

NON-MELANOMA SKIN CANCER | ANTIPSYCHOTICS FOR DEMENTIA | BIOLOGICS | PERFORMANCE FRAMEWORK

# Best Practice

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Issue 57 December 2013



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Patients with severe immune-mediated inflammatory diseases, e.g. rheumatoid arthritis, Crohn's disease or psoriasis, often respond well and relatively quickly to treatment with biologic medicines such as tumour necrosis factor (TNF) inhibitors. For a patient to qualify for subsidy for these medicines, treatment must be initiated by a relevant specialist, e.g. Rheumatologist, Gastroenterologist or Dermatologist. The role of the primary care team is to facilitate discussion between the patient and the treating specialist, to reduce the risk of complications, e.g. serious infection, to provide repeat prescriptions and in some cases to monitor the patient's response to treatment. General Practitioners may also be involved in applications for the renewal of Special Authority subsidy for patients taking biologic medicines.



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# Have a happy new year...

Every year around this time, people start to indulge with reckless abandon, knowing that in the New Year, things will be different – we will eat one pudding instead of two, make a fleeting attempt to lose weight, and cut back on the alcohol to pre-Christmas soak levels. It is estimated that around 50% of people make a New Year's resolution...8% of people are successful in achieving their New Year's resolution.

A quick Google search shows that the most common New Year's resolutions are:

- Lose weight and get fit
- Spend more time with family
- Drink less alcohol
- Eat healthy food
- Quit smoking
- Save money
- Learn something exciting
- Make new friends/fall in love

The Time magazine top 10 most commonly broken New Year's resolutions are:

- Lose weight and get fit
- Spend more time with family
- Drink less
- Eat healthier and diet
- Get out of debt and save money
- Quit smoking
- Learn something new
- Travel to new places
- Be less stressed
- Volunteer

Why do we fail so badly when it comes to making resolutions? The main reasons are that we set goals that are sweeping and unrealistic, which usually involve stopping doing something, which is so much more challenging than taking up something new. We also lack the motivation to follow through on these resolutions, or make the fatal mistake of using guilt or fear as our motivation, which is unlikely to work for maintaining willpower in the long-term.

So what is the secret to success? Follow these rules and you may be sailing right through February with your resolution, unlike the majority of your peers:

- Keep it simple – make only one resolution at a time and focus on this until you have achieved it
- Make it tangible – your goal should be something that realistically can be achieved, there is no point in making a resolution to be the owner of a yellow Lamborghini when you are currently driving a Camry station wagon
- Make it specific – a vague goal is a stab in the dark, instead of saying you are going to “get fit”, make your goal that you will walk your dog for thirty minutes each day, five days of the week
- Be accountable – tell your family and friends about your goal so they can act as hall monitors when you slip up in your quest. Apparently this one works especially well for the female goal setters.
- Keep believing you can do it – it's all in your head

Now that you are all motivated to make your goals and see them through the year, I shall leave you with the most important fact of all: **There is no correlation between happiness and achieving New Year's resolutions.**

We hope you have enjoyed your year with Best Practice Journal and we look forward to providing you with your staple of evidence-based, thought-provoking, forward-thinking – some say trail blazing – articles next year. We would like to give a special mention to Dr Peter Moodie, Medical Director of PHARMAC who retires from this role at the end of the year. Peter has provided us with some truly memorable moments and we value and respect his support and input into Best Practice Journal and bpac<sup>nz</sup> over the years.

*Merry Christmas from the bpac<sup>nz</sup> team*

**Our offices will be closed from 1 pm, December 24th and re-open at 8.30 am January 6th, 2014.**

Managing  
**NON-MELANOMA  
SKIN CANCER**  
in primary care



**A focus on topical treatments**

*When a patient presents with a suspicious skin lesion the first step is to assess the likelihood of melanoma being present and then to provisionally identify the type of lesion. Surgical excision with histology is the first-line treatment for all skin cancer. It has the highest cure rate among available treatments. Referral, according to local guidelines, to a General Practitioner with a Special Interest (GPSI) in skin lesions, a Dermatologist, a Plastic Surgeon or an ENT Surgeon may be appropriate for patients with large lesions or lesions with an aggressive growth pattern. Patients with superficial basal cell carcinoma or intraepidermal carcinoma (squamous cell carcinoma in situ) may be safely managed with cryotherapy or topical treatments, i.e. fluorouracil or imiquimod creams, when excision is not appropriate because of the location of the lesion or due to cosmetic considerations. Topical treatments should not be considered if the diagnosis is uncertain.*

## **Skin cancer: Causes, risk factors and treatment**

Skin cancer is estimated to account for over 80% of new cancers in New Zealand each year.<sup>1</sup> The majority of these are non-melanoma skin cancers, i.e. basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). However, as BCC and SCC are not required to be reported to the New Zealand Cancer Registry the impact of these cancers on New Zealand communities is difficult to quantify. Non-melanoma skin cancers are rarely fatal, however, they can grow if not treated early and result in substantial destruction of local tissue and disfigurement.

### **Why does New Zealand have high rates of skin cancer?**

New Zealand has one of the highest rates of skin cancer in the world which is reflected in the relatively high rates of melanoma. In 2010, there were 2341 new registrations and 324 deaths due to invasive melanoma in New Zealand.<sup>2</sup> High levels of ultraviolet radiation (UVR) and an outdoor lifestyle combine with four interrelated factors to determine a person's risk of developing skin cancer:

1. Increasing age (the greatest risk factor for developing skin cancer)
2. Individual patterns of exposure to sunlight
3. Skin type and genetic makeup
4. Immune system function

In New Zealand, approximately twice as many males as females die from melanoma. Males aged over 50 years have a higher incidence of melanoma and tend to present with thicker melanomas, which are associated with poorer outcomes.<sup>1,2</sup> Having an outdoor occupation is likely to be one contributing factor for the increased skin cancer mortality rates among males.

### **Ultraviolet radiation and patterns of sun exposure**

Ultraviolet radiation is electromagnetic radiation that, unlike visible light and thermal heat, cannot be detected by the human body.<sup>2</sup> UVR is divided into UVB (290 – 315 nm) and UVA (315 – 400 nm).<sup>3</sup> UVB can cause skin cancer by damaging DNA in P53 tumour suppressor genes, which are involved in DNA repair, or by activating genes that promote cancer (oncogenes).<sup>4</sup> UVA is present in greater amounts in sunlight and penetrates more deeply into the skin than UVB due to its longer wave length.<sup>3</sup> UVA is also able to pass through glass, unlike UVB.<sup>3</sup> UVA radiation has been shown to be involved in the carcinogenesis of skin stem cells.<sup>3</sup> DNA damage due to UVR accumulates over time and the risk of malignancy increases with age.

Differing patterns of UVR exposure are associated with different types of skin cancer in susceptible people. Intermittent, high-dose sun exposure, e.g. during recreational activities, is associated with an increased risk of developing melanoma in younger adults, especially those with many melanocytic naevi (moles) and BCC.<sup>5</sup> Cumulative exposure, which is generally



higher in people with chronic exposure to sunlight, e.g. people with outdoor occupations, is the most significant risk factor for developing pre-cancerous solar keratoses and SCC.<sup>4</sup> Chronic exposure to UVR can also cause slow-growing melanomas to develop on patches of sun-damaged skin in older people.

### Skin type and risk factors for skin cancer

Darker skin pigmentation reduces the risk of developing skin cancer because melanin protects skin cells by absorbing UVB. Skin cancer is rare in Māori and Pacific peoples, but can occur. When Māori or Pacific peoples do present with melanoma they often have thicker lesions and more extensive disease at diagnosis.<sup>6</sup> Māori and Pacific peoples are also more likely than New Zealand Europeans to develop nodular and acral (generally on the soles of feet, palms of hands or under the nails) melanomas, which tend to grow more rapidly and be more difficult to diagnose.<sup>7</sup>

Multiple melanocytic naevi, e.g. more than 100, and more than five atypical naevi (large and unusual looking moles) are risk factors for melanoma. A family history of melanoma approximately doubles a person's risk of developing melanoma.<sup>8</sup>

Features that are commonly associated with a fair complexion are also risk factors for skin cancer, e.g. Celtic ancestry, a tendency to burn easily, blonde or red hair and green or blue eyes.<sup>4</sup>

### The role of the immune system in skin cancer

The immune system plays an important role in preventing skin cancer. This is illustrated by the increased incidence of skin cancer in people who are immunosuppressed, e.g. over 80% of patients who have received a kidney transplant will develop skin cancer within 20 years.<sup>5</sup>

Ultraviolet radiation can cause immunosuppression by: disturbing the way antigens are processed by the immune system, stimulating cytokines that can suppress the immune system and by altering contact and delayed hypersensitivity reactions.<sup>3</sup> UVR therefore initiates and accelerates the progression of skin cancer.

## First, assess for melanoma

When a patient with a suspicious skin lesion presents in general practice the first step is to assess the risk of a melanoma being present. Reassurance should only be given where there is confidence that the lesion is not melanoma. A complete skin examination should be conducted with a good light source and magnification, although another consultation

may need to be scheduled for this. The examination should note the extent of the sun damage and the distribution and morphology of skin lesions.

### Red-flags: Is this melanoma?

Approximately half of all melanomas are first identified by the patient themselves and a discussion about the lesion's history will often provide clinically useful information.<sup>6</sup>

**The ABCDE of melanoma** has been developed to help people recognise when they should seek medical advice about a skin lesion:<sup>6</sup>

A = Asymmetry

B = Border irregularity

C = Colour variation

D = Diameter greater than 6 mm

E = Evolution, i.e. change

**“How long has it been there?”** This is the most important question to ask a patient who reports a suspicious skin lesion. If the lesion is new and the patient reports changes over days or weeks then the lesion is likely to be due to inflammation rather than malignancy. Stable lesions that have been present for years can be monitored by observation at the next consultation and their cancer risk reassessed.<sup>9</sup> However, if the patient reports **the lesion has developed and persisted over a period of months then the clinical suspicion of either melanoma or non-melanoma skin cancer should be increased.**

**“Have you noticed any changes in size, shape or colour?”** These symptoms and signs are suggestive of melanoma, particularly if the patient reports change or growth over a period of months. However, they may also be present in benign lesions, e.g. seborrhoeic keratoses (brown warts).<sup>10</sup> Seborrhoeic keratoses usually have a warty or waxy surface with a sharp border and appear stuck on the skin surface. Patients with melanoma may report intermittent itch in and around the lesion.<sup>6</sup> Pain and/or bleeding are rare features of early melanoma but are often reported in advanced or nodular melanoma.<sup>6</sup>

**“Does this mole appear different to others that you have?”** Melanomas stand out as being different from other pigmented skin lesions and are often described as having an “ugly duckling” appearance.<sup>6</sup>

Flat or superficial (Figure 1) are the most common types of melanoma, characterised by an asymmetrical structure




and multiple colours, e.g. black, brown or pink.<sup>6</sup> Areas of depigmentation are also often present and are indicators of regression.<sup>6</sup> Amelanotic melanoma is mostly pink but often has a small focal point of irregular pigmentation on the periphery of the lesion.<sup>10</sup>


Nodular melanoma (Figure 2) is suggested by progressive enlargement, symptoms, e.g. pain and bleeding, and a firm and raised appearance.<sup>6</sup> Nodular melanomas usually have a single colour, e.g. black, steel blue or red, and are usually uniform in shape. They are often misdiagnosed resulting in a disproportionate number of deaths from this type of melanoma.<sup>6</sup>

**Diagnostic excision with a narrow 2 mm margin or referral to an appropriate specialist** should be strongly considered for patients with skin lesions that are unusual, new, changing or difficult to diagnose (see: "Treatments for cancerous skin lesions"; Page 14).<sup>6</sup> A second excision with a wider margin will be required if a diagnosis of melanoma is confirmed on histology, and depending on the staging of the melanoma this may need to be as wide as 2 cm.<sup>6</sup>

Observation for one to two months (but no more than three months) may be appropriate for some patients with flat, pigmented lesions where there is clinical uncertainty.<sup>6</sup> This approach is not appropriate for undiagnosed growing nodules. Tumours less than 1 mm thick and without histological evidence of mitoses or ulceration are considered to be at low-risk of metastasis and can be managed in primary care.<sup>6</sup>

Digital imaging is recommended to assist in identifying changes over a short interval, to accompany requests for histology and to request advice from, or make referrals to, other clinicians. Patients with suspected or known invasive melanoma, i.e. lesions that extend deeper than the epidermis, should be urgently referred to specialist care, and prioritised as having a high suspicion of cancer to ensure they receive treatment within 62 days of receipt of referral. Local guidelines may vary for referral to a Surgical Dermatologist, Plastic Surgeon, ENT Surgeon or General Surgeon.

 For further information see: "Detecting malignant melanoma", BPJ 34 (Feb, 2011).

 The Ministry of Health will shortly be releasing standards for the provision of services for patients with melanoma, see: [www.health.govt.nz](http://www.health.govt.nz)



**Figure 1 :** Superficial melanoma – the most common type of melanoma. Image provided by DermnetNZ



**Figure 2:** Nodular melanoma – the second most common type of melanoma. Image provided by DermnetNZ



**Figure 3:** Flat pink-red keratosis – suitable for topical treatment. Image provided by DermnetNZ

## Pre-cancerous lesions – solar keratoses



**Figure 4:** Hyperkeratotic solar keratoses – cryotherapy recommended. Image provided by DermnetNZ

Once there is confidence that melanoma is not present the patient can be assessed for the presence of non-melanoma skin cancer. Solar keratoses, also known as actinic keratoses, are frequently encountered, particularly in older patients. These lesions are considered to be pre-cancerous or an early form of SCC and are an indication of chronic exposure to UVR.<sup>10</sup> Solar keratoses appear as multiple, pink-red flat spots (Figure 3), or skin coloured, rough, scaly spots (Figure 4). Sometimes they are more easily felt than seen. Over 80% of solar keratoses occur on the head, neck, back of the hands and forearms.<sup>11</sup> Patients often report tenderness with solar keratoses, but they may cause no symptoms other than being aesthetically undesirable. Keratolytic emollients (Table 1) can be applied to provide symptomatic relief only. The probability of an individual solar keratosis transforming to SCC is unknown; reports range widely from almost negligible to 16% per year.<sup>11</sup>

A Cochrane review found that a wide range of topical treatments were generally comparable in the treatment of solar keratoses, however, there was some evidence that fluorouracil cream may be more effective long-term than cryotherapy.<sup>11</sup> Imiquimod cream is often tolerated better than fluorouracil and may provide better cosmetic results than either fluorouracil or cryotherapy, however, it may cause hypopigmentation and is unsubsidised for this indication.<sup>12</sup> Ingengol gel and photodynamic treatment cause tissue reactions of shorter duration than fluorouracil or imiquimod and have similar response rates. These treatments are not currently available in primary care (Page 14).

