

**REPORT OF THE PSYCHIATRIC DRUG SAFETY
EXPERT ADVISORY PANEL**

2009

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Executive Summary

In August 2008, the TGA established the Psychiatric Drug Safety Expert Advisory Panel (the Panel) to undertake a scientific review a series of case reports submitted to the TGA by a psychiatrist with a special interest in forensic and medico-legal psychiatry. Most of the reports described complicated medication and adverse event histories, in which numerous psychotropic medications had been administered over considerable time periods.

The Panel was asked to assess which of the case reports submitted to the TGA described 'new' or 'unrecognised' adverse events caused by antidepressant and antipsychotic medications of interest. To avoid potential bias in the assessment of the case reports, each report was assessed and rated independently by two of the three Panel members. Once the rating process was completed the co-raters undertook a series of consensus meetings at which each item was discussed until agreement was reached on the rating for each case.

The Panel found the reports were most valuable for highlighting a number of issues associated with the use of psychotropic medicines, including:

- the extent of and problems associated with polypharmacy - the presence of polypharmacy in the majority of the cases was of major concern given the lack of evidence for the use of many of the prescribed combinations and the increased potential for adverse effects when multiple medications are used concurrently;
- the difficulties for clinicians in distinguishing some side effects, such as akathisia, from underlying psychiatric disorders; and
- inconsistencies between current Australian Product Information documents and international monographs for some of these medicines.

Panel members were unable to draw any further conclusions on the information provided in this series of case reports. Polypharmacy and concurrent poly-substance use complicated the issue in the majority of these cases. As a result, a connection between the medication and the adverse report could be made only in a small proportion of case reports. In these cases there was usually clear evidence of a temporal relationship between the onset of symptoms (e.g. akathisia or suicidal ideation) and the use of medication and evidence that the symptom improved on discontinuation or reduction in dose of the drug. The other cases typically involved clear descriptions of serotonin syndrome occurring in a patient taking multiple serotonergic medications, including drugs like tramadol. None of these cases, however, was a new adverse report.

The Panel also undertook extensive literature reviews, with a view to examining the current state of knowledge of the following topics and reconciling this with the appropriateness of information in existing Australian prescribing information documents such the Product Information:

- SSRI antidepressants and suicidal mortality, including in children;
- Antidepressants and the induction hypomania/mania;
- Serotonin syndrome arising from polypharmacy;
- Akathisia and antipsychotic medicine;

- Weight gain, obesity and diabetes;
- Interactions between antipsychotic and antidepressant medications; and
- SSRI antidepressants and pregnancy

Based on the collective findings of these all activities, the Panel has made recommendations in three main areas:

- Changes to Australian Product Information documents;
- Prescriber education activities; and
- Enhancement of pharmacosurveillance activities

A consolidated list of recommendations follows this summary.

Consolidated list of recommendations

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 at 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 SOC)

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

Part A Context

Chapter 1 Terms of Reference

Chapter 2 Background

2.1 What is an adverse drug reaction?

2.2 Methods of assessing adverse drug reactions

Chapter 3 Approach to the assessment of the reports

Chapter 1 Terms of Reference

In August 2008, the TGA established the Psychiatric Drug Safety Expert Advisory Panel (the Panel) to undertake a scientific review a series of case reports submitted to the TGA by a psychiatrist with a special interest in forensic and medico-legal psychiatry.

The reports contained details of the experiences of several healthcare professionals involved in the management of patients who had received a variety of psychiatric medicines and experienced adverse events. In correspondence the psychiatrist had raised particular concerns over the safety of selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotic medicines, drawing attention to problems that may occur with polypharmacy.

The PDSEAP was asked to:

- identify and document the reported adverse effects that may be reasonably attributed to the medicines specified therein;
- review the relevant literature for those drugs and document their adverse effects with, wherever possible, quantitative information about incidence;
- provide a commentary on the degree of congruence or dissonance between the recognised adverse effects of each of the identified medicines and those attributed to them in the case reports;
- provide advice on the clinical importance of any adverse effects recorded in the case reports but not identified in the literature review; and
- provide advice as to whether the adverse effects identified through the literature reviews are adequately described in the approved Australian product Information documents.

The members of the Panel were:

- Professor Wayne Hall, a pharmacoepidemiologist who is an NHMRC Australia Fellow, Professor of Public Health Policy at the University of Queensland and Chair of the Drug Utilisation Subcommittee of the Pharmaceutical Benefits Advisory Committee (PBAC);
- Professor Steve Kisely, a psychiatrist, epidemiologist and public health physician from the University of Queensland and Director of the Queensland Centre for Health Data Services; and
- Dr Frances Wilson, a consultant psychiatrist at Westmead Hospital.

Chapter 2 Background

2.1 What is an adverse drug reaction?

The Panel noted the TGA has well established guidelines setting out requirements for the reporting of adverse drug reactions ¹. Although these guidelines outline the regulatory responsibilities of sponsors, they nevertheless provide insight into the TGA's approach to the assessment of adverse drug reactions and identification of possible safety signals as well as its expectation of the key information required in order to adequately assess the causality of events observed.

An adverse event is any untoward medical occurrence in a patient administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the outcome is considered to be related to that medicinal product.

A reaction, in contrast to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected. It follows that the minimum information required of a report of a suspected adverse drug reaction is an identifiable patient, an identifiable reporter, a suspected reaction and a suspect medicine. The key data elements required to enable evaluation of reports and attribution of causality include:

- Patient Details – initials, gender, age or date of birth, concomitant conditions, medical history and relevant family history;
- Suspected Medicinal Product(s) - brand or generic name, batch/lot number, indication(s) for which suspect medicinal product was prescribed, dosage form and strength, daily dose and regimen, route of administration, starting date and stopping date or duration of treatment;
- Other Treatment(s) – for medicines, the same information as for the suspected medicine, as well as details of any medical devices used; and
- Details of the suspected adverse drug reaction(s) - full description of reaction(s), including body site and severity and a description of the reported signs and symptoms, specific diagnosis for the reaction, onset and stop date of the reaction or duration of reaction, de-challenge and rechallenge information, relevant diagnostic test results and laboratory data, outcome (recovery and any sequelae), including for a fatal outcome, stated cause of death or relevant autopsy or post-mortem findings.

The submission of an individual report does not in itself constitute evidence of a safety issue. Although most reports are implicitly attributed to one or more medicines, any individual report may have several possible explanations that include confusion with complications due to the underlying illness (so-called confounding by indication), confounding by other co-morbidities, prescription errors and the chance occurrence of a new illness unrelated to either the original condition being treated or the medicine (especially if it has been used long term).

Thus, it is important to assess not only the individual reports but all similar reports collectively and robustly for evidence of a safety signal. Sir Bradford Hill established the

following nine criteria for causation (does factor A cause disorder B) which are relevant to the detection of safety signals from adverse drug reaction reports ²:

- *Strength of the association*: How large is the effect?
- *The consistency of the association*: Has the same association been observed by others, in different populations, using a different method?
- *Specificity*: Does altering only the cause alter the effect?
- *Temporal relationship*: Does the cause precede the effect?
- *Biological gradient*: Is there a dose response?
- *Biological plausibility*: Does it make sense?
- *Coherence*: Does the evidence fit with what is known regarding the natural history and biology of the outcome?
- *Experimental evidence*: Are there any clinical studies supporting the association?
- *Reasoning by analogy*: Is the observed association supported by similar associations?

References

1. Australian Guideline for Pharmacovigilance Responsibilities of Sponsors of Registered Medicines Regulated by Drug Safety and Evaluation Branch (July 2003 – Amended 31 May 2005).
2. Bradford-Hill A. The environment and disease: Association or causation? *Proc R Soc Med* 1965; 58: 295-300.

2.2 Methods of assessing adverse effects of prescribed medicines¹

Generally, drugs are only approved for medical use if they have been shown to be safe and effective in randomised controlled trials (RCTs). Although data from RCTs provide good reasons for expecting that widely prescribed medicines may improve health outcomes, outcomes observed in such trials may not occur in routine clinical use. Controlled clinical trials may therefore provide optimistic estimates of effectiveness under routine clinical care because the medicines are used to treat more seriously ill patients in the community than were studied in clinical trials^{1, 2}. Drugs may also be prescribed inappropriately, or patients not comply with recommended use of the drugs. Clinical trials will also only detect common adverse drug reactions (ADRs); uncommon ADRs will often only be detected after a drug has been approved and widely used. This section evaluates the research methods that can be used to assess the adverse effects of prescribed medicines on health outcomes in the community. It reviews methods used to make causal inferences about the relationships between medicine use and adverse health outcomes (e.g.^{3,4}).

2.2.1 Research methods

Making Causal Inferences

When we say that medicine use is a cause of an adverse health outcome we mean that it is a contributory cause of that outcome in the sense that use of the medicine is one of a complex set of conditions that jointly produced it. In order to infer that medicine use is a contributory cause in this sense we need evidence that: (1) medicine use and the health outcome co-vary; and (2) evidence that other explanations of the relationship are implausible, leaving medicine use as the most plausible explanation of the adverse health outcome⁵⁻⁷.

Assessing Covariation

We can assess whether medicine use and an adverse outcome co-vary in experiments (such as randomised controlled trials) or in observational studies (e.g. ecological, case-control, cohort, time series and cross-sectional studies).

Excluding Alternative Explanations

A and B may be correlated without being causally related. Hence, in order to make a case for a causal relationship we must exclude plausible alternative explanations of the relationship⁶⁻⁸. Experiments provide the strongest basis for excluding alternative explanations of covariation but they are expensive and difficult to conduct. Observational designs are easier to enact but provide a weaker warrant for causal inferences because of their limitations in excluding the following alternative explanations^{7,9}.

Chance?

We can assess the plausibility of chance by constructing a confidence interval around the measure of covariation between medicine use and the health outcome. If the

¹ This chapter is based on the following article: Hall W and Lucke J. Assessing the impact of prescribed medicines on health outcomes. *Australia and New Zealand Health Policy* 2007, 4:1 doi 10.1186/1743-8462-4-1.

confidence interval does not include the value consistent with the absence of a relationship between medicine use and the health outcome, then we can infer that medicine use and health outcome co-vary^{10,11}.

Cause or Consequence?

If medicine use is a cause of an adverse health outcome, then medicine use should occur before the deterioration. Experiments and cohort studies (which measure medicine use before assessing the health outcome) provide the best basis for deciding which is cause and which is consequence².

A Common Cause?

If medicine use and the health outcome co-vary, and medicine use precedes the health outcome, we then have to exclude the possibility that a common cause explains the relationship between the two. Experiments provide the best evidence against a common cause because randomisation to an active medicine or a placebo ensures that subjects differ only in whether or not they have been exposed to the medicine^{11,12}. When subjects are randomly assigned to a medicine or a placebo then all other causal factors will be equally distributed between the two groups¹³ and hence, any difference between the two groups can be attributed to medicine use.

Causal Inferences from Observational Data

When experiments and intervention studies cannot be done for ethical and practical reasons common causes must be excluded by indirect means. The logic of the approach is conceptually straightforward: we see whether A and B co-vary when possible common causes are statistically “controlled for”.

One approach to this goal is to control potentially confounding variables in the **study design**. For example, we could rule out the hypothesis that any relationship between non-steroidal anti-inflammatory drug (NSAID) use and coronary heart disease (CHD) was due to the concurrent use of another medicine by: (i) excluding individuals who used that medicine from the cohort study; or (ii) by matching cases and controls on the use of that medicine^{2,14}.

Another approach to dealing with confounding in epidemiology is **covariate adjustment**. In this approach, all study participants are measured on potentially confounding variables (covariates) and statistical methods are used to estimate the association between A and B while controlling for the covariates¹⁴⁻¹⁷.

Propensity score analysis can be used to assess the plausibility of selection bias as an explanation of relationships in observational studies where patients select their own treatment^{12,14}. In studies using this approach, covariates are used to predict the exposure condition that each individual had the greatest propensity to receive. The resulting “propensity score” can be used either as a matching variable or as a covariate in regression analyses^{12,18}.

Sensitivity analyses can be used when we do not have measures of potential confounders for covariate adjustment or propensity score analysis. Such analyses explore the plausibility of confounding as an explanation of observed outcomes^{12,14,19}. These analyses involve modelling the relationship between medicine use and the health outcome under various scenarios in which a confounding variable is related in varying degrees to both medicine use and the outcome. If the relationship between the two persists when

allowance is made for plausible degrees of confounding then we can be more confident that the relationship is likely to be causal (²⁰, pp 193-6).

The major limitation of all these strategies is that they can only rule out specified alternative hypotheses. That is, we have to identify a candidate common cause that we can then match on, measure and adjust for using covariate adjustment or propensity scores, or model in sensitivity analyses. Randomisation is superior to all these strategies because it rules out all possible common causes, including ones that have not been measured or thought of¹¹.

Causal Inferences from Individual Data on Health Outcomes and Medicine Use

Ideally we would examine relationships between medicine use and health outcomes in large samples of individuals who comprised a representative sample of the population about which we wish to make inferences. These data may be collected in very large-scale special-purpose longitudinal studies of representative samples of the population (e.g. ²¹), but such studies are very expensive to mount and time-consuming to conduct²². Unless they collect comprehensive data on health outcomes, they may only be able to examine the health outcomes that they were primarily designed to study. Even then they often rely upon self-reports of both health outcomes and medicine use.

An alternative approach that has been used in Canada, Europe and the USA ²³⁻²⁸ is to link electronic data on medicine use and health outcomes in identified individuals that is routinely collected in administrative health care databases ²⁹. These linked databases typically link data on identified individuals in separate data sets, such as, hospital morbidity collections, mortality data, disease registers, records of outpatient care, and records of prescribed medicines. These data sets are usually linked without individual consent because of the impracticality of obtaining it ³⁰. A view often taken by research ethics committees is that individual data can only be obtained for research purposes with the consent of the person on whom the data have been collected. This is impractical with large administrative data sets because of the costs and logistical challenges in contacting individuals and the fact that personally contacting individuals to obtain their consent may be arguably more intrusive than using their data without their consent.

These data sets can be linked without individual consent if a mechanism for de-identification has been included in the process. In Australia, for example, such data are classified as 'de-identified' and consent is no longer required for public interest research. A protocol has been designed for the Western Australian data linkage project to permit health data to be linked in ways that are acceptable to ethics committees and consistent with the relevant legislation ³⁰. These arrangements have been extended nationwide.

Administrative databases may not include data on patient characteristics that predict treatment outcome ³¹. Key missing data may include: individuals' use of alcohol and tobacco; individuals' use of over-the-counter medications; and the presence of comorbid conditions that will affect treatment outcome ³¹. The latter may have to be assessed indirectly via proxy indicators, such as hospital treatment for a comorbid condition.

The major statistical challenge in studying the effects of medicine use via linked data is dealing with "confounding by indication" ^{3, 32-34}. Because patients who have particular diseases are more likely to be prescribed medicines, those who receive the medicines

usually have an higher risk of experiencing adverse health outcomes that are attributable to their disease, or other common comorbid conditions, regardless of their treatment, than patients who do not have the disease³³. If account is not taken of such confounding, then observational studies may misleadingly suggest that the medicine use produces harm when in fact it may be beneficial^{18, 34, 35}. For example, in observation studies patients who take antihypertensive drugs will have higher average blood pressures than those who do not; if we did not take account of their blood pressure before they took the medication then we would mistakenly conclude that the medication had raised their blood pressure. The analytical approaches outlined above can also be used to address confounding in linked data sets, that is, covariate adjustment and analyses using propensity scores, and sensitivity analyses to assess the impact of sample selection bias on relationships between medicine use and health outcomes^{14, 18, 34}.

An additional complication in Australia is that some data are held by States and Territories (e.g. hospital morbidity and psychiatric service contacts), and others by the Commonwealth (e.g. PBS and Medicare data).

The capacity of covariate adjustment and propensity analysis to adequately control for confounding by indication depends upon the quality of data available in the database on potential confounders³⁶, and the extent of the overlap of distributions on key covariates between individuals exposed to the two or more treatments that are being compared^{18, 34}. A major limitation of both methods is that they are only as good as the covariates that are available to control for confounding. If key covariates that predict the outcome (e.g. tobacco and alcohol use, comorbid conditions, etc) are not measured then neither of these approaches can be used to control for confounding by indication^{34, 36}. In the absence of measures of key potential confounders, we are limited to sensitivity analyses and epidemiological modelling to assess the seriousness of the threat that confounding by indication poses to the validity of any inferences that can be draw from the data on the benefits of medicines¹⁴.

Causal Inferences from Aggregate Data on Health Outcomes and Medicine use

When individual linked data on pharmaceutical use and health outcomes are not available we can only assess associations between (1) population data on pharmaceutical use and (2) population health outcomes such as mortality or morbidity attributable to a specific disease⁴. The analysis of aggregate data on medicine use and health outcome comprises a type of “ecological analysis” that uses data on groups to make inferences about the health of individuals^{37, 38}. If we assume, in the absence of good reasons for so doing, that individual level relationships can be inferred from aggregate level relationships, then we are said to have committed the “ecological fallacy”^{39, 40}.

