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ORIGINAL ARTICLE

Adverse reactions with levamisole vary according to its indications and misuse: A systematic pharmacovigilance study

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Levamisole was initially prescribed for the treatment of intestinal worms. Because of immunomodulatory properties, levamisole has been used in inflammatory pathologies and in cancers in association with 5-fluorouracil. Levamisole is misused as a cocaine adulterant. Post-marketing reports have implicated levamisole in the occurrence of adverse drug reactions (ADRs) and its use is now limited in Europe and North America. In contrast, all other parts of the World continue to use single-dose levamisole as an anthelmintic. The aim of this study was to identify ADRs reported after levamisole exposure in VigiBase, the World Health Organisation's pharmacovigilance database, and analyse their frequency compared to other drugs and according to levamisole type of use.

Methods: All levamisole-related ADRs were extracted from VigiBase. Disproportionality analyses were conducted to investigate psychiatric, hepatobiliary, renal, vascular, nervous, blood, skin, cardiac, musculoskeletal and general ADRs associated with levamisole and other drugs exposure. In secondary analyses, we compared the frequency of ADRs between levamisole and mebendazole and between levamisole type of use.

Results: Among the 1763 levamisole-related ADRs identified, psychiatric disorders (reporting odds ratio with 95% confidence intervals: 1.4 [1.2–2.6]), hepatobiliary disorders (2.4 [1.9–4.3]), vasculitis (6.5 [4.1–10.6]), encephalopathy (22.5 [17.4–39.9]), neuropathy (4.3 [2.9–7.1]), haematological disorders, mild rashes and musculoskeletal disorders were more frequently reported with levamisole than with other drug. The majority of levamisole-related ADRs occurred when the drug was administered for a non-anti-infectious indication.

Conclusion: The great majority of the levamisole-related ADRs concerned its immunomodulatory indication and multiple-dose regimen. Our results suggest that single-dose treatments for anthelmintic action have a good safety profile.

KEYWORDS

adverse drug reactions, disproportionality, levamisole, pharmacovigilance

1 | INTRODUCTION

Levamisole is an old drug derived from imidazothiazole, discovered in 1966 and originally used in veterinary medicine as an anthelmintic and then marketed for the same indication in humans. The anthelmintic action of levamisole is mainly used against *Ascaris lumbricoides*, *Trichuris trichiura* and hookworms (*Necator americanus* and *Ancylostoma duodenale*), the 3 main soil-transmitted helminths (STH) belonging to the World Health Organisation's (WHO's) list of Neglected Tropical Diseases. Because of levamisole's broad spectrum activity and safety, as well as the fact that it is relatively inexpensive and requires only a single oral dose to treat STH, it has been included in the WHO list of essential medicines in 1988.¹ From the early 1980s, national programmes to control STH have typically implemented annual mass drug administration with any of the following anthelmintic drugs: albendazole, mebendazole, levamisole or pyrantel (the exact drug is at the discretion of each country).² However, since 2003, the 3 drugs used by national programmes are albendazole, mebendazole and praziquantel (only in combination with 1 of the other 2 treatments), while levamisole is no longer used in mass drug administration according to the WHO data.^{3,4} This is due to 3 main reasons: (i) contrarily to levamisole, benzimidazoles (especially mebendazole) are very little absorbed by the organism and remain in the intestine where they kill the intestinal parasites, which is a guarantee of safety; (ii) since 2010, 2 pharmaceutical companies have been donating large quantities of mebendazole (Johnson & Johnson) and albendazole (GlaxoSmithKline) to countries where STH are endemic, thus promoting the use of these molecules from an economic perspective; (iii) albendazole and mebendazole do not require weight adjustment, unlike levamisole, which is used at 2.5 mg/kg. In 2008, Albonico *et al.* reported that "no literature was found specifically on the use of levamisole in pre-school age children" (i.e. as part of mass drug administration for STH infections).⁵ However, it appears that the last documented uses of levamisole in national control programmes were in China, Iran, Vietnam, Brazil, Kenya and Nigeria in the 1990s.^{5,6}

Besides these national control programmes, levamisole can be purchased with or without a medical prescription for personal use in many countries around the world, particularly in areas where STH are highly endemic (South America, Asia and Africa). For both individual treatment and mass drug administration, levamisole is usually administered as a single oral dose of 2.5 mg/kg or 80 mg for all school-age children to treat STH.⁷

The mechanisms of action of levamisole are multiple and not yet fully elucidated. Levamisole is able to paralyze nematode muscles, leaving the worms unable to attach themselves to the mucous membranes, and causing them to be expelled through the intestine.⁸ Levamisole has several other effects on human organisms: it exerts immunomodulatory properties and acts on the dopaminergic, cholinergic and noradrenergic systems.⁹ Levamisole was subsequently used for its immunomodulatory action in certain forms of rheumatoid arthritis and in association with 5-fluorouracil in patients with colon cancer or melanoma.¹⁰ In some countries,

What is already known about this subject

- Levamisole has had many different indications, has been misused and has been associated in the occurrence of serious adverse drug reactions (ADRs).
- This association has led several countries to suspend its use. Nevertheless, other countries still use it daily for its antiparasitic indication and do not report serious ADRs.

