



The Differential Diagnosis of Opioid Poorly-Responsive Cancer Pain  
Robert Arnold, MD and Tamara Sacks, MD

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**Case:** Mrs. Smith is a 52-year-old woman with metastatic lung cancer diagnosed two months ago when she developed chest wall and right arm pain. Since then she has seen her primary care physician, an oncologist, and a palliative medicine physician. Her opiate dose was escalated from nothing to 200 micrograms of fentanyl without any pain relief. She was admitted to the hospital two days ago for uncontrolled pain and placed on a hydromorphone PCA. She is currently using 10mg/hr (continuous and bolus), still rates her pain as a 10 out of 10, and has developed nausea.

She describes her pain as a throbbing of the right chest wall and numbness, burning, and tingling down her right arm. Her physical exam is consistent with a lower brachial plexopathy. Her radiographic studies reveal metastases to the sternum and ribs and a right upper lobe mass invading the brachial plexus.

Given the patient is currently using almost 5 grams of oral morphine equivalents a day with no relief and probable opioid induced nausea, what is the next step?

**Discussion:** While cancer pain can be relieved in 80-90% of patients using the WHO analgesic ladder, this case raises the question of what should be done when a patient's pain is uncontrolled even on very high opiate doses. In this discussion, we will assume the pain is caused by tumor rather than distress from psychological causes (delirium, anxiety, addiction) or spiritual/existential suffering.

A key question is whether the patient has ever been responsive to opiates for this condition. If the answer is yes, the increased pain should lead to a search for a worsening of the underlying disease or a new cause of pain. Prior to concluding that a patient's pain is not opioid responsive, one needs to make sure that the patient has had an adequate trial. The dose should be increased until the patient has pain relief or unacceptable toxicities develop. Aggressively treating the opiate's side effects may improve the analgesic window. Control of the patient's vomiting, hyperalgesia, myoclonus, delirium or drowsiness may make it possible to increase the opiate dose to an effective level. In addition, a Cochrane review suggests that rotating from one opiate to another may help decrease side effects and widen the therapeutic window. In addition, recent studies have shown that for patients with opioid responsive pain and uncontrolled side effects, an epidural pump leads to better pain management and is cost-effective.

If analgesia is still ineffective, one can add a drug that produces independent analgesic effects. For example, this patient seems to have both bone and neuropathic pain syndromes. The former may respond to steroids, non-steroidals, or biphosphonates, the latter to topical lidocaine, antidepressant, or antiepileptic drugs. While the strongest evidence supports tri-cyclic antidepressants, gabapentin, and serotonergic neuroepinephrine reuptake inhibitors for the treatment of neuropathic pain, one may have to try five or six agents (including agents such as clonidine, intravenous lidocaine, or mexelitine) to get a significant decrease in pain. A combination of these may also be needed. One should systematically add a co-analgesic and increase the dose until the maximal dose, pain relief, or intolerable side effects occur. A medication should be continued if it results in at least a 50% decrease in pain.

One should also consider non-pharmacological analgesic interventions. Acupuncture and behavioral interventions have been shown to help with pain syndromes. Radiation to the patient's sternum and ribs may help with bone related pain, while a regional nerve block may help the neuropathic component. In addition radiopharmaceuticals such as samarium, can be considered in patients with pain secondary to diffuse bone metastases.

In very difficult cases, one may need to try and enhance the opiate's analgesic effect. Drugs that antagonize the NMDA receptor, for example, have both direct analgesic effects or may reverse opiate tolerance, resulting in better pain management. The three drugs that are most commonly used are ketamine, methadone, and dextromethorphan. The use of these drugs should only be done with a pain or palliative care consultation.

While opiate unresponsive pain is not that common, it is very frustrating. Systematically approaching the problem will ensure that one develops the best treatment plan.

**References:**

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4. Acknowledgments: We appreciate input from David Weissman who helped us think through and provide part of the algorithm for this article.

For further information please contact the Palliative Care Program at PUH/MUH, 647-7243, beeper 8511,, Shadyside Dept. of Medical Ethics and Palliative Care, 623-3008, beeper 263-9041, Perioperative/ Trauma Pain 647-7243, beeper 7246, UPCI Cancer Pain Service, beeper 644 – 1724, Interventional Pain 784-4000, Magee Women's Hospital, 641-2108, beeper 917-9276, VA Palliative Care Program, 688-6178, beeper 296. For ethics consultations at UPMC Presbyterian-Montefiore, and Children's call 647-5700 or pager 958-3844. With comments about "Case of the Month" call David Barnard at 647-5701.