

Evidence-to-Decision table 5.2.1

In adults (including older persons) and adolescents with bone metastases, what is the evidence for the use of bisphosphonates compared no treatment 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 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.
INTERVENTION:	Bisphosphonates	
COMPARISON:	Placebo (no treatment)	
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> 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

- **Forty randomized controlled trials** compared bisphosphonates to placebo. Most trial participants had either breast or prostate cancer. Fifteen of the trials were restricted to people (women or men) with breast cancer (or included mostly people with breast cancer). Ten trials were restricted to men with prostate cancer. The third most common cancer across studies was lung cancer. Thirteen trials evaluated clodronate, nine zoledronate, five each ibandronate and pamidronate, and one each etidronate and risendronate.

BENEFITS and HARMS

- **Three trials** provided **moderate strength of evidence favoring use of bisphosphonates to provide bone pain relief**; RR = 1.61 (95% CI 0.89, 2.93)
Four trials provided **moderate strength of evidence favoring use of bisphosphonates to improve bone pain**; RR = 1.24 (95% CI 0.90, 1.71).
Fourteen trials provided **moderate strength of evidence** when evaluating pain on continuous scales (which were each converted to a 100 point scale, with 100 = worst pain). The studies, overall, **indicated decrease in pain with bisphosphonates**, with an overall net difference of -11.8 (95% CI -17.6, -6.1).
- **No trial** reported on **pain relief speed**.
- **One trial** provided **low strength of evidence** suggesting **no difference in duration of pain relief** between risendronate and placebo in people with prostate cancer (HR = 1.27; 95% CI 0.84, 1.92), nominally favoring placebo (3.4 month median duration with risendronate, 5.5 months with placebo).
- **Five studies** provide **moderate strength of evidence** that **bisphosphonates improve QoL compared with placebo**. One provided moderate strength of evidence of reduced and delayed deterioration in quality of life with clodronate (RR = 0.81; 95% CI 0.67, 0.99 and HR = 0.71; 95% CI 0.56, 0.92). The five trials, overall, provided very low strength of evidence of no significant difference in changes in quality of life scores measured on a variety of scales (summary net difference on a 0 to 100 [best] scale = 8; 95% CI -6, 22).
- **Two trials** provided **very low to low strength of evidence in functional outcomes favoring bisphosphonates**. One trial each found net differences (all transformed to 100 point scale where 100 = best score) in ECOG performance status of -7.7 (95% CI -17.0, 1.7), in FACT-P physical well-being of 1.4 (95% CI 0.5, 3.3), in FACT-P social well-being of 1.8 (95% CI 1.0, 2.6), and in FACT-P functional well-being of 1.8 (95% CI 0.6, 2.9).
- **Twenty trials** provided **moderate strength of evidence** that **bisphosphonates reduce the risk of any skeletal-related events**; 18 of these trials yielded a summary RR of 0.81 (95% CI 0.76, 0.86). Six trials provided moderate strength of evidence of that reported hazard ratios for time to first skeletal-related event (any) in comparisons of zoledronate (4 studies) or ibandronate (2 studies) found a statistically significant benefit of bisphosphonates over placebo (HR = 0.71; 95% CI 0.61, 0.84).
- **Twelve trials** provided **moderate strength of evidence** of **reduction in risk of fracture with bisphosphonates** (RR = 0.75; 95% CI 0.67, 0.84).

- **Eight trials** provided **moderate strength of evidence** nominally **favoring bisphosphonates to reduce the risk of spinal cord compressions** (RR = 0.74; 95% CI 0.49, 1.12). The three zoledronate trials together found a statistically significant reduction in risk of spinal cord compression (RR = 0.52; 95% CI 0.27, 0.99), but this result was not significantly different than the nonsignificant summary of the pamidronate studies (RR = 1.07; 95% CI 0.60, 1.90; P=0.72 between studies of different medications).
- **Twelve trials** provided **moderate strength of evidence** that the risk of **bone radiotherapy was significantly reduced risk with bisphosphonates** (RR = 0.71; 95% CI 0.63, 0.81).
- **Nine trials** provided **moderate strength of evidence** of a **significantly reduced risk of bone surgeries with bisphosphonates** (RR = 0.62; 95% CI 0.44, 0.89). A significantly greater risk reduction was found in the four studies of pamidronate (RR = 0.53; 95% CI 0.39, 0.74) than the two studies of zoledronate (RR = 1.23; 95% CI 0.60, 2.51; P=0.042 between studies of different medications).
- **Thirteen trials** provided **moderate strength of evidence** of **reduced risk of hypercalcemia with bisphosphonates compared to placebo** (RR = 0.47; 95% CI 0.37, 0.60). The trials of zoledronate (RR = 0.30; 95% CI 0.12, 0.74) and pamidronate (RR = 0.41; 95% CI 0.29, 0.57) showed a nominally stronger effect on hypercalcemia than trials of clodronate (RR = 0.65; 95% CI 0.43, 0.96), but the differences among studies of different medications were not statistically significant (P=0.072).
- **Four trials** provided **low strength of evidence** and **reported on the risk of osteonecrosis of the jaw**. Across the trials, there were no occurrences of this adverse event with either bisphosphonates (N=460) or placebo (N=450).

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

Bisphosphonates probably reduce bone pain and the risk of skeletal-related events and improve QoL. They may improve functional outcomes, but may make little or no difference to duration of pain relief. Rates of osteonecrosis of the jaw may be rare with bisphosphonates.

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 presented.</p> <p><u>Additional considerations</u> The GDG believed that most patients would prefer bisphosphonates over placebo.</p> <p>The GDG deemed bisphosphonates acceptable to clinicians.</p>
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FEASIBILITY / RESOURCE USE	<p>How large are the resource requirements?</p> <p>Major <input type="checkbox"/> Minor <input type="checkbox"/> Uncertain <input type="checkbox"/></p> <p>Yes <input type="checkbox"/> No <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 type="checkbox"/></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. Almost all 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"/></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	<p>Current recommendation: None</p> <p>New (draft) recommendation: In adults (including older persons) and adolescents with bone metastases, a bisphosphonate should be used to prevent and treat bone pain.</p>
Strength of Recommendation	Strong
Quality of Evidence	<p>➤ MODERATE [Pain (critical) = moderate Pain reduction maintenance (critical) = low QoL (critical) = very low (continuous), moderate (categorical) Skeletal-related events (important) = moderate (any, fracture, spinal cord compression, radiotherapy, bone surgery, hypercalcemia) Functional outcomes (important) = low, very low (physical, social, functional) Osteonecrosis of jaw (important) = low others omitted for no data or indeterminate findings]</p>
Justification	<p>The GDG felt that the balance of effect fell strongly in favour of prescribing bisphosphonates to appropriate populations. Osteonecrosis of the mandible, considered a serious adverse event, was deemed sufficiently rare (no cases were observed in the eligible trials) that the expected benefits outweighed the risks of harm. Consideration was given to the issue that administration of the bisphosphonates should be IV, but this was not deemed to be a significant enough barrier to administration that the strength of the recommendation should be attenuated.</p>
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	