What this study adds

- Most levamisole-related ADRs concern its immunomodulatory properties.
- Single-dose treatments of levamisole for an antiparasitic indication appear to have a good safety profile.
- The use of levamisole in specific areas where benzimidazole resistance is feared could be an important resource to overcome the possible occurrence of resistance.

levamisole is also used in the treatment of paediatric nephrotic syndrome.¹¹

The majority of levamisole-related adverse drug reactions (ADRs) reported when used as an anthelmintic treatment were mild and transient.^{12–15} During 1994–2000, some cases of nervous system disorders were reported in North Vietnam but levamisole was produced locally, which, according to the Centre for Adverse Drug Reaction of the Vietnam ministry of health, "raises the issue of quality assurance".⁶ In 2009, for the first time, 16 cases of multifocal inflammatory leucoencephalopathy were reported from China after a single dose of levamisole.¹⁶

The scientific literature also reports various ADRs after levamisole treatment for other purposes than anthelmintic indication. In cancer treatments, levamisole is generally used at high doses (50 mg every 8 h for 3 d) every 2 weeks for at least 1 year¹⁷ and in combination with 5-fluorouracil. Several authors reported cases of multifocal inflammatory leucoencephalopathy,^{18–34} vasculitis,³⁵ agranulocytosis³⁶ and thrombocytopenia³⁷ associated with this regimen.

As part of paediatric nephrotic syndrome or rheumatoid polyarthritis, the recommended dose of levamisole is 2 or 2.5 mg/kg on alternate days for 12–24 months.¹¹ In studies concerning immunomodulatory properties of levamisole, some serious ADRs have been reported: nervous system disorders,³⁸ vasculitis^{39–43} and agranulocytosis.^{44,45}

Since 2009, levamisole has been involved in case reports as a cocaine adulterant; the amphetamine-like substance aminorex (an anorectic stimulant) being its metabolite.⁴⁶ Several hypotheses have been made to explain cocaine adulteration with levamisole: its cheapness, the large quantity available, its chemical properties, which enable it to go undetected in typically used street purity tests, and/or potentiation of cocaine effects.⁴⁷ Severe somatic complications widely reported in users of levamisole-adulterated

cocaine include leucopenia, agranulocytosis, leucoencephalopathy, arthritis, thrombotic vasculopathy and vasculitis.⁴⁸ Cardiac complications, cognitive impairments and cerebral toxicities were also recently described.^{49–51} As the percentage of levamisole in cocaine powder and the amount of cocaine consumed is never known at the time of consumption, it is very difficult to estimate the level of levamisole exposure in the cases.

Although levamisole is considered as an essential medicine by the WHO, the USA and Europe decided to withdraw its marketing authorization in 2004 and 1998 respectively, and to regulate its use (temporary authorization) for specific indications such as nephrotic syndrome or (as an adjuvant) cancer therapy.

Encephalopathies, vasculitis and agranulocytosis are post-levamisole ADRs which seem related to the type of use of the drug, and thus to the dosage regimen. Besides the adulterated cocaine, information regarding the extent of levamisole use, both in general (including in automedication) and specifically for treatment of STH (i.e. at single dose of 2.5 mg/kg) is scarce. As levamisole has been used in many indications, with very different administration schemes and various coadministered drugs, it is likely that the ADRs occurring varies according to each use. The prescription drug information mentions the following ADRs: neutropenia, thrombocytopenia, leucoencephalopathy, hypersensitive reactions, nervousness, sleepiness, depression, nausea, vomiting, reduced appetite, diarrhoea, constipation, pancreatitis, skin rash and inflammation, muscle and joint pain, inflammation of the mouth, and change of odour.⁵² Finally, with the emergence of the COVID-19 pandemic, levamisole has been proposed as a therapeutic strategy option on the basis of its immunomodulatory properties, which were thought to improve clinical status of patients with COVID-19.⁵³ In this context, we searched the WHO global pharmacovigilance database, VigiBase, for all the suspected ADRs reported after levamisole treatment. We then conducted disproportionality analyses considering the types of use. More specifically, the aims of this study were: (i) to identify new pharmacovigilance signals (increased reporting of suspected ADRs after treatment with levamisole compared to other treatments); (ii) to compare ADRs after levamisole according to its type of use (and therefore its regimen); and (iii) to assess, using all available information, the safety of a single dose. Finally, an overview of the known mechanisms of action of levamisole is provided.

2 | METHODS

2.1 | Data source

Data were extracted from the WHO Global Individual Case Safety Report (ICSR) database VigiBase,⁵⁴ which includes >24 million cases of suspected ADRs reported by national pharmacovigilance centres in >130 countries participating in the WHO Program for International Drug Monitoring.⁵⁵ An ICSR is an anonymized report for a single individual who experienced adverse event(s) that may be linked to the use of 1 or more drugs. ICSR contains sociodemographic

information (age, sex, reporter qualification, country of origin, year of report), information about the drug administration (frequency, dosage, comedications) and information about the reported adverse event(s). The latter includes the seriousness according to the criteria of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH),⁵⁶ adverse event verbatim description and associated terms from the Medical Dictionary for Regulatory Activities (MedDRA) developed by the ICH. From VigiBase, all reports of suspected ADRs associated with levamisole from 27 February 1977 (first ever report of levamisole-related suspected ADR recorded) up to 7 February 2021 were extracted. Primary analysis used all reports from VigiBase, comparing levamisole-related ADRs to all ADRs reported in the database (any drugs). Mebendazole-related cases were also extracted and used as control cases because of this drug has similar anthelmintic indications. Prior to analysis, suspected duplicate reports identified by an automated screening were excluded.⁵⁷ Suspected ADRs were classified following the MedDRA classification,⁵⁸ grouped at the system organ class (SOC) level and at the individual preferred term (PT) level.

2.2 | Study design

We performed disproportionality analyses using the case–noncase method, which allows to identify disproportionate reporting, i.e. a higher-than-expected number of adverse reaction reports compared to other reactions recorded in the database by calculating reporting odds ratios (RORs). ROR compares the odds of exposure to levamisole between cases and noncases.^{59,60}

Cases were defined as reports of each suspected ADR of interest identified by a MedDRA PT. ADRs of interest were identified from the scientific literature or from the drug official information (summary of product characteristics) and include vasculitis, encephalopathies, peripheral neuropathy, convulsions, agranulocytosis, leucopenia, neutropenia, thrombocytopenia, vertigo, fever, tachycardia, failures (cardiac arrest, cardiorespiratory arrest, heart attack and chest pains), arthritis or synovitis, arthralgia or myalgia and hypothermia. Because of the small number of PT reported among some SOC, a global analysis was performed for all PT reported among the 3 following SOC: “psychiatric disorders”, “hepatobiliary disorders” and “renal and urinal disorders”. For “skin and subcutaneous tissue disorders” SOC, we conducted 2 separated analyses, 1 on severe skin disorders: Stevens–Johnson syndrome, or toxic epidermal necrolysis or acute generalized exanthematous pustulosis; and 1 on all mild skin disorders (rash or erythema).