**Table 1:** Topical treatment regimens in primary care for solar keratoses<sup>12</sup>

Treatment type	Regimen for solar keratoses
Keratolytic emollients, e.g. urea cream (10%)	Apply to all affected areas, twice daily. Provides short-term symptomatic benefit only.
Cryotherapy	Apply liquid nitrogen in a single freeze for two to five seconds. <sup>13</sup> Repeat in four weeks or as necessary. Cryotherapy can remove approximately 70% of treated solar keratoses, depending on the intensity of treatment. <sup>13</sup> Unsuitable for large or numerous lesions.
Fluorouracil (5%) cream	Apply once or twice daily, for two to four weeks. Monitor weekly.
Imiquimod cream (5%) (unsubsidised for this indication)	Apply two or three times a week for four weeks to six weeks. Assess local response after three weeks and adjust treatment frequency if necessary. Review again after a four week treatment-free interval. Treatment can be repeated if the lesion persists.

Table 1 shows the recommended topical treatment regimens for solar keratoses managed in primary care. If a patient presents with numerous keratoses and it is impractical to treat all of them, target symptomatic, hyperkeratotic (Figure 4) or thickened lesions with cryotherapy as these lesions have a greater risk of transforming to SCC.<sup>10</sup> Treatment of wider areas of skin with fluorouracil cream or imiquimod cream may be appropriate. Ingenol gel or photodynamic therapy is more suitable for flat keratoses or larger areas of sun-damaged skin. It can be useful to freeze thicker, tender lesions two to three weeks before starting treatment as this can increase absorption of topical medicines. Follow-up may be necessary to repeat cryotherapy or biopsy lesions that do not respond to treatment or continue to enlarge. It is important to ensure that persistent lesions are in fact solar keratoses. Seborrhoeic keratoses do not respond to topical treatment.

All patients with solar keratoses should be advised to protect themselves from the sun year-round and to use high protection, broad spectrum SPF 50+ sunscreens when they are exposed to high levels of UVR.

For more detailed information about the topical treatments for non-melanoma skin cancer, see: "Treatment options for cancerous skin lesions", Page 14. For information on diagnosing suspicious skin lesions using dermatoscopy see: "Diagnosing solar keratoses and non-melanoma skin cancer using dermatoscopy, Page 13.

## Non-melanoma skin cancers – basal cell carcinoma

Basal cell carcinoma is the most frequently occurring cancer in humans and, although locally invasive, it rarely metastasises and is almost never fatal. People with a personal history of BCC also have an increased risk of developing melanoma.

Approximately 80% of BCCs occur on the face and neck, but lesions may also be found on the back of the hands, forearms and on the back and lower legs.<sup>14</sup> The classic appearance of a BCC is a "rodent ulcer", which is a lesion with raised pearly edges and central atrophy or ulceration (Figure 5). A pearly (Figure 6), shiny nodule with prominent capillary networks is common. Superficial BCC may also present as an irregular red, scaly patch or plaque with short linear blood vessels (Figure 7). Pigmented forms of BCC may be observed in people with dark skin or people who tan easily.



**Figure 5:** Nodular basal cell carcinoma (BCC) – excision recommended. Image provided by DermnetNZ



**Figure 6:** Stretching basal cell carcinoma (BCC) reveals a pearly appearance. Image provided by DermnetNZ



**Figure 7:** Superficial basal cell carcinoma (BCC) suitable for cryotherapy or topical treatment. Image provided by DermnetNZ



BCCs are generally slow growing over months or years.<sup>10</sup> Morphoeic (infiltrative with poorly defined edges) or sclerosing (scar-like) BCCs may go unnoticed until they are several centimetres in diameter and have penetrated deeply. Advanced BCCs may appear as large, deep ulcers. BCC located near the eyes, nose and ear can invade the orbital rim, nasal vault and middle ear respectively and may be larger than expected. Consider early referral of any patient with a BCC in these locations to a General Practitioner with a Special Interest (GPSI) in skin lesions, a Dermatologist, a Plastic surgeon or an ENT surgeon.

**Surgical excision with histology is the first-line treatment for BCC**, as this has superior cure rates to topical treatments and histology results can guide the need for further investigation or treatment. Patients with aggressive, recurrent or large tumours, e.g. diameter greater than 6 mm on the face,<sup>14</sup> may require referral to a Dermatologist for consideration of Mohs margin-controlled micrographic surgery (see: "Treatments for cancerous skin lesions", Page 14).

**Superficial BCC, i.e. restricted to the outermost layers of skin**, may be treated topically (Table 2) if the lesion's location, the patient's general health or the presence of co-morbidities mean excision is impractical or associated with an increased risk of complications or poor cosmetic outcome. A punch biopsy may be considered, prior to initiating topical treatments,

for superficial BCC to assess tumour thickness and confirm diagnosis. Non-surgical treatments should not be used if the diagnosis of BCC is unclear.<sup>13</sup>

Cryotherapy delivered in freeze-thaw cycles (Table 2) is effective at destroying malignant cells in superficial BCC because cellular damage occurs both during the freezing process and during the slower thaw, due to the osmotic gradient across the cell membrane. Superficial confirmed BCC can be treated with imiquimod (subsidised under Special Authority criteria) when standard treatment options, including surgical excision, are contraindicated or inappropriate (Table 2).<sup>12</sup> Imiquimod is not indicated for recurrent, invasive, infiltrating or nodular BCC.<sup>12</sup> There is insufficient evidence to compare the effectiveness of cryotherapy with imiquimod for the treatment of superficial BCC. Fluorouracil is not routinely used to treat BCC as there is insufficient evidence to assess treatment effectiveness,<sup>15</sup> however, occasionally it is used to treat small, very superficial BCCs.

Photodynamic therapy is available in some specialist centres for superficial BCC, including BCCs on the face that are unsuitable for surgery. Photodynamic therapy (unsubsidised) can also be used to treat large thin superficial BCCs on the lower leg. Photodynamic treatment for BCC is repeated after one to two weeks.

**Table 2:** Topical treatments regimens in primary care for superficial basal cell carcinoma (BCC)<sup>12,13</sup>

Treatment type	Regimen for BCC
<b>Cryotherapy</b>	Apply liquid nitrogen to the skin for 20 – 30 seconds, allow to thaw for three to five minutes, then refreeze for another 20 – 30 seconds. Unsuitable for facial lesions, due to poor response rates, or distal lower limbs, due to persistent ulceration. Recurrence at the lesion margin may develop following cryotherapy.
<b>Imiquimod cream</b> (Special Authority)	Apply to the lesion and 1 cm beyond, once daily on five days each week, for six weeks. Treatment should be reviewed by at least the third week, to adjust the frequency of application. After a four week treatment break, treatment can be repeated for another six weeks if the response to the first course is incomplete. Imiquimod can cure 70 – 80% of small, superficial BCCs. <sup>10</sup> A punch biopsy should be performed where possible to confirm a diagnosis to qualify for Special Authority subsidy criteria. Imiquimod is indicated for superficial BCC on the neck, chest and distal upper limbs, but it appears to be less effective when used on the distal limbs. Imiquimod can be used to treat facial lesions but as local tissue reaction may be prolonged it may not be a desirable option for all patients.
<b>Fluorouracil (5%) cream</b>	Apply thinly to the affected area, twice daily, for 12 weeks. <sup>10</sup> Not routinely used to treat BCC, however, prolonged courses of treatment are occasionally used to treat small, very superficial BCCs. <sup>10</sup>



## Squamous cell carcinoma (SCC)

Squamous cell carcinomas (SCC) develop from the flat, scale-like (squamous) cells that form the outermost layer of the epidermis. When a SCC is limited to the epidermis it is referred to as intraepidermal carcinoma (IEC – also known as SCC in situ, Figure 8). The term Bowen's disease is no longer used. IECs are generally flat, but can be several millimetres in thickness and slow-growing over months or years. There are usually multiple irregular orange-red or brown plaques with variable scaling or crusting. SCC will often be tender and will rarely go unnoticed. The presence of chronic leg ulcers and infection with human papillomavirus (HPV) increase the risk of developing SCC.<sup>10</sup> Chronic leg ulcers may progress into aggressive ulcerating SCC, referred to as Marjolin's ulcer.<sup>10</sup> Smoking increases the risk of developing SCC on the lip and genitalia and is likely to be a risk factor for developing SCC in other sites.<sup>10</sup> People with a history of SCC also have an increased risk of developing malignant melanoma.<sup>10</sup>

Approximately 80% of invasive SCCs develop on the face and neck, but lesions may also be found in other areas exposed to the sun.<sup>14</sup> The clinical characteristics of invasive SCC are dependent on the keratin producing cells within the tumour. Well differentiated SCC appear as firm slow-growing skin-coloured nodules with scaling or a protruding horn (Figure 9).<sup>10</sup> SCC that are less differentiated grow more quickly and have an irregular crusted plaque that is often ulcerated (Figure 10).<sup>10</sup> Keratoacanthoma appear as symmetrical nodules with a central crater or keratin core. They grow rapidly, reaching a diameter of 2 cm in few weeks. Keratoacanthoma can cause an immune reaction and resolve within months, but may be indistinguishable from aggressive tumours and should be excised.

SCC will metastasise in approximately 5% of cases, but this risk is higher if the lesion is large or deep, or is located on the ear, lip, genitals or on mucosal surfaces, or involves nerve fibres.<sup>10,14</sup> Metastasis of SCC is also more likely if the immune system is suppressed, e.g. in people with chronic leukaemia or people who have received an organ transplant.<sup>14</sup>

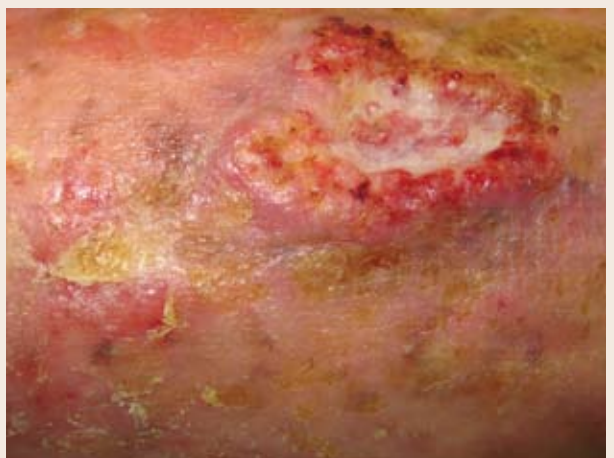
**A regional lymph node examination should be considered whenever invasive SCC is suspected.**<sup>14</sup> Nodal metastasis is more likely to occur in patients with SCC with poor differentiation and perineural invasion.<sup>14</sup> Symptoms such as pain, burning, stinging, anaesthesia, paraesthesia, facial paralysis, diplopia and blurred vision are suggestive of neurological involvement. The role of sentinel node biopsy in the investigation of suspected SCC is uncertain.<sup>14</sup>



**Figure 8:** Typical red crusted plaque of intraepidermal carcinoma (IEC). Image provided by DermnetNZ



**Figure 9:** Cutaneous horn suitable for excision. Image provided by DermnetNZ



**Figure 10:** Poorly differentiated and ulcerated squamous cell carcinoma (SCC) for wide excision. Image provided by DermnetNZ

**Surgical excision is the first-line treatment for SCC** and is indicated for all invasive SCC. For clinically well defined, low risk tumours that are less than 2 cm in diameter, a 4 mm margin of unaffected tissue around the tumour is sufficient to completely remove 95% of all primary SCCs.<sup>16</sup> At least a 6 mm margin of unaffected tissue should be removed, or referral to a Plastic Surgeon, ENT Surgeon or Dermatologist for Mohs margin-controlled micrographic surgery is recommended for tumours that have one or more of the following features:<sup>16</sup>

- Greater than 2 cm in diameter
- Classified as moderately or poorly differentiated
- Extending into subcutaneous tissues
- Present on the ear, lip, scalp, eyelid or nose
- Recurrent

**Cryotherapy or fluorouracil** can be used to treat IEC where the diameter, location or number of lesions make surgery unsuitable (Table 3). A skin punch biopsy may be considered, if practical, before beginning topical treatment for IEC to assess tumour risk and confirm diagnosis. A Cochrane review found that there was insufficient evidence to compare the effectiveness of cryotherapy with fluorouracil in the treatment of IEC.<sup>17</sup> Imiquimod is not registered for the treatment of IEC in New Zealand and there is a lack of quality studies investigating its effectiveness for this condition. However, many clinicians report that imiquimod is useful for treating IEC.

Photodynamic therapy is also a treatment option for large flat areas of IEC on the face, neck and lower legs, however, this treatment is unsubsidised and unregistered for this indication and not available in primary care.

## Follow-up of patients treated for non-melanoma skin cancer

Patients with a history of pre-cancerous or cancerous skin lesions should be advised that the risk of treated lesions becoming recurrent, or new lesions developing, is increased if they are exposed to excessive UVR. Encourage regular self-examination of the skin, using a mirror or involving their partner or carer. Any new or changing lesions should be reported, particularly if they stand out as being different, or are growing, crusting or bleeding. Photography of the lesions may help patients and clinicians with surveillance and follow-up.


It is particularly important that “sun smart” behaviour is encouraged in people with a history of skin cancer. The Metservice sun protection alert for each centre in New Zealand is available online. This informs people of the time of day when there is a risk of being harmed due to UVR, i.e. the ultraviolet index (UVI) is greater than three, and the following measures should be taken:

- Slip into a long-sleeved shirt
- Slop on broad-spectrum (SPF 30+) sunscreen 15 minutes before going outdoors
- Slap on a hat with a wide brim
- Wrap on a pair of wrap-around sunglasses

 The Metservice sun protection alert is available from: [www.metservice.com/national/home](http://www.metservice.com/national/home)

**Table 3:** Topical treatments regimens in primary care for intraepidermal carcinoma (IEC)<sup>12, 13</sup>

Treatment type	Regimen for IEC
<b>Cryotherapy</b>	Apply liquid nitrogen in a single freeze to the skin for five to ten seconds
<b>Fluorouracil (5%) cream</b>	Apply thinly to the affected area, once or twice daily, for an initial duration of three to four weeks. Treatment can be applied for eight weeks, or longer. An occlusive dressing should be used to increase penetration if tissue reaction is minimal.
<b>Imiquimod (5%) cream</b> (unsubsidised and unregistered for this indication)	Apply to the lesion and 1 cm beyond, once daily on five days each week, for six weeks. Treatment should be reviewed by at least the third week, to adjust the frequency of application. After a four week treatment break, treatment can be repeated for another six weeks if the response to the first course is incomplete.

