

Medication

This section describes the medications used in IBD, how they work, when they are used and their more common and important side effects. The list of side effects is not all-inclusive. If you think one of your medications is causing a side effect, consult your doctor. It is important not to treat yourself.

This section does not discuss any non-drug therapies such as dietary changes, surgery or psychological support. They are addressed in other chapters.

Many medications are used to treat IBD. They may be given for a variety of reasons including to:

- suppress inflammation in those with active disease
- prevent flare-ups in those with inactive disease
- control symptoms such as pain or diarrhoea
- replace or supplement essential nutrients that are poorly absorbed because of extensive disease or surgery.

The goal of most medications is to bring the inflammation from Crohn's disease and ulcerative colitis under control. By reducing the inflammation, they can relieve the symptoms of IBD, allow the bowel to heal, and reduce the chances that long-term complications will develop.

Remember that all treatments used in medicine (medications, surgery, radiation) have risks. Every time a doctor prescribes a medication to a person with IBD, the

risks of the medication must be weighed against the risks of continuing or worsening symptoms and the risk of developing complications.

It is best not to be too alarmed by the long list of possible side effects with some medications. Most side effects are uncommon and are fully reversible with cessation of the medication. Prior to starting on any new medication, the potential benefits and risks of any therapy should be fully discussed between you and the medical team. Be sure to ask questions and discuss any concerns.

Your clinical team will work out a treatment plan based on your own individual circumstances. It is quite common for people with IBD to require a combination of medications to achieve the best result. As IBD is a chronic condition, many people will need to take medications for long periods of time. Stopping your medications can result in a flare-up of symptoms so always consult with your doctor before stopping medication, even if you feel well.

The medications are given in a number of ways depending on the location and severity of disease: as tablets or capsules, intravenously or by injection, and sometimes as enemas, rectal foam or suppositories.

If you are on a medication that suppresses the immune system, you should avoid vaccines that contain a live virus like the chicken pox and measles vaccines. The flu jab and Covid vaccines are not live vaccines. They are safe and are recommended for people with IBD.

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Medications that reduce inflammation

1. 5-aminosalicylic acid (5-ASA), also called mesalazine.

Nearly all individuals with ulcerative colitis and some with Crohn's disease take 5-aminosalicylic acid, or 5-ASA, which is chemically related to but not the same as aspirin.

5-ASA is useful for the treatment of mild attacks of ulcerative colitis or Crohn's disease, but its main role is in patients with inactive ulcerative colitis, where it markedly reduces the chance of a flare-up.

Taking 5-ASA does not guarantee that you will remain well, but it does significantly lower the risk of a flare-up. This effect probably persists indefinitely and many patients with ulcerative colitis take a 5-ASA-containing medication for life. There is no evidence that long-term use of 5-ASA is harmful. In fact, there is some evidence that taking these medications long-term may lower the risk of colon cancer in patients with ulcerative colitis.

To be effective in reducing inflammation, the 5-ASA must get to the colon, where it has a direct anti-inflammatory effect. Since pure 5-ASA is completely absorbed from the upper gut, long before it reaches the colon, all the 5-ASA medications have been formulated to prevent absorption high up in the digestive tract. There are

four 5-ASA preparations available in New Zealand. Most studies have found them to be equally effective, both in the treatment of mild attacks of ulcerative colitis and in preventing flare-ups.

Sulphasalazine (Salazopyrin®)

Sulphasalazine is 5-ASA chemically linked to a sulfa drug. The linkage to the sulfa molecule prevents the medication from being absorbed in the upper intestinal tract. It was the first 5-ASA drug and has been around since the 1950s. It is rarely used today as many people have allergies to sulfa and it can cause infertility in men.

5-ASA or mesalazine (Pentasa® and Asacol® and Dipentum)

There are several varieties of mesalazine, each with different mechanisms of 5-ASA release. The most commonly used brands in NZ are Pentasa and Asacol.

Asacol tablets are coated with a polymer that prevents absorption until the tablets reach the end of the small intestine.

Pentasa tablets have prolonged-release granules that slowly dissolve and release the mesalazine throughout the gastrointestinal tract, ensuring that most of the medication reaches the colon. Pentasa tablets may be dispersed in 50ml of cold water. Stir and drink immediately. Pentasa also comes in a 'granule' form, rather than a tablet, which some patients find easier to swallow.

