

Evidence-to-Decision table 5.2.5

In adults (including older persons) and adolescents with bone metastases, what is the evidence for the use of monoclonal antibodies (monoclonals) compared to bisphosphonates to prevent and treat pain?

POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	<p>Background:</p> <p>Bone pain is the most common type of pain from cancer and is present in approximately one out of three patients with bone metastases.^{129,139} The pain is commonly a mixture of background pain and incident/episodic pain, which is commonly associated with weight bearing or movement.¹³⁰ Bone metastases can weaken bone sufficiently to greatly increase patients' risk of fracture.</p> <p>Bisphosphonates and monoclonal antibodies are two classes of medication reported to relieve bone pain in cancer patients.</p> <p>Bisphosphonates inhibit osteoclasts, and their use in cancer patients prevents the elevated bone resorption common in metastatic bone disease. They thus reduce complications or skeletal related events (SREs), and reduce bone pain and analgesic requirements.¹³¹</p> <p>There are reports that monoclonal antibodies designed to target Nerve Growth Factor (NGF) and osteoclasts reduce pain scores in patients with metastatic bone pain¹⁴¹ or fracture risk¹⁴².</p> <p>Current WHO recommendation: None</p>
INTERVENTION:	Monoclonals	
COMPARISON:	Bisphosphonates	
MAIN OUTCOMES:	<ul style="list-style-type: none"> • Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Skeletal-related events • Osteonecrosis of the jaw (adverse event) 	
STRATIFICATIONS:	<ul style="list-style-type: none"> • Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain 	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	<p>Is the problem a priority? Yes</p>	<p><u>Research evidence</u> None</p> <p><u>Additional considerations</u> WHO does not have recommendations for treating bone pain and should investigate the various methods by which it might be treated, including both bisphosphonates and monoclonal antibodies.</p>

Do the desirable effects outweigh the undesirable effects?

Yes No Uncertain

- **No randomized controlled trials** compared monoclonals to bisphosphonates in patients with metastatic bone lesions, mostly from breast or prostate cancer, but also non-small cell lung cancer, multiple myeloma, and other cancers; although most studies did not report the cancer types. All evaluated the monoclonal denosumab; most evaluated zoledronate, but also pamidronate, or a variety of bisphosphonates (based on local practice). Patient ages varied widely across trials.

BENEFITS and HARMS

- **One trial** provided **low strength of evidence** that **there was no difference between monoclonals (denosumab) and bisphosphonates (zoledronate) in the percentage of people who had decreases in their pain scores** of at least 2 (of 10) points (RR = 0.89; 95% CI 0.67, 1.10); the trial did not evaluate complete pain relief.
- **One trial** provided **low strength of evidence** that found **no difference between monoclonals (denosumab) and bisphosphonates (zoledronate) in average time until this pain outcome was reached** (2.7 vs. 2.6 months).
- **No trial** reported on **pain relief maintenance**.
- **Six trials** provide **high strength of evidence favoring monoclonals over bisphosphonates to prevent any skeletal-related events** (summary RR = 0.86; 95% CI 0.81, 0.91).
- **Two trials** provided **high strength of evidence favoring monoclonals over bisphosphonates to prevent fractures** (summary RR = 0.88; 95% CI 0.78, 0.96).
- **One trial** provided **moderate strength of evidence favoring monoclonals over bisphosphonates to prevent spinal cord compression** (summary RR = 0.88; 95% CI 0.65, 1.20).
- **Two trials** provided **high strength of evidence favoring monoclonals over bisphosphonates to prevent bone radiation therapy** (summary RR = 0.80; 95% CI 0.73, 0.88).
- **One trial** provided **moderate strength of evidence favoring monoclonals over bisphosphonates to prevent bone surgery** (summary RR = 0.87; 95% CI 0.62, 1.23).
- **Two trials** provided **high strength of evidence favoring monoclonals over bisphosphonates to prevent hypercalcemia** (summary RR = 0.58; 95% CI 0.34, 0.81).
- **One trial** provided **very low strength of evidence** regarding **QoL**. As assessed by an improvement of at least 5 (of 108) points in FACT-G (Functional Assessment of Cancer Therapy–General, RR = 1.08; 95% CI 0.95, 1.23). We are uncertain of any difference.
- **Two trials** provided **low strength of evidence** regarding **functional outcomes, favoring monoclonals (denosumab) over bisphosphonates (zoledronate): time to increase (worsening) in interference due to pain (16 vs 14.9 months) and ECOG performance status** (RR = 1.07 [95% CI 0.99, 1.16]).
- **Three trials** provide **high strength of evidence** that **the risk of osteonecrosis of the jaw was more common with monoclonals than bisphosphonates**, with a summary RR = 1.40 (95% CI 0.92, 2.13).

