Australian Prescriber

AN INDEPENDENT REVIEW
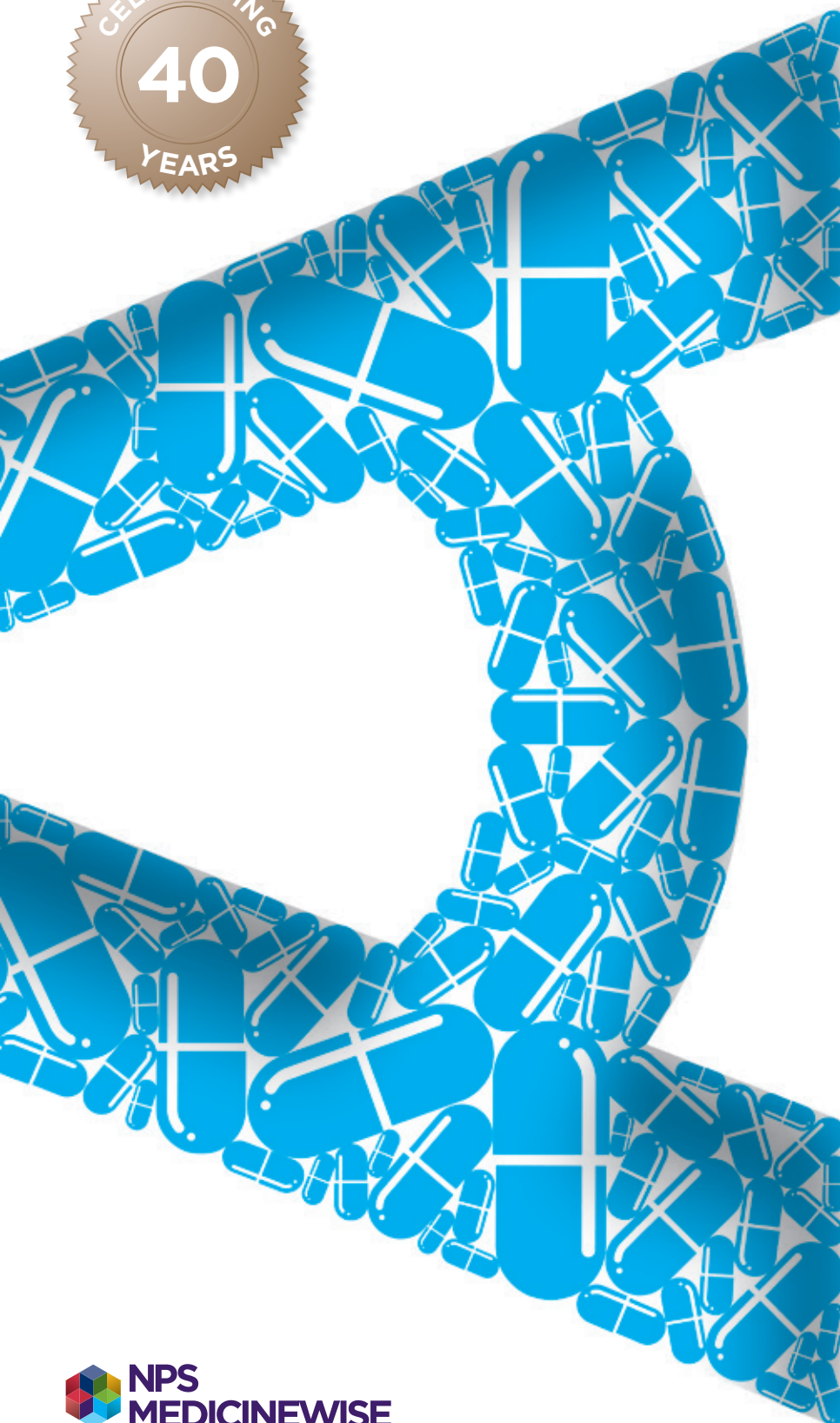
CELEBRATING 40 YEARS

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NPS MEDICINEWISE

Conflict of interest in medical journals

John Dowden
Editor
Australian Prescriber

Competing interests are everywhere. Everyone has a range of interests and these interests have the potential to conflict with each other. These conflicts are of particular concern in medical publishing because biased information can have adverse effects on practice. The competing interest may be personal, academic or intellectual, but most attention is paid to direct financial conflicts of interest.[1] For many medical journals, particularly those focused on therapeutics, the influence of the pharmaceutical industry has to be considered.

There is evidence of the widespread influence of the industry. A systematic review found that 23–28% of academic investigators receive industry funding, and industry-funded studies are likely to produce pro-industry conclusions.[2] An Australian study of 1500 clinicians found that while only 6% had been paid by industry, 23% had served on an industry advisory panel, 52% had accepted travel sponsorship and 96% had accepted gifts.[3] The gifts that have been commonly offered to Australian medical specialists include food and items for the office or for personal use.[4]

Conflicts of interest may be hidden or not reported. A review of 29 meta-analyses of 509 drug trials found that the authors' financial interests were only disclosed in 26% of the trials. None of the meta-analyses reported on the financial links between authors and industry in the trials they analysed.[5] A 2011 review of guidelines listed by the National Health and Medical Research Council found that only 15% had published conflict of interest statements.[6] While many Australian universities have policies on conflicts of interest, few require their staff to make regular declarations of their interests.[7]

Asking authors to declare their interests over the previous three years is one way medical journals identify competing interests. The International Committee of Medical Journal Editors has produced a standard form authors can use.[1] Since 1996, *Australian Prescriber* has been asking authors to declare any conflicts of interest. This policy was later extended to include the specialist referees who review the articles. The members of the Editorial Executive Committee have to make annual declarations of their interests in accordance with the policies of our publisher NPS MedicineWise.

The International Society of Drug Bulletins (ISDB), of which *Australian Prescriber* is a founder member, encourages its members to have policies on conflicts of interest. Members without their own policies can use an adapted version of the conflict of interest form produced by the International Committee of Medical Journal Editors. There is, however, now a view within ISDB that this is insufficient to prevent the publication of possibly biased information. A proposal that member bulletins should not publish material written by authors with competing interests is being considered. This would include the editorial team as well as external authors. While only publishing articles written by authors with no competing interest is a noble aim, is it practical?

In the 1990s, the New England Journal of Medicine decided that authors of its editorials and review articles should have no financial interests in the companies whose products are discussed in the journal. This policy had to be revised in 2002 because of the difficulties in finding authors with no conflicts of interest. In a two-year period the journal was only able to publish one article about a new drug therapy.[8] If finding authors with no conflict of interest is difficult in the USA, with its huge population, how hard will it be in Australia? With limited access to other sources of funding, it is highly likely that anyone involved in researching new drugs in Australia will have received some support from a pharmaceutical company.

During 2014 *Australian Prescriber* published 35 editorials and articles. In 11 of these, one or more authors declared an interest. Should we be as

From the Editor

Welcome to the 40th anniversary year of *Australian Prescriber*. While there have been many advances since 1975, the clinical challenges are similar. Mary Stewart and Kirsten Black advise on how to choose a combined contraceptive pill, while Barry McGrath discusses the diagnosis of hypertension.

Vitamin D testing is more frequent nowadays, but Paul Glendenning explains the problems in measuring vitamin D concentrations. Measuring the QT interval on the ECG can also be problematic and Geoffrey Isbister reviews the risks related to QT prolongation.

1975 also saw the first publication of the bulletin of the Adverse Drug Reactions Advisory Committee in *Australian Prescriber*. The successor to that publication, Medicines Safety Update, has appeared in *Australian Prescriber* since 2010, but this issue will be the last in print. Medicines Safety Update will continue to be available on the website of the Therapeutic Goods Administration.

All our authors are asked to declare any conflicts of interest. While this was not routine practice in 1975, it is a common cause for concern in modern medical publishing. Managing any competing interests is one way *Australian Prescriber* will continue to provide independent information 40 years on.

concerned about an author who declares funding from the National Health and Medical Research Council as we might be about someone who obtains research funding from a pharmaceutical company? What about an author who works in an academic institution that holds a global licence for a product? Should we exclude someone who is an adviser to the Therapeutic Goods Administration, but has also been an adviser to industry? There are many possible questions about potential conflicts of interest, but the Editorial Executive Committee believes that those 11 articles should still have been published.

While publishing declarations of interest at the end of articles may not solve all the difficulties of competing interests, it informs readers. Journal readers are quick to comment if their perceptions about a conflict of interest differ from those of the authors.[9-12]

The Editorial Executive Committee does not think it should refuse to deal with people who may be very knowledgeable about a treatment because they have participated in industry-funded research. Often their expertise is the source of the conflict. Although assessing conflicts of interest can be difficult, the Editorial Executive Committee believes that the disclosure and peer-review processes of *Australian Prescriber* should mitigate the risk of bias.

Competing interests are everywhere, but they can be managed. ◄

John Dowden is Editor of Australian Prescriber.

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Letters to the Editor

Janus kinase inhibitors – holistically seeing two faces

Editor, - I was interested to read the recent article on Janus kinase inhibitors by Paul Kubler (Aust Prescr 2014;37:154-7). In addition to being pro-cancer, the Janus kinase-Signal Transducer and Activation of Transcription (JAK-STAT) pathway is part of a central physiological pro-survival mechanism.[1] Thus pharmacological targeting of this signalling cascade may pose potential threats, for example to cardiac integrity.[2] Targeting JAK-STAT will also potentially challenge neuroprotection.[3] Conversely, activation of JAK-STAT is proposed as a tangible approach to managing heart disease.[4]

The message is that there is a clinically highly relevant 'crossroads' between physiology and cancer, thus maintaining the truly holistic viewpoint. Therefore treatments aimed at targeting cancer necessarily target normal tissues and in turn define burgeoning fields within cancer-related therapy such as cardio-oncology. Activating a pro-survival pathway such as JAK-STAT therapeutically to manage heart disease removes a barrier in the multiple-step process of oncogenesis. Targeting the JAK-STAT pathway is in a sense 'non-specifically specific'. The target may be a defined one, but the target itself is universally expressed.

Future developments in therapeutics must be designed to be 'specifically specific' to the disease target to be effective, yet with little fear of resultant adverse reaction.

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The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

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Paul Kubler, the author of the article, comments:

It is not surprising that therapies targeting the JAK-STAT pathway have the potential for diverse applications, as over 500 kinases have been identified in the human kinome. Janus kinases belong to the tyrosine kinase family, of which there are at least 90 recognised members.

Although there is a large volume of published data about the JAK-STAT pathway, it is mostly pre-clinical. Currently, very few drugs targeting Janus kinase signalling have been approved by regulatory authorities and are in clinical use. The focus of the article was on those mechanisms which have current clinical applications.

The statement of whether specifically targeting selective errors of the immune system (that is being specifically specific) versus inhibiting multiple cytokines (that is being non-specifically specific) is a better way of improving effectiveness and reducing adverse effects, is a vexed question with no clear answer. The clinical data in the treatment of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus do not consistently support this hypothesis. The patho-aetiology of many autoimmune diseases is characterised by multiple abnormalities of the immune system with cascading effects over time and alternative pathways of disease perpetuation after onset, hence I would suggest specifically specific therapies are less likely to be effective from a biological plausibility perspective as the disease progresses. If we could identify and treat disease in a pre-clinical phase, specifically specific therapies have the potential to be more effective. However, the answer to this is unknown.

Cost shifting and the quality use of medicines

Editor, – The recent editorial by Andrew McLachlan (Aust Prescr 2014;37:110-1) overlooked an interesting point about reforms to the Pharmaceutical Benefits Scheme (PBS) in public hospitals. In some states, the reforms have seen patients discharged with one month's supply of their medications, in place of the traditional few days' supply currently given in hospitals not affected by the reform.[1] The model of minimal supply forces patients to visit their GP and pharmacy as soon as possible after discharge.[1] This has significant impacts on continuity of care – if a month is left from discharge to visiting their GP, problems due to changes in medications at discharge may not be identified.[1,2]

PBS reform is intended to decrease confusion about changes to medications. However, it will not achieve this as hospitals will continue to keep only the single contracted brand of medication and there may be an increase in readmissions due to patients not being followed up by the GP after discharge.[1] Further to this, the PBS reforms in public hospitals have given pharmacy departments the opportunity to profit from patients' discharge medications, causing hospital pharmacies to focus on supply rather then clinical practices.[3,4] This draws pharmacists away from important clinical roles including medication safety, counselling and education services, not to mention liaison with community services including the GP and pharmacy about the changes to patients' medication regimens.[3,4]

Given that it has been shown that clinical pharmacists in hospitals reduce adverse drug events and improve patient safety, funding systems should focus on streamlining processes, community liaison and integration with community-based programs, not on increasing the burden on already short-staffed hospital pharmacy departments.[3,4]

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Andrew McLachlan, author of the article, comments:

Mary Wilkin has identified some important realities and possible implications related to medication access and transition of care. Her comments about the possibility of continued confusion related to medicines, and remuneration shifting the clinical role of pharmacists is well made and further highlights the need to carefully consider the implication of change in a complex health system. Mary Wilkin's letter further highlights the

need to design well thought out solutions guided by relevant medicines policy.