 The Sunsmart skin cancer awareness programme has information available on how patients can reduce their risk of developing skin cancer.

Available from: <http://sunsmart.org.nz/being-sunsmart>

### Follow-up of non-melanoma skin cancer

Patients who have been treated for non-melanoma skin cancer require follow-up every six to 12 months.<sup>13</sup> It is reported that between one-third and one-half of all patients with a non-melanoma skin cancer will develop another malignancy within five years.<sup>14</sup> Surveillance in the two years following treatment for SCC is particularly important as 70 – 80% of recurrent SCC develops within this time period.<sup>14</sup> Patients with a history of skin cancer who are immunosuppressed are at increased risk of developing further malignancies and a follow-up schedule for these patients should be discussed with an appropriate specialist, e.g. a Dermatologist.<sup>14</sup> Patients who have a history of invasive skin cancer should also be taught to regularly self-examine their lymph nodes.<sup>14</sup>

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### Diagnosing solar keratoses and non-melanoma skin cancer using dermatoscopy

Dermatoscopy can provide more confidence in discriminating between benign lesions that can be left untreated and malignancy that should be excised. A dermatoscope with strong polarised light and ×10 magnification is used to assess the symmetry of pigmented structures, e.g. lines, dots, circles and clods, and their patterns, e.g. reticular, dotted or without structure. Lack of symmetry of colour and structure, i.e. chaos, indicate a high suspicion of malignancy, once seborrhoeic keratosis has been excluded.

On dermatoscopy:

- Solar keratoses may contain small, irregular white circles. Facial keratoses may contain a “strawberry pattern” of concentric red and white rings.
- Basal cell carcinoma will show a loss of normal skin features and asymmetry of structure and colour. Microerosions may also be present. Pigmentation tends to be at the edge of the lesion in the form of irregular light brown, grey or blue structures. The blood vessels of BCC appear as branched lines. Polarised dermatoscopy of BCC shows white lines without a pigmented network.
- Intraepidermal carcinoma shows light pigmentation in a linear array. The blood vessels appear as groups of irregular large, red dots and coils.



# Treatments for non-melanoma cancerous skin lesions

When considering potential treatments for skin cancer it is important to discuss patient preference as well as the effectiveness of the treatment. For example, an older patient with multiple co-morbidities may prefer not to have a slow growing BCC removed.

**Surgical excision with histology is the first-line treatment for all skin cancers.** This will generally completely remove the tumour as well as guide the need for any further investigations or treatment once the histology is known. Superficial non-melanoma skin cancer should only require a single excision if an adequate margin of normal skin is removed with the tumour (see below). Excision also has the advantage over topical treatments of being a one-off treatment that does not rely on patients adhering to a dosing regimen. An increased risk of bleeding should always be considered in patients taking medicines such as aspirin, clopidogrel, ticagrelor, dabigatran or warfarin. The use of antithrombotic medicines does not greatly increase the risk of complications due to minor surgery, however, in individual patients, e.g. a patient taking warfarin with an elevated or unstable INR, non-surgical treatment may be preferable.


The tumour margin should be identified before administering local anaesthetic. As a general rule the margin of normal skin around the tumour should not be less than 3 – 4 mm. Margins that are smaller result in increased rates of recurrence, especially of BCC, which can be difficult to remove. Shaving, curettage (scraping out the malignant tissue) and cautery may be appropriate for thick solar keratoses, some IEC and small, well defined nodulocystic or superficial BCC. A deeper incision with simple or complex wound closure, e.g. use of skin flaps, is likely to be necessary for larger lesions or lesions that have been confirmed on histology to be incompletely excised. The cosmetic outcome of sutured wounds is improved if they are covered with an occlusive dressing for at least four days.<sup>9</sup>

Mohs margin-controlled micrographic surgery is generally performed by a specially trained Dermatologist. This involves removing horizontal sections of skin tissue, examining them

under a microscope, colour coding specimens and then creating a map to locate remaining cancer cells. The cure-rate for Mohs margin-controlled micrographic surgery can be as high as 99% for primary skin cancer and 95% for recurrent skin cancer.<sup>10</sup> This procedure is mainly used for facial lesions and is useful for:<sup>10</sup>

- Recurrent or incompletely excised BCC and SCC
- BCC and SCC without clearly defined borders
- Areas where sensory function is important, e.g. eyelids, nose, ears and lips
- BCC and SCC that is larger than 2 cm in diameter or rapidly growing
- High-risk or aggressive SCC, e.g. infiltrative histology or poorly differentiated

**A punch biopsy should be considered for suspicious non-melanocytic skin lesions that will not be surgically removed** to confirm a diagnosis and guide treatment.<sup>10</sup> However, this is not necessary for low-risk tumours with classical features seen on dermatoscopy (see: “Diagnosing solar keratoses and non-melanoma skin cancer using dermatoscopy”, Page 13). When performing a punch biopsy, stretch the skin perpendicular to the direction of least skin tension as this will allow for an elliptical wound that is easily closed with a single suture or steri-strip. The biopsy site should be on the wound margin so as to include tissue from the tumour and surrounding, non-affected skin.<sup>18,19</sup> The use of forceps should be minimised when handling the sample as this may crush tissue, making histological analysis difficult.

 For further information on punch biopsy and other surgical procedures see:

<http://dermnetnz.org/doctors/lesions/procedures.html>

**Cryotherapy using liquid nitrogen is widely used in general practice** to treat solar keratoses, low-risk superficial BCC or IEC less than 1 cm in diameter on the trunks and limbs.<sup>13</sup> Spray devices have the advantage of allowing the freeze to be controlled using different applicators. If a spray device



is not available a cotton-tipped stick can be dipped into a flask of liquid nitrogen. The disadvantages of this technique are: contamination, rapid thaw, inadvertent drip, inaccurate application and under or over-treatment. Some degree of hypopigmentation is inevitable following cryotherapy and this may be more noticeable in people with darker skin.

Liquid nitrogen is applied for a length of time dependent on the type, diameter and thickness of the lesion. Superficial lesions, i.e. solar keratoses and IEC, can be removed with a freeze lasting a few seconds, however, superficial BCC requires longer and repeat applications aiming for a cumulative tumour freeze-time of approximately 60 seconds. Within a few hours the patient will develop a clear, red or purple blister. Generally, these do not require special attention, but should be kept clean and intact. Dressing is recommended if the area is likely to be rubbed, e.g. the neck, or knocked, e.g. the hand, or where discharge onto clothing is a concern.<sup>10</sup> Eschar (scabs) on the face often peel off after five to ten days, hands may take three weeks to heal and eschar on the lower leg may remain for up to three months.<sup>10</sup> Due to the longer healing rates cryotherapy is not suitable on the lower leg for patients with impaired circulation.<sup>13</sup> Caution is recommended when applying liquid nitrogen to the back of hands as damage to the extensor tendons can occur. Infection following cryotherapy is rare.<sup>10</sup> If freezing occurs over a sensory nerve, e.g. the sides of the fingers, numbness may result with normal sensation generally returning over weeks to months.<sup>10</sup>

**Fluorouracil (5%) cream is indicated and fully subsidised for the treatment of pre-cancerous and superficial malignant skin lesions.**<sup>12</sup> It is toxic to dividing cells as it is incorporated into DNA and RNA; stopping the cell cycle. The area of skin being treated should not be larger than 22 × 22 cm.<sup>12</sup>

Patients applying fluorouracil must avoid exposure to the sun as this can make adverse effects worse; it is best used during the winter months.<sup>10</sup> Patients should avoid contact with eyes and mucous membranes while using fluorouracil.<sup>12</sup> The use of gloves and/or cotton-tipped applicators when applying the cream is also recommended and hands should be washed thoroughly after application if these are not used. Hyperkeratotic lesions being treated with fluorouracil should be covered with an occlusive dressing, but this is not necessary on thin flat lesions on facial skin.<sup>12</sup> Topical use of fluorouracil should be expected

to cause local irritation and photosensitivity and may result in permanent hyperpigmentation and scarring. Erythema multiforme may also occur.<sup>12</sup> Inflammation is likely to last for one to two weeks after treatment has finished.<sup>13</sup> Patients can be reassured that the greater the inflammatory reaction, the more effective the treatment is likely to be, but pain can be substantial and treatment is often discontinued early.<sup>12</sup> Severe discomfort that is associated with an inflammatory response may be treated with a topical corticosteroid and analgesia.<sup>12</sup> Patients should be advised to store fluorouracil safely so it will not be inadvertently used by other members of the household.

Fluorouracil is contraindicated in women who are pregnant or breast feeding and in people with a dihydropyrimidine dehydrogenase deficiency, which slows the rate at which uracil is metabolised. The prevalence of this deficiency is reported to be approximately 3%, however, people who are severely affected by this deficiency are likely to display neurological symptoms, e.g. seizures or intellectual disability.<sup>20</sup> Adverse effects due to uracil toxicity following topical application are extremely rare and estimated to occur in one in 100 000 people.<sup>20</sup> Fluorouracil should be used with caution in patients with inflammatory skin conditions, e.g. eczema, as adverse reactions may be more severe.<sup>12</sup> Dermatitis may also occur in patients with no history of sensitive skin.

**Imiquimod (5%) cream is subsidised under Special Authority criteria for the treatment of confirmed superficial BCC** when standard treatment options, including surgical excision, are contraindicated or inappropriate.<sup>12</sup> Imiquimod is an immune modifier that causes the removal of skin cells by inducing local cytokine production. Imiquimod causes local irritation and should not be applied to broken skin. The cream is provided in packs of 12 sachets and each sachet can treat an area of skin up to 25 cm<sup>2</sup>. The cream is well absorbed and should be left on the treated area for eight hours (typically over night), then any residue washed off with a mild soap and water.<sup>12</sup>

Skin treated with imiquimod may become inflamed, itchy, ulcerated and flaky. Painful erosions can occur on mucous membranes and cream should not be applied within 1 cm of the eyes, nose and lips. Inflammation may vary between patients and treatment should be monitored.<sup>10</sup> Occlusion of the treated lesion is not necessary. Advise patients that because

imiquimod activates the immune system locally, inflammation is an expected result which indicates that the cream is likely to be effective. Reassurance can be given that the inflammation will settle leaving an acceptable cosmetic result. The patient should be advised to stop treatment if black coloured ulceration or systemic flu-like symptoms occur.<sup>10</sup> Topical steroidal cream may reduce treatment efficacy and should not be used to treat reactions.<sup>13</sup> Imiquimod is also effective for treating locally occurring subclinical lesions. Patients with mild symptoms following treatment with imiquimod can be treated with paracetamol.<sup>10</sup> Assess the patient's response 12 weeks after they have completed the regimen to determine if there is a need for further treatment.<sup>12</sup>

### Treatment options generally not used in primary care

**Photodynamic therapy** is performed by private providers and in some hospital clinics. It can produce good cosmetic results, but it is painful and can be expensive. Treatment involves the application of methyl aminolevulinate (16%) cream thickly to the lesion and a 1 cm margin. This is occluded for three hours and then exposed to a wavelength of light that matches the absorption spectrum of the active component within the cream and penetrates to the required depth. Sunlight can be used to treat the skin as this contains multiple wavelengths of light. After absorbing light the active component reacts with O<sub>2</sub> to form destructive single oxygen atoms that destroy the lesion.<sup>20</sup>

Photodynamic therapy has a relatively short treatment duration (approximately 15 minutes) and may also reduce other visible signs of photo-damage.<sup>20</sup> Adverse effects of treatment may include discomfort and intense inflammation; in these patients pain and pruritus may be reported during exposure. Local anaesthetic, analgesia or breaks in treatment may be required. After treatment a tissue reaction may persist for one to two weeks.

**Ingenol mebutate gel** is an extract of milk weed (*Euphorbia peplus*) that has been shown to be useful in the treatment of superficial skin cancers and solar keratoses.<sup>10</sup> This medicine was registered in October, 2013, and is expected to be available (unsubsidised) in New Zealand in February, 2014. Ingenol gel (0.015%) is applied to the face and scalp once daily, for three days. Ingenol gel (0.05%) is applied on the trunk and extremities once daily, for two days.<sup>10</sup> The reaction to treatment is variable and will last one to two weeks.

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# BIOLOGIC MEDICINES

for the treatment of  
inflammatory conditions:

What does primary care need to know?



*Patients with severe immune-mediated inflammatory diseases, e.g. rheumatoid arthritis, Crohn's disease or psoriasis, often respond well and relatively quickly to treatment with biologic medicines such as tumour necrosis factor (TNF) inhibitors. For a patient to qualify for subsidy for these medicines, treatment must be initiated by a relevant specialist, e.g. Rheumatologist, Gastroenterologist or Dermatologist. The role of the primary care team is to facilitate discussion between the patient and the treating specialist, to reduce the risk of complications, e.g. serious infection, to provide repeat prescriptions and in some cases to monitor the patient's response to treatment. General Practitioners may also be involved in applications for the renewal of Special Authority subsidy for patients taking biologic medicines.*

## **What are biologic medicines?**

Biologics are a class of medicine that are derived from biological systems as opposed to being synthesised in a chemical process. The term includes a wide range of medical products such as immunomodulators, vaccines, blood products and chemotherapy agents. Biologic immunomodulators are often used to treat immune-mediated inflammatory disease, e.g. rheumatoid arthritis and inflammatory bowel disease. A feature of this type of medicine is that unlike other immunosuppressive medicines, e.g. methotrexate, specific cell signalling pathways involved in the disease are targeted. The most well known biologics used to treat immune-mediated diseases are the tumour necrosis factor (TNF) inhibitors (see: "What are TNF inhibitors?").

## **The effectiveness of biologic medicines can vary between patients**

Treatment with biologic medicines can produce a marked beneficial response in many patients with inflammatory conditions. For example, in patients with rheumatoid arthritis, TNF inhibitor treatment can decrease synovitis and prevent joint erosions within months, and sometimes induce disease remission.<sup>1</sup> However, approximately one-third of patients do not respond to treatment.<sup>2</sup> A lack of response may be due to differences in the pathophysiology of the patient's condition, differences in genetics or the treatment being only effective at certain stages of a disease.

