CASE IN POINT

# Naltrexone: a Novel Approach to Pruritus in Polycythemia Vera

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**Background:** Pruritus is a characteristic and often debilitating clinical manifestation reported by about 50% of patients with polycythemia vera (PV). Interventions for PV-associated pruritus include phlebotomy, antidepressants, antihistamines, phototherapy, interferon α, myelosuppression, and signaling pathway–specific agents.
**Case Presentation:** A 40-year-old man presented with Janus kinase 2 (Jak2)–positive PV complicated by intractable pruritus that was not alleviated by multimodal therapy and lifestyle modifications. Following the initiation of naltrexone, the patient experienced immediate relief that has persisted for 2 years.
**Conclusions:** This case demonstrates a novel approach to the management of PV-associated pruritus. Notably, naltrexone is an affordable, accessible, and potentially effective option for patients with intractable PV pruritus. Future directions involve consideration of case series or randomized clinical trials investigating the efficacy and pathophysiology of naltrexone in treating PV-associated pruritus.

Pruritus is a characteristic and often debilitating clinical manifestation reported by about 50% of patients with polycythemia vera (PV). The exact pathophysiology of PV-associated pruritus is poorly understood. The itch sensation may arise from a central phenomenon without skin itch receptor involvement, as is seen in opioid-induced pruritus, or peripherally via unmyelinated C fibers. Various interventions have been used with mixed results for symptom management in this patient population.[1]

Selective serotonin reuptake inhibitors (SSRIs), such as paroxetine and fluoxetine, have historically demonstrated some efficacy in treating PV-associated pruritus.[2] Alongside SSRIs, phlebotomy, antihistamines, phototherapy, interferon α, and myelosuppressive medications also comprise the various current treatment options. In addition to lacking efficacy, antihistamines can cause somnolence, constipation, and xerostomia.[3,4] Phlebotomy and cytoreductive therapy are often effective in controlling erythrocytosis but fail to alleviate the disabling pruritus.[1,5,6] More recently, suboptimal symptom alleviation has prompted the discovery of agents that target the mammalian target of rapamycin (mTOR) and Janus kinase 2 (Jak2) pathways.[1]

Naltrexone is an opioid antagonist shown to suppress pruritus in various dermatologic pathologies involving histamine-independent pathways.[3,7,8] A systematic search strategy identified 34 studies on PV-associated pruritus, its pathophysiology and interventions, and naltrexone as a therapeutic agent. Only 1 study in the literature has described the use of naltrexone for uremic and cholestatic pruritus.[9] We describe the successful use of naltrexone monotherapy for the treatment of pruritus in a patient with PV.

## CASE PRESENTATION

A 40-year-old man with Jak2-positive PV treated with ruxolitinib presented to the outpatient Michael E. DeBakey Veterans Affairs Medical Center Supportive Care Clinic in Houston, Texas, for severe refractory pruritus. Wheals manifested in pruritic regions of the patient's skin without gross excoriations or erythema. Pruritus reportedly began diffusely across the posterior torso. Through the rapid progression of an episode lasting 30 to 45 minutes, the lesions and pruritus would spread to the anterior torso, extend to the upper extremities bilaterally, and finally descend to the lower extremities bilaterally. A persistent sensation of heat or warmth on the patient's skin was present, and periodically, this would culminate in a burning sensation comparable to "lying flat on one's back directly on a hornet's nest…[followed by] a million stings" that was inconsistent with erythromelalgia given the absence of erythema. The intensity of the pruritic episodes was subjectively also described as "enough to make [him] want to jump off the roof of a building… [causing] moments of deep, deep frustration… [and] the worst of all the symptoms one may encounter because of [PV]."

Pruritus was exacerbated by sweating, heat, contact with any liquids on the skin, and sunburns, which doubled the intensity. The patient reported minimal, temporary relief with cannabidiol and cold fabric or air on his skin. His current

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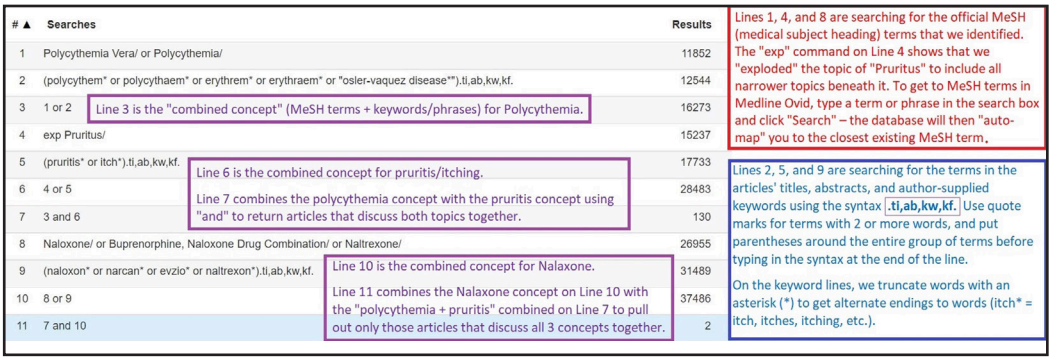
**FIGURE** Literature Review Search Results