Noncases were defined as reports of any other suspected ADR.

2.3 | Exposure definition

Exposure was identified in the ICSR by the use of levamisole (Anatomical Therapeutic Chemical [ATC] code P02CE) preceding the onset of the adverse reaction.

2.4 | Statistical analysis

Descriptive statistics were used to summarize the basic characteristics according to the indication of levamisole: anti-infectious, immunomodulator, adulterant or unknown/unprecise indication.

The indication categories were retrieved based on the information available in Vigibase and defined as follows. The *anti-infectious* category includes cases where the drug was administered for any infection according to the market authorization, i.e. for parasitic infections, or off-market authorization, i.e. at the discretion of the prescribing physician, for viral or bacterial infections. The *adulterant* category includes all cases where cocaine was part of the coadministered molecules or where the reporter notified that it was a misuse. The *immunomodulator* category includes all cases where levamisole is defined as an adjuvant, immunomodulator or anti-cancer treatment or where 5-fluorouracil was part of the coadministered drugs. Finally, the *unknown/unprecise* category includes all other cases where the reporter did not report any specific indication.

An analysis of characteristics associated with each ADR of interest where levamisole was suspected, including sex ratio, age, percentage of cases considered as serious, median time from initiation of levamisole to effect, reported use, reported period of notification and frequency of administration (single dose or multiple doses), was conducted. The reporting period was categorized into 4 categories (before 1990, between 1990 and 1999, between 2000 and 2009 and after 2009) according to important dates in the history of levamisole (approved in 1970 for its anthelmintic action; approved in 1990 for its immunomodulatory action; loss of marketing authorizations in the 2000s; first case of levamisole uses as a cocaine adulterant in 2009).

Our primary analyses consisted in calculating the ROR of each suspected ADR of interest (and corresponding 95% confidence interval [95% CI]) for levamisole compared to all other drugs reported in Vigibase using logistic regression models. A first secondary stratified analysis consisted in calculating the ROR of each suspected ADR of interest for levamisole compared to mebendazole but only when the indication was anti-infectious. In 2 last secondary analyses, ADRs were compared according to levamisole type of use: immunomodulatory indication vs. anti-infectious indication, and adulterant use vs. anti-infectious indication.

Analyses were conducted using STATA v.15.1 software (StatCorps, LP, College Station, TX, USA).

2.5 | Description of the mechanisms of action of levamisole

A separate literature review was performed using the Medline database to search information on the mechanisms of action of levamisole, their potential implication in occurrence of ADRs and their potential synergy with cocaine or 5-fluorouracil.

3 | RESULTS

3.1 | Descriptive analysis of the ADRs reported with levamisole

Among the 24 217 750 cases reported in Vigibase and after elimination of duplicates, 1763 suspected ADRs after administration of levamisole were reported between 27 February 1977 and 7 February 2021. Among them, 265 (15.0%) were reported as serious, 89 (5.0%) resulted in death, 82 (4.6%) involved cocaine, 142 (8.0%) occurred after use for an anti-infectious indication, 953 after use for immunomodulatory action (54.1%) and 586 (33.2%) had no specified indication. Within immunomodulatory cases, 51 (5.3%) concerned treatment of paediatric nephrotic syndrome and 902 (94.7%) concerned cancer treatment in association with 5-fluorouracil. Table 1 shows the distribution of cases according to levamisole use by age, sex, dosage regimen, seriousness, reporter type, geographical area and reporting period.

Most cases concerned adults (64.0%) and were reported by healthcare professionals (98.9%). Mean age was 35.7 ± 23.9 years for all cases, 35.7 ± 12.7 years for adulterant cases, 23.4 ± 19.5 years for anti-infectious cases, 59.0 ± 16.7 years for immunomodulator cases, 9.0 ± 3.3 years for nephrotic syndrome and 61.9 ± 11.8 years for cancer therapy. Suspected ADRs were more frequently fatal in adulterant cases (55 deaths; 68.7%) than in other indications. All deaths that occurred in cases where levamisole was used as an adulterant also cited cocaine as a potential suspect. The 4 countries that reported the highest number of cases were the USA (958 cases, 54.2%), the UK (98, 5.5%), France (75, 4.2%) and India (75, 4.2%). Single dose was more frequent in anti-infectious cases than in immunomodulator or unknown indication cases. The 3 most reported SOC were general disorders and administration site conditions (25.8%), nervous system disorders (23.9%) and skin and subcutaneous tissue disorders (20.9%; Table 2).

3.2 | Description of ADRs related to levamisole

Description of adverse events where levamisole was suspected are presented in Table 3.

With the exception of convulsions, thrombocytopenia, neuropathy, severe skin disorders and failures, the majority of ADRs were more frequently reported in women than in men. The median time to onset of ADR was lower than 2 weeks for vasculitis, convulsions, thrombocytopenia, severe skin disorders, rashes, vertigo, fever, failures, arthralgia/myalgia and hypothermia, and higher than 2 weeks for encephalopathy, agranulocytosis, neutropenia, tachycardia and arthritis/synovitis. Relatively few levamisole-related ADRs were reported for the anti-infectious indication and adulterant use, comprising <8% and 5% of reported cases, respectively. Similarly, relatively few ADRs were reported following a single dose of levamisole.

