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MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Te Kāwanatanga o Aotearoa
New Zealand Government

MANATŪ HAUORA
MINISTRY OF HEALTH

Targeting SARS-CoV-2: An overview of COVID-19 treatments

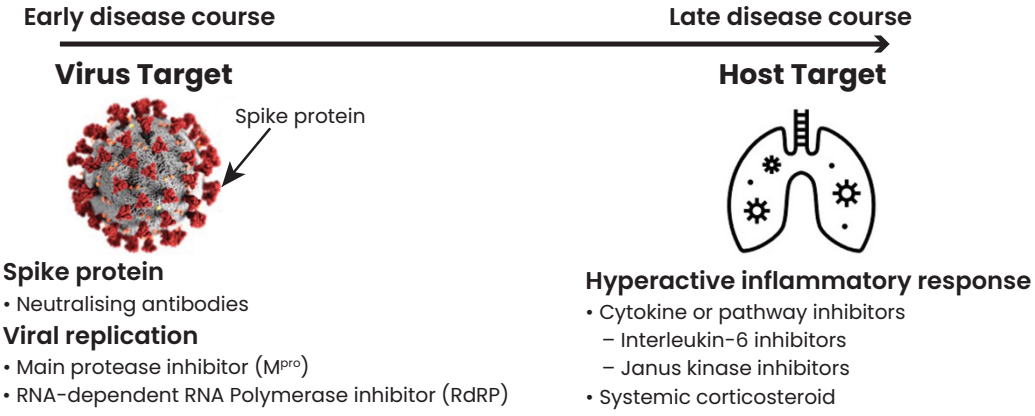
The number of COVID-19 treatments approved for use in New Zealand is increasing. Here we provide a summary of when they are used, how they work, and list examples from each drug class.

COVID-19 treatments in the different stages of infection

Early in COVID-19 infection, viral replication is thought to drive many of the initial signs and symptoms. Therefore, neutralising antibodies that prevent the virus from attaching or entering the cell and small molecule direct-acting antivirals that inhibit viral replication are anticipated to have the greatest effect on limiting disease severity (Figure 1).[1]

In the later course of infection, immune modulators are likely to be beneficial, particularly if disease is driven by immune dysregulation leading to excessive inflammation (Figure 1).[1,2]

Figure 1: SARS-CoV-2 virus and human host targets and potential COVID-19 treatments



Neutralising antibody treatments targeting the SARS-CoV-2 spike protein

The spike (S) protein on the surface of SARS-CoV-2 mediates attachment and entry of the virus to the host cell. Targeting this interaction with neutralising antibodies, such as monoclonal antibodies, can interfere with the virus entering the host cell.[3]

As the virus replicates, spontaneous mutations arise in the viral code. These mutations become selected, known as selective pressure, when they confer a survival advantage in the presence of the drug.[4] The S protein is under heavy selective pressure, which has led to variant mutations occurring within the S protein.[5] For example, the highly transmissible Omicron variant has up to 32 mutations in the S protein. Neutralising antibodies may have reduced activity against different variants of SARS-CoV-2. The susceptibility of circulating variants must be considered when prescribing a neutralising antibody treatment.[6]

Some medicines combine two types of neutralising monoclonal antibodies to reduce the risk of resistance associated with monotherapy.[7]

Small molecule direct-acting antiviral treatments

Small molecule direct-acting antivirals target critical stages of the viral replication cycle to suppress or inhibit viral replication.[7] Some targets for this class include the viral main protease (M^{pro}) and RNA-dependent RNA polymerase (RdRp).

M^{pro} inhibitors

The SARS-CoV-2 virus M^{pro}, also known as 3C-like protease (3CLpro), performs the first major step of viral replication.[3] It activates the proteins needed to form the viral replication complex.[3] Therefore, inhibiting M^{pro} prevents the virus from replicating.

The SARS-CoV-2 virus M^{pro} structure is different from that of human proteases, making it a highly specific target for therapeutics and reducing the risk of severe side effects.[3] Nirmatrelvir (with ritonavir) is a SARS-CoV-2 M^{pro} inhibitor.