Ian Coombes, Director of Pharmacy, Royal Brisbane and Women's Hospital, and member of the Australian Prescriber Editorial Executive Committee

Mary Wilkin has highlighted that there are risks when introducing Pharmaceutical Benefits Scheme (PBS) reforms to public hospitals. The reforms could shift the pharmacy's focus towards satisfying PBS regulations for reimbursement. This raises questions about the purpose of each pharmacy department. If public hospitals do not focus on patient-centred review, reconciliation and facilitation of medication liaison with primary care, the quality use of medicines is at risk.

I believe our department learnt the harsh reality that if the hospital pharmacy's primary role becomes dispensing PBS prescriptions and it focuses more on optimising our reimbursement than ensuring appropriateness, then safety and continuity of treatment become secondary. This places the patients at risk of adverse events.[1]

As a result of our experience, we chose to actively disinvest in dispensing drugs at discharge where feasible without compromising patient care. We realigned our roles on ensuring early clinical review, completion of medication action plans and close collaboration with patients, carers and hospital staff to optimise medication outcomes in hospital. On discharge our goal is to reconcile all PBS discharge prescriptions and only dispense what is required. We should focus on providing medication information for patients and carers and facilitating medication liaison with the primary care team.

Pharmacy has to use any healthcare reforms as a trigger to re-evaluate its role in a complex system in order to maintain its ability to optimise the quality use of medicines. As we stated in our previous article, 'a focus on tasks and processes in hospitals runs the risk of removing the patient as the focus of care.'[1]

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Book review

AMH Aged Care Companion

This companion is intended primarily for general practitioners, nurses and pharmacists working in aged-care settings. It is also relevant to the care of frail older people living in the community.

The book contains almost 70 chapters, each addressing one or more common clinical problems in aged care. The chapters are arranged by organ system, and structured to cover key diagnostic issues, considerations before starting treatment, non-drug and drug treatments, safety and useful resources. The book has a number of helpful tables and appendices. The advice is based on best available evidence, although neither this nor the recommendations are graded. The Editorial Advisory Committee and reviewers are an impressive group of experts.

It is odd that there is no chapter about chronic kidney disease. Prescribing in renal impairment is discussed briefly in the introduction, but with no mention of strategies to slow progression or avoid nephrotoxicity (although the risk from non-steroidals is stated in the chapter on osteoarthritis).

The other notable gap is lack of a chapter on quitting smoking. Although a number of the chapters recommend smoking cessation, nicotine replacement and other pharmaceutical aids are not discussed.

Some chapters are more comprehensive than others. The chapter on depression recommends psychosocial interventions and physical activity, but does not mention other lifestyle changes, including quitting smoking and a healthy diet, for which there is growing evidence. The chapter on diabetes does not discuss management of albuminuria. Absolute vascular risk assessment and management is a particularly challenging area in elderly patients but is not covered in detail. A future edition of the companion could usefully provide more comprehensive guidance.

Any textbook is inevitably incomplete. The Aged Care Companion is of undoubted value in the care of older people, but even alongside the Australian Medicines Handbook does not provide all the answers.

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Choosing a combined oral contraceptive pill

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CPD

FOR PHARMACISTS

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SUMMARY

The combined oral contraceptive pill is an effective contraceptive method which can also offer other benefits. However, other contraceptive options should be discussed. If the pill is the chosen method, prescribe a pill with the lowest effective dose of oestrogen and progestogen.

Pills containing levonorgestrel or norethisterone in combination with ethinyloestradiol 35 microgram or less are considered first-line. They are effective if taken correctly, have a relatively low risk of venous thromboembolism, and are listed on the Pharmaceutical Benefits Scheme.

The pill is usually taken in a monthly cycle. Some women may prefer an extended pill regimen with fewer or no inactive pills.

Introduction

The combined oral contraceptive pill contains oestrogen and progestogen. It was introduced into Australia just over 50 years ago. Australia was the second country in the world to have access to 'the pill'. Women rapidly adopted the pill as it allowed the reliable separation of sex and reproduction and gave them the opportunity to plan when to have children. Since then the pill has been further developed to ensure good efficacy while minimising the adverse effects.

A key advance was a decrease in the dose of oestrogen to the currently used low-dose formulation (standard dose of ≤35 microgram ethinyloestradiol).[1] Subsequently it has been found that formulations with ethinyloestradiol 20 microgram are likely to be as effective as the 30–35 microgram pills while possibly reducing the oestrogenic effects such as nausea, bloating and breast tenderness.[2] However, there may be an increase in unscheduled bleeding.[3] More recent developments, which may improve the safety and efficacy of the combined oral contraceptive pill, include using oestradiol instead of ethinyloestradiol and extended pill regimens with fewer or no inactive pills.[4–6]

The pill today

The pill is the most commonly used contraceptive method and approximately 50–80% of Australian women use it at some stage during their reproductive lives.[7] There is now a large range of products available with over 30 different registered brands. While many of these pills contain similar hormones and doses, there are multiple formulations for the prescriber to consider (Table 1). These pills contain an oestrogen component (ethinyloestradiol, mestranol, oestradiol or its pro-drug oestradiol valerate) and a progestogen (levonorgestrel, norethisterone, gestodene, desogestrel, drospirenone, nomegestrol, dienogest or cyproterone).

Oestrogens

Ethinyloestradiol, a derivative of 17 beta-oestradiol, has been the predominant oestrogen in contraceptive pills because of its high oral bioavailability. Until recently oestradiol had not been used due to its rapid inactivation by the liver, short half-life and the occurrence of breakthrough bleeding when combined with older progestogens. However, formulations that combine oestradiol (1.5 mg) in a micronised form with a newer progestogen (nomegestrol) appear to offer good cycle control.[8] Oestradiol has also been combined with a synthetic ester in the form of oestradiol valerate to improve its oral bioavailability and extend its half-life.[9] At the doses prescribed in pills, oestradiol may have a more favourable impact on haemostasis and lipid and carbohydrate metabolism (and therefore on cardiovascular risk) when compared with ethinyloestradiol.[10,11] However, there is insufficient evidence to preferentially prescribe these pills to women with cardiovascular risk factors.[12]

Progestogens

Pills containing levonorgestrel or norethisterone have been used since the 1960s. The combination of these progestogens with 35 microgram or less of ethinyloestradiol is considered the 'gold standard' in relation to their safety profile. As most of these combinations are listed on the Pharmaceutical Benefits Scheme (PBS) they are an effective first-line option for women preferring an oral contraceptive.

Newer progestogens such as gestodene and desogestrel are structurally related to progesterone, but have greater specificity for progesterone receptors than the older progestogens. They reduce the potential for androgenic, oestrogenic and glucocorticoid effects. Drospirenone is a

Table 1   **Combined oral contraceptive pills**

Brand name	Oestrogen	Progestogen	PBS listing
Femme-Tab ED 20/100 Microgynon 20 ED Microlevlen ED Loette Micronelle 20 ED	20 microgram ethinyloestradiol	100 microgram levonorgestrel	Only Femme-Tab ED 20/100 PBS listed
Femme-Tab ED 30/150 Levlen ED Microgynon 30 ED Monofeme Nordette Evelyn 150/30 ED Eleanor 150/30 ED Micronelle 30 ED	30 microgram ethinyloestradiol	150 microgram levonorgestrel	PBS listed
Microgynon 50 ED	50 microgram ethinyloestradiol	125 microgram levonorgestrel	
Logynon ED Trifeme 28 Triphasil Triquilar ED	6 x 30 microgram ethinyloestradiol 5 x 40 microgram ethinyloestradiol 10 x 30 microgram ethinyloestradiol	6 x 50 microgram levonorgestrel 5 x 75 microgram levonorgestrel 10 x 125 microgram levonorgestrel	
Brevinor 21 and 28 Day Norimin 28 Day	35 microgram ethinyloestradiol	500 microgram norethisterone	PBS listed
Brevinor-1 21 and 28 Day Norimin-1 28 Day	35 microgram ethinyloestradiol	1000 microgram norethisterone	
Norinyl-1 21 and 28 Day	50 microgram mestranol	1000 microgram norethisterone	
Improvil 28 Day Synphasic 28	7 x 35 microgram ethinyloestradiol 9 x 35 microgram ethinyloestradiol 5 x 35 microgram ethinyloestradiol	500 microgram norethisterone 1000 microgram norethisterone 500 microgram norethisterone	
Marvelon 28 Madeline	30 microgram ethinyloestradiol	150 microgram desogestrel	Not PBS listed
Minulet	30 microgram ethinyloestradiol	75 microgram gestodene	
Brenda-35 ED Carolyn-35 ED Diane-35 ED Estelle-35 ED Jene-35 ED Juliet-35 ED Laila-35 ED	35 microgram ethinyloestradiol	2 mg cyproterone acetate	
Yaz Yaz Flex	20 microgram ethinyloestradiol	3 mg drospirenone	
Isabelle Petibelle Yasmin	30 microgram ethinyloestradiol	3 mg drospirenone	
Valette	30 microgram ethinyloestradiol	2 mg dienogest	
Qlaira	2 x 3 mg oestradiol valerate 5 x 2 mg oestradiol valerate 17 x 2 mg oestradiol valerate 2 x 1 mg oestradiol valerate	– 5 x 2 mg dienogest 17 x 3 mg dienogest –	
Zoely	1.5 mg oestradiol	2.5 mg nomegestrol acetate	

PBS Pharmaceutical Benefits Scheme

spironolactone analogue and has a mild diuretic effect. Cyproterone has anti-androgenic effects which may be beneficial in women with severe acne.

Guiding pill prescription

The guiding principles when considering which pill to prescribe for an individual woman are to choose a formulation that:

- has the lowest dose of oestrogen and progestogen to provide good cycle control and effective contraception
- is well tolerated
- has the best safety profile
- is affordable
- offers additional non-contraceptive benefits if desired.

Effective regimens

The first available formulation of the combined oral contraceptive pill contained 50 microgram of ethinyloestradiol for cycle control. However, an association between the pill and venous thromboembolism soon emerged. This was due to the effect of oestrogen on the synthesis of clotting factors.[13] To mitigate this risk, and reduce oestrogenic adverse effects, the dose of ethinyloestradiol was reduced to 35 and 30 microgram and more recently 20 microgram without an apparent loss of contraceptive efficacy.[3]

> Women with significant risk factors for venous thromboembolism are not suitable for any combined hormonal method

The pills available in Australia are mostly in 28-day packs with 21 active and 7 inactive pills, to mimic the menstrual cycle. Some formulations contain 24 active and 4 inactive pills (24/4 regimes) which may reduce the chance of contraceptive failure and breakthrough ovulation.[4] Extended pill-taking regimens are used by many women to delay or avoid a withdrawal bleed. This is most easily achieved with monophasic regimens in which each active pill contains the same amount of oestrogen and progestogen and the inactive pills are skipped. Typically this is done for three months at a time. Indeed evidence is available to support the safety of continuous use of the contraceptive pill for up to 12 months.[14]

Another approach is called a 'menstrually signalled' regimen. Women take the pill continuously until they experience four days of vaginal spotting or bleeding after which they have a four-day pill break.

Triphasic pills are commonly prescribed in Australia, but have no evidence-based advantage over monophasic pills in relation to their adverse effect profile or cycle control. A quadriphasic combined oral contraceptive pill that contains oestradiol valerate and desogestrel is formulated with an oestrogen step-down and progestogen step-up sequence.[15]

The pill is a user-dependent method. Its failure rate therefore differs between 'perfect use' (0.3% annually) by women who take it consistently and correctly and 'typical use' (9% annually) when the pill is used inconsistently or incorrectly.[16]

Safety and tolerability

Long-term cohort studies show that, compared to non-users of the combined oral contraceptive pill, users have lower rates of death from any cause. They also have significantly lower rates of death from cancer, cardiovascular disease and other diseases.[17]

Women may experience a range of adverse effects and managing these can be challenging. Table 2 outlines some common adverse effects and strategies that may improve the symptoms should the woman wish to continue with the pill.

Although trying another oral formulation can be helpful, sometimes a change to another form of contraception may be appropriate. This includes a progestogen-only method, such as the contraceptive implant or levonorgestrel intrauterine system, or the non-hormonal copper intrauterine device. These long-acting reversible contraceptive methods are much more effective at preventing unintended pregnancy compared to the pill. They should be discussed with all women requesting contraception, particularly those who cannot take the pill because of adverse effects or identified risk factors or who find it difficult to remember to take the pill daily.

The combined oral contraceptive pill is not recommended during lactation as it may affect breast milk volume.