TABLE 1 Characteristics of levamisole-related adverse drug reactions reported in VigiBase according to indication

	Levamisole use				
	Adulterant (n = 82)	Anti-infectious (n = 142)	Immunomodulator (n = 953)	Unknown/Unprecise (n = 586)	Total (n = 1763)
Age					
<18 y	1 (1.4%)	31 (23.3%)	49 (6.0%)	66 (13.4%)	147 (9.7%)
18–65 y	69 (97.2%)	96 (72.2%)	449 (55.2%)	353 (71.6%)	967 (64.0%)
>65 y	1 (1.4%)	6 (4.5%)	315 (38.7%)	74 (15.0%)	396 (26.2%)
Missing data	11	9	140	93	253
Sex					
Female	33 (42.9%)	72 (51.0%)	452 (51.9%)	310 (58.0%)	867 (53.4%)
Male	44 (57.1%)	69 (49.0%)	419 (48.1%)	224 (42.0%)	756 (46.6%)
Missing data	5	1	82	52	140
Dosage regimen					
Single dose	0	72 (60.0%)	5 (1.5%)	105 (37.1%)	182 (25.0%)
Multiple doses	0	48 (40.0%)	319 (98.5%)	178 (62.9%)	545 (75.0%)
Missing data	82	22	629	301	1036
Seriousness					
Yes	80 (97.6%)	19 (21.3%)	42 (70.0%)	124 (65.3%)	265 (62.9%)
No	2 (2.4%)	70 (78.7%)	18 (30.0%)	66 (34.7%)	156 (37.1%)
Missing data	0	53	893	396	1342
Seriousness criterion					
Caused/prolonged hospitalization	19 (23.7%)	5 (38.5%)	8 (20.0%)	82 (66.7%)	114 (44.5%)
Death	55 (68.7%)	0	3 (7.5%)	31 (25.2%)	89 (34.8%)
Disabling/incapacitating	0	0	2 (5.0%)	0	2 (0.8%)
Life threatening	2 (2.5%)	2 (15.4%)	1 (2.5%)	5 (4.1%)	10 (3.9%)
Other important condition	4 (5.0%)	6 (46.1%)	26 (65.0%)	5 (4.1%)	41 (16.0%)
Reporter					
Health professionals	74 (96.1%)	108 (99.0%)	213 (100%)	433 (98.9%)	828 (98.9%)
Other occupations	3 (3.9%)	1 (1.0%)	0	5 (1.1%)	9 (1.1%)
Missing data	5	33	740	148	926
Continent					
Africa	0	22 (15.5%)	0	70 (11.9%)	92 (5.2%)
North America	55 (67.1%)	1 (0.7%)	794 (83.3%)	147 (25.1%)	997 (56.6%)
South America	0	15 (10.6%)	0	56 (9.6%)	71 (4.0%)
Asia	1 (1.2%)	79 (55.6%)	8 (0.8%)	63 (10.7%)	151 (8.6%)
Australia	0	4 (2.8%)	40 (4.2%)	27 (4.6%)	71 (4.0%)
Europa	26 (31.7%)	21 (14.8%)	111 (11.7%)	223 (38.0%)	381 (21.6%)
Reporting period					
Before 1990	0	15 (10.6%)	1 (0.1%)	143 (24.4%)	159 (9.0%)
1990–1999	0	10 (7.0%)	816 (85.6%)	140 (23.9%)	966 (54.8%)
2000–2009	5 (6.1%)	26 (18.3%)	88 (9.2%)	100 (17.1%)	219 (12.4%)
After 2010	77 (93.9%)	91 (64.1%)	48 (5.0%)	203 (34.6%)	419 (23.8%)

TABLE 2 Levamisole-related adverse drug reactions: frequency of reported system organ class (SOC) by indications and in total. Multiple SOCs can be reported in a single Individual Case Safety Report (ICSR)

SOC, n (% of ICSR with mention of the SOC)	Adulterant (n = 82)	Anti-infectious (n = 142)	Immunomodulator (n = 953)	Unknown/Unprecise (n = 586)	Total (n = 1763)
General disorders and administration site conditions	30 (37.0%)	28 (19.7%)	221 (23.2%)	174 (29.7%)	455 (25.8%)
Nervous system disorders	8 (9.9%)	36 (25.4%)	246 (25.8%)	132 (22.5%)	422 (23.9%)
Skin and subcutaneous tissue disorders	3 (3.7%)	30 (21.2%)	180 (18.9%)	154 (26.3%)	369 (20.9%)
Gastrointestinal disorders	3 (3.7%)	79 (55.6%)	151 (15.8%)	118 (20.1%)	352 (19.9%)
Blood and lymphatic system disorders	13 (16.0%)	7 (4.9%)	118 (12.4%)	96 (16.4%)	234 (13.3%)
Psychiatric disorders	32 (39.5%)	14 (9.9%)	81 (8.5%)	56 (9.6%)	183 (10.4%)
Musculoskeletal, connectives tissues disorders	6 (7.4%)	5 (3.5%)	98 (10.3%)	62 (10.6%)	171 (9.7%)
Investigations	9 (11.1%)	0	92 (9.7%)	26 (4.4%)	127 (7.2%)
Metabolism and nutrition disorders	3 (3.7%)	4 (2.8%)	99 (10.4%)	20 (3.4%)	126 (7.1%)
Vascular disorders	9 (11.1%)	5 (3.5%)	45 (4.7%)	27 (4.6%)	86 (4.9%)
Injury, poisoning, procedural complications	57 (70.4%)	0	8 (0.8%)	20 (3.4%)	85 (4.8%)
Respiratory, thoracic, mediastinal disorders	12 (14.8%)	4 (2.8%)	34 (3.6%)	28 (4.8%)	78 (4.4%)
Infections and infestations	5 (6.2%)	1 (0.7%)	53 (5.6%)	16 (2.7%)	75 (4.2%)
Hepatobiliary disorders	0	0	59 (6.2%)	13 (2.2%)	72 (4.1%)
Renal and urinal disorders	5 (6.2%)	4 (2.8%)	39 (4.1%)	17 (2.9%)	65 (3.7%)
Cardiac disorders	15 (18.5%)	1 (0.7%)	26 (2.7%)	21 (3.6%)	63 (3.6%)
Eye disorders	0	3 (2.1%)	37 (3.9%)	18 (3.1%)	58 (3.3%)
Immune system disorders	0	4 (2.8%)	10 (1.0%)	8 (1.4%)	22 (1.2%)
Neoplasm benign, malignant and unspecified	0	0	15 (1.6%)	2 (0.3%)	17 (1.0%)
Ear and labyrinth disorders	0	2 (1.4%)	6 (0.6%)	8 (1.4%)	16 (0.9%)
Endocrine disorders	2 (2.5%)		9 (0.9%)	1 (0.2%)	12 (0.7%)
Reproductive system and breast disorders	0	2 (1.4%)	4 (0.4%)	2 (0.3%)	8 (0.5%)
Pregnancy, puerperium, perinatal disorders	1 (1.2%)	2 (1.4%)	0	1 (0.2%)	4 (0.2%)
Product issues	2 (2.5%)	0	0	1 (0.2%)	3 (0.2%)
Congenital, familial and genetic disorders	0	1 (0.7%)	1 (0.1%)	0	2 (0.1%)
Surgical and medical procedures	1 (1.2%)	0	0	1 (0.2%)	2 (0.1%)
Social circumstances	1 (1.2%)	0	0	0	1 (0.1%)

