EOSINOPHIL COUNTS & ICS FOR COPD | NEWLY-SUBSIDISED MEDICINES FOR COPD | VALACICLOVIR

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Treatment of depression and anxiety in young people

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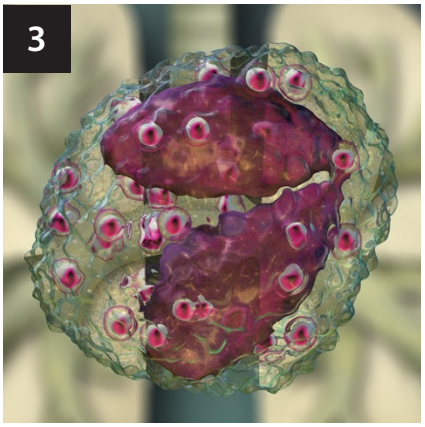

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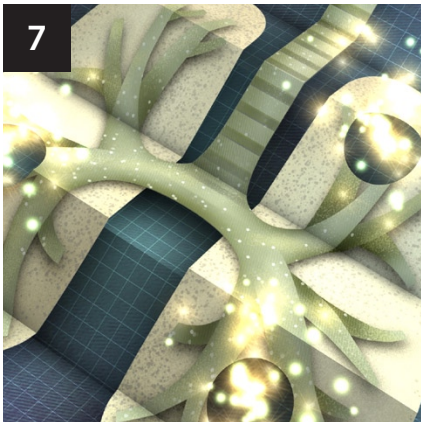
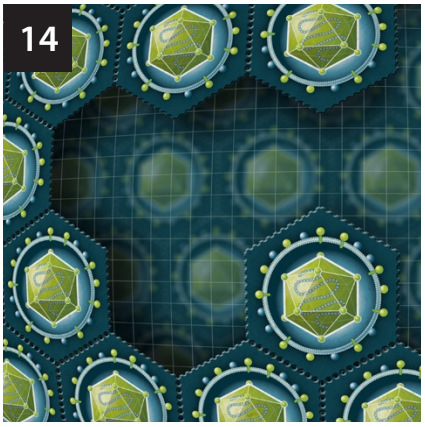


7 **Newly-subsidised medicines for the treatment of patients with COPD**

Subsidy changes for medicines used to treat patients with COPD came into effect on March 1, 2016. In this article we discuss how these changes affect the management of patients with COPD and introduce prescribers to medicines new to the New Zealand market, highlight inhaled combination medicines and an inhaler device that were not previously available and provide updates on access and subsidies.



14 **Valaciclovir – a first line antiviral medicine**

Valaciclovir is an antiviral medicine which can be used for the treatment of Herpes simplex infections and herpes zoster. As of 1 March, 2016, Special Authority approval is no longer required. Valaciclovir is as effective as aciclovir across the same range of indications, and has a simpler dosing regimen which may improve patient adherence.

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19 **The role of medicines for the treatment of depression and anxiety in patients aged under 18 years**

Psychological and behavioural approaches are the cornerstone of treatment for young people with depression or anxiety. When pharmacological treatment for a patient aged under 18 years is required due to severe or ongoing symptoms it is almost always "off-label". Medicines may be initiated in secondary care, with monitoring and follow up in primary care, or they may be initiated by a general practitioner. In this final article of a three-part series focusing on mental health issues for young people, the recommendations and evidence for the use of medicines in people aged under 18 years with depression and anxiety are discussed.

27 **Correspondence:**

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LABA without ICS in patients with COPD

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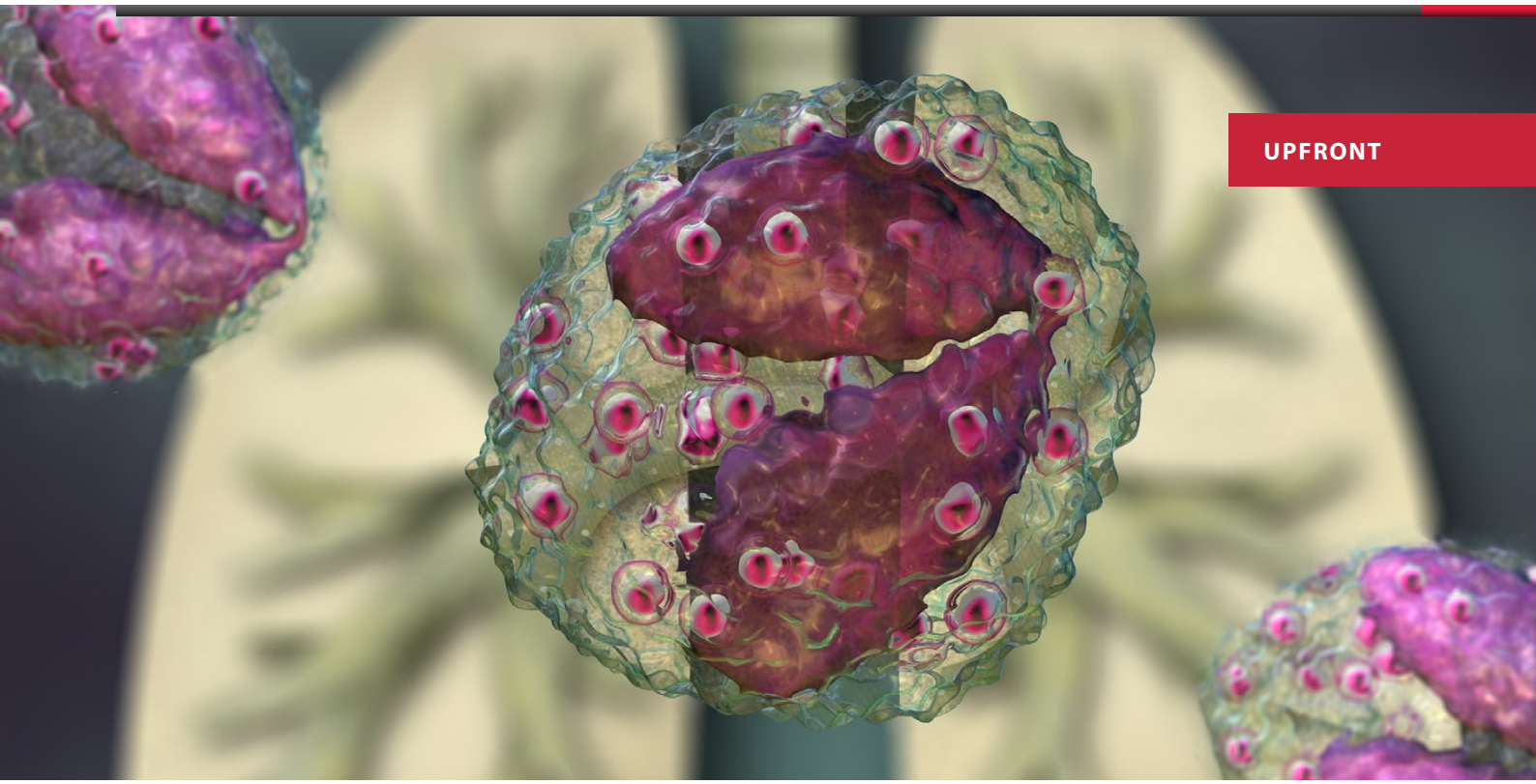


Are blood eosinophil counts helpful in predicting patient responses to **inhaled corticosteroids in COPD?**

The risks and benefits of COPD treatment with inhaled corticosteroids (ICS) are different for individual patients. There is currently debate within the respiratory literature as to whether blood eosinophil counts can be used as a biomarker to determine which patients with COPD are most likely to benefit from treatment with an ICS. In this article, we examine whether there is currently a role for this test in primary care.

Management of patients with chronic obstructive pulmonary disease (COPD) is changing. There is increasing recognition that COPD is a heterogeneous disease which may have distinct phenotypes, a growing realisation that inhaled corticosteroids (ICS) may be overused, new medicines are more readily available (see: "Newly-subsidised medicines for the treatment of patients with COPD", Page 7) and there is some evidence that biomarkers may be able to guide treatment.

The use of biomarkers to enable targeted treatment for patients with COPD is an evolving area of research. The idea that airway inflammation, characterised by elevated eosinophil levels in sputum or blood, may be important in COPD pathophysiology is not new. Initially, research was driven by the observation that corticosteroid treatment modified eosinophilic airway inflammation and was associated with improved outcomes in patients with asthma.[1] This led some researchers to question whether stable patients with COPD and elevated eosinophil levels might respond better to corticosteroids compared with patients without elevated eosinophil levels.[2, 3] Translation of this research into clinical practice is now being discussed in the belief that a raised blood eosinophil level may identify which subset of patients are most likely to benefit from ICS use.[4–6]

The use of blood eosinophil counts to guide ICS treatment is controversial

Despite the promise shown in a number of studies, questions remain as to exactly how blood eosinophil counts could, or should, be applied in clinical practice. For example, should blood eosinophils be assessed by absolute count or relative percentage, and what level should be used as a cut-off,

bearing in mind that most definitions of elevated eosinophil levels in the context of the research are within the "normal" range (see: "Raised eosinophil levels", next page). Also, does a raised eosinophil level detect all patients who are likely to respond to ICS treatment? Should assessment of eosinophils levels only occur when patients are stable, as during COPD exacerbations patients can have elevated levels, and can eosinophil levels guide treatment with oral corticosteroids during an exacerbation? Furthermore, should patients without an increased eosinophil blood level be withdrawn from ICS treatment?

Some respiratory physicians feel more research is required to clinically define elevated eosinophil levels to determine if ICS use in patients with COPD leads to better outcomes.[7, 8]

The concept of COPD phenotypes

Asthma and COPD have traditionally been considered as separate clinical entities; in reality they are both heterogeneous diseases which can be difficult to differentiate. A new taxonomy for chronic airway diseases may eventually be needed to acknowledge this reality as respiratory care becomes increasingly personalised and precise.[9]

The overlap between asthma and COPD has long been recognised, although it was only recently that the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy included a clinical definition for identifying patients with Asthma-COPD Overlap Syndrome (ACOS).[10] In addition, other "phenotypes" of COPD have begun to emerge, such as patients with eosinophilic airway inflammation which cannot be attributed to asthma, and patients who have frequent exacerbations.[8, 11] What is not clear is the extent to which these phenotypes reflect the natural progression of COPD, disease severity, responsiveness to treatment and the presence of co-morbidities, and to what extent they are stable and distinct clinical subsets of patients.[8, 12]

The changing role of ICS in COPD

Patients with COPD have been routinely treated with ICS; largely due to the effectiveness of ICS in patients with asthma, rather than clinical evidence of benefit in COPD.[12, 13] Most guidelines now suggest that ICS should only be used for patients with more severe disease who are at risk of exacerbations and for selected patients with ACOS.[10, 14] The legacy of past practice remains, however, and many patients who do not meet these criteria are continuing to be prescribed ICS which may result in more harm than benefit.[13]

The risks and benefits of ICS in COPD

Epidemiological evidence and the retrospective analysis of several large randomised controlled trials indicate that the use of an ICS, either alone or in combination with a long-acting beta$_2$ agonist (LABA), increases the risk of patients with COPD developing pneumonia.[10, 15] The long-term use of ICS is also associated with an increased prevalence of oral candidiasis, hoarse voice, skin bruising and possibly reduced bone density.[10] Respiratory physicians in New Zealand now tend to reduce or withdraw ICS treatment in patients with COPD, rather than initiate it. One study reported that in stable patients with severe COPD withdrawal of ICS resulted in no difference in the exacerbation rate compared with patients who continued ICS treatment.[16]

The decision to prescribe an ICS needs to balance the risks and the benefits for individual patients. Approximately fourteen patients need to be treated for one year to prevent one COPD exacerbation (number needed to treat [NNT]= 14).[17] For the same period there will be one additional case of pneumonia for every 20 – 30 patients treated with an ICS (i.e. number needed to harm [NNH] may be as low as 20).[17] When the heterogeneous nature of COPD is considered, however, these numbers are less helpful as not all patients with COPD will receive the same benefit from ICS treatment.[12] The availability of a reliable biomarker to help predict response to ICS would assist clinicians and patients in making better treatment decisions.


For further information on COPD, see: "The optimal management of patients with COPD – Parts 1 & 2", BPJ 66 (Feb, 2015).

The role of eosinophilic airway inflammation in COPD

Eosinophilic airway inflammation is generally considered to be a hallmark of patients with asthma rather than COPD, however, it is also found in patients with COPD.[10, 18] Elevated sputum eosinophil levels, due to eosinophilic airway inflammation, are found in up to 80% of corticosteroid-naïve and 50% of corticosteroid-treated patients with asthma, compared with between 10 and 40% in patients with COPD.[18] This data was taken from stable patients, but there is also evidence that patients with COPD have elevated sputum eosinophil levels during exacerbations.[18]

Blood eosinophil levels have been suggested as a practical, quick, cost-effective surrogate marker for sputum eosinophil levels as sputum samples for eosinophil analysis are often unavailable outside of a research setting.[5, 6] However, there are difficulties with using blood eosinophil levels as a biomarker in this context, including:

- The link between eosinophilic airways inflammation and blood eosinophils has been questioned with one study reporting only a moderate correlation between the two[18]
- An individual's blood eosinophil levels change over time and are influenced by COPD phenotype, medicines and co-morbidities, e.g. obesity[18]

- Depending on what cut-off is used, a large number of patients with COPD may have "elevated" blood eosinophil counts; a review of three large trials found that 57–75% of patients with COPD had blood eosinophil levels ≥ 2%.[6]

Research has been hampered by methodological problems

In addition to the problems relating directly to eosinophil levels, issues have been raised regarding the methodology of some of the research that has been conducted, including:

- Variability in the outcomes used to measure ICS treatment efficacy, e.g. a decrease in exacerbations or a slower rate of decline in FEV_1.[6, 19]
- Inconsistencies in the medicines that are used. Some studies have used ICS monotherapy, others have used combination medicines, e.g. a LABA/ICS;[6, 19] earlier studies used oral corticosteroids[2]
- The exclusion of patients with mild COPD and those with any features suggestive of asthma, i.e. patients with ACOS type COPD