The dominant view in the epidemiological literature is that ecological studies should only be conducted when individual level data are unavailable. Even then they are only seen as providing, at best, inexpensive and relatively efficient ways of generating hypotheses that need to be tested in analyses of relationships between these variables measured in individuals (e.g.^{4, 9, 37, 41}).

2.2.2 Conclusions

There is no “gold standard” method for assessing the impact of medicine use on health outcomes. In its absence, a convergence of evidence from different types of studies using multiple methods of independent imperfection provides the best reason for attributing improvements in health outcomes to the use of medicines (see Table 2.1).

The major requirement for being able to do so is good evidence that:

- a safe and effective medicine is being appropriately prescribed in clinical practice;
- there is covariation between medicine use and health outcomes; and
- we can discount alternative explanations of the covariation, leaving medicine use as a plausible explanation of the health outcomes.

Table 2.1 Approaches to studying the effects of medicines on health outcomes

Method of study	Strengths	Limitations
Randomised Controlled Trials and meta-analyses of such trials	<ul style="list-style-type: none"> · Gold standard evidence for causal relationship by virtue of randomisation to treatment 	May not predict effects of medicines on health outcomes because: <ul style="list-style-type: none"> · May be too small to detect rare adverse events · May be too short to detect long term adverse effects · May exclude high risk patients e.g. those with comorbidity · May involve optimal treatment and compliance
Linked data on individuals	<ul style="list-style-type: none"> · Links data on medicine use and health outcomes in individuals · Closer to routine clinical practice than evidence from RCTs · Cheap and quick to do retrospectively 	<ul style="list-style-type: none"> · Confounding by indication: patients who use medicines are at a higher risk of a disease · Limited assessment of confounders e.g. comorbidity, OTC drugs, alcohol & tobacco · Often uses treated morbidity as a proxy for comorbidity
Ecological studies	<ul style="list-style-type: none"> · Simple and cheap to do because use existing data on medicines and health outcomes · Directly examine relationships between population medicine use and health outcomes 	<ul style="list-style-type: none"> · Use aggregate rather than individual level data · Crude measures of medicine use e.g. drug sales or scripts · Limited capacity to exclude alternative explanations such as changes in risk factors, and increased use of other treatments
Epidemiological modelling	<ul style="list-style-type: none"> · Mathematical synthesis of epidemiological data on the disease and clinical trial data on safety and efficacy of medicines 	<ul style="list-style-type: none"> · Simplifications of complex natural history of disease · Uncertainties about long term effects of medicines (addressed by sensitivity analyses) · Underdeveloped in studies of effects of medicines on health outcomes

The strongest possible evidence for an inference that the use of a medicine has adversely affected population health outcomes would be provided by the coherence of the following types of evidence:

- individual linked data showing that patients are prescribed the medicine, there are reasonable levels of patient compliance, and there is a relationship between medicine use and adverse impacts on health that is not explained by other factors;
- evidence of aggregate deteriorations in these health outcomes in the population in which the medicine is used;
- the replication of these results in comparable countries;
- consistent trends in population vital statistics in countries that have introduced the medicine; and

epidemiological modelling that changes observed in population health outcomes are plausible, given the epidemiology of the condition, and the clinical effectiveness of the medicines (after discounting for the decline in efficacy observed in RCTs to that expected in routine clinical practice).

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Chapter 3 Approach to the assessment of the reports

A total of eighty eight case reports were submitted to the TGA, of which eighty three described a side effect and an associated medicine(s) and could, therefore, be considered evaluable. Of the remaining reports, two were duplicates, one had no details of either an event or medicine, and two described clinical events with no specific medicine identified.

Most of the evaluable reports contained complicated medication and adverse event histories, in which numerous psychotropic medications had been administered over considerable time periods. A total of sixty one medicines were identified across the eighty three reports, with an average of 4.6 medicines per report (median 4; range 1 to 16).

The Panel was asked by the TGA to concentrate on the following specified list of psychotropic medicines as they were the main focus of the reports:

amisulpride	fluvoxamine	quetiapine
aripiprazole	mirtazapine	reboxetine
citalopram	moclobemide	risperidone
escitalopram	olanzapine	sertraline
fluoxetine	paroxetine	venlafaxine

A total of seventy three case reports identified at least one of these ‘medicines of interest’ and were subject to detailed assessment by the Panel. Panel members were each provided with PDF documents of the de-identified case reports. The task confronting the Panel was to assess which of the case reports submitted to the TGA described ‘new’ or ‘unrecognised’ adverse events caused by the antidepressant and antipsychotic medications of interest. This would then allow the Panel to flag deficiencies in each individual medicine’s Australian Product Information.

To avoid potential bias in the assessment of the case reports, each ‘evaluable’ report (identified by folio and case number, e.g. folio 1, case 3) was assessed and rated independently by two of the three Panel members, recording the following information:

The target medication

If multiple medicines were mentioned, where there was a sense of a predominant medicine this was recorded as the target medication.

The adverse event class

Only side effects with a clear link to the case were recorded. Where multiple effects were described for the antipsychotic agents and appeared to be collapsible, a category titled ‘drug-induced neurotoxicity’ was recorded.

The adverse event description

Panel members recorded a description of the event associated with the target medicine and any assertions about that medicine. In reports where assertions were made about medicines that were not the target medicine but still required scientific challenge, such assertions were also recorded (quotations were often used).

Relevant references

Any published literature known by the Panel member to be relevant to and useful for clarifying ambiguous statements or correcting incorrect scientific assertions were listed by the Panel member.

Evidence of polypharmacy

Reports were assessed from the point of view of whether there was polyantipsychotic prescribing (PAP) and/or polypsychotropic prescribing (PPP) in order to ascertain the ability to relate the adverse event to a particular medicine or class of medicines.

Rating scores

Ratings of reported adverse effects were made on three dimensions:

- known link as reported in the literature on a scale of 7, from none (0) to strong (6);
- strength of the link in this particular case on a scale of 4, from none (0) to strong (3); and
- veracity on a scale of 4, from none (0) to strong (3). Veracity was an overall rating based on the previous two that measured the need to investigate the reported adverse effect more fully. A rating of three implied that it required further examination in depth.

Once the data recording and rating process was completed, each pair of co-raters undertook a series of telephone-based consensus meetings. At these meetings each rater's comments and their scores for each of the four variables in the individual reports were presented and recorded in a spreadsheet prior to discussion. If the scores differed, discussion ensued until agreement was reached.

Part B Findings

Chapter 4 Challenges in evaluating the reports

Chapter 5 Summary of the drug reactions reported

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5.2 Findings in relation to antidepressant medicines of interest

Chapter 6 The literature on these adverse drug reactions

6.1 SSRI antidepressants and suicidal mortality

6.2 Induction of manic states

6.3 Serotonin syndrome arising from polypharmacy

6.4 Akathisia and antipsychotic medicine

6.5 Weight gain, obesity and diabetes

6.6 Interactions between antipsychotic and antidepressant medications

6.7 SSRI antidepressants and pregnancy

Chapter 7 Review of Australian Product Information (PI) documents

7.1 SSRI antidepressants and suicidal mortality

7.2 Induction of manic states

7.3 Serotonin syndrome arising from polypharmacy

7.4 Akathisia and antipsychotic medicine

7.5 Weight gain, obesity and diabetes

7.6 Interactions between antipsychotic and antidepressant medications

7.7 Antidepressants and pregnancy

Chapter 4 Challenges in evaluating the reports

There were a number of challenges in evaluating the adverse drug reports provided by the reporter. First, the majority of the adverse reports were embedded in legal reports written for the courts.

Second, the putative adverse drug reactions were usually not observed by the reporter but based on retrospective histories of symptoms and medication use provided by the patient. These reports often covered periods of years and, in some cases, decades preceding the interview in which the reports were obtained. Consequently, it was often difficult to judge the temporal relationship between the symptoms attributed to drug use and the drug use. The reporter also attributed adverse effects to medications not just immediately after initiation or during dose escalation but sometimes months after cessation.

Third, it was often not clear how compliant patients had been with prescriptions, i.e. whether they had taken the prescribed drugs to which adverse drug effects were attributed, and if so, for how long and whether they were taking them at the time of the putative adverse drug reaction.

Fourth, polypharmacy was a major complicating issue in many cases. These patients were prescribed multiple antidepressant and antipsychotic drugs, often by different practitioners (GP and psychiatrists) who were not always aware that other doctor's were prescribing for the patient or that the patient was still taking previously prescribed drugs.

Fifth, recreational poly-drug use was an additional complication in some patient histories. This was most often heavy alcohol use but on occasion included psychotogenic illicit drugs like cannabis, cocaine and amphetamines.

All of these factors made the task of judging the connection between prescribed drugs and putative adverse reactions difficult to assess.

Chapter 5 Assessment of the reported drug reactions

Although there were 83 evaluable reports, a number of these referred to both antidepressant and antipsychotic medicines and so were evaluated by both pairs of raters.

Steve Kisely and Wayne Hall independently assessed 37 case reports for patients who were prescribed one or more of the antipsychotic medicines of interest. A further two reports describing the use of antipsychotic medicines of interest were excluded as they were based on past records of deceased patients rather than direct observation or clinical interviews with the patient.

Frances Wilson and Wayne Hall independently assessed 54 case reports for patients who were prescribed one or more of the antidepressant medicines of interest. A further four reports describing the use of antidepressant medicines of interest were excluded because they described symptoms in deceased patients that were based on assessments of clinical records rather than clinical interviews with the patient.

Each pair of reviewers met to compare ratings and resolved any minor discrepancies after discussion.

5.1 Findings in relation to antipsychotic medicines of interest

5.1.1 Diagnosis

About 50% (n=19) had a diagnosis of schizophrenia or other psychosis. The remainder had affective disorder, post-traumatic stress disorder and personality disorder. Comorbidity with alcohol or substance use disorders (most commonly marijuana or amphetamines) was present in 51% (n=19).

5.1.2 Medicines used

Olanzapine was the commonest antipsychotic medication mentioned in the reports (73%) followed by risperidone and quetiapine (Figure 1, page 18).

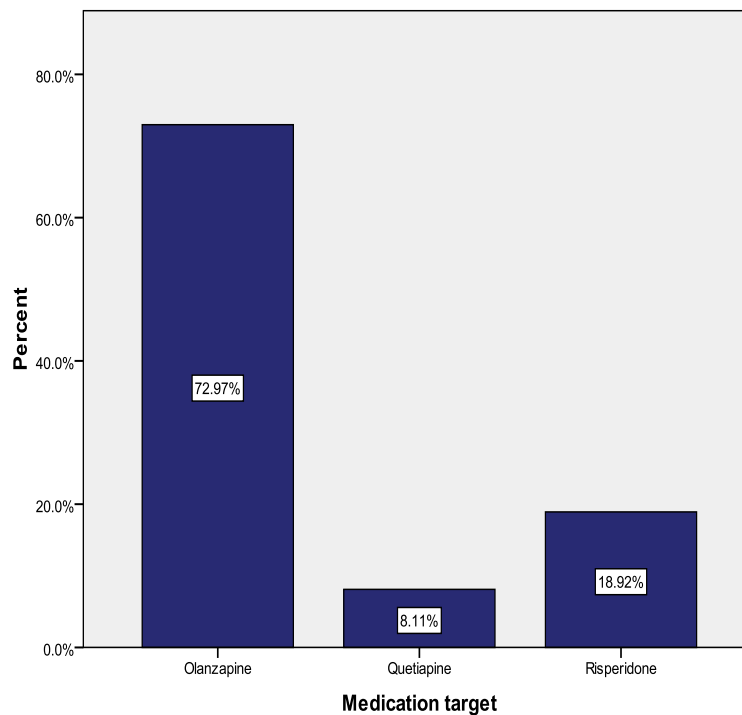
5.1.3 Adverse effects reported - their ratings and links with the literature

The most common adverse effect was akathisia and agitation followed by decreased concentration (Figure 2, page 19). The problems described as akathisia, agitation and concentration were often associated with symptoms such as withdrawal, 'toxic confusion', 'dementia', 'supersensitivity psychosis', suicidal ideation and, in one case, 'hypomania'. Weight gain reported was in less than 3%.

Ratings of reported adverse effects were made on three dimensions:

- known link as reported in the literature on a scale of 7 from none (0) to strong (6);
- strength of the link in this particular case on a scale of 4 from none (0) to strong (3); and
- veracity on a scale of 4 from none (0) to strong (3). Veracity was an overall rating based on the previous two that measured the need to investigate the reported adverse effect more fully. A rating of three implied that it required further examination in depth.

Figure 1: Medication type



Ratings of the two raters were very similar and were no more than one point apart. Consensus was achieved in 100% of cases. In terms of the known links in the literature between medications and the reported adverse effect, there was a mild to moderate link between the symptoms reported and the medication of interest in over 80% of cases (Figure 3). In only 8% of cases, was there only a weak link or none at all.

Of interest was the finding of differences in the details provided in product monographs between Australia and other jurisdictions. For instance in the case of olanzapine, the product monograph for the United States contained more information on potential adverse effects than the one for Australia. This included important adverse effects such as the possibility of withdrawal symptoms, which was missing from the Australian document. This issue was highlighted by the reporting psychiatrist.

However, it was much more difficult to establish links between adverse effects as presented in the case reports and any of the antipsychotics under review. This was because the reported adverse effect often occurred in the context of polypharmacy with patients prescribed multiple psychotropic and other medications in over two thirds of the 37 cases. Other prescribed psychotropics included: antidepressants, benzodiazepines, mood stabilisers and other atypical or conventional antipsychotics. It was therefore difficult to disentangle effects of other medications, or of drug interactions, from those attributed to the antipsychotic medication of interest. Poly-substance abuse was also common in the case series, as well as other risk factors for the described symptoms including adverse life events and co-morbid personality disorder. In addition a clear description of time course or cause effect was often missing. As a consequence, there was there only a weak link or none at all in 81% of cases (Figure 4).