Nucleoside analogues

RdRp is an enzyme responsible for replicating the SARS-CoV-2 RNA genome. After replication, the RdRp translates and transcribes the RNA to structural and accessory proteins.[3]

RdRp incorporates nucleoside analogues into the viral RNA strand. Remdesivir causes chain termination, which stops RNA synthesis. Molnupiravir causes mutations to accumulate over cycles, leading to viral error catastrophe (ie, where there are so many mutations that the virus is no longer viable).[7]

Resistance

M^{pro} and RdRp are highly conserved across coronaviruses and have a high barrier to resistance, as significant mutations in these enzymes would likely reduce pathogen virulence.[3] However, there is little published evidence on the potential for SARS-CoV-2 to develop resistance to therapies that target these enzymes. In other viral infections, resistance to nucleoside analogue monotherapies emerges extremely readily, whereas the inhibitory activity of protease inhibitors is more durable.[7]

Immune modulators

Immune modulators have an important role during the later course of infection, if a hyperactive inflammatory response occurs.[1] Interleukin-1 and interleukin-6 are likely the most relevant pro-inflammatory cytokines involved.[8] The choice of modulator ranges from non-specific and broad, such as corticosteroids, to very targeted, such as inhibiting one specific cytokine.[8]

Summary

Table 1 provides examples of COVID-19 medicines from each drug class. Note that some medicines may not be approved for use in New Zealand. The Medsafe website has the approval status of COVID-19 treatment applications.

Refer to the medicine data sheet for prescribing and adverse event information for approved medicines.

Table 1: Examples of COVID-19 medicines from each drug class

Drug class	Medicine[a]	Notes[b]
Neutralising antibodies targeting S protein	Casirivimab + imdevimab	See the Ronapreve data sheet. • Approved on 21 December 2021. • Two monoclonal antibodies that bind to non-overlapping areas of the S protein. • Indicated for the treatment and post-exposure prophylaxis of COVID-19. • Reduced neutralisation activity against the Omicron variant.

Drug class	Medicine[a]	Notes[b]
	Tixagevimab + cilgavimab	Two long-acting monoclonal antibodies that bind to non-overlapping areas of the S protein.[c]
	Sotrovimab	Single monoclonal antibodies that bind to the S protein.[d]
	Bebtelovimab	
M^{pro} inhibitors (Small molecule direct-acting antivirals)	Nirmatrelvir + ritonavir	See the Paxlovid data sheet. • Provisionally approved on 2 March 2022. • Nirmatrelvir is pharmacokinetically boosted with ritonavir. • 5-day course to be taken orally within 5 days of first symptoms. • Dose adjustment required in moderate renal impairment. Contraindicated in severe renal and hepatic impairment. • Consider drug-drug interactions due to cytochrome P450 3A inhibition.
Nucleoside analogues (Small molecule direct-acting antivirals)	Molnupiravir	See the Lagevrio data sheet. • Provisionally approved on 14 April 2022. • 5-day course to be taken orally within 5 days of first symptoms. • Causes lethal mutagenesis to viral genome. • Based on animal data, molnupiravir may cause fetal harm when administered to pregnant women.
	Remdesivir	Undergoing assessment. Proposed to cause RNA chain termination. See the New Zealand Formulary remdesivir drug monograph.
Immune modulators	Tocilizumab	See the Actemra data sheet. Extension of indications to treat COVID-19 was approved on 12 May 2022. A monoclonal antibody that blocks interleukin-6 receptors.[e]
	Baricitinib	A Janus kinase (JAK) inhibitor that may also have antiviral properties.[e] See the New Zealand Formulary baricitinib drug monograph.
	Dexamethasone	See the Dexmethsone data sheet. Extension of indications to treat COVID-19 was approved on 16 November 2020. Indicated in adults and adolescent patients (aged 12 years and older with body weight at least 40 kg) who require supplemental oxygen therapy.

Notes:

a. Examples given may not have approval for use in New Zealand. Information current to 12 May 2022. Emerging variants of concern and the efficacy of certain medicines may reduce. Refer to national or local guidelines for the latest information.

b. Unless otherwise referenced, the medicine information is sourced from the respective New Zealand data sheet.

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More information

- New Zealand Formulary: COVID-19 treatments
- Ministry of Health: COVID-19: Advice for all health professionals
- Pharmac: COVID-19 treatments portfolio and Access criteria

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WE NEED YOUR HELP!

Please send your reports to CARM for the potential safety issues* listed in the table below.