Patients may also develop antibodies against biologic medicines that limit their effectiveness. This is more likely to occur with the use of chimeric biologics, e.g. infliximab (Table 1, over page), which contain a combination of human

and animal-derived amino acids, as opposed to humanised biologics which contain only human derived amino acids.<sup>1</sup> If a patient does not respond to one biologic medicine, they may respond to another.<sup>1</sup>

## **Biologic medicines subsidised in New Zealand to treat inflammatory diseases**

In New Zealand several biologic medicines are funded under Special Authority criteria or subject to restrictions on the Hospital Medicines List (HML) for the treatment of immune-mediated inflammatory disease (Table 1). These medicines are usually initiated when patients have not responded sufficiently to conventional treatment and remain severely affected by an inflammatory condition. To qualify for subsidy the initial application for treatment must come from an appropriate named specialist, e.g. a Rheumatologist, Gastroenterologist or Dermatologist.

## **Supporting the treatment of patients with biologic medicines**

When initiation of treatment with a biologic is being considered for a patient the role of the primary care team is to facilitate discussion between the patient and the treating specialist, to reduce the patient's risk of complications through the course of their treatment and to provide repeat prescriptions where appropriate.

Methotrexate is often co-prescribed with immunosuppressive biologic medicines. This is to reduce the development of antibodies that may neutralise the effectiveness of treatment and because an additional disease-modifying anti-rheumatic drug (DMARD) is likely to provide further clinical benefit.<sup>1</sup>

**Table 1:** Immunosuppressive biologic medicines available in New Zealand under Special Authority criteria and/or Hospital Medicines List (HML) restrictions for the treatment of inflammatory diseases<sup>2,3</sup>

Medicine	Classification	Mode of action	Administration	Subsidised indications (inflammatory conditions)
<b>Biologic medicines for inflammatory disease subsidised in the community and on the HML</b>				
<b>Etanercept</b>	Human fusion protein	Decoy for soluble TNF- $\alpha$ receptors that competitively binds to TNF- $\alpha$	Subcutaneous injection, once or twice weekly, in a community setting	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and severe plaque psoriasis
<b>Adalimumab</b>	Humanised monoclonal antibody	Binds to TNF- $\alpha$	Subcutaneous injection, usually every two weeks, in a community setting	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (including fistulising) and severe plaque psoriasis
<b>Biologic medicines for inflammatory disease subsidised on the HML only</b>				
<b>Infliximab</b>	Chimeric monoclonal antibody containing approximately 25% mouse-derived amino acids <sup>4</sup>	Binds to TNF- $\alpha$	Intravenous infusion at zero, two and six weeks, then every eight weeks, in a secondary care setting	Where treatment with adalimumab or etanercept has been intolerable or ineffective, used in combination with methotrexate (if possible) for: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (including fistulising), ulcerative colitis, severe plaque psoriasis and ocular inflammation
<b>Rituximab</b>	Chimeric monoclonal antibody	Binds to a CD20 protein mainly found on antibody-producing B cells	Intravenous infusion, in two-dose courses, in a secondary care setting	Rheumatoid arthritis where treatment with a TNF inhibitor has failed or is contraindicated
<b>Tocilizumab</b>	Humanised monoclonal antibody	Binds to interleukin-6 receptors	Intravenous infusion, every two weeks, in a secondary care setting	Systemic juvenile idiopathic arthritis

 The New Zealand Formulary or Pharmaceutical Schedule has details of Special Authority subsidy criteria.

## Precautions with the use of biologic medicines

Biologic medicines are usually contraindicated in patients with any of the following:<sup>2,6,8</sup>

- Severe active infections
- Moderate to severe heart failure
- Multiple sclerosis or optic neuritis
- Untreated or latent tuberculosis
- Hepatitis B
- Malignancy within the last five years

## Testing for latent infection

**Patients should be tested for latent tuberculosis infection** prior to starting a biologic medicine using an interferon gamma release assay (QuantiFeron Gold).<sup>8</sup> This test is reported to be more sensitive in people who are immunocompromised than Tuberculin Skin Testing (TST/Mantoux), e.g. in patients who have been taking corticosteroids or methotrexate.<sup>8</sup> The specificity of the QuantiFeron Gold test is also higher than Mantoux testing in patients who have previously had a BCG vaccination and the test only requires one patient visit.<sup>8</sup> Infliximab is most frequently associated with tuberculosis reactivation, but reactivation can occur with other biologics.<sup>9</sup>

## Check the patient's vaccination history

Before patients are prescribed biologic medicines they should have their immunisation status reviewed to ensure they have received all vaccinations recommended on the New Zealand immunisation schedule.

**For some patients it may be necessary to plan an immunisation catch-up.** Live vaccinations, e.g. varicella vaccine, tuberculosis (BCG) and measles, mumps rubella (MMR), are contraindicated in patients who are undergoing immunosuppressive treatment and should be completed in advance of treatment.<sup>10,11</sup>

**Hepatitis A and B vaccination** is recommended in patients who will be taking biologic medicines who do not have confirmed immunity to viral hepatitis.<sup>10,11</sup> Reactivation of hepatitis B in patients taking biologics is increasingly reported in the literature.

**Influenza vaccination** should be provided annually to people taking biologic medicines. People who are immunosuppressed, people aged over 65 years and people with rheumatoid arthritis are currently eligible for free annual influenza vaccinations. Vaccination against pneumococcal infection

## What are TNF inhibitors?

Tumour necrosis factor (TNF) inhibitors are used to treat immune-mediated inflammatory diseases, e.g. rheumatoid arthritis, inflammatory bowel disease and psoriasis, by blocking the action of TNF- $\alpha$ , a pro-inflammatory cytokine.<sup>2</sup> TNF- $\alpha$  is a transmembrane protein that is cleaved by an enzyme to produce a soluble form of the protein.<sup>5</sup> Soluble TNF- $\alpha$  is released by activated T cells.<sup>6</sup> Both the soluble and transmembrane forms of TNF- $\alpha$  bind to TNF receptors causing activation of inflammatory genes that result in:<sup>5,6</sup>

- Increased blood flow and permeability of blood vessels; and
- Guidance of neutrophils to sites of infection

Soluble TNF- $\alpha$  also:<sup>6,7</sup>

- Causes macrophages to phagocytose pathogens
- Stimulates leukocytes and endothelial cells in blood vessels to release cytokines
- Increases expression of cell-surface attachment molecules for neutrophils
- Increases production of leukotrienes (cell signalling molecules that cause contraction of smooth muscle)

TNF- $\alpha$  levels are increased in areas of immune-mediated inflammation in people with conditions such as rheumatoid arthritis.<sup>4</sup> TNF inhibitors block the pro-inflammatory action of TNF- $\alpha$  and usually reduce the severity of the patient's symptoms, and sometimes induce disease remission.<sup>1</sup> Each TNF inhibitor blocks binding of both soluble and membrane forms of TNF- $\alpha$  to TNF receptors resulting in any one, or combination, of the following events occurring:<sup>2</sup>

1. Neutralisation of soluble TNF, therefore reducing inflammation. This action mimics the body's own ability to prevent fatal shock during infection and inflammation via the production of endogenous soluble receptors.
2. Cell lysis through serum protein-dependent or antibody-dependent cell-mediated cytotoxicity
3. Intracellular signalling which can reduce cytokine production, reduce cell growth or induce apoptosis (programmed cell death) of inflammatory cells following binding to membrane receptors


The adverse effects of the TNF inhibitors can be serious because they potentially involve all the immune-mediated pathways that interact with TNF- $\alpha$  (Page 22).




is also recommended, but not funded, for patients taking biologics. To achieve a maximum immune response against pneumococcal infection the Immunisation Advisory Centre recommends that Prevenar 13 (unsubsidised) be given eight weeks before Pneumovax 23, in patients at high-risk of an infection.<sup>12</sup> Patients at high-risk of infection should also receive a second Pneumovax 23 vaccine after three to five years.

**Varicella vaccination** is recommended by New Zealand gastroenterology guidelines for patients who will be taking biologic medicines who do not have demonstrated varicella immunity.<sup>10</sup> However, rheumatology guidelines do not make this recommendation as greater than 90% of the adult population are reported to have evidence of serological immunity and most instances of varicella infection are due to reactivation.<sup>13</sup>

**HPV vaccination** is recommended before beginning treatment with biologic medicines for females aged nine to 26 years, based on current guidelines.<sup>10</sup> This vaccine is fully subsidised for females prior to their twentieth birthday.

 The New Zealand Immunisation Schedule has advice and examples to help plan an immunisation catch-up programme. See: [www.health.govt.nz/publication/immunisation-handbook-2011](http://www.health.govt.nz/publication/immunisation-handbook-2011)

 For further information see: "How to plan a catch-up immunisation", BPJ 45 (Aug, 2012).

## The safety of biological medicines during pregnancy

The use of biologic medicines in women who are pregnant is not recommended as their safety has not been established.<sup>13</sup> Most guidelines suggest females treated with biologics be prescribed effective contraception during treatment and also for several months after treatment has been discontinued.<sup>3,13</sup> In the event of a pregnancy occurring while a female is being treated with a biologic, the decision to discontinue the medicine should take into account the current activity of the condition being treated, the risks of a flare if treatment is discontinued and the potential for harm to the foetus.<sup>13</sup> However, there is a lack of data and consensus regarding the adverse effects of biologics during pregnancy. There have been reports in the literature of an increased risk of miscarriage and foetal abnormality but also instances where the pregnancy has progressed normally and there has been no harm to the infant.<sup>13</sup>

## Monitoring patients being treated with biologics

Reducing the risk of infection in patients taking biologics is an important role for the primary care team. Patients prescribed biologics should be made aware that they have an increased risk of acquiring infections and to report any symptoms early. Strategies such as good food hygiene to reduce the likelihood of food-borne infections, e.g. listeria, and good personal hygiene to reduce the risk of opportunistic infection, e.g. candidiasis, can be discussed.<sup>13</sup> Once the patient is stabilised on treatment, General Practitioners will be involved with ongoing monitoring for adverse effects.

### Monitoring for adverse events during administration

**Subcutaneous administration of adalimumab and etanercept** is usually performed by the patient themselves, but may be performed by a Practice Nurse. The most frequent reactions include: redness, rash, swelling, itching and bruising, however, more severe gastrointestinal and cardiovascular effects can also occur.<sup>3,10</sup> To reduce injection site reactions patients can be advised to space each new injection site at least 3 cm from the previous site and to apply a damp towel or ice pack to the site for ten to fifteen minutes after the injection, if required.

**IV infusions of infliximab, rituximab and tocilizumab are administered in secondary care.** Patients require monitoring during the procedure and for one hour afterwards.<sup>10</sup> Infusion reactions are rare, but can be marked and may occur up to 12 days following treatment including: hypertension, hypotension, headache, skin rashes and urticaria and flu-like symptoms.<sup>3,10</sup>

### Monitoring for complications

If a patient taking a biologic medicine develops symptoms of a serious disease or infection then prompt action is required; the treating specialist should be contacted and the possibility of withdrawing the biologic discussed.<sup>13</sup>

**Patients taking biologic medicines have an increased risk of developing serious infections.** For example, in the first six months of treatment there is an increased likelihood of pneumonia, soft tissue infections and opportunistic infection, particularly latent infections that have been controlled by the production of granulomas (foreign material surrounded by macrophages), e.g. *Mycobacterium tuberculosis* and *Listeria monocytogenes*.<sup>6</sup> Depending on the type and severity of the infection, there may be a lower threshold for prescribing antibiotics.<sup>2</sup> The rate of infection is dependent on baseline risk and is also influenced by age, other medicine use and co-morbidities, e.g. chronic obstructive pulmonary disease (COPD).<sup>6</sup>

**Heart failure may occur or be exacerbated in patients taking biologic medicines.**<sup>13</sup> Treatment with biologics should be discontinued if heart failure develops and patients with mild heart failure should be regularly monitored and treatment withdrawn if the condition worsens.<sup>13</sup> Etanercept and infliximab are known to be associated with an increased risk of heart failure.<sup>13</sup> It is not known if there is an association between adalimumab use and heart failure as no trials have been conducted, however, it is generally assumed a similar risk is associated with its use.<sup>13</sup>

**Interstitial lung disease is associated with rheumatoid arthritis** and can be life threatening. Patients should be monitored for shortness of breath or dry cough.<sup>14</sup> The incidence of interstitial lung disease is increased with the use of etanercept, infliximab and adalimumab.<sup>13</sup> It is likely that the risk of a patient developing interstitial lung disease is also influenced by the concomitant use of methotrexate,<sup>13</sup> which can itself cause pulmonary fibrosis.

**A periodic skin examination for non-melanoma skin cancer is appropriate** for patients who are at increased risk, e.g. patients with a history of psoriasis or those treated with photochemotherapy (PUVA).<sup>14</sup>

People with rheumatoid arthritis are also approximately 2 – 2.5 times more likely than people in the general population to develop lymphoma.<sup>13</sup> In addition, there have been studies suggesting that the risk of developing lymphoma may be increased in patients taking biologics for inflammatory conditions, however, the overall evidence for this is mixed.<sup>13</sup>

**The use of etanercept, infliximab and adalimumab has been associated with both peripheral and central demyelination.**<sup>13</sup> These medicines should not be prescribed to patients with multiple sclerosis and should be used with caution in patients with a history of other demyelinating diseases.<sup>13</sup>

**Treatment with biologics has also occasionally been associated with autoimmune diseases,** e.g. lupus-like syndrome, autoimmune uveitis, vasculitis or inflammatory bowel disease.<sup>13, 15</sup>

#### **Laboratory investigations**

Guidance varies on the type and frequency of laboratory tests required for patients taking biologic medicines. Laboratory tests may include:<sup>16</sup>

- CRP – to monitor the inflammatory response
- FBC – the use of biologics has been associated with various cytopenias, e.g. neutropaenia, thrombocytopaenia

- LFTs – due to reports of hepatotoxicity
- Creatinine and electrolytes – as a baseline, particularly prior to IV infusion

Depending on the clinical situation, laboratory testing should be repeated every three to six months, or more frequently if the patient is being treated with other DMARDs.<sup>14</sup> When interpreting the results it is important to note that although the absolute laboratory values are important, any consistent trend in values, such as a steady downward pattern or a rapid fall or rise in a parameter may signal the need for clinical assessment and further investigations.<sup>14</sup>

#### **Managing patients who require surgery**

There is some evidence that the risk of peri-operative infection is increased in patients taking biologics, although this varies, e.g. with the type of surgical procedure and the co-morbidities of the patient. There is a potential for a flare of the condition being treated when treatment is withheld, e.g. in rheumatoid arthritis activity, however, most guidelines advocate stopping TNF inhibitors before and after surgery.<sup>13</sup>

It is recommended that if patients require major surgery during treatment with biologics the medicine should be withheld prior to surgery for three to five times the half-life of the medicine being used.<sup>13</sup> The half-life of the most commonly used biologics is: 100 hours for etanercept, 15 – 19 days for adalimumab and 8 – 9.5 days for infliximab.<sup>13</sup> For example, a patient undergoing a major procedure should have etanercept withdrawn for 13 – 21 days and adalimumab 45 – 95 days prior to the operation. The medicine can be resumed 10 – 14 days after surgery provided there are no signs of infection and the wound is healing satisfactorily. The risk of post-operative infection is likely to be influenced by the type of procedure the patient is undergoing and the presence of comorbidities. Infection risk should therefore be assessed on a case-by-case basis.