Venous thromboembolism

There is a risk of venous thromboembolism associated with the combined hormonal contraception, but the risk is much less than that during pregnancy and the immediate postpartum period. Non-users of hormonal contraception have a baseline risk for venous thromboembolism of around 20 per 100 000 woman-years. Current research points to a three-fold increased risk of venous thromboembolism for women using a combined pill over baseline (Table 3).[19,20]

Women should be informed of the risk of venous thromboembolism with combined oral contraceptive pills and be aware of the signs. The factors that influence the risk include age, smoking, body mass index, immobilisation, and a personal or family history of thromboembolism or thrombogenic mutations. These factors need to be assessed when considering

Table 2 **Managing common adverse effects associated with the combined oral contraceptive pill**

Problem	Management strategies based on practice
Nausea	Reduce oestrogen dose Exclude pregnancy Take pills at night Change to progestogen-only method
Breast tenderness	Reduce oestrogen and/or progestogen dose Change progestogen Consider using a pill containing drospirenone
Bloating and fluid retention	Reduce oestrogen dose Change to progestogen with mild diuretic effect (i.e. drospirenone)
Headache	Reduce oestrogen dose and/or change progestogen If headache occurs in hormone-free week, consider: • extended use or • giving oestradiol 50 microgram transdermal patch in this week or • try oestradiol valerate/dienogest pill[18]
Dysmenorrhoea	Extended pill regimen to reduce the frequency of bleeding
Decreased libido	No evidence supports a benefit of one type of oral contraceptive pill over another
Breakthrough bleeding	If taking an ethinyloestradiol 20 microgram pill, increase oestrogen dose to a maximum of 35 microgram Change progestogen if already taking an ethinyloestradiol 30–35 microgram pill Try another form of contraception. Consider the vaginal ring.

Table 3 **Risk of venous thromboembolism** [19,20]

	Rate of venous thromboembolism per 10 000 women–years (10 000 women studied for one year)
Non contraceptive users and not pregnant	2
Oral contraceptive users of pills	7–10
Pregnancy	29
Immediately postpartum	300–400

the safety of the combined oral contraceptive pill. If a woman has a significant risk factor for venous thromboembolism, she is not suitable for any combined hormonal method. Progestogen-only methods are safer for women with risk factors for venous thromboembolism.

The risk of venous thromboembolism appears to vary with oestrogen dose and progestogen type. Pills containing 50 microgram ethinyloestradiol have the highest risk. Compared with pills containing levonorgestrel, those with desogestrel, gestodene, cyproterone acetate and drospirenone may have a higher risk, although the evidence is conflicting.[21-23]

Arterial disease

Combined oral contraceptive pills are associated with an increase in the risk of myocardial infarction and ischaemic stroke. While the odds ratio for these events is around 1.7 (compared to non-users), the absolute risk is very low and depending on age lies between 2 and 20 per million women.[24-26]

Women with significant risk factors for arterial disease such as a personal history of arterial disease, obesity, smoking (if over 35 years old), migraine with aura, diabetes with vascular complications or uncontrolled hypertension should not use any combined hormonal method.[27]

Affordability

Only the pills containing levonorgestrel and norethisterone are listed on the PBS (Table 1). The out-of-pocket expense for a four-month subsidised supply is approximately $20 compared to up to $120 or more for the newer non-PBS-listed pills.

Non-contraceptive benefits

There is not a great deal of evidence for the benefit of one pill type over another. Although the newer combined oral contraceptives have been marketed on their non-contraceptive benefits, it is important to understand which claims are well substantiated.

Acne and hirsutism

Most women with acne and hirsutism find that their skin improves when they take the combined oral contraceptive pill. This is in part because of a rise in sex hormone binding globulin. Pills containing cyproterone acetate, drospirenone, gestodene or desogestrel are often recommended, but the evidence for a benefit over levonorgestrel-containing pills is limited.

The pills containing cyproterone acetate and ethinyloestradiol appear to improve acne (judged by inflammatory lesions and global assessments) better than those containing levonorgestrel.[28] Studies comparing pills containing cyproterone acetate with pills containing drospirenone, gestodene or desogestrel have had conflicting results.[29] Women with hirsutism may benefit from pills containing one of the anti-androgenic progestogens, including cyproterone acetate or drospirenone, which have been found to result in improvements in clinical hirsutism scores.[30]

Heavy menstrual bleeding

All combined contraceptive pills can reduce the duration and heaviness of menstrual blood loss. Extending the days women take active pills while reducing or eliminating inactive pills can be useful for heavy menstrual bleeding.

The oestradiol valerate with dienogest pill has a quadriphasic regimen which reduces menstrual blood loss through its effect on the endometrium. It has an indication for the management of heavy menstrual bleeding. This pill appears to be more effective at reducing the number of days of bleeding and the amount of blood loss when compared to combinations of ethinyloestradiol and levonorgestrel.[10,31,32]

Premenstrual syndrome and premenstrual dysphoric disorder

Menstrual-related symptoms are commonly reported, but a proportion of women will experience more severe cyclic symptoms, known as premenstrual syndrome. A further subset of women will experience severe dysphoric symptoms, which have been labelled as premenstrual dysphoric disorder.

Combined oral contraceptives, by regulating hormonal fluctuations, improve the physical symptoms of menstruation such as breast discomfort and primary dysmenorrhoea, but there is little evidence on their effect on mood and behavioural symptoms.[33] The exception is the pill containing drospirenone 3 mg plus ethinyloestradiol 20 microgram, which may be more effective in treating severe premenstrual symptoms. Compared to placebo, it has been found to reduce impairment in productivity, social activities and relationships.[34,35]

Conclusion

Contraceptive counselling should involve the provision of evidence-based information on the safety, efficacy, advantages and disadvantages of all methods of contraception. This enables women to make choices based on their personal preferences and medical suitability.

All combined oral contraceptive pills in Australia have high efficacy provided they are taken regularly. There is little evidence for superior non-contraceptive benefits of the newer pills. The pills containing levonorgestrel or norethisterone in combination with ethinyloestradiol at doses equal to or below 35 microgram are considered first-line due to their possible lower risk of venous thromboembolism and their PBS listing. Other pills can be used if adverse effects develop, however 50 microgram pills are not recommended due to the risk of venous thromboembolism. ◄

Q:

SELF-TEST QUESTIONS

True or false?

1. Users of the combined oral contraceptive pill have a higher cancer mortality rate than other women.

2. The risk of venous thromboembolism is higher with combined oral contraceptive pills containing 50 microgram ethinyloestradiol compared to those containing 35 microgram or less.

Answers on page 35

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Measuring vitamin D

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Key words

vitamin D tests,
vitamin D deficiency,
vitamin D supplements,
25-hydroxyvitamin D

SUMMARY

When assessing vitamin D status, measure serum 25-hydroxyvitamin D concentration as this reflects total body vitamin D reserves.

Recent Australasian guidelines outline who should be tested for vitamin D deficiency, who should be treated and when repeat testing should be performed.

A 25-hydroxyvitamin D threshold of at least 50 nanomol/L at the end of winter is a suitable treatment target. Measurement can be repeated after three months of repletion, and thereafter less frequently unless new risk factors for vitamin D deficiency arise.

When interpreting vitamin D pathology reports, practitioners should be aware that some laboratories quote reference limits which are based on overseas rather than Australian guidelines.

Introduction

Vitamin D is an important hormone required for bone and muscle development as well as preservation of musculoskeletal function.[1,2] Vitamin D deficiency can be detected by measuring 25-hydroxyvitamin D in serum.

Vitamin D physiology

Multiple metabolites of vitamin D are present in the circulation (see Fig.). Vitamin D is synthesised in the skin following ultraviolet B radiation exposure. It can also be obtained from the diet. There are two major circulating forms of vitamin D: 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. Two steps are involved in the metabolic activation of vitamin D in the body. The second step produces 1,25-dihydroxyvitamin D and occurs in the kidney plus many other body tissues.

Vitamin D has three main functions:

- enhancing intestinal calcium and phosphate absorption
- inhibiting parathyroid hormone production
- formation and mineralisation of bone.

While 1,25-dihydroxyvitamin D is the functionally active vitamin D metabolite, deficiency is defined according to the measured concentration of circulating 25-hydroxyvitamin D. The serum concentration of 25-hydroxyvitamin D and not 1,25-dihydroxyvitamin D is associated with fracture risk.[1] 25-hydroxyvitamin D is a good reflection of substrate available for local synthesis of 1,25-dihydroxyvitamin D. Due to diminishing ultraviolet B light exposure, 25-hydroxyvitamin D concentrations decline in winter.

Vitamin D deficiency

Moderate to severe vitamin D deficiency (25-hydroxyvitamin D <30 nanomol/L) is causally associated with osteomalacia and rickets in children. Mild vitamin D deficiency (25-hydroxyvitamin D <50 nanomol/L) was first associated with hip fracture and subsequently other osteoporotic fractures. Correction of vitamin D deficiency and adequate calcium intake have been cornerstones of osteoporosis management. Most evidence for fracture reduction with current antiresorptive therapies has been from trials where participants were vitamin D and calcium replete, or if not, they were receiving adequate supplementation.

Vitamin D receptor expression has been found in tissues other than bone. Conversion to the active metabolite can be achieved through local enzymatic action. Consequently, vitamin D may exert paracrine or autocrine extra-skeletal effects.[3] These effects have generated much research but most studies are observational. Outcomes from these studies have several inherent biases. The major bias is that illness can result in reduced outside activities, diminished sunlight exposure and low 25-hydroxyvitamin D. Low concentrations of 25-hydroxyvitamin D could be a consequence, rather than a cause, of disease. Two recent systematic reviews have concluded there is insufficient evidence to establish a role for vitamin D replacement in extra-skeletal disease. Several large randomised clinical trials in Australia and overseas are planned or underway and may help resolve this issue definitively.[4,5]

When should 25-hydroxyvitamin D be measured?

The Royal College of Pathologists of Australasia published a position statement to clarify the role of vitamin D testing in vitamin D deficiency, with guidelines for who should be tested, and when repeat testing should be performed.[6] The recommendations, broadly consistent with current evidence, advocate testing in individuals at increased risk of vitamin D deficiency and provide clinical indications for vitamin D measurement (see Box).
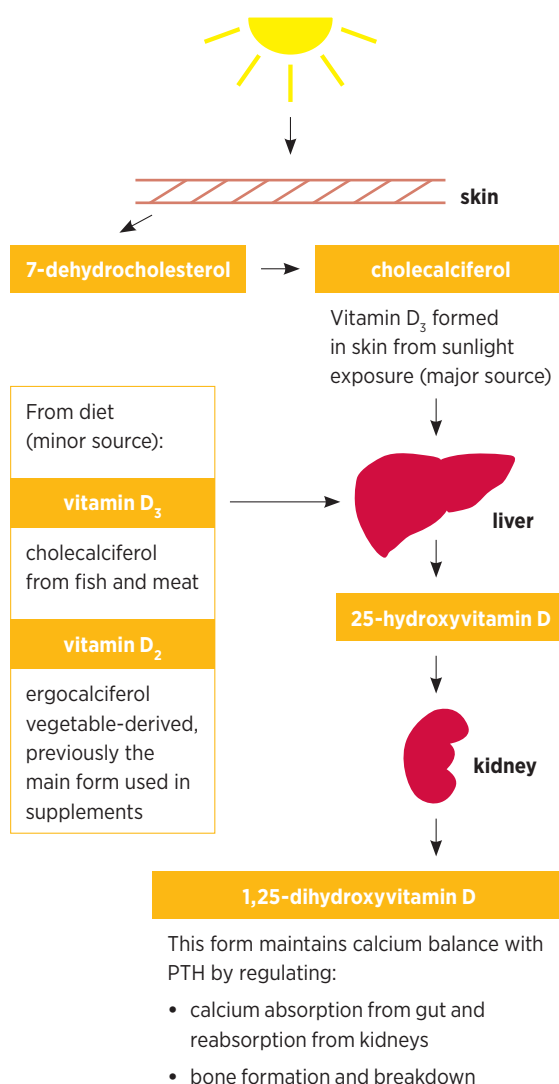
Re-testing

Repeat testing is commonly advised, because the nadir of parathyroid hormone suppression following supplementation with cholecalciferol (25-hydroxyvitamin D_3) can take at least three months and the response can vary between individuals. Consequently, repeat testing after three months is recommended in most guidelines. In patients already taking long-term replacement (including when combined with other treatments such as a bisphosphonate) or those who have a higher fracture risk, repeat testing annually at the end of winter may be helpful, especially if risk factors for vitamin D deficiency have changed.

Methods of measuring 25-hydroxyvitamin D

Initial methods using liquid chromatography or competitive protein binding were cumbersome and not suited to routine laboratory analysis. Subsequent assays used a simpler extraction method which separated 25-hydroxyvitamin D from its binding protein and allowed quantification of total 25-hydroxyvitamin D using a radio-labelled antibody.