3.3 | Disproportionality analysis

The results of the disproportionality analyses of levamisole-related ADRs of interest compared to any other drugs are presented in Table 4.

The relative frequencies of psychiatric disorders, hepatobiliary disorders, encephalopathies, neuropathy, agranulocytosis, leucopenia, neutropenia, thrombocytopenia, fever, arthritis/synovitis, arthralgia/myalgia, hypothermia and vasculitis were significantly higher with levamisole than with other drugs (see all ROR values and 95% CI in Table 4). Psychiatric disorders were significantly more frequently

reported after levamisole-adulterated cocaine intake than after levamisole intake for anti-infectious indication. No cases of hepatobiliary disorders, encephalopathy, neuropathy, agranulocytosis, serious skin disorders (Stevens–Johnson syndrome, or toxic epidermal necrolysis and acute generalized exanthematous pustulosis), arthritis/synovitis, tachycardia, failures or hypothermia were reported when levamisole was given for an anti-infectious indication. Encephalopathies and leucopenia were more frequently reported when levamisole was used for an immunomodulatory action than when it was used for an anti-infectious indication. Neutropenia was more frequently reported when levamisole was misused than when it was used for its

TABLE 3 Description of adverse drug reactions related with levamisole

Adverse events	Sex Ratio ^a	Serious ^b	Time of occurrence ^c	Age (n, %)			Use (n, %)			
				<18 y	18–65 years	> 65 years	Adulterant	Anti-infectious	Immunomodulator	Unknown indication
Vasculitis	0.31	91.7%	9	2 (11.8%)	14 (82.4%)	1 (5.9%)	4 (23.5%)	1 (5.9%)	3 (17.5%)	9 (52.9%)
Encephalopathy	0.49	100%	53	1 (1.7%)	32 (54.2%)	19 (32.2%)	1 (1.7%)	1 (1.7%)	50 (84.8%)	7 (11.9%)
Neuropathy	1.30	100%	47.5	0 (0%)	10 (40.0%)	7 (28.0%)	1 (4.0%)	0 (0%)	21 (84.0%)	3 (12.0%)
Convulsions	1.37	50.0%	8	1 (4.5%)	10 (45.5%)	6 (27.3%)	0 (0%)	1 (4.5%)	13 (59.1%)	8 (36.4%)
Agranulocytosis	0.39	100%	38	3 (5.0%)	35 (58.3%)	14 (23.3%)	4 (6.7%)	3 (5.0%)	18 (30.0%)	35 (58.3%)
Leucopenia	0.72	66.7%	19	3 (4.3%)	43 (61.4%)	20 (28.6%)	1 (1.4%)	1 (1.4%)	47 (67.1%)	21 (30.0%)
Neutropenia	0.74	73.7%	26	16 (28.6%)	24 (42.9%)	13 (23.2%)	7 (12.5%)	2 (3.6%)	17 (30.4%)	30 (53.6%)
Thrombocytopenia	1.00	75.0%	9	3 (9.4%)	15 (47.0%)	11 (34.4%)	2 (6.3%)	1 (3.1%)	22 (68.8%)	7 (21.9%)
SJS/TEN/APEG ^d	1.50	100%	9.5	1 (20.0%)	4 (80.0%)	0 (0%)	0 (0%)	0 (0%)	3 (60.0%)	2 (40.0%)
Rashes	0.65	33.3%	11	21 (11.2%)	95 (50.8%)	51 (27.3%)	0 (0%)	12 (6.4%)	109 (58.3%)	67 (35.6%)
Vertigo	0.80	58.3%	1	5 (6.7%)	54 (72.0%)	11 (14.7%)	0 (0%)	16 (21.3%)	25 (33.3%)	34 (45.3%)
Fever	0.65	68.4%	9	11 (8.3%)	84 (63.4%)	29 (22.0%)	5 (3.8%)	14 (10.6%)	54 (40.9%)	59 (44.7%)
Tachycardia	0.36	100%	35	1 (6.3%)	13 (81.2%)	1 (6.3%)	1 (6.2%)	0 (0%)	9 (56.2%)	6 (37.5%)
Failures	1.16	95.5%	2	0 (0%)	34 (80.9%)	5 (11.9%)	10 (23.8%)	0 (0%)	16 (38.1%)	16 (38.1%)
Arthritis/synovitis	0.75	MD	30	1 (6.3%)	7 (43.7%)	4 (25.0%)	0 (0%)	0 (0%)	12 (66.7%)	6 (33.3%)
Arthralgia/myalgia	0.74	86.0%	2	7 (7.0%)	68 (68.0%)	15 (15.0%)	3 (3.0%)	4 (4.0%)	57 (57.0%)	36 (36.0%)
Hypothrombinaemia	0.78	MD	16.5	0 (0%)	11 (35.5%)	13 (41.9%)	0 (0%)	0 (0%)	27 (87.1%)	4 (12.9%)

MD, missing data.

