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Medicines Safety Update

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In this issue

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Combined hormonal contraceptives and risk of venous and arterial thromboembolism

Health professionals are advised that a TGA review has found the risk of venous thromboembolism is increased in women taking a combined hormonal contraceptive containing ethinyloestradiol and a progestogen and that, based on current data, the risk varies according to the progestogen used. The risk of arterial thromboembolism is also increased, however, there is currently no evidence that risk varies according to the progestogen used.

As part of its review, the TGA sought advice from the Advisory Committee on the Safety of Medicines (ACSOM). The meeting statement from the relevant ACSOM meeting (Meeting 27) is available on the TGA website.

The TGA's review found that while the risk of venous thromboembolism (VTE), such as deep vein thrombosis and pulmonary embolism, for women is generally rare – about two cases in every 10,000 women per year – the risk was slightly increased for women using combined hormonal contraceptives (CHCs).

It was recommended that Product Information (PI) and Consumer Medicine Information (CMI) documents for CHCs should be updated to ensure clearer and more consistent information is provided across products.

The review also found that, based on currently available data, the increase in risk of VTE varied according to the progestogen included in the CHC (see table below).

Approximate risk of developing a VTE in a year, per 10,000 women

Progestogen component of CHC	Risk
levonorgestrel, norethisterone, norgestimate	5-7
etonogestrel, norelgestromin	6-12
drospirenone, gestodene, desogestrel, cyproterone*	9-12
drospirenone, gestodene, desogestrel, cyproterone*	Not yet known

* While cyproterone is indicated for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism, it is known to have efficacy as a contraceptive. The risk of developing a blood clot associated with cyproterone use is considered to be 1.5 to 2 times higher than for CHCs containing levonorgestrel and may be similar to the risk with contraceptives containing gestodene, desogestrel or drospirenone.

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

The risk of arterial thromboembolism (ATE), such as myocardial infarction or stroke, is also increased with the use of CHCs, however, it is still very rare, and there is no evidence for differences in risk between CHCs.

The risk of ATE from using CHCs increases with age, smoking and obesity (BMI > 30kg/m^2).

The European Medicines Agency (EMA) also recently undertook a review of this issue and came to similar conclusions.

Sponsors of some CHCs have already incorporated updated information in their PI and CMI documents. The TGA is now working with other sponsors to update their PIs and CMIs.

Information for health professionals

If you are considering prescribing a CHC or are treating a patient who is taking a CHC, ensure that you are familiar with information provided in this article. In particular be aware of the contraindications and precautions relating to the risk of VTE.

Educate patients regarding the signs and symptoms of VTE and ATE and instruct them to contact you if they experience aggravation, exacerbation or first appearance of any of the conditions/risk factors listed below.

If any of the conditions appear for the first time during use, the CHC should be stopped immediately.

Contraindications relating to the risk of thromboembolic disorders are:

- Presence or risk of VTE:
  - Current VTE (on anticoagulants) or history of deep venous thrombosis or pulmonary embolism, or other thrombotic disorder.
  - Known hereditary or acquired predisposition for venous thromboembolism, such as activated protein C-resistance (including Factor V Leiden), antithrombin III-deficiency, protein C deficiency, and protein S deficiency.
  - Major surgery with prolonged immobilisation.
  - A high risk of VTE due to the presence of multiple risk factors.
- Presence or risk of ATE:
  - Current ATE or history of ATE (for example myocardial infarction or stroke) or prodromal condition (for example angina pectoris or transient ischaemic attack; transient ischaemic attack).
  - Known hereditary or acquired predisposition for ATE, such as hyperhomocysteinaemia and antiphospholipid-antibodies (for example anticardiolipin antibodies and lupus anticoagulant).
  - History of migraine with focal neurological symptoms.
  - A high risk of ATE due to multiple risk factors or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia.

Antidepressants – communicating risks and benefits to patients

Health professionals are reminded of the importance of effectively communicating to patients the potential risks and benefits of treatment with antidepressants before prescribing these medicines.

Concerns have been raised about an increased risk of suicidal thinking and behaviour when patients begin treatment with antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs).

It is important to note that suicidal thoughts and acts are a common symptom of depression and that it can take a few weeks for an antidepressant to begin working after initiating therapy.