Fig. **Vitamin D metabolism**

From diet (minor source):

vitamin D_3
cholecalciferol from fish and meat

vitamin D_2
ergocalciferol vegetable-derived, previously the main form used in supplements

Vitamin D_3 formed in skin from sunlight exposure (major source)

This form maintains calcium balance with PTH by regulating:
- calcium absorption from gut and reabsorption from kidneys
- bone formation and breakdown

PTH   parathyroid hormone

Box   **Major risk factors for vitamin D deficiency** [6]

Adults
- Signs, symptoms and/or planned treatment of osteoporosis or osteomalacia
- Increased alkaline phosphatase with otherwise normal liver function tests
- Hyperparathyroidism, hypo- or hypercalcaemia, hypophosphataemia
- Malabsorption (e.g. cystic fibrosis, short bowel syndrome, inflammatory bowel disease, untreated coeliac disease, bariatric surgery)
- Deeply pigmented skin, or chronic and severe lack of sun exposure for cultural, medical, occupational or residential reasons
- Drugs known to decrease 25-hydroxyvitamin D (mainly anticonvulsants)
- Chronic renal failure and renal transplant recipients

Children
- Signs, symptoms and/or planned treatment of rickets
- Infants of mothers with established vitamin D deficiency
- Exclusively breastfed babies in combination with at least one other risk factor
- Siblings of infants or children with vitamin D deficiency

However, as test requests increased, this manually intensive method became impractical.

Automated assays use a variety of proprietary reagents to release 25-hydroxyvitamin D from its binding protein, and different antibody detection methods. These methods have been problematic and subject to interference from other antibodies present in the sample. These can cause falsely high results, or suboptimal release of 25-hydroxyvitamin D from its binding protein resulting in falsely low results. Initial automated immunoassays were also not optimally standardised.[7]

To resolve these limitations, newer assays using liquid chromatography and more specific detectors containing two mass spectrometers were developed. These methods have not been widely adopted as they require expensive hardware and technical expertise. The lack of a reference standard also meant that disagreement between these methods was still a problem.

The US National Institute for Standards and Technology developed separate serum-based standard reference materials to help minimise inter-method disagreement and reduce bias. A reference method using liquid chromatography tandem mass spectrometry measurement from the University of Ghent has been adopted by the US Centers for Disease Control and Prevention. The first vitamin D standardisation certification program administered by the US Centers for Disease Control and Prevention is now in place. More than eight methods have achieved certification in this program including several automated, commercially available immunoassays. To achieve annual certification, tests must have a bias of ±5% (closeness to the true result) and an imprecision (reproducibility) of 10% or less. Consequently, routine immunoassay methods are improving and inter-method disagreement is diminishing as testified in external quality assurance programs, such as the one administered by the Royal College of Pathologists of Australasia and the Australasian Association of Clinical Biochemists. All Australian laboratories providing routine laboratory testing are required to be enrolled in appropriate external quality assurance programs.

What is the target concentration of 25-hydroxyvitamin D?

Surrogate measures indicate that a 25-hydroxyvitamin D threshold of 50 nanomol/L is a suitable target for treatment. Supplementation of patients at highest risk for fracture should aim to achieve above this target.

No clinical studies investigating the effectiveness of calcium and vitamin D treatment on fracture reduction have recruited people based on their 25-hydroxyvitamin D concentrations. Also, no intervention studies with calcium and vitamin D targeted the 25-hydroxyvitamin D concentration required for fracture prevention. Consequently, the threshold of 50 nanomol/L is determined by surrogate measures which relate fracture risk factors to vitamin D concentrations.

Fractures

An observational study of American women found hip fractures were more common in women with 25-hydroxyvitamin D concentrations below 47.5 nanomol/L.[8]

Parathyroid hormone

Parathyroid hormone was the first biomarker to indicate that a 25-hydroxyvitamin D threshold of 50 nanomol/L was adequate based on the change in parathyroid hormone with cholecalciferol and calcium therapy.[9] This threshold has been verified in a larger study.[10]

Bone turnover markers and bone density

Data using biochemical bone turnover markers show that the 25-hydroxyvitamin D threshold for higher bone resorption and hence higher fracture risk is closer to 50 nanomol/L than to 75 nanomol/L.[11]

Data from over 1200 community-dwelling men over the age of 65 years found a 25-hydroxyvitamin D below 49 nanomol/L was associated with higher rates of loss of hip bone density.[12]

Calcium absorption

The change in serum calcium following oral calcium loading has been used as a surrogate measure of fractional calcium absorption.[13] This estimate is less accurate than dual stable isotopic calcium studies which use two calcium isotopes – one isotope is ingested and one is infused to correct for renal and gastrointestinal recycling. A study assessing fractional calcium absorption (using dual stable isotopic calcium) in individuals before and after cholecalciferol supplementation found that absorption was 3% higher when 25-hydroxyvitamin D was above 100 nanomol/L compared to when it was 55 nanomol/L, a negligible difference.[14]

Interpreting test results

Practitioners should pay attention to the measured amount of 25-hydroxyvitamin D but be cautious of quoted reference limits reported by some laboratories. The different threshold limits quoted by laboratories are not due to methodological differences, but to differences in the interpretation of data from surrogate measures and to the use of overseas, rather than Australian, guidelines.

Vitamin D supplementation

Most supplements in Australia provide cholecalciferol 500–1000 IU (vitamin D$_3$) either as a single supplement or combined with calcium. Some clinicians advise a higher dose in patients with severe vitamin D deficiency (25-hydroxyvitamin D <12.5 nanomol/L) compared with less severe forms. A higher dose may also be required in patients taking anticonvulsant drugs, those with obesity or nephrotic syndrome, or following biliopancreatic bypass surgery.

Daily calcium with 800 IU of cholecalciferol was effective at preventing non-vertebral and hip fractures in elderly French women.[15] In a West Australian study of hip fractures in patients with vitamin D deficiency, a daily dose of cholecalciferol 1000 IU was sufficient to attain 25-hydroxyvitamin D concentrations greater than 50 nanomol/L in patients adherent to treatment.[16]

Evidence from an Australian randomised controlled study in 2200 women at high risk of hip fracture has questioned the use of annual high-dose cholecalciferol therapy.[17] Risk was based on maternal history of hip fracture, past personal fracture history or self-reported falls. Women receiving oral cholecalciferol 500 000 IU annually experienced 26% more fractures than those receiving placebo. This was attributed to a 31% higher rate of falls in the first three months after dosing. In view of these results, daily, weekly or even monthly vitamin D replacement therapy can probably be safely used, but annual high-dose replacement should be avoided.

Conclusion and recommendations

Vitamin D is one of the most commonly requested tests. Replacement of vitamin D should be started when circulating levels of 25-hydroxyvitamin D are low (<50 nanomol/L at the end of winter) and when patients are at increased risk of falls or fractures. Annual testing of 25-hydroxyvitamin D at the same laboratory, at the end of winter in patients who are concerned about fracture risk or falls is appropriate management in 2014. ◁

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Home monitoring of blood pressure

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SUMMARY

Home blood pressure monitoring is the self-measurement of blood pressure by patients. In the diagnosis and management of high blood pressure it is complementary to 24-hour ambulatory blood pressure monitoring and clinic blood pressure measurements. Home monitoring can also help to identify white-coat and masked hypertension.

Home monitoring has good reproducibility, is well tolerated and relatively inexpensive. It is superior to blood pressure taken in the clinic in predicting cardiovascular events and mortality.

Twice-daily measurements are recommended, usually in the morning and evening for a minimum of five days. The threshold for defining hypertension is an average home blood pressure of 135/85 mmHg or above.

Patients are engaged with their management when they monitor their own blood pressure. This results in increased adherence to therapy and lower blood pressure.

Introduction

Blood pressure measurements taken by a doctor are often higher than the patient's usual blood pressure. Uncertainty surrounding a patient's blood pressure outside the doctor's office is a recognised barrier to treating hypertension in Australian general practice.[1] This uncertainty can be alleviated by using 24-hour ambulatory blood pressure monitoring.[2,3] An alternative is to instruct the patient to measure their own blood pressure for several days. This home blood pressure monitoring is more likely to reflect the patient's underlying blood pressure, than measurements in the clinic.

Rationale for home monitoring

An Australian consensus statement has promoted 24-hour ambulatory blood pressure monitoring as the reference standard for optimal care in uncomplicated hypertension.[2] However, home blood pressure monitoring has better reproducibility.[4-6] Compared with 24-hour ambulatory blood pressure monitoring, home monitoring is less expensive, much more widely available and provides information about the day-to-day variability of blood pressure.[7]

An advantage of 24-hour ambulatory blood pressure monitoring is the detection of nocturnal hypertension or 'non-dipping' blood pressure patterns, which are associated with a worse prognosis.[8] However, newer devices for home blood pressure monitoring may enable nocturnal measurements. At this stage the two methods should be considered as complementary clinical tools.

Compared to clinic measurements, home measurements are more reproducible, more strongly predict hypertensive end-organ disease,[9-12] and are stronger predictors for cardiovascular events and mortality.[13-16] Several international guidelines recommend using home blood pressure monitoring for hypertension diagnosis, evaluation of suspected white-coat hypertension and masked hypertension, and for guiding management.[7,17-19] Substantial evidence for the benefits of home blood pressure monitoring comes from studies in Japan.[19]

Method

The blood pressure measurements are recorded by the patient using a validated, automated blood pressure device. Devices with a storage memory have advantages over self-recording for ensuring the validity of measurements.

Home blood pressure is optimal when the patient takes readings while seated, around the same time each morning and evening. Monitoring is usually over a period of one week, with a five day minimum. Standing blood pressures can also be measured if needed to assess postural changes in blood pressure.

The patient should sit quietly (no talking or distractions such as television) for five minutes in a comfortable ambient temperature. The blood pressure cuff selected should be appropriate for body size. Feet should be flat on the floor, legs uncrossed, upper arm bare, back and arm supported with the cuff at heart level. Readings should not be taken if the patient feels uncomfortable, stressed or in pain. Smoking or caffeine drinks are to be avoided for 30 minutes before the measurement. Readings should be done before eating or taking medication. Two readings are taken one minute apart with the

second reading being recorded in a diary or electronic spreadsheet. The average measurement over the monitoring period is used to determine the patient's underlying blood pressure. An average weekly home blood pressure above 135/85 mmHg is considered to be the cut point for hypertension.

White-coat hypertension

White-coat hypertension is defined as a blood pressure of at least 140/90 mmHg measured at the doctor's office on at least three occasions, but with a normal blood pressure measured outside the office. An average weekly home blood pressure below 135/85 mmHg or two 24-hour ambulatory blood pressure recordings with daytime ambulatory blood pressure below 135/85 mmHg would rule out the diagnosis of hypertension.

The population prevalence of white-coat hypertension is approximately 15%.[20] It is more common in women and non-smokers and is associated with increased waist circumference, glucose intolerance, and increased left ventricular mass.[20,21] White-coat hypertension is a risk factor for sustained hypertension[22] with 36% of patients progressing to established hypertension within five years. Those who progress are more likely to have a higher waist circumference, a higher plasma glucose two hours post-loading and an increased resting aorto-femoral pulse wave velocity.

Patients with white-coat hypertension have a significantly increased risk of developing type 2 diabetes.[23-25] This highlights the importance of monitoring and managing the cardiovascular risk in white-coat hypertension, particularly glucose intolerance and obesity, and not just the blood pressure alone.

Masked hypertension

Masked hypertension is defined as a blood pressure in the clinic below 140/90 mmHg, but high blood pressure elsewhere, for example a blood pressure of 135/85 mmHg or more on home monitoring.

The population prevalence is 10–17%,[7] but may be up to 29% in untreated patients with diabetes.[26] These patients commonly have subclinical cardiovascular disease and the risk for incident cardiovascular events is similar to that of sustained hypertension.[27-29] A particular at-risk group are patients with obstructive sleep apnoea.

Thorough assessment of cardiovascular risk is key to managing masked hypertension. In addition to home monitoring, management will require 24-hour ambulatory blood pressure monitoring if there is nocturnal hypertension or non-dipping.

Blood pressure variability

Home blood pressure monitoring is a good method for assessing long-term variability in blood pressure. Increased variability and episodic hypertension have been shown to have adverse consequences in patients with stroke or transient cerebral ischaemia.[30,31] Moreover, different drug classes may have different effects on variability. This is an important area for further research.

Assessing treatment

Home blood pressure monitoring provides a reliable estimate of the effectiveness of antihypertensive treatment,[32] and the measurements are relatively unaffected by placebo.[33] Therapy guided by home blood pressure monitoring compared with usual care can lead to better blood pressure control and higher patient satisfaction with medical care.[33,34] Additional support for the patient such as educational materials or counselling increases the benefit.[35] Home blood pressure monitoring can also be used to assess the duration of the antihypertensive effect and identify hypertension that is resistant to treatment.[36]

Adherence

Home blood pressure monitoring engages the patient in their management and increases adherence to therapy.[37-40] This can lead to a lower blood pressure than standard care.[37,38] However, home blood pressure monitoring was not as successful at improving adherence to treatment in primary care as it was in hospital-based or non-clinical (community centre/workplace) settings.[41] Additional support strategies may be needed in primary care.