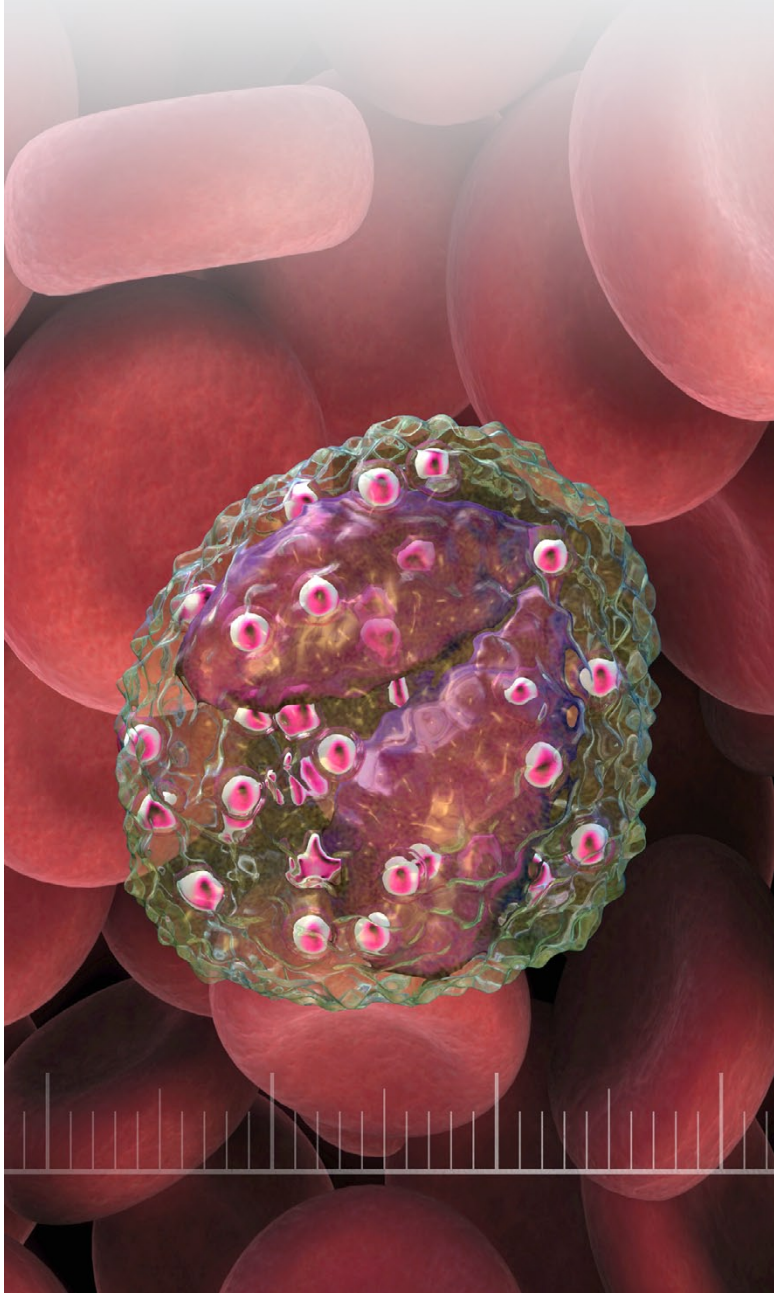
More research is required before eosinophil testing becomes a routine part of management

There is currently a lack of consensus amongst respiratory physicians, in New Zealand and worldwide, regarding the usefulness of blood eosinophils as a marker for ICS responsiveness in patients with COPD. The research appears to suggest that COPD patients with a blood eosinophil level > 2% may benefit from ICS (or combination) treatment. However, it remains unclear whether a blood eosinophil level >2% will identify all patients with COPD who will respond to an ICS. To date, no prospective randomised controlled trials have been published. Expert opinion currently suggests that it is premature to offer specific advice on the usefulness of a raised blood eosinophil level to guide individual ICS treatment in primary care; this issue will be revisited if the evidence-base for the recommendation changes.[6–8]

Acknowledgement: Thank you to **Professor John Kolbe**, Respiratory Medicine Physician, University of Auckland and Auckland DHB for expert review of this article.

Raised eosinophil levels

Eosinophils typically account for 1–6% of an individual's total white blood cell count.[20] The >2% cut-off used by many researchers investigating ICS response in patients with COPD therefore falls within the normal range.[18] The reference range for eosinophils in adults on full blood count is $0 - 0.5 \times 10^9$/L.[21] Most research in the context of COPD focuses on a "raised blood eosinophil level" rather than "eosinophilia" *per se*. Alternative causes for elevated blood eosinophil counts include: allergies, skin diseases, e.g. eczema, parasitic infections of the gastrointestinal tract, e.g. hookworm, reactions to medicines, e.g. aspirin, malignancy, as well as a range of non-parasitic infections, e.g. scarlet fever, and autoimmune disorders.[21]



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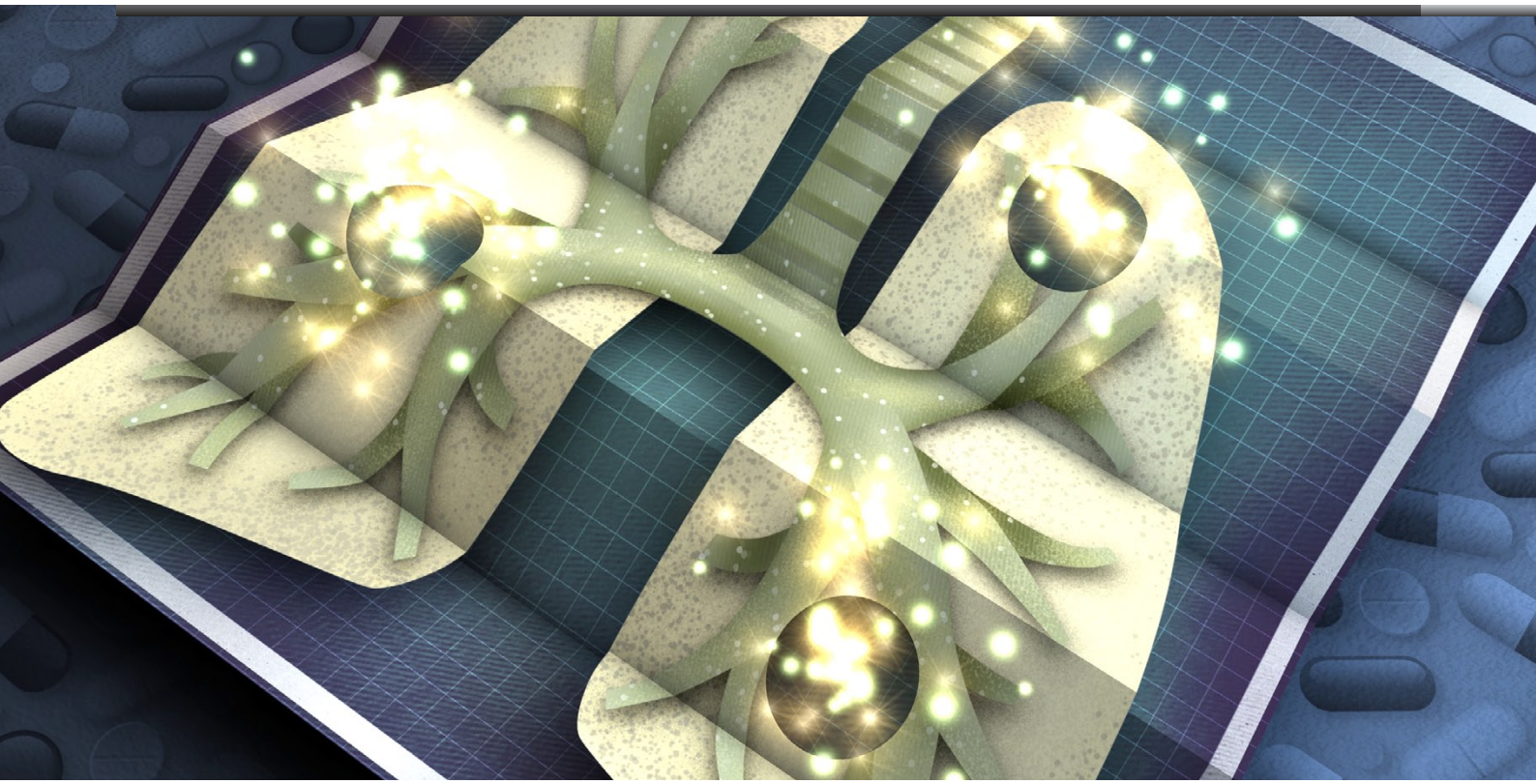
References

1. Evans PM, O'Connor BJ, Fuller RW, et al. Effect of inhaled corticosteroids on peripheral blood eosinophil counts and density profiles in asthma. J Allergy Clin Immunol 1993;91:643–50.
2. Brightling CE, Monteiro W, Ward R, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. Lancet Lond Engl 2000;356:1480–5. doi:10.1016/S0140-6736(00)02872-5
3. Leigh R, Pizzichini MMM, Morris MM, et al. Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment. Eur Respir J 2006;27:964–71. doi:10.1183/09031936.06.00072105
4. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med 2011;184:662–71. doi:10.1164/rccm.201104-0597OC
5. Pascoe S, Locantore N, Dransfield MT, et al. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Respir Med 2015;3:435–42. doi:10.1016/S2213-2600(15)00106-X
6. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting β-2 agonist efficacy in COPD. Thorax 2016;71:118–25. doi:10.1136/thoraxjnl-2015-207021.
7. Groenke L, Disse B. Blood eosinophil counts as markers of response to inhaled corticosteroids in COPD? Lancet Respir Med 2015;3:e26. doi:10.1016/S2213-2600(15)00258-1.
8. Miravitlles M, Vogelmeier C, Roche N, et al. A review of national guidelines for management of COPD in Europe. Eur Respir J 2016;47:625–37. doi:10.1183/13993003.01170-2015
9. Bateman ED, Reddel HK, van Zyl-Smit RN, et al. The asthma-COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases? Lancet Respir Med 2015;3:719–28. doi:10.1016/S2213-2600(15)00254-4
10. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2016). 2016. Available from: www.goldcopd.org/uploads/users/files/WatermarkedGlobal%20Strategy%202016%281%29.pdf (Accessed Mar, 2016)
11. Singh D, Kolsum U, Brightling CE, et al. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. Eur Respir J 2014;44:1697–700. doi:10.1183/09031936.00162414
12. Ernst P, Saad N, Suissa S. Inhaled corticosteroids in COPD: the clinical evidence. Eur Respir J 2015;45:525–37. doi:10.1183/09031936.00128914
13. Kaplan AG. Applying the wisdom of stepping down inhaled corticosteroids in patients with COPD: a proposed algorithm for clinical practice. Int J Chron Obstruct Pulmon Dis 2015;10:2535–48. doi:10.2147/COPD.S93321
14. Abramson M, Frith P, Yang I, et al. COPD-X concise guide for primary care. 2014. Available from: www.copdx.org.au (Accessed Mar, 2016).
15. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. In: The Cochrane Collaboration, ed. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd 2014. Available from: http://doi.wiley.com/10.1002/14651858.CD010115.pub2 (Accessed Mar, 2016).
16. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med 2014;371:1285–94. doi:10.1056/NEJMoa1407154
17. Suissa S. Number needed to treat in COPD: exacerbations versus pneumonias. Thorax 2013;68:540–3. doi:10.1136/thoraxjnl-2012-202709
18. George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. Ther Adv Chronic Dis 2016;7:34–51. doi:10.1177/2040622315609251
19. Barnes NC, Sharma R, Lettis S, et al. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. Eur Respir J 2016; [Epub ahead of print]. doi:10.1183/13993003.01370-2015
20. Curry C. Differential blood count. Medscape 2015. Available from: http://emedicine.medscape.com/article/2085133-overview (Accessed Mar, 2016).
21. Kyle C (Ed). Sonic pathology handbook: a guide to the interpretation of pathology tests. New South Wales: Sonic Healthcare 2014. Available from: www.snp.com.au/ (Accessed Mar, 2016).



Newly-subsidised medicines for the treatment of patients with COPD

Subsidy changes for medicines used to treat patients with COPD came into effect on March 1, 2016. In this article we discuss how these changes affect the management of patients with COPD and introduce prescribers to medicines new to the New Zealand market, highlight inhaled combination medicines and an inhaler device that were not previously available and provide updates on access and subsidies.

KEY PRACTICE POINTS

- Umeclidinium (Incruse*) and glycopyrronium (Seebri) may become the most common LAMAs** for patients with COPD who are not already receiving treatment with a LAMA as they do not require Special Authority approval
- Three combination LAMA/LABA inhalers, olodaterol + tiotropium (Spiolto), umeclidinium + vilanterol (Anoro) and glycopyrronium + indacaterol (Ultibro) are now available; combination LAMA/LABAs were not previously subsidised in New Zealand
- The choice of inhaled LAMAs and combination LABA/LAMAs is largely based on the ability of patients to use the various devices and patient and clinician preference; there is no robust evidence that one of these medicines has greater clinical efficacy than any other
- A new ICS/LABA, fluticasone + vilanterol (Breo) that only requires once-daily dosing is now available for patients with COPD; previous subsidised options required twice daily dosing, i.e. fluticasone + salmeterol (Seretide, Rexair) and budesonide + formoterol (Symbicort, Vannair)

* Generally, bpac^{nz} does not use trade names where referring to medicines. An exception has been made in this article, as there is the potential for prescriber confusion. The trade names of the various inhaler devices are included in Table 2.

** Abbreviations used for inhaled medicines: LAMA = Long-acting muscarinic receptor antagonist, LABA = Long-acting beta$_2$ agonist, DPI = Dry powder inhaler, MDI = metered dose inhaler, ICS = Inhaled corticosteroid, SABA = Short-acting beta$_2$ agonist, SAMA = Short-acting muscarinic receptor antagonist.

Treatment options for patients with COPD have increased

The range of subsidised medicines used to treat patients with COPD in New Zealand has been transformed over the past 18 months. In November, 2014, glycopyrronium (Seebri DPI), a LAMA, and indacaterol (Onbrez DPI), a LABA, were added to the pharmaceutical schedule. On 1 March, 2016, the number of subsidised medicines available to patients in New Zealand with COPD was further increased:

- Two new medicines may now be prescribed that were not previously available:

- **Umeclidinium** (Incruse DPI), a LAMA, is a new medicine to New Zealand and is subsidised in single medicine and combination inhalers
- **Olodaterol**, a LABA, is a new medicine to New Zealand and is subsidised as a combination inhaler

- Three combination LAMA/LABAs inhalers, **glycopyrronium + indacaterol** (Ultibro DPI), **olodaterol + tiotropium**, (Spiolto MDI) and **umeclidinium + vilanterol** (Anoro DPI) are now subsidised. Combination LAMA/LABA inhalers were not previously subsidised in New Zealand.
- A new combination inhaled corticosteroid (ICS)/LABA, **fluticasone + vilanterol** (Breo DPI) t**hat only requires once-daily dosing** is now available for patients with COPD. Previously subsidised ICS/LABA inhalers required twice daily dosing, i.e. fluticasone + salmeterol (Seretide, Rexair MDIs) and budesonide + formoterol (Symbicort DPI, Vannair MDI). Vilanterol has only recently become available in New Zealand and is also available as a LAMA/LABA in combination with umeclidinium.
- The Special Authority approval criteria has been removed from the LAMA inhaler glycopyrronium (Seebri DPI) and the combination ICS/LABA budesonide + formoterol (Symbicort DPI, Vannair MDI)
- A new type of tiotropium inhaler (Spiriva MDI) is also now available

Umeclidinium: a new LAMA not previously available

Umeclidinium (Incruse DPI) is a LAMA that is new to the New Zealand market. As of March 1, 2016 umeclidinium is available without restriction for patients with COPD, provided the prescription is endorsed* by the prescriber that the patient has been diagnosed with COPD by spirometry.

