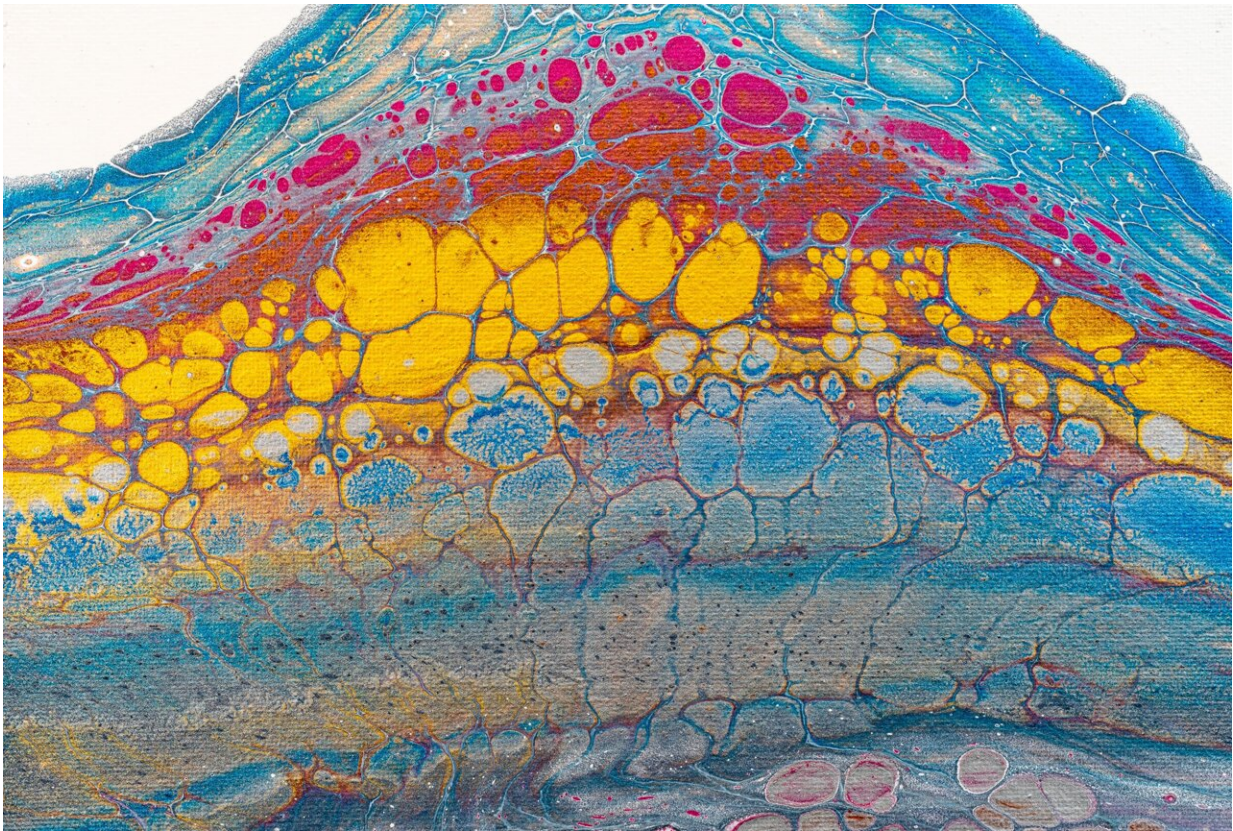


Lorazepam treatment may be linked to worse outcomes for pancreatic cancer patients

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Patients with pancreatic cancer who took the benzodiazepine lorazepam (Ativan), commonly prescribed to treat anxiety during cancer treatment, had a shorter progression-free survival than patients who did not,

according to results published in *Clinical Cancer Research*.

In contrast, patients who took the benzodiazepine alprazolam (Xanax) had a significantly longer progression-free survival than patients who did not.

Benzodiazepines are a class of drugs that suppress the activity of the central nervous system, which can relieve symptoms of anxiety, insomnia, and seizures. Cancer patients are frequently prescribed benzodiazepines to help with such issues resulting from their disease or treatment. However, there is little comprehensive research about how benzodiazepine use may affect cancer outcomes, said Michael Feigin, Ph.D., an associate professor of pharmacology and therapeutics at Roswell Park Comprehensive Cancer Center and senior author of the study.