Cost-effectiveness

Most home blood pressure monitoring devices are relatively cheap (approximately $100), reliable and widely available. There are also lending schemes in some general practice and specialist clinics.

Home monitoring has been shown to be cost neutral, after taking into account the number of consultations, drugs, referrals, equipment and training expenses.[42] It is cost-effective in terms of reducing the drugs needed to maintain blood pressure control.[43] Telemonitoring of the measurements may be more costly, although this may be offset by having better healthcare outcomes.[44]

Adverse effects

Some patients with anxiety may become stressed about their readings, particularly if these are high, and this may affect subsequent measurements. Then there are those patients who change their treatment according to readings without medical consultation,

Q:

increasing the risk of adverse consequences. Others may become obsessed and perform excessive numbers of readings.

Conclusion

Ambulatory blood pressure monitoring is the current gold standard for assessing hypertension. Home blood pressure monitoring is a complementary method. Hypertension is diagnosed if the average of twice-daily measurements for at least five days is 135/85 mmHg or higher. Home blood pressure monitoring can help to detect patients who have white-coat or masked hypertension. As the price of blood pressure monitors reduces, home monitoring by patients will become a routine part of their management. An Australian consensus statement on the role of home blood pressure monitoring is being prepared. ◁

Conflict of interest: none declared

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Book review

Therapeutic Guidelines: Endocrinology. Version 5.

Melbourne: Therapeutic Guidelines Limited; 2014
419 pages
Electronic version also available

The strength of this guideline is its concise and yet thorough approach to the management of the more common endocrinological conditions. For example, strategies for the different types of diabetes are explained in great detail. The guidance for diabetic ketoacidosis and hyperosmolar hyperglycaemia is excellent. The numerous tables provided throughout the book are useful and easy to read.

However, there are areas of weakness. There are too many cross references throughout the book, making it difficult to read in parts. Reference to further information in the electronic version of the Therapeutic Guidelines, eTG, is common. This is problematic as not every user has access to the electronic version. I do think a guide needs to be able to stand alone.

The recommendations about blood glucose monitoring are too vague and generalised. Also, the advice on sunlight exposure for patients with vitamin D deficiency lacks detail.

Despite some shortcomings, overall I think this book is excellent. I like its pocket size format, and the treatment recommendations are detailed, practical and easy to follow. I recommend this endocrinology guide to health practitioners working in a hospital or in general practice.

Heinz Tilenius
GP
Melbourne
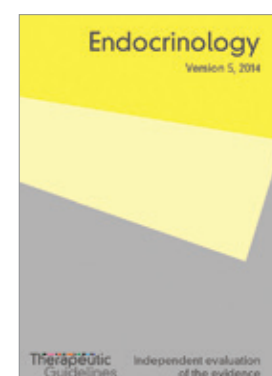
Risk assessment of drug-induced QT prolongation

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SUMMARY

Drugs can cause prolongation of the QT interval, alone or in combination, potentially leading to fatal arrhythmias such as torsades de pointes.

When prescribing drugs that prolong the QT interval, the balance of benefit versus harm should always be considered.

Readouts from automated ECG machines are unreliable. The QT interval should be measured manually.

Changes in heart rate influence the absolute QT interval. Heart rate correction formulae are inaccurate, particularly for fast and slow heart rates.

The QT nomogram, a plot of QT interval versus heart rate, can be used as a risk assessment tool to detect an abnormal QT interval.

Introduction

Over the last two decades, intense research has improved our knowledge of the mechanisms and risks of drug-induced QT prolongation.[1] Most of this research has been conducted by the pharmaceutical industry and has arisen following market withdrawals of medicines that caused torsades de pointes arrhythmia, such as cisapride and some non-sedating antihistamines. Little of this information has flowed to clinicians and there remains a paucity of clinically relevant data to guide patient management.

The QT interval is the duration between the start of the Q wave and the end of the T wave on an ECG (Fig. 1). Methods of measuring the QT interval, correcting for heart rate and determining what is an abnormal interval are outdated and provide a poor risk assessment for patients.[1] Confusion also remains about the safety and level of risk with many drugs that have been associated with QT prolongation.

Drug regulatory bodies and pharmaceutical companies have placed restrictions on some drugs which appear to have a low risk of torsades de pointes (for example quetiapine). Conversely, other drugs with clear evidence of risk have the same level of restriction (for example amisulpride).

Drugs implicated in QT prolongation and torsades de pointes

Most drugs known to cause QT prolongation block the rapid component of the delayed rectifier potassium channel. This prolongs the action potential and lengthens the QT interval (Fig. 2).[2] Delayed ventricular repolarisation will lead to early after-depolarisations, which can result in re-entrant pathways or focal activity and torsades de pointes (Fig. 3).

Many drugs have been implicated in QT prolongation, but the actual risk of this occurring is unclear in most cases. Table 1 lists common drugs which cause QT prolongation and have been associated with torsades de pointes. Other sources provide longer lists of drugs, but in many cases the evidence for QT prolongation is a single case report in which only the QTc interval (QT interval corrected for heart rate) is long. In some cases, this is due to over-correction with Bazett's formula. To complicate matters there are some drugs, such as amiodarone, that cause QT prolongation, but rarely, if ever, cause torsades de pointes.

For some drugs, such as sotalol, amisulpride and citalopram or escitalopram, there is a lot of information on the risk of QT prolongation and torsades de pointes (Fig. 4). Conversely, for other drugs such as quetiapine, venlafaxine and risperidone there is a large amount of normal QT interval data to support a very low risk of torsades des pointes.[1]

Drug interactions

QT prolongation may be due to multiple factors or more than one drug. It is important to consider both pharmacodynamic and pharmacokinetic drug interactions when prescribing drugs.

Concomitant use of two drugs that prolong the QT interval, such as escitalopram and sotalol, will

increase the risk of QT prolongation and torsades de pointes due to a pharmacodynamic interaction.

Pharmacokinetic interactions can also lead to QT prolongation, such as erythromycin inhibiting the metabolism of cisapride via cytochrome P450 (CYP) 3A4.[3]

Other factors that increase the QT interval

Congenital long QT syndromes and a number of acquired conditions cause QT prolongation. Congenital cardiac channelopathies include autosomal dominant Romano-Ward syndrome and the rarer Jervell and Lange-Neilsen syndrome.[4]

Genetics account for a large amount of the variability in the QT interval in healthy individuals.[1,5] This may explain why some individuals are more predisposed to QT prolongation. Physiological factors also influence the QT interval. Female sex and older age are associated with longer QT intervals, and there is diurnal variation in the QT interval.[6]

QT prolongation is also associated with a number of pathological conditions, including electrolyte abnormalities (hypokalaemia, hypocalcaemia, hypomagnesaemia), cardiac ischaemia, cardiomyopathies, hypothyroidism and hypoglycaemia.[1]

When is the QT interval long or abnormal?

Many different cut-offs have been suggested to determine if the QT interval is abnormal. A QT or QTc interval greater than 500 millisecond (msec) is sometimes regarded as abnormal, but this is problematic for patients with tachycardia and it is unclear which heart rate correction formula should be used.

One study of Holter measurements in healthy volunteers showed that the 95% confidence limit of the average 24-hour QTc interval was 440 msec in men and 460 msec in women (450 msec overall).[7] Lower cut-offs, such as 440 msec, are too sensitive and a considerable number of patients would require evaluation (outpatient) or monitoring (inpatient) because they have a QT interval greater than 440 msec, when actually they have no risk of torsades de pointes (false positives). These cut-offs are difficult to apply in clinical practice, and a sensitive and specific cut-off that incorporates heart rate correction is required.
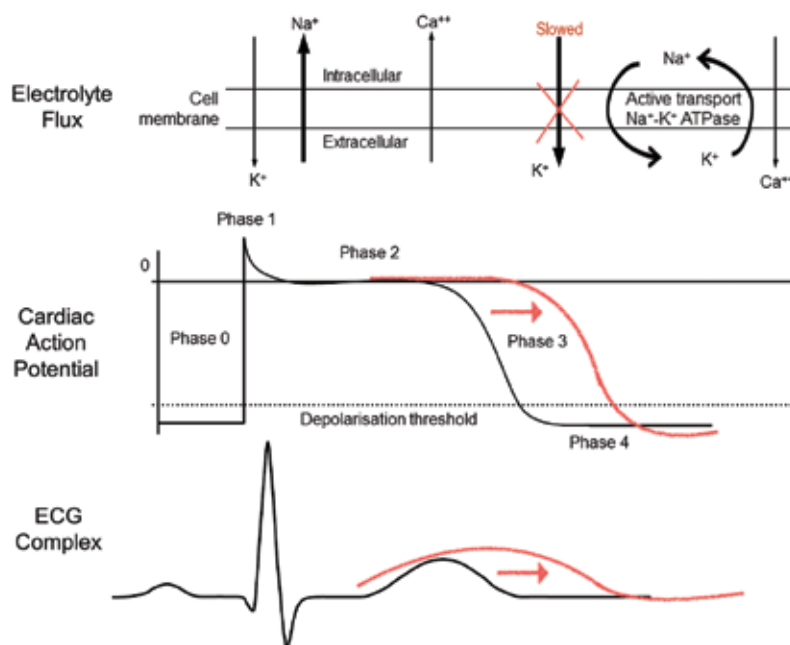
Measuring the QT interval

There continues to be debate over the best method for measuring the QT interval. Standard ECG machines

Fig. 1 ECG showing the different intervals during a heart beat
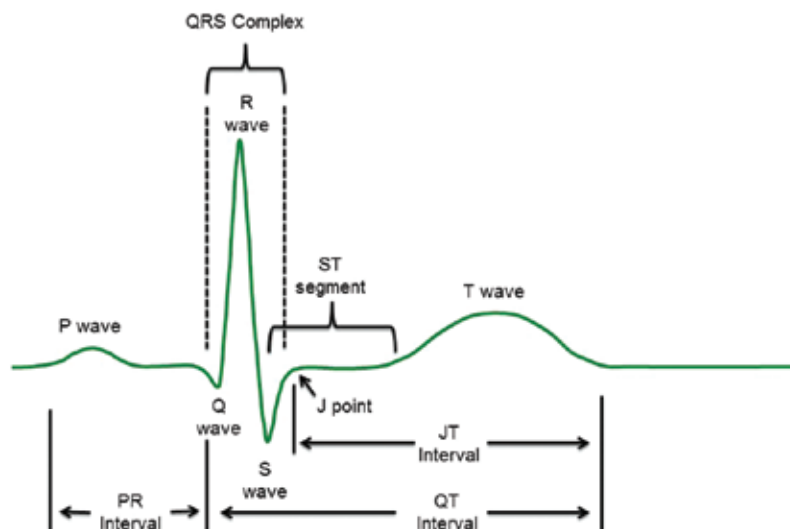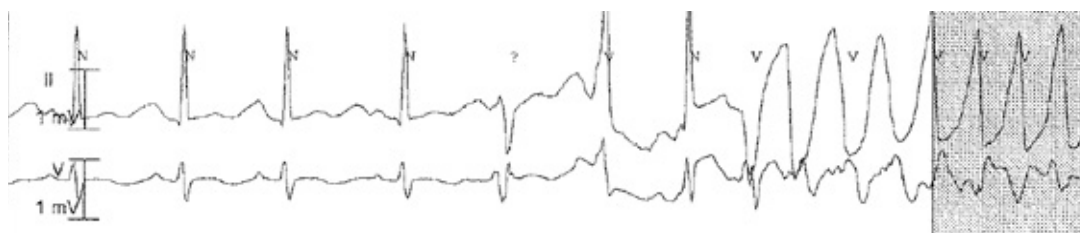

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Fig. 2 QT prolongation showing electrolyte fluxes, action potentials and ECG phases 0–4 on the electrocardiogram

phase 0   rapid depolarisation due to rapid sodium influx
phase 1   initial repolarisation due to potassium and chloride efflux
phase 2   the plateau where there is a balance of potassium efflux and calcium influx
phase 3   rapid repolarisation due to potassium efflux
phase 4   the resting membrane potential before the next depolarisation
———   indicates QT prolongation and its associated pathophysiology

Reproduced and adapted from WikiTox www.wikitox.org

Fig. 3   **Torsades de pointes on a rhythm strip**

ECG tracing of leads II and V in a patient with a prolonged QT and then onset of torsades de pointes showing the R on T phenomena
Reproduced and adapted from WikiTox www.wikitox.org

Table 1   **Drugs that have been associated with a high risk of QT prolongation and torsades de pointes**