Figure 2: Types of adverse effect

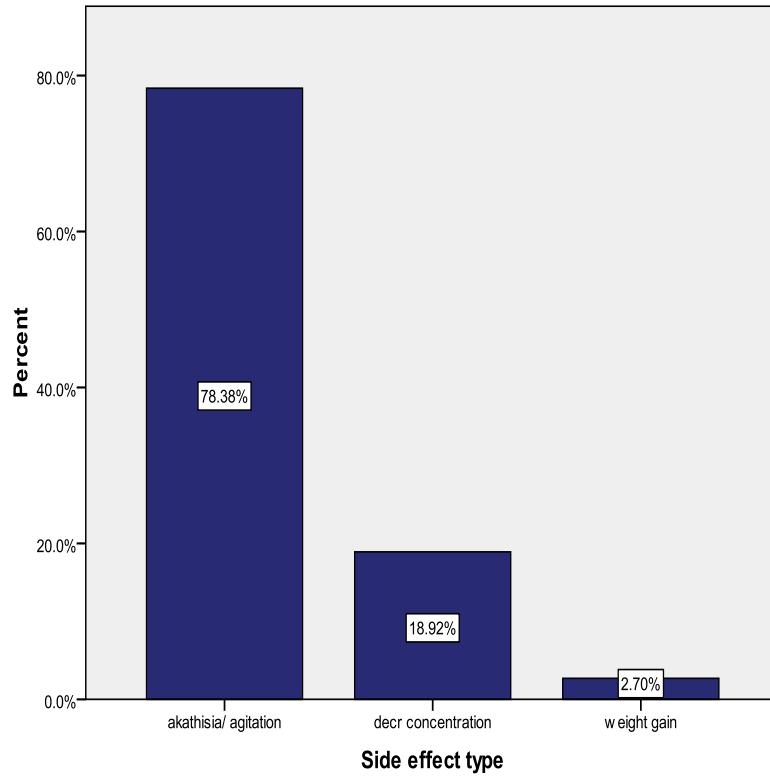


Figure 3: Known link between the reported side effect and the literature

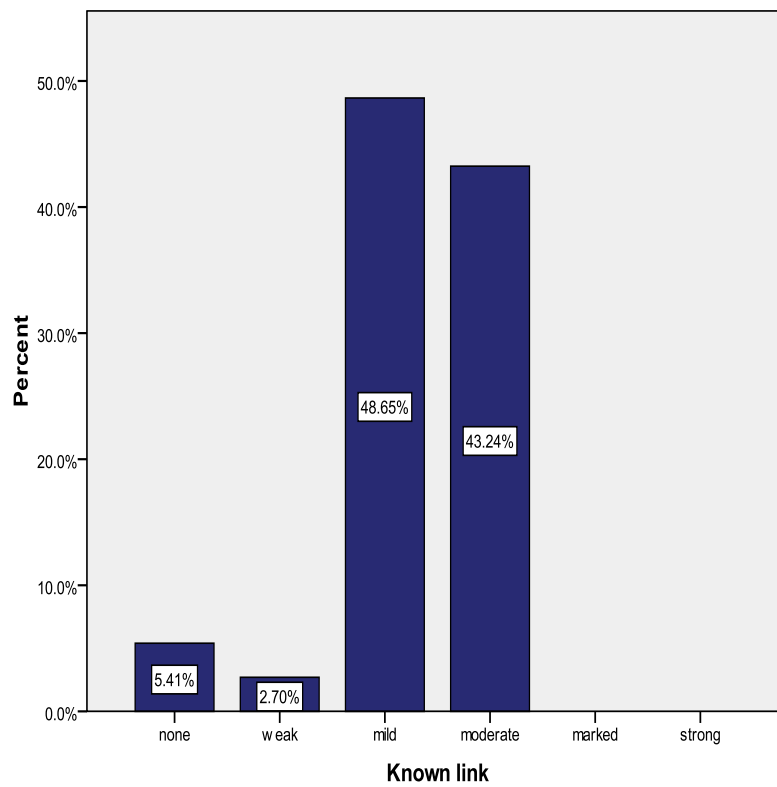
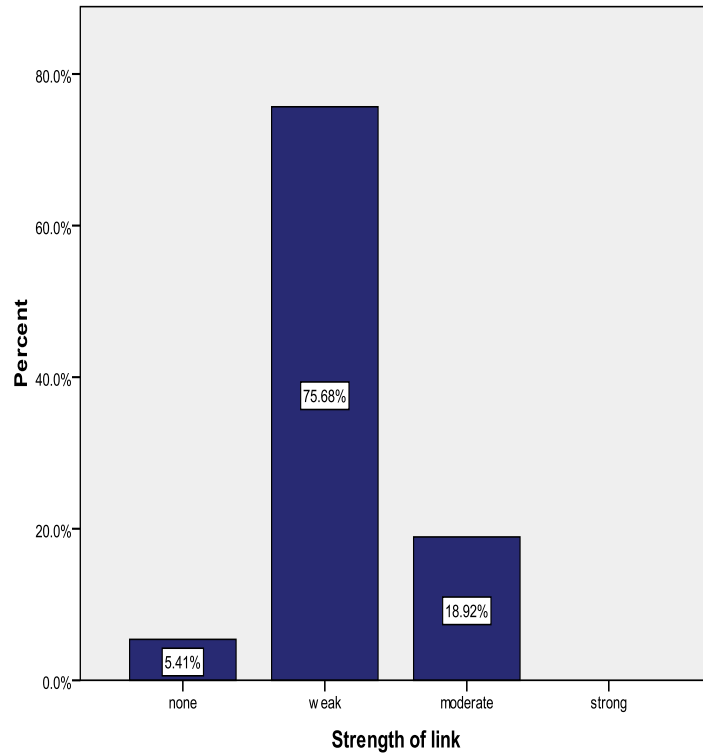
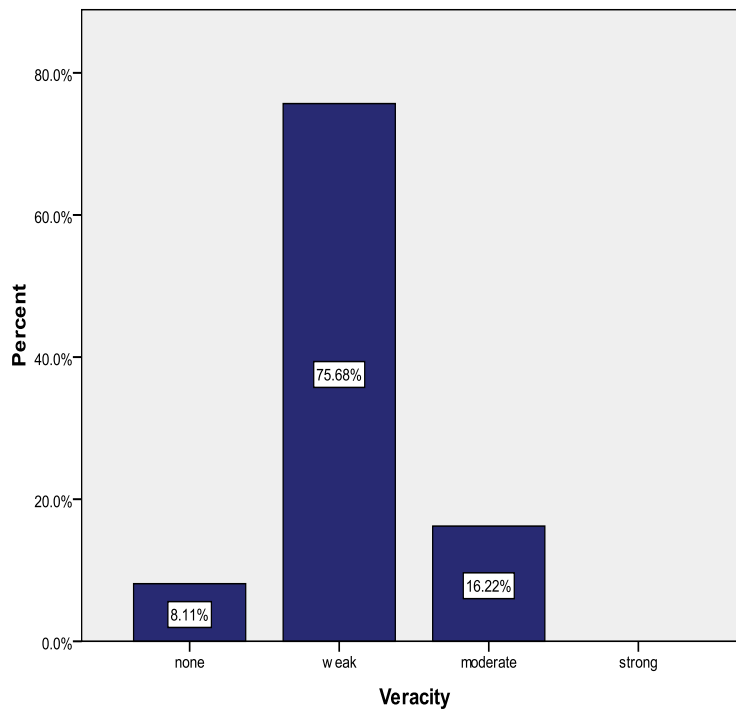


Figure 4: Strength of link as rated in the case reports



The above findings for the observed link between adverse effects and medication were reflected in the ratings for veracity where there was again a weak link, or none at all, in 83% of cases (Figure 5).

Figure 5: Veracity



5.1.4 Comments

It was difficult to draw firm conclusions on the information provided in this series of case reports which were primarily reports prepared for medico-legal reasons rather than detailed case histories collected in the course of treatment. Polypharmacy and concurrent polysubstance use also complicated the issue in the majority of these cases. The presence of polypharmacy in over two thirds of the cases was of major concern given the lack of evidence for the use of many of the prescribed combinations and the increased potential for adverse effects when multiple medications are used concurrently. We also found variation in the information on adverse effects in product monographs between jurisdictions, the reason for which is unclear.

5.2 Findings in relation to antidepressant medicines of interest

5.2.1 Diagnosis

The most common diagnoses of the patients who were prescribed antidepressant medications were: anxiety spectrum disorders (32%), major depressive disorder (30%), schizophrenia spectrum disorder (13%), bipolar disorder (11%), personality disorder (8%), and an organic disorder (5%). In half of these cases there was a co-occurring substance use disorder such as alcohol, cannabis or amphetamine abuse or dependence. In half of the cases with a substance use disorder, there was a history of polydrug abuse, most often a combination of alcohol, cannabis and amphetamine abuse, with some cases of benzodiazepine and opioid abuse.

5.2.2 Medicines used

The most commonly mentioned antidepressant medications were in order of frequency: venlafaxine (21%), mirtazapine (19%), sertraline (14%), paroxetine (13%), citalopram (12%) and fluoxetine (12%). The remaining cases were made up of small numbers of reports on other drugs.

5.2.3 Adverse effects reported - their ratings and links with the literature

The most common adverse effect reported was “akathisia”. This was reported in 63% of the case reports. This term was used by the reporter to describe a constellation of symptoms that included agitation, restlessness, pacing, aggressive thoughts, worsening depression, suicidal ideation, anxiety, panic attacks and nightmares. The serotonin syndrome was reported in 9% of cases. This term was typically used to describe symptoms of a serotonin overdose such as, myoclonic jerks, confusion, sweating, anxiety, depression, and panic attacks. Homicidal impulses were described in 9% of cases, a manic switch (i.e. emergence of hypomania in a patient treated for depression) in 6%, and there were single case reports of a range of other adverse effects that included emotional blunting, increased sleep, increased sex drive, panic attacks, nausea and vomiting, suicide attempts and worsening depression.

Ratings of reported adverse effects were made on three dimensions as described above. Ratings of the two raters were no more than one point apart for most cases and consensus was achieved in all of cases in which there was any discrepancy. In terms of the known links in the literature between medications and the reported adverse effect, there was a mild to strong link between the symptoms reported and the medication of interest in 57% of cases (comprising 33% with mild, 17% moderate, 5% marked and

1% strong evidence of a link). In 43% of cases there was only a weak link or no evidence of a link

It was difficult to assess the links between the adverse effects described in the case reports and many of the antidepressant drugs under review. This was because the reported adverse effect often occurred in the context of polypharmacy: patients were prescribed multiple antidepressant and other psychotropic medications, and in some cases other medications that could have interacted with their antidepressant medications, such as tramadol. The other prescribed psychotropic medications included: tricyclic and MAOI antidepressants, benzodiazepines, mood stabilisers, sleep medications (e.g. Stilnox) and atypical and conventional antipsychotic medications. There was polypharmacy in 65 out of 76 reports and in 30 cases there was polypharmacy in patients who were polydrug abusers. These patterns of medication and substance use made it very difficult to decide whether the effects reported were due to the medication identified by the reporter, the effects of other medications, or of interactions between the other drugs and the antidepressant medication of interest.

Substance abuse was reported in half of the case series, including polydrug use in nearly a quarter of all cases. Many of these patients were cognitively impaired (e.g. because of chronic cannabis or benzodiazepines use) and were understandably described as “unreliable historians” because they could not clearly remember what medications they had been prescribed or when. Patients often had a history of other risk factors for the described symptoms which included serious adverse life events (such as major accidents, violence, abuse during childhood) and pre-existing personality disorders. A clear description of the time course of the symptoms or any direct evidence of a causal relationship to taking medication was usually missing. As a consequence, there was there only a weak link or none at all in 83% of the cases.

5.2.4 Comments

The challenges identified above in assessing the putative links between the reported adverse effects and medication were reflected in the overall ratings for the veracity of the reports. This was judged to be either weak or none in 84% of cases. There was a reasonable case made for a connection between the medication and the adverse report in 14% of case reports. In these cases there was usually clear evidence of a temporal relationship between the onset of symptoms (e.g. akathisia or suicidal ideation) and the use of medication and evidence that the symptom improved on discontinuation or reduction in dose of the drug. The other cases typically involved clear descriptions of serotonin syndrome occurring in a patient taking multiple serotonergic medications, including drugs like tramadol. None of these cases was a new adverse report.

There was one new report that was seen as requiring further examination. This was a case of a substantial weight gain and the development of diabetes in a patient taking the antidepressant mirtazapine in the absence of any other medications (e.g. atypical antipsychotic medications) that might have contributed to the weight gain or a metabolic disorder.

Chapter 6 The literature on these adverse drug reactions

6.1 SSRI Antidepressants and Suicide Mortality

Two very different claims have been made about the effects that the selective serotonin reuptake inhibitor (SSRI) antidepressants have on suicide risk in depressed patients¹. First, some authors have argued that increased SSRI use has *reduced* population suicide rates, supporting their case with evidence that suicide rates have fallen as SSRI prescribing has increased (e.g.^{2, 3}). Second, other authors have claimed that SSRIs *increase* suicide risk among a minority of depressed patients^{4,5}.

Meta-analyses of randomised controlled trials (RCTs) have generally established the effectiveness of SSRIs in treating depression in adults^{6, 7, 8, 9}, although publication bias may have contributed to over-estimation of their average efficacy¹⁰. However, these trials have provided limited data on the impact of SSRIs on suicide risk for a number of reasons. First, the sample sizes sufficient to establish efficacy in reducing depressive symptoms (typically fewer than 100 in each arm) are too small to detect changes in suicide risk^{11, 12, 13}. Second, the chances of detecting changes in suicide risk are reduced further by the fact that RCTs often exclude patients who are adjudged to be at high risk of suicide¹⁴. Third, these studies have not been designed to investigate the iatrogenic effects of SSRIs (or other antidepressants) on suicidal thoughts and behaviour¹⁴.

Evidence relating to these two causal claims about SSRIs and suicide comes from three study types: (1) meta-analyses of randomised controlled trials of the safety and efficacy of SSRIs; (2) observational studies of the relationships between suicidal behaviour and SSRI and other antidepressant prescribing; and (3) ecological studies of the relationships between SSRI prescribing and suicide mortality. Each of these methods has its strengths and limitations¹⁵ (see Table 1, page 30). In assessing the evidence it is necessary to look for a convergence of results from these three types of studies while taking account of their complementary advantages and disadvantages.

6.1.3 Meta-analyses of Randomised Controlled Trials

A small number of meta-analyses found no evidence of increased suicide risk from SSRI antidepressants^{16, 17}. An analysis of data from 17 RCTs of fluoxetine conducted in the late 1980s found no evidence that SSRIs increased suicidal thoughts in depressed people more than placebo or other antidepressants¹⁶. Analyses of the aggregate data from trials of antidepressants submitted to the FDA from 1985 to 2000 failed to find any difference in suicide rates between SSRIs (0.15% [95% confidence interval (CI): 0.10, 0.20]), other antidepressants (0.20% [95% CI: 0.09, 0.27]) and placebo (0.10% [95% CI: 0.01, 0.19])¹⁷. A meta-analysis of RCTs funded by Lilly that compared the efficacy of fluoxetine and placebo in major depression in adults¹⁸ found lower rates of suicidal ideation in patients receiving fluoxetine than placebo. These studies, however, have included relatively small aggregate numbers of patients, have often only included published studies, and study authors have not always performed statistical analyses¹¹.

More recent meta-analyses of larger sets of trials (including unpublished ones) have found an increased risk of self-harm in depressed patients given SSRIs or placebos. Gunnell et al 2005 reported a meta-analysis of 342 randomised controlled trials comparing SSRIs with placebo that had been submitted by pharmaceutical companies to the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK¹¹. They

found suggestive evidence that SSRIs increased self-harm (RR = 1.57 [95% CI: 0.99, 2.55]) but the evidence on suicide risk was inconclusive because there were only 16 suicides among 40,826 patients in these studies (RR = 0.85 [95% CI: 0.20, 3.40]). They estimated that two million people would need to be randomised to either SSRI or placebo to provide an 80% chance of detecting a clinically significant increase in suicide mortality.

Fergusson et al 2005¹⁹ reported a systematic review and meta-analysis of 702 RCTs that included 87,650 patients. They found a higher rate of suicide attempts among patients receiving SSRIs compared with placebo (RR = 2.28 [95% CI: 1.14, 4.55]) but no difference between SSRIs and tricyclic antidepressants (TCA) (RR = 0.88 [95% CI: 0.54, 1.42]). There was no difference in suicide rate between SSRI and placebo but the small number of events produced wide confidence intervals around this estimated risk (RR = 0.95 [95% CI: 0.24, 3.78]). Paradoxically, despite no difference in suicide attempts between SSRIs and TCAs, and no difference in suicide rate between SSRIs and placebo, Fergusson et al 2005 found a higher elevated risk of suicide in patients receiving SSRIs compared to TCAs (RR = 7.27 [95% CI: 1.26, 42.03])¹⁹.

Meta-analyses partially overcome the problem of the limited statistical power of RCTs by aggregating large numbers of studies but they still have a number of limitations. First, they still lack sufficient statistical power to detect clinically significant effects on completed suicide as against suicidal ideation. As Gunnell and colleagues noted, 2 million individuals would need to be randomised to SSRI or placebo in order to detect an increase in completed suicide¹¹. The total sample sizes in the largest meta-analysis are less than 100,000. Second, meta-analyses are also subject to the limitations of the individual RCTs they summarise, namely, their short duration and exclusion of patients at high risk of suicide (e.g. ¹¹). Third, without access to the individual data, meta-analyses cannot adjust for differences between the patients in different trials. This may lead to an underestimation of the variance between trials and subsequent masking of effects¹¹. Fourth, analyses of published studies may overestimate SSRI efficacy because studies with null results are less likely to be published.

6.1.2 Observational Studies of Suicide and SSRIs

Observational studies typically use record linkage in administrative and clinical data bases to assess the strength of associations between SSRI and other antidepressant use and suicide attempts or episodes of self-harm. This type of evidence is inferior to that from RCTs because patients are not randomly assigned to receive an antidepressant drug or not, thereby raising doubts about the equivalence in suicide risk before exposure to the antidepressant. The potential confounding by indication can only be imperfectly addressed by statistical methods such as covariate adjustment and propensity score analysis. The strength of observational studies is that they often involve large numbers of patients who are prescribed these drugs under conditions of routine clinical practice, precisely the situation in which we wish to make inferences about suicide risk.

Valuck et al 2004²⁰ compared suicide risk among adolescents aged 12 – 18 years who received a diagnosis of major depressive disorder and either did or did not receive a prescription for an antidepressant. Participants were treated in a large HMO in the USA over a six year period and the outcome measured was suicide attempts in the six months following diagnosis. Two thirds (68%) of the antidepressant prescriptions were

for a SSRI. A crude analysis showed an increased risk of a suicide attempt among adolescents who were prescribed any antidepressant (OR = 1.93 [95% CI: 1.56, 2.39]) or an SSRI (OR = 1.95 [95% CI: 1.53, 2.49]). A propensity analysis that adjusted for potential confounding by indication showed that the relationship was still elevated but no longer statistically significant (OR = 1.59 [95% CI: 0.89, 2.82]). A separate analysis found a reduction in suicide attempts among those were treated with an antidepressant for greater than 180 days (OR = 0.34 [95% CI: 0.21, 0.55]) compared to those treated for less than 180 days.

