R13/708115

Committee-in-confidence

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Advisory Committee on the Safety of Medicines

Meeting 16
8 March 2013

Item 2.2: Update on Psychiatric Drug Safety Expert Advisory Panel recommendations

Source: Dr Jane Cook, Head, Office of Product Review

Purpose of item	For information.
Background	In 2008, the TGA established the Psychiatric Drug Safety Expert Advisory Panel (PDSEAP) to undertake a scientific review of case reports submitted to the TGA by a psychiatrist. The case reports examined by the PDSEAP mainly related to complicated medication and adverse event histories, in which numerous psychotropic medicines had been administered over considerable time periods. In addition, the PDESAP also undertook extensive literature reviews into the current state of knowledge, with a view to reconciling that information with information presented in Australian prescribing documents including the Product Information. In response, the PDSEAP developed a consolidated list of recommendations (attachment 1). A summary table of the recommendations and status to date is provided at attachment 2. The actions taken by OPR in response to recommendations to update the Product Information are included in Attachment 3. The full PDSEAP report 2009 can be accessed via http://www.tga.gov.au/pdf/alerts-medicine-ssri-pdseap-091224.pdf
Attachments	1. List of the PDSEAP recommendations 2. Implementation status of PDSEAP recommendations 3. Update on innovator PI changes associated with PDSEAP recommendations

List of Recommendations by PDSEAP

Recommended changes to Australian PI documents

Recommendation 1: Consideration should be given to requiring sponsors of all antidepressant medicines to include, as a minimum, standard text about the risks of inducing mania/hypomania in the Product Information documents, as follows:

"A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression."

Recommendation 2: Consideration should be given to requiring PI documents of the SSRIs and SNRIs to have, as a minimum, standardised text in the Contraindications and Precautions sections, as follows:

Contraindications

Monoamine oxidase inhibitors (MAOI)

[Drug name] should not be used in combination with monoamine oxidase inhibitors (MAOI) or the reversible MAOI (RIMA), moclobemide, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least [insert washout period] should be allowed after stopping [Drug name] before starting a MAOI. Cases of serious reactions, such as potentially life-threatening serotonin syndrome (characterised by neuromuscular excitation, altered mental status and autonomic dysfunction) have been reported in patients receiving an [SSRI/SNRI] in combination with MAOIs and RIMA, and in patients who have recently discontinued an [SSRI/SNRI] and have been started on a MAOI. (see also Precautions)"

Precautions

Serotonin syndrome

Development of serotonin syndrome may occur in association with treatment with SSRIs and SNRIs, particularly when given in combination with MAOIs or other serotonergic agents. Symptoms and signs of serotonin syndrome include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with [Drug name] should be discontinued if such events occur and supportive symptomatic treatment initiated."

Recommendation 3: Consideration should be given to requiring PI documents of the atypical antipsychotic medicines to have, as a minimum, standardised text about akathisia in the Precautions section, as follows:

"The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse."

Recommendation 4: The TGA should give consideration to including recommended glycaemic monitoring regimes in the PI documents of the atypical antipsychotic medicines.

Recommendation 5: The TGA should review the consistency and appropriateness of advice about monitoring of patients with diabetes mellitus contained within the PI documents of the SSRI class of antidepressants.

Recommendation 6: The TGA should give consideration to standardising the way in which important drug-drug interaction information is presented in the PI. A possible format is:

Pharmacodynamic interactions

- Interactions relevant to site of intended action (i.e. same system organ class SOC))

- Interactions at other sites (i.e. other SOCs)

Pharmacokinetic interactions

- Potential for other medicines to inhibit the metabolism of the medicine in question, with reference to metabolic pathway(s), and genetic polymorphism if relevant

- Potential for the medicine in question to inhibit the metabolism of other drugs, with reference to relevant metabolic pathway(s), and genetic polymorphism if relevant

- Interaction with highly protein bound medicines if relevant

- Other

Recommendation 7: The TGA should consider instituting a program in which Australian Product Information documents of medicines are routinely reviewed for consistency with international monographs throughout their life cycle.

Recommendation 8: The *Use in Pregnancy* section in the reboxetine PI should be amended to include advice about the potential for neonatal effects.

Recommendation 9: The *Use in Pregnancy* section in the PI documents of all the SSRIs should include advice about the risk of Persistent Pulmonary Hypertension in the Newborn.

Recommendations regarding prescriber education and quality use of psychotropic medicines

Recommendation 10: The TGA should consider instituting an outreach program (through its Principal Medical Adviser) to liaise with the National Prescribing Service and the various professional colleges on matters pertaining to medicines safety and quality use issues.