Antidepressants	selective serotonin reuptake inhibitors: citalopram, escitalopram
	moclobemide
	tricyclic antidepressants[†]
	lithium[‡]
Antihistamines	loratadine
	diphenhydramine
Antimicrobials	ciprofloxacin, moxifloxacin
	erythromycin, clarithromycin
	fluconazole, voriconazole
	pentamidine
Antipsychotics	amisulpride
	chlorpromazine
	haloperidol
	ziprasidone
Cardiac drugs	amiodarone[‡]
	sotalol
	disopyramide
Other drugs	cisapride
	ondansetron, dolasetron
	methadone
	arsenic
	chloroquine

† Although QT prolongation is traditionally associated with tricyclic antidepressants, this is almost always due to QRS widening without lengthening of the JT interval (QT interval minus the QRS duration)

‡ Drugs where there appears to be QT prolongation, but a much lower risk of torsades de pointes

A longer list of drugs associated with QT prolongation can be found at http://crediblemeds.org, but many may only have a low risk of torsades de pointes and possibly no risk

can be unreliable and taking the automated reading from the ECG machine in clinical practice may be inaccurate, particularly in patients with a long QT. The best method is to use continuous digital 12-lead Holter recordings, extracting multiple 12-lead ECGs and using a combination of computer algorithms and onscreen manual measurement with overlapped views and calipers.[8] However, this is not possible in clinical practice and manual methods using standard ECGs have been shown to be reproducible[9] and close to digital Holter methods.[8] A simple manual method is presented in Table 2.[1] The QT interval is measured from the beginning of the Q wave to the end of the T wave (Fig. 1). Although it requires measuring the QT interval in six leads and taking the median, this can be done in a few minutes or less with practice, and its value and importance make this worthwhile.
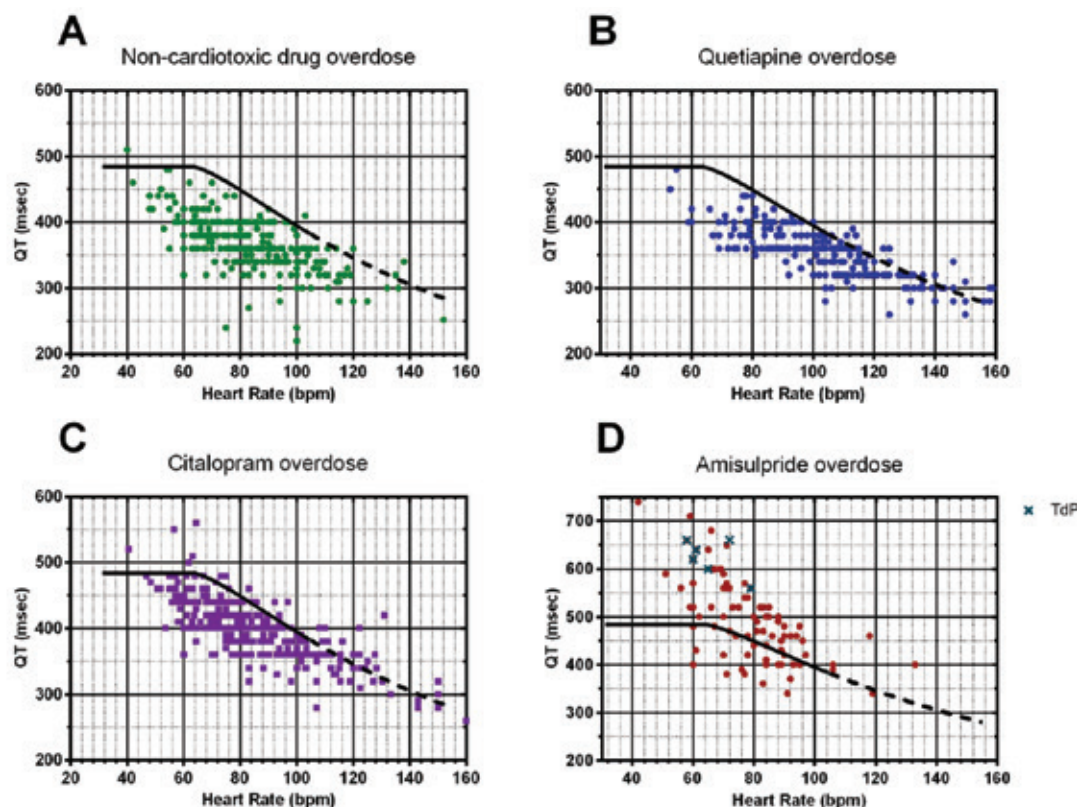
Heart rate correction

Changes in heart rate influence the absolute QT interval and therefore influence assessment of whether it is long.[6] Many heart rate formulae exist and the most commonly used is Bazett's formula. However, this is really only useful for a narrow range of heart rates and significantly over-corrects for fast heart rates and under-corrects for slow heart rates.[1,10] Fridericia's formula is better, but is still problematic for fast heart rates. Over-correction for fast heart rates is a major problem with overdoses that cause tachycardia, such as sympathomimetics (including selective noradrenergic reuptake inhibitors such as venlafaxine) and anticholinergic drugs (including drugs for which this is not their primary effect like antihistamines, antidepressants and antipsychotics such as quetiapine).[11]

QT nomogram: a risk assessment tool

An effective alternative to heart rate correction is to not correct the QT interval using a formula but

*Fig. 4* **QT nomograms for various drugs in patients after overdose**

Examples of plots of QT vs heart rate for:

A   non-cardiotoxic drugs (temazepam, oxazepam, diazepam, paracetamol)
B   quetiapine
C   citalopram
D   amisulpride

● is the QT–HR pair from the ECG for an individual patient who did not develop torsades de pointes

x is the QT–HR pair from the ECG for a patient who developed torsades de pointes

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instead plot the QT interval against the heart rate on the QT nomogram (Fig. 5).[12,13] This approach incorporates heart rate correction and risk assessment in the same process. It also avoids the issue of which cut-off to use.

To use the nomogram the QT interval is measured manually (as described in Table 2) and then plotted against the heart rate. If the QT–heart rate pair is above the cut-off line then the QT is prolonged.

For patients with drug-induced torsades de pointes, a retrospective evaluation of the QT nomogram found it had a sensitivity of 97% and a specificity of 99%. This was compared to using Bazett's formula and cut-offs of QTc=440 msec (sensitivity 99%, specificity 67%) and QTc=500 msec (sensitivity 94%, specificity 97%).[12] There is some evidence that the further above the line the QT–heart rate pair is, the greater the risk of torsades de pointes. However, other factors such as hypokalaemia or individual (genetic) susceptibility may also play a role.

In addition to its role of providing a risk assessment tool for individuals, the QT nomogram has been used in a number of toxicology studies to provide a risk assessment for particular drugs in overdose (see Fig. 4).

Fig. 5 **QT nomogram**
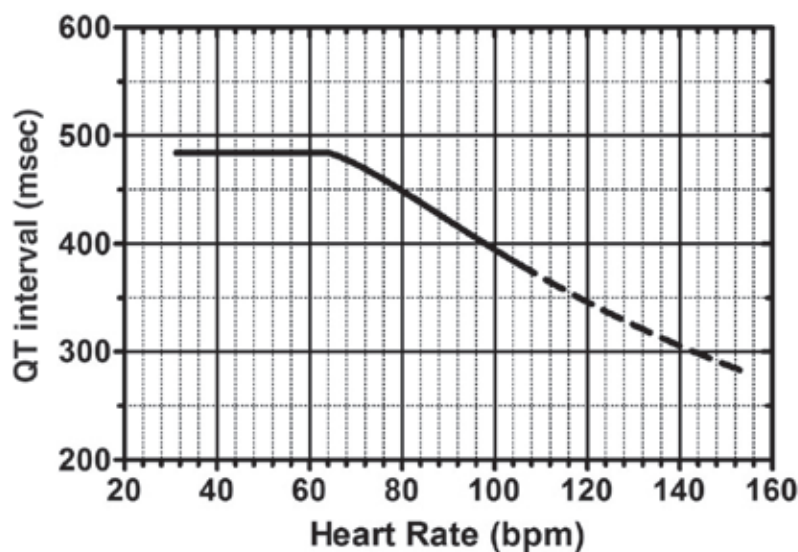
──────   solid line indicates heart rates that are not tachycardic[12]

- - - - -   dashed line is extrapolated to allow assessment of faster heart rates

The QT nomogram is a plot of the QT interval versus the heart rate. A QT–heart rate pair above the line is associated with an increased risk of torsades de pointes.[13]
Reproduced and adapted from WikiTox www.wikitox.org

Table 2   **Step by step approach for using the QT nomogram to determine if a QT interval is abnormal** [1]

Steps	Approach
Obtain ECG	The QT interval length is manually measured in 6 leads on the ECG, usually: • 3 limb leads: I, II and aVF • 3 chest leads: V2, V4 and V6
Measure the absolute QT interval	The QT interval is manually measured from the start of the Q wave until the T wave returns to baseline On a standard ECG at 25 mm per second this is best done by counting the number of small squares • 5 small squares = 200 milliseconds • 8 small squares = 320 milliseconds Do not use the ECG automated readout or QTc
Calculate the median QT	The median is the middle number of all 6 measured QT intervals when arranged in numerical order If there are 2 middle numbers, e.g. position 3 and 4, then the average of these 2 measurements is the median
Determine heart rate	The heart rate is the average measurement derived from the RR interval on the 12 lead ECG and is most accurate when read from an automated ECG
Plot on QT nomogram	The median QT length is then plotted against the heart rate on the QT nomogram (Fig. 4). If the QT–heart rate pair is above the line on the nomogram it is a prolonged QT and there is an increased risk of torsades de pointes.

RR   the distance from one R wave to the next R wave   Modified from reference 1

Recommendation

Clinicians from a variety of specialities are faced with assessing whether a QT interval is abnormal. A recommended approach to the measurement of the QT interval, heart rate correction and determining if the QT is abnormal is shown in Table 2.

In addition to assessing a single QT–heart rate pair on a nomogram, it is important to consider the known risk of the drug involved and whether the patient has an underlying abnormal QT interval. This may be difficult to determine, but if old ECGs can be obtained this will provide a useful comparison.

Before prescribing a drug that causes QT prolongation and torsades de pointes, it is essential to undertake a baseline assessment. A reasonable minimum would be a single baseline ECG, but in situations where the risk is high or there are other risk factors, taking several measurements at different times of the day or a Holter recording will provide a more accurate assessment. This initial assessment establishes if the patient has an abnormal QT interval 'off' the drug which would contraindicate the use of a QT-prolonging drug. If the patient is commenced on the drug, they require serial ECGs during treatment to check for QT prolongation. It is important to avoid other drugs known to cause QT prolongation as well as preventing other causes of QT prolongation such as electrolyte abnormalities. ◄

Conflict of interest: none declared

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Medicines Safety Update

TGA Health Safety Regulation

Volume 6, Number 1, February 2015

Combined oral contraceptives and hormone replacement therapy – inflammatory bowel disease

Health professionals are advised that the TGA is working with sponsors of combined oral contraceptives and hormone replacement therapy to ensure information regarding inflammatory bowel disease is included in the Product Information documents.

The TGA has evaluated recently published research that describes a link between the use of combined oral contraceptives (COCs) and an increased risk of developing inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease.[1,2,3]

During assessment of this information, the TGA identified corresponding data that suggested hormone replacement therapy (HRT) was also a potential risk factor for development of IBD.

The literature also suggested that these risks may be increased in women who were smokers.[4]

Related products

Progestogen-only contraceptive and HRT products and products containing tibolone as the active ingredient were not specifically considered in the data evaluated, therefore the TGA could not determine whether or not those products were associated with a potential increased risk of IBD.

One paper concluded that there was no difference in the IBD risk between oestrogen-only HRT products and oestrogen/progestogen combination HRT.[1]

TGA assessment

The TGA found that the literature had limitations. While the research did not confirm a causal relationship and the pathogenesis of IBD remained incompletely defined, the TGA concluded that health professionals should be made aware of this information.

While the Product Information (PI) documents for most COC products include a reference to the association between these drugs and IBD, this information is not consistent across all products.

Meanwhile, no PI documents for oestrogen/progestogen combination HRT products contain information about a potential association with IBD.

The TGA is negotiating with the sponsors of COCs and oestrogen/progestogen combination HRT products to ensure adequate information is provided in their PI.

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TGA Health Safety Regulation

Metoclopramide and neurological adverse events

The Product Information for metoclopramide has been updated to include a new contraindication and changes to dosing and duration of use to reduce the risk of neurological adverse events.

Metoclopramide is a widely used antiemetic and gastroprokinetic drug. It has a number of approved indications, the most common being to control nausea and vomiting which may be associated with the following conditions:

- intolerance to essential drugs with emetic properties
- uraemia
- radiation sickness
- malignant disease
- postoperative vomiting
- labour
- infectious diseases.

There are 30 metoclopramide and metoclopramide-containing products included on the Australian Register of Therapeutic Goods. These are available as prescription and pharmacist-only medicines.

European review

The TGA has recently completed an analysis of the findings of a European Medicines Agency (EMA) review of metoclopramide.