Dipentum (olsalazine) is an older form of 5-ASA. It is two 5-ASA molecules connected by a chemical bond that prevents



absorption in the small intestine. Bacteria in the colon are able to break the bond that activates the medication in the large intestine. It is rarely used today as it can cause diarrhoea in about 15% of people. This can sometimes be avoided by starting on a low dose and gradually increasing the dosage over time. Due to the issue with diarrhoea, people are usually started on the other two forms of 5-ASA that are available in New Zealand: Pentasa or Asacol.

Side effects of Pentasa and Asacol are relatively uncommon, but nausea, abdominal pain, headaches, diarrhoea and rashes do occasionally occur. There have been a few reports of kidney damage, presumably due to the small amount of 5-ASA absorbed from the small bowel. For this reason, doctors will monitor your kidney blood tests periodically. These formulations of mesalazine/salazine do not cause male infertility. You should tell your doctor if you think you are allergic to aspirin.

5-ASA enemas and suppositories (Topical preparations)

Ulcerative colitis confined to the rectum and lower part of the large bowel can be treated by medications inserted into the rectum. These preparations come in both enema and suppository forms. This method of treatment has the advantage of delivering large amounts of the medication to the site of inflammation with very little absorption into the blood (and therefore very low rate of side effects).

5-ASA (mesalazine) enemas and suppositories are sometimes used in combination with oral 5-ASA (Pentasa or Asacol tablets), since taking the 5-ASA from 'above and below' often works better than either route alone.

While the 5-ASA suppositories are easier to use than enemas, they are most useful for disease that is confined to the lowest part of the bowel (the rectum).

2. Corticosteroids (steroids)

Corticosteroids are medications used in the treatment of moderate to severe IBD. Steroids are very effective and fast-acting in suppressing inflammation but have the drawback of having several potential side effects. The most common preparation is prednisone, which is a tablet that is usually given to control bad flare-ups in the outpatient setting.

Another oral form of steroids is budesonide (Entocort, Cortiment), which tends to cause fewer side effects. It is currently only funded for people with Crohn's disease who have involvement in the small intestine, right side of the colon and who have experienced serious side effects to prednisone in the past (your doctor needs to make a special application to prescribe budesonide as it is more expensive).

If you are in the hospital, you may be given hydrocortisone, which is a steroid that can be given through the vein (intravenously). These steroids should not be confused



While it is important to be aware of the side effects of your medications, it is important to remember that they do not always occur.



with steroid sex hormones or with anabolic steroids used by body builders and athletes.

Although steroids are an effective treatment for more severe IBD, their use is restricted by important side effects. Therefore, high doses are used to bring attacks under control, after which they are gradually withdrawn over weeks to months. Prolonged use of oral steroids should be avoided, and they have no role in preventing flare-ups in those with inactive disease.

Side-Effects of Corticosteroids

Corticosteroids affect a number of different body systems and, as a result, there is a wide range of possible side effects. While it is important to be aware of the side effects, it is also important to remember that they do not always occur and for most people these are temporary problems that tend to resolve once the dosage is reduced or treatment discontinued.

Patients with IBD are often reluctant to take steroids because of their possible effects on bodily appearance. The most common changes are increased appetite and weight gain, rounding (or 'mooning') of the face, redness of the skin, acne, facial hair, easy bruising and ankle swelling. Rapid changes in weight can cause stretch marks. Some people develop weakness of the

muscles of the upper arms and legs with long-term use.

Mood changes can also occur, usually a feeling of wellbeing, but occasionally agitation, irritability, sleep disturbance, psychosis or depression.

There are a number of less visible side effects. Steroids weaken the body's resistance to infection. You should always consult your doctor if you develop an infection while you are taking steroids. They also cause thinning of the skin and impair healing after cuts or surgery.

While steroids do not cause diabetes, they may raise blood sugar levels. Some patients with a predisposition to diabetes may require treatment for diabetes after starting steroids. Those with pre-existing diabetes may need to have their medications adjusted. Steroids can also raise blood pressure and lower the level of potassium and phosphate in the blood, occasionally causing fatigue and weakness.