Medicine(s)	Potential safety issue	Active monitoring ends
Vildagliptin	Possible risk of vasculitis with vildagliptin products	22 August 2022

- M² (Medicines Monitoring) is a Medsafe scheme designed to collect more information on potential safety signals for specific medicines.

  Please send your report to CARM (as for any suspected adverse reaction). This can be done even if the reaction happened some time ago. Please include as much information as possible as this helps the medical assessors at CARM to investigate whether the medicine caused the reaction.

- For further information about M², see the Medsafe website.

* The appearance of a possible safety issue in this scheme does not mean Medsafe and CARM have concluded that this medicine causes the reaction.

Quarterly summary of recent safety communications

The table below is a summary of recent safety communications to health care professionals and consumers, published on the Medsafe website.

Date	Communication	Topic
10/05/2022	Dear Healthcare Professional Letter	Change in appearance of Motetis 25 mg tablets (PDF, 169 KB, 1 page)
08/04/2022	Alert	Reminder: Miracle Mineral Solution has dangerous and potentially life-threatening side effects
05/04/2022	Dear Healthcare Professional Letter	Supply of PAXLOVID (nirmatrelvir 150 mg/ ritonavir 100 mg), film coated tablets (PDF, 292 KB, 5 pages)
29/03/2022	Dear Healthcare Professional Letter	New improvements occurring on the ClopineCENTRAL™ website (PDF, 168 KB, 2 pages)
03/03/2022	Information leaflet	Risks of opioid medicines (PDF, 320 KB, 2 pages)
24/02/2022	Dear Healthcare Professional Letter	Supply of Nuvaxovid COVID-19 vaccine in New Zealand (PDF, 222 KB, 1 page)
22/02/2022	Monitoring	Possible risk of vasculitis with vildagliptin products (Galvus, Galvumet)

MARC's remarks: March 2022 meeting

The Medicines Adverse Reactions Committee (MARC) convened via videoconference on 10 March 2022.

The Committee reviewed the risk of drug-induced liver injury (DILI) with **glucagon-like peptide-1 receptor agonists** (GLP1-RAs). The Committee did not consider that the current evidence supports an association between GLP1-RAs and DILI. The Committee recommended removing the requirement for monitoring of liver enzymes from the liraglutide data sheet to align with the product information for other GLP1-RAs.

The Committee discussed the use of **venlafaxine** in pregnancy and whether the current evidence supports an increased risk of congenital malformations or gestational hypertension. The Committee agreed that the risk of gestational hypertension is biologically plausible, and while the available evidence may suggest an association, it is inconclusive. The Committee considered that the existing information on hypertension and gestational diabetes in the venlafaxine data sheets is sufficient. The Committee noted that the data sheets include the Australian 'Pregnancy – Category B2' heading. However, pregnancy category B2 is not consistent with the information in the data sheets on congenital abnormalities, and the Committee recommended removing the heading. The Australian pregnancy categorisation system is no longer used in New Zealand clinical practice and is not required in New Zealand data sheets.

The Committee reviewed the safety of **non-steroidal anti-inflammatory drug** (NSAID) exposure during the third trimester of pregnancy. The Committee recommended this review following the September 2021 meeting where they discussed the safety of NSAIDs during the second trimester. At that meeting, the Committee noted that the NSAID data sheets had inconsistent information regarding safety during the third trimester and recommended reviewing this topic at a future meeting. At the March 2022 meeting, the Committee concluded that all NSAIDs should be contraindicated in the third trimester of pregnancy. They recommended that Medsafe consult with the Committee to develop information for all NSAID data sheets that reflects the risks of use throughout pregnancy. This information will also be communicated in *Prescriber Update* when available.

See the Medsafe website for the MARC meeting minutes and the reports presented to the MARC.

Drug-drug interaction: Levothyroxine and ciprofloxacin

Key messages

- Case reports in the literature describe situations where concomitant use of levothyroxine and ciprofloxacin led to changes in thyroid function tests.
- If concomitant use is indicated, an interval of six hours between the administration of these medicines is recommended.

The Centre for Adverse Reactions Monitoring (CARM) received a report (CARM ID: 139087) where a patient taking levothyroxine had symptoms of hypothyroidism after taking a course of ciprofloxacin. The reported symptoms were a low heart rate, extreme fatigue and feeling cold. The symptoms improved upon stopping ciprofloxacin and temporarily increasing the levothyroxine dose. The reporter suspected an interaction between these medicines.