The pharmacology of umeclidinium

Umeclidinium, like tiotropium, preferentially binds to M_3 acetylcholine muscarinic receptors to induce bronchodilation.[1] The medicine has an effect within 5 to 15 minutes of inhalation, peak efficacy is at three hours and therapeutic levels last for more than 24 hours.[1] Patients achieve a steady-state concentration of umeclidinium after 14 days of dosing.[1]

Umeclidinium is reported to have been used in multiple clinical trials with similar frequencies of adverse effects as placebo and tiotropium.[1] Umeclidinium should be used cautiously with patients who have urinary retention or narrow-angle glaucoma due to its antimuscarinic activity.[1]

Combination LAMA/LABA inhalers are now available in New Zealand

Three LAMA/LABA combination inhalers are now subsidised with Special Authority approval for patients with COPD with the diagnosis confirmed by spirometry (See: "The importance of spirometry in COPD diagnosis"):

- Glycopyrronium + indacaterol (Ultibro Breezhaler)
- Tiotropium + olodaterol (Spiolto Respimat)
- Umeclidinium + vilanterol (Anoro Ellipta)

Glycopyrronium (Seebri DPI – a LAMA) and **indacaterol** (Ombrez DPI – a LABA) have been subsidised in New Zealand since November, 2014 as single medicine inhalers.

For further information see: "Medicine updates", BPJ 65 (Dec, 2014).

The pharmacology of olodaterol

Olodaterol, a LABA, is new to the New Zealand market and is only available in combination with tiotropium.

Olodaterol was specifically designed for use in combination with tiotropium.[2] Peak plasma concentration occurs 10–20 minutes after inhaling the medicine and patients experience bronchodilation lasting at least 24 hours.[3]

Olodaterol is associated with similar adverse effects to other LABAs, including increased heart rate, raised blood pressure and hypokalaemia. Caution is required if olodaterol is prescribed to patients with cardiovascular disorders, QT prolongation, thyrotoxicosis or convulsive disorders.[4]

The pharmacology of vilanterol

Vilanterol, a LABA, is relatively new to the New Zealand market and was previously available only in combination with fluticasone as an ICS/LABA inhaler (Breo DPI). Vilanterol is now available in combination with umeclidinium.

Vilanterol has greater selectivity for beta2-adrenergic receptors than formoterol and indacaterol.[5] The onset of vilanterol occurs within five minutes of inhalation and it is effective when taken once daily, due to its long-lasting action.[5]

Vilanterol is associated with similar adverse effects as other LABAs. In a short study in patients with moderate-to-severe COPD there were no changes in blood pressure, ECG, blood glucose or potassium levels in patients taking vilanterol.[5]

* Prescription endorsements should be handwritten or computer-generated by the prescriber and include "certified condition" on the prescription or a statement confirming that the patient has been diagnosed with COPD by spirometry.

How will the changes in medicine subsidy affect the management of patients with COPD?

Smoking cessation, physical activity (including pulmonary rehabilitation) and maintenance of normal body weight remain essential aspects in the management of patients with COPD.

Medicines are prescribed to help patients manage symptoms and reduce their risk of exacerbations. Treatments are introduced in a stepwise manner depending on the severity of the patient's symptoms, the results of spirometry and the patient's quality of life (Table 1).

Step 1: For all patients with symptomatic COPD

Short-acting bronchodilators, i.e. inhaled SABAs and SAMAs, are appropriate for patients with mild COPD for use during periods of acute breathlessness.[6, 7] The medicine subsidy changes do not affect the availability of treatment options for these patients:[6, 7]

- Inhaled SABAs, i.e. salbutamol (Respigen, Salair, Salamol, Ventolin MDIs) or terbutaline (Bricanyl DPI)
- An inhaled SAMA, i.e. ipratropium (Atrovent MDI]); or
- An inhaled combination SABA/SAMA, i.e. ipratropium + salbutamol (Duolin HFA MDI)

Table 1: The assessment of COPD severity and the stepwise escalation of pharmacological treatment, adapted from Abramson *et al*, 2014.[6]

Severity	**Mild**	**Moderate**	**Severe**
	■ Few symptoms ■ Breathless on moderate exertion ■ Recurrent chest infections ■ Little or no effect on daily activities ■ FEV_1 = 60 – 80% of predicted	■ Increasing dyspnoea ■ Breathless walking on level ground ■ Increasing limitation of daily activities ■ Cough and sputum production ■ Infections requiring corticosteroids ■ FEV_1 = 40–59% of predicted	■ Dyspnoea on minimal exertion ■ Daily activities severely restricted ■ Experiencing regular sputum production ■ Chronic cough ■ FEV_1 < 40% of predicted
Medicines management	**Check technique of device use and adherence at each visit** – up to 90% of patients do not use devices correctly		
Step 1	**For all patients with COPD** for use during periods of acute breathlessness prescribe an: ■ Inhaled SABA, i.e. salbutamol (Respigen, Salair, Salamol, Ventolin MDIs), terbutaline (Bricanyl DPI) ■ Inhaled SAMA, i.e. ipratropium (Atrovent); or ■ A combination SABA/SAMA, i.e. ipratropium + salbutamol (Duolin HFA MDI)		
Step 2	**For patients with COPD and persistent troublesome dyspnoea** who do not have adequate symptom control while using a short-acting bronchodilator, consider prescribing: ■ A LABA, i.e. salmeterol (Meterol MDI, Serevent MDI and DPI), indacaterol (Onbrez DPI), formoterol ◐ (Foradil, Oxis DPIs) ■ A LAMA, i.e. glycopyrronium2 (Seebri DPI), umeclidinium ● (Incruse DPI), tiotropium ● (Spiriva DPI and MDI)		
Step 2.5	**For patients who are unable to achieve symptom control with a single long-acting bronchodilator** consider a newly-subsidised combination LABA/LAMA inhaler: ■ Glycopyrronium + indacaterol ● (Ultibro DPI) ■ Olodaterol + tiotropium ● (Spiolto MDI) ■ Umeclidinium + vilanterol ● (Anoro DPI)		
Step 3	**For patients with an FEV_1 < 50% of predicted and two or more exacerbations in a 12-month period:** Consider prescribing a fixed-dose combination ICS/LABA: ■ Fluticasone + vilanterol (Breo DPI), once daily ■ Budesonide + formoterol (Symbicort DPI, Vannair MDI), twice daily ■ Fluticasone + salmeterol (Seretide, Rexair MDIs), twice daily		

◐ Partially subsidised without restriction ● Prescription endorsement required for full subsidy ● Special Authority approval required for full subsidy

Step 2: For patients with COPD and persistent troublesome dyspnoea

Long-acting bronchodilators, i.e. inhaled LABAs and LAMAs, are appropriate for patients with persistent and troublesome dyspnoea who do not receive adequate symptom control while using a short-acting bronchodilator.[6]

The medicine subsidy changes have made treatment with inhaled LAMAs and inhaled combination LABA/LAMAs more accessible to patients with COPD. There is no robust evidence that one inhaled LAMA or inhaled combination LABA/LAMA has greater clinical efficacy than any other; treatment decisions may be guided by the patient's ability to operate the various devices and patient and clinician preference.

Subsidised treatment options for LAMAs are:

- **Glycopyrronium** (Seebri DPI) prescribed as one inhalation, once daily, of 50 micrograms of glycopyrronium
- **Umeclidinium** (Incruse DPI) prescribed as one inhalation, once daily, of 62.5 micrograms of umeclidinium bromide
- **Tiotropium** (Spiriva DPI and MDI mist-inhaler) prescribed as either 18 micrograms, once daily (Spiriva Handihaler) or 5 micrograms, once daily (Spiriva Respimat); both provide patients with similar levels of systemic exposure to tiotropium[9]

Subsidised inhaled LABA treatment options remain salmeterol (Meterol MDI, Serevent MDI and DPI), indacaterol (Onbrez DPI) or formoterol (Foradil, Oxis DPIs – partially subsidised).

Umeclidinium and glycopyrronium may become the most common LAMAs

Due to the subsidy change, rather than any evidence of clinical benefit, umeclidinium (Incruse DPI) or glycopyrronium (Seebri DPI) may become the most common LAMAs for patients with COPD who are not already taking a LAMA as they do not require Special Authority approval. Both of these LAMAs are now available without restriction provided the prescription is endorsed by the prescriber that the patient has been diagnosed with COPD by spirometry. Special Authority approval is still required for subsidised treatment with tiotropium. Patients in New Zealand can only receive subsidised treatment with one LAMA at any one time.

Previously, patients with COPD needed to meet Special Authority approval criteria to receive treatment with a LAMA. It is estimated that 1200 people in New Zealand with COPD, who were previously unable to access subsidised LAMA treatment, will benefit from access to umeclidinium or glycopyrronium.[8]

Tiotropium continues to be subsidised under Special Authority approval for patients with COPD who have an FEV_1 < 60% of predicted on spirometry. However, the Special Authority renewal for tiotropium no longer includes the requirement for recent spirometry. General practitioners applying for subsidy renewal for tiotropium must only be satisfied that the patient is adherent with treatment and that their symptoms have improved with treatment.

There is no clear evidence to help decide the preferred LAMA for treatment initiation in patients with COPD; head-to-head trials for these medicines are lacking. For patients with COPD and an FEV_1 < 60%, who have not been previously prescribed a LAMA, i.e. those eligible for treatment with any of the three LAMAs, treatment decisions may be guided by the patient's ability to operate the various devices and patient and clinician preference.

Step 2.5: Combination LABA/LAMAs are now available

An inhaled combination LABA/LAMA is appropriate for patients with COPD who are unable to achieve symptom control with a single long-acting bronchodilator. Three combination LABA/LAMAs that were not previously subsidised in New Zealand are now subject to Special Authority approval (Table 2):

- **Glycopyrronium + indacaterol** (Ultibro DPI) prescribed as 110 + 50 micrograms, once daily
- **Olodaterol + tiotropium** (Spiolto MDI) prescribed as 2.5 + 2.5 micrograms, once daily
- **Umeclidinium + vilanterol** (Anoro DPI) prescribed as 62.5 + 25 micrograms, once daily

The addition of a combination LAMA/LABA inhaler has been reported by a number of studies to improve lung function on spirometry in patients with COPD who are not adequately controlled with a single bronchodilator.[7] The use of combination LAMA/LABAs is thought to decrease the risk of adverse effects compared with increasing the dose of a single bronchodilator.[7]

There is no clear evidence to help decide the preferred combination LABA/LAMA for treatment initiation in patients with COPD; head-to-head trials for these medicines are lacking. Treatment decisions may be guided by the patient's ability to operate the various devices and patient and clinician preference.

Step 3: For patients with an FEV_1 < 50% of predicted and two or more exacerbations in a 12-month period

Fixed-dose inhaled ICS/LABA combinations are appropriate for patients with an FEV_1 < 50% of predicted and two or more exacerbations in 12-month period.[6] Subsidised combination ICS/LABAs for these patients include:[11]

- **Fluticasone + vilanterol** (Breo DPI) a new ICS/LABA inhaler requiring once daily dosing is subsidised without restriction and is prescribed as: one inhalation, once daily, of fluticasone + vilanterol (100 + 25 micrograms)
- **Budesonide + formoterol** (Symbicort DPI, Vannair MDI)

no longer has Special Authority approval criteria* for the treatment of COPD and is available without restriction
The DPI is more appropriate for the treatment of patients with COPD and is prescribed as:
  - Two inhalations, twice daily, of budesonide + formoterol (200 + 6 micrograms); maximum of four inhalations daily
  - One inhalation, twice daily, of budesonide + formoterol (400 + 12 micrograms); maximum of two inhalations daily
- **Fluticasone + salmeterol** (Seretide MDI and DPI, Rexair MDI), twice daily, continues to be subsidised without restriction for patients with COPD (Table 2)

* Prior to March 1, 2016, to receive subsidised treatment with budesonide + formoterol, patients needed to be aged over 12 years and to have been treated with an ICS of at least 800 micrograms per day beclomethasone or budesonide, or 500 micrograms per day fluticasone, and assessed as likely to gain additional benefit from a combination product.

Which combination ICS/LABA inhalers are most effective?

There is no clear evidence to help decide the preferred ICS/LABA combination for patients with COPD; head-to-head trials of these medicines are lacking. The decision of which ICS/LABA is most appropriate for patients who have not been previously treated with an ICS/LABA may be guided by the patient's ability to operate the various devices and patient and clinician preference.

Consider the increased risk of pneumonia before initiating ICS treatment in patients with COPD. The annual risk of pneumonia associated with vilanterol alone in patients with COPD was 3%, compared with 6–7% in patients taking fluticasone + vilanterol.[12]

For further information see: "The optimal management of patients with COPD – Part 1: The diagnosis" and "The optimal management of patients with COPD – Part 2: Stepwise escalation of treatment", BPJ 66 (Feb, 2015).

For further information see: "Are blood eosinophil counts helpful in predicting patient responses to inhaled corticosteroids in COPD?", Page 3.