Recommendation 11: The TGA should include items on serotonin syndrome and akathisia in upcoming issues of its Adverse Drug Reactions Bulletin.

Recommendations for enhanced pharmacosurveillance

Recommendation 12: The TGA should be able to commission epidemiological studies using linked databases.

Recommendation 13: The TGA should consider implementing a post market surveillance system with the following elements:

· Research networks, including strengthened relationships with researchers

· Public oversight of independently conducted post-market research

· Phased introduction of new drugs with potential for large scale use

· A flexible and enforceable tool kit of regulatory options

· Adequate funding

· Active surveillance

· Regional pharmacovigilance centres

Psychiatric Drug SafetyExpert Advisory Panel (PDSEAP) Recommendations – Summary table (to 1 March 2013)

Recommendation	Action taken to date/Response
Recommendation 1: Consideration should be given to requiring sponsors of all antidepressant medicines to include, as a minimum, standard text about the risks of inducing mania/hypomania in the Product Information documents, as follows: "A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression."	Completed for all but one reference product, generics in progress.
Recommendation 2: Consideration should be given to requiring PI documents of the SSRIs and SNRIs to have, as a minimum, standardised text in the Contraindications and Precautions sections, as follows: ***Contraindications*** **Monoamine oxidase inhibitors (MAOI)** [Drug name] should not be used in combination with monoamine oxidase inhibitors (MAOI) or the reversible MAOI (RIMA), moclobemide, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least [insert washout period] should be allowed after stopping [Drug name] before starting a MAOI. Cases of serious reactions, such as potentially life-threatening serotonin syndrome (characterised by neuromuscular excitation, altered mental status and autonomic dysfunction) have been reported in patients receiving an [SSRI/SNRI] in combination with MAOIs and RIMA, and in patients who have recently discontinued an [SSRI/SNRI] and have been started on a MAOI. (see also Precautions)" ***Precautions*** **Serotonin syndrome** Development of serotonin syndrome may occur in association with treatment with SSRIs and SNRIs, particularly when given in combination with MAOIs or other serotonergic agents. Symptoms and signs of serotonin syndrome	Completed for reference products, generics in progress.

include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with [Drug name] should be discontinued if such events occur and supportive symptomatic treatment initiated."	
Recommendation 3: Consideration should be given to requiring PI documents of the atypical antipsychotic medicines to have, as a minimum, standardised text about akathisia in the Precautions section, as follows: "The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse."	Completed for eight reference products and in train for remaining two reference products. Generic products in train where reference product has made PI update.
Recommendation 4: The TGA should give consideration to including recommended glycaemic monitoring regimes in the PI documents of the atypical antipsychotic medicines.	Completed
Recommendation 5: The TGA should review the consistency and appropriateness of advice about monitoring of patients with diabetes mellitus contained within the PI documents of the SSRI class of antidepressants.	Completed
Recommendation 6: The TGA should give consideration to standardising the way in which important drug-drug interaction information is presented in the PI. A possible format is: Pharmacodynamic interactions - Interactions relevant to site of intended action (i.e. same system organ class SOC)) - Interactions at other sites (i.e. other SOCs) Pharmacokinetic interactions - Potential for other medicines to inhibit the metabolism of the medicine in question, with reference to metabolic pathway(s), and genetic polymorphism if relevant - Potential for the medicine in question to inhibit the metabolism of other drugs, with reference to relevant metabolic pathway(s), and genetic polymorphism if relevant	This is general recommendation regarding the presentation of drug-drug interactions, it will be considered when a review of the PI content is undertaken.

- Interaction with highly protein bound medicines if relevant - Other	
Recommendation 7: The TGA should consider instituting a program in which Australian Product Information documents of medicines are routinely reviewed for consistency with international monographs throughout their life cycle.	To be considered as part of MCG 5 (response to Transparency Rec 17)
Recommendation 8: The *Use in Pregnancy* section in the reboxetine PI should be amended to include advice about the potential for neonatal effects.	At this stage the TGA have not found sufficient evidence to support the inclusion of additional advice about the potential for neonatal effects in the reboxetine PI.
Recommendation 9: The *Use in Pregnancy* section in the PI documents of all the SSRIs should include advice about the risk of Persistent Pulmonary Hypertension in the Newborn.	Completed
Recommendation 10: The TGA should consider instituting an outreach program (through its Principal Medical Adviser) to liaise with the National Prescribing Service and the various professional colleges on matters pertaining to medicines safety and quality use issues.	TGA meets on a weekly basis with NPS to discuss safety issues under investigation and prescriber and consumer education. Liaison with professional colleges considered under TGA communication strategy.
Recommendation 11: The TGA should include items on serotonin syndrome and akathisia in upcoming issues of its Adverse Drug Reactions Bulletin.	Completed
Recommendation 12: The TGA should be able to commission epidemiological studies using linked databases.	Noted. The TGA has the ability to commission small observational studies (for example the association of intussusception with rotavirus vaccine administration)