Background

Ciprofloxacin is a fluoroquinolone antibiotic indicated in adults for infections caused by ciprofloxacin-sensitive pathogens.[1]

Levothyroxine is indicated for the treatment of hypothyroidism.[2]

The interaction

There is limited evidence in the literature explaining this interaction.

A case report describes two patients on stable levothyroxine therapy who began concomitant ciprofloxacin.[3] Both patients subsequently experienced decreased free thyroxine and increased thyroid-stimulating hormone (TSH), which resolved upon stopping ciprofloxacin or separating administration by six hours.

A randomised cross-over study suggests that co-administration of ciprofloxacin reduces the intestinal absorption of levothyroxine.[4]

If concomitant use is indicated

Systemic ciprofloxacin may decrease the serum concentration of levothyroxine. Therefore, if patients taking levothyroxine require concomitant ciprofloxacin:

- instruct them to separate administration by six hours
- inform them about this potential interaction and the signs and symptoms to look out for (eg, fatigue, lethargy or feeling cold)
- monitor them for any changes in thyroid function.

Data sheet update

The ciprofloxacin and levothyroxine data sheets are being updated to include information about this possible interaction.

References

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Recent approvals: New active ingredients or new indications

For the period 16 January to 15 April 2022.

Recent approvals of medicines with new active ingredients

Trade name (active ingredient)	Dose form and strength(s)	Therapeutic area
Ajovy (fremanezumab)	Solution for injection 225 mg/1.5 mL	Migraine
Evrysdi (risdiplam)	Powder for oral solution 750 mcg/mL	Spinal muscular atrophy
Zejula (niraparib)	Capsule 100 mg	Epithelial ovarian, fallopian tube, or primary peritoneal cancer
Nuvaxovid* (COVID-19 vaccine with Matrix-M adjuvant)	Solution for injection 10 mcg/mL	COVID-19 prevention
Paxlovid* (nirmatrelvir; ritonavir)	Film-coated tablet 150 mg/100 mg	COVID-19 treatment
Lagevrio* (molnupiravir)	Capsule 200 mg	COVID-19 treatment

* Provisional approval.

Approved medicines with new indications

Trade Name (active ingredient)	Dose form and strength(s)	New therapeutic area(s)
Lenvima (lenvatinib)	Capsule 4 mg 10 mg	Endometrial carcinoma
Xolair (omalizumab)	Solution for injection 75 mg 150 mg	Chronic rhinosinusitis with nasal polyps
Yervoy (ipilimumab)	Concentrate for injection 50 mg/10 mL 200 mg/40 mL	Malignant pleural mesothelioma
Winglore (ipilimumab)	Concentrate for injection 50 mg/10 mL 200 mg/40 mL	Malignant pleural mesothelioma
Keytruda (pembrolizumab)	Concentrate for infusion 25 mg/mL (100 mg/4 mL)	Endometrial carcinoma
Opdivo (nivolumab)	Concentrate for infusion 40 mg/4 mL 100 mg/10 mL	Malignant pleural mesothelioma Oesophageal squamous cell carcinoma

See the Medsafe website for:

- more information about these medicines
- data sheets of currently marketed medicines.

Can Vitamin E cause bleeding?

Key messages

- Although the data is limited, there are plausible mechanisms whereby vitamin E may cause bleeding:
  - the main oxidation product of alpha-tocopherol (a type of ingestible vitamin E) is tocopheryl quinone, which has anticoagulant properties
  - vitamin E may inhibit platelet aggregation.
- The recommended daily intake of vitamin E is 10 mg for men and 7 mg for women. Exceeding the recommended dose could theoretically cause clinically significant bleeding.

The Centre for Adverse Reactions Monitoring (CARM) received a report of vitamin E toxicity. A patient experienced easy bruising after finishing a dietary supplement containing high levels of vitamin E.