Prolonged use of steroids in children may retard growth. However, children with active IBD will not grow normally until the disease is brought under control. The long-term effects of withholding treatment may be significantly greater than the side effects of steroids, especially as children with IBD



often experience a growth spurt after their disease is controlled. Therefore, the potential benefits of steroids in children must be weighed against the risks.

All of the side effects mentioned so far are reversible. They resolve when the steroids are stopped. However, there are also a small number of irreversible side effects. These include development of cataracts and, most importantly, effects on the bones.

Corticosteroids can lead to osteoporosis, or softening of bones, with the result that bones can break more easily. Osteoporosis develops gradually, particularly when high doses have been used for long periods of time and is more likely in those with other risk factors (e.g. women after menopause).

Treatment to prevent osteoporosis, such as combinations of calcium and vitamin D supplements are sometimes given in conjunction with a course of steroids. Rarely, steroids can cause a sudden loss of blood supply to the bone of the hip joint (avascular necrosis of the head of the femur) and cause damage to the joint.

The body's normal steroid production can slow or stop after you have been on steroids

for a period of time. This occurs because the body senses that there are more steroids around than normal. Since steroids are necessary for the body to function, when an attack of IBD is under control, the dose of steroids should be reduced gradually to allow the body to take over again.

As increased levels of corticosteroids are necessary for your body to cope with physical stresses such as surgery or severe illness, you should always tell your doctor, dentist or any paramedical person treating you if you are on steroids or have taken them recently. You should never stop taking steroids suddenly unless advised to do so by your doctor.

3. Immunomodulators

These medications work by suppressing the normal function of the immune system to reduce inflammation in the body and, in particular, in the gastrointestinal tract. On their own, these agents do not usually suppress the immune system to the extent it is unable to defend the body against everyday infections. They can sometimes take several weeks (or even months) to start working.

These medications are used in people with moderate-to-severe IBD to keep people in remission. The exception is Cyclosporin which is begun in the hospital and used in very severe disease which is not responding to corticosteroids.

Azathioprine (Imuran®) and 6-mercaptopurine (6-MP, Azasan), Thioguanine

Azathioprine and 6-mercaptopurine are the most commonly used immunosuppressive agents in IBD. Azathioprine is converted to 6-mercaptopurine by the body and then to thioguanine. It is thioguanine that has is the active 'metabolite' that reduces inflammation.

These medications are generally started when the disease is not responding to steroids or controlled only by repeated courses of steroids. Sometimes they are started after surgery to make sure people stay in remission. These medications are available in tablet form.

Azathioprine, 6-MP and thioguanine have been shown to control difficult Crohn's disease and ulcerative colitis, and to prevent flare-ups of both diseases. They have a 'steroid sparing' effect, often allowing people to come off steroids and, hopefully, avoid flares which might require more steroid use in the future. Most people, once started on these medications, take them for many years.

Side-effects of azathioprine and 6-MP

Approximately 10% of individuals are unable to continue taking these medications because of side effects. However, these side effects resolve on stopping the medication. It is not possible to predict who will get side effects, although some patients are deficient in the enzyme (TPMT) that breaks down the medications. If people have low levels of this enzyme, the medication needs to be started at a much lower dose.

The most important side effect is suppression of the bone marrow, leading to reduced production of blood cells, particularly white blood cells, which are the body's main defence against infection. Bone marrow suppression can also cause easy bruising.

All patients taking this medication require regular blood tests and should report any signs of infection (e.g. fever, chills or sore throat), bleeding or bruising immediately. Bone marrow suppression is uncommon and is reversible if the medication is stopped.

Other side effects include nausea and vomiting, flu-like illness with or without fever and rashes, hair loss, inflammation of the liver and abdominal pain due to inflammation of the pancreas (pancreatitis).

It needs to be mentioned that there is also a very, very slight increased risk of developing certain cancers such as lymphoma (a cancer of the lymph glands) and non-melanoma skin cancers. For the latter reason and because New Zealanders have a high risk of skin cancer, people should use



You should always tell your doctor, dentist or any medical professional treating you what medications you are currently taking.

sun block, cover up clothing, and wear a hat when they are out in the sun.