For age, indication, reporting period and dosage regimen, the lines contain the number of cases and the percentage over all cases. Missing data are not described but are included in the percentage calculations.

^aRatio male/female.^bPercentage of cases reported as serious.^cMedian time to onset of effect from initiation of treatment (in days).^dStevens–Johnson syndrome, toxic epidermal necrolysis or acute generalized exanthematous pustulosis.

TABLE 3 Continued

Adverse events	Notification period			Dosage regimen		
	Before 1990	1990–1999	2000–2009	After 2010	Single dose	Multiples doses
Vasculitis	2 (12.5%)	2 (12.5%)	0 (0.0%)	12 (75.0%)	0 (0%)	5 (29.4%)
Encephalopathy	0 (0.0%)	42 (71.2%)	9 (15.2%)	8 (13.6%)	0 (0%)	27 (45.8%)
Neuropathy	2 (8.0%)	15 (60.0%)	6 (24.0%)	2 (8.0%)	0 (0%)	8 (32.0%)
Convulsions	1 (4.5%)	19 (86.4%)	0 (0%)	2 (9.1%)	1 (4.5%)	12 (54.5%)
Agranulocytosis	21 (35.0%)	24 (40.0%)	6 (10.0%)	9 (15.0%)	0 (0%)	28 (53.3%)
Leucopenia	15 (21.4%)	46 (65.7%)	6 (8.6%)	3 (4.3%)	0 (0%)	31 (44.3%)
Neutropenia	21 (37.5%)	5 (8.9%)	11 (19.6%)	19 (33.9%)	0 (0%)	32 (57.1%)
Thrombocytopenia	5 (15.6%)	20 (62.5%)	3 (9.4%)	4 (12.5%)	0 (0%)	14 (43.8%)
SJS/TEN/APEG ^d	0 (0%)	3 (60.0%)	0 (0%)	2 (40.0%)	0 (0%)	1 (20.0%)
Rashes	28 (15.0%)	124 (66.3%)	14 (7.5%)	21 (11.2%)	12 (6.4%)	67 (35.8%)
Vertigo	3 (4.0%)	28 (37.3%)	15 (20.0%)	29 (38.7%)	27 (36.0%)	20 (26.7%)
Fever	34 (25.8%)	60 (45.5%)	20 (15.1%)	18 (13.6%)	15 (11.4%)	49 (37.1%)
Tachycardia	2 (12.5%)	10 (62.5%)	1 (6.2%)	3 (18.8%)	0 (0%)	5 (31.3%)
Failures	0 (0%)	17 (40.5%)	3 (7.1%)	22 (52.4%)	9 (21.4%)	11 (26.2%)
Arthritis/synovitis	1 (6.2%)	12 (75.0%)	3 (18.8%)	0 (0%)	0 (0%)	6 (37.5%)
Arthralgia/myalgia	12 (12.0%)	57 (57.0%)	11 (11.0%)	20 (20.0%)	17 (17.0%)	25 (25.0%)
Hypothrombinaemia	0 (0%)	31 (100%)	0 (0%)	0 (0%)	0 (0%)	6 (19.4%)

MD, missing data.

For age, indication, reporting period and dosage regimen, the lines contain the number of cases and the percentage over all cases. Missing data are not described but are included in the percentage calculations.

^aRatio male/female.^bPercentage of cases reported as serious.^cMedian time to onset of effect from initiation of treatment (in days).^dStevens–Johnson syndrome, toxic epidermal necrolysis or acute generalized exanthematous pustulosis.

TABLE 4 Disproportionality analysis of levamisole-related adverse reactions at preferred term (PT) level