#### **Application for renewal of Special Authority subsidy**

Special Authority subsidy for the treatment of inflammatory conditions with biologics can be renewed by General Practitioners who have written confirmation from a relevant specialist recommending that treatment be continued. This is dependent on specific renewal criteria (Table 2, over page). For some General Practitioners renewal may also involve monitoring a patient's clinical response to treatment when patient access to specialist assessment is limited or difficult, e.g. a rural location. For example, in patients with rheumatoid arthritis this may include: a regular clinical assessment of the

number of inflamed joints, any improvements in the patients daily function, the need for any additional anti-inflammatory agents and requests for laboratory tests, e.g. CRP, FBC and LFTs.<sup>1,16</sup>

Patients who require specialist assessment prior to the renewal of a Special Authority need to be seen by the treating specialist before the approval expires. Most renewals are valid for six months.

**ACKNOWLEDGEMENT** Thank you to **Dr Rebecca Grainger**, Rheumatologist, Wellington Regional Rheumatology Unit, Hutt Valley DHB and Senior Lecturer, Department of Medicine, University of Otago, Wellington for expert review of this article.

**Table 2 :** Special Authority renewal criteria for biologic medicines for the treatment of inflammatory conditions<sup>3,17</sup>

Condition	Medicine	Renewal criteria*
<b>Rheumatoid arthritis</b>	Etanercept or adalimumab	At least a 50% decrease in active joint count (number of swollen or tender joints) from baseline. After the initial response the patient is assessed six-monthly and treatment withdrawn if a response is not maintained.
<b>Juvenile idiopathic arthritis</b>	Etanercept or adalimumab	At least a 50% decrease in active joint count following three to four months of treatment and improvement in overall clinical condition
<b>Ankylosing spondylitis</b>	Etanercept or adalimumab	At least a 50% decrease in active joint count from baseline, or at least four points on the ten point Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). For further information on calculating BASDAI see: <a href="http://www.basdai.com">www.basdai.com</a>
<b>Crohn's disease</b>	Adalimumab	A reduction in the Crohn's Disease Activity Index (CDAI) of 100 points or a score of 150 or less. Patients with fistulising Crohn's disease require additional confirmation from a Gastroenterologist that there has been a decrease in the number of open draining fistulae by at least 50%, or a marked reduction based on the Fistula Assessment score in addition to a decrease in induration and pain.† For further information on calculating CDAI see: <a href="http://www.ibdjohn.com/cdai">www.ibdjohn.com/cdai</a>
<b>Chronic plaque psoriasis</b>	Etanercept or adalimumab	Requirements vary. Patients with "whole body" severe chronic plaque psoriasis prior to treatment require an ongoing reduction in the Psoriasis Area and Severity Index (PASI) of 75% or more. Patients with localised disease, e.g. of the face or sole of the foot at the start of treatment, must have a reduction in the PASI symptom subscore for erythema, thickness and scaling compared to baseline or a reduction of 75% or more in the area affected. For further information on calculating PASI see: <a href="http://www.dermnetnz.org">www.dermnetnz.org</a>
<b>Psoriatic arthritis</b>	Etanercept or adalimumab	A clinically significant result and at least a 50% reduction in active joint count after three to four months of treatment

\* Including written confirmation from the treating specialist. † A form to calculate a fistula assessment score is available from: [www.pharmac.health.nz/ckeditor\\_assets/attachments/435/fistula-assessment-form-nz.pdf](http://www.pharmac.health.nz/ckeditor_assets/attachments/435/fistula-assessment-form-nz.pdf)



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## bestpractice Holiday Hours

Tuesday 24th Dec	8.30am-5pm
Wednesday 25th Dec	Closed
Thursday 26th Dec	Closed
Friday 27th Dec	8.30am-5pm
Monday 30th Dec	8.30am-5pm
Tuesday 31st Dec	8.30am-5pm
Wednesday 1st Jan	Closed
Thursday 2nd Jan	Closed
Friday 3rd Jan	8.30am-5pm
Monday 6th Jan	Normal Hours Resume

## Thank you for your support in 2013

We wish you a safe and happy holiday period and look forward to working with you in the new year.



# Managing patients with dementia:

What is the role of antipsychotics?

Concerns have been raised, both in New Zealand and internationally, about the increasing off-label use of antipsychotics, and their safety profile in older people. Antipsychotics should not be considered in older people with dementia before non-pharmacological treatment strategies have been trialled. The potential benefit of antipsychotics needs to be weighed against the significant likelihood of adverse effects. The choice of antipsychotic is also important and needs to take into account both relative efficacy and safety. Antipsychotics are only useful for specific behaviours associated with dementia, such as psychosis and agitation. If antipsychotics are prescribed, response to treatment and adverse effects must be carefully monitored.

## The behavioural and psychological symptoms of dementia

The behavioural and psychological symptoms of dementia (BPSD) are defined as symptoms of disturbed perception, thought, mood or behaviour in a person with dementia, which are not due to another major neuropsychiatric disorder, such as a major depressive episode.<sup>1</sup> Almost all people with dementia experience inappropriate behavioural and psychological symptoms at some point during their illness. This can cause significant stress to family and caregivers and result in institutionalisation. As there is no cure for dementia, appropriate treatment of BPSD can have a significant impact on the quality of life of the patient, their families and caregivers.

There is concern that antipsychotics are being over-prescribed to control inappropriate behaviour in people with dementia.<sup>2</sup> The first approach to managing BPSD is to try to understand why the behaviour is occurring, and, where possible, control for these factors.


Although the evidence base for non-pharmacological treatments of BPSD is not strong, there are generally less risks associated with these interventions and they should always be considered first. Non-pharmacological interventions should be tailored to the individual patient and the target behaviour(s) and the impact carefully monitored.

### Identify target behaviours

There are a variety of challenging behaviours and symptoms that may present in older people with dementia. As different behaviours are often best managed using different approaches, it is critical to first decide which behaviours are being targeted for management. Identifying target behaviours also allows the response to treatment to be more accurately monitored.<sup>2</sup>

Common target problems and behaviours observed in elderly people with dementia or other mental illnesses include:<sup>2</sup>

- Calling out
- Aggression
- Agitation
- Hallucinations and illusions
- Delusions
- Wandering
- Depression
- Elevated mood
- "Sundowning", e.g. increased agitation in the late afternoon
- Insomnia
- Apathy/lack of motivation
- Extreme anxiety
- Resistance or unease towards carers
- Intrusive behaviours
- Inappropriate sexualised behaviour
- Inappropriate urination or defaecation
- Other inappropriate social behaviours

 Record the target problem(s) and the response to treatment in the patient's notes.

### Assess underlying causes and contributing factors

Medical and environmental factors can often precipitate or exacerbate BPSD. Patients presenting with BPSD should be assessed to exclude reversible causes, minimise precipitating factors, and to develop an individualised plan.



Assessment should include consideration of the following factors:<sup>3</sup>

- Are the symptoms explained by another psychiatric condition such as depression or delirium?
- Is the patient taking any medicines that may be causing or contributing to the symptoms?
- Is the patient in otherwise good physical health? Is there a possibility of undetected pain, infection, constipation or discomfort?
- Are there any factors in the patient's living environment, i.e. their home/care facility, or unmet personal needs which may be exacerbating behaviours?

### Differential diagnosis: The 3Ds

Depression and delirium can also be associated with BPSD-like symptoms, therefore it is important to distinguish dementia from these conditions (referred to as the 3Ds). Differential features of the 3Ds are presented in Table 1, but

there is considerable overlap and the 3Ds often co-exist. Severe depression can present as a dementia-like illness (pseudodementia). Delirium can be caused by infections, drug toxicity, alcohol withdrawal and metabolic disturbances.

### Medicines that could precipitate or worsen BPSD

If an older person presents with new or worsening BPSD, current medicines should be excluded as a possible precipitant.

Medicines which can be associated with cognitive impairment include:<sup>5</sup>

- Anticholinergics, e.g. amitriptyline, oxybutynin
- Anticonvulsants, e.g. carbamazepine, phenytoin
- Lithium
- Systemic corticosteroids, especially high doses
- H2 antagonists, e.g. ranitidine
- Some antibiotics, e.g. ciprofloxacin, norfloxacin, metronidazole, clarithromycin

**Table 1:** Differential features of the 3Ds: delirium, dementia and depression<sup>4</sup>

Feature	Delirium	Dementia	Depression
Onset	Hours to days Usually sudden, often in the evening	Months to years Chronic and generally insidious	Weeks to months Sometimes relatively abrupt and coinciding with life changes, but may also be insidious and not clearly linked to life events
Duration	Hours to less than one month, rarely longer	Months to years	Months
Progression	Abrupt, fluctuating	Slow but generally steady	Variable and uneven
Thinking	Disorganised, slow, incoherent	Paucity of thought, poor judgment; words hard to find	Intact with themes of helplessness, generally negative
Memory	Impaired, sudden	Impaired	Selective or patchy
Sleep	Nocturnal confusion	Often disturbed; nocturnal wandering	Reduced sleep with early morning waking, or may oversleep
Awareness	Reduced	Clear	Clear
Alertness	Fluctuates; lethargic or hypervigilant	Generally normal	Normal
Attention	Impaired, fluctuates	Generally normal	Minimal impairment but easily distracted

- Analgesics, particularly opioids
- Anti-Parkinson's medicines
- ACE inhibitors
- Digoxin

#### Undetected medical conditions

The following medical conditions can potentially cause, contribute to or mimic BPSD and should be considered:<sup>3</sup>

- Pain (see opposite)
- Infection (especially urinary tract infection)
- Dehydration or hyponatraemia
- Constipation
- Urinary retention
- Anxiety
- Fatigue
- Hearing/visual impairment
- Poor dental health

#### Personal or environmental factors that can cause or exacerbate BPSD

Problems in the design and configuration of the patient's home or residential facility can cause or exacerbate restlessness, frustration, anxiety and disorientation. Simple changes in the environment can be beneficial and may be worth discussing with the patient's family, carer or residential care manager, including:<sup>3,8</sup>


- Promote a calm, tranquil environment, i.e. avoid overstimulation
- Ensure that the patient's home/room is at a comfortable temperature
- Ensure easy access to the toilet
- Have well lit surroundings
- Use signs and memory aids for objects within the home that the patient commonly uses
- Improve time orientation, e.g. prominent calendar/clock
- If the patient is in a residential care facility, make their environment as "home-like" and reassuring as possible, by ensuring the patient is surrounded by their personal belongings, including culturally significant items
- Encourage involvement in group activities to prevent boredom and loneliness
- If possible, ensure consistency of carers
- Ensure the patient has privacy

Encouraging people with dementia to participate in activities which are meaningful and enjoyable to them may improve their sense of wellbeing and communication and lead to

### Untreated pain may be a cause of BPSD

Pain is estimated to occur in up to 83% of patients with dementia.<sup>6</sup> It is often poorly recognised and undertreated due to the patient's difficulty in communicating their needs. Symptoms of BPSD, e.g. calling out, agitation and restlessness, can be due to undertreated pain.

Regularly ask the patient whether they have any pain. Keep questions simple, e.g. "is it sore"? or "does it hurt"? It may be necessary to observe breathing patterns, facial expression or vocalisations to assess pain in a patient with dementia. There are several tools available to help establish if a patient with cognitive impairment is in pain, if they cannot tell you in words. A New Zealand study found that the Pain Assessment Scale for Seniors with Limited Ability to Communicate (PACSLAC) was easily used by caregivers, and resulted in increased use of "as needed" analgesic medicines and reduced levels of caregiver stress.<sup>7</sup>

 PACSLAC is available from: [www.rgpc.ca](http://www.rgpc.ca)




reductions in BPSD. This might include exercising, gardening, music, dancing, art or interactions with a pet. There is some limited evidence that aromatherapy can improve symptoms of BPSD and increase quality of life in people with dementia.<sup>9</sup>

## Behaviour management

Behaviour management is defined as a structured intervention, usually carried out by family or other caregivers, under the supervision of a professional with expertise in this area. This might involve providing reinforcement for increased social activity or removing reinforcement for attention seeking behaviour. Behavioural management involving scheduling enjoyable events or engagement in problem-solving activities has been shown to improve symptoms of depression in people with dementia.<sup>10</sup>

Inappropriate sexual behaviour can be particularly challenging to address. Strategies include separating the patient from a person who might be a trigger for the behaviour and distraction with other activities, e.g. craft work to occupy the hands.<sup>11</sup>

## Antipsychotics are second-line

 Antipsychotics may be considered for treating aggression, agitation or psychotic symptoms. They are not useful for wandering, shouting, touching or social withdrawal.

Antipsychotics are only appropriate for patients with BPSD if aggression, agitation or psychotic symptoms are causing severe distress or an immediate risk of harm to the patient or others.<sup>8, 10</sup> Unless emergency treatment is required, non-pharmacological treatment should always be tried first and continued concurrently with antipsychotics.

Antipsychotics are not recommended for patients with mild to moderate BPSD,<sup>10</sup> and are not usually effective for other symptoms such as wandering, social withdrawal, shouting, pacing, touching or incontinence.<sup>12</sup> Antipsychotics do not appear to improve overall functioning, care needs or quality of life in patients with dementia.<sup>13</sup>

If an antipsychotic is prescribed, it should be given on a trial basis, and response and adverse effects regularly reviewed. An appropriate trial of an antipsychotic for patients with aggression or agitation is up to four weeks and up to three months for patients with psychotic symptoms, e.g. delusions or hallucinations.<sup>2</sup> If possible, antipsychotics should not be used long-term for patients with dementia.