While these risks can be scary, remember that the chance of developing a cancer as a result of being on these medications is extremely unlikely. If your medical team recommends these medications, it is likely because they feel that the risks of having your disease not under control far outweighs the risks of being on these medications.

Cyclosporin (Neoral®, Sandimmun®)

Cyclosporin has the advantage of a rapid onset of action. Cyclosporin is most commonly used in people with severe ulcerative colitis that are not improving on high dose intravenous steroids in the hospital and are at risk of needing urgent surgery. Side effects are more likely to occur when cyclosporin blood levels are high so regular monitoring of blood levels is essential (blood test just before a dose of cyclosporin).

Cyclosporin has a number of side effects that are often reversible with a dose reduction or cessation of this medication. Side effects include high blood pressure, impaired kidney function, susceptibility to infections, nausea, loss of appetite, facial hair, tremor, pins and needles or numbness of the fingers and toes, headaches, gum swelling and epileptic seizures.

Methotrexate (Ledertraxate®, Methoblastin®)

Methotrexate may be helpful for IBD that is not responding to other medications or in patients who cannot tolerate medications like azathioprine and 6-mercaptopurine. It is usually given as a weekly tablet or injection.

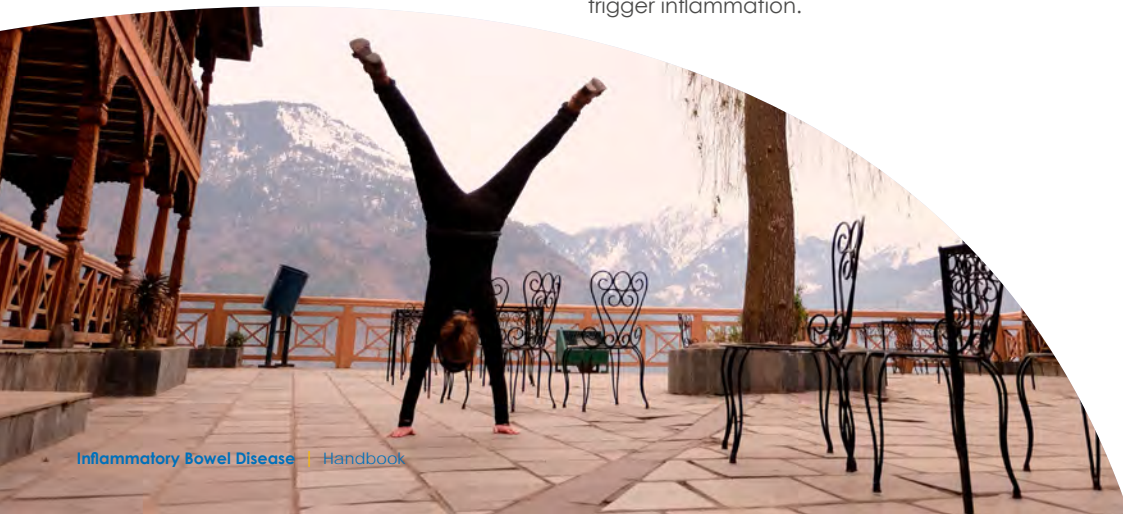
The most common side effect is nausea and mouth ulceration, which can improve with folic acid supplements. Folic acid is also necessary for blood formation. Other less common but more serious side effects include liver or lung damage and low blood counts due to bone marrow suppression.

If you are on this medication, you should limit your alcohol intake as this greatly reduces your risk of liver damage.

Methotrexate is a known teratogen, meaning it can cross the placenta and damage an unborn child. It is crucial not to get pregnant on this agent (a reliable contraceptive is needed) and, regardless of your sex, if you are planning a family in the near future and you have been prescribed this medication, you should discuss this with your doctor.

Biological agents – Infliximab (Remicade®) and Adalimumab (Humira®)

Biologicals are a newer category of immunomodulator that work by blocking the effects of specific substances (inflammatory mediators) that are produced by the immune system and trigger inflammation.