References

1. Manickam R, Asija A, Aronow WS. Umeclidinium for treating COPD: an evaluation of pharmacologic properties, safety and clinical use. Expert Opin Drug Saf 2014;13:1555–61. doi:10.1517/14740338.2014.968550
2. Schlueter M, Gonzalez-Rojas N, Baldwin M, et al. Comparative efficacy of fixed-dose combinations of long-acting muscarinic antagonists and long-acting β2-agonists: a systematic review and network meta-analysis. Ther Adv Respir Dis 2016; [Epub ahead of print]. doi:10.1177/1753465815624612
3. Australian Prescriber. Olodaterol for chronic obstructive pulmonary disease. 2014;37. Available from: www.australianprescriber.com/magazine/37/6/214/21/new-drugs/1075/olodaterol-for-chronic-obstructive-pulmonary-disease (Accessed Mar, 2016).
4. Ramadan WH, Kabbara WK, El Khoury GM, et al. Combined bronchodilators (tiotropium plus olodaterol) for patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2015;10:2347–56. doi:10.2147/COPD.S88246
5. Spyratos D, Sichletidis L. Umeclidinium bromide/vilanterol combination in the treatment of chronic obstructive pulmonary disease: a review. Ther Clin Risk Manag 2015;11:481–7. doi:10.2147/TCRM.S67491
6. Abramson M, Frith P, Yang I, et al. COPD-X concise guide for primary care. 2014. Available from: www.copdx.org.au (Accessed Mar, 2016).
7. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2016). 2016. Available from: www.goldcopd.org/uploads/users/files/WatermarkedGlobal%20Strategy%202016%281%29.pdf (Accessed Mar, 2016).
8. PHARMAC. Proposal to list new respiratory products and changes to some currently listed products. 2015. Available from: www.pharmac.health.nz/news/consultation-2015-12-18-respiratory-products/ (Accessed Mar, 2016).
9. van Noord JA, Cornelissen PJG, Aumann J-L, et al. The efficacy of tiotropium administered via Respimat® Soft MistTM Inhaler or HandiHaler® in COPD patients. Respir Med 2009;103:22–9. doi:10.1016/j.rmed.2008.10.002
10. Tricco AC, Strifler L, Veroniki A-A, et al. Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis. BMJ Open 2015;5:e009183. doi:10.1136/bmjopen-2015-009183
11. New Zealand Formulary (NZF). NZF v45. 2015. Available from: www.nzf.org.nz (Accessed Mar, 2016).w
12. Australian Prescriber. Fluticasone furoate with vilanterol for asthma, chronic obstructive pulmonary disease. Aust Prescr 2015;38. Available from: www.australianprescriber.com/magazine/38/1/28/34/new-drugs/1080/fluticasone-furoate-with-vilanterol-for-asthma-chronic-obstructive-pulmonary-disease (Accessed Mar, 2016).

The importance of spirometry in COPD diagnosis

COPD cannot be confidently diagnosed in a patient by the presence of symptoms alone; spirometry is required to confirm a diagnosis.[7] Patients in New Zealand with COPD may need to be assessed with spirometry before they are eligible for subsidised treatment with some of the inhaled medicines (Table 2). The peak expiratory flow rate (PEFR) should not be used to diagnose COPD as this is a measure of airflow in the patient's large airways and does not access airflow in the bronchioles.

Spirometry can be reliably performed in primary care, although training in technique and equipment maintenance is required. When performing spirometry a FEV_1/FVC ratio < 0.7 indicates an airflow limitation consistent with COPD.[7] The results of spirometry are used to assess the severity of COPD, in combination with the clinical symptoms and signs of hypoxaemia, hypercapnia, pulmonary hypertension, heart failure and polycythaemia.[6] Spirometry is not recommended to "screen" patients without significant symptoms;[7] testing should be reserved for patients suspected of having COPD.

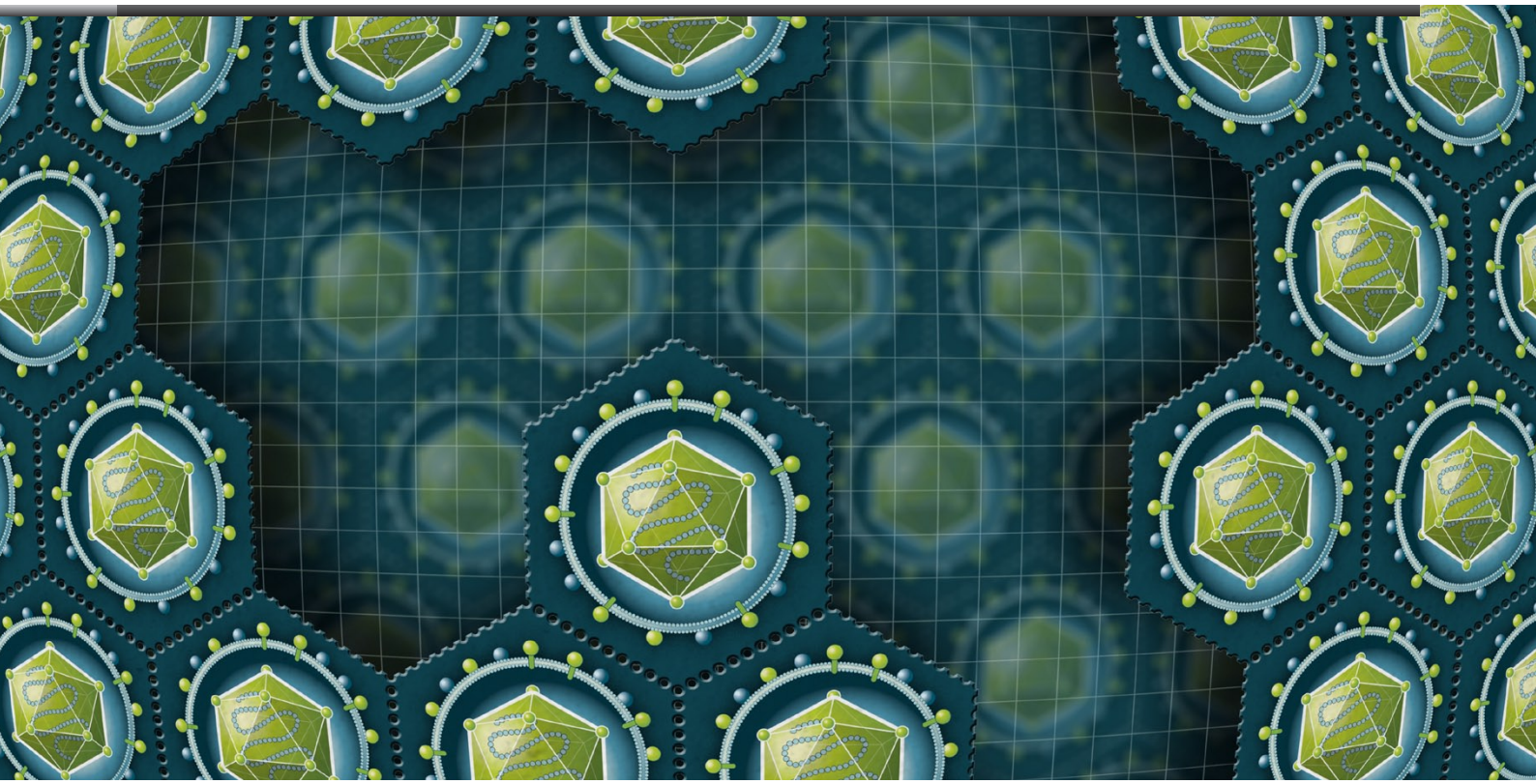
Table 2: Inhaled medicines subsidised in New Zealand for the treatment of patients with COPD from March 1, 2016 (newly-subsidised medicines are high-lighted ●).[11]

Medicine	Dose and frequency	Inhaler device (trade name)	Subsidy status
Short acting beta$_2$-agonists (SABA)			
Salbutamol	100 – 200 micrograms (one to two inhalations of 100 micrograms), as needed, up to four times daily	Metered dose inhaler (MDI) with use of a spacer recommended (Respigen, Salair, Salamol, Ventolin)	Fully subsidised without restriction and available on Practitioner Supply Order (PSO)
Terbutaline	250 – 500 micrograms (one to two inhalations of 250 micrograms), as needed Maximum single dose: six inhalations Maximum daily dose: 24 inhalations	Breath-activated dry powder inhaler (DPI) loaded when base of device is turned (Bricanyl Turbuhaler)	Fully subsidised without restriction
Long-acting beta$_2$-agonists (LABA)			
Salmeterol	50 micrograms (two inhalations of 25 micrograms), twice daily	MDI (Meterol, Serevent) and breath-activated DPI (Serevent Accuhaler) with each dose contained in a disc of eight doses	Fully subsidised without restriction
Indacaterol	150 – 300 micrograms (one capsule of 150 micrograms or one capsule of 300 micrograms), once daily	Breath-activated DPI with each dose contained in a capsule (Onbrez Breezhaler)	Fully subsidised without restriction
Formoterol (Eformoterol)	12 micrograms (two inhalations of 6 micrograms, or one capsule of 12 micrograms), once or twice daily	Breath-activated DPI loaded when base of device is turned (Oxis Turbuhaler) and breath-activated device with each dose contained in a capsule (Foradil)	Partially subsidised without restriction
Anticholinergics (SAMA or LAMA)			
Ipratropium (short-acting)	40 micrograms (two puffs of 20 micrograms), four times daily Maximum single dose: 80 micrograms. Maximum daily dose: 240 micrograms	MDI with use of a spacer recommended (Atrovent)	Fully subsidised without restriction
Glycopyrronium (long-acting)	50 micrograms (one inhalation of 50 micrograms), once daily	Breath-activated DPI with each dose contained in a capsule (Seebri Breezhaler)	Both fully subsidised with an endorsement on the prescription that the patient has been diagnosed with COPD with spirometry. These medicines will not be subsidised if the patient is already taking another subsidised LAMA.
● **Umeclidinium** (long-acting)	62.5 micrograms (one inhalation of 62.5 micrograms), once daily	Breath-activated DPI automatically loaded when opened (Incruse Ellipta)	
Tiotropium (long-acting)	18 micrograms (one capsule of 18 micrograms), once daily	Breath-activated DPI with each dose contained in a capsule (Spiriva HandiHaler)	New prescriptions are fully subsidised with Special Authority for patients with all of the following: ■ Have trialled a short-acting bronchodilator of at least 40 micrograms ipratropium, four times daily for one month ■ Have grade 4 or 5 breathlessness ■ Recent FEV$_1$ below 60% of predicted ■ Have been offered smoking cessation counselling if currently smoking ■ Have been offered influenza immunisation
	● 5 micrograms (two inhalations of 2.5 micrograms), once daily	MDI containing a solution delivered as mist that does not include propellants (Spiriva Respimat)	

Continued on next page

Medicine	Dose and frequency	Inhaler device (trade name)	Subsidy status
		Tiotropium continued from previous page	This medicine will not be subsidised if the patient is already taking another subsidised LAMA. Prescription renewals require that the patient be adherent with treatment and to have experienced an improvement in COPD symptoms.
Combination bronchodilators			
Ipratropium + salbutamol (SABA/SAMA)	20 + 100 micrograms, two puffs, four times daily	MDI with use of a spacer recommended (Duolin HFA)	Fully subsidised without restriction
● **Olodaterol + tiotropium** (LABA/LAMA)	2.5 + 2.5 micrograms, two puffs, once daily	MDI containing a solution delivered as a mist (Spiolto Respimat)	Fully subsidised with Special Authority for patients previously treated with a LAMA who are likely to gain additional benefit from a combination LAMA/LABA. Special Authority renewal requires that patient is adherent and has improved COPD symptom control.
● **Umeclidinium + vilanterol** (LAMA/LABA)	62.5 + 25 micrograms, one puff, once daily	Breath-activated DPI automatically loaded when opened (Anoro Ellipta)	
● **Glycopyrronium + indacaterol** (LAMA/LABA)	110 + 50 micrograms, one puff, once daily	Breath-activated DPI with each dose contained in a capsule (Ultibro Breezhaler)	
Combination ICS/bronchodilators			
● **Fluticasone furoate + vilanterol** (ICS/LABA) Note: the 200 + 25 micrograms inhaler is not indicated for COPD	100* + 25 micrograms, one puff, once daily	Breath-activated DPI automatically loaded when opened (Breo Ellipta)	Fully subsidised without restriction
Budesonide + formoterol (Eformoterol) (ICS/LABA) Note: budesonide + formoterol (100 + 6 micrograms) is used for the treatment of asthma, not COPD	200 + 6 micrograms; two inhalations, twice daily	Breath-activated DPI loaded when base of inhaler is turned (Symbicort Turbuhaler) and MDI with use of a spacer recommended (Vannair)	Fully subsidised without restriction
	400 + 12 micrograms; one inhalation, twice daily	Breath-activated DPI loaded when base of inhaler is turned (Symbicort® Turbuhaler®)	
Fluticasone + salmeterol (ICS/LABA) Note: the 100 + 50 micrograms DPI inhaler is not indicated for COPD	125 + 25 micrograms; two inhalations, twice daily 250 + 25 micrograms; up to two inhalations, twice daily, if symptoms not controlled with 125 + 25 micrograms	MDI with use of a spacer recommended (Seretide, Rexair)	Fully subsidised without restriction
	250 + 50 micrograms; one inhalation, twice daily	Breath-activated DPI with each dose contained in a disc of eight doses (Seretide Accuhaler) Note: MDI 250 + 50 micrograms is not subsidised	

* Important: One inhalation of fluticasone furoate 100 micrograms once daily is approximately equivalent to fluticasone propionate 250 micrograms twice daily.



Valaciclovir – a first line antiviral medicine

Valaciclovir is an antiviral medicine which can be used for the treatment of Herpes simplex infections and herpes zoster. As of 1 March, 2016, Special Authority approval is no longer required. Valaciclovir is as effective as aciclovir across the same range of indications, and has a simpler dosing regimen which may improve patient adherence.

Valaciclovir is now available without restriction

Valaciclovir and aciclovir are antiviral medicines that interfere with replication of Herpes viruses including Herpes simplex and Varicella zoster.[1] General practitioners in New Zealand are more likely to be familiar with aciclovir than valaciclovir as it has been fully subsidised and used in clinical practice for longer.

Valaciclovir consists of a valine amino acid attached to an aciclovir molecule. Following administration, the amino acid is cleaved and valaciclovir is converted into aciclovir. Due to increased bioavailability oral valaciclovir can be taken less frequently than oral aciclovir, e.g. two to three times daily instead of five times daily.[2, 3]

Prior to 1 March, 2016, Special Authority approval was required for patients to receive subsidised treatment with valaciclovir, 500 mg tablets; the Special Authority criteria has been removed and valaciclovir is now available without restriction for:

- The treatment of first and recurrent episodes of genital herpes
- Suppression of genital herpes recurrences
- The treatment of herpes zoster

This article provides clinical guidance for the use of valaciclovir in patients with each of these conditions.

Prescribing valaciclovir

Dosing and duration of treatment

The recommended doses, frequency and duration of valaciclovir treatment differ according to the condition being treated. For prescribing information refer to the specific conditions below or to the New Zealand Formulary (NZF).