STRATIFICATIONS

		<ul style="list-style-type: none">• 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 regarding refractory pain. <p>SUMMARY</p> <p>Monoclonals reduce the risk of skeletal-related events and may improve functional outcomes more than bisphosphonates, but increase the risk of osteonecrosis of the jaw. The choice of monoclonals or bisphosphonates may make little or no difference to bone pain, or time to pain relief.</p>
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ACCEPTABILITY & PREFERENCES	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Major variability <input checked="" type="checkbox"/> Yes</p> <p>Minor variability <input type="checkbox"/></p> <p>Uncertain <input type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	<p>Research evidence None</p> <p>Additional considerations Monoclonal antibody regimens involve a lower medication-administration burden than bisphosphonates, which patients would prefer. But they also have a higher cost, which patients would <u>not</u> prefer. Osteonecrosis of the jaw (higher with monoclonal antibodies) is an outcome sufficiently adverse that the GDG believe it could affect patient preferences, but its expected disutility to patients must be weighed against the expected disutility of skeletal-related events (higher with bisphosphonates).</p> <p>The therapies were both deemed acceptable to clinicians and other key stakeholders.</p>
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FEASIBILITY / RESOURCE USE	<p>How large are the resource requirements?</p> <p>Major <input checked="" type="checkbox"/> Minor <input type="checkbox"/> Uncertain <input type="checkbox"/></p>	<p style="text-align: center;">Price (USD) per vial or tablet</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;"><u>Medication</u></th> <th style="text-align: center;"><u>International Medical Products Price Guide, Median price*</u></th> <th style="text-align: center;"><u>Drugs.com*</u></th> <th style="text-align: center;"><u>Pharmacy checker.com*</u></th> <th style="text-align: center;"><u>Goodrx.com*</u></th> <th style="text-align: center;"><u>Green et al. 2010¹⁵¹</u></th> </tr> </thead> <tbody> <tr> <td>Zoledronate (4mg/5ml IV solution, 5ml)</td> <td style="text-align: center;">\$ 23.4501</td> <td style="text-align: center;">\$ 45.52</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Clodronate (800mg)</td> <td style="text-align: center;">Not present</td> <td style="text-align: center;">NA</td> <td style="text-align: center;">\$ 3.87</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Ibandronate (3mg/3mL IV solution, 3ml)</td> <td style="text-align: center;">Not present</td> <td style="text-align: center;">\$ 218.56</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Pamidronate (3mg/ml IV solution, 10ml)</td> <td style="text-align: center;">Not present</td> <td style="text-align: center;">\$ 20.16</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Etidronate (200mg oral tablet)</td> <td style="text-align: center;">Not present</td> <td style="text-align: center;">\$ 3.17</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Risendronate (35mg tablet)</td> <td style="text-align: center;">Not present</td> <td style="text-align: center;">\$ 38.75</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Denosumab (60mg/ml, 1ml syringe)</td> <td style="text-align: center;">Not present</td> <td style="text-align: center;">Not present</td> <td style="text-align: center;">\$ 553.68</td> <td style="text-align: center;">\$1121.15</td> <td style="text-align: center;">\$990.00</td> </tr> </tbody> </table>					<u>Medication</u>	<u>International Medical Products Price Guide, Median price*</u>	<u>Drugs.com*</u>	<u>Pharmacy checker.com*</u>	<u>Goodrx.com*</u>	<u>Green et al. 2010¹⁵¹</u>	Zoledronate (4mg/5ml IV solution, 5ml)	\$ 23.4501	\$ 45.52	-	-	-	Clodronate (800mg)	Not present	NA	\$ 3.87	-	-	Ibandronate (3mg/3mL IV solution, 3ml)	Not present	\$ 218.56	-	-	-	Pamidronate (3mg/ml IV solution, 10ml)	Not present	\$ 20.16	-	-	-	Etidronate (200mg oral tablet)	Not present	\$ 3.17	-	-	-	Risendronate (35mg tablet)	Not present	\$ 38.75	-	-	-	Denosumab (60mg/ml, 1ml syringe)	Not present	Not present	\$ 553.68	\$1121.15	\$990.00
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	<p>Is the option feasible to implement?</p> <p>Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Uncertain <input type="checkbox"/></p>	<p>*All accessed 16th January 2018. Prices reported here are the lowest prices reported at the sources.</p>																																																				
<p>Would the option improve equity in health?</p> <p>Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Uncertain <input type="checkbox"/></p>	<p>Research evidence None</p> <p>Additional considerations There is a major equity issue with the recommendation of denosumab.</p>																																																					

Recommendation	<p>Current recommendation: None</p> <p>New (draft) recommendation: None</p>
Strength of Recommendation	None
Quality of Evidence	<p>➤ MODERATE/LOW [Pain (critical) = low Skeletal related events (important) = high (any, fracture, bone radiation therapy, hypercalcemia), moderate (spinal cord compression, bone surgery) Functional outcomes (important) = moderate Osteonecrosis of the jaw (important) = high]</p>
Justification	<p>Monoclonals reduce the risk of skeletal-related events and may improve functional outcomes more than bisphosphonates, but increase the risk of osteonecrosis of the jaw. The choice of monoclonals or bisphosphonates may make little or no difference to bone pain, or time to pain relief. Although there are relative benefits to the use of denosumab compared with bisphosphonates, the relative cost of denosumab is disproportionate to the benefits. The GDG felt that they could not recommend one medication over the other on these grounds.</p>
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	