One inflammatory mediator known to promote inflammation in people with IBD is called tumour necrosis factor (TNF). Therefore, these medications are commonly called TNF blockers or anti-TNF agents. They work by blocking the activity of TNF and prevent inflammation. They often work very quickly and are usually very effective in reducing inflammation and improving symptoms.

These agents are used in the treatment of moderate to severe Crohn's disease and ulcerative colitis unresponsive to other therapies. They can also be effective in treating fistulae in patients who have Crohn's disease involving the anal region.

Infliximab is given as an intravenous infusion and adalimumab is self-administered by the patient via an injection under the skin. Once you are on these medicines, your doctor can monitor the levels of the medications in your blood. They can adjust the dose if the level is too low.

The most common side effect of the anti-TNF agents is an infusion or injection site reaction, which is usually minor and can be managed by your doctor or IBD nurse. Rarely, a severe allergic-type reaction can occur. Since these medications suppress the immune system, there is an increased

risk of getting infections. Serious infections are unlikely, but can occur, so it is important to notify your doctor if you feel ill or have a fever. Serious infections are more common if people are on more than one immunosuppressant medication, especially if one of those is a steroid.

Before starting you on a biological, your doctor or nurse will check and make sure you have immunity to common illnesses like chicken pox and do not have tuberculosis, HIV, or hepatitis.

Like some of the immunomodulator medications, there is also a very, very minimal increased risk of certain cancers. Your doctor or IBD nurse will discuss these risks in more detail.

There are newer biologicals that work differently from the anti-TNF agents, infliximab (Remicade®) and adalimumab (Humira®). One of these is ustekinumab (Stelara®) and the other is vedolizumab (Entyvio®). Rather than interfering with the actions of TNF, ustekinumab interferes with the inflammatory-causing effects of other mediators of inflammation called interleukins. Vedolizumab interferes with the inflammatory-causing effects of integrin $\alpha_4\beta_7$.

Since these newer biologicals work differently for the anti-TNF medications, they can be very useful if infliximab and adalimumab are not working or if they lose effectiveness over time, which occurs in about 50% of people over five years.

We hope to have these newer biologicals available in New Zealand soon.

4. Antibiotics

Metronidazole (Flagyl®) and Ciprofloxacin

Metronidazole and ciprofloxacin are both antibiotics that have a role in the treatment of IBD. They are used almost exclusively in patients with Crohn's disease – most commonly to control anal complications such as abscesses or fistulae (abnormal channels, usually between intestine and the skin or other organs). Additionally, metronidazole is also used in some patients shortly after surgery for Crohn's disease (alone or in combination with azathioprine)

to prevent early recurrence of Crohn's disease in their remaining intestine.

The most common side effects of metronidazole are nausea, loss of appetite, a metallic taste in the mouth, diarrhoea and headache. Prolonged treatment with metronidazole can damage the nerves in the feet and arms, leading to tingling and numbness. This is mostly reversible on stopping the medication but may take some months to return to normal.

Some people have an unpleasant reaction to the combination of metronidazole and alcohol (flushing of the face, severe nausea, headache, palpitations, shortness of breath and drowsiness) so it is recommended to abstain from alcohol while on this medication.

Ciprofloxacin is mostly well tolerated, with the most common side effect being diarrhoea or taste disturbance. Rarely, inflammation of the tendons and inflammation of the liver can occur.



The best treatment is to suppress the activity of the disease using one of the specific medications already discussed. However, it is perfectly safe to use common analgesics such as paracetamol.

Medicines that do not treat inflammation, but are used for symptom control or replacement of vitamins and other nutrients

1. Anti-diarrhoeal medications

Loperamide (Imodium[®], Dicap[®]), diphenoxylate + atropine (Diastop[®]) and codeine phosphate reduce diarrhoea but have no effect on the inflammation that is causing diarrhoea. They are related to morphine but have a much lower risk of addiction, especially loperamide and Diastop.

They work mainly by reducing the contraction of the muscle in the bowel wall, slowing the movement of bowel contents through the gut. They also cause some reduction of the amount of fluid produced by the lining of the gut.

These medications should not be used in a severe attack of ulcerative colitis, as in this situation, on rare occasion, they can cause the bowel to stop working entirely, with a risk having a perforation. However, they can be useful to control diarrhoea during milder attacks of IBD, or in patients who have diarrhoea even though their disease is inactive. The main side-effect is constipation.