In December 2013, the European Commission adopted the EMA's recommended changes to restrict the dose and duration of use of metoclopramide to reduce the risk of potentially serious neurological adverse events, including extrapyramidal disorders and tardive dyskinesia, as well as rare cardiac conduction disorders.[1]

Extrapyramidal disorders, including tardive dyskinesia, may continue even after cessation of metoclopramide and may not be reversible.

Adverse events

From January 1971 to 16 October 2014, the TGA received 2190 adverse event case reports associated with metoclopramide. Among these reports were 16 cases of tardive dyskinesia associated with metoclopramide use, and 86 cases of other extrapyramidal disorders. There were also nine reports of cardiac arrest and a further 63 reports of cardiac arrhythmias.

Product Information changes

The TGA has worked closely with the sponsor to update the Product Information (PI) for prescription metoclopramide products to include information about the risk of neurological adverse events.

The TGA will also be assessing labelling requirements for the over-the-counter metoclopramide products.

Information for health professionals

Health professionals are advised of the risk of neurological adverse events, including extrapyramidal disorders and tardive dyskinesia, associated with the use of metoclopramide. A risk of rare cardiac conduction disorders has also been identified.

In response to these identified risks, the following changes have been made to the PI for prescription metoclopramide:

- it is contraindicated for children aged under one year
- for young adults (aged under 20 years) and children over one year of age, it is only indicated as second-line therapy
- the total daily dosage, especially for children and young adults, should not normally exceed 0.5 mg/kg bodyweight, with a maximum of 30 mg daily
- the maximum dose for adults is 10 mg three times daily
- the maximum recommended treatment duration is now five days in all age groups.

Please report any suspected neurological adverse events and cardiac conduction disorders associated with metoclopramide to the TGA.

REFERENCE

1. European Medicines Agency. European Medicines Agency recommends changes to the use of metoclopramide. Changes aim mainly to reduce the risk of neurological side effects. 2014.

Publication changes for Medicines Safety Update

After this issue, publication of the TGA's bimonthly safety bulletin Medicines Safety Update will be changing. It will no longer be included within *Australian Prescriber*.

Medicines Safety Update will continue to be published on the TGA's website at www.tga.gov.au/publication/medicines-safety-update during the months of February, April, June, August, October and December.

Through that webpage, you can subscribe to an email list and receive a notification when each new edition becomes available.

Medicines Safety Update provides health professionals with practical information and advice on drug safety and emerging safety issues. It replaced the *Australian Adverse Drug Reactions Bulletin*, which was published from 1974 to 2009. It also provides information on adverse event reporting and how health professionals can contribute to safety monitoring in Australia.

Further important safety information for health professionals regarding all types of therapeutic goods is available on the TGA website at www.tga.gov.au/safety-information-health-professionals. This includes *Medicines Safety Update's* companion publication, *Medical Devices Safety Update*, which is published during the months of January, March, May, July, September and November.

The TGA wishes to acknowledge the ongoing collaboration and support of the publisher of *Australian Prescriber*, NPS MedicineWise, and thanks *Australian Prescriber* readers for their ongoing interest in and commitment to drug safety.

What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website
- **online** at www.tga.gov.au
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Office of Product Review on 1800 044 114.

For the latest safety information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

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DISCLAIMER

New drugs

Enzalutamide

Approved indication: metastatic prostate cancer
Xtandi (Astellas)
40 mg capsules
Australian Medicines Handbook section 14.3.1

Prostate cancer is an androgen-dependent malignancy. Although medical or surgical castration reduces progression in the earlier stages, the cancer eventually becomes resistant and requires chemotherapy. The median survival time for men with castration-resistant disease is 1–2 years.

Androgen receptor signalling is increased at this late stage of the disease and is thought to be driven, in part, by over-expression of the androgen receptor. Anti-androgen treatments have therefore become a focus of research. Like abiraterone (Aust Prescr 2012;35:128-35), enzalutamide has been approved for patients with metastatic castration-resistant prostate cancer. Enzalutamide is an inhibitor of androgen receptor signalling and works by competitively blocking the binding of androgen to its receptor.

The efficacy and safety of enzalutamide has been assessed in a phase III trial.[1] Men who had already been treated with docetaxel were randomised to enzalutamide 160 mg once daily (800 patients) or placebo (399 patients). Corticosteroids were allowed during the study and patients continued androgen deprivation therapy.

Enzalutamide treatment was continued until the disease progressed. The median duration of treatment was 8.3 months in the enzalutamide group versus 3 months in the placebo group. Median overall survival was significantly longer for enzalutamide than with placebo (18.4 vs 13.6 months, p<0.001). Because of the observed benefit, the study was stopped at the prespecified interim analysis and patients in the placebo group were offered enzalutamide.

The most common adverse events with enzalutamide were asthenia or fatigue (50.6% of people), back pain (26.4%), arthralgia (20.5%), hot flushes (20.3%), peripheral oedema (15.4%), musculoskeletal pain (15%) and headache (12.1%). These were more frequent with enzalutamide than with placebo. Neutropenia was also more common with enzalutamide than with placebo (15% vs 6%), and 1% of men in the enzalutamide group died from an infection compared to 0.3% in the placebo group. Falls

or injuries from falls (4.6% vs 1.3%) and hallucinations (1.6% vs 0.3%) were also more frequently reported with enzalutamide.

Enzalutamide comes with a warning about seizures. In the trial, 7 of 800 men given enzalutamide had a seizure, compared to no seizures with placebo.[1] Caution is urged in patients with a history of seizures, brain injury, stroke, tumours in the brain, alcoholism or concomitant use of medicines that reduce the seizure threshold.

Cardiac disorders were reported in 6% of those taking enzalutamide[1] even though men with recent cardiovascular disease were excluded from the trial (recent myocardial infarction or unstable angina, a long QT interval, bradycardia or uncontrolled hypertension). Hypertension (6.6%) has also been reported with enzalutamide.

Following oral administration of enzalutamide, maximum plasma concentrations are observed within 1–2 hours. Oral bioavailability is high (≥84.2%). The mean terminal half-life is approximately six days and steady state is reached after a month. Most of the dose is excreted in the urine (71%), with a minor portion excreted in the faeces (13.6%).

Caution is urged when prescribing enzalutamide to people with moderate hepatic impairment and it is not recommended in those with severe impairment. Care should also be taken in those with severe renal impairment or end-stage renal disease.

Enzalutamide is extensively metabolised, mainly by cytochrome P450 (CYP) 2C8, so strong inhibitors (gemfibrozil) or inducers (rifampicin) of this enzyme should be avoided if possible. If a CYP2C8 inhibitor is co-prescribed, the enzalutamide dose should be halved. Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19 so there is potential for drug interactions with substrates of these enzymes such as midazolam, warfarin and omeprazole. Enzalutamide may also affect P-glycoprotein so substrates of this transporter with a narrow therapeutic range (e.g. colchicine, dabigatran, digoxin) may require dose adjustment. There may be an increased risk of liver injury with paracetamol in patients being treated with enzyme inducers.

Enzalutamide provides another option for men with metastatic castration-resistant prostate cancer. Although it prolongs survival by a median of 4.8 months, enzalutamide carries a risk of seizures as well as numerous drug interactions. It is not known

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Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

how it will compare to abiraterone. Enzalutamide is also being investigated in the treatment of metastatic prostate cancer before chemotherapy.[2]

⊠ manufacturer did not supply data

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First published online 1 December 2014

Fluticasone furoate with vilanterol

Approved indications: asthma, chronic obstructive pulmonary disease
Breo Ellipta (GlaxoSmithKline)
100/25 microgram, 200/25 microgram powder for inhalation
Australian Medicines Handbook section 19.1

In asthma a long-acting beta agonist can be added to treatment if an inhaled corticosteroid is insufficient to control the patient's symptoms. Inhaled corticosteroids can be added to long-acting beta agonists to try and reduce exacerbations in patients with chronic obstructive pulmonary disease (COPD). Fluticasone propionate is already available in combination with salmeterol for both conditions, so the combination of fluticasone furoate with vilanterol trifenatate is just another option for delivering a corticosteroid and a long-acting beta agonist by inhalation. These combinations have anti-inflammatory effects and relax bronchial smooth muscle.

A specific device is needed to inhale the powder formulation. Following inhalation, some of the dose is absorbed through the lung into the systemic circulation. The subsequent metabolism of both drugs includes cytochrome P450 (CYP) 3A4. Vilanterol has a half-life of 2.5 hours with most of its metabolites being excreted in the urine, while fluticasone has an elimination half-life of 24 hours with most of its metabolites being excreted in faeces. No dose reduction is needed in renal impairment, but in moderate or severe hepatic impairment the maximum dose is limited to fluticasone furoate 100 microgram and vilanterol 25 microgram.

Efficacy

There have been multiple studies of the combination in more than 17 000 patients. These have established the usual dose of fluticasone furoate/vilanterol to be 100/25 microgram once daily. Some patients with asthma will need 200/25 microgram, but this dose is not indicated in patients with COPD.

Asthma

The efficacy of the combination was compared with fluticasone products in patients with persistent asthma. These patients were at least 12 years old and had a forced expiratory volume in one second (FEV_1) that was 40–90% of the predicted value. Following a run-in period, 197 patients were randomised to use the combination (200/25 microgram daily), 194 inhaled fluticasone furoate (200 microgram daily) and 195 inhaled fluticasone propionate (500 microgram twice daily). The mean pre-dose (trough) FEV_1 at baseline was 2.153 L. After 24 weeks this had improved by 394 mL with the combination, by 201 mL with fluticasone furoate and by 183 mL with fluticasone propionate. The combination of fluticasone furoate and vilanterol therefore had a significantly greater effect on lung function than fluticasone alone.[1]

Another trial studied the effect of the combination on exacerbations of asthma. The 2020 adolescents and adults in the study had FEV_1 values that were 50–90% of their predicted value, and a history of at least one exacerbation in the previous year. They were randomised to receive fluticasone furoate/vilanterol 100/25 microgram or fluticasone furoate 100 microgram daily. At least one severe exacerbation occurred in 340 patients. At one year, the risk of having an exacerbation was reduced by 20% in the patients inhaling the combination.[2]

The combination of fluticasone furoate and vilanterol (100/25 microgram) has been compared with the combination of fluticasone propionate and salmeterol (250/50 microgram). After a run-in period, 806 patients, with FEV_1 40–85% of the predicted value, were randomised to inhale the drugs for 24 weeks. The mean FEV_1 increased by 341 mL with the vilanterol combination and by 377 mL with the salmeterol combination. This difference is not statistically significant and there was also no difference in asthma control or exacerbations.[3]

Chronic obstructive pulmonary disease

Two placebo-controlled, parallel group trials studied different doses of fluticasone furoate and vilanterol in patients with COPD. These patients were at least 40 years old, had a smoking history of at least 10 pack-years and an FEV_1 that was 70% or less than the predicted value after using a bronchodilator. In addition to the different doses of the combination, both trials had arms which included fluticasone furoate alone and vilanterol alone.[4,5]

The first trial randomised 1030 patients. After 24 weeks the mean trough FEV_1 had increased by 33 mL with fluticasone furoate and by 67 mL with vilanterol, compared to placebo. The 100/25 microgram combination increased trough FEV_1 by 115 mL more than placebo. This combination also significantly increased the mean FEV_1 in the four hours following the inhalation (see Table).[4]

The second trial randomised 1224 patients. Compared to placebo, the trough FEV_1 increased by 44 mL with fluticasone furoate, 100 mL with vilanterol and by 144 mL with the 100/25 microgram combination. After 24 weeks this combination had also increased the mean FEV_1 in the four hours following the inhalation (see Table).[5]

Another two trials in similar groups of patients assessed the effect of vilanterol 25 microgram and different doses of the combination on exacerbations. These patients had a history of at least one exacerbation in the previous year. The first study randomised 1622 patients and the second study randomised 1633. A pooled analysis after one year showed that 48.9% of the patients taking vilanterol and 41.9% of those taking the 100/25 microgram combination had an exacerbation. This combination also significantly reduced the rate of moderate and severe exacerbations.[6]

Safety

In addition to data from the clinical trials, the safety of fluticasone furoate and vilanterol has been investigated in safety studies. One study followed 503 patients with asthma for a year. One hundred patients took fluticasone propionate and the remainder took the 100/25 or 200/25 microgram combination. The most frequent adverse effects in all groups were headache, upper respiratory tract infection and nasopharyngitis.[7] This reflects the observations seen in the clinical trials in asthma and COPD. Oral candidiasis was the most frequent treatment-related adverse effect. A few cases of dysphonia and extrasystoles were seen with the combination, but not with fluticasone propionate.[7] Inhaling a beta agonist can increase the pulse rate.