Recommendation 13: The TGA should consider implementing a post market surveillance system with the following elements: · Research networks, including strengthened relationships with researchers · Public oversight of independently conducted post-market research · Phased introduction of new drugs with potential for large scale use · A flexible and enforceable tool kit of regulatory options · Adequate funding · Active surveillance · Regional pharmacovigilance centres	Will be considered as part of wider TGA Blueprint Reforms and Senate Inquiry recommendations on post-market surveillance.

Update on innovator PI changes associated with PDSEAP recommendations

Medicine	Trade Name	PDSEAP recommended PI Changes Required*	Action Taken^
Atypical Antipsychotics			
Amisulpride	Solian	PDSEAP Rec 4 (diabetes)	PI updated
Aripiprazole	Abilify	PDSEAP Rec 4 (diabetes)	PI updated
Asenapine	Saphris	PDSEAP Rec 3 (akathisia) PDSEAP Rec 4 (diabetes)	PI updated
Clozapine	Clozaril	PDSEAP Rec 3 (akathisia)	PI updated
Olanzapine	Zyprexa	PDSEAP Rec 3 (akathisia)	PI updated
Paliperidone	Invega	PDSEAP Rec 3 (akathisia)	PI update in progress
Risperidone	Risperdal	PDSEAP Rec 3 (akathisia)	PI updated
Quetiapine	Seroquel	PDSEAP Rec 3 (akathisia)	PI update in progress
Sertindole	Serdolect	PDSEAP Rec 4 (Diabetes)	PI updated
Ziprasidone	Zeldox	PDSEAP Rec 3 (akathisia)	PI updated
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Citalopram	Cipramil		No PI update required
Escitalopram	Lexapro		No PI update required
Paroxetine	Aropax	PDSEAP Rec 5 (diabetes)	PI updated
Fluvoxamine	Luvox		No PI update required
Fluoxetine	Prozac		No PI update required
Sertraline	Zoloft		No PI update required
Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)			
Venlafaxine	Efexor	PDSEAP Rec 2 (MAOI and Serotonin Syndrome)	PI updated
Desvenlafaxine	Pristiq	PDSEAP Rec 2 (MAOI and Serotonin Syndrome)	PI updated
Duloxetine	Cymbalta	PDSEAP Rec 1 (bipolar) PDSEAP Rec 2 (MAOIs and serotonin syndrome)	PI updated
Noradrenaline Reuptake Inhibitor (NRIs)			
Reboxetine#	Edronax	PDSEAP Rec 1 (mania)	PI updated
Noradrenaline-Serotonin Specific Antidepressants (NaSSAs)			
Mirtazepine	Avanza		No PI update required
Mianserin	Tolvon	PDSEAP Rec 1 (mania)	PI updated
Tricyclic Antidepressants (TCAs)			
Clomipramine	Anafranil	PDSEAP Rec 1 (mania)	PI updated
Doxepin	Sinequen	PDSEAP Rec 1 (mania)	PI updated
Imipramine	Tofranil	PDSEAP Rec 1 (mania)	PI updated

Medicine	Trade Name	PDSEAP recommended PI Changes Required*	Action Taken^
Nortriptyline	Allergon	PDSEAP Rec 1 (mania)	PI updated
Trimipramine	Surmontil	PDSEAP Rec 1 (mania)	PI updated
Dothiepine	Prothiaden		No PI update required
Amitriptyline	Endep	PDSEAP Rec 1 (mania)	PI updated
Monoamine Oxidase Inhibitors (MAOIs)			
Moclobemide	Aurorix	PDSEAP Rec 1 (mania)	PI updated
Phenelzine	Nardil		No PI update required
Tranylcypromine	Parnate		No PI update required
Melatonergic Agonist			
Agomelatine	Valdoxan	PDSEAP Rec 1 (mania)	PI update in progress

Additional notes:

*refers to PI updates required to bring the PI in line with the PDSEAP recommendations. If not listed, other relevant PDSEAP recommendations were already incorporated in the PI.

^changes have only been made to the innovator PI of each medication. The TGA has processes to update the PIs for all generics. The Office of Medicines Authorisation are working with the sponsor's of generics to update the PIs accordingly.

PDSEAP recommendation 8 relates to reboxetine, at this stage the TGA have not found sufficient evidence to support the inclusion of additional advice about the potential for neonatal effects.