Jick et al 2004 ²¹ compared the risk of suicide and suicide attempts in patients who received the four most common antidepressants prescribed in UK general practice between 1993 and 1999, namely, the tricyclic antidepressants amitriptyline and dothiepin, and the SSRIs fluoxetine, and paroxetine. They selected cases and controls from the UK General Practice database that included 159,810 patients who had been prescribed one of these drugs during this period. They compared 555 cases who attempted suicide within 90 days of being prescribed one of these drugs and 2062 controls who had attempted suicide but had not been prescribed one of these drugs (matching cases and controls for sex, age, and general practice). Patients with a previous history of suicide attempts were more likely to receive an SSRI than the most commonly prescribed tricyclic. There was also a higher risk of a suicide attempt in the first nine days after a prescription (OR = 4.07 [95% CI: 2.89, 5.74]) but there were no marked differences in risk between the four drugs. The relative risks (compared to dothiepin) were 0.83 [95% CI: 0.61, 1.13] for amitriptyline, 1.16 [95% CI: 0.80, 1.50] for fluoxetine, and 1.29 [95% CI: 0.99, 1.70] for paroxetine. There were too few suicides (17) in the cohort to detect any differences in suicide risk between the different drugs.

Martinez et al 2005 ²² reported an observational study of suicide risk from SSRIs, tricyclic antidepressants and other antidepressants in the UK GP database. They selected cases (of persons who had had an episode of self-harm) and up to 20 controls (who had not) for each case from 146,095 patients who received an antidepressant prescription between 1995 and 2001. They found that patients with a history of self-harm were more likely to receive an SSRI but there was no difference in the risk of self-harm between patients receiving an SSRI and those receiving a TCA (OR = 0.99 [95% CI: 0.86, 1.14]). There was possibly a higher risk among patients in the 10 – 19 year age group, with an OR of 1.50 [95% CI: 1.01, 2.50]. Among the 69 suicides in this cohort the risk of suicide did not differ between those prescribed an SSRI and those prescribed a TCA (OR = 0.57 [0.26, 1.25]).

Isacsson et al 2005 ²³ compared toxicological evidence of use of SSRIs, TCAs and other antidepressants in 14,857 suicides and 26,422 controls who died from natural causes or accidents in Sweden between 1992 and 2000. Antidepressants were detected in 20% of suicides (compared to 6% of the controls) but the SSRIs were *less* likely to be detected in suicides than newer antidepressants (OR = 0.83 [95% CI: 0.77, 0.90]) and just as likely to be detected as TCAs (OR = 1.01 [95% CI: 0.90, 1.14]). SSRIs were also less likely to be found among suicides in persons younger than 19 years (OR = 0.14 [95% CI: 0.05, 0.43]). Treatment refractory depressed patients were more likely to be prescribed the newest antidepressant at the time of their treatment. This was fluvoxamine in the early 1990s and moclobemide, mianserin, reboxetine and venlafaxine in the late 1990s.

Simon et al 2006 ²⁴ used computerised medical records in a HMO in Washington state and Idaho to conduct an observational study of the association between antidepressant use and suicide and suicide attempts in 82,285 episodes of depression involving 65,103 patients who were prescribed an antidepressant between January 1992 and June 2003. They examined the risk of suicide attempts in the six months after the index prescription. There were 31 suicides and 76 suicide attempts that led to hospitalisation during the 10.5 years of observation. They found the highest risk of suicide attempts in the month after a prescription (OR = 2.5 [95% CI: 1.6, 3.8]) but no increase in suicide deaths in the first month of treatment (OR = 1.2 [95% CI: 0.5, 2.9]). Nor was there any increased risk attributable to the specific antidepressants that had been included in the FDA warning about increased suicide risk. There were higher rates of suicide attempts among adolescents than adults but no evidence (within limitations of the small numbers involved) of an increased risk in the first month of treatment.

Sondergard 2006 ²⁵ reported a small pharmacoepidemiological study of antidepressant use among adolescents age 10 – 17 years in Denmark between 1995 and 1999. During this period prescribing of SSRIs in this age group increased substantially. A linked study of antidepressant prescriptions and suicide found an increased risk of suicide in adolescents prescribed an SSRI but the number of suicides was very small (19), and there was marked confounding by indication in that adolescents with a history of past psychiatric hospitalisation for depression were most likely to be prescribed antidepressants (and a variety of other psychotropic medications). The study had limited capacity to adjust for the effects of this confounding. The fact that there was no increase in suicide rate among Danish adolescents during the period that SSRI use increased suggests that this relationship probably reflected increased pharmacological treatment of severely depressed adolescents in Denmark over the study period.

Gibbons et al 2007 ²⁶ reported an observational study of the risk of serious suicide attempts leading to treatment among depressed males in the US Veterans Health Administration Data Sets. They compared suicide risk in the 6 months before and after diagnosis of depression in 226,866 veterans who received a diagnosis of depression and received no antidepressant or an antidepressant prescription for an SSRI, tricyclic antidepressant or non-serotonergic-specific (non SSRI) antidepressant. They found a lower suicide rate after diagnosis in patients treated with an antidepressant than those who did not receive an antidepressant, with patients receiving SSRIs (OR = 0.38 [95% CI: 0.30, 0.49]) and non-SSRIs (OR = 0.40 [95% CI: 0.30, 0.52]) showing significantly lower rates. This was true for all age ranges except that of 18 – 25 years where too few patients were observed to provide a good estimate of risk.

Barbui et al 2009 ²⁷ have reported a systematic review of 8 observational studies that passed minimum quality criteria and compared rates of attempted or completed suicide in moderate to severely depressed patients who received an SSRI antidepressant, and depressed patients who did not. They found that prescription of an SSRI reduced attempted or completed suicide in adults aged 18 – 64 years (OR = 0.57 [95% CI: 0.47, 0.70]) and older adults aged 65 plus (OR = 0.46 [95% CI: 0.27, 0.79]) but increased the risk among children and adolescents (OR = 1.92 [95% CI: 1.51, 2.44]). The same pattern of results was found when the analysis was confined to completed suicides, with wider confidence intervals reflecting the rarity of this outcome.

All of the observational studies are subject to the problem of confounding by indication^{28,29}. That is, patients who were at increased risk of suicide were more likely

to be prescribed SSRIs. Despite many of these studies having only limited ability to adjust for such confounding (e.g. via the use of a limited number of variables in covariate adjustment and propensity analyses) most have found a reduction in suicide risk among adults with depression; the same may not be true with children and adolescents where there may well be an association between the SSRIs and self-harmful acts. The effect of antidepressants on completed suicides was less clear because the numbers of suicides involved in all of these studies has been too small to permit one to infer that the absence of evidence of increased suicide risk is equivalent to evidence of the absence of an increased suicide risk.

6.1.3 Ecological Studies of Suicide and SSRI Use

Ecological studies have explored associations between (1) population indicators of SSRI use (e.g. total SSRI sales in kg or daily dose equivalents) and (2) population suicide mortality, (3) controlling where possible for changes in other factors that might explain the associations (or lack thereof) ³⁰.

A number of studies have found that suicide mortality has declined as SSRI use has increased. Ohberg et al 1998 ³¹ found that suicide mortality declined between 1990 and 1995 in Finland as SSRI use increased but they did not have any quantitative data on rates of SSRI use and they were unable to assess alternative explanations of the trend. Carlsten 2001 ³² found that suicide rates in Sweden decreased by 31% in men and 34% in women between 1977 – 1979 and 1995 – 1997 while SSRI use increased markedly between 1993 and 1996. The decline in suicide rates could not be wholly attributed to SSRI use because it began before their introduction. Fazel et al 2006 ³³ have more recently reported an ecological study of trends in suicide in Sweden between two five year periods, 1989 – 1994 and 1995 – 2000. Over this period, rates of SSRI prescribing increased 10-fold in Swedish adults while suicide rates declined in all age groups and both sexes.

Rihmer and colleagues ³⁴ found that suicide deaths declined in Hungary after antidepressant prescribing increased in the early 1990s, despite steep *increases* in unemployment and per capita alcohol consumption, factors that would be expected to predict an increased suicide rate. Hall et al 2003 ³⁵ found a dose-response relationship between SSRI use and suicide rates in Australian men and women between 1991 and 2000: in males and females the higher the exposure to antidepressants in each age group, the larger the decline in suicide rate between 1991 and 2000. These trends were not explained by changes in per capita alcohol consumption or unemployment rate.

Four studies in the USA have found associations between increased SSRI use and declining suicide rate. Olfson et al 2003 ³⁶ examined the relationship between regional trends in antidepressant use and suicide mortality among adolescents between 1990 and 2000 in the USA. They found that a 1% increase in antidepressant use in a region was associated with a decrease of 0.23 suicides per 100,000 per year. Grunebaum et al 2004 ³⁷ analysed the relationship between adult suicide rates between 1985 and 1999 and SSRI sales data, controlling for the effects of unemployment and per capita alcohol use. They found that suicide rates declined as SSRI use increased. Gibbons et al 2005 ³⁸ studied the relationship between US county suicide rates and SSRI and TCA sales over the period 1996 to 1998, controlling for county, age, sex, race and median income.

Antidepressant sales were uncorrelated with suicide rates overall but different types of antidepressants had different types of relationships to suicide rates: higher sales of

TCAAs were correlated with higher country suicide rates while higher sales of non-TCAAs (which included the SSRIs and all other newer antidepressants) were associated with lower country suicide rates. Milane et al 2006 ³⁹ conducted a time series regression analysis of the relationship between US suicide rates between 1960 and 2002 and sales data for fluoxetine. They found that suicide rates declined in proportion to increased sales of fluoxetine after its introduction to the US market in 1988. Their results showed a stronger relationship for female than male suicide rates.

Other ecological studies have found more mixed results. Barbui and colleagues ⁴⁰ found that while SSRI use increased 53% in Italy between 1988 and 1996, suicide rates increased in males and only marginally declined in females. In Iceland a time series analysis by Helgason et al 2004 ⁴¹ found that sales of SSRIs increased by 16% per year after 1989 but rates of suicide did not change while psychiatric treatment rates and rates of disability from depressive disorders increased. Sondergard et al 2006 ²⁵ did not find any change in suicide rates among Danish adolescents as SSRI use increased between 1995 and 1999.

In Northern Ireland, Kelly et al 2003 ⁴² did not find an association between antidepressant use and suicide in adults under 30 years but suicide rates declined as antidepressant use increased among those over the age of 30. Similar trends emerged from a time-series analysis of suicide between 1950 and 1998 in the United Kingdom⁴³. This study found that antidepressant use was associated with declines in suicide among adults over the age of 60 years but not among younger males (aged 25 – 34 years) who had much smaller increases in antidepressant use than older males and females. Morgan et al 2004 ⁴⁴ reported an inverse correlation between antidepressant prescribing in England between 1993 and 2001 but did not examine the relationship by age or gender.

Ludwig and Marcotte 2005 ² have reported the largest ecological study of SSRI use and suicide to date. They analysed the relationship between SSRI sales data and suicide rates in 27 countries between 1980 and 2000 while controlling for different ways of coding cause of death (e.g. ICD-9 vs. ICD-10) and for differences between populations in age and sex, employment and divorce rates. They also assessed the robustness of their findings to the method of statistical analysis and to the measures of suicide and SSRI exposure that were used. They generally found an inverse relationship between per capita SSRI sales and population suicide mortality, indicating that the higher the sales of SSRIs in a country, the lower the suicide rate. An increase of one pill per capita was associated with a 2.5% reduction in suicide rate. These findings have largely been replicated in further analyses using rates of diffusion of new non-psychiatric drugs (statins, proton pump inhibitors, and CCBs and ACE inhibitors for high blood pressure) in each country as an instrumental variable to address uncontrolled confounding³.

These ecological studies have a number of limitations ⁴⁵. First, antidepressant sales data do not necessarily describe patterns of drug use and sales data typically do not partition SSRI use by age and sex (e.g. ²). Second, most studies have not been able to control for the effects of risk factors for suicide, such as alcohol and other substance use ^{32, 36, 40}. The most likely effect of these limitations would be to reduce the magnitude of associations observed between SSRI use and suicide. It is therefore impressive that increased SSRI use has so often been correlated with declining suicide rates. An analysis of data from 27 countries over 20 years has supported the findings of the majority of the analyses in individual countries in finding that suicide deaths declined as SSRI use

increased, although an independent critical analysis of the same data failed to find any clear relationship ⁴⁵.

6.1.4 High Risk Populations: Children and Adolescents

Concern about the risk of SSRI use was originally prompted by cases of suicide in adults but attention has more recently focused on the risk of self-harm and suicide among depressed adolescents treated with SSRIs ^{46, 47, 48}. Because there have been many fewer placebo controlled RCTs of SSRIs in adolescents, the evidence of the efficacy of SSRIs other than fluoxetine is less impressive in adolescents than in adults ^{49, 50}. Recent meta-analyses of clinical trials have found evidence of increased suicide ideation or suicide attempts like that in trials in adults ⁴⁹. An FDA-commissioned study that reviewed 24 placebo controlled trials with over 4582 children and adolescents found a higher incidence of suicidal ideation in those receiving SSRIs compared to placebo (RR= 1.66 [95% CI: 1.02, 2.68]) ⁵¹. A meta-analysis of 22 paediatric trials submitted to the European registration authorities found a similar increase in the risk of events related to suicidality (RR = 1.33 [95% CI: 0.33, 5.35]) ⁵².

Adolescents have not been well represented in the larger observational and ecological studies so the effect of SSRI use on suicidal risk is less certain in adolescents than in adults ^{47, 48}. Jick et al 2004 ²¹ found only equivocal evidence of an increased risk of suicide in adolescents, while Isacson et al 2005 ²³ found evidence of a protective effect of SSRIs in young adults. The results of recent observational studies in adolescent populations have been more equivocal: Simon et al 2006 ²⁴ and Valuck et al 2004 ²⁰, for example, did not find a large increase in the rate of suicide attempts among adolescents who had been prescribed an SSRI, after account was taken of confounding by indication. Sondergaard et al 2006 ²⁵ did find an increased risk of suicide among adolescents prescribed an SSRI. It was no longer significant after adjustment for confounding by indication but the upper limit of the confidence interval did not exclude an increased rate of suicide. The systematic review of the observational studies by Barbui et al 2009 ²⁷ did find an increased risk of attempted and completed suicides among children and adolescents who were prescribed an SSRI. They suggested that this may reflect uncontrolled confounding by indication among younger patients, whereby suicidal adolescents were more likely to be prescribed an SSRI.

6.1.5 Summary

A reasonably coherent picture is emerging from such research about the effects of SSRI use on suicide risk. Concerns that SSRIs may increase suicide risk in the short term were raised by case studies and volunteer studies and have been supported by the biological plausibility of the hypothesis that SSRIs have a short term activating effect ⁴ that may increase suicidal impulses ^{13, 53} or may improve patients' energy before they improve mood, thereby making it easier for depressed patients to act on suicidal thoughts ¹.

In principle, the best evidence comes from RCTs of the effects of SSRIs on depressed patients but these trials have involved too few patients, been observed for too short a time, and not been well assessed on suicidal ideation ⁴⁷. The most recent and largest meta-analyses of placebo-controlled RCTs of SSRIs have found suggestive evidence that SSRIs increase suicidal ideation and attempts early in treatment. RCTs are unlikely to assist in deciding whether SSRIs increase suicide mortality because an extremely large

number of patients (of the order of several million) would need to be randomised to detect effects on a rare outcome like suicide ^{11, 12}. It is uncertain whether suicidal ideation as assessed in clinical trials predicts suicide mortality well enough to serve as a useful surrogate marker for suicide mortality risk ¹².

The evidence that SSRIs increase suicidal ideation in the meta-analyses has not generally been supported by observational studies of self-harm and suicide or ecological studies of suicide trends in adults. Several observational studies have found an increased risk of self-harmful acts within nine days to a month of an antidepressant drug being prescribed but the increase in risk has been similar for the older TCAs and SSRIs. The observational studies have found more suggestive evidence of increased suicide attempts among children and adolescents who are prescribed SSRIs.

If SSRIs increase suicide risk in some patients, then the number of additional suicide deaths is very small because no increase in suicide rates has been detected in the case-control studies or ecological studies to date. The ecological studies also suggest that the risks of SSRIs are outweighed by their benefits in reducing suicide among adults since suicide rates in adults have declined as SSRI use has increased in most developed countries.

The observational studies provide support for the clinical wisdom that suicide risk increases as psychomotor retardation begins to lift, an effect that may occur before mood improves, thereby enabling depressed patients to act on suicidal thoughts ⁵⁴. A plausible hypothesis is that any increase in suicide risk arising from initial improvement in depression would be more noticeable during induction onto SSRI antidepressants because (1) SSRIs are the most commonly prescribed antidepressant drugs; (2) they are more likely to be prescribed to patients at risk of suicide, and (3) their lower side effect profile means that patients are more likely to take them for long enough to experience a therapeutic effect than was the case with older antidepressants.

