Australian Government
Department of Health
Therapeutic Goods Administration

# Medicines Safety Update

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## Bupropion and serious cardiovascular adverse events

The Product Information for bupropion is being updated to provide further information about the risk of serious cardiovascular adverse events.

Bupropion is a selective inhibitor of the neuronal reuptake of catecholamines, noradrenaline and dopamine. It is registered for use in Australia as a short-term adjunctive therapy, used in conjunction with counselling and abstinence, for nicotine dependence to assist in smoking cessation.

The Product Information (PI) for bupropion had previously contained information regarding hypertension. However, the TGA has identified postmarket spontaneous reports of more serious cardiovascular events, including myocardial infarction. To address this, the TGA is working closely with the innovator sponsor to update and strengthen the precautions for serious cardiovascular adverse events in the PI.

### Information update

The updated information will advise that there have been reports of patients receiving bupropion (alone and in combination with nicotine replacement therapy) experiencing severe hypertension requiring acute treatment, in patients both with and without pre-existing hypertension.

The updated information will also advise that there is limited clinical experience establishing the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, health professionals should exercise care if using bupropion in such patients.

It is recommended that blood pressure be monitored while the patient is taking bupropion, especially in patients with pre-existing hypertension, and consideration be given to discontinuing treatment if a clinically significant increase is observed.

A higher rate of hypertension has been observed when treatment with bupropion is combined with use of nicotine transdermal system products (patches).

If bupropion is used in combination with nicotine patches, caution must be exercised and weekly monitoring of blood pressure is recommended.

### Adverse events

As at 1 July 2014, the TGA has received a number of cardiovascular adverse event reports associated with use of bupropion. This includes 24 reports of myocardial infarction, five reports of cerebrovascular accident, and one report of transient ischaemic attack.

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

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

# Methylphenidate and priapism

Health professionals are advised that in very rare cases treatment with methylphenidate may potentially lead to prolonged and sometimes painful erections (priapism).

Methylphenidate is a central nervous system stimulant and is indicated for the treatment of attention deficit hyperactivity disorder (ADHD). It is marketed in Australia as Ritalin and Concerta.

A US Food and Drug Administration review of methylphenidate products resulted in priapism being added as a class warning to the drug's labelling. Subsequent investigation by the TGA found that, while there had been no reports of this adverse event in Australia, the risk of untreated priapism was potentially serious.

A precaution for priapism has recently been added to the Product Information (PI) for methylphenidate.

While this risk applies to all use in males, the greatest concern is regarding pre-pubertal boys, who might not recognise the problem or may be too embarrassed to seek help if it occurs. Health professionals should consider educating parents and caregivers of pre-pubertal boys being treated with methylphenidate about this issue, while reassuring them that it is very rare.

Priapism can develop some time after starting the drug, often following an increase in dose, and has also been observed during a period of methylphenidate withdrawal.

Health professionals who are considering switching patients to another drug due to this issue are advised that atomoxetine, which is also used to treat ADHD, has been associated with priapism. The PI for atomoxetine lists painful or prolonged erection and male genital pain as potential, but very rare, adverse events.

# Propranolol – prescribing to patients who may be at risk of self-harm

A recent case investigated by the Coroners Court of Victoria has prompted a warning regarding prescribing propranolol for patients who are suspected of being at risk of self-harm.

Propranolol is a beta-adrenoreceptor blocking drug which has a number of indications, the most common of which are:

- angina pectoris
- hypertension
- prevention of migraine
- essential tremor, including familial and senile tremor
- management of some cardiac dysrhythmias.

Propranolol is available in Australia in 100-tablet pack sizes of 10 mg and 40 mg tablets, as well as a 50-tablet pack of 160 mg tablets. If repeats are provided with a prescription for propranolol, the patient could accumulate a large number of tablets at one time.

The coroner recommended that the TGA advise health professionals to exercise caution when prescribing propranolol for patients suspected of being at risk of self-harm, particularly by overdose. Overdosage of propranolol can result in bradycardia, hypotension, bronchospasm and/or acute cardiac failure.

If propranolol is prescribed, consider providing prescriptions for smaller quantities or make other arrangements to reduce the amount of the drug that the patient has access to at one time.

## Adverse events

From 1972 to 1 July 2014, the TGA has received 829 reports of adverse events involving propranolol. Of these reports, five involved overdose and/or intentional overdose. Two of these cases resulted in the patient's death.

Health professionals are encouraged to report to the TGA all suspected adverse events relating to propranolol, particularly if they involve overdose and potential self-harm.