Vitamin E

Vitamin E is a lipid-soluble antioxidant.[1] It has an important role as a free radical scavenger to protect polyunsaturated fatty acids from oxidation.[2,3] Humans cannot synthesise vitamin E and must ingest it from the diet, primarily from fats and oils.[2,4] Olive and sunflower oils have high levels of alpha-tocopherol, the primary bioactive form of vitamin E.[2,4]

The recommended daily intake of vitamin E (as alpha-tocopherol equivalents) for adults in New Zealand is 10 mg for men and 7 mg for women.[3,4]

Bleeding

There are biologically plausible mechanisms whereby vitamin E may cause bleeding. Tocopheryl quinone is an oxidised form of alpha-tocopherol with anticoagulant activity.[4,5] It can interfere with vitamin K metabolism, theoretically causing bleeding.[5] Vitamin E may also inhibit platelet aggregation.[2,6] However, there is limited data to support high vitamin E levels causing bleeding, and the clinical significance of high vitamin E levels is also unknown.

In the case report mentioned above, the product ingested contained about 30 times the recommended daily intake of Vitamin E. The side effects also occurred within a plausible time frame. Consideration should be given to the theoretical possibility of vitamin E as a cause of bleeding.

Further information

The Medicines Adverse Reactions Committee discussed this topic at the 188th meeting in December 2021. For further information, see the meeting minutes and meeting report.

References

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Gathering knowledge from adverse reaction reports: June 2022

Adverse reaction reporting is an important component of medicine safety monitoring. Case reports can highlight significant safety issues concerning therapeutic products and their use.

The table below presents a selection of recent informative cases from the Centre for Adverse Reactions Monitoring (CARM) database.

Case details[a,b]	Reaction description and data sheet information[b,c]
CARM ID: 141803 **Age:** 68 **Gender:** Female **Medicine(s):** Alendronic acid + Colecalciferol **Reaction(s):** Uveitis	Two weeks after starting alendronic acid + colecalciferol, the patient developed gritty, red eyes, photophobia and reduced visual acuity, which worsened following each weekly dose. She was diagnosed with bilateral anterior uveitis.
	Uveitis is listed as a rare ADR in the Fosamax Plus data sheet.
CARM ID: 142360 **Age:** 12 **Gender:** Female **Medicine(s):** Lamotrigine **Reaction(s):** Stevens Johnsons syndrome	Approximately three weeks after starting lamotrigine, the patient developed lesions on her lips. Lamotrigine was discontinued but the lesions continued. She also developed erythematous maculopapular lesions on her skin, back, face, chest, arms and palms. SJS was confirmed on biopsy.
	The Logem data sheet states serious potentially life-threatening skin rashes, including Stevens-Johnson syndrome, have been reported. The risk of serious skin rashes in children is higher than in adults. Physicians should consider the possibility of a medicine reaction in children that develop symptoms of rash and fever during the first eight weeks of therapy. In patients taking lamotrigine, the overall risk of rash is strongly associated with: • high initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy • concomitant use of valproate.

Case details[a,b]	Reaction description and data sheet information[b,c]
CARM ID: 142835 **Age:** 39 **Gender:** Female **Medicine(s):** Ethinylestradiol + Levonorgestrel **Reaction(s):** Cerebral infarction	A patient taking long-term ethinylestradiol + levonorgestrel experienced a cerebral infarct. The Levlen ED data sheet contains warnings about the risks of arterial and venous thromboembolism (ATE and VTE, respectively) and combined oral contraceptives (COCs). Inform COC users of the symptoms of ATE and VTE and advise them to seek urgent medical attention if symptoms develop. See also: • the *Prescriber Update* article: Reminder: Counsel patients about symptoms and signs of venous thromboembolism when prescribing combined oral contraceptives • the bpac[nz] article: Oral contraceptives: selecting a pill.
CARM ID: 143058 **Age:** 72 **Gender:** Female **Medicine(s):** Omeprazole **Reaction(s):** Drug rash with eosinophilia and systemic symptoms (DRESS)	Three weeks after starting omeprazole, the patient developed a macular rash on her lower limbs that spread to her entire body. Blisters developed, and her eosinophil count was slightly raised. DRESS is listed in the Omeprazole Actavis data sheet. See also the *Prescriber Update* articles: • DRESS: a pleat for help • DRESS syndrome – monitor for long-term sequelae
CARM ID: 143176 **Age:** 59 **Gender:** Male **Medicine(s):** Clobetasol propionate **Reaction(s):** Cushing's syndrome	The patient applied clobetasol propionate over his entire body for almost 6 weeks. He developed iatrogenic Cushing's syndrome, with a moon face, adrenal suppression and diabetes. Clobetasol propionate is a very potent topical corticosteroid. The Dermol data sheet states manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary adrenal (HPA) axis suppression, leading to glucocorticosteroid insufficiency, can occur in some individuals as a result of increased systemic absorption of topical steroids. Risk factors for increased systemic effects include potency and formulation of the corticosteroid, duration of exposure and application to large surface areas. See also the *Prescriber Update* article: Adrenal suppression associated with the use of topical steroids.