Table 6.2 Strengths and weaknesses of available evidence on SSRIs and suicide

Study type	Findings	Strengths	Limitations
Meta-analyses of RCTs	Evidence of increased suicidal ideation and acts	<ul style="list-style-type: none"> Aggregated N from small RCTs increases statistical power 	<ul style="list-style-type: none"> Short study periods Uncertainty about suicidal ideation as a surrogate for suicide risk
Observational studies	Increased suicide risk in first week but no greater risk for SSRIs than TCAs	<ul style="list-style-type: none"> Larger than RCTs Observe risks under routine clinical use 	<ul style="list-style-type: none"> Confounding by indication: higher risk patients given SSRIs Too few suicides
Ecological studies	Suggestive evidence that suicide rates have declined as SSRI prescriptions have increased	<ul style="list-style-type: none"> Able to detect small effects aggregated over large exposed populations 	<ul style="list-style-type: none"> Limited capacity to test alternative explanations e.g. role of other causes such as alcohol use and unemployment

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6.2 Antidepressants and induction of mania/hypomania

The reports detail a number of instances of SSRI and SNRI induced “mania”. The reports describe brief periods of agitation, overactivity and lability of mood. There is no description of patients being psychotic or requiring hospitalisation. Thus the clinical picture described is closer to hypomania than mania. This review will focus on the question of induction of hypomania and on questions surrounding hypomania in Bipolar II disorder. The continuing controversies in the definition of mood shifts in Affective Disorders and the inherent cycling pattern of Bipolar Disorder both make the evaluation difficult.

There are three possible mechanisms in the reported frequent switch to hypomania. The reported periods of hypomania may be a true side effect of the antidepressant in those with unipolar depression, albeit at a much higher rate than that reported in the literature. Secondly, the periods of hypomania may represent an induction of a “switch” in a patient with unrecognised bipolar disorder, again at a much higher rate than that reported in the literature. The third possibility is that in some of these patients, the hypomania described more readily fits a picture of affective instability, thus suggesting trait rather than state disturbance.

The literature suggests a very low “switch” rate to either mania or hypomania in those identified as having unipolar depression treated with SSRIs. Peet 1994 ¹ found SSRIs induced mania in only 0.72% of a group of patients carefully identified as having “non-bipolar” depression. Benvenuti 2008 ² found a higher rate of 3% with SSRI treatment compared to 0.9% in unipolar patients treated with a psychotherapy alone. (The higher rate may have been due to the use of escitalopram as well as citalopram.) Bipolar II appears to have a much lower switch rate. Amsterdam 2004 ³, Leverich 2004 ⁴ and Altshuler 2006 ⁵ report a low switch rate when specifically looking at a switch into hypomania with SSRI treatment. The rates appear similar for SNRIs: Amsterdam 1998 ⁶ reports no mania or hypomania in 17 BP II patients treated with venlafaxine and Dunner 2005 ⁷ reports a switch rate of 0.2% with duloxetine compared to 0.1% with placebo.

Chun and Dunner’s review ⁸ comments that in 89% of studies of antidepressants in major depressive disorder, patients reported no cases of treatment-induced hypomania, even in those with chronic depression. No instances of treatment-induced hypomania were reported in three large studies reviewed by them.

If a true side effect, the phenomenon should be at least sometimes dose related. Ramasubba 2001 ⁹ provides a case report of only two patients in whom the switch was dose related and the mood elevation responded to simple dose reduction. Both patients had been treated with higher than the recommended doses.

Chun and Dunner 2004 ⁸ conclude that the rate of antidepressant-induced hypomania in Major Depressive Disorder is within the rate of misdiagnosis of bipolar depression as unipolar. The misidentification of bipolar patients as unipolar is presumably common given 50% of bipolar patients first present with depression ¹⁰ although the spontaneous shift into hypomania without mania is lower than BPI. Coryell 1995 ¹¹ reported a shift of 7.2%. Akiskal 1995 ¹² reported a rate of 8.6% after an eleven year follow up.

Identification of hypomanic episodes is often difficult, perhaps particularly when recall is affected by a current depressed state. Identification in family members is

presumably still more difficult with the subtleties of elevated mood and irritability and the difficulty of separating hypomania from personality.

There are identified pre-morbid personality features, personal and family history, age of onset, chronicity of depression, history of previous below threshold episodes and the pattern of the current depressive episode that may indicate bipolarity^{12, 13}, although these are not upheld in all studies². When identified, these appear to be different for Bipolar I and II¹².

The third possible explanation is that these periods described as “mania” are indicative of an underlying affective instability. The features that set Bipolar II disorder apart from Bipolar I disorder make the distinction between Axis I and II more difficult and BPII is clinically and genetically heterogenous.

The clinical picture, particularly the relationship to Cluster B Personality Disorders, remains unclear. The literature includes many features of BPII that could be seen as due to Borderline PD¹⁴. Benazzi 2002¹⁵ describes a syndrome of a BPDII mixed depression with racing thoughts, irritability, increased risky and goal directed activities but does not distinguish this from the patients’ inter-episode state. The best point of separation between unipolar and BPII depression appears to be a past history of suicide attempts, both patterns consistent with Borderline Personality Disorder^{16, 7}.

Akiskal 1995¹² identifies clear differences between unipolar depressed and BPII. Again these characteristics – poor long term education and social adjustment, likely substance use, marital disruption, significantly longer periods of illness, shorter periods of “wellness”, social withdrawal, minor antisocial acts, lower self reported “ego resilience” and “emotional stability” and an earlier age of onset of symptoms – could be seen as identifying personality disorder. Four personality factors emerged; most prominently “mood lability”. Akiskal’s “daydreaming” could represent dissociation.

Overall, those patients with brief periods of elevated and dysphoric mood, often characterised as Bipolar II, represent a group with a complex mood disorder potentially related to temperamental affective dysregulation.

In summary, the literature reports a very low or no development of hypomania due to SSRIs and many of the vignettes presented could be viewed through a lens of personality disorder and or substance use, rather than affective illness.

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6.3 Serotonin syndrome arising from polypharmacy

6.3.1 Serotonin syndrome or a spectrum of serotonin toxicity?

Serotonin syndrome is the term used to describe a potentially life-threatening adverse drug reaction characterised by the clinical triad of altered mental status (confusion, agitation, hypomania), autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering) and neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), caused by excessive central nervous system and peripheral serotonergic activity.

The characteristic symptoms were first described by Sternbach 1991¹ who suggested that at least three of them were needed to be present before classifying the reaction as the serotonin syndrome rather than the neuroleptic malignant syndrome. Serotonin syndrome has since been most commonly reported with exposure to two or more serotonergic agents. It can develop shortly after one serotonergic agent is added to another, but may also occur when one agent is replaced with another without allowing a long enough wash out period in between. It has also been reported to occur with a single serotonergic agent².

The exact pathophysiological and molecular mechanisms are unclear. No single receptor appears responsible for development of the condition, although most evidence points to a substantial contribution from agonism of 5-HT_{2A} receptors, with some lesser contribution from 5-HT_{1A} receptors via a pharmacodynamic interaction in which increased synaptic concentrations of serotonin agonist saturate all receptor subtypes. There is also some evidence that other neurotransmitters such as noradrenaline, γ -aminobutyric acid and N-methyl-D-aspartate receptor antagonists may play a role³. Furthermore, it is not entirely clear if serotonin syndrome arises simply as a result of additive effects or whether a degree of synergism or other, as yet unidentified factors are involved in its aetiology. It is generally understood that only in a small number of patients who take two or more serotonergic medicines actually develop the condition and, furthermore, only a very small number actually develop life threatening manifestations².

More recently, as our understanding of the mediation of side effects of serotonergic medicines has improved, there has been growing recognition that the triad of clinical features is better described as serotonin toxicity which can be mild (i.e. there are serotonergic features that may or may not be of concern to the patient but are not clinically significant), moderate (a level of toxicity that causes distress to the patient and requires treatment); or severe (a life-threatening emergency in which there is rapid onset of severe hyperthermia, muscle rigidity and multiple organ failure)⁴.

6.3.2 Polypharmacy and serotonin toxicity

Toxicity resulting from excessive intra-synaptic serotonin, historically referred to as serotonin syndrome, is now understood to be an intra-synaptic serotonin concentration-related phenomenon⁵. It appears that only combinations of serotonergic drugs acting by different mechanisms are capable of raising intra-synaptic serotonin in the brain stem and spinal cord to a level that constitutes life-threatening serotonin syndrome^{5, 6}. The most commonly reported life-threatening situations involve the use of monoamine oxidase inhibitors (MAOIs) in combination with serotonin re-uptake inhibitors, such as SSRIs and the phenylpiperidine series opioids.

Medicines implicated in severe serotonin syndrome have been ⁷:

- inhibitors of serotonin metabolism:
 - § irreversible monoamine oxidase inhibitors – phenelzine and tranylcypromine
 - § reversible monoamine oxidase inhibitors – moclobemide
 - § others – linezolid, an antibiotic which is also a reversible non selective MAOI
- inhibitors of re-uptake of serotonin by nerve terminals:
 - § selective serotonin re-uptake inhibitors – fluoxetine, fluvoxamine, paroxetine, citalopram, escitalopram, sertraline
 - § other serotonin reuptake inhibitors
 - other antidepressants
 - tricyclic antidepressants - clomipramine, imipramine
 - atypical antidepressants - venlafaxine
 - phenylpiperidine series opioids, such as pethidine, tramadol, methadone, dextromethorphan and propoxyphene
 - St John's Wort
- serotonin precursors:
 - § L-tryptophan
- serotonin releasing agents:
 - § amphetamines
 - § MDMA, ecstasy
- serotonin agonists:
 - § LSD, buspirone
- others (mechanism unknown): lithium

Less severe (i.e. non life-threatening) serotonin toxicity can be expected to occur with combinations of medicines with the same serotonergic mechanism of action, overdoses of individual serotonergic medicines, and with single therapy in susceptible individuals ⁶. That single serotonergic agents are unlikely to cause life-threatening serotonin toxicity was confirmed in the study of SSRI overdoses by Isbister et al 2004 in which moderate serotonin toxicity occurred in 15% of overdoses but none were severe enough to be life-threatening ⁸.

There is some debate as to whether triptans, such as sumatriptan, are associated with the potential to cause severe life-threatening serotonin toxicity. Whilst they are regarded as serotonergic agents, they have significantly lower affinity for 5-HT_{1A} than 5-HT_{1D} receptors, thereby limiting their intrinsic ability to mediate a serotonergic response alone. Furthermore, sumatriptan does not appreciably cross the blood-brain barrier. A number of case reports have linked sumatriptan to serotonin syndrome when used in combination with other serotonergic agents but an extensive review of the literature found the reports indicated a mild to moderate, self limiting course only with some features consistent with serotonin syndrome ⁹. However, in 2006, the US FDA issued information to healthcare professionals alerting them to the potential for life-threatening serotonin syndrome with combined use of SSRIs or SNRIs (such as venlafaxine) and triptans. The alert was based on the FDA's analysis of 27 reports received by them over a period of 5 years, in which there were thirteen cases requiring hospitalisation, including two considered to be life-threatening. However, these

diagnoses have subsequently been challenged as not meeting validated criteria for serotonin syndrome ¹⁰ (see additional discussion regarding atypical antipsychotics, below).

A somewhat more contentious issue is whether atypical antipsychotic agents are associated with the development of serotonin toxicity. The atypical antipsychotics olanzapine ^{11, 12}, risperidone ^{13, 14} and quetiapine ^{13, 15} have been reported rarely in association with the serotonin syndrome. However, some authors have argued that atypical antipsychotic drugs cannot cause serotonin excess because of their anti-serotonergic action as non selective 5-HT₂ antagonists and suggest that use of the non specific clinical features described by Sternbach as diagnostic criteria has led to reported associations with medicines that clearly do not cause serotonin excess ⁴. Duggal and Fetchko 2002 reported of a case of serotonin syndrome precipitated by the addition of olanzapine to a mirtazapine and tramadol combination¹². In that case, 8 days after commencing olanzapine the patient developed confusion, tachycardia, flushing, facial twitching, tremors, myoclonus and hyperreflexia. The patient recovered within 12 hours of withdrawal of all medication. The authors considered neuroleptic malignant syndrome was a possibility but the absence of hyperthermia and rigidity, the presence of normal serum creatinine phosphokinase levels and rapid recovery were considered to be more consistent with serotonin syndrome. Furthermore, they postulated that olanzapine, which is an antagonist at 5-HT₂ and 5-HT₃ receptors could have potentiated the effect of mirtazapine. Mirtazapine is known to increase serotonin release, whereby the effect of released serotonin is exerted via 5-HT₁ receptors because 5-HT₂ and 5-HT₃ type receptors are specifically blocked by mirtazapine ¹⁶.

Others have subsequently argued that the putative mechanism for serotonin syndrome with atypical antipsychotics is 5-HT_{1A} receptor modulation in the face of 5-HT₂ antagonism and that in a comparison of such drugs, quetiapine has the lowest theoretical risk (although there is still clinical significance at the upper dosage range), with 100 to 200 times less potency at 5-HT₂ receptors than risperidone, olanzapine and clozapine, and ziprasidone has the greatest theoretical potential because of its direct 5-HT_{1A} receptor agonism ¹⁵.

The divergence of opinion as to whether particular agents can or can't cause serotonin syndrome on the basis of their individual pharmacological actions serves to reinforce that the exact pathophysiological and molecular mechanisms are unclear and vigilance for serotonin toxicity is needed when prescribing polypharmacy involving at least one serotonergic agent.

6.3.3 Clinical challenges

It has been estimated that more than 85% of physicians are unaware of the serotonin syndrome as a clinical diagnosis ³. Furthermore, even when a clinician is cognisant of the possibility of such a pharmacodynamic interaction, the difficulty is that mild, early symptoms of serotonin toxicity may be easily overlooked or, in the case of altered mental status, be interpreted as an aggravation of the underlying disorder, such as depression. In the latter case, this can lead to an increase in dose of the causative agent or the addition of another serotonergic drug, which may provoke a dramatic clinical deterioration. One such example was described by Munhoz 2004 ¹⁷ who reported the onset of life-threatening serotonin syndrome presenting as altered consciousness and dysautonomia after venlafaxine was added to an existing combination of bupropion and

sertraline for treatment of depression. Venlafaxine had been added to treat emergent forgetfulness, confusion, and alternating agitation and lethargy that was interpreted as worsening depression. Apparently myoclonic jerks were also present prior to the addition of venlafaxine but had seemingly been overlooked.

There are a number of specific neurological features of serotonin toxicity not usually seen with other conditions that should alert clinicians to the presence of serotonin toxicity. The most important of these is generalised hyperreflexia, followed by sustained ankle clonus and ocular clonus. Also, generalised spontaneous clonus may occur in moderate to severe cases and is rarely seen in any other condition ⁴. On the other hand, the mental state and autonomic features, although usually present to some degree, are less specific and indistinguishable from that observed with other causes of an agitated delirium. The differential diagnosis for serotonin toxicity is shown in Table 6.3.

Table 6.3 Differential diagnosis of serotonin syndrome

Differential diagnosis	Distinguishing features
Neuroleptic malignant syndrome	Absence of neuromuscular excitation, presence of bradykinesia, lead pipe rigidity and extrapyramidal signs
Non convulsive seizures	EEG features, readily responsive to benzodiazepines
Acute baclofen withdrawal	History of baclofen pump, responsiveness to baclofen
CNS infection	Absence of neuromuscular excitation
Anticholinergic delirium	Absence of neuromuscular excitation, absent bowel sounds, dry skin
Sympathomimetic toxicity	Absence of neuromuscular excitation
Malignant hyperthermia	anaesthetic exposure, absence of neuromuscular excitation

In patients with suspected serotonin toxicity/serotonin syndrome, a careful clinical assessment is required, including a focused neurological examination (including mental state; upper and lower limb tone, clonus and reflexes; pupillary size, reaction and extraocular movements), observation for tremor, myoclonic jerks and diaphoresis, and assessment of vital signs (heart rate, blood pressure and temperature) ⁴. An accurate diagnosis cannot be made on observation or history alone.

In Australia, clinicians have been alerted to the risk of serotonin syndrome as an adverse drug reaction on a number of occasions via different publications:

- serotonin syndrome with tramadol was the subject of an Adverse Drug Reactions Bulletin article in 2001 ¹⁸. This was followed in 2004 by a more general Adverse Drug Reactions Bulletin article on the features of and medicines associated with Serotonin Syndrome ¹⁹. The latter article highlighted the need for health professionals to note the drugs that may cause serotonin syndrome, alone or in combination with other serotonergic agents, and be alert to the features of syndrome. It also stressed that patients should be informed of the risk and symptoms of serotonin syndrome when serotonergic agents are prescribed.
- the Australian Prescriber magazine carried a review article in 2003 ⁷ and has on three other occasions reported cases of serotonin syndrome arising from polypharmacy ²⁰⁻²².