System organ class	Preferred term	Primary analysis ^a			Secondary analysis 1 ^b			Secondary analysis 2 ^c			Secondary analysis 3 ^d		
		n	ROR (95% CI)	P	n	ROR (95% CI)	P	n	ROR (95% CI)	P	n	ROR (95% CI)	P
Psychiatric disorders	All PT	183	1.4 (1.2–2.6)	.050	13	4.0 (2.0–7.8)	<.001	72	0.8 (0.4–1.5)	.509	32	7.4 (3.5–15.3)	<.001
Hepatobiliary disorders	All PT	72	2.4 (1.9–4.3)	.009	0	No cases [*]		58	No cases [*]		0	No cases [*]	
Renal and urinary disorders	All PT	65	1.3 (1.0–2.3)	.065	3	1.4 (0.4–4.7)	.608	42	2.1 (0.6–6.9)	.209	5	3.3 (0.8–14.2)	.108
Vascular disorders	Vasculitis	17	6.5 (4.1–10.6)	<.001	1	8.3 (0.5–133)	.136	3	0.4 (0.1–4.3)	.485	4	7.9 (0.9–72.4)	.066
Nervous system disorders	Encephalopathy	59	22.5 (17.4–39.9)	<.001	1	No cases ^{**}		50	7.8 (1.1–57.0)	.043	1	1.9 (0.1–30.9)	.650
Nervous system disorders	Neuropathy	25	4.3 (2.9–7.1)	<.001	0	No cases [*]		21	No cases [*]		1	No cases [*]	
Nervous system disorders	Convulsions	22	1.4 (0.9–2.4)	.064	1	0.4 (0.1–3.4)	.444	13	1.9 (0.2–15.0)	.521	0	No cases ^{***}	
Blood and lymphatic system disorders	Agranulocytosis	60	25.2 (19.5–44.7)	<.001	3	No cases ^{**}		18	0.9 (0.2–3.1)	.857	4	2.6 (0.6–12.0)	.217
Blood and lymphatic system disorders	Leucopenia	70	9.8 (7.7–17.5)	<.001	1	4.1 (0.4–46.0)	.247	47	7.3 (1.0–53.5)	.050	1	1.9 (0.1–30.9)	.650
Blood and lymphatic system disorders	Neutropenia	56	4.8 (3.7–8.5)	<.001	2	3.3 (0.6–17.3)	.153	17	1.3 (0.3–5.6)	.749	7	7.2 (1.4–35.6)	.015
Blood and lymphatic system disorders	Thrombocytopenia	32	2.8 (2.0–4.8)	<.001	1	4.1 (0.4–46.0)	.247	22	3.3 (0.4–24.9)	.241	2	3.9 (0.3–43.3)	.273
Skin and subcutaneous tissue disorders	SJS/TEN/AGEP ^e	5	1.3 (0.6–1.9)	.093	0	No cases [*]		3	No cases [*]		0	No cases [*]	
Skin and subcutaneous tissue disorders	All rashes ^f	187	1.5 (1.3–2.8)	.042	12	0.7 (0.4–1.4)	.337	109	1.4 (0.7–2.6)	.290	0	No cases ^{***}	
General disorders	Vertigo	75	1.1 (0.8–1.9)	.088	16	1.8 (1.0–3.2)	.038	25	0.2 (0.1–0.4)	<.001	0	No cases ^{***}	
General disorders	Fever	132	2.4 (2.0–4.4)	.008	14	2.7 (1.5–5.1)	<.001	54	0.5 (0.3–1.0)	.057	5	0.65 (0.2–1.9)	.432
Cardiac disorders	Tachycardia	16	1.3 (0.8–2.2)	.074	0	No cases [*]		9	No cases [*]		1	No cases [*]	
Cardiac disorders	Failures ^g	42	1.0 (0.7–1.7)	.101	0	No cases [*]		16	No cases [*]		10	No cases [*]	
Musculoskeletal disorders	Arthritis/synovitis	18	3.9 (2.4–6.3)	<.001	0	No cases [*]		12	No cases [*]		0	No cases [*]	
Musculoskeletal disorders	Arthralgia/myalgia	100	2.3 (1.9–4.2)	.010	4	4.2 (1.2–14.2)	.020	57	2.2 (0.8–6.1)	.134	3	1.4 (0.3–6.6)	.641
Investigations	Hypothrombinaemia	31	41.5 (29.1–70.6)	<.001	0	No cases [*]		27	No cases [*]		0	No cases [*]	

n: number of exposed cases; ROR: reporting odds ratio; CI: confidence interval.

^{*}No cases when levamisole is used as an anti-infective.^{**}No cases in mebendazole group.^{***}No cases when levamisole is used as an adulterant.^aPrimary analysis comparing levamisole-related cases with all cases reported in the World Health Organization pharmacovigilance database.^bSecondary analysis comparing adverse drug reactions (ADRs) after use of levamisole for an anti-infective indication with those occurring after use of mebendazole (control group).^cSecondary analysis comparing ADRs after use of levamisole for an immunomodulatory indication with those after its use for an anti-infective indication (control group).^dSecondary analysis comparing ADRs after use of levamisole for an adulterant action with those after its use for an anti-infective indication (control group).^eStevens–Johnson syndrome, toxic epidermal necrolysis or acute generalized exanthematous pustulosis.^fRegroups all rashes and all erythema.^gRegroups cardiac arrest, cardiorespiratory arrest, heart attack and chest pains.

anti-infectious action. The association between vasculitis and levamisole intake disappeared in the 3 secondary analyses. Arthralgia/myalgia were also more frequently reported with levamisole compared to mebendazole for anti-infectious purposes. Serious skin and subcutaneous tissue disorders were not more frequently reported with levamisole than with other drugs. Vertigo was more frequently reported with levamisole than with mebendazole and when levamisole was used for an anti-infectious purpose than for an immunomodulatory purpose.

3.4 | Levamisole mechanisms of action

Table 5 summarizes the mechanisms of action of levamisole identified from the scientific literature, their potential implication in the

occurrence of ADRs and their potential synergy with cocaine or 5-fluorouracil. We identified 11 different pharmacological mechanisms for levamisole. For each identified mechanism, we summarized the pharmacological effects both on worms and humans.

4 | DISCUSSION

Our study used a case–noncase approach to analyse data collected in the WHO drug adverse events database from 1977 to 2021 to assess the association between levamisole use and the reporting of suspected ADRs of interest. To our knowledge, it is the first study to review the main ADRs associated with levamisole. Significant disproportionality signals were found, with our results showing more frequent reporting of psychiatric disorders, hepatobiliary disorders,

TABLE 5 Mechanisms of action of levamisole and their potential synergy of action with 5-fluorouracil and cocaine