This makes it difficult to determine whether experiencing suicidal thinking and behaviour shortly after commencing antidepressant treatment is an adverse event caused by the medicine or a symptom of the underlying condition.[1]

However, treatment with antidepressants has been linked with a small increase in the risk of suicidal thinking and behaviour in children and adolescents

with Major Depressive Disorder and other psychiatric disorders.[1]

Precautions relating to suicidal thinking and behaviour in children and adolescents are included in the Product Information (PI) documents of all SSRIs registered for use in Australia. These warnings are supported with information for patients included in Consumer Medicine Information (CMI) documents for those products.

Risks and benefits

A decision to prescribe an antidepressant, as with any prescription medicine, should be based on an assessment of the risks and benefits for each individual patient, as well as consideration of any other treatment options available. Prescribers can refer to the relevant PI for specific information about the medicine being considered.

In addition, prescribers should effectively communicate to patients – and when appropriate their families or carers – the expected risks and benefits of a proposed new medicine to enable them to make an informed decision about their treatment options.

Several studies have shown that patients with mental illness and their carers feel that they have not received enough information about their medicines.[2]

One survey found that just over half of the inpatients and one third of community-based patients reported that they did not receive any medicines information. Carers were even less likely to report receiving medicines information or to be included in discussions or decisions regarding medicine use.[2]

With this in mind, health professionals are strongly encouraged to provide patients with the relevant CMI, which is available through medical and pharmacy software as well as from the TGA website, for any new antidepressant they are prescribed.

Discontinuation symptoms

Another important topic to discuss with patients when appropriate is discontinuation and potential discontinuation symptoms. Discontinuation symptoms can include headache, nausea, sleep disturbance, dizzinesss, irritability, anxiety symptoms and abnormal sensations such as numbness, tingling and 'electric shock-like' sensations.

To avoid discontinuation symptoms, once a decision has been made to stop antidepressant treatment, the dose of an antidepressant will often need to be reduced gradually. It is important for patients and carers to be educated about the importance of not suddenly stopping antidepressant treatment.

Additional education

Health professionals are also encouraged to consider providing additional education to patients who are taking antidepressants.

A review of international literature on the effect of educational interventions for patients with mental illness found that multiple, structured educational sessions delivered at frequent intervals were more effective than one-off interactions.[3]

There are additional resources available for health professionals and consumers to help them make informed decisions about the use of antidepressants and to better education patients and carers about their treatment, including information on the NPS MedicineWise website.

NPS MedicineWise has also launched a new health professional learning program on the management of depression.

REFERENCES

1. Antidepressants and suicide risk. NPS MedicineWise. 20 Nov 2012. http://www.nps.org.au/conditions/mental-health-conditions/mood-disorders/depression/for-individuals/medicines-for-depression-antidepressants/managing-side-effects-of-antidepressants/antidepressants-and-suicide-risk (accessed 23 Nov 2016)
2. Tran N, Castle D. Outcomes from a regular medication information programme for consumers with a mental illness. Australasian Psychiatry. 2012;20(2):143-7
3. Cleary M, Freeman A, Hunt GE, Walter G. What patients and carers want to know: an exploration of information and resource needs in adult mental health services. Australian and New Zealand Journal of Psychiatry. 2005;39(6):507-13

Medicine shortages information

The Medicine Shortages Information Initiative provides information about a temporary or permanent disruption to the supply of a prescription medicine. Health professionals and consumers are invited to subscribe to the Medicine Shortages email list to receive an alert when there is new or updated medicine shortage information reported to the TGA.

ACSOM and ACSOV coming to an end

The TGA would like to publicly acknowledge the contributions of the members of its Advisory Committee on the Safety of Medicines and Advisory Committee on the Safety of Vaccines. Current appointments to both committees are being concluded at the end of 2016, with a new consolidated advisory committee structure to be implemented in early 2017.

Seven new committees will replace the current eleven advisory committees, consolidating the premarket and post-market functions of those bodies.

The functions of the Advisory Committee on the Safety of Medicines (ACSOM) and Advisory Committee on the Safety of Vaccines (ACSOV) will be incorporated into the Advisory Committee for Medicines and Advisory Committee for Vaccines respectively.