## Antipsychotics can modestly improve BPSD in some patients

Antipsychotics are only modestly effective in managing BPSD, and the level of effectiveness varies between patients. They should not be regarded as a “cure” for BPSD. Traditionally, older antipsychotics (referred to as typical antipsychotics) such as haloperidol were used to manage symptoms in patients with dementia. Newer, atypical antipsychotics, such as risperidone, olanzapine, quetiapine and aripiprazole are now used. They are no more effective than typical antipsychotics for BPSD, but are regarded as being better tolerated and safer (in terms of adverse effects) to use in older people.<sup>2</sup>


A meta-analysis which measured improvement in psychosis (e.g. delusions and hallucinations) and agitation (e.g. aggression, excitability, oppositional behaviours or excessive motor activity) with use of atypical antipsychotics found that the overall observable change was a 35% improvement in behaviour compared to baseline.<sup>14</sup> A 30% improvement in behaviour is regarded as the minimum clinically observable change.<sup>14</sup> Risperidone, olanzapine and aripiprazole had a small, but statistically significant, beneficial effect on symptoms. The effect of quetiapine was not significant.<sup>14</sup> In contrast, a 2011 meta-analysis found that patients using quetiapine had a statistically significant improvement in BPSD, but the improvement was of questionable clinical significance.<sup>15</sup>

## Which antipsychotic to choose for BPSD?

The choice of antipsychotic is based on their relative efficacy and adverse effects, along with subsidy status. Common adverse effects associated with all antipsychotics include sedation, dizziness, postural hypotension and confusion, which may increase the risk of falls in older people.<sup>5, 16</sup> The anticholinergic properties of antipsychotics can worsen cognition or cause delirium. Extrapyramidal adverse effects occur more commonly with typical antipsychotics, but can occur with risperidone even at relatively low doses. Rarely, tardive dyskinesia can occur. Metabolic changes, e.g. significant weight gain, hyperglycaemia and effects of increased prolactin (e.g. galactorrhoea), have also been associated with antipsychotics, but this is not observed to occur as frequently in older people. Many of these effects can be potentiated by interactions with other medicines and co-morbid conditions.<sup>16</sup>

**Risperidone** is the most extensively studied antipsychotic for use in BPSD, and is the only atypical antipsychotic approved for this use in New Zealand. Risperidone is, therefore, the first-line choice when an antipsychotic is prescribed for BPSD.<sup>14</sup>

If risperidone is not tolerated or not appropriate, then other antipsychotics may be considered in some patients. Other atypical antipsychotics are not approved for use in BPSD in New Zealand, so are regarded as being used “off-label” for this indication. Table 2 shows a comparison of adverse effects for antipsychotics commonly used in the treatment of BPSD.

 For further information about off-label prescribing, including prescriber obligations, see: “Unapproved medicines and unapproved use of medicines: keeping prescribers and patients safe”, BPJ 51 (Mar, 2013).

**Quetiapine** appears to be increasingly used in older people, and evidence from cohort studies suggests it is safer than other antipsychotics (including risperidone) in terms of mortality risk, but it may not be as effective.<sup>14, 15</sup> Quetiapine at low doses (< 100 mg/day) is generally well tolerated in older people.

**Olanzapine** has been shown to be modestly effective for treating agitation, however, the evidence is not as robust as it is for risperidone.<sup>18</sup> Olanzapine is associated with more metabolic adverse effects, including rapid and significant weight gain, dyslipidaemia and type 2 diabetes, than other antipsychotics.<sup>14, 16</sup>

**Aripiprazole** has been shown to be modestly effective for symptoms of agitation and psychoses associated with BPSD.<sup>18</sup> However, it is not subsidised for this use as a Special Authority is required for subsidised prescription and the criteria do not cover BPSD. If aripiprazole is being considered, this should be discussed with a Psychiatrist or Geriatrician.

**Haloperidol** has traditionally been used for BPSD and does not differ significantly in effectiveness from atypical antipsychotics. However, it should generally be avoided in older people given the high risk of extrapyramidal adverse effects and increased mortality compared to atypical antipsychotics.<sup>2, 16</sup> Low-dose haloperidol has a restricted place in the short-term management of the acute symptoms of delirium (except in people with Parkinsonism of any cause).

The newer antipsychotics **amisulpride**, **paliperidone** (not subsidised) and **ziprasidone** (not subsidised for this indication) do not yet have an evidence base to support their use in BPSD.

**Table 2:** Comparative risk of adverse effects of antipsychotics commonly used wfor BPSD.<sup>16, 19</sup>

	Risperidone	Quetiapine	Olanzapine	Aripiprazole	Haloperidol
Anticholinergic effects	+	+	+	•	+
Dyslipidaemia	++	++	+++	•	+
Extrapyramidal symptoms	++	•	+	+	+++
Hyperprolactinaemia	+++	+	+	•	+++
Neuroleptic malignant syndrome	+	+	+	+	++
Postural hypotension	++	++	+	+	+
Prolonged QT interval	+	+	+	+	++
Sedation	+	++	++	+	+++
Seizures	+	+	+	+	+
Sexual dysfunction	+	+	+	+	+++
Type 2 diabetes	+	+	++	+	+
Weight gain	++	++	+++	•	++

• = rare, + = lower risk, ++ = medium risk, +++ = higher risk



## Lewy Body dementia and dementia associated with Parkinson's disease

Approximately 10% of people with dementia have Parkinson's disease or significant Parkinsonian symptoms.<sup>20</sup> Some of these people have Lewy Body dementia. Core symptoms of Lewy Body dementia include complex visual hallucinations, fluctuating cognitive impairment and Parkinsonism that is neither stroke nor drug-induced. It is recommended that a Psychiatrist or Geriatrician is consulted before considering prescribing any medicines for BPSD in people with Lewy Body dementia.

Typical antipsychotics such as haloperidol should not be used in people with Lewy Body dementia or dementia associated with Parkinson's disease as they can cause dangerous extrapyramidal symptoms. There is also an increased risk of neuroleptic malignant syndrome, which is a life-threatening disorder induced by dopamine antagonists, characterised by hyperthermia, hypertonia ("lead pipe" rigidity in all muscle groups), changes in mental state, hyporeflexia and haemodynamic instability.<sup>21</sup> Atypical antipsychotics, especially olanzapine, are also best avoided, as they can result in severe sensitivity reactions (e.g. marked extrapyramidal effects, confusion, autonomic instability, falls and increased mortality).<sup>20</sup> Quetiapine may be used at low doses with extreme caution, in consultation with a Geriatrician or Psychiatrist, if cholinesterase inhibitors and non-pharmacological treatments have failed.<sup>22</sup>

## Safety concerns with antipsychotics in older people

Antipsychotics are associated with additional serious safety concerns when used in older people with dementia, such as an increased risk of stroke and overall mortality. When considering antipsychotic treatment, these risks need to be balanced against the risk of injury (due to BPSD) for individual patients.

### Increased risk of cerebrovascular events

Atypical antipsychotics, such as risperidone and olanzapine, have been associated with an increased risk of cerebrovascular adverse events, such as stroke, in older people with dementia, particularly those with more advanced dementia. It is not known what the exact mechanism for this association is. There is evidence to suggest that the risk of stroke may be greatest in the first weeks of use of an atypical antipsychotic, and people with a past history of cerebrovascular events are particularly at risk.<sup>23</sup> The risk of stroke may not return to baseline until six months after a patient ceases antipsychotic treatment (depending on the length of treatment).<sup>24</sup> Typical antipsychotics are also associated with an increased risk of stroke, but there is some evidence that this risk is less than that with atypical antipsychotics.<sup>24</sup> Antipsychotics should be prescribed with caution in elderly people with dementia who have an increased cardiovascular risk or personal or family history of cerebrovascular events.


An analysis of trials found an increased odds ratio of 2.13 for cerebrovascular adverse events in people taking antipsychotics for dementia. This risk was especially high with risperidone (odds ratio 3.43).<sup>25</sup> Another systematic review and meta-analysis also found that risperidone was associated with an increased risk of stroke (odds ratio 3.12).<sup>14</sup> The number needed to harm was 53.<sup>14</sup> A comparative study found that there was no difference in risk of stroke between patients taking risperidone and patients taking olanzapine, i.e. suggesting that olanzapine has the same increased risk.<sup>17</sup> Patients taking quetiapine had a smaller risk of cerebrovascular adverse events than those taking olanzapine.<sup>17</sup>

### Increased mortality

Atypical antipsychotics have been associated with an increased overall mortality rate in older people with dementia. In 2005, the United States Food and Drug Administration (FDA) stated that the risk of mortality was increased 1.6-1.7-fold in patients treated with atypical antipsychotics for BPSD.<sup>26</sup> A subsequent meta-analysis also found a similar mortality rate with atypical antipsychotics.<sup>4</sup> For every 87 patients treated with an antipsychotic for dementia, one patient will die.<sup>14</sup>

The risk of death is significantly lower for quetiapine compared to risperidone or olanzapine, which in turn has a lower risk of death than haloperidol.<sup>27,28</sup> The highest increase in mortality is in the first four months of treatment and in the first 30 days for haloperidol, although study participants receiving haloperidol may have been more unwell, and had received the medicine during an inpatient hospital admission.<sup>27</sup> This finding contrasts to that of the DART-AD study which found that the risk of death may increase with long-term treatment.<sup>29</sup>

The most common conditions associated with cause of death appear to be pneumonia (see below) or cardiac failure or arrest.<sup>30</sup> Antipsychotics prolong the QT interval, which can result in ventricular tachyarrhythmia and sudden cardiac death. The risk of cardiac death increases with increasing dose, and the risk is similar between typical and atypical antipsychotics.<sup>31</sup> The risk is no longer elevated when use of antipsychotics ceases.<sup>31</sup> Antipsychotics should be prescribed with caution in patients taking other medicines which prolong the QT interval, e.g. erythromycin, citalopram, venlafaxine.

 A full list of medicines with the potential to cause prolonged QT interval is available from: [www.qtdrugs.org](http://www.qtdrugs.org)

### Potential increased risk of pneumonia

Population based studies have suggested that there is an increased risk of pneumonia in older people (with or without dementia) treated with antipsychotics. The risk is thought to be greater with atypical antipsychotics, and the risk may be highest during the first week of treatment.<sup>32</sup>

It is not known how antipsychotics increase the risk of pneumonia, however, dysphagia (due to H1 receptor blockade), dry mouth (due to the anticholinergic effect), sedation (facilitating aspiration pneumonia) and direct or indirect effects on the immune system have been suggested as possible mechanisms.<sup>32</sup>

## Guidance for prescribing antipsychotics in elderly people

### Obtain informed consent

Before prescribing an antipsychotic for BPSD, a full discussion should take place regarding the possible benefits and risks of treatment, including the increased risk of stroke and all-cause mortality in people with dementia.<sup>2,10</sup> Many patients

**Table 3:** Recommended starting and maintenance doses for antipsychotics in older people<sup>2,5</sup>

Medicine	Dose	Comments
<b>Risperidone</b>	0.25 – 0.5 mg initially, titrated to maximum 2 mg daily in patients with dementia (6 mg daily may be tolerated in other patients), in one or two divided doses	Only approved atypical antipsychotic for BPSD. At higher doses it may behave more like a typical antipsychotic in terms of a higher incidence of extrapyramidal effects.
<b>Quetiapine</b>	12.5 mg initially, titrated to maximum 100 mg daily in patients with dementia (300 mg daily may be tolerated in other patients), in two or more divided doses	Current evidence suggests limited effectiveness for BPSD, although possibly safer in terms of mortality risk
<b>Olanzapine</b>	2.5 mg initially, titrated to maximum 10 mg daily (less in patients with dementia), in one or two divided doses	May be modestly effective for treating agitation, but generally not recommended in people with dementia. Associated with greater comparative risk of adverse metabolic effects.
<b>Aripiprazole</b>	5 mg – 10 mg daily	Not subsidised for use in BPSD
<b>Haloperidol</b>	0.25 mg, twice daily, titrated up to 3 mg daily	Effective for the short-term management of the acute symptoms of delirium (except in people with Parkinsonism of any cause). Not recommended for long-term use. High risk of extrapyramidal adverse effects and increased mortality compared to atypical antipsychotics.

with dementia will lack competency to decide on their own treatment, therefore the person legally responsible for the patient's medical decisions must be given information that is easily understood so they can make an informed decision.<sup>2</sup>

### “Start low and go slow”

If a trial of antipsychotic treatment is considered necessary, the starting dose should be as low as possible (Table 3). The starting dose can be divided or timed according to the behaviour, e.g. a lunchtime dose for patients exhibiting increased agitation towards the end of the day (“sundowning”).

The dose can be slowly increased at no less than weekly intervals, depending on response. High doses should be avoided, and treatment should be stopped if it has not significantly improved the target behaviour.<sup>2</sup>

### Monitor closely for adverse effects

Older people are especially vulnerable to the adverse effects of antipsychotics, and these may outweigh any benefits. Adverse effects are generally dose-related and can be minimised by keeping the dose as low as possible.

Monitor for:

- CNS depression – sedation, increased confusion or cognitive impairment. Concurrent medicines may worsen effects, including benzodiazepines, opioids, antihistamines, antidepressants, anti-Parkinson's medicines.
- Anticholinergic effects – dry mouth, constipation, urinary retention, blurred vision, delirium. Concurrent medicines may worsen effects, including tricyclic antidepressants, oxybutynin and opioid analgesics.
- Dizziness and postural hypotension – increases risk of falls. Concurrent medicines may worsen effects, including antihypertensives, diuretics, SSRIs (causing hyponatraemia).
- Extrapyramidal effects – dyskinesias, dystonias
- Metabolic changes – monitor weight and monitor HbA<sub>1c</sub> at baseline, then every three months in year one (or fasting glucose monthly for first three months in patients at high risk)\*, and annually for subsequent years
- Infection – in particular urinary tract infections and pneumonia

### Regularly review the need for continuing treatment

Gradual dose reduction and eventual withdrawal should be tried every three months. There have been very few studies done to measure the effectiveness of antipsychotics for BPSD longer than three months. In addition, BPSD may be temporary. A recent Cochrane review concluded that antipsychotics could be routinely withdrawn without adversely affecting behaviour, in all patients apart from those with severe symptoms.<sup>33</sup>

Longer-term use of antipsychotics is reported to be associated with a higher risk of relapse of symptoms. A study found that in patients who had been treated with risperidone for BPSD for four to eight months, discontinuation was associated with an increased risk of relapse.<sup>34</sup> The risk of recurrence of symptoms may also be higher in people with previously severe symptoms and if discontinuation has caused recurrence before.