Mechanisms	Potential effects		Potential synergy	References
	On worms	On humans		
Nicotinic receptor agonist and allosteric modulator	Reduces the capacity of male worms to control their reproductive muscles and limits their ability to copulate	Mimics the effects of acetylcholine on nicotine receptors	Increases the pleasurable and behaviour reinforcing effects of cocaine	47,61
Inhibition of cyclic AMP-mediated glycogenolysis	Increases glucose incorporation into glycogen and decrease glycogen phosphorylase activity ratios			62
Selective inhibition of MAO-A and COMT		Resembles certain antidepressant drugs Limits the degradation of dopamine Increases dopamine concentration in the cerebral reward pathway	Potentiates the dopamine level due to cocaine inhibitory action in dopamine reuptake	63–65
Decrease of norepinephrine reuptake		Resembles certain antidepressant drugs Convulsions at high doses	Potentiates the norepinephrine release due to cocaine at sympathetic synapsis level	63,66,67
Anticholinesterase activity	Increases the concentration of acetylcholine	Increases the concentration of acetylcholine	Increases the pleasurable and behaviour reinforcing effects of cocaine	64,67
Endogenous opioid synthesis		Increases endogenous opioid concentrations in specific areas of the brain and in peripheral tissues	Potentiates cocaine effects	65
Metabolization into an amphetamine-like compound (aminorex)		Modulates norepinephrine, dopamine and serotonin levels	Potentiates cocaine effects	68–70,78
Local anaesthetic properties				79
Stimulation of T-cell		Activates and induces proliferation of T-cells	Potentiates 5-fluorouracil immunomodulatory activities	9,71
Potentialization of monocyte and macrophage functions		Increases phagocytosis and chemotaxis		
Increase neutrophil functions		Increases mobility, adherence and chemotaxis		

MAO-A: monoamine oxidase type A; COMT: catechol-omethyl transferase.

vasculitis, encephalopathies, neuropathies, agranulocytosis, leucopenia, neutropenia, thrombocytopenia, mild rashes, fever, arthritis, arthralgia and hypothermia. When comparing levamisole to mebendazole in anti-infectious indications, we identified new pharmacovigilance signals regarding hepatobiliary disorders, neuropathy, serious skin disorders, tachycardia, failures, arthritis and hypothermia. In addition, some other known ADR were not retrieved: leucopenia, neutropenia, thrombocytopenia, rashes and hypothermia. One of our main hypotheses is that levamisole is used at single dose in the vast majority of anti-infectious indications and that this administration regimen results in far fewer ADRs, with this reduction likely to be most significant for serious ADRs. This hypothesis is supported by 2 secondary analyses. Encephalopathies and leucopenia were more frequently reported when levamisole was used for an immunomodulatory action compared to when it was used for an anti-infectious action, and psychiatric disorders and neutropenia were more frequently reported when it was used as an adulterant than for its anti-infectious activity.

The majority of the levamisole-related ADRs concerned either its use in immunomodulatory indications, or when delivered as a multiple-dose regimen. The median times to onset of each ADR suggest that the drug induces short-term effects (vasculitis, convulsions, thrombocytopenia, rashes, vertigo, fever, failures, arthralgia, hypothermia) as well as delayed effects (encephalopathy, neuropathy, agranulocytosis, leucopenia, neutropenia, tachycardia and arthritis). These delayed effects could be immuno-mediated effects, potentially induced by the immunomodulatory properties of levamisole. If clinical trials on the use of levamisole in patients with COVID-19 give good results, its benefit-risk balance as an immunomodulator in this infection will have to be re-evaluated to enable its use in hospital or ambulatory settings. In June 2021, 4 clinical trials evaluating levamisole in the management of COVID-19 were reported in ClinicalTrials.gov, and the results of 1 of them have been published. The authors conclude that levamisole could potentially improve the cough and dyspnoea of patients with COVID-19 but no benefit could be demonstrated on mortality or aggravation of the disease.⁵³

The mechanisms of action of levamisole are multiple. It acts at the level of nicotinic receptors,^{47,61} the glucose pathway,⁶² dopaminergic pathways,^{63–65} norepinephrine and acetylcholine.^{63,64,66,67} In addition, secondary mechanisms exist such as its capacity to increase endogenous opiate synthesis,⁶⁵ to metabolize into an amphetamine-like compound,^{68–70} and to act on the immune system.^{9,71} Some of its mechanisms of action are synergistic with those of 5-fluorouracil, used in the treatment of cancers, or with those of cocaine. The fact that levamisole is often administered in combination with cocaine or 5-fluorouracil and the potential synergy of action between these molecules make it difficult to differentiate the molecule most likely to cause certain adverse effects.

Our study has several strengths. First, we used the global ADRs database VigiBase to collect information on suspected ADRs from nearly all national pharmacovigilance systems in the world, allowing us to identify new pharmacovigilance signals for rare events with

sufficient statistical power and to stratify on levamisole indication in secondary analyses. Second, our results are consistent with already known risks associated with levamisole (encephalopathy, agranulocytosis and vasculitis). Third, the analysis of real-life surveillance data with disproportionality analyses have already demonstrated their usefulness for detecting drug risks.^{72,73}

One of the main limitations of this study, inherent to all studies using pharmacovigilance databases,^{74,75} is related to the potential missing information. Under-reporting of suspected ADRs, differences in the capacity of reporting between countries and the lack of information about the total number of patients exposed to the drug may cause biased estimates. Nevertheless, there is no apparent reason why, in a specific region, ADRs would be more or less reported with levamisole than those occurring after treatment with any other drugs. Whilst this might mitigate potential bias in the results presented here, these results should be still interpreted with caution because of this potential missing information. Additionally, pharmacovigilance systems are not yet well established in African countries. In 2017, only 30% of these countries had specific procedures for the monitoring of ADRs and only 28% had a national platform for coordinating pharmacovigilance activities.⁷⁶ Despite the widespread usage of levamisole in some African, Latin American or Asian countries, there remains little information about its use or potential ADRs arising from this use. However, our analyses suggest a good safety profile of single-dose levamisole for anthelmintic treatment and its use could be considered in some focal areas where emergence of benzimidazole resistance may occur, due to the high drug pressure caused by mass administration of albendazole or mebendazole.⁷⁷

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COMPETING INTEREST

The authors claim to have no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from VigiBase. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from <https://vigilize.who-umc.org/> with the permission of VigiBase.

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