For more information see: **www.nzf.org.nz/nzf_3443**

Adverse effects and cautions for prescribing

The adverse effects most commonly experienced by patients taking valaciclovir are headaches, rhinitis and flu-like symptoms. These symptoms are usually mild to moderate, although some patients may discontinue treatment as a result. In randomised controlled trials the incidence of these symptoms is only slightly higher than in patients taking placebo.[4, 5]

Patients taking valaciclovir should be advised to maintain adequate hydration. There have been isolated case reports of older patients or patients with severely reduced renal function developing acute kidney injury following treatment with 1 g three times daily, for as little as one day.[6, 7]

Rarely, valaciclovir use can cause aciclovir-induced neurotoxicity.[6] Symptoms of aciclovir-induced neurotoxicity include hallucinations, involuntary movements and characteristic delusions of death: either that the patient or someone else is going to die or has already died.[8] Withdraw treatment in patients suspected of having aciclovir-induced neurotoxicity, especially if they have reduced renal function.[8]

Dose adjustments are required for some patients

Reduced dosing is required in patients with renal impairment. Dose adjustments are required in patients with renal impairment, as the half-life of valaciclovir is extended from two to three hours in healthy individuals, up to 14 hours in patients with end-stage renal failure.[1, 8]

Immunocompromised patients require an increased dose and longer duration of valaciclovir treatment.[2, 9]

For specific information on dose adjustments in patients with renal impairment see: **www.nzf.org.nz/nzf_3443**

Valaciclovir for the treatment of genital herpes

Without treatment the symptoms of genital herpes can last for up to three weeks.[3] Treatment with valaciclovir or aciclovir reduces the time to healing, the severity and duration of symptoms and viral shedding.[1] In one large randomised controlled trial the median time to symptom resolution for patients taking either valaciclovir or aciclovir was approximately nine days; with almost all patients having symptom resolution and lesion healing by two weeks.[10]

Oral valaciclovir, 1000 mg, twice daily, produces the same clinical benefit as oral aciclovir, 200 mg, five times daily, when taken for the same duration, with similar duration of symptoms, pain, viral shedding and time to healing.[10]

Continuous valaciclovir treatment can reduce the incidence of symptomatic episodes

Patients who regularly experience recurrent genital herpes, e.g. six episodes or more per year, may trial preventative treatment to reduce the impact of the disease and to provide a sense of control over the disease process.[3, 11] There is evidence that continuous treatment with valaciclovir can reduce the number of recurrent episodes of genital herpes by approximately 60%.[11] The clinical threshold at which continuous treatment with valaciclovir could be offered is influenced by the patient's ability to tolerate recurrences and their willingness to adhere to treatment.[9]

How to prescribe valaciclovir for the treatment of genital herpes

Valaciclovir dosing recommendations* differ depending on the intended use:[3, 9]

- **For first episodes:** valaciclovir 500 mg, twice daily, for seven days, or longer if new lesions appear or lesions are not fully healed (consider 1000 mg, twice daily, for seven to ten days in immunocompromised patients)
  - All patients with suspected first episodes of genital herpes should receive empiric treatment with valaciclovir, without waiting for confirmatory test results (see: "The role of testing in the diagnosis and treatment of genital herpes", over page)
- **For recurrent episodes (episodic treatment):** valaciclovir 500 mg, twice daily, for three days
  - Consider providing the patient with a prescription to be used as soon as symptoms begin
- **For prevention of recurrences (suppressive treatment):** valaciclovir 500 mg, daily
  - Only recommended if HSV confirmed on testing
  - Withdraw treatment every 6–12 months to reassess the recurrence frequency; consider restarting treatment after two recurrences
  - Dosing may be increased to 500 mg, twice daily, or 1 g, once daily, for patients who continue to experience multiple recurrences (unapproved dose)

* Valaciclovir doses in this article may differ from those in the Medicine Data Sheet and the NZF. This dosing information is endorsed by the New Zealand Herpes Foundation.

Valaciclovir for pregnant women or women planning pregnancy

Transmission of the herpes virus to neonates during delivery is a potentially serious event. Women who have had symptomatic herpes before pregnancy can be assured that the risk of passing the infection on to their baby is very small (approximately 0.05%), if they have no signs or symptoms at the time of delivery.[3] Suppressive therapy to avoid a recurrence

The role of testing in the diagnosis and treatment of genital herpes

Testing should be requested for patients with first episodes of genital herpes (and atypical recurrences) to confirm the diagnosis and determine the type of virus involved. This can provide prognostic information, e.g. HSV-2 is associated with more frequent recurrences of genital herpes than HSV-1 infections. Approximately 70–90% of patients who have symptomatic HSV-2 genital infections and 20–50% of patients with genital HSV-1 infections experience a recurrence within the first year.[12]

After removing the covering tissue with a needle or scalpel, swabs are taken from the base of the lesion to collect virus-infected cells and vesicular fluid. Polymerase chain reaction (PCR)-based detection is now the preferred method for herpes virus testing. If this is not available viral culture is an alternative method of testing; culture has a higher specificity, but lower sensitivity, than PCR-based detection and usually takes longer to receive a result.

Arrange a follow-up appointment at five to seven days for patients with test results positive for genital herpes to provide counselling and future lifestyle advice (see: "Advice for patients with genital herpes").

Herpes virus serology, i.e. testing for the presence of antibodies to HSV-1 or HSV-2, is not recommended as a routine test. Herpes antibodies typically take two to six weeks to develop and sometimes longer. Patients presenting with new infections are therefore likely to test negative for antibodies. A positive serology result may indicate that the patient has previously had an asymptomatic infection but would not change how they are managed. Serology may be useful in specific circumstances, such as to test whether a pregnant woman has antibodies to herpes virus if their partner develops symptomatic genital herpes during the pregnancy (see: "Valaciclovir for pregnant women or women planning pregnancy").[3]

near the time of delivery can be considered in women with a history of genital herpes; consultation with an obstetrician or gynaecologist is recommended.[3]

The greatest risk of neonatal transmission occurs when a woman has a first episode of symptomatic herpes near or at the time of delivery. For women who develop symptomatic genital herpes during pregnancy, particularly during the third trimester, consultation with an obstetrician or gynaecologist is recommended. For women who develop symptomatic genital herpes during the first or second trimester, standard treatment with antiviral medicines and vaginal delivery is possible. Delivery by caesarean section is recommended for women with a first episode during the third trimester.[3] A first episode of herpes symptoms during pregnancy may not be a new infection, due to changes in immune function, this may be the first symptomatic episode in a woman previously infected.[3]

If a pregnant woman, without a prior history of symptomatic genital herpes, has a partner with a history of herpes symptoms, serological testing of both partners may be beneficial. If the male partner is seropositive for HSV-2 infection and the female seronegative, suppressive treatment of the male partner could reduce the risk of transmission; this regimen has been shown to reduce the risk of transmission between partners by approximately 50%.[3, 9] The use of valaciclovir to prevent transmission in this way is an unapproved indication.

Advice for patients with genital herpes [3, 9, 13]

Inform patients that there is no cure for herpes virus infection; valaciclovir can reduce the severity of symptoms and the incidence of recurrences, but does not clear the infection.

Transmission risk is highest during recurrences and patients should avoid sexual contact while they have symptoms, even if they are taking valaciclovir. Transmission can also occur when people are asymptomatic. Infected people will need to discuss the approach they wish to take if they want to avoid transmission to an uninfected partner; condoms can reduce but not eliminate the risk of transmission.

Herpes recurrences may be preceded by symptoms such as tingling, burning or pain in the anogenital region, which may extend to hips or legs for two to five days before visible lesions develop. Patients should begin taking valaciclovir to treat a recurrence at the onset of these symptoms.

Salt baths may relieve pain and improve the healing of lesions, e.g. half a cup of salt in a bath. Patients often experience pain during urination and application of lignocaine gel a few minutes prior to urination may lessen discomfort. Topical lignocaine products are not subsidised for this indication. Sensitisation to topical lignocaine occurs rarely but patients should be aware of the possibility of irritant hypersensitivity.

Patient information and support is available from:
www.herpes.org.nz

Valaciclovir for the treatment of herpes zoster (shingles)

Herpes zoster, also known as shingles, is caused by reactivation of latent Varicella zoster virus in individuals who have previously had varicella, and usually occurs in people aged 40 years and over.[14]

Patients with herpes zoster often describe an itching or burning, shooting pain which precedes a characteristic rash by three to four days. Typically, patients display a unilateral rash with a distribution corresponding to the affected dermatome.[14] Diagnosis can usually be made on the basis of this dermatomal rash with accompanying pain, without the need for further investigation. Testing may be necessary if there is uncertainty, e.g. to differentiate between Herpes simplex infection and herpes zoster or if herpes zoster without rash (zoster sine herpete) is suspected.

Post-herpetic neuralgia occurs in 10–18% of patients with herpes zoster and causes ongoing pain after the resolution of other symptoms and signs.[14]

Valaciclovir is more effective at reducing pain due to herpes zoster than aciclovir

Antiviral medicines reduce the severity and duration of acute pain for patients with herpes zoster; valaciclovir may result in improved symptoms compared with the use of aciclovir. A study of over 1,000 patients, using comparable doses of valaciclovir or aciclovir, reported that resolution of pain was on average 25% quicker for patients taking valaciclovir than patients taking aciclovir (p=0.001). The duration of cutaneous symptoms and signs was similar for both groups of patients.[15]

Valaciclovir is unlikely to prevent post-herpetic neuralgia, as this has not been observed in studies of aciclovir for the treatment of herpes zoster, although clinical trials assessing this end-point with valaciclovir have not been conducted.[16]

How to prescribe valaciclovir for the treatment of herpes zoster:[17]

- Valaciclovir, 1g, three times daily, for seven days to reduce the pain associated with symptomatic episodes; lower doses are required in patients with reduced renal function, see: **www.nzf.org.nz/nzf_3443**
- Immunocompromised patients should continue dosing for at least two days after lesions have crusted, which may result in treatment for longer than seven days

Red flag: Patients with herpes zoster and signs of involvement of the ophthalmic branch of the trigeminal nerve (herpes zoster ophthalmicus) should be discussed with an ophthalmologist.[18] Herpes zoster ophthalmicus can result in serious sequelae including keratitis, uveitis, glaucoma and blindness.[2]

Advice for patients with herpes zoster

Advise patients with herpes zoster to avoid physical contact with others to reduce the risk of transmission, especially infants aged one year and under, pregnant women and immunocompromised people. Lesions should be kept clean and dry and can be covered with a dressing without an adhesive backing.[2] Patients should refrain from scratching the rash to reduce transmission and scarring.

Following the resolution of cutaneous symptoms and signs patients may experience ongoing pain that may resolve over months to years, but can often continue despite treatment.[19] In clinical trials in patients with post-herpetic neuralgia, fewer than half of patients treated with analgesia have a 50% or greater reduction in pain.[19] Treatment options in primary care for chronic pain due to herpes zoster include topical capsaicin creams (0.075%), paracetamol, or for more severe pain, medicines such as tricyclic antidepressants or anticonvulsants may be of benefit.[20]

For further information on the diagnosis and management of herpes zoster, see: "The diagnosis and management of herpes zoster and its complications", BPJ 59 (Mar, 2014).

Vaccination reduces the risk of developing herpes zoster

Zoster vaccine (Zostavax, a live attenuated vaccine) is recommended but not subsidised in New Zealand for people aged 50 years and over.[14]

Vaccination can prevent the development of herpes zoster by approximately 50% and reduce the incidence of post-herpetic neuralgia by approximately 40%.[21, 22] Patients aged 60–69 years may receive a greater benefit from vaccination (64% reduction in risk) than patients aged 70 years and over (36% reduction in risk).[21] The number-needed-to-treat is 50, in patients aged 60 years and over, for vaccination to prevent one case of herpes zoster. Adverse effects include mild to moderate injection site reactions.[21] The vaccine is effective for at least five years, but it is not known how long protection lasts beyond this time and if, or when, repeat vaccination is necessary.[14]

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Problematic cold sores (herpes labialis)

Most patients with herpes labialis experience no more than one recurrence per year, although 5–10% of patients experience six or more episodes per year.[23] The majority of patients who have recurrences will have episodes that are not sufficiently problematic for them to seek medical attention. Triggers for recurrence include sun exposure, stress, hormonal fluctuations and minor trauma or cosmetic procedures.[23]

For patients who present with particularly painful or extensive cold sores, clinicians may advise the use of a topical product containing aciclovir (available unsubsidised in pharmacies and supermarkets) or consider prescribing oral valaciclovir:

- Topical aciclovir 5% creams have been shown to produce statistically significant but clinically small effects in patients with cold sores, reducing pain and symptoms by approximately half a day[24]
- Oral valaciclovir, 2 g twice daily for one day, reduces healing time by approximately one day.[24] However, this is an unapproved use of oral valaciclovir.[17]

There is little evidence to support the use of antiviral medicines to prevent recurrences of cold sores in patients without underlying conditions, e.g. immunocompromised patients.[23] For patients with recurrent cold sores, wearing sunscreen on the affected area during periods of remission may reduce recurrences.[23] Stress management techniques may also be beneficial as recurrence of cold sores has been associated with periods of psychological stress. Recent research has identified a molecular mechanism by which stress signals in neurons can induce reactivation of the Herpes virus.[25]

References:

1. Brantley JS, Hicks L, Sra K, et al. Valacyclovir for the treatment of genital herpes. Expert Rev Anti Infect Ther 2006;4:367–76. doi:10.1586/14787210.4.3.367
2. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. Clin Infect Dis 2007;44 Suppl 1:S1-26. doi:10.1086/510206
3. New Zealand Herpes Foundation. Guidelines for the management of genital herpes in New Zealand. 11th edition. 2015. Available from: www.herpes.org.nz/files/8114/5003/2005/genital_herpes_guidelines_2015.pdf (Accessed Jan, 2016).
4. Reitano M, Tyring S, Lang W, et al. Valaciclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale dose range-finding study. International Valaciclovir HSV Study Group. J Infect Dis 1998;178:603–10.
5. Fife KH, Warren TJ, Ferrera RD, et al. Effect of valacyclovir on viral shedding in immunocompetent patients with recurrent herpes simplex virus 2 genital herpes: a US-based randomized, double-blind, placebo-controlled clinical trial. Mayo Clin Proc 2006;81:1321–7. doi:10.4065/81.10.1321
6. Carlon R, Possamai C, Corbanese U. Acute renal failure and severe neurotoxicity following valacyclovir. Intensive Care Med 2005;31:1593. doi:10.1007/s00134-005-2808-9
7. Sugimoto T, Yasuda M, Sakaguchi M, et al. Oliguric acute renal failure following oral valacyclovir therapy. QJM 2008;101:164–6. doi:10.1093/qjmed/hcm154
8. Gentry III JL, Peterson C. Death delusions and myoclonus: acyclovir toxicity. Am J Med 2015;128:692–4. doi:10.1016/j.amjmed.2015.03.001
9. Patel R, Alderson S, Geretti A, et al. European guideline for the management of genital herpes, 2010. Int J STD AIDS 2011;22:1–10. doi:10.1258/ijsa.2010.010278
10. Fife KH, Barbarash RA, Rudolph T, et al. Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection. Results of an international, multicenter, double-blind, randomized clinical trial. The Valaciclovir International Herpes Simplex Virus Study Group. Sex Transm Dis 1997;24:481–6.
11. Le Cleach L, Trinquart L, Do G, et al. Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients. Cochrane Database Syst Rev 2014;8:CD009036. doi:10.1002/14651858.CD009036.pub2
12. Gupta R, Warren T, Wald A. Genital herpes. Lancet 2007;370:2127–37. doi:10.1016/S0140-6736(07)61908-4
13. Johnston C, Saracino M, Kuntz S, et al. Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, cross-over trials. Lancet 2012;379:641–7. doi:10.1016/S0140-6736(11)61750-9
14. Ministry of Health (MoH). Immunisation handbook. 2014. Available from: www.health.govt.nz/publication/immunisation-handbook-2014 (Accessed Mar, 2016).
15. Beutner KR, Friedman DJ, Forszpaniak C, et al. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. Antimicrob Agents Chemother 1995;39:1546–53. doi:10.1128/AAC.39.7.1546
16. Chen N, Li Q, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. Cochrane Database Syst Rev 2014;2:CD006866. doi:10.1002/14651858.CD006866.pub3
17. New Zealand Formulary (NZF). NZF v44. 2015. Available from: www.nzf.org.nz (Accessed Mar, 2016).
18. Wehrhahn M, Dwyer D. Herpes zoster: epidemiology, clinical features, treatment and prevention. Aust Prescr 2012;35:143–7.
19. Johnson RW, Rice ASC. Clinical practice. Postherpetic neuralgia. N Engl J Med 2014;371:1526–33. doi:10.1056/NEJMcp1403062
20. Scottish Intercollegiate Guidelines Network (SIGN). Management of chronic pain. Edinburgh: SIGN 2013. Available from: www.sign.ac.uk/pdf/SIGN136.pdf (Accessed Mar, 2016).
21. Gagliardi AMZ, Gomes Silva BN, Torloni MR, et al. Vaccines for preventing herpes zoster in older adults. Cochrane Database Syst Rev 2012;10:CD008858. doi:10.1002/14651858.CD008858.pub2
22. Langan SM, Smeeth L, Margolis DJ, et al. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. PLoS Med 2013;10:e1001420. doi:10.1371/journal.pmed.1001420
23. Chi C-C, Wang S-H, Delamere FM, et al. Interventions for prevention of herpes simplex labialis (cold sores on the lips). Cochrane Database Syst Rev 2015;8:CD010095. doi:10.1002/14651858.CD010095.pub2
24. Chon T, Nguyen L, Elliott TC. Clinical inquiries. What are the best treatments for herpes labialis? J Fam Pract 2007;56:576–8.
25. Hofer U. Viral pathogenesis: Stressing out over herpes. Nat Rev Microbiol 2016;14:62–3. doi:10.1038/nrmicro.2015.19

The role of **medicines for the treatment of depression** and **anxiety** in patients aged under 18 years

Psychological and behavioural approaches are the cornerstone of treatment for young people with depression or anxiety. When pharmacological treatment for a patient aged under 18 years is required due to severe or ongoing symptoms it is almost always "off-label". Medicines may be initiated in secondary care, with monitoring and follow up in primary care, or they may be initiated by a general practitioner. In this final article of a three-part series focusing on mental health issues for young people, the recommendations and evidence for the use of medicines in people aged under 18 years with depression and anxiety are discussed.

KEY PRACTICE POINTS:

- Non-pharmacological approaches are preferred for patients aged under 18 years with anxiety disorders or depression; treatment should acknowledge the ongoing importance of family support, sleep, good nutrition and exercise
- Clinicians in primary care should consider consulting with a child and adolescent psychiatrist or paediatrician before prescribing a psychoactive medicine to a patient aged under 18 years; these should only be prescribed if symptoms are severe and/or other treatments have been ineffective and they are used alongside psychological therapy
- There is evidence that selective serotonin reuptake inhibitors (SSRIs) may be effective for some young people with severe or persistent anxiety or depression. These medicines are only approved for use in patients aged over 18 years and their use in children and adolescents with depression or anxiety is almost always "off-label".
- Fluoxetine offers the greatest benefit for young people with depression and is the only SSRI that should be initiated in primary care without consulting with a child and adolescent psychiatrist. General practitioners may be involved in continuing treatment with other SSRIs initiated in secondary care.
- The pharmacological treatment of mental health conditions in young people should be accompanied by increasing, rather than decreasing, clinical contact. Frequent follow-up, e.g. weekly face-to-face or telephone contact, is recommended for the first month of use.

For previous articles in this series, see: "Addressing mental health and wellbeing in young people", BPJ 71 (Oct, 2015) and "Managing frequently encountered mental health problems in young people: non-pharmacological strategies", BPJ 72 (Dec, 2015)

The use of psychoactive medicines in young people is increasing

The use of psychoactive medicines in people aged under 18 years has increased in New Zealand over the last five years (Figure 1):[1]

- Dispensings of antidepressants to patients aged 10–17 years were 44% higher in 2014 than 2010. Fluoxetine accounted for 56% of SSRI dispensings in this age group in 2014.
- Antipsychotic dispensing to people aged 10–17 years increased by 48% in 2014 compared with 2010. Quetiapine and risperidone are the most frequently dispensed antipsychotic medicines in this age group.

The individual medicines included in each group in Figure 1 are available from: **www.pharmac.govt.nz/healthpros/PharmaceuticalSchedule/Schedule?code=A22**

Why is dispensing of psychoactive medicines to young people increasing?

The most likely reason for the increase in dispensing of SSRIs to young people is a greater awareness of depression. Clinicians may also be adopting a lower threshold for prescribing, as only small changes in the prevalence of mental health conditions among young people have occurred.[2,3]

Guidance regarding the pharmacological treatment of mental health conditions in young people has not changed substantially in the past five years. Furthermore, the number of people aged 10–17 years in New Zealand has decreased slightly from 2010 to 2014; therefore population change cannot account for the increase.[4]

Medicines for mental health are often initiated in secondary care

Some classes of medicines used for the treatment of mental health conditions in young people are almost exclusively initiated in secondary care. For example, antipsychotic medicines may be prescribed by child and adolescent psychiatrists for the treatment of psychosis, bipolar disorder, anxiety and disruptive behaviours associated with autism,

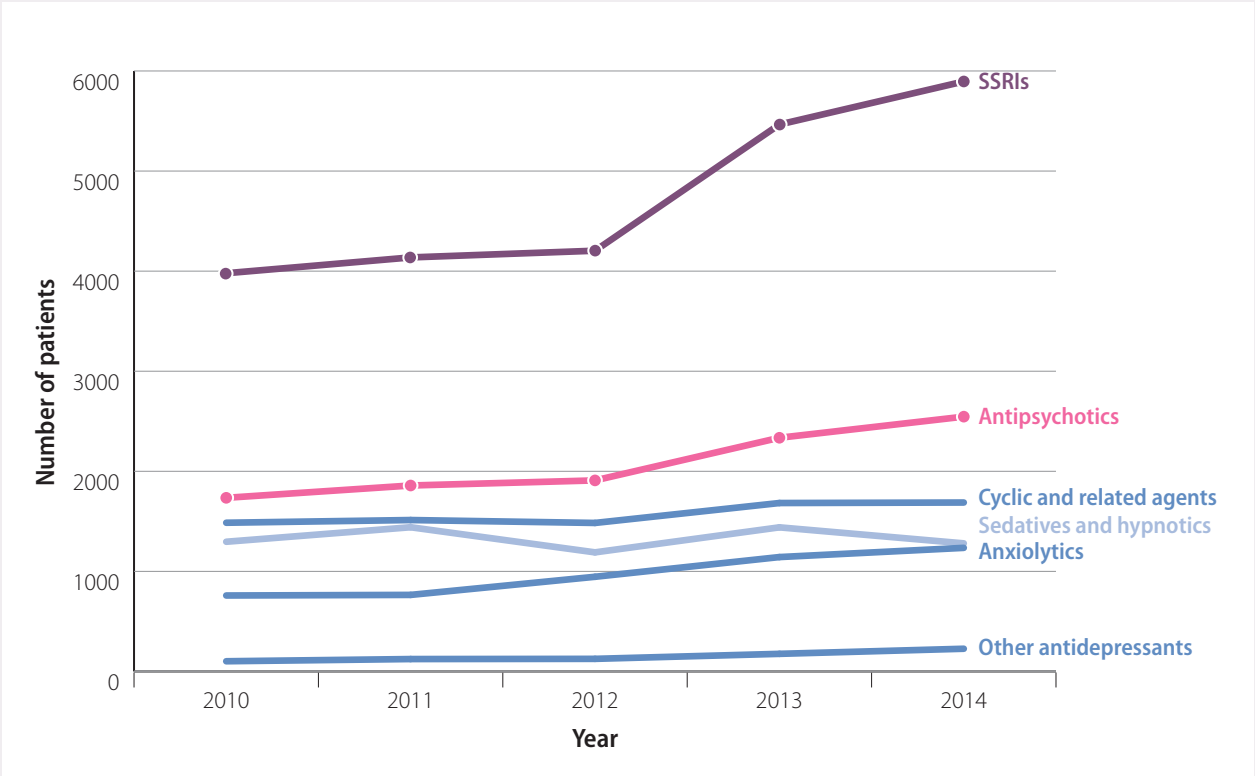

Figure 1: New Zealand community dispensing for medicines used in the treatment of mental health conditions to people aged 10–17 years, from 2010 to 2014.[1]

neurodevelopmental disorders and conduct disorder in patients aged under 18 years. The majority of these medicines are not initiated in primary care, but general practitioners may be required to continue treatment in consultation with the clinician who initiated treatment (see: "Caring for patients aged under 18 years taking antipsychotic medicines", Page 24).

Most patients taking antidepressants will experience adverse effects

Most patients of any age who take an antidepressant experience at least one adverse effect. In short-term clinical trials nausea is the most common adverse effect reported, occurring in approximately one in five patients, usually in the first weeks of treatment and often resolving shortly after.[5, 6] Other adverse effects frequently reported include:[7]

- Agitation
- Changes in sexual function, such as erectile dysfunction and failure to orgasm
- Dizziness
- Drowsiness
- Dry mouth
- Headaches
- Psychological and emotional changes, such as blunted emotions or aggression
- Weight gain

Adverse events in young patients are more common and more severe

Younger patients are more likely to experience adverse effects while taking antidepressants than adults and these adverse effects may be more severe.[7, 8] The evidence supporting SSRI use in young people has been questioned following recent re-analyses of clinical trials which concluded that the harms of treatment appear to have been underestimated.[8, 9]

Antidepressant treatment approximately doubles the rate of suicidal ideation and attempted suicide in children and young people. However, the rates recorded in clinical trials are relatively low, e.g. 11 incidents per 1000 patients taking placebo and 30 incidents per 1000 patients taking antidepressant medicines.[8, 10] This increase is larger than that seen in adults taking antidepressants and involves suicidal thinking or suicide attempts: no studies have reported an increase in the number of completed suicides for patients aged under 18 years using antidepressants.[8, 10]

Antidepressants are not the first-line treatment for most young patients with depression or anxiety

For young people with depression or anxiety disorders, the use of counselling, psychological treatment, self-help and online resources are the preferred first-line treatment options.[11, 12] Five or six out of every ten young people with moderate to severe depression achieve remission with psychological treatment.[13] In situations where treatment with non-pharmacological approaches is unsuccessful, or difficult to access, other approaches may be necessary. Second-line treatments can involve medicines or, where available, other non-pharmacological approaches, e.g. an escalation from self-help to face-to-face counselling, or from counselling with a general practitioner to cognitive behavioural therapy with a psychologist.

The evidence supporting antidepressant treatment in young people is limited

There are no medicines currently approved for the treatment of depression, generalised anxiety, social anxiety or panic disorders in patients aged under 18 years in New Zealand.[14] Although results from some clinical trials suggest antidepressants are effective in patients aged under 18 years, worldwide few manufacturers have sought approval for their use in young people.

For the treatment of depression fluoxetine is preferred in patients aged under 18 years due to its superior risk-benefit profile. In patients aged under 18 years with depression the placebo effect, or natural rate of remission, is larger than the effect produced by fluoxetine: two out of ten young people taking fluoxetine for depression will experience natural remission or placebo effect, one will experience remission due to fluoxetine treatment and seven will not experience a clinically significant improvement in symptoms.[10] Antidepressant treatment is, however, more likely to be effective for young patients with severe depression than those with mild to moderate depression.[15]

Fluoxetine has marketing authorisation in the United Kingdom for use in patients aged eight to 18 years, and is the only antidepressant recommended for use in patients in this age group with severe or ongoing depression by the National Institute for Health and Care Excellence (NICE).[12] The Royal Australian and New Zealand College of Psychiatrists also recommends that fluoxetine be considered, in addition to psychological treatment, in young people when depression is moderate to severe or when psychotherapy has been ineffective.[15]

Paroxetine and venlafaxine should not be used in patients aged under 18 years; three placebo-controlled studies have

Case study: Lachie

Lachie, aged 16 years, presents with his mother. He reports low mood, insomnia, and lethargy worsening over the preceding two months. His mother is concerned: Lachie has missed school most days in the past fortnight. He was working through the online SPARX (Smart, Positive, Active, Realistic, X-factor thoughts) programme with some benefit, but recently has felt too low to continue.

Lachie has a strong family history of depression, with his older brother committing suicide at age 19 years. Lachie denies any thoughts or plans of suicide or self harm at this time, but his mother is anxious.

Lachie is moderately depressed and risk factors include having a family member who committed suicide.[18] On balance it is reasonable to trial fluoxetine and the local adolescent psychiatrist agrees with this assessment and treatment plan. Lachie is encouraged to continue with the SPARX programme and to make use of online or telephone support. He is also referred to a child and adolescent psychologist to ensure that psychological therapy is continued.