Withdrawal of antipsychotics should be done gradually, e.g. by reducing the dose by 50% every two weeks then stopping after two weeks on the minimum dose. Withdrawal may be slower if the antipsychotic has been prescribed for a longer period of time. Monitor for recurrence of target behaviours or the emergence of new symptoms.


Challenging behaviours or symptoms can persist over time and in certain circumstances it may be justifiable to continue antipsychotics. Reasons for continuing antipsychotics include:<sup>2</sup>


- A high risk of adverse consequences if medicines are withdrawn, especially if treatment has only been partially effective or prior relapses have occurred
- When the consequences of symptom relapse are deemed to be unacceptably severe
- When no alternative treatment approaches have been possible or effective in the past

Alternatives to antipsychotics may also be considered; discussion with a Geriatrician or Psychiatrist is recommended. There is a small body of evidence to support the use of SSRIs, such as citalopram and sertraline, for agitation and psychosis in people with dementia, with no statistically significant differences found between the effectiveness of SSRIs and antipsychotics.<sup>35</sup> There is some limited emerging evidence that levetiracetam may be useful for the behavioural symptoms of dementia.<sup>36</sup>

\* HbA<sub>1c</sub> should be used in preference to a fasting glucose test for investigating for diabetes in most clinical situations. However, HbA<sub>1c</sub> is not reliable when blood glucose levels rise too rapidly to affect HbA<sub>1c</sub> such as in some patients newly initiated on atypical antipsychotics. Therefore, in patients with other risk factors for diabetes, fasting blood glucose is recommended at baseline, and monthly for the first three months. HbA<sub>1c</sub> can be used for long-term monitoring.

## Further reading

 The Faculty of Psychiatry of Old Age (NZ) guidelines for the use of antipsychotics in residential aged care can be downloaded from: [www.ranzcp.org/Files/ranzcp-attachments/About\\_Us/College\\_Structure/Faculties/RANZCP\\_Clinical\\_recommendations-pdf.aspx](http://www.ranzcp.org/Files/ranzcp-attachments/About_Us/College_Structure/Faculties/RANZCP_Clinical_recommendations-pdf.aspx)

 The Health Quality and Safety Commission's Atlas of Healthcare Variation contains data on polypharmacy in older people, including the prescription of antidepressants. For further information, see: [www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/polypharmacy-in-older-people/](http://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/polypharmacy-in-older-people/)

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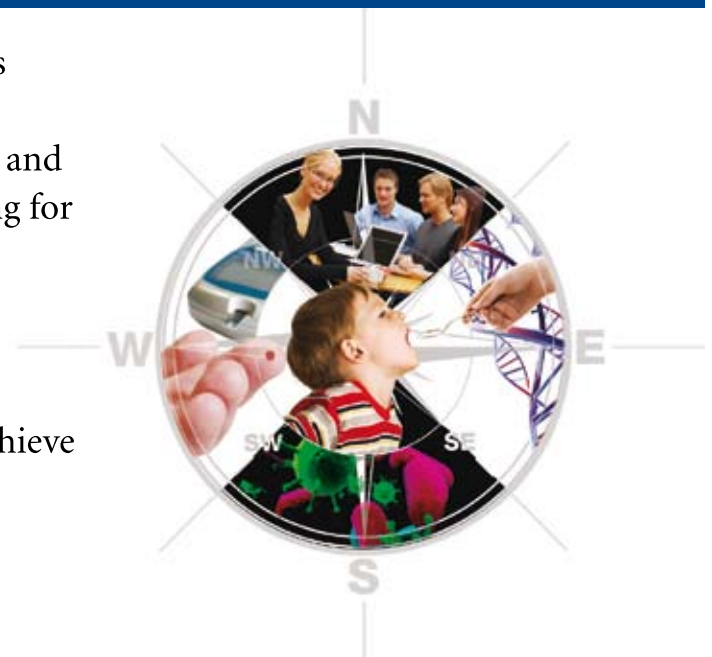
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# The New Zealand Formulary for Children

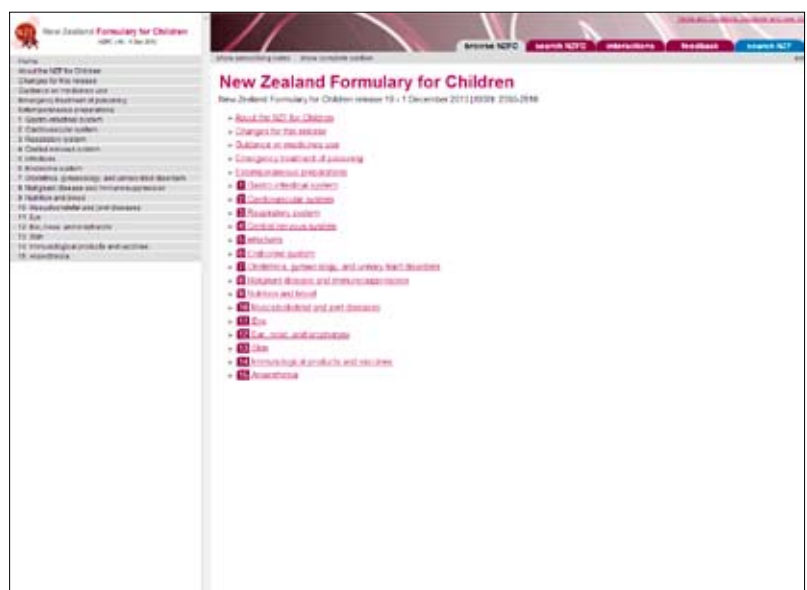
## The New Zealand Formulary for children is now available

In November 2013, the New Zealand Formulary launched the NZFC – a New Zealand adaptation of the British National Formulary for Children.

The NZFC is available from: [www.nzfchildren.org.nz](http://www.nzfchildren.org.nz) or click the pink tab on the NZF home page.

## The NZFC

- Easily navigated, with searchable medicines information specifically for children
- Indications and doses reflect current New Zealand practice, with expert advice from New Zealand Paediatricians
- Adapted from the British National Formulary for Children, incorporating PHARMAC and Medsafe information
- Additional information from reputable sources on drug interactions, drugs in pregnancy, breastfeeding
- Updated monthly and freely available to all healthcare professionals within New Zealand
- Feedback welcomed via feedback tab



## Prescribing notes for children

- Each section begins with prescribing notes followed by relevant drug monographs and preparations. Drugs are classified in a section according to their pharmacology and therapeutic use. Information can be found using the search NZFC tab.
- Prescribing notes are divided into 15 chapters, each of which is related to a particular system of the body or to an aspect of medical care

**5.1.5 Macrolides**

These medicines have an antibiotic spectrum that is similar but not identical to that of penicillins. They are less an alternative in penicillin-allergic patients. They are active against many gram-positive bacteria, but are not active or are less active against the macrolides.

Indications for the macrolides include campylobacter infections, respiratory infections (including pneumonia, whooping cough, Legionella, chlamydia, and Mycoplasma infections) and skin infections.

**Erythromycin** has an antibiogram spectrum that is similar but not identical to that of penicillin. It is thus an alternative in penicillin-allergic patients. It has poor activity against Haemophilus influenzae.

**Erythromycin** is a macrolide with slightly less activity than erythromycin against Gram-positive bacteria but enhanced activity against some Gram-negative organisms, including H. influenzae. Plasma concentrations are very low but tissue concentrations are much higher. It has a long tissue half-life and once daily dosage is recommended. Azithromycin is also used in the treatment of pertussis.

**Clarithromycin** is an erythromycin derivative with slightly greater activity than the parent compound. Tissue concentrations are higher than with erythromycin. It is given twice daily.

**Azithromycin** is a macrolide with slightly less activity than erythromycin against Gram-positive bacteria but enhanced activity against some Gram-negative organisms, including H. influenzae. Plasma concentrations are very low but tissue concentrations are much higher. It has a long tissue half-life and once daily dosage is recommended. Azithromycin is also used in the treatment of pertussis.

**Cautions**  
Macrolides should be used with caution in children with a predisposition to QT interval prolongation (including electrolyte disturbances) and concurrent use of drugs that prolong the QT interval.

**Adverse effects**  
Nausea, vomiting, abdominal discomfort, and diarrhoea are the most common adverse effects of the macrolides, but they are mild and less frequent with azithromycin and clarithromycin than with erythromycin. Hypokalaemia (including idiopathic hypokalaemia) and tachycardia are frequent. Other adverse effects reported rarely in any form include conjunctivitis, arthritis, associated colitis, QT interval prolongation, arrhythmias, generally reversible hearing loss (sometimes with tinnitus) after large doses, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Nervousness (often) may cause loss of consciousness and paresthesia.

**Interactions**  
+ azithromycin  
+ clarithromycin  
+ erythromycin  
+ roxithromycin

## Monographs & more

- Drug monographs are summaries of the important practical information about individual drugs
- More information can be revealed by clicking or hovering the cursor over some sections of the text, e.g. interactions, pregnancy and breast feeding
- Clicking on the + sign at the bottom of the drug monograph shows products available, funding information, links to medicines data sheets and consumer medicines information

**azithromycin**

**Cautions** children with a predisposition to QT interval prolongation (including electrolyte disturbances, concurrent use of drugs that prolong the QT interval), neonates under 2 weeks (risk of hypotriglyceridaemia, pyloric stenosis), avoid in acute porphyria (caution 3.6.2).

**Interactions** flecainide, sotalolol, azetimicin, SNF, sumatriptan, azetimicin.

**Hepatic impairment** caution in severe liver disease, consider dose reduction.

**Renal impairment** use with caution if estimated glomerular filtration rate less than 30 mL/minute/1.73 m<sup>2</sup>. Important: see [Prescribing in renal impairment](#) in children.

**Pregnancy** **3** manufacturers advise use only if adequate alternatives not available.

**Breast feeding** **3** compatible, may cause diarrhoea in infant's stools.

**Adverse effects** nausea, vomiting, abdominal discomfort, diarrhoea, anorexia, dyspepsia, flatulence, dysphagia, headache, drowsiness, conjunctivitis, otitis media, sinusitis in toddler and school-age children, hepatomegaly (including cholestatic jaundice), rash, tingling or very itchy complexion, conjunctivitis, arthritis associated colitis, QT interval prolongation, arrhythmias, sprague, myositis, agranulocytosis, anorexia, anaphylaxis, parosmia, hyperkalemia, thrombocytopenia, haemolytic anaemia, interstitial nephritis, acute renal failure, hearing loss (sometimes with tinnitus, usually reversible), Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity, tooth and tongue discoloration.

**Approved status** approved for use in children (age range not specified by manufacturer).

**Indications and dose**

**Chronic Pseudomonas aeruginosa infection in cystic fibrosis**

**Child 6-18 years**  
 • **Body-weight 20-40 kg** 250 mg 2 times a week  
 • **Body-weight over 40 kg** 500 mg 2 times a week

**Uncomplicated genital chlamydial infections and non-gonococcal urethritis**

**Child**  
 • **Body-weight under 40 kg** 200 mg as a single dose  
 • **Body-weight over 40 kg** 1 g as a single dose

**Treatment of pertussis, other susceptible infections**

**Child**  
 • **Body-weight under 40 kg** 10 mg/kg on day 1, then 5 mg/kg on days 2-5  
 • **Body-weight over 40 kg** 500 mg on day 1, then 250 mg on days 2-5

**+** azithromycin  
 not listed possible for:  
 • 250 mg 5 mL full safety (week 10)  
 • 250 mg 5 mL full safety (week 10)  
 • 500 mg 5 mL full safety (week 10)

## Interactions

- Interactions in the NZF and NZFC are provided by Stockley's interaction alerts which are derived from the full Stockley's drug interactions database. This gives health care professionals a quick way to check for potential interactions and management advice in a clinical setting.

Drugs	Interaction	Action	Evidence
erythromycin (systemic) and clarithromycin (systemic)	Clarithromycin appears to have the concentrations of erythromycin which is expected to reduce its antibiotic effects.	Consider an alternative antibiotic if possible. Note that clarithromycin should be avoided in patients with a history of colitis.	Severe Formal only
erythromycin (systemic) and clarithromycin (systemic)	Erythromycin raises clarithromycin levels to as much as 10-fold, which has resulted in toxicity in several cases.	Avoid concurrent use unless clarithromycin levels can be monitored. Symptoms commonly begin within 10 to 72 hours of starting erythromycin. In most cases toxicity resolves after 3 to 5 days of stopping the erythromycin.	Severe Clinical only
paracetamol (systemic) and clarithromycin (systemic)	The metabolism of paracetamol is increased in patients being erythromycin or clarithromycin, such as clarithromycin.	Consider an interaction as a possible cause of any reduction in paracetamol efficacy.	Moderate Formal only
paracetamol (systemic) and erythromycin (systemic)	Erythromycin accelerates gastric emptying and might increase paracetamol absorption, but any effect is small and unlikely to be clinically relevant.	No action needed. Any interaction is likely to be beneficial, particularly in patients with impaired gastric emptying.	Sublingual Formal only
erythromycin (systemic) and azithromycin (systemic)	The manufacturers of erythromycin state that erythromycin may inhibit the metabolism of azithromycin by CYP3A4, including the two 12-hydroxy-erythromycin esters, but all evidence is conflicting and inconclusive.	The clinical relevance of this prediction is unclear as the main route for azithromycin metabolism is CYP3A4. Until more is known, the possibility of an interaction in renal should only be noted if clinically adverse effects (such as otitis media, sinusitis, diarrhoea etc.) occur.	Mild Formal only

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# The Integrated Performance and Incentive Framework:

## An introduction

### A change in performance measurement

In October, 2013, the first draft of the Integrated Performance and Incentive Framework (IPIF) was released. It has been developed for the Ministry of Health by the IPIF Expert Advisory Group. The IPIF represents a significant change to the way that the performance of primary care, and the rest of the healthcare system, is monitored and incentivised. Until the final document is released, it is difficult to say what the full impact will be for primary care, but it is important to be aware of the Framework's development.