"When we study response to therapy, we think of treatments like chemotherapy or immunotherapy, but patients are also given a lot of medicines for anxiety and pain," Feigin said. "We wanted to understand the impact of some of these palliative care drugs on the tumor."

Feigin and colleagues first evaluated how many patients take benzodiazepines during [cancer treatment](#). Among patients treated at Roswell Park for prostate, pancreatic, ovarian, kidney, head and neck, endometrial, colon, breast, or brain cancer or melanoma, 30.9% had received benzodiazepines; patients with [pancreatic cancer](#) had the highest rate of benzodiazepine use at 40.6%.

The researchers then examined the relationship between benzodiazepine use and survival in patients with pancreatic cancer. When they adjusted for age, race, sex, disease stage and progression, and treatments received, any benzodiazepine use was associated with a 30% lower risk of pancreatic cancer-related death.

However, when Feigin and colleagues studied the relationship between individual benzodiazepines and pancreatic cancer outcomes, they found stark differences. Apart from short-acting benzodiazepines used as part of surgical anesthesia, the two most commonly used benzodiazepines were lorazepam (40 patients) and alprazolam (27 patients). Patients who took alprazolam had a 62% lower risk of disease progression or death compared with those who did not take alprazolam (42 patients). Conversely, patients taking lorazepam had a 3.83-fold higher risk of disease progression or death than patients who did not take lorazepam (29 patients).

When the researchers investigated the associations between lorazepam and alprazolam use and patient outcomes in other cancer types, they found that alprazolam was rarely associated with significantly different outcomes. However, lorazepam use correlated with significantly worse overall survival in prostate, ovarian, head and neck, uterine, colon, and breast cancer, as well as melanoma, with effects ranging from a 25% increased risk to a 116% increased risk.

Feigin and colleagues investigated why. "Some prior studies examined the effect of benzodiazepines on tumor cell growth using models without a microenvironment," Feigin said. "Since the tumor microenvironment plays a big role in pancreatic cancer biology, we wanted to know what the benzodiazepines are doing to the microenvironment."

Abigail Cornwell, first author of the study and a graduate student in Feigin's lab, led mechanistic studies showing that lorazepam may activate a protein called GPR68, which is highly expressed on fibroblasts that support the tumor. GPR68 boosts expression of the cytokine IL-6, which promotes inflammation in the pancreatic [tumor microenvironment](#), leading to increased tumor growth.

However, only one class of benzodiazepines, called n-unsubstituted

benzodiazepines (including lorazepam, clonazepam, nordiazepam, and oxazepam), could activate GPR68. N-substituted benzodiazepines (including alprazolam, diazepam, and temazepam) had no effect on GPR68 activation.

"We think the mechanism comes down to a difference in structure between different [benzodiazepines](#)," Feigin said. "Alprazolam has the opposite effect as lorazepam; it has no impact on GPR68, but it potently decreases IL-6, and we think this decreases the inflammatory potential of these tumors."

"I think it's too early to say patients should stop taking one drug or start taking another drug," Feigin said, clarifying that this was a correlative analysis. "There's a lot more to learn in terms of the clinical implications."

Feigin said the next step would be a clinical trial to prospectively evaluate the effects of [lorazepam](#) and alprazolam on pancreatic cancer outcomes and the human pancreatic cancer microenvironment.

Limitations of this study include differences in optimal benzodiazepine dosing between mice and humans, as well as differences in benzodiazepine doses given to human patients for different indications, which was not accounted for in this study. Further, some of the mouse experiments were performed on subcutaneously implanted tumors, which have a different microenvironment than tumors that develop in the pancreas.

More information: Lorazepam stimulates IL-6 production and is associated with poor survival outcomes in pancreatic cancer, *Clinical Cancer Research* (2023). [DOI: 10.1158/1078-0432.CCR-23-0547](https://doi.org/10.1158/1078-0432.CCR-23-0547)

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