The risks and benefits of fluoxetine are discussed with Lachie and his mother and its off-label use explained. Lachie and his mother are warned about the potential for increased suicidality. Arrangements are made to see Lachie in one week or sooner if required, and both Lachie and his mother are given the local psychiatric emergency phone number to call if there is a sudden change in his condition.

A directory of local mental health and support services is available from: **www.werrycentre.org.nz/service/locations?tid=168**

Parents, family members and friends of young people with mental health issues are likely to be affected by their change in mood and behaviour. Given the family history of suicide in this case, Lachie's family members are likely to benefit from additional support. Lachie's mother is given the details of a local support service and encouraged to use online resources such as Common Ground, available from: **www.commonground.org.nz**

been conducted for each of these medicines which suggest they have limited efficacy.[12] Tricyclic antidepressants should not be used in patients aged under 18 years; it is unlikely they produce clinically significant benefits and they are potentially toxic in overdose.[12]

For the treatment of anxiety disorders, e.g. panic disorder, social phobia or generalised anxiety disorder, there is a wider range of antidepressants that may be appropriate in patients aged under 18 years, e.g. fluoxetine, sertraline, venlafaxine.[16,17] Generally, the use of these medicines is reserved for patients with severe or ongoing symptoms who are likely to be referred to secondary care.

There is a strong placebo effect or natural rate of remission in young people with anxiety; response rates in placebo groups in clinical trials range from 31–39%.[16, 17] In young patients with anxiety disorders SSRIs are almost twice as effective as placebo.[16, 17]

Balancing the risks and benefits of antidepressant treatment

It is unknown which patients with depressive symptoms will benefit prior to starting pharmacological treatment. This makes it difficult to balance the risk versus the benefits of treatment, especially in young patients where the potential harms may be greater. On one hand, the greatest risk associated with depression is suicide. On the other, antidepressants increase the risk of suicidal ideation. Furthermore, suicide risk can be difficult to judge, is often highly variable and can change rapidly in a young person.[18]

Similarly, the use of antidepressants may increase anxiety and agitation and patients with anxiety may experience a worsening of symptoms.[14]

Consider how the patient's condition affects their quality-of-life

For some young patients with mental health issues the concern may not be suicide risk but rather their long-term development. In young people with persistent anxiety the principal concern could be the effect on their education and relationships. It is also important to consider symptoms which are ongoing despite treatment, the concern of family members, relationships or work commitments (see: "Case study: Lachie").

Involve the patient's family where appropriate

Involve the family or carers of young people, wherever possible, in treatment discussions for mental health conditions if the patient consents; the observations of those closest to them are likely to be helpful, especially if a trial of pharmacological treatment is initiated.

Situations where added caution is advised before initiating treatment

Situations where extra caution is advised before initiating antidepressant treatment for a young person in primary care are shown in Table 1.

Situations where it may be appropriate to initiate pharmacological treatment in primary care

While patients with mild to moderate depression or anxiety should be treated with non-pharmacological approaches before medicines are trialled (see below), there may be situations where clinicians in primary care feel that more needs to be done to help a young person.

The initiation of antidepressant treatment in primary care will often involve the input of a child and adolescent psychiatrist. However, if the availability of psychological treatment is limited or if it is difficult for young people to attend therapy sessions and online resources are insufficient, general practitioners may need to consider initiating a trial of pharmacological treatment. In each case, clinicians will need to take an individualised approach taking into account the patient's age, history and circumstances, severity of symptoms, access to other treatments, wider family/whānau support and how they have responded to non-pharmacological treatments.

Table 1: Situations and reasons why trialling an antidepressant in primary care may not be appropriate.

Scenario	Factors for consideration
Patient is a younger adolescent	The evidence for treatment benefit is less certain in younger patients; the mean age of participants in clinical trials for the treatment of depression in young patients with antidepressants ranges from 12 to 16 years[10]
Patient has a crisis which triggers an abrupt onset of depression, e.g. relationship ending	It is important to differentiate between low mood arising from an event, e.g.grief or acute trauma, and long-term changes in mood. The onset of action of fluoxetine is gradual; several weeks of treatment is required before a clinical effect is experienced. Short-term pharmacological treatment is unlikely to be helpful for patients with an acute change in mood caused by factors out of their control; counselling services and strong support is preferred in these situations.
Patient is using alcohol or substances	Alcohol and substance use are risk factors for suicide.[18] The combination of antidepressant treatment and alcohol or substance use may result in additional harm; young people with substance or alcohol use problems should be referred to secondary care.
Follow-up and monitoring is likely to be difficult	The development of adverse effects may be difficult to detect in these situations, particularly if the patient has limited family involvement, a history of non-attendance or is difficult to contact
Patient has a pre-existing condition that increases the risk of adverse effects	■ Epilepsy; SSRIs antagonise the effect of antiepileptic medicines ■ A history of mania ■ Bleeding disorders or taking medicines which increase the risk of bleeding ■ A high risk of QT prolongation*

* For information on the risk of QT prolongation with antipsychotic or antidepressant medicines, see: www.medsafe.govt.nz/profs/PUArticles/DrugInducedQTProlongation.htm

Caring for patients aged under 18 years taking antipsychotic medicines

Young people treated with antipsychotics are at an increased risk of metabolic adverse effects, in particular rapid weight gain, compared with adults using the same medicines.[23] Weight gain in young people with mental health conditions may have a negative effect on interactions with peers and their quality of life. Young people taking antipsychotics are also two to three times more likely to develop type 2 diabetes than their peers.[24]

Before initiating antipsychotic medicines in young people, the following examinations are recommended:[25]

- Lipid levels: triglycerides, total cholesterol and total:HDL cholesterol ratio
- Fasting glucose
- Blood pressure
- BMI and waist circumference
- Baseline ECG for patients with risk factors for QT prolongation*

Where appropriate, repeat these measurements at suggested intervals of:[25]

- Six weeks after starting antipsychotic medicines: BMI and waist circumference
- Then 12 weeks after initiation: all measures
- Then annually thereafter: all measures

Additional tests may be needed depending on the patient's symptoms and signs, e.g. prolactin levels may be assessed in young people with symptoms suggestive of hyperprolactinaemia: e.g. changes in sexual function in teenagers who are sexually active, menstruation changes or the production of breast milk.[25]

Ask about or examine the patient for the development of:[26, 27]

- Extrapyramidal effects, e.g. tardive dyskinesia
- Drowsiness
- Nocturnal enuresis (bed wetting)

Treatment should be discontinued if tardive dyskinesia develops. For the management of other extrapyramidal adverse effects, options include dose reduction, discontinuing medicines, or the use of anticholinergic medicines to reduce extrapyramidal symptoms. If a patient develops any of these symptoms consultation with the psychiatrist who is managing their care is recommended.[28]

* See:www.medsafe.govt.nz/profs/PUArticles/DrugInducedQTProlongation.htm

Trialling pharmacological treatment in a young patient

Before initiating pharmacological treatment for depression or anxiety in a young person ensure that:

1. Alternative treatment options, including available psychological therapies, and lifestyle advice regarding sleep, nutrition and exercise have been discussed
2. Consider whether a child and adolescent psychiatrist should be consulted, or an experienced colleague in primary care if this is not possible
3. The patient is not already taking an antidepressant prescribed by another clinician
4. A plan is established for follow-up and monitoring in order to maintain contact with the patient

 For further information about healthy lifestyle advice which may improve a young person's mood, see: "Managing frequently encountered mental health problems in young people BPJ 72 (Dec, 2015)

Antidepressants are initiated as a trial

Whenever antidepressant medicines are initiated in patients aged under 18 years their use should be regarded as a trial. Close contact and frequent follow-up are important in the weeks following initiation.

Advice for young people and their parents or carers should cover:[12, 19]

- That the use of the medicine is "off-label" and what this means
- The need for psychological therapy to continue alongside pharmacological treatment
- The risks and benefits of treatment, particularly the increased risk of suicidal ideation or self-harm behaviours
- The contact details of a local emergency psychiatric service should the patient's condition deteriorate or they develop suicidal ideation or aggression
- That any benefits may take three to four weeks to occur; emphasise the importance of adherence to treatment
- That withdrawal symptoms may occur if a dose is missed or treatment is stopped suddenly

Remind patients to avoid using alcohol or illicit drugs as they may increase the risk of suicide due to their disinhibiting effects.[18] St. John's wort or supplements containing tryptophan should also be avoided as they may increase the risk of serotonin syndrome.[20]

 For further information on the use of medicines for unapproved indications, see: "Unapproved medicines and unapproved uses of medicines", BPJ 51 (Mar, 2013)

Dosing starts low with regular follow-up

Fluoxetine, initially 10 mg, daily, is suggested for the treatment of severe or ongoing depression in patients aged under 18 years in primary care; this can be increased to 20 mg, daily, after one week if necessary; evidence is limited regarding the efficacy of doses above 20 mg.[12] Follow up should be weekly for the first month, then monthly.[12]

There is a wider range of antidepressants that may be effective for the treatment of anxiety disorders in young patients.[17, 21] Clinicians in primary care should consult with a child and adolescent psychiatrist to determine whether initiating one of these medicines is likely to be beneficial in a patient aged under 18 years with severe or ongoing anxiety.

Clinicians should review patients within one week of initiating antidepressants, and be alert for the development of suicidal thinking or self-harm, particularly during the first month of use.[12] Include the patient's parents/carers in the treatment plan, with the patient's consent, as they may be well placed to judge treatment response and to monitor the young person for adverse effects; consent from the patient may not be necessary if they are at risk of harming themselves.

If the patient shows an improvement with antidepressant treatment it may be continued with follow-up consultations every one to two months.[22] Treatment duration is typically at least six months.[12] The decision to continue treatment after a trial will depend on shared decision making with patients and parents/carers.

If patients develop adverse effects management strategies include:[19]

- Monitoring of symptoms, if they are mild and tolerable
- Discontinuing the medicine and increasing the use of psychological treatment
- Reducing the dose of the medicine for a period then increasing it if tolerated
- Switching to another medicine: if patients wish to trial another antidepressant referral to a child and adolescent psychiatrist is recommended

If the patient develops an increase in suicidal ideation or self-harm, antidepressant medicines should be discontinued. The patient should be urgently referred to child and adolescent mental health services;[12, 22] consultation with a child and adolescent psychiatrist is also helpful to determine whether dose tapering is required to minimise any adverse effects of withdrawal (see below). If a young patient develops an increase in suicidal ideation or self-harm while using antidepressants more intensive psychological treatment or an alternative pharmacological approach may be necessary.

If there is no improvement with antidepressant treatment, or worsening of symptoms consultation with a child and adolescent psychiatrist is recommended; dose adjustment, intensification of psychological approaches or a trial of another antidepressant medicine may be necessary.

Fluoxetine withdrawal does not usually require dose tapering

In general, antidepressant medicines should be discontinued over the course of at least four weeks.[6] However, fluoxetine may be stopped in some patients without the need for dose tapering due to its long half-life and lower risk of withdrawal symptoms.[6] For young patients who have been taking a high dose of fluoxetine, i.e. 40 mg daily, or a long course, e.g. months, dose tapering may be necessary.

The most common withdrawal symptoms for SSRIs include:[14]

- Gastro-intestinal disturbances
- Headache
- Dizziness
- Anxiety
- Paraesthesias, such as a sensation of an electric shock in neck, head or spine
- Tinnitus
- Fatigue
- Influenza-like symptoms
- Sweating

Clinicians should provide patients and family members or carers with a written action plan of who to contact if negative changes in the young person's behaviour, agitation or irritability occur during antidepressant withdrawal.[22]

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References:

1. Ministry of Health. Pharmaceutical Claims Collection. 2015.
2. Fleming TM, Clark T, Denny S, et al. Stability and change in the mental health of New Zealand secondary school students 2007-2012: results from the national adolescent health surveys. Aust N Z J Psychiatry 2014;48:472–80. doi:10.1177/0004867413514489
3. Ministry of Health. Tier 1 statistics 2014/15: New Zealand Health Survey. Ministry of Health NZ. 2015. Available from: www.health.govt.nz/publication/tier-1-statistics-2014-15-new-zealand-health-survey (Accessed Mar, 2016).
4. Statistics New Zealand. Infoshare, Population estimates – DPE, estimated resident population by age and sex, 1991+, annual-Jun. 2015. Available from: www.stats.govt.nz/infoshare/default.aspx (Accessed Mar, 2016).
5. Greist J, McNamara RK, Mallinckrodt CH, et al. Incidence and duration of antidepressant-induced nausea: duloxetine compared with paroxetine and fluoxetine. Clin Ther 2004;26:1446–55. doi:10.1016/j.clinthera.2004.09.010
6. National Collaborating Centre for Mental Health (UK). Depression: the treatment and management of depression in adults (updated edition). Leicester (UK): British Psychological Society 2010. Available from: www.ncbi.nlm.nih.gov/books/NBK63748/ (Accessed Mar, 2016).
7. Read J, Cartwright C, Gibson K. Adverse emotional and interpersonal effects reported by 1829 New Zealanders while taking antidepressants. Psychiatry Res 2014;216:67–73. doi:10.1016/j.psychres.2014.01.042
8. Sharma T, Guski LS, Freund N, et al. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ 2016;352:i65. doi:10.1136/bmj.i65
9. Le Noury J, Nardo JM, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. BMJ 2015;351:h4320. doi./10.1136/bmj.h4320
10. Hetrick SE, McKenzie JE, Cox GR, et al. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database Syst Rev 2012;11:CD004851. doi:10.1002/14651858.CD004851.pub3
11. National Institute for Health Care Excellence (NICE). Social anxiety disorder: recognition, assessment and treatment. London: NICE 2013. Available from: www.nice.org.uk/guidance/cg159 (Accessed Mar, 2016).
12. National Institute for Health and Care Excellence (NICE). Depression in children and young people: identification and management. London: NICE 2005. Available from: www.nice.org.uk/guidance/cg28 (Accessed Mar, 2016).
13. Cox GR, Callahan P, Churchill R, et al. Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database Syst Rev 2014;11:CD008324. doi:10.1002/14651858.CD008324.pub3
14. New Zealand Formulary for Children. NZFC v44. 2016. Available from: www.nzfchildren.org.nz/ (Accessed Mar, 2016).
15. Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2015;49:1087–206. doi:10.1177/0004867415617657
16. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 2007;297:1683–96. doi:10.1001/jama.297.15.1683
17. Ipser JC, Stein DJ, Hawkridge S, et al. Pharmacotherapy for anxiety disorders in children and adolescents. Cochrane Database Syst Rev 2009;3:CD005170. doi:10.1002/14651858.CD005170.pub2
18. New Zealand Guidelines Group. Assessment and management of people at risk of suicide. Ministry of Health NZ 2003. Available from: www.health.govt.nz/publication/assessment-and-management-people-risk-suicide (Accessed Mar, 2016).
19. National Institute for Health and Care Excellence (NICE). Generalised anxiety disorder and panic disorder in adults. London: NICE 2011. Available from: www.nice.org.uk/guidance/cg113 (Accessed Mar, 2016).
20. Ables AZ, Nagubilli R. Prevention, recognition, and management of serotonin syndrome. Am Fam Physician 2010;81:1139–42.
21. Strawn JR, Welge JA, Wehry AM, et al. Efficacy and tolerability of antidepressants in pediatric anxiety disorders: a systematic review and meta-analysis. Depress Anxiety 2015;32:149–57. doi:10.1002/da.22329
22. New Zealand Guidelines Group (NZGG). Identification of common mental disorders and management of depression in primary care. Wellington: NZGG 2008. Available from: www.health.govt.nz/system/files/documents/publications/depression_guideline.pdf (Accessed Mar, 2016).
23. De Hert M, Dekker JM, Wood D, et al. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). Eur Psychiatry 2009;24:412–24. doi:10.1016/j.eurpsy.2009.01.005
24. Galling B, Roldán A, Nielsen RE, et al. Type 2 diabetes mellitus in youth exposed to antipsychotics: A systematic review and meta-analysis. JAMA Psychiatry 2016;73:247–59. doi:10.1001/jamapsychiatry.2015.2923
25. De Hert M, Vancampfort D, Correll CU, et al. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. Br J Psychiatry 2011;199:99–105. doi:10.1192/bjp.bp.110.084665
26. Cohen D, Bonnot O, Bodeau N, et al. Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis. J Clin Psychopharmacol 2012;32:309–16. doi:10.1097/JCP.0b013e3182549259
27. Barnes TRE, Drake MJ, Paton C. Nocturnal enuresis with antipsychotic medication. Br J Psychiatry 2012;200:7–9. doi:10.1192/bjp.bp.111.095737
28. Pringsheim T, Doja A, Belanger S, et al. Treatment recommendations for extrapyramidal side effects associated with second-generation antipsychotic use in children and youth. Paediatr Child Health 2011;16:590–8.