Notes:

a. Only the medicines suspected to have caused the reaction are listed in the table.

b. The reactions listed in the 'Case details' column are coded according to the Medical Dictionary for Regulatory Activities (MedDRA), an internationally used set of standardised terms relating to medical conditions, medicines and medical devices. The reactions listed in the 'Reaction description' column are based on what was reported to CARM, and do not always match the MedDRA term.

c. If the suspect medicine's brand name is not described in the report to CARM, only the data sheet for the funded medicine is included in the table.

Information about suspected adverse reactions reported to CARM is available on the Medsafe website using the Suspected Medicines Adverse Reaction Search (SMARS).

By selecting the ingredient of a medicine, you can find out:

- the number of reports and suspected adverse reactions for that ingredient. The suspected reactions are grouped by body system or organs (Summary report)
- single case reports, listing the medicines involved that contain the ingredient and the suspected adverse reactions (Detail report).

Reminder: Potential for abuse, dependence and withdrawal with benzodiazepines

Key messages

- Benzodiazepines have the potential to be misused – even when taken at the recommended dosages. Counsel patients about these risks when initiating treatment with benzodiazepines.
- Regularly review the ongoing need for treatment.
- Following continuous or high-dose use, benzodiazepines must be gradually tapered to reduce the risk of withdrawal reactions.

The New Zealand benzodiazepine data sheets were recently updated with additional information about the potential for abuse, dependence and withdrawal. This article is a reminder of these risks.

Benzodiazepines have the potential to be misused

Benzodiazepine use can lead to misuse, abuse, and dependence, even when taken at recommended dosage.[1] Dependence can occur with continuous use over several days to weeks, even when taken as prescribed.[1] Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with opioids, alcohol or illicit drugs.[1] Counsel patients about these risks when initiating treatment with benzodiazepines.[2,3]

Before prescribing and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.[2] Use caution when prescribing benzodiazepines to patients with a history of alcohol or drug abuse, those known to be addiction prone or with a history that suggests they may increase the dosage on their own initiative.[2]

When prescribing a benzodiazepine for anxiety or insomnia, ensure the patient understands that these medicines are intended for short-term use (2-4 weeks).[3] Non-pharmacological approaches are generally preferred for first-line treatment. Long-term use of benzodiazepines for these indications is not recommended.[4]

New Zealand dispensing data shows that diazepam and lorazepam are the most dispensed benzodiazepines. The total amount of dispensing of these medicines for all indications has increased over the period of available dispensing data (2016–2020),[5] which may suggest frequent and/or long-term use.[3]

Regularly review the ongoing need for treatment

Ongoing use of benzodiazepines may lead to dependence.[2] The risk of dependence increases with dose and duration of treatment and in patients with a history of alcohol or drug abuse or a marked personality disorder.[2]

Regularly review the ongoing need for treatment, particularly if the patient is at high risk of dependence.[2]

Slowly discontinue treatment to prevent withdrawal reactions

Abrupt discontinuation or rapid dosage reduction of benzodiazepines after continued use may lead to withdrawal reactions.[2]

The likelihood and degree of severity of withdrawal depends on the duration of treatment, dose and degree of dependency.[2] Sudden cessation of benzodiazepines that have been used continually and/or at high doses is associated with serious withdrawal reactions, such as convulsions, delirium or psychosis.[4] Inform patients of these risks and advise them to consult their doctor before decreasing the dose or abruptly stopping the medicine.[2]

Discontinuing a benzodiazepine following continuous use must be gradual. Advise patients that stopping treatment requires an individualised tapering schedule that is supervised by their doctor.[2,4]

New Zealand case reports

Between August 1969 and March 2022, the Centre for Adverse Reactions Monitoring received 23 case reports for benzodiazepines where the reported reactions included withdrawal and/or dependence. Clonazepam (9 cases) was the most frequently reported benzodiazepine, followed by lorazepam (5), diazepam (3) and triazolam (3).