The IPIF is a performance and quality improvement programme which will monitor a broad range of measures across the whole of the New Zealand healthcare system. The aim of the IPIF is to encourage innovation and improvement within the New Zealand healthcare system and implement the New Zealand adaptation of the Triple Aim goals (see: "What is the Triple Aim?").

The IPIF will address broad health and disability performance and quality measures. The framework will include system level

### What is the "Triple Aim"?

The Triple Aim is a healthcare improvement policy that was initially developed in the United States. It outlines a plan for better healthcare systems by pursuing three aims: improving patients' experience of care, improving the overall health of a population and reducing the per-capita cost of health care.

In New Zealand the policy has been adapted by the Health Quality and Safety Commission and is one of the key tenants of the IPIF. The three aims developed by the HQSC are:

- Improved quality, safety and experience of care
- Improved health and equity for all populations
- Best value for public health system resources




measures, which will consist of composite levels and will be organised according to the triple aim domains and life stages ranging from early start to supportive end of life. There will be a menu of standardised contributory measures that district alliances will select, that are meaningful for their districts and that show a logical link to the system level measures.

One of the expected outcomes from the IPIF is that the PHO Performance Programme (PPP) will be phased out. However, it is likely that many of the current PPP indicators will also be indicators in the IPIF. The PPP continues to be in operation, and primary care should still be working toward improving indicator performance. Funding for the PPP is currently unchanged and can continue to be claimed.

One of the goals of the IPIF is to reduce the burden of reporting and other administrative tasks for practitioners. This may be achieved through better use of IT and greater integration between higher-level services, such as PHOs with DHBs and DHBs with the Ministry of Health.

It is expected that the IPIF will be fully integrated within practice management systems (PMS), similar to the PPP is currently, prior to the Framework's roll-out. The PMS can then be used to monitor individual indicators and track the performance of a practice within the Framework.

It is anticipated that the IPIF will be finalised in early 2014, and will begin to be implemented from 1 July, 2014.

 Full documentation of the IPIF is available from:  
[www.hiirc.org.nz/page/42610](http://www.hiirc.org.nz/page/42610)

For any questions or comments about the IPIF, contact Cathy O'Malley, Deputy Director General, Sector Capability and Implementation, email: [cathy\\_omalley@moh.govt.nz](mailto:cathy_omalley@moh.govt.nz) or Kate Charles, Director, Systems and Integration, email: [kate\\_charles@moh.govt.nz](mailto:kate_charles@moh.govt.nz)



# Pyrethroid toxicity and its management

Contributed by Dr Michael Beasley and Dr Wayne Temple, National Poisons Centre

Pyrethroids are insecticides that are synthetic modifications of natural pyrethrins, which are extracts from the flowers of some *Chrysanthemum* species.

Pyrethroids have been developed for the control of household and agricultural insects, and human lice. Pyrethroids have a very high “selective toxicity” for insects compared to mammals, which is due to higher insect nerve sensitivity, lower mammalian skin absorption and more efficient mammalian hepatic metabolism. Traditionally, pyrethroids have been considered as having relatively low toxicity, particularly when compared to organophosphate insecticides. However ingestion of concentrated pyrethroid-containing products can cause severe, and occasionally fatal, effects.

Pyrethroid formulations include aerosol sprays, smoke coils, electric mats, oil formulations, emulsifiable concentrates and wettable and dustable powders. A shampoo and lotion

formulation is also available for the control of human lice. The formulated products often combine the synthetic pyrethroids with a synergist, such as piperonyl butoxide (which inhibits their metabolism), and they may also contain other insecticides.

## Physiologic effects of pyrethroids

Pyrethroids are ion channel toxins that interfere with the function of the nervous system. They modify the “gating” characteristics of neuronal voltage-sensitive sodium channels to delay their closure,<sup>1</sup> thereby prolonging neuronal excitation.

The toxic effects of pyrethroids result from this neuronal excitation and include a wide spectrum of signs and symptoms from paraesthesia and increased salivation, through to seizures and potentially death (Table 1). Allergic reactions, including contact dermatitis or asthma, are only rarely reported with synthetic pyrethroids.

Table 1: Toxic effects of pyrethroids

Mild pyrethroid toxicity	Moderate pyrethroid toxicity	Severe pyrethroid toxicity
Paresthaesia	CNS depression	Seizures
Nausea	Increased salivation	Coma
Headache	Fasciculations	Pulmonary oedema
Vomiting	Fever	Respiratory failure
Dizziness	Diaphoresis	
Fatigue	Blurred vision	
Anorexia		



## Enquiries to the National Poisons Centre about pyrethroids

In the five year period between 2008 and 2012, the New Zealand National Poisons Centre (NZNPC) received 1544 enquiries about synthetic pyrethroids; 106 of these were from medical centres. Medical centres enquired about a range of pyrethroid products including agricultural insecticides, household aerosol fly sprays, household bug bombs and household liquid insecticides. Typical calls included:

- A patient who developed immediate nausea and rhinorrhoea, and a delayed skin rash, when treating livestock with a cypermethrin (synthetic pyrethroid) product without using protective measures
- A patient who developed a burning and tingling sensation on his face and neck after spraying his house with a pyrethroid insecticide
- An asymptomatic child who briefly activated an aerosol spray into her mouth.



## Typical clinical presentation of patients with pyrethroid exposure

The largest risk of pyrethroid toxicity is from the ingestion of undiluted formulations. The presentation of patients with exposure to pyrethroids depends somewhat on the setting of exposure.

### Occupational exposure to pyrethroids


Most reports on the adverse effects of pyrethroid exposure have arisen from occupational settings, particularly where insufficient precautions are taken during pyrethroid preparation and application.<sup>2</sup> People using pyrethroids in this setting may develop cutaneous paraesthesia as well as ocular and upper respiratory tract irritation. The cutaneous sensation, typically described as stinging or burning, may not develop until several hours post-exposure, and can be associated with erythema but not usually other skin lesions. Acute systemic symptoms have also been reported in cases of careless use of pyrethroids. There are few studies which have investigated the possibility of long-term adverse effects in people exposed to pyrethroids occupationally.

### Household/indoor exposure to pyrethroids

The risk of pyrethroid toxicity is low when pyrethroids are sprayed indoors, e.g. in the home or office, by professional applicators. However, anecdotally it is not uncommon for some people to complain of a range of symptoms from such exposures. There is general agreement that a period of several hours (ideally at least 24 hours) should be observed between pyrethroid application and re-occupation of the building. Spray droplets can settle on furnishings, causing potential ongoing skin exposures, but it appears that re-entrainment of particles into air is minimal. If measured, floor or other surface levels can be an unreliable guide to air levels of pyrethroids.

The use of permethrin as a topical treatment or shampoo for head lice or scabies is associated with relatively low risk of toxicity, if used according to directions. However, the NZNPC is aware of some caregivers using pyrethroid-containing fly sprays to treat children's head lice. There is some risk with this; adverse effects can include scalp and face burning and itching, and ocular discomfort if sprayed into the eyes.

## Management of pyrethroid exposure

 If a patient presents with signs and symptoms of toxicity and a history of exposure to a pyrethroid, it is recommended to phone the National Poisons Centre for advice on management.

Patients with significant pyrethroid ingestion can present with severe symptoms and signs (Table 1) which would constitute a medical emergency, and should be immediately referred to hospital for life support measures and ongoing monitoring. General practitioners may occasionally need to commence standard emergency care. Seizures can be resistant to benzodiazepines and other pharmacotherapy; thiopental may be used in a hospital setting.<sup>3</sup>

Patients with an occupational exposure to pyrethroids may require symptomatic treatment for cutaneous paresthesia or upper respiratory tract irritation. While controversial, the use of creams containing vitamin E has been claimed to be useful for paresthesia,<sup>4</sup> although this treatment is more likely to be helpful if applied prior to exposure. Relief may be obtained by the use of lipophilic agents, such as cooking oil or white soft paraffin. A cool cloth or ice may also be helpful.


Persistent symptoms following indoor pyrethroid exposure may be reported, even when a period of time away from the environment has been observed. Complex psychosocial factors can play a role in this, similar to that seen with “sick building syndrome”. The patient can be reassured that the presence of paraesthesia does not correlate with a high level of exposure, and that chronic neurotoxicity is unlikely from such exposures.<sup>5</sup>


## Notification of pyrethroid toxicity


Cases of pyrethroid toxicity must be notified to the Medical Officer of Health, under the Hazardous Substances and New Organisms Act 1996.

A short electronic notification form is located on the *bestpractice* dashboard (log in at [www.bestpractice.org.nz](http://www.bestpractice.org.nz) or go directly through MedTech) – look for “Hazardous Substances & Lead Notifications”. Primary care practices that do not use *bestpractice* Decision Support software, should still inform their Public Health Unit of any notifications. Access to the notification form for non-MedTech Patient Management Systems will be available in early 2014.

### Further information

 For advice on toxic exposures to pyrethroids, phone the National Poisons Centre on 0800 POISON (0800 764 766).

 For information on the treatment of head lice see: “Treating head lice”, *BPJ* 14 (Jun, 2008).

 For information on the treatment of scabies see: “Scabies – diagnosis and management”, *BPJ* 19 (Feb, 2009).

### References

1. Bradberry SM, Cage SA, Proudfoot AT, Vale JA. Poisoning due to pyrethroids. *Toxicol Rev* 2005;24(2):93-106.
2. He F, Wang S, Liu L, et al. Clinical manifestations and diagnosis of acute pyrethroid poisoning. *Arch Toxicol* 1989;63: 54-8.
3. Giampreti A, Lampati L, Chidini G, et al. Recurrent tonic-clonic seizures and coma due to ingestion of type I pyrethroids in a 19-month old patient. *Clin Toxicol* 2013;51:497-500.
4. Flannigan SA, Tucker SB, Key MM, et al. Synthetic pyrethroid insecticides: a dermatological evaluation. *Br J Ind Med* 1985;42:363-72.
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## Hazardous Substances

### Hazardous Substances Disease & Injury Notification

GPs in all regions of New Zealand are now able to use e-notification to inform your Medical Officer of Health about hazardous substances, diseases and injuries.

By law, injuries from hazardous substances, lead absorption and poisoning arising from chemical contamination of the environment (including from agricultural spraydrift) are required to be notified.

Look for 'Hazardous Substances & Lead Notifications' on the Module list of your BPAC dashboard.

For more information on these notifications see the article on page 34 of the April **Best Practice** journal <http://www.bpac.org.nz/BPJ/2013/April/docs/BPJ52.pdf>.

If you have any questions regarding a patient or notification, please contact your local public health unit.



## CORRESPONDENCE



### NSAIDs and renal toxicity: Prescribe all NSAIDs with caution

Dear Editor

In your article "NSAIDs: Making safer treatment choices", BPJ 55 (Oct, 2013), the article opened saying that COX-1 was concentrated in the kidney and that COX-1 activity controlled renal perfusion through catalysing prostaglandins.

Later in the same article you state that medicines that block COX-2 are nephrotoxic because they reduce renal blood flow by preventing prostaglandin-mediated vasodilation.

My questions are:


1. Is renal blood flow COX-1 or COX-2 mediated?
2. Are COX-2 inhibitors safer to use in renal impairment?

*Dr Bruce Sutherland, General Practitioner  
Warkworth*

The article "Non-steroidal anti-inflammatory drugs (NSAIDs): Making safer treatment choices", BPJ 55 (Oct, 2013), began with a brief overview of the function of the cyclo-oxygenase (COX) enzymes, with more detailed information in later sections. Clarification about the role of the COX enzymes in renal function may be necessary to emphasise that all non-selective non-steroidal anti-inflammatory drugs (NSAIDs) and all COX-2 inhibitors have the ability to cause adverse renal effects, particularly in patients who are at increased risk.

1. Renal blood flow is mainly controlled by the vasodilatory action of prostaglandins produced by the COX-1 enzyme, which is concentrated in the vascular endothelium.<sup>1</sup> However, the flow of blood to the kidney is also influenced by the activity of the COX-2 enzyme. COX-2 in the kidney largely functions to maintain water and electrolyte balance and if homeostasis is not maintained then renal perfusion can decrease.<sup>1</sup> Studies also indicate that there is significant overlap between the function of the COX enzymes and that COX-2 also produces prostaglandins that can cause vasodilation of the renal artery.<sup>1,2</sup>
2. Clinical trials have demonstrated that non-specific NSAIDs and COX-2 inhibitors have similar risk profiles for people with reduced glomerular filtration rate (GFR) and in people at risk of pre-renal failure.<sup>1</sup> This is because the vasodilatory effect of COX-1 derived prostaglandins and the ability of COX-2 derived prostaglandins to maintain water and electrolyte balance is important to maintain renal function. Inhibiting COX-2 reduces the ability of the kidney to maintain homeostasis which increases the risk to the kidney further by reducing renal perfusion. It would have perhaps been clearer if it had been specified in the article that both COX-2 inhibitors and non-selective NSAIDs are potentially nephrotoxic. The statement “medicines that block COX-2 are nephrotoxic” was intended to convey the potential adverse effects of both types of NSAIDs, because both non-selective NSAIDs and COX-2 inhibitors block COX-2 activity. The statement was not meant to imply that any NSAID-induced renal toxicity was caused exclusively by inhibition of the COX-2 enzyme.

It is important to remember that the use of either non-selective NSAIDs or COX-2 inhibitors is not recommended in people at increased risk of renal complications. It should also be kept in mind that the selectivity of NSAIDs is only relative. For example, meloxicam, a COX-2 inhibitor, mainly inhibits COX-2 at low concentrations but as the concentration of meloxicam increases adverse effects attributed to inhibition of COX-1 are experienced by patients.<sup>3</sup>

 For further information on the effect of NSAIDs on renal physiology see: NSAIDs, Coxibs, and Cardio-Renal Physiology: A Mechanism-Based Evaluation: Coxibs and Renal Physiology. Available from: [www.medscape.org/viewarticle/422939\\_3](http://www.medscape.org/viewarticle/422939_3)

### References

1. DeMaria A. NSAIDs, coxibs, and cardio-renal physiology: A mechanism based evaluation. Available from: [www.medscape.org/viewarticle/422939](http://www.medscape.org/viewarticle/422939) (Accessed Nov, 2013).
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3. Singh G, Lanes S, Triadafilopoulos G. Risk of serious upper gastrointestinal and cardiovascular thromboembolic complications with meloxicam. *Am J Med.* 2004;117(2):100–6.

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