- a tramadol alert was disseminated in 2000 by the NSW Therapeutic Assessment Group²³.
- independently prepared and published *Therapeutic Guidelines: Psychotropic* are a comprehensive guide for doctors prescribing psychotropic medicines and include, among other information, information on distinguishing between SSRI discontinuation syndrome, adverse effects, depression symptoms and serotonin syndrome.

The extent of potential polypharmacy of serotonergic medicines, particularly among elderly Australians, cannot be underestimated. Ringland et al 2008²⁴ examined Australian Department of Veterans' Affairs (DVA) data for July 2000 to June 2004 from 273,228 veterans, war widows, widowers and dependents aged \geq 55yrs to assess the level of concomitant use of serotonergic medicines and therefore potential risk of serotonin toxicity. They found that 42% (115,969) of the cohort were dispensed at least one serotonergic medicine over the 4 year period and 8% (20,658) had received at least one episode of potential concomitant use. Most concerning was the observation that 0.7% (1,811) patients had at least one overlapping period of potentially life-threatening combinations (MAOIs + SSRI; MAOIs + TCA; MAOIs + tramadol) and of these 937 had the combinations dispensed in the washout period (including 317 who were dispensed the medications on the same day). Thus, the number of individuals potentially at risk of mild to moderate serotonin toxicity was considerable and potentially life-threatening combinations were not infrequent, indicating ongoing prescriber education is essential.

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6.4 Akathisia and antipsychotic medicines

The traditional antipsychotics have been associated with a range of disabling extrapyramidal side effects such as akathisia, acute dystonic reactions, (pseudo)parkinsonism and tardive dyskinesia. There is now a large body of evidence to show that newer, atypical antipsychotic medicines have a more favourable neurological side-effect profiles and cause fewer extrapyramidal effects than typical neuroleptic medicines. This body of evidence comprises both individual published articles¹⁻⁵ and numerous Cochrane systematic reviews⁶⁻¹². However, there are reports of extrapyramidal effects with atypical antipsychotics^{13, 14} and, indeed, a dose-response relationship has been demonstrated for extrapyramidal side effects with some of them¹⁵. Akathisia is a particularly problematic and disabling side effect as it often goes undiagnosed, distresses patients, is associated with poor compliance with treatment and, thus, is ultimately associated with an increased risk of relapse.

6.4.1 Pathophysiology

While the complete pathophysiology of neuroleptic-induced acute akathisia remains unknown, it is generally accepted that antagonism of mesocortical and mesolimbic dopaminergic pathways is necessary for the development of akathisia. The notion that dopaminergic blockade underlies the emergence of akathisia is supported by PET studies¹⁶. In one study investigators examined striatal dopamine D₂ receptor occupancy in patients who had responded to antipsychotic medication and found that in those who exhibited extrapyramidal side-effects (Parkinsonism or akathisia) the D₂ receptor occupancy ranged from 77-89%, while the range for those without such symptoms was 74-80%. These findings link D₂ occupancy to extrapyramidal side effects¹⁶.

Other neurotransmitters implicated in the pathophysiology of akathisia include acetylcholine, γ -aminobutyric acid, noradrenaline and serotonin. The involvement of serotonergic mechanisms in the pathophysiology of akathisia is supported by the reported efficacy of ritanserin, a selective 5-HT₂ antagonist and the lower liability for akathisia with newer antipsychotic drugs with relatively potent 5-HT₂-receptor blockade. Further, the occurrence of akathisia during treatment with SSRI antidepressants, which potentiate 5-HT neurotransmission, has been reported^{17, 18}.

Different drug classes, particularly serotonin-dopamine antagonists, have a more distinct dose-response curve because they are intensive dopamine blockers with their extrapyramidal effects partially modified at lower doses by serotonin (5-HT_{2A}) blockade. For example, with risperidone, akathisia can be detected beginning at dosages of ~3 mg and increasing from that point. Although olanzapine appears to be relatively free of extrapyramidal side effects, onset of akathisia is noted as patients take higher doses. Some of the other serotonin-dopamine antagonists, such as clozapine and quetiapine, which are reported to be largely free of extrapyramidal side effects (e.g. Parkinsonism) at normal doses, may cause akathisia^{19, 20}. For example, it has been reported that clinicians observe akathisia in ~7% of patients taking clozapine²¹.

6.4.2 Diagnostic challenges with akathisia

Identifying and diagnosing akathisia can be quite difficult. Iqbal et al 2007²¹ highlighted many of these difficulties and discussed how our understanding of the phenomenology of akathisia has changed from it being thought of as a straight forward movement

disorder involving the legs to being a complicated intrapsychic and motor disorder that involves distress. It is now thought that akathisia comprises *subjective akathisia*, in which there are subjective complaints of restlessness and an overwhelming urge to move, and either *distress* or *motor phenomena* such as pacing, swinging the legs while seated, rocking from foot to foot, or both.

The presentation of akathisia can also be highly variable. For example, subjective aspects may dominate without any motor phenomena. Consequently, the diagnosis is often missed because many clinicians still mistakenly believe that akathisia is not present unless the legs are moving ²¹. Furthermore, the psychological components are often mistaken for other psychiatric conditions. For example, patients' psychoses can appear to worsen because they become quite agitated. Akathisic distress can also be highly variable. In moderately severe cases patients report experiencing "a horrible feeling," which causes agitation and spurs them to try to rid themselves of negative energy and in the most severe cases this can be associated with suicidality. On the other hand, some patients become inured to the subjective feelings of restlessness and stop being distressed. These patients may even lose their motor movements to a degree. However, the subjective component is always present ²¹.

Akathisia may be difficult to distinguish from psychotic agitation or anxiety, especially if the person describes a subjective experience of akathisia in terms of being controlled by an outside force ²². If akathisia is mistaken for psychosis, the antipsychotic drug dose may be increased leading to a worsening of the condition. The use of standardized scales can assist in identifying and diagnosing akathisia.

It is also useful for clinicians to distinguish between different types of akathisia as this assists with choosing the appropriate treatment and in the understanding of prognosis. Barnes et al 1985 ²³ divided patients who received neuroleptics and developed akathisia into three main groups on the basis of their clinical features – acute akathisia, pseudoakathisia and chronic akathisia. This classification has been further refined ²¹:

- acute akathisia – acute response to start of neuroleptic dosing, manifesting with subjective restlessness and motor phenomena;
- pseudoakathisia – response to chronic neuroleptic dosing in schizophrenic patients with negative symptoms, comprising overt motor phenomena without subjective restlessness;
- chronic akathisia type 1 – persistent acute akathisia with onset since last increase in neuroleptic dose, comprising subjective and motor restlessness; and
- chronic akathisia type 2 – tardive akathisia; withdrawal akathisia.

The importance of distinguishing between different types of akathisia is particularly highlighted with respect to tardive akathisia. Tardive akathisia is characterized by longer-term akathisia manifestations, which develop after ≥ 3 months of treatment. It is accompanied by motor phenomena associated with dyskinesia (which is poorly responsive to anticholinergic treatments, which along with benzodiazepines, β blockers and dose reduction are usually considered first line treatments, and which is used if Parkinsonism is present). It persists or in some cases, gets worse, when antipsychotic treatment is discontinued or reduced. It has been reported to be responsive to treatment with moclobemide ²⁴. Furthermore, some cases of tardive akathisia may be a form of tardive dyskinesia rather than akathisia. Symptoms may be due to withdrawal

dyskinesia from previous treatment, or may represent a different type of entity than what clinicians understand akathisia to be in its acute form.

In addition, it is important to distinguish akathisia from psychotic anxiety, activation syndrome that occasionally occurs with atypical antipsychotics (particularly some new partial dopamine agonists), drug withdrawal states (e.g. opiates, cannabis), neuroleptic rebound syndrome and restless legs syndrome. For example, akathisia can be differentiated from activation by seeking information from the patient about inner, pervasive restlessness, which is very characteristic of akathisia but absent in those with activation syndrome. Progressive restlessness and tremulousness while sitting can help clinicians separate between activation and akathisia. In addition, β -blockers have no effect for these patients and their responsiveness to benzodiazepines is a time-limited phenomenon ²¹.

Clearly, the diagnosis of akathisia has to be based on both an interview and examination, preferably aided by a standardised screening instrument (e.g. Barnes Akathisia Rating Scale (BARS) ²⁵; General Akathisia Tardive Phenomena and Extrapyrimal Scale (GATES) ²⁶), rather than observation alone.

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6.5 Weight gain, obesity and diabetes

Increasing numbers of Australians are either overweight (age-standardized body mass index (BMI) 25.0-29.9) or obese (age-standardized BMI \geq 30.0). This growing prevalence of obesity and obesity-related chronic disorders, most commonly coronary heart disease, stroke, type 2 diabetes mellitus, and hypertension, is a major public health concern ^{1, 2}. Other conditions that have been associated with obesity include gallbladder disease, osteoarthritis, and some cancers (colorectal and prostate in men, and breast, cervical, endometrial, gall bladder and ovarian in women) ¹.

In Australia, obesity rates range from 17.0% in Victoria to 19.6% in South Australia, and overweight rates from 34.2% in Queensland to 36.3% in Victoria ^{3, 4}. Analysis of AusDiab data found that 19% of males and 22% of females aged 25 years or over were obese, and an additional 48% of males and 30% of females were overweight in 1999–2000 ^{3, 5}. Males were more likely than females to be overweight or obese (67% versus 52%). The prevalence of obesity was found to be highest among those aged 55–64 (29%), with the lowest rates being among those aged 25–34 (15%) or 75 years and over (14%). Prevalence patterns for all overweight people were similar, with the prevalence increasing with age to 65–74 years, and declining thereafter ^{3, 6}.

Aside from diet and physical activity, prescribed medication can promote weight gain ⁶. The largest group of medications associated with weight gain are those used for psychiatric conditions such as schizophrenia, bipolar disorder, depression and anxiety ⁶. These include the most commonly used antipsychotic agents and mood stabilizers and several antidepressants. As one in five Australians has a psychiatric disorder, it is possible that psychotropic medications are contributing to the prevalence of obesity. Using the Framingham Heart Study 30 year dataset, Fontaine et al.⁷ estimated the effect of psychotropic weight gain on public health. They estimated that a 7.5kg weight gain related to antipsychotic drug usage would be associated with an additional 264 deaths, 1296 cases of impaired glucose tolerance or diabetes, and 5556 cases of hypertension per 100,000 people over 10 years. These results support the proposal that psychotropic-induced weight gain is contributing to the higher rates of mortality in psychiatric patients ⁸⁻¹¹.

6.5.1 Summary of literature review

There is a significant association between psychological disorders and weight gain ¹. Obesity is associated with an increased prevalence of stress symptoms and prescription of antidepressants ¹. Although some drugs, such as fluoxetine, isocarboxazid, and topiramate, can result in weight loss, many psychotropic medications produce weight gain.^{6,13-17} Major categories of concern are the antipsychotics, antidepressants and mood stabilizers. Low-potency (e.g. chlorpromazine and thioridazine) and atypical antipsychotic agents (e.g., clozapine, olanzapine, quetiapine and risperidone) and selected antidepressant agents, such as tricyclic antidepressants and monoamine oxidase (MAO) inhibitors, are most often associated with weight gain ^{13, 18-20}. Mood stabilizers, such as lithium carbonate, valproic acid and carbamazepine, are also commonly associated with weight gain ^{13, 18-20}. In addition, higher than expected rates of obesity-related chronic diseases such as diabetes, heart disease, dyslipidaemia, hypertension and stroke have been described in a number of case reports among patients taking antipsychotic medications ²¹⁻²³.

Conventional neuroleptics

Weight gain associated with chlorpromazine and thioridazine has been well described^{6, 13-16}. High-potency neuroleptics have less weight-promoting effects than low-potency neuroleptics²⁴. There is little evidence that haloperidol promotes weight gain²⁴, though weight gain of varying degrees has been observed, albeit in uncontrolled observation trials, with other high to mid potency agents including fluphenazine, pimozide, perphenazine, and loxapine^{24, 25}. The weight gain associated with depot medication has been observed to continue for at least 2 years following treatment initiation^{26, 27}. The putative mechanism of neuroleptic-associated weight gain relates to receptor antagonism at anticholinergic, serotonergic, and histaminergic sites, all of which are related to appetite stimulation²⁴. Haloperidol has a low affinity for these receptors, which may explain its low potential for inducing weight gain. Though there are several trials that have assessed their effect on weight, there have been few investigations measuring the prevalence of obesity-related disorders such as diabetes, dyslipidaemia, hypertension and stroke in patients taking conventional antipsychotic. One recent controlled trial did suggest that non-depot conventional neuroleptics but not depot preparations increased the risk for diabetes in patients with schizophrenia²⁸. There are no data on other obesity-related disorders.

Atypical antipsychotic drugs

Clozapine has been strongly associated with weight gain^{6, 13-16, 29}. A retrospective study showed that patients gained an average of 8 kg while taking clozapine³⁰. The accumulations were substantial and exceeded those associated with the use of conventional neuroleptics. Weight gain was most rapid during the early months of drug treatment, but continued to gain at a slower rate for several years. Clozapine's pharmacological effects include antagonism at serotonin 5-HT₂, alpha-adrenergic, histaminergic, and muscarinic receptors, as well as effects on endocrine and metabolic systems^{30, 31}. Clozapine may impair glucose homeostasis through altered secretion or utilization of insulin and growth hormone, which is mediated by serotonin and histamine receptors^{32, 33}. Abnormal glucose tolerance and adverse changes to lipids have been documented among patients being treated with clozapine^{21, 34}.

Olanzapine has also been shown to have a potent effect on weight gain^{6, 13-16}; up to 94 percent of persons who take olanzapine may experience this side effect. Several studies found that patients who were receiving long-term treatment with olanzapine gained an average of 12 kg during the course of one year. It has also been associated with increased rates of hyperlipidaemia and diabetes^{21, 28, 35}. The drug's mechanism of action involves antagonism at serotonergic 5-HT₂, muscarinic, histaminic, alpha-adrenergic, and dopamine D₁ and D₂ receptors.

Quetiapine has been associated with smaller increases in weight^{6, 13-16}. In clinical trials, average weight gain was 1-4 kg during the initial months of treatment³⁶. Although continued gains have not been documented, a 7 percent increase in weight from baseline was reported for 25 percent of quetiapine-treated patients in one study³⁷. The drug acts mainly at histaminic and alpha₁- and alpha₂-adrenergic receptors^{31, 38}. Quetiapine use is relatively small compared with olanzapine and risperidone.

The data on risperidone's effect on weight suggest some weight gain potential but less than with clozapine, olanzapine, and quetiapine^{39, 40}. In a meta-analysis of short-term trials (mean follow up of 10 weeks), risperidone was associated with a mean increase in

weight of 2.0kg⁴⁰. Risperidone is a combined dopamine D₂ and serotonin 5-HT₂ antagonist and has little affinity for other receptors, which may account for its reduced effect on weight. Risperidone is the most frequently used of all antipsychotics. It is used commonly in the management of children and elderly patients with behavioural problems, but its most common use is in adults with chronic psychotic disorders.

Several case reports, of diabetes, heart disease, stroke, and sudden death, point to the potential harms associated with antipsychotic-induced weight gain ^{21, 41}. However, the frequency of case reports, which suffer from many limitations and reporting biases, is neither a true indication of incidence nor a measure of the attributable risk for developing these disorders. Other reports, including small randomised controlled trials and observational studies demonstrating higher than expected rates, support a causal association between antipsychotic use and adverse cardiovascular and metabolic outcomes ^{21, 23, 28, 35, 41}. One study demonstrated an increased risk of diabetes and hyperlipidaemia in younger patients on clozapine (20-34 years) compared to those on conventional antipsychotics ⁴². In another, the risk of type 2 diabetes for risperidone-treated patients was not significantly different from that for untreated patients after 12 months, whereas patients receiving other antipsychotics such as olanzapine, clozapine, high-potency conventionals, and low-potency conventionals had a significantly greater risk of diabetes than untreated patients ⁴³. Older age and greater use of non-antipsychotic psychotropic medications also contributed to risk of type 2 diabetes. Olanzapine also showed significantly higher odds of diabetes associated with increasing dose ^{35, 43}.