More information

See the following bpac^{nz} articles:

- Benzodiazepines and zopiclone: is overuse still an issue? - February 2021
- Withdrawing patients from long-term use of benzodiazepines or zopiclone – February 2021

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Febrile seizures in children are rare

Key messages

- A febrile seizure is a convulsion caused by a rise in body temperature in infants and young children. Febrile seizures have been reported following vaccination.
- Nearly all children who experience a febrile seizure will recover quickly. There is no evidence to suggest that a simple febrile seizure causes long-term neurological harm.
- Children with a history of febrile seizures following vaccination can safely continue vaccination in their usual setting.

Febrile seizures occur in children with fever and have been reported following vaccination. The Centre for Adverse Reactions Monitoring (CARM) receives about eight reports per year of febrile seizures associated with childhood vaccines.

Febrile seizures

Febrile seizures (also called febrile convulsions) are seizures that occur when a child has a fever.[1] They are an age-dependent phenomenon occurring in 2 to 4 percent of young children, one-third of whom may experience another febrile seizure in the future. Commonly identified risk factors include high fever, viral infection, recent immunisation and a family history of febrile seizures.[2]

Febrile seizures can occur with any condition that causes a fever. In children, fevers are commonly caused by colds, influenza, nd various infections, such as ear infections. There is a small increased risk of febrile seizures following vaccination with inactivated or live-attenuated vaccines. Overall, febrile seizures following vaccination remain a rare adverse event.[3–5]

Diagnosis and management

A febrile seizure is a clinical diagnosis defined by the following features:[2]

- a convulsion associated with an elevated temperature of greater than 38°C
- a child older than 6 months and younger than 6 years of age
- absence of central nervous system infection or inflammation
- absence of acute systemic metabolic abnormality that may produce convulsions
- no history of afebrile seizures.

The majority of febrile seizures end spontaneously, and the child recovers quickly. In these cases, febrile seizures do not require treatment with medicines. More complex cases may require treatment with benzodiazepines.[6]

Children diagnosed with febrile seizures do not generally require follow-up unless they have one or more features of concern:

- more than three seizures
- under 6 months or older than 6 years of age
- seizures lasting longer than 30 minutes
- seizures with focal signs
- seizures that are not tonic-clonic.

In these cases, children should be referred to a paediatrician for additional investigation.[1,6]

Information for parents and caregivers

Prescribers should inform parents and caregivers that febrile seizures are generally self-limiting and do not cause long-term brain damage or epilepsy. However, the child may have another febrile seizure in future. Provide parents and caregivers with information on what to do if their child experiences another fever or febrile seizure.[7,8]

- There is no way to prevent febrile seizures. Keeping the child cool when they have a fever will make them more comfortable but not prevent a seizure.
  - Antipyretics (paracetamol) may help to reduce the fever. Always follow the dosage instructions on the bottle.
  - Use simple cooling measures to reduce body temperature (eg, undress to a single layer, make sure the room is not too hot or cold).
- In the event of another seizure, lie the child down on their side, do not put anything in their mouth, wait a few minutes for the seizure to stop and seek medical care as advised. If the seizure does not resolve within 5 minutes, call an ambulance.

The KidsHealth and Health Navigator websites have information for parents and caregivers about febrile seizures.

New Zealand case reports

Between March 1989 and 31 March 2022, the Centre for Adverse Reactions Monitoring (CARM) received 184 reports of febrile seizures/convulsions associated with vaccines. The most frequently reported vaccines were measles-mumps-rubella (MMR), meningococcal B, diphtheria-tetanus-acellular pertussis-polio (DTaP-IPV) and diphtheria-tetanus-acellular pertussis-polio-hepatitis B/Hib (DTaP-IPV-HepB/Hib). It is important to note that multiple vaccines can be administered to a child concomitantly. Therefore, a febrile seizure cannot be isolated to any one vaccine.

Conclusion

Febrile seizures can occur in children with fever, usually due to systemic viral or bacterial infection but may, in rare cases, arise from recent vaccination. Vaccines are a key measure to prevent and reduce the burden of various diseases in children and the wider community. The prognosis for children with febrile seizures is favourable, and therefore, future vaccinations should be encouraged and can be safely administered to children in their usual setting.[5]

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