

Evidence-to-Decision table 5.2.2

In adults (including older persons) and adolescents with bone metastases, what is the evidence for the use of bisphosphonates compared to other bisphosphonates in order 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 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.^{131,132}</p> <p>Current WHO recommendation:</p> <ul style="list-style-type: none"> • The WHO 1996 cancer pain relief guidelines do not address the use of bisphosphonates. There are no GRC approved guidelines on the use of bisphosphonates for pain relief. • Zoledronic acid was added to the WHO Model list of essential medicines for adults in 2017. • 5.2.1 recommends that bisphosphonates be administered over placebo. This question is concerned about choice of bisphosphonate.
INTERVENTION:	Bisphosphonates	
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	Is the problem a priority?	<p><u>Research Evidence</u> None</p> <p><u>Additional considerations</u> Bisphosphonates are commonly used in for pain relief in clinical practice. Yet WHO does not have guidance on their use.</p>

Do the desirable effects outweigh the undesirable effects?

Yes
 No
 Uncertain

 Yes

- **Seven randomized controlled trials** compared different bisphosphonates in patients with various cancers with bone metastases—mostly breast, prostate, and non-small cell lung cancer. The trials evaluated **clodronate, ibandronate, pamidronate, and zoledronate**. Trial participants were generally older, with mean ages ranging from 53 to 73 years old.

BENEFITS and HARMS

- **One trial** provided **low evidence** reported **no difference in average or worst pain between different bisphosphonates** (between group differences -2.6 [95% CI -11.8, 6.6] and -0.1 [95% CI -9.3, 9.1], respectively), and in percentage of people who achieve pain relief (by at least 50%) (RR = 1.38 [95% CI 0.55, 3.49]).
- **No trial** reported on **pain relief speed**.
- **Two trials** provided **very low strength of evidence regarding duration of pain relief**. One study found no difference in average duration of pain relief in patients with a variety of cancers (about half with lung cancer) between ibandronate (5.5 months) and pamidronate (5.2 months). One trial reported that in patients with prostate cancer those taking clodronate had longer duration of pain relief (13 months) than those taking zoledronate (9 months, P=0.03).
- **No trial** reported on **QoL**.
- **No trial** reported on **functional outcomes**.
- **Six trials** provided **very low strength of evidence** that **skeletal-related events were similar across bisphosphonates** (18-26%, no data on pamidronate).
- **Four trials** provided **very low strength of evidence** that **fracture rates were similar between bisphosphonates**, except in one trial of people with breast cancer in which 16% of those taking clodronate had fractures compared with 7% taking pamidronate (P=0.03).
- **Three trials** provided **very low strength of evidence** of **no significant differences in rates of spinal cord compression across bisphosphonates**.
- **Two trials** provided **very low strength of evidence** of **no significant differences in rates of bone radiotherapy across bisphosphonates**.
- **Three trials** provided **very low strength of evidence** of **no significant differences in rates of bone surgery across bisphosphonates**.
- **Three trials** provided **very low strength of evidence** of **rare rates of osteonecrosis of the jaw for clodronate (1.5%), ibandronate (0.7%), and zoledronate (1.2%)**; ibandronate vs. zoledronate (2 studies; RR = 0.52; 95% CI 0.19, 1.45); clodronate vs. zoledronate (1 study; RR = 3.09; 95% CI 0.12, 77.2).

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 regarding refractory pain.

SUMMARY

The choice of bisphosphonate may make little or no difference in bone pain relief. We are uncertain whether there are differences in effects of different bisphosphonates on other outcomes.