MEDICINES SAFETY UPDATE

# Valproate – fetal exposure and cognitive impairment

The TGA has reviewed updated information regarding the association between use of valproate during pregnancy and cognitive impairment in children.

Valproate is an anticonvulsant that is indicated for the treatment of primary generalised epilepsy and partial epilepsy. It is also indicated for the treatment of mania, where other therapy has proven inadequate or is inappropriate.

Earlier studies examined the effect of fetal exposure to valproate on cognitive outcomes in children and these risks are reflected in the Product Information (PI).

In particular, an interim analysis by the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study had found that fetal exposure to valproate was associated with a range of cognitive deficits at three years of age. In 2013, the NEAD study published its final analysis, which found fetal valproate exposure had dose-dependent associations with reduced cognitive abilities across a range of domains at six years of age.[1]

Meanwhile, another study found a link between use of valproate during pregnancy and autism spectrum disorders and childhood autism in the offspring, even after adjusting for maternal epilepsy.[2]

## NEAD study

The NEAD study was a prospective observational study that aimed to determine how fetal exposure to different antiepileptic drugs affected cognitive outcomes at various ages. Pregnant women with epilepsy receiving antiepileptic drug monotherapy were enrolled in the study, and their children's IQs were measured at 2, 3, 4.5 and 6 years of age.

There were 305 mothers and 311 live births included in the primary analysis, and 221 mothers and 225 children were included in the age six analysis.

Children with fetal exposure to valproate demonstrated reduced IQ at six years of age compared with other antiepileptic drugs. An increased valproate dose was associated with a range of cognitive deficits, including decreased verbal IQ.

While the mean valproate IQ was in the normal range, the 7–10 IQ point reduction for this drug compared with other antiepileptic drugs observed in the study was considered clinically significant.

## Autism study

Christensen et al. conducted a population-based cohort study on the risk of autism in children exposed to prenatal valproate.

Of 655 615 children born in Denmark between 1996 and 2006, 5437 were identified with autism spectrum disorder, including 2067 with childhood autism. The estimated absolute risk after 14 years of follow-up was 1.53% (95% confidence interval [CI] 1.47–1.58%) for autism spectrum disorder and 0.48% (95% CI 0.46–0.51%) for childhood autism. Overall, the 508 children exposed to valproate had an absolute risk of 4.42% (95% CI 2.59–7.46%) for autism spectrum disorder (adjusted hazard ratio [HR] 2.9 [95% CI 1.7–4.9]) and 2.50% (95% CI 1.30–4.81%) for childhood autism (adjusted HR 5.2 [95% CI 2.7–10.0]).

## Information update

The PI for valproate contains a warning about autism spectrum disorders and information about fetal exposure and the risk of developmental delay in the Use in Pregnancy section. However, the TGA's review of the updated information in the NEAD study has found that the information about cognitive impairment should be updated to show that cognitive deficits have been observed at six years of age.

The sponsor has agreed to update the PI and intends to incorporate any recommendations that may result from an ongoing review being conducted in the European Union.[3]

## REFERENCES

1. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurology 2013;12:244-52.
2. Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA 2013;309:1696-703.
3. European Medicines Agency. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7-10 July 2014. Update on the ongoing review of valproate and related substances.

MEDICINES SAFETY UPDATE

# Medicine shortages information resource

Drug shortages can have significant implications for the quality use of medicines and, in rare cases, can be a risk to public health.

Launched in May 2014, the Medicine Shortages Information Initiative aims to improve the communication and management of drug shortages in Australia.

In partnership with Medicines Australia and the Generic Medicines Industry Association, the TGA is providing information to assist health professionals and their patients when there is a temporary or permanent disruption (discontinuation) to the supply of a drug.

Changes to the access of any drug, even when a substitute medicine or therapeutic alternative is available, can have serious impacts.

You and your patients can search the Medicine Shortages Information Initiative website at www.tga.gov.au/hp/information-msi.htm for information about the nature, anticipated duration and status of prescription drug shortages.

The predicted shortage start and end dates are included on the website as soon as the TGA receives the information from the sponsor. In most cases, this will be sufficient to help you and your patients during a shortage period.

Once the shortage is resolved, it will be displayed in the 'Resolved' area for a period of three months.

In extreme cases, the TGA has a number of regulatory options to assist your patients, including the supply of a substitute medicine or therapeutic alternative through the Special Access Scheme. Where it is in the interests of public health, the TGA can also authorise the supply of an otherwise unapproved medicine.

## 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 and with the October issue of *Australian Prescriber*
- **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.

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