| # ▲ | Searches | Results |
|---|---|---|
| 1 | Polycythemia Vera/ or Polycythemia/ | 11852 |
| 2 | (polycythem* or polycythaem* or erythrem* or erythraem* or "osler-vaquez disease*").ti,ab,kw,kf. | 12544 |
| 3 | 1 or 2 | 16273 |
| 4 | exp Pruritus/ | 15237 |
| 5 | (pruritis* or itch*).ti,ab,kw,kf. | 17733 |
| 6 | 4 or 5 | 28483 |
| 7 | 3 and 6 | 130 |
| 8 | Naloxone/ or Buprenorphine, Naloxone Drug Combination/ or Naltrexone/ | 26955 |
| 9 | (naloxon* or narcan* or evzio* or naltrexon*).ti,ab,kw,kf. | 31489 |
| 10 | 8 or 9 | 37486 |
| 11 | 7 and 10 | 2 |

regimen and nonpharmacologic efforts provided no relief and included oatmeal baths, cornstarch after showers, and patting instead of rubbing the skin with topical products. Trials with nonprescription diphenhydramine, loratadine, and calamine and zinc were not successful. He had not pursued phototherapy due to time limitations and travel constraints. He had a history of phlebotomies and hydroxyurea use, which he preferred to avoid and discontinued 1 year before presentation.

Despite improving hematocrit (< 45% goal) and platelet counts with ruxolitinib, the patient reported worsening pruritus that significantly impaired quality of life. His sleep and social and physical activities were hindered, preventing him from working. The patient's active medications also included low-dose aspirin, sertraline, hydroxyzine, triamcinolone acetonide, and pregabalin for sciatica. Given persistent symptoms despite multimodal therapy and lifestyle modifications, the patient was started on naltrexone 25 mg daily, which provided immediate relief of symptoms. He continues to have adequate symptom control 2 years after naltrexone initiation.

## LITERATURE REVIEW

A systematic search strategy was developed with the assistance of a medical librarian in Medline Ovid, using both Medical Subject Heading (MeSH) terms and synonymous keywords. The strategy was then translated to Embase, Web of Science, and Cochrane to extract publications investigating PV, pruritus, and/or naltrexone therapy. All searches were conducted on July 18, 2022, and the results of the literature review were as follows: 2 results from Medline Ovid; 34 results from Embase (2 were duplicates of Medline Ovid results); 3 results from Web of Science (all of which were duplicates of Medline Ovid or Embase results); and 0 results from Cochrane (Figure). Although 34 total results met inclusion criteria, the search revealed the absence of any literature that discussed the use of naltrexone for PV-associated pruritus.

## DISCUSSION

Although pruritus is a common and often excruciating manifestation of PV, its pathophysiology remains unclear. Some patients with decreasing or newly normal hematocrit and hemoglobin levels have paradoxically experienced an intensification of their pruritus, which introduces erythropoietin signaling pathways as a potential mechanism of the symptom.[8] However, iron replacement therapy for patients with exacerbated pruritus after phlebotomies has not demonstrated consistent relief of pruritus.[8] Normalization of platelet levels also has not been historically associated with improvement of pruritus.[8,9] It has been hypothesized that cells harboring Jak2 mutations at any stage of the hematopoietic pathway mature and accumulate to cause pruritus in PV.[9] This theory has been foundational in the development of drugs with activity against cells expressing Jak2 mutations and interventions targeting histamine-releasing mast cells.[9-11]

The effective use of naltrexone in our patient suggests that histamine may not be the most effective or sole therapeutic target against pruritus in PV. Naltrexone targets opioid receptors in all layers of the epidermis, affecting cell adhesion and keratinocyte production, and exhibits anti-inflammatory effects through interactions with nonopioid receptors, including Toll-like receptor 4.[12] The efficacy of oral naltrexone has been documented in patients with pruritus asso-

ciated with immune checkpoint inhibitors, psoriasis, eczema, lichen simplex chronicus, prurigo nodularis, cholestasis, uremia, and multiple rheumatologic diseases.[3,4,7-9,12-14] Opioid pathways also may be involved in peripheral and/or central processing of pruritus associated with PV.

Importantly, patients who are potential candidates for naltrexone therapy should be notified and advised of the risk of drug interactions with opioids, which could lead to symptoms of opioid withdrawal. Other common adverse effects of naltrexone include hepatotoxicity (especially in patients with a history of significant alcohol consumption), abdominal pain, nausea, arthralgias, myalgias, insomnia, headaches, fatigue, and anxiety.[12] Therefore, it is integral to screen patients for opioid dependence and determine their baseline liver function. Patients should be monitored following naltrexone initiation to determine whether the drug is an appropriate and effective intervention against PV-associated pruritus.

## CONCLUSIONS

This case study demonstrates that naltrexone may be a safe, effective, nonsedating, and cost-efficient oral alternative for refractory PV-associated pruritus. Future directions involve consideration of case series or randomized clinical trials investigating the efficacy of naltrexone in treating PV-associated pruritus. Further research is also warranted to better understand the pathophysiology of this symptom of PV to enhance and potentially expand medical management for patients.

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## Ethics and consent

The authors obtained written informed consent for publication of this case report. This case report was exempt from institutional review board (IRB) requirements at the Baylor College of Medicine.

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