Risk factors for type 2 diabetes and impaired glucose tolerance include abdominal adiposity, age, ethnic status, and certain neuropsychiatric conditions ^{16, 42}. In turn, diabetes is an independent risk factor for cardiovascular and metabolic morbidity and mortality ⁴⁴. The mechanisms are unclear. Increased abdominal adiposity may explain some treatment-related changes in glucose metabolism, although clozapine and olanzapine treatment may also be associated with adverse effects on glucose metabolism independent of changes in adiposity ⁴⁴. Dyslipidaemia is a feature of type 2 diabetes, and antipsychotics such as clozapine and olanzapine have also been associated with hypertriglyceridaemia, in contrast to agents such as haloperidol, risperidone, and ziprasidone that may be associated with reductions in plasma triglycerides. There is an association between weight gain and impaired glucose tolerance and hypertension, and it has been estimated that the use of clozapine may lead to 416 additional deaths per 100,000 patients with schizophrenia over 10 years, a rate that would essentially reverse its benefits from suicides prevented ¹¹. Diabetes mellitus is associated with increased morbidity and mortality due to both acute (e.g., diabetic ketoacidosis) and long-term (e.g., cardiovascular disease) complications ⁴⁴. A progressive relationship between plasma glucose levels and cardiovascular risk (e.g., myocardial infarction, stroke) begins at glucose levels that are well below diabetic or "impaired" thresholds ⁴⁴.

Mood stabilizers

Most mood stabilizers, including lithium, valproic acid derivatives, carbamazepine, gabapentin, and lamotrigine, can cause weight gain. In contrast, topiramate, which is currently used infrequently as a mood stabilizer, has been associated with weight loss ^{13, 18-20}. The mechanism for lithium-induced weight gain could include hypothyroidism, increased consumption of high-calorie liquids due to lithium-induced polydipsia, oedema, and increased storage of carbohydrates and lipids ⁴⁵. Weight gain in the case of

the other mood stabilizers may be explained by increased food intake, decreased energy expenditure, reduction of thermogenesis, and greater availability of long-chain fatty acids as a result of competitive binding to serum albumin ⁴⁵. Although the link between the most commonly used mood stabilizers and weight gain is well established, there are no data on their association with obesity-related disorders.

Antidepressants

Most antidepressants are associated with increased weight although some of this may be related to improved appetite as symptoms of depression diminish ⁴⁶. Aside from their antidepressant action, older antidepressants have a direct action on appetite and can induce a craving for carbohydrates ^{24, 45}. Tricyclic antidepressants cause weight gain more often than do monoamine oxidase inhibitors. Tricyclic antidepressants have multiple pharmacological effects including blockade of norepinephrine, dopamine, and serotonin reuptake at presynaptic sites and antagonism at muscarinic, alpha1-adrenergic, and histaminic receptors. Although several mechanisms for weight gain have been proposed, the strongest association has been with their antihistaminic effects ¹³. Anticholinergic activity may also contribute secondary to drug induced dry mouth, which may lead to excessive consumption of high-calorie beverages. A craving for sweets has been reported among patients taking amitriptyline, nortriptyline, and imipramine ⁴⁷. The effects of amitriptyline on body mass have been extensively investigated. In one study involving 51 women taking amitriptyline, the average weight gain was 4 kg ²⁴. In another study, the average gain was 7 kg, and 73 percent of the study participants reported an increase in their desire for sweets ⁴⁸. Amitriptyline remains the most commonly prescribed tricyclic in Canada and is second only to paroxetine in terms of number of prescriptions. ⁶ Its widespread use and association with weight gain indicate that it may contribute to obesity-related disorders.

Selective serotonin reuptake inhibitors (SSRIs) selectively block the reuptake of serotonin into presynaptic nerve terminals. Minimal weight gain and decreases in appetite have been associated with the use of SSRIs ⁴⁹. Fluoxetine and sertraline have been used in the treatment of obesity, albeit with limited success ⁵⁰. Although there are few data on weight changes during treatment with fluvoxamine or paroxetine, anecdotal evidence and a single controlled trial indicate that paroxetine, Canada's most prescribed antidepressant, can promote weight gain ^{6, 51, 52}. Overall, the effects of SSRIs on weight and obesity-related diseases have not been adequately studied ⁵³.

Mirtazapine, the most recently marketed antidepressant, has been associated with an increase in appetite and weight ⁵⁴. These side effects may be a result of mirtazapine's potent antihistaminic and noradrenergic effects. An average gain of about 2 kg after six weeks of treatment has been reported ⁵⁵. A dose-dependent relationship between mirtazapine and increased appetite and weight has also been demonstrated.⁵⁶

Other antidepressants can lead to weight loss or are weight neutral. Bupropion, in a three-month trial with 58 depressed patients, was associated with a mean decrease in weight of 3 kg ⁵⁹. Forty-two patients who had complained of increased appetite or weight gain with previous antidepressant therapy lost an average of 4 kg each. Bupropion is a rational choice when stability or loss of weight is important ⁶⁰. Venlafaxine does not appear to cause weight changes ^{50, 56}.

There are no data on the prevalence of obesity-related disorders in this group of medications.

6.5.2 Possible confounding factors

The measured association between psychotropic drug use and obesity related disorders might be affected by a number of confounders. First, patients with chronic psychiatric illnesses (e.g., schizophrenia) may not be at the same baseline risk for several outcomes of interest including diabetes and cardiovascular disease ⁶¹. This may relate to differences in lifestyle and other less well understood mechanisms. Second, use of other drugs that affect weight and/or modulate the risk for metabolic and cardiovascular outcomes may be different in the population of interest and/or across its subgroups compared to the general public. For example, topiramate and fluoxetine, may cause weight loss and will be used long-term primarily by patients with chronic mood disorders. Alternatively, medical treatments associated with weight gain, such as corticosteroids, insulin therapy, sulfonylurea derivatives, antineoplastic agents, and migraine prevention therapies, may be relatively under represented in the population of patients with chronic psychiatric disorders ⁶². Furthermore, drug therapies (e.g., statins, thiazides, beta blockers) that reduce the risk for the development of certain outcomes of interest (e.g., total mortality, stroke, myocardial infarction) may also be relatively underused by patients with chronic psychiatric disorders. Third, patient related factors that may alter risk include abdominal adiposity, age, ethnic status, tobacco use and certain neuropsychiatric conditions. For instance, there is an independent association between schizophrenia and diabetes. The association between psychotropic medication and some cardiac disease such as cardiac sudden death may be mediated by effects on the QT interval rather than by weight gain ⁶³.

In conclusion, there is good evidence that a range of psychotropic medications can induce weight gain even though this side effect does not feature prominently on the series of reports submitted to the TGA.

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6.6 Interactions between antipsychotic and antidepressant medications

When combining medications for the management of patients, physicians face a potentially complex treatment strategy. In particular, antipsychotics and antidepressants are often used concomitantly in both mood disorder and schizophrenia. Available agents have different mechanisms of action, routes of metabolism and excretion, therapeutic effects and side effects. Whilst combining treatments can be advantageous as a result of therapeutic synergy, there may be increased side effects.

6.6.1 Pharmacodynamic antidepressant-antipsychotic drug interactions

Pharmacodynamic drug-drug interactions are usually intuitively straight forward and if one has a sense of the mechanism of action and receptor occupancies of the various medicines, these interactions can often be predicted and avoided. Atypical antipsychotic drugs have diverse pharmacological actions. All are dopamine and serotonin 5HT receptor antagonists (with the exception of aripiprazole, which has partial agonist activity at dopamine D₂ and serotonin 5HT_{1A} receptors and antagonist activity at serotonin 5HT_{2A} receptors), and possess varying α -adrenergic muscarinic and histaminic receptor antagonistic activity.

The action of the newer antidepressants (a diverse group of chemical compounds) is mediated via effects on monoamine reuptake, enhancing serotonin and/or noradrenaline function. They possess minimal or no affinity for dopamine, muscarinic, histaminic or adrenergic receptors. Mirtazapine increases serotonin and noradrenergic activity by more complex action being a presynaptic adrenoceptor antagonist and serotonin 5HT₂ antagonist. It also has antihistaminic action.

Pharmacodynamic interactions of potential clinical importance are:

- increased appetite and weight gain - particularly with antipsychotics olanzapine and quetiapine in combination with mirtazapine. This may increase risk of metabolic syndrome;
- sedation - the antihistamine effects of antidepressants, particularly mirtazapine, may potentiate sedative effects with atypical antipsychotics such as quetiapine;
- extrapyramidal effects and the risk of akathisia may be increased as a result of the interaction of the antipsychotics and antidepressant drugs;
- cardiovascular effects - blood pressure control may be compromised through adrenergic effects particularly in patients with pre-existing cardiovascular disease;
- sexual dysfunction - decreased libido, erectile dysfunction and anorgasmia may occur with both groups of drugs. Hyperprolactinaemia, particularly with risperidone, and paliperidone can also contribute to sexual dysfunction.

6.6.2 Pharmacokinetic antidepressant-antipsychotic drug interactions

It is often more difficult to predict pharmacokinetic interactions, which are most predominantly concerned with metabolic alterations. There are several key enzymatic systems involved in pharmacokinetic interactions, the most prominent of which is the cytochrome P450 system that perform oxidative (phase I) metabolism. Inhibitors of the various members of the family of mostly hepatic CYP450 enzymes impair the ability of the specific enzyme to metabolise the substrate drug, producing increased plasma levels. This effect is usually immediate. CYP450 inducers, on the other hand usually

require several days to weeks to increase the production of the particular enzymes before the metabolism of substrates is increased. Conjugative (phase II) metabolism, which most prominently involves the uridine 5'-diphosphate glucuronosyltransferases (UGTs), generally renders substances that have already undergone oxidative metabolism more hydrophilic and thus more readily excreted. The contribution of phase II metabolism to drug-drug interactions is typically not as significant as that of phase I metabolism. However, the metabolism of some psychotropic drugs involves a considerable contribution from the UGTs. For example, there is a significant contribution from UGT1A4 to the metabolism of olanzapine ¹.

Increasingly, non-metabolic systems, such as the P-glycoprotein transporter, are being recognised as important mechanisms of pharmacokinetic interaction. P-glycoprotein is an important regulator of drug absorption and bioavailability (through its presence in the plasma membrane of enterocytes), excretion (through its presence in cells lining renal tubules), as well as the ability of medicines to cross the blood-brain barrier. The P-glycoprotein transporter has substrates, inhibitors and inducers. P-glycoprotein functions by extruding of substrates from the cell cytosol of enterocytes back into the gut lumen and from capillaries of the blood brain barrier into the bloodstream. Inhibitors of P-glycoprotein block these actions, thereby causing retention and absorption of P-glycoprotein substrates, resulting in increased blood levels ¹.

Table 6.6A summarises the current knowledge of the various substrates and inhibitors of the CYP450 system. In the table, medicines that are metabolised primarily by a particular CYP450 enzyme are shown in normal font. Where the medicine is metabolised secondarily by the enzyme a lighter font is used. It can be appreciated that most antidepressants and antipsychotic medicines are substrates of multiple CYP450 enzymes, with some, such as haloperidol, having particularly complex pathways. Furthermore, many of these medicines are also inhibitors (with varying degrees of affinity) of one or more of the enzymes. Fluoxetine gives rise to a special concern as both the parent drug and its metabolite have a long half life, with potential to cause interactions weeks after administration of the parent drug is ceased.³

However, whilst the myriad of potential interactions is, therefore, theoretically quite large, this does not mean that there will inevitably be clinically significant interactions. For example, the combination of quetiapine (metabolised almost entirely by CYP3A4) and fluoxetine (an inhibitor of CYP3A4) reliably produces increased peak and trough concentrations of quetiapine that are statistically significantly higher than with quetiapine alone, but such an interaction does not result in a clinically significant increase in adverse effects ⁴. Also, moclobemide is an inhibitor of CYP1A2, CYP2C19 and CYP2D6 and it could be expected that this would be of particular relevance to olanzapine, which is metabolised via CYP1A2 and, to an insignificant extent, CYP2D6. However, few drug interactions involving moclobemide have been reported ⁵, including with olanzapine (most likely on account of the primary contribution of UGT1A4 to olanzapine metabolism).

To further illustrate this point, Table 6.6B provides a summary of the clinically significant (real and theoretical) interactions between antidepressants and antipsychotic medicines that have been identified by published, extensive reviews of the literature ^{1, 3, 6}. On the whole there are relatively few clinically significant effects from pharmacokinetic interactions between antipsychotics and antidepressant medicines and these can be characterised under four main types, mostly involving the SSRI

antidepressants. Importantly, there do not appear to be any clinically significant pharmacokinetic interactions involving the newer antidepressants reboxetine, venlafaxine or mirtazapine and antipsychotic medicines.

Table 6.6A Antidepressants and antipsychotics as substrates and inhibitors of CYP450 enzymes*

Substrates			Inhibitors		
CYP	Antidepressants	Antipsychotics	Potent	Mild to moderate	Weak to Mild
1A2	fluvoxamine duloxetine mirtazapine amitriptyline clomipramine imipramine	clozapine olanzapine haloperidol pimozide	fluvoxamine	fluoxetine norfluoxetine moclobemide	sertraline paroxetine citalopram
2C19	amitriptyline clomipramine citalopram escitalopram moclobemide	clozapine	fluvoxamine	fluoxetine norfluoxetine sertraline moclobemide	amitriptyline imipramine citalopram
2D6	amitriptyline imipramine desipramine nortriptyline mianserin paroxetine fluoxetine fluvoxamine citalopram escitalopram mirtazapine duloxetine moclobemide venlafaxine	haloperidol (low doses) perphenazine thioridazine zuclopenthixol pimozide aripiprazole risperidone clozapine olanzapine	fluoxetine norfluoxetine (fluoxetine metabolite) paroxetine sertraline >150mg/day bupropion thioridazine reduced haloperidol	secondary amine TCAs (eg desipramine, nortriptyline) escitalopram sertraline 100- 150mg/day duloxetine pimozide risperidone moclobemide	tertiary amine TCAs (eg amitriptyline, imipramine, doxepin) sertraline <100mg/day clozapine fluvoxamine citalopram venlafaxine
3A4	mirtazapine reboxetine buspirone venlafaxine amitriptyline imipramine citalopram paroxetine	quetiapine pimozide haloperidol (high doses) aripiprazole ziprasidone risperidone clozapine		fluoxetine norfluoxetine fluvoxamine pimozide	paroxetine reboxetine

* Adapted from Bertilsson (2007)², Baxter (2008)³, Sandson et al (2005)¹ and approved PI documents.

Table 6.6B Clinically significant antidepressant – antipsychotic drug interactions**

Antidepressant /interacting antipsychotic	Mechanism(s) of interaction	P/K results	Clinical consequences	Comments	
citalopram, escitalopram					
Phenothiazine antipsychotics	Pharmacokinetic – inhibition of CYP2D6 by citalopram and escitalopram (weak)	Increased levels of phenothiazine antipsychotics	Increased EPS	Combination of citalopram or escitalopram with thioridazine may increase its arrhythmogenic potential (theoretical risk)	
pimozide	Citalopram - unclear effect, in vitro enzyme inhibition data did not reveal inhibitory effect of citalopram on CYP3A4 and only mild inhibition of 1A2 Escitalopram – inhibition of CYP2D6	Racemic citalopram increased pimozide AUC and Cmax	Increase in QT interval prolongation		
fluoxetine					
aripiprazole	Pharmacokinetic – inhibition of CYP 2D6 and 3A4 by parent and its metabolite norfluoxetine	Increased levels of aripiprazole	Increased EPS, report of neuroleptic malignant syndrome	Aripiprazole plasma levels 44% higher in patients receiving potent CYP2D6 inhibitors Clozapine levels typically increased by ~50%	
clozapine	Pharmacokinetic – inhibition of CYP 1A2, 2C9, 2C19, 2D6 and 3A4 as well as P-glycoprotein by parent and norfluoxetine	Increased levels of clozapine	Increased sedation and anticholinergic effects, seizure risk		
haloperidol	Pharmacokinetic – inhibition of multiple CYP450 enzymes - 1A2, 2D6 and 3A4 as well as P-glycoprotein by parent and norfluoxetine	Increased levels of haloperidol	EPS, reports of akathisia, increased antimuscarinic effects		
pimozide	Pharmacokinetic - inhibition of CYP 1A2 and 3A4 by parent and norfluoxetine	Increased levels of pimozide	Increased EPS and arrhythmogenic potential		Case of serious bradycardia reported
risperidone	Pharmacokinetic – inhibition of CYP 2D6 and 3A4 as well as P-glycoprotein by	Increased level of risperidone	EPS, increased prolactin		Average increase in risperidone active moiety of ~75%

Antidepressant /interacting antipsychotic	Mechanism(s) of interaction	P/K results	Clinical consequences	Comments
typical antipsychotics	parent and norfluoxetine Pharmacokinetic – inhibition of multiple CYP450 enzymes - 1A2, 2D6 and 3A4 as well as P-glycoprotein by parent and its metabolite norfluoxetine	Increased levels of most atypical antipsychotics	Increased EPS	Combination of fluoxetine with thioridazine or pimozide can increase arrhythmogenic potential
fluvoxamine				
clozapine	Pharmacokinetic – inhibition of CYP 1A2, 2C9, 2C19, 2D6 and 3A4 as well as P-glycoprotein by fluvoxamine	Increased levels of clozapine	Increased sedation and anticholinergic effects, seizure risk. Also reports of increased EPS (rigidity, tremor, akathisia)	Clozapine levels typically increase three to four fold (literature reports of up to ten fold increase)
olanzapine	Pharmacokinetic – inhibition of CYP1A2 (strong), 2D6 (weak) and P-glycoprotein by fluvoxamine	Increased level of olanzapine	Increased sedation and risk of EPS	
pimozide	Pharmacokinetic - inhibition of CYP 1A2 and 3A4 by fluvoxamine	Increased levels of pimozide (probably)	Increased EPS and arrhythmogenic potential	Theoretical concern
haloperidol	Pharmacokinetic - inhibition of CYP1A2, 2D6, 3A4 and P-glycoprotein by fluvoxamine	Increased levels of haloperidol	Increased EPS, sedation and worsening of cognitive function	Haloperidol levels increased by fluvoxamine in dose dependent manner – 20% at 25mg fluvoxamine daily, 39% at 75mg and 60% at 150mg daily.
typical antipsychotics	Pharmacokinetic – inhibition of multiple CYP450 enzymes - 1A2, 2D6 and 3A4 as well as P-glycoprotein (weak) by fluvoxamine	Increased levels of most atypical antipsychotics	Increased EPS	Combination of fluvoxamine with thioridazine or pimozide can increase arrhythmogenic potential
paroxetine				
aripiprazole	Pharmacokinetic - inhibition of CYP2D6 and P-glycoprotein by paroxetine	Increased levels of aripiprazole expected	Increased EPS	Theoretical risk on basis of potent inhibition of CYP2D6 by paroxetine.