ACCEPTABILITY & PREFERENCES	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Major variability <input type="checkbox"/></p> <p>Minor variability <input checked="" type="checkbox"/> Yes</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><u>Research evidence</u> None</p> <p><u>Additional considerations</u> The GDG did not think patients would have major reasons to prefer one bisphosphonate to another and thought there would only be minor variability.</p> <p>Clinicians might differ in their preferences for use of certain bisphosphonates, since there is evidence of differences in renal adverse effects and therefore the degree to which renal pathologies are considered to be contraindications.¹⁴⁰ This being the case, the options were all nevertheless considered acceptable to key stakeholders.</p>
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FEASIBILITY / RESOURCE USE	<p>How large are the resource requirements?</p> <p>Major <input type="checkbox"/> Yes Minor <input type="checkbox"/> Uncertain <input type="checkbox"/></p> <p>Is the option feasible to implement?</p> <p>Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain <input checked="" type="checkbox"/> Yes</p>	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2" style="text-align: left; vertical-align: bottom;">Medication</th> <th colspan="3" style="text-align: center;">Price (USD) per vial or tablet</th> </tr> <tr> <th style="text-align: center;">International Products Price Guide, Median price</th> <th style="text-align: center;">Medical Price Guide, Drugs.com</th> <th style="text-align: center;">Pharmacychecker.com</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> </tr> <tr> <td>Clodronate (800mg)</td> <td style="text-align: center;">NA</td> <td style="text-align: center;">NA</td> <td style="text-align: center;">\$ 3.87</td> </tr> <tr> <td>Ibandronate (3mg/3mL IV solution, 3ml)</td> <td style="text-align: center;">NA</td> <td style="text-align: center;">\$ 218.56</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Pamidronate (3mg/ml IV solution, 10ml)</td> <td style="text-align: center;">NA</td> <td style="text-align: center;">\$ 20.16</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Etidronate (200mg oral tablet)</td> <td style="text-align: center;">NA</td> <td style="text-align: center;">\$ 3.17</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Risendronate (35mg tablet)</td> <td style="text-align: center;">NA</td> <td style="text-align: center;">\$ 38.75</td> <td style="text-align: center;">-</td> </tr> </tbody> </table> <ul style="list-style-type: none"> The GDG recognized the high costs of bisphosphonate medications. Most of the RCTs were conducted with intermittent intravenous administration. Using this method could be considered as a potential feasibility issue according to the GDG. 	Medication	Price (USD) per vial or tablet			International Products Price Guide, Median price	Medical Price Guide, Drugs.com	Pharmacychecker.com	Zoledronate (4mg/5ml IV solution, 5ml)	\$ 23.4501	\$ 45.52	-	Clodronate (800mg)	NA	NA	\$ 3.87	Ibandronate (3mg/3mL IV solution, 3ml)	NA	\$ 218.56	-	Pamidronate (3mg/ml IV solution, 10ml)	NA	\$ 20.16	-	Etidronate (200mg oral tablet)	NA	\$ 3.17	-	Risendronate (35mg tablet)	NA	\$ 38.75	-
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<p>Would the option improve equity in health?</p> <p>Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain <input checked="" type="checkbox"/> Yes</p>	<p>Research Evidence</p> <p>The use of bisphosphonates in populations of older women with osteoporosis and in breast cancer patients with bone metastases has been deemed cost-saving or cost effective (depending on population) in a number of high income countries.¹³³⁻¹³⁵ It remains to be seen whether these savings would apply to lower income settings.</p> <p>Additional considerations</p> <p>Bisphosphonates are expensive throughout the world. In most settings, their use is often prohibitively expensive.</p> <p>Combining these considerations, the GDG felt that equity could be affected in either direction, and therefore opted for uncertainty in this regard.</p>																																

Recommendation	Current recommendation: None
	New (draft) recommendation: None

Strength of Recommendation	None
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Quality of Evidence	➤ VERY LOW [Pain (critical) = low Pain reduction maintenance (critical) = very low Skeletal-related events (important) = very low (any, fracture, spinal cord compression, bone radiation therapy, bone surgery, hypercalcemia) Osteonecrosis of jaw (important) = low other outcomes omitted for no data]
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Justification	The GDG did not feel the evidence permitted recommending one bisphosphonate over another.
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Subgroup considerations

Implementation considerations
[incl. M&E]

Research priorities