Combinations containing fluticasone furoate initially had less effect than fluticasone propionate on 24-hour urinary cortisol, but by 52 weeks there was no significant difference between the treatments.[7] In patients with COPD there were more fractures with the combination than in patients taking vilanterol alone. There were also more cases of pneumonia, some of which were fatal. The incidence of pneumonia was 6–7% with the combination compared to 3% in patients taking vilanterol alone.[6] In the trial which compared the combination to fluticasone propionate/salmeterol there was no significant difference in adverse effects.[3]

Conclusion

The studies show that the combination of fluticasone furoate and vilanterol has more effect on lung function than its individual components given alone.

Table **Efficacy of fluticasone furoate/vilanterol combination in COPD**

	Fluticasone furoate 100 microgram	Vilanterol 25 microgram	Fluticasone furoate/ vilanterol 100/25 microgram
Study 1 [4]			
Number of patients	206	205	206
Baseline trough FEV_1	1.166 L	1.285 L	1.246 L
Change compared to placebo at 24 weeks			
trough FEV_1	33 mL	67 mL	115 mL
mean FEV_1 (0–4 hours post-dose)	53 mL	103 mL	173 mL
Study 2 [5]			
Number of patients	204	203	204
Baseline trough FEV_1	1.412 L	1.371 L	1.357 L
Change compared to placebo at 24 weeks			
trough FEV_1	44 mL	100 mL	144 mL
mean FEV_1 (0–4 hours post-dose)	46 mL	185 mL	214 mL

FEV_1 forced expiratory volume in one second

These differences were not always statistically significant. While the combination reduces exacerbations, the absolute reduction is small. In asthma the rate of severe exacerbations was 0.14/patient/year with 100/25 microgram, compared with 0.19/patient/year with fluticasone furoate 100 microgram.[2] In COPD the rate of severe exacerbations was 0.09/year with the combination and 0.1/year with vilanterol 25 microgram.[6]

At the time of writing, neither fluticasone furoate nor vilanterol was available separately in Australia. This means that patients cannot have their doses individually titrated and then be changed to the combination. It would be inappropriate to start treating asthma or COPD with this combination. This means patients who are prescribed the combination are likely to be switching from other drugs. The comparative study in asthma suggests that fluticasone furoate/vilanterol 100/25 microgram once daily is similar to fluticasone propionate/salmeterol 250/50 microgram twice daily.[3] A once-daily dose may help some patients adhere to their treatment. The fluticasone furoate/vilanterol combination is not indicated for treating acute symptoms, so patients will still need a short-acting beta agonist. It is also not approved for treating asthma in children less than 12 years old.

T manufacturer provided the product information

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First published online 1 December 2014

Pomalidomide

Approved indication: multiple myeloma
Pomalyst (Celgene)
1 mg, 2 mg, 3 mg and 4 mg capsules
Australian Medicines Handbook section 14.2.4

Multiple myeloma is characterised by abnormal plasma cells in the bone marrow. The disease is generally considered incurable and most patients eventually become refractory to treatment. Pomalidomide is indicated for those who have already received at least two treatments, including bortezomib (Aust Prescr 2006;29:84-7) and lenalidomide (Aust Prescr 2008;31:49-55). Median overall survival in this group is around nine months with treatment and three months without treatment.

Pomalidomide is structurally related to thalidomide and lenalidomide. Its exact mechanism of action is unknown, but like other drugs in the class, it is thought to have antimyeloma, anti-angiogenic, immunomodulatory and stromal cell effects. In a phase II trial, the efficacy of pomalidomide was enhanced when given with low-dose dexamethasone (see Table).[1]

The approval of pomalidomide is mainly based on an open-label phase III trial which enrolled patients who

Table **Efficacy of pomalidomide[‡] in relapsed or refractory multiple myeloma**

Phase II trial [1]		
Outcomes (after a median of 14 months of follow-up)	**Pomalidomide plus low-dose dexamethasone[§]** (108 patients)	**Pomalidomide monotherapy** (113 patients)
Median progression-free survival	4.2 months	2.7 months
Median overall survival	16.5 months	13.6 months
Overall response	33% (3% were complete responses)	18% (2% were complete responses)
Phase III trial [2]		
Outcomes (after a median of 10 months of follow-up)	**Pomalidomide plus low-dose dexamethasone[§]** (302 patients)	**High-dose dexamethasone[#]** (153 patients)
Median progression-free survival	4 months	1.9 months
Median overall survival	12.7 months	8.1 months
Overall response	31% (1% were complete responses)	10% (no complete responses)

‡ pomalidomide 4 mg/day was taken orally on days 1–21 of a 28-day cycle
§ dexamethasone 40 mg once a week during each 28-day cycle
# dexamethasone 40 mg given on days 1–4, 9–12 and 17–20 of a 28-day cycle. Dose reduced to 20 mg in people aged 75 years and older.

had relapsed or progressed despite a median of five previous treatments. Participants were randomised to 28-day cycles of pomalidomide with low-dose dexamethasone (302 patients), or to high-dose dexamethasone alone (153 patients). Treatment was continued until disease progressed or patients developed unacceptable toxicity. After 10 months, pomalidomide and low-dose dexamethasone was found to significantly improve response rates, progression-free and overall survival compared to high-dose dexamethasone (see Table).[2]

After a median follow-up of 10 months, most people had discontinued treatment (80% of the pomalidomide group, 93% of the comparator group). Progressive disease was the most common reason for stopping, but approximately 10% of people discontinued because of an adverse event.[2]

Serious adverse events, defined as resulting in hospitalisation, disability or incapacity, occurred in 61% of patients in the pomalidomide group and 53% of those in the comparator group. The most common adverse events of any grade with pomalidomide were infections (68% of people), anaemia (52%), neutropenia (51%), fatigue (34%), thrombocytopenia (30%), fever (27%), diarrhoea (22%) and constipation (22%).[2] Peripheral neuropathy occurred in 12% of patients. Adverse events were more likely to occur during the first two cycles of treatment. There were 11 treatment-related deaths with pomalidomide – eight cases of infections, two cases of multi-organ failure or sudden death, and one nervous system disorder.[2]

Because of its structural similarity to thalidomide, pomalidomide is contraindicated in pregnancy. It is available under a restricted distribution program, which includes measures to prevent pregnancy. Women should be using a recommended form of contraception and have a negative pregnancy test before starting pomalidomide and men must use a condom throughout treatment, even if they have had a vasectomy.

Regular monitoring of blood counts is recommended with pomalidomide because anaemia, neutropenia and thrombocytopenia are so common and patients often need their dose reduced or interrupted. Dizziness and confusion have been reported and patients should be warned not to drive or operate machinery if this occurs.

Deep vein thrombosis occurs with pomalidomide so prophylaxis is recommended in patients with a high risk. There is no experience of this drug in patients with significant heart problems such as congestive heart failure, recent myocardial infarction or poorly controlled angina, as they were excluded from trials. Close monitoring is recommended in patients with an increased risk of tumour lysis syndrome (those with a high tumour burden or renal impairment).

Following oral administration, maximum plasma concentrations are reached after 2–3 hours. Pomalidomide's plasma half-life is 7.5 hours in patients with multiple myeloma. After metabolism in the liver, the drug is eliminated in the urine (73%) and faeces (15%). It is unclear if the dose needs to be reduced in renal disease as patients with moderate to severe impairment were excluded from the trials. Patients with hepatic impairment (serum bilirubin >34.2 micromol/L) and elevated transaminases (>3 x upper limit of normal) were also excluded.

Pomalidomide is predominantly metabolised by cytochrome P450 (CYP) 1A2 and 3A4 and is also a substrate of P-glycoprotein. Co-administration of strong CYP1A2 inhibitors, such as fluvoxamine, may increase pomalidomide exposure and monitoring is recommended. Close monitoring is also advised in patients taking concomitant warfarin as there is a potential drug interaction with dexamethasone.

For patients with few options left, pomalidomide with low-dose dexamethasone may offer longer progression-free and overall survival compared to treatment with high-dose dexamethasone. However, haematological toxicity and infections are very common and may limit treatment.

T T manufacturer provided additional useful information

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First published online 14 November 2014

Retapamulin

Approved indication: skin infections
Altargo (GlaxoSmithKline)
tubes containing 1% ointment
Australian Medicines Handbook section 8.4.3

Retapamulin is a topical pleuromutilin antibiotic. It is indicated for impetigo and mild secondary skin infections arising from lacerations, abrasions, sutured wounds, psoriasis or dermatitis. These infections are mainly caused by *Staphylococcus aureus*, but can also be due to *Streptococcus pyogenes*.

In vitro, retapamulin is bacteriostatic against *S. aureus* and *S. pyogenes*. It is thought to act by inhibiting protein synthesis through the 50S bacterial ribosomal unit. From in vitro studies, the likelihood of *S. aureus* and *S. pyogenes* becoming resistant to retapamulin is predicted to be low.

The recommended dose is a thin layer of ointment, twice a day for five days. Systemic exposure following application to intact skin is generally very low. However, detectable concentrations were observed in 69% of babies aged 2–9 months. Retapamulin is therefore contraindicated in babies under nine months. As this drug is metabolised by cytochrome P450 (CYP) 3A4, inhibitors of this enzyme (e.g. ketoconazole) may increase retapamulin exposure in children under two years.

The efficacy of retapamulin 1% ointment in patients aged nine months and older has been studied in several phase III trials (see Table).

Impetigo

There have been two comparative trials of retapamulin for impetigo – one with a placebo[1] and the other with sodium fusidate ointment 2% (3 times daily for 7 days).[2] The median age of the participants was 7–9 years and most of them had only one impetigo lesion. Clinical success was defined as drying up (without crusts) or resolution of the lesion, or an improvement such that no further treatment was needed. The efficacy of retapamulin was significantly better than placebo and was non-inferior to sodium fusidate (see Table).

Infected wounds

Retapamulin has also been compared to a 10-day course of oral cephalexin 500 mg (twice a day) in people with secondarily infected wounds caused by trauma.[3] Two identical trials enrolled participants who had wounds less than 10 cm long with no more than 2 cm of surrounding erythema. Response to treatment was scored using a skin infection rating scale which assessed exudates, crusting, inflammation, tissue warmth, oedema, itching and pain. The efficacy of retapamulin appeared to be non-inferior to oral cephalexin, with most patients requiring no further treatment at the end of the study period (see Table).

In another trial, retapamulin did not reach statistically significant superiority over placebo for people with secondarily infected wounds. This was presumably because clinical success rates were quite high in the placebo arm (see Table).[4]

Infected dermatoses

A single trial investigated retapamulin for secondary infections arising from psoriasis or dermatitis (atopic or allergic). The ointment was found to have comparable efficacy to oral cephalexin 500 mg twice a day for 10 days (see Table).[5]

MRSA infections

Evidence that retapamulin is effective against infections caused by methicillin-resistant *S. aureus* (MRSA) is limited. In one of the studies of secondarily infected wounds, clinical success rates were lower

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Table **Efficacy of topical retapamulin 1% for superficial skin infections in phase III trials**

Indication	Trial	Treatment[‡]	Number of patients	Clinical success rates[§]
Impetigo	Koning[1]	retapamulin	139	85.6%
		placebo	71	52.1%
	Oranje[2]	retapamulin	345	94.8%
		sodium fusidate	172	90.1%
Secondarily-infected wounds	Free[3]	retapamulin	1268	86.3%
		oral cephalexin	636	85.7%
	Tomayko[4]	retapamulin	246	74.8%
		placebo	113	66.4%
Secondarily-infected dermatoses	Parish[5]	retapamulin	363	82.9%
		oral cephalexin	183	86.3%

[‡] retapamulin ointment was applied twice a day for 5 days, sodium fusidate ointment was applied 3 times a day for 7 days, oral cephalexin 500 mg was given twice a day for 10 days

[§] clinical success was reported in the intention-to-treat population and defined as resolution or improvement in signs and symptoms such that no further treatment was needed at the end of the study period

for MRSA infections than for methicillin-sensitive *S. aureus* infections – 68.6% (35/51) versus 92.2% (330/358).[3]

In an unpublished study of people with impetigo or secondarily infected wounds caused by MRSA, clinical success rates were significantly lower with retapamulin than with oral linezolid (63.9% vs 90.6%).

Safety and precautions

Application site reactions were the most frequently reported adverse events with retapamulin and included irritation, pruritus, paraesthesia and pain. In most of the trials, these were reported by less than 2% of people.[1-5] In comparative trials with oral cephalexin, diarrhoea was less common with retapamulin than with oral cephalexin (1.6% vs 2.7%).[3,5]

Retapamulin should not be used to treat abscesses or cellulitis and should not be applied to mucosal membranes or eyes. When prescribing antibiotics for skin infections, geographical variations in antibiotic susceptibility should be considered. If a patient is not responding to retapamulin, they may need to be switched to the appropriate systemic therapy.

Conclusion

Retapamulin ointment is better than placebo for impetigo, however, it has not been compared to mupirocin ointment. Retapamulin may be a preferable alternative to oral antibiotic therapy for mild secondary skin infections. Clinical evidence does not support the use of this drug for MRSA infections.

T manufacturer provided the product information

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First published online 6 November 2014

The Transparency score (**T**) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov)

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu)

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