

## What is Levamisole?

Levamisole is a veterinary antihelminthic (commonly referred to as “pig de-wormer”). It was withdrawn from the Canadian market for patient use around 2003 after reports of vasculitis, leukopenia and agranulocytosis. Levamisole was previously used as an immunomodulatory drug for the treatment of colorectal cancer, autoimmune diseases and nephrotic syndrome. It remains on WHO’s essential list of medicines.

## What is the link with cocaine?

Levamisole is one of the most frequently detected adulterants of cocaine, because it is:

- Relatively inexpensive and an easily accessible means of adding bulk
- Colorless, tasteless, and has a lower melting point than cocaine (does not leave any residues), and can pass “purity” tests

Aminorex, a levamisole metabolite, was developed in the 1970’s as an appetite suppressant medication in Europe. It was discontinued in early 1970’s after pulmonary hypertension-related deaths. Aminorex analogues were popular in the 1980’s due to amphetamine-like behaviour, and slightly longer half-life than cocaine, that can potentially prolong euphoric effects.

## How often is levamisole detected in cocaine?

Approximately 5% of cocaine/crack samples tested by the BC Centre for Substance Use’s drug checking services from January 2019 to January 2021 were found to contain levamisole. A BC Centre for Disease Control led harm reduction client survey with urinalysis found 24.4% (32 of 131) and 10.7% (23 out of 215) of samples that tested positive for cocaine also contained levamisole in 2018 and 2019 respectively .

## Levamisole Toxicity: Typical presentation and findings

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|---|---|
| <p>Retiform purpura</p>                   | <ul style="list-style-type: none"> <li>• <b>Pathognomonic: ears.</b> Also the cheeks, arms and legs.</li> <li>• Dusky purple, with erythematous margins and necrotic centers that can progress to bullae, necrosis and possibly eschar.</li> <li>• Can be rapid and extensive, progressing to full-skin thickness ulcers.</li> </ul> <div style="display: flex; justify-content: space-around; align-items: center;">     </div> |
| <p>Leukopenia</p>                         | <ul style="list-style-type: none"> <li>• Neutropenia (&lt;1.0x10<sup>9</sup> granulocytes/L)</li> <li>• Agranulocytosis (≤0.5 x 10<sup>9</sup> granulocytes/L): otherwise not often seen outside of cancer and related therapy</li> <li>• May present with opportunistic infections, including bacterial and fungal infections and fever</li> </ul>   |
| <p>May see evidence of autoantibodies</p> | <ul style="list-style-type: none"> <li>• Antineutrophil cytoplasmic (ANCA), p- and c-antibodies.</li> <li>• May also see Proteinase 3 (PR3), myeloperoxidase (MPO), Neutrophilic cytoplasmic antigen (NCA) and Human neutrophil elastase (HNE).</li> <li>• Note: Human leukocyte antigen B27 (HLA-B27) may predispose to complications.</li> </ul>  |

**Note:** Cocaine and levamisole have similar and synergistic toxic effects. Cocaine induced toxicity related to snorting or inhalation is less likely to present with systemic symptoms, and more likely to present with involvement of ears, nose and throat, specifically “Cocaine-induced midline destruction” (CIMD), oral or tracheal ulceration and rhinitis. Hard palate perforation is pathognomonic for CIMD that can result in communication between oral and nasal cavities. Consider referral for further testing, including ultrasound of sinuses.

## What are possible clinical findings?

Prompt identification of levamisole toxicity can avoid unnecessary invasive investigations, such as bone marrow biopsies, and can lead to more effective care and management. In the context of cocaine use, findings of retiform purpura on the ears, neutropenia, and agranulocytosis can help to distinguish levamisole toxicity from other differential diagnoses.



Clinical findings can also include rash, nausea, vomiting, diarrhea, flu-like symptoms, headache, fever, arthralgia, night sweats, weight loss, alopecia, dysgeusia (metallic taste), pulmonary infection, and liver and renal toxicities.



- **CBC differential**
- If otherwise unexplained fever, neutropenia or agranulocytosis: order bacterial and fungal cultures, and urgent hematology referral.
- If wanting to confirm recent crack/cocaine use, cocaine metabolites can be detected routine urine drug screens for up to 5 days after use.

Consider:

- Autoantibodies (e.g., ANCA)
- Histopathology to exclude malignancy
- CXR, CT sinuses
- TB, HIV and syphilis testing

**Note:** Testing for levamisole is not recommended, as clinical management remains supportive regardless of results.

## What can happen when cocaine or crack is tainted with levamisole?

Serious adverse events include neutropenia, agranulocytosis, leukoencephalopathy and vasculitis, with subsequent risk for infection, sepsis and death. Reconstructive surgery may be required if there is extensive skin damage. For unknown reasons, women appear to be more susceptible to experiencing serious adverse events.

There is no clear dose-response effect, but it is likely that toxic effects are more likely after prolonged use. A review of 32 cases of neutropenia identified in Alberta and BC in 2008, found almost three-quarters of cases reported smoking as the mode of ingestion of cocaine. Adverse events have been found to be genetically determined. Agranulocytosis is associated with HLA-B27. Therefore it is important to inform patients that the condition may be genetically determined and can reoccur with continued use of cocaine/crack cut with levamisole.

## Follow-up care

Engage into comprehensive care. Consider crack/cocaine prescription alternatives and addiction counselling, as around 50% experience neutropenia again upon re-exposure. Most lesions resolve spontaneously within 3 weeks, while neutropenia generally improves after 5-10 days, but can take longer. Recovery can be prolonged and outcomes worsened if use of crack/cocaine cut with levamisole continues. Recommend use drug-checking services and a different drug supply.

Regular wound care is required to manage any lesions. Refer to dermatology as needed, if larger areas of skin are affected and/or full skin thickness loss has occurred. Broad spectrum antibiotics may be required if there is risk for infection, especially if immune compromised.

## Recommend use of drug-checking services

- For current information and locations, see the Toward the Heart website: [towardtheheart.com/for-pwus](http://towardtheheart.com/for-pwus)
- For testing by mail or in person: [Getyourdrugstested.com](http://Getyourdrugstested.com)

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