Installing the NZF icon on the Medtech toolbar

Dear Editor,
How do we go about linking with the New Zealand Formulary in Medtech 32 PMS? Another surgery I worked at had an icon in Medtech that we clicked on and it came through to the website.

Practice Manager
Tauranga

Response from bpac^{nz} editorial team:
The New Zealand Formulary (NZF) provides health professionals in New Zealand with free, clinically validated information about medicines which enables them to select safe and effective treatments for individual patients. A number of clinicians prefer to be able to access the NZF directly from their Patient Management System. Instructions on how to install the NZF icon on the Medtech toolbar are available from:

www.nzformulary.org/wp-content/uploads/2012/10/NZFIcon.pdf

This process needs to be performed for each work station in the practice that requires an NZF icon installed.

Can urine dipstick be used to "rule-out" kidney disease in patients with mildly reduced renal function?

Greetings,
I am under a tree in Tapawera pursuing my usual holiday habit of catching up on bpac journals [Best Practice Journal] (which incidentally is why I prefer hard copy) and have reached the CKD article in Issue 66 [BPJ Feb, 2015]. My question is about dipsticks for patients with an eGFR between 60 and 89 mL/min/1.73m^2. Currently, if the lab reports a mildly reduced eGFR when performing cardiovascular risk assessments or testing renal function prior to medicine initiation, I arrange a urine dipstick and if negative for protein I just put them on annual recall. The article would suggest I should be sending the urines to the lab for ACR. There are quite a lot of these. Is a dipstick sufficient?
Thanks

Dr Emma Dunning, General Practitioner
Wellington

Response from bpac^{nz} editorial team:
Proteinuria is a sign of chronic kidney disease (CKD) as well as being an indicator for progressive CKD and future cardiovascular events.[1] Many clinicians will routinely use urine dipstick to test for proteinuria. However, New Zealand guidelines now recommend assessing patients with risk factors for CKD with urinary albumin:creatinine ratio (ACR), serum creatinine and blood pressure testing;[2] the addition of these tests to all diabetes screening and cardiovascular risk assessments is also recommended.[3] The frequency of CKD testing for patients with risk factors is:[2]

- At least every one to two years for patients without CKD
- At least every 12 months for patients with diabetes

ACR is the preferred method for quantifying proteinuria because:[1]

- Urinary dipstick is not sensitive enough to reliably detect proteinuria (see below)
- Albumin is the main protein excreted in the vast majority of proteinuric kidney disease
- ACR provides greater sensitivity in the detection of lower, but clinically significant, proteinuria compared with measures of total protein, i.e. protein:creatinine ratio (PCR)

Despite it being a rapid and simple point-of-care test the ability of urine dipstick to detect anything other than overt proteinuria is limited.[4] In a sample of urinalysis results for more than 10,000 Australian adults aged 25 years and older, a dipstick test result ≥ 1+ protein identified ACR ≥ 3.4 mg/mmol, i.e. microalbuminuria, with 57.8% sensitivity and 95.4% specificity, meaning four out of ten patients with microalbuminuria would be expected to return a false-negative result on urine dipstick testing.[5] When the threshold for detection was raised to ACR ≥ 33.9 mg/mmol, i.e. macroalbuminuria, the sensitivity of dipstick was increased to 98.9% with a specificity of 92.6%.[5]

The concern in using a negative result on urine dipstick to effectively "rule-out" clinically significant proteinuria in patients with reduced renal function is that while patients with

macroalbuminuria, who are admittedly at the highest risk, are likely to be identified, some patients with microalbuminuria may be missed.

Urine dipstick can, however, provide useful information in some situations in patients with reduced renal function. For example, dipstick testing for haematuria can provide useful diagnostic information.

It is acknowledged that routine ACR testing in all patients with a mildly reduced eGFR, i.e. 60–89 mL/min/1.73m^2, will include a substantial number of patients and an associated cost. It is important to remember that in New Zealand 7–10% of the adult population is estimated to have CKD;[3] with future rates of CKD expected to rise secondary to the increasing prevalence of obesity and diabetes, early detection in primary care is a priority. The overarching aim of CKD surveillance is to reduce the number of people reaching end-stage kidney disease and the resultant need for patient dialysis and kidney transplants.

For further information, see: "Interpreting urine dipstick tests in adults: a reference guide for primary care", BT (Jun, 2013) and "The detection and management of patients with chronic kidney disease in primary care", BPJ 66 (Feb, 2015).

References

1. National Health Service (NHS). Proteinuria: detection and quantification in adults using ACR - information for GPs. NHS: UK,. 2009. Available from: www.birminghamquality.org.uk/DLopen/proteinuria_GPs.pdf (Accessed Jun, 2015).
2. Kidney Health New Zealand. Chronic kidney disease (CKD): management in General Practice. 2013. Available from: www.kidneys.co.nz/resources/file/ckd_management_in_general_practice._2014_version.pdf (Accessed Dec, 2015).
3. Ministry of Health (MOH). Managing chronic kidney disease in primary care: national consensus statement. Wellington: Ministry of Health. 2015. Available from: www.health.govt.nz/publication/managing-chronic-kidney-disease-primary-care (Accessed Jun, 2015).
4. BMJ Best Practice. Assessment of proteinuria. 2015. Available from: http://bestpractice.bmj.com/best-practice/monograph/875.html
5. White SL, Yu R, Craig JC, et al. Diagnostic accuracy of urine dipsticks for detection of albuminuria in the general community. Am J Kidney Dis 2011;58:19–28. doi:10.1053/j.ajkd.2010.12.026

LABA without ICS in patients with COPD

Dear Editor

I have a question regarding COPD from issue 66 [BPJ Feb, 2015]. I was clearly in need of this article because I must be well out of date – in asthma we were told no LABA without ICS due to risk of sudden death – is this not the case for COPD?

Thanks

Emma Dunning, General Practitioner
Wellington

Response from bpac^{nz} editorial team:

Concerns about the use of long-acting beta$_2$-agonist (LABA) monotherapy for patients with asthma were first raised in the 1990s and confirmed by the Salmeterol Multicenter Asthma Research Trial (SMART), published in 2006. This was a 28-week, randomised, double-blind, placebo-controlled study comparing the safety of adding salmeterol or placebo to usual care in more than 26 000 patients with asthma aged over 12 years.1 The investigators found small, but statistically significant increases in respiratory-related deaths or life-threatening events in patients with asthma who were prescribed a salmeterol inhaler in addition to their normal treatment, which for some patients included inhaled corticosteroids (ICS);[1] the study was not designed to assess the effect of ICS treatment on patient outcomes. The finding from the SMART study was replicated and it was subsequently found that the increased risk of death in patients with asthma taking salmeterol was reduced with concomitant ICS treatment.[2] This resulted in the United States Food and Drug Administration (FDA) recommending that LABA monotherapy be contraindicated in the treatment of asthma.[3] The FDA also advised that LABAs should only be used as additional treatment for patients with asthma who were taking, but not receiving adequate control from, a long-term asthma control medicine such as ICS.[3]

In contrast to patients with asthma, LABA monotherapy has not been found to increase the risk of serious adverse events for patients with COPD.[3] Monotherapy with a LABA or long-acting muscarinic receptor antagonist (LAMA) is recommended in the stepwise management of COPD for patients with persistent dyspnoea.[4] Specifically, guidelines state that treatment with formoterol or salmeterol significantly improves FEV$_1$, lung volumes, dyspnoea, quality of life and exacerbation rate in patients with COPD, with no effect on mortality.[5] However, it is important to note that patients with asthma-COPD overlap syndrome (ACOS), i.e. patients with features of both asthma and COPD, should not be treated with LABA monotherapy.[5]

The reason why monotherapy with a LABA increases the risk of adverse events in patients with asthma but not in patients with COPD is uncertain. Eosinophilic airway inflammation due to allergic sensitisation and a T helper 2 lymphocyte-mediated immune response is a characteristic of asthma.[6] In the airways of patients with COPD a neutrophil response is typically present involving T helper 1 lymphocytes, often in association with bacterial colonisation.[6] However, some patients with COPD and ACOS also display eosinophilic airway inflammation.[6] Given the heterogeneity of asthma and COPD it is perhaps not surprising that different groups of patients with chronic airway diseases may not receive the same benefit from the same medicine.

For further information, see: "Are blood eosinophil counts helpful in predicting patient responses to inhaled corticosteroids in COPD?", Page 3 and "Newly-subsidised medicines for the treatment of patients with COPD", Page 7.

References

1. Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129:15–26. doi:10.1378/chest.129.1.15
2. Weatherall M, Wijesinghe M, Perrin K, et al. Meta-analysis of the risk of mortality with salmeterol and the effect of concomitant inhaled corticosteroid therapy. Thorax 2010;65:39–43. doi:10.1136/thx.2009.116608
3. United States Food and Drug Administration (FDA). FDA Drug Safety Communication: Drug labels now contain updated recommendations on the appropriate use of long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs). 2010. Available from: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm
4. Abramson M, Frith P, Yang I, et al. COPD-X concise guide for primary care. 2014. Available from: www.copdx.org.au (Accessed Mar, 2016).
5. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2016). 2016. Available from: www.goldcopd.org/uploads/users/files/WatermarkedGlobal%20Strategy%202016%281%29.pdf (Accessed Mar, 2016).
6. George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. Ther Adv Chronic Dis 2016;7:34–51. doi:10.1177/2040622315609251

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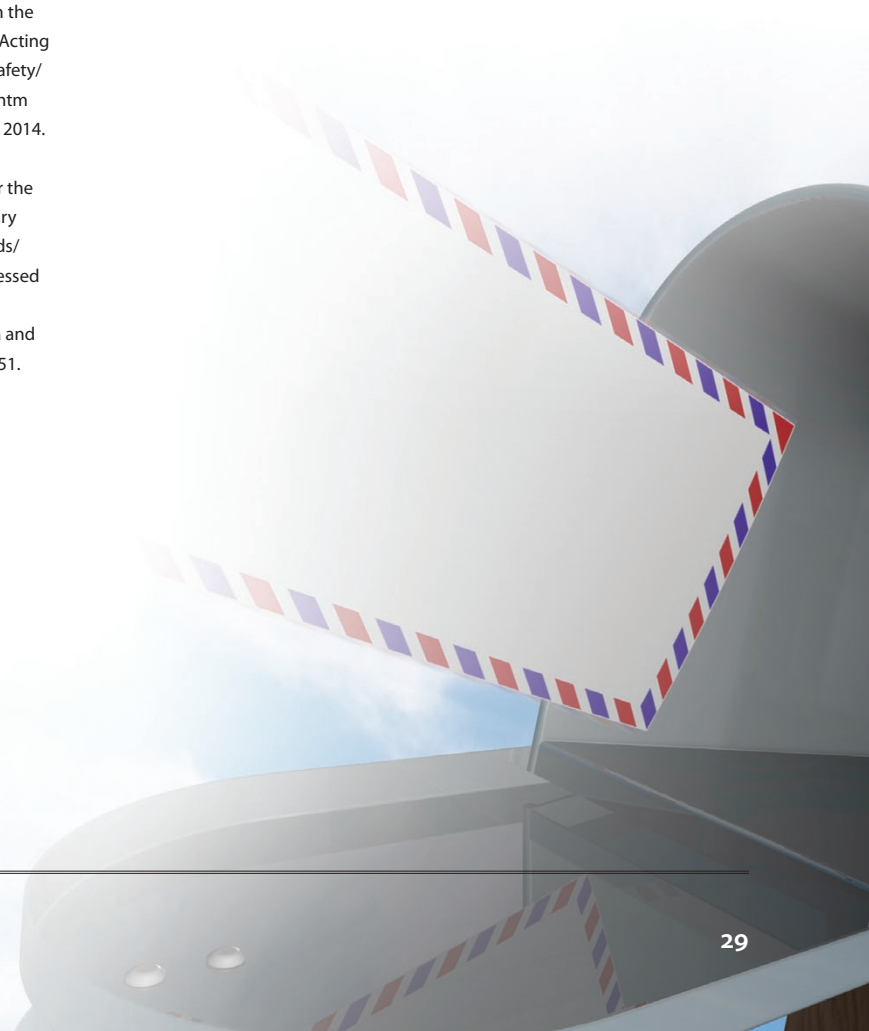

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