoerythroblastic anaemia

	• Rectal discharge (give per rectum) • Sweating Either prednisolone or dexamethasone are recommended, the dose depending on clinical situation. 7mg of prednisolone is equivalent to 1mg of dexamethasone. For nerve compression pain, prescribe 20-40mg prednisolone/4-6mg of dexamethasone per day. Reduce dose step by step to a maintenance dose after one week. The maintenance dose will depend on the amount necessary to relieve pain, but could be as low as 15mg prednisolone or 2mg dexamethasone. Occasionally, a higher dose may be necessary to achieve significant benefit. In patients with raised intracranial pressure, an initial daily dose of 8-16mg dexamethasone is appropriate. It may be possible to begin to reduce this to a maintenance dose after one week. With spinal cord compression, even higher doses have been used in some centres – up to 100mg per day initially, reducing to 16mg during radiation therapy. Adverse events include oedema, dyspeptic symptoms, and occasionally gastrointestinal bleeding. Proximal myopathy, agitation, hypomania, and opportunistic infections may also occur. The incidence of adverse gastrointestinal effects is increased if corticosteroids are used in conjunction with NSAIDs. **New (draft) recommendation:** In adults (including older persons) and adolescents, with pain related to active cancer, adjuvant steroids should be given to achieve pain control, based on clinical indications.
Strength of Recommendation	**Strong**
Quality of Evidence	➢ **MODERATE** [Pain (critical) = moderate QoL (important) = low others omitted for no data, conflicting, no difference, or indeterminate findings]

Justification	The GDG noted that while some side effect and adverse events from steroids can be serious, the balance of effects is evidently strongly in favour of their use when indicated. Care should be taken with regard to patient selection for the prescription of steroids to avoid contraindications. The GDG also agreed that in the text of the guidelines, in line with good clinical practice, the steroids should only be prescribed for as short a period as possible.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	