Other side effects are unusual, although probably more common with codeine phosphate than with loperamide and Diastop. Drowsiness, headache, dry mouth, difficulty urinating and mood changes are occasional side effects.

2. Bile salt binders

Cholestyramine (Questran[®]) and colestipol (Colestid[®])

Bile salts are a normal component of bile that is secreted from the liver into the upper gut to aid in the absorption of food. They are normally resorbed in the lower part of the small bowel, the terminal ileum. However, if the terminal ileum is damaged

by Crohn's disease or has been removed surgically, bile salts cannot be resorbed and pass into the large bowel where they can cause diarrhoea.

Cholestyramine (Questran) and colestipol (Colestid) are two medications that bind to bile salts, preventing them from causing diarrhoea. Both are powders that are dissolved in fluid before taking. Their most frequent side effects are constipation, abdominal discomfort and abdominal distension. Heartburn, nausea and loss of appetite can also occur.

3. Analgesics (pain killers)

Paracetamol (Panadol[®])

Pain most commonly occurs during a flare-up. The best treatment is to suppress the activity of the disease using one of the specific medications already discussed. However, it is perfectly safe to use common analgesics such as paracetamol. It is best to avoid aspirin, and nonsteroidal anti-inflammatory medications such as ibuprofen (Nurofen[®]) and diclofenac (Voltaren[®]), which can occasionally aggravate IBD.

Occasionally the pain from IBD can be persistent and severe. It is important to notify your doctor or IBD nurse if this is the case as the pain could be due to a serious complication. You will need to discuss how to effectively manage the pain.

4. Vitamins and minerals

All patients with IBD need a well-balanced, nourishing diet. Vitamin and mineral supplements are generally unnecessary, especially if the disease is inactive. However, there are a few exceptions.

The most important is the use of regular vitamin B12 injections in some patients with

Crohn's disease. Vitamin B12 is essential for blood formation and for nerve and brain function. It is absorbed from the lower part of the small bowel, the terminal ileum, a common site of Crohn's disease. If there is extensive Crohn's disease of the terminal ileum or if a significant length of terminal ileum has been surgically removed, vitamin B12 absorption will be compromised and replaced with regular injections. A blood test will show if your vitamin B12 is low.

Most other vitamins and minerals are absorbed in the upper part of the small bowel, which is less commonly affected by Crohn's disease. However, a few individuals with extensive disease or surgery require supplements, most commonly iron or folic acid. Iron supplements are commonly necessary in patients who become deficient in iron because of chronic bleeding from the bowel.

Iron tablets may cause the bowel motions to turn very dark. They can also cause indigestion, constipation, diarrhoea or nausea. Iron can also be replaced very effectively through an intravenous line. This can be arranged through your GP or specialist. Vitamin D and calcium tablets are also commonly prescribed, for patients who are taking corticosteroids (prednisone) to help protect the bones against steroid-induced osteoporosis (see corticosteroid section of this chapter).

5. Alternative therapies

Many people with chronic conditions grow tired of their disease and look for alternative solutions to what conventional medicine has to offer. There is a common misconception that all 'natural' remedies are safe. However, this is not necessarily the case. So, while some alternative therapies may be harmless, or even helpful, others may have their own side effects.

If you're already using or are considering using alternative approaches to manage you IBD, be open about this and discuss it with your doctor. You will find that most doctors will be happy to work with your alternative or complementary practitioners.

6. Drug treatment and pregnancy

Women with IBD who become pregnant are naturally concerned that their medications will be harmful to the baby. In general, it is best to take as few medications as possible during pregnancy, but it is important to realise that uncontrolled disease is a much greater threat to the baby than the medications used to treat it.

For further information on specific medications and pregnancy, please consult the '**Sexuality, fertility and pregnancy**' chapter. If you are concerned about taking any medications during pregnancy, please discuss this with your doctor.

Conclusion

This chapter describes the most common medications used in the treatment of IBD. Don't be alarmed by the list of possible side effects. Most are uncommon and the majority of IBD patients have few problems with their medications.

You should consult your doctor if you have any questions about your medications or if you are concerned about side effects.