The new committees will provide advice on specific clinical and scientific matters to aid regulatory decision making, in particular on applications for the market approval of new products and safety issues relating to particular products or product groups.

ACSOM history

The ACSOM was established on 1 January 2010 and the first meeting was held in March 2010.

The ACSOM evolved from the Adverse Drug Reaction Advisory Committee.

The ACSOM worked with the TGA to develop a successful new approach to providing advice to the TGA in a manner consistent with the new regulations and took into account the changes in the way post-market functions were carried out by the TGA, including the introduction of Risk Management Plans (RMPs).

Advice from the ACSOM has now contributed to decisions by delegates on 136 RMPs and such advice may be quoted in the published Australian Public Assessment Reports (AusPARs).

Advice from the committee has also contributed to 44 safety reviews, including: cardiovascular risks with hormonal contraceptives; drug interactions with warfarin; and the safety of codeine and of non-steroidal anti-inflammatory drugs NSAIDs.

The inaugural, and current, chair is Professor Emily Banks. Two other members have also served since the committee's commencement in 2010 – Ms Alison Marcus and Professor Nick Buckley.

ACSOV history

The ACSOV was established on 10 November 2012 following a recommendation from the 'Review of the management of adverse events associated with Panvax and Fluvax in 2012'.

It replaced the ACSOM in providing advice on vaccine regulation, as well as replacing various ad hoc arrangements of expert panels and individuals working in the field.

Advice from the ACSOV has contributed to decisions by delegates regarding 13 RMPs for new vaccines or extensions of the patient population and such advice may be quoted in published AusPARs.

Advice from the committee has also contributed to 14 safety reviews, including acute adverse events following immunisation with human papillomavirus (HPV) vaccine and aluminium adjuvants given at birth to premature or low birth weight neonates.

The ACSOV has also provided advice to the Department of Health's Immunisation Branch, including on the vaccine safety plan to extend the National Immunisation Program to include trivalent (and subsequently, quadrivalent) influenza vaccine for Aboriginal and/or Torres Strait Islander children aged 6 months to less than 5 years of age, and on the draft national shingles vaccination program vaccine safety plan for adults aged 70 years.

The inaugural chair was Dr Nicole Gilroy, and Professor Banks was appointed chair in early 2016. Four members have served throughout the life of the committee – Ms Karen Booth, Ms Hazel Clothier, Associate Professor Kristine Macartney and Dr Nicole Pratt.

Acknowledgement

The TGA would like to thank each member of these advisory committees for providing independent expert advice to help ensure the continued safe use of medicines and vaccines for the benefit of the Australian public.

Further information about the new advisory committee structure can be found on the TGA website.

Adrenaline autoinjectors for single use only

Health professionals are reminded that adrenaline autoinjectors are designed for single use only and should not be disassembled under any circumstances. You are encouraged to ensure that patients and caregivers are also aware of this information to promote the safe use of these medicines.

The TGA is aware of reports that some first aid providers are recommending disassembly of adrenaline autoinjectors after use to access any remaining medicine.

Disassembly of these devices can pose significant risks to patients and first aid providers, including needlestick injury, inappropriate administration and/or delay in accessing emergency medical care.

Adrenaline autoinjectors are indicated for the emergency treatment of anaphylaxis. They are preloaded to deliver an exact dose of adrenaline and include safety features that protect against needlestick injury. Adrenaline autoinjectors should be prescribed in accordance with relevant clinical guidelines, and should always be used according to the instructions in the Product Information (PI).

You are encouraged to advise patients and caregivers to regularly review the injection technique and other information in the instructions for these medicines to ensure they are familiar with their correct use. Also advise patients to review the relevant Consumer Medicine Information (CMI) leaflet.

Whenever adrenaline autoinjector treatment is administered, patients and caregivers should always call 000 for an ambulance, as further medical treatment may be required.

It may be appropriate to also advise patients and caregivers to carry (or otherwise have access to) a second adrenaline autoinjector to ensure that a back-up is available if needed.

PI and CMI documents for adrenaline autoinjectors are available on the TGA website.

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 Pharmacovigilance and Special Access Branch on 1800 044 114.

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

For correspondence or further information about Medicines Safety Update, contact the TGA's Pharmacovigilance and Special Access Branch at ADR.Reports@tga.gov.au or 1800 044 114

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