Antidepressant /interacting antipsychotic	Mechanism(s) of interaction	P/K results	Clinical consequences	Comments
clozapine	Pharmacokinetic – inhibition of CYP 1A2, 2C9, 2C19, 2D6 (weak) and 3A4 as well as P-glycoprotein by paroxetine	Increased levels of clozapine and norclozapine	Increased sedation and antimuscarinic effects. Report of fatality from NMS	PI recommends dose reduction. Reports of variable effects on clozapine levels, ranging from little effect to doubling of clozapine levels
phenothiazine antipsychotics	Pharmacokinetic - inhibition of CYP2D6 and P-glycoprotein by paroxetine	Increased levels of phenothiazine antipsychotics	Increased EPS	Combination of paroxetine with thioridazine or pimozide can increase arrhythmogenic potential
pimozide	Pharmacokinetic – inhibition of CYP 1A2, 2D6 and 3A4 by paroxetine	Increased levels of pimozide	Increased arrhythmogenic potential in pimozide which has low therapeutic index.	PI for paroxetine reports a single 2mg dose increased pimozide Cmax by 62% and AUC by 115%.
risperidone	Pharmacokinetic – inhibition of CYP 2D6 > 3A4 as well as P-glycoprotein by paroxetine	Increased level of risperidone	EPS, increased prolactin	Average increase in risperidone active moiety of ~45%
sertraline				
aripiprazole	Pharmacokinetic - inhibition of CYP2D6 and P-glycoprotein by sertraline	Increased levels of aripiprazole expected	Increased EPS	Sertraline a moderate to potent inhibitor of CYP2D6 at doses >150mg/day. Report of akathisia when aripiprazole 10mg/day added to sertraline 200mg/day, with resolution after withdrawal of aripiprazole.
pimozide	Unclear – possible inhibition of CYP3A4 and 1A2 by sertraline.	Unclear – possible increased level of pimozide	Increased EPS and arrhythmogenic potential	
MAOIs				
clozapine	Pharmacodynamic – decreased	NA	Hypertension	Case known to Sandsom et al 2005

Antidepressant /interacting antipsychotic	Mechanism(s) of interaction	P/K results	Clinical consequences	Comments
ziprasidone	metabolism of noradrenaline by MAOIs, combined with increased serum noradrenaline due to clozapine's α_2 blockade Pharmacodynamic – decreased metabolism of serotonin and noradrenaline by MAOIs, combined with ziprasidone's intrinsic serotonergic and noradrenergic reuptake blockade.	NA	Serotonin syndrome and/or hypertensive crisis.	Theoretical concern for this combination but potentially fatal
TCAs				
haloperidol	Pharmacokinetic – inhibition of CYP2D6 and P-glycoprotein by haloperidol and reduced haloperidol metabolite	Increased levels of TCAs	Increased arrhythmia risk and anticholinergic symptoms	Theoretical concern – usually not clinically significant
phenothiazine antipsychotics	Pharmacokinetic – inhibition of CYP2D6 and P-glycoprotein by phenothiazines. Moderate inhibition of CYP2D6 by secondary amine TCAs and mild inhibition of CYP2D6 by tertiary amine TCAs. Also possible additive pharmacodynamic effects	Increased levels of TCAs Increased levels of the antipsychotic medicines	Increased arrhythmia risk, hypotension, sedation and anticholinergic symptoms	Theoretical concern – usually not clinically significant. Combination of TCAs with thioridazine may increase arrhythmogenic potential
pimozide	Pharmacokinetic – inhibition of CYP2D6, 3A4 and P-glycoprotein by pimozide Pharmacodynamic – synergistic QT prolongation	Increased levels of TCAs	Increased arrhythmogenic potential	Theoretical concern
ziprasidone	Pharmacodynamic – synergistic QT prolongation	NA	Increased arrhythmogenic potential	

** Adapted from Sandson et al (2005)¹, supplemented by information from Baxter (2008)³ and Australian PI documents.

1. Interaction between SSRIs and antipsychotics resulting in increased antipsychotic levels and extrapyramidal effects

Movement disorders associated with raised antipsychotic levels from SSRI co-administration appear most common with fluoxetine, fluvoxamine and paroxetine. Fluoxetine (and its active metabolite norfluoxetine) and fluvoxamine are CYP450 pan inhibitors.

Fluoxetine, norfluoxetine and paroxetine are potent inhibitors of CYP2D6. CYP2D6 is the primary metabolic pathway for many antipsychotics, including haloperidol and risperidone. There are a number of reports of increased extrapyramidal effects from concomitant use of fluoxetine with haloperidol ⁷, fluvoxamine with clozapine⁸, and fluvoxamine and olanzapine⁹. Risperidone levels have been found to be raised by fluoxetine (associated with reports of severe akathisia and extrapyramidal effects ^{10, 11}), and with paroxetine (associated with parkinsonian effects and increased extrapyramidal effects ^{12, 13}). Aripiprazole levels have been shown to be 44% higher in patients also receiving CYP2D6 inhibitors, including fluoxetine ¹⁴ and the reported clinical effects from such a combination have included extrapyramidal effects ¹⁵ and neuroleptic malignant syndrome ¹⁶.

Clozapine and olanzapine unusual among the antipsychotics in the sense that they are metabolized primarily by CYP1A2 and not to any significant extent by CYP2D6. Furthermore UGT1A4 is a primary pathway for olanzapine. Fluvoxamine is a potent inhibitor of CYP1A2 has the greatest impact on the levels of these two antipsychotics ³ - see also interaction between clozapine and SSRIs, below.

2. Interaction between pimozide/thioridazine and SSRIs, with the potential for cardiac arrhythmia

Both pimozide and thioridazine have low therapeutic index because of their arrhythmogenic potential and administration of these agents alone can cause QT_c interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes and sudden death.

Pimozide levels are expected to rise when used with inhibitors of CYP3A4 (which is its primary metabolic pathway (with secondary contribution from 2D6 and 1A2)).

The marketing applications of several of the currently approved SSRIs included pharmacokinetic interaction studies that demonstrated altered pharmacokinetic parameters of pimozide with a single 2mg dose of pimozide when co-administered with the SSRI as follows (as stated in approved Product Information documents):

- fluoxetine - increased pimozide levels
- racemic Citalopram (40mg/day for 11 days) - increased pimozide AUC and C_{max} and mean increase in QT_c interval by 10msec

In view of the potentially very severe interaction that could arise from such a combination, concomitant use of SSRIs with pimozide has been generally contraindicated. Not surprisingly, therefore, there is only a single case report of serious bradycardia with the combination of fluoxetine and pimozide ¹⁷. It should be noted that pimozide is not currently entered in the Australian Register of Therapeutic Goods and is therefore not available for commercial supply.

Thioridazine levels are expected to rise when used with inhibitors of CYP2D6, its primary metabolic pathway. Carrillo et al 1999¹⁸ found the addition of fluvoxamine 50mg daily (a weak inhibitor of CYP2D6) to schizophrenic patients on established treatment with thioridazine 30 to 200mg daily (n=10) was associated with an increase in thioridazine plasma levels by 225% but this was not associated with any reported change in clinical status or adverse effects in those patients. There is an absence of further studies and adverse reaction reports pertaining to SSRI-thioridazine interactions. However, it has been generally recognised that caution should be exercised when coadministering thioridazine and inhibitors of CYP2D6, especially paroxetine, which along with thioridazine is a potent inhibitor of that enzyme.

3. Interaction between clozapine and SSRIs, resulting in clozapine toxicity

The interaction between SSRIs and clozapine, whereby co-administration of SSRIs may cause serum levels of clozapine to rise, is well established³. Fluoxetine, paroxetine, sertraline and fluvoxamine all have been reported as causing increased clozapine levels. For example, several studies and case reports have shown fluoxetine increased clozapine levels by between 30 to 75%, with increased levels of its metabolite norclozapine of between 34 to 52% after fluoxetine was added to clozapine^{19, 20}. Reported clinical effects associated with these changes have included hypertension and myoclonic jerks.

However, the effect appears greatest with fluvoxamine which potently inhibits the primary CYP1A2 pathway for clozapine. Concomitant administration of fluvoxamine and clozapine has been reported to cause up to ten fold increases in clozapine levels³. The significance of such elevated clozapine levels has been quite variable though, with one study reporting the absence of any significant adverse effects, even following prolonged treatment with such a combination²¹. However, there have been reports of extrapyramidal effects (including rigidity, tremors and akathisia)⁸ and sedation within days of commencement of such a combination and in one study there was also a trend toward decreased granulocyte levels in patients receiving the combination (n=11), but not in those receiving clozapine alone (n=12)²².

4. Interaction between tricyclic antidepressants and typical antipsychotics, resulting in risk of arrhythmia

Co-administration of tricyclic antidepressants (TCAs) and typical antipsychotics can result in creases in plasma levels of both medicines, mostly from interaction via CYP2D6^{1,6}. Phenothiazine antipsychotics are metabolised primarily by CYP2D6 and most of these agents also exhibit moderate to potent CYP2D6 inhibition. As a class they also appear to be P-glycoprotein inhibitors. Secondary amine TCAs such as nortriptyline and desipramine are primary substrates of CYP2D6 as well as being moderate inhibitors of the enzyme and of P-glycoprotein. The tertiary amine TCAs (amitriptyline, clomipramine, imipramine) whilst relying on CYP2D6 for hydroxylation, also undergo demethylation via CYPs 1A2, 2C19 and 3A4. They also exhibit only mild inhibition of CYP2D6.

This interaction is more of a theoretical concern in relation to coadministration of drugs with a narrow therapeutic index, such as thioridazine and is usually not clinically significant. However, additive effects, such as hypotension, sedation and anticholinergic effects may occur.

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6.7 SSRIs and Pregnancy

The use of SSRIs in pregnancy is of ongoing and current interest. In 2006, the US FDA notified healthcare professionals and consumers of the outcomes of two studies that needed to be considered when making treatment decisions in pregnant women who take antidepressants:

- the first study examined the potential risk of relapsed depression after stopping antidepressant medication during pregnancy and found that women who stopped their medicine were five times more likely to have a relapse of depression during their pregnancy than were women who continued to take their antidepressant medicine while pregnant ¹;
- the second study found that persistent pulmonary hypertension (PPHN), a serious and life-threatening lung condition, was six times more common in babies whose mothers took an SSRI antidepressant after the 20th week of pregnancy compared to babies whose mothers did not take an antidepressant ².

As a result the FDA asked the sponsors of all SSRIs to change prescribing information to describe the potential risk for PPHN. At about the same time, the FDA also changed the labelling for paroxetine to include information that exposure to the drug in the first trimester of pregnancy may be associated with an increased risk of cardiac birth defects.

More recently this year, media attention has focussed on pending legal action in the US in which it has been claimed that insufficient attention was paid to the effects of SSRIs (and in particular paroxetine) in pregnancy.

Two of the reports received by the TGA alluded to adverse effects, such as congenital abnormalities, having occurred with exposure to SSRIs during pregnancy, although there were no specific details of those events.

6.7.1 Review of the literature

The examination of the use of SSRIs in pregnancy needs to be divided into a number of areas of possible risk: teratogenic effects, premature birth, early effects on the neonate and longer term effects on development of the child. Most studies are burdened with recall and selection bias and there are continuous difficulties with sample size. The indication for SSRI use and the psychiatric illness itself have been little taken into account.

The evidence for teratogenesis is not clear. Most reports focus on cardiovascular abnormalities although other rare defects have been reported: sertraline with omphalocele ³ and anencephaly ⁴, fluoxetine with craniosynostosis ⁴ and paroxetine with omphalocele ⁴. The absolute risk, although increased, remains small.

Most focus has been on cardiovascular abnormalities but the risk remains unclear. A number of studies found no increase in heart defects with SSRI use overall ^{3, 4, 5, 6}. However, an association between paroxetine and right ventricle outflow obstruction ⁵, and associations of both paroxetine and fluoxetine with cardiovascular abnormalities ⁷ have been found.

Gentile 2009 ⁸ in a review of the question of defects with paroxetine, comments on the inconsistency of the findings and limitations of the methodology of the published studies and concludes that the teratogenic potential of paroxetine remains unproven.

Bar-Oz et al 2007 ⁹ also provide some caveats in examining this literature, again focusing on paroxetine. Based on their review, paroxetine was associated with a significant increase in the risk of major cardiac malformations. However, women using antidepressants in pregnancy had a 30% higher rate of use of ultrasound in pregnancy and their infants had twice as many echocardiograms in the first year of life compared to infants not exposed. As many of the reports are of spontaneously closing VSDs, this observation shows an important bias. They also examined for indication. Paroxetine was used more for anxiety and panic than other SSRIs; the significance is not clear.

Premature birth has been more consistently reported ¹⁰ as have lower birth weights ^{7, 11} and lower gestational age ¹⁰. Depression itself appears to increase the risk of premature birth ¹². Wisner et al 2009 ¹⁰ examine the limitations in the literature by comparing groups of women without SSRI exposure or depression, women with untreated depression and women with varying periods of SSRI exposure. There were many confounding factors but both SSRI use and untreated depression carried risk of premature birth.

The evidence for neonatal toxicity and discontinuation is much clearer. Common perinatal effects were respiratory problems, sleepiness, decelerations on foetal monitor, excessive crying, tremor, meconium stained fluid, floppy infant and jitteriness ^{7, 11}. The most serious effect, convulsions, was seen more in the paroxetine group ⁷. Most resolved with support but mean length of stay in hospital was much longer than that of unexposed neonates ^{13, 14}. There does appear to be some lack of precise delineation between discontinuation and toxicity: paroxetine appears most implicated in the former, fluoxetine, with its long half life, in the latter ¹⁰. There are also limitations in using the Finnegan score, developed for opiate withdrawal, in recognising all effects of SSRIs in the neonate ¹⁴.

An increased risk of Persistent Pulmonary Hypertension, a rare but potentially fatal complication, was reported in infants exposed to SSRIs after the 20th week of gestation. Chambers 2006 ² first reported, in a case control study, an increased rate of Persistent Pulmonary Hypertension in neonates exposed to SSRI in the third trimester. This study generated an adjusted (for maternal diabetes, race, maternal BMI) odds ratio of 6.1. Another study, conducted through the Swedish Medical Birth Register, including 831,324 women, found a relative risk of 3.7 ¹⁵. There was no increased risk apparent in a number of further studies ^{13, 16, 17}.

Gentile 2005¹⁸ reviewed the literature on long-term neuro-cognitive development of children exposed to SSRIs in utero. 11 studies (306 children) showed no impairment of infant neurodevelopment; 2 studies (81 children) suggested unwanted effects on motor development and motor control. Gentile comments the former research is more rigorous than the latter but cautions against generalising the findings, suggesting there will be extensive individual differences. The effects of the illnesses for which SSRIs were prescribed are not adequately examined.

6.7.2 Summary

In summary, there appears to be an increase of a number of rare malformations with first trimester SSRIs. The absolute risk is very low. The risk of cardiac abnormalities, although again not consistently found, does seem to be higher, with paroxetine and fluoxetine the most clearly implicated. In women on SSRIs in the third trimester, there is an increased rate of pre-term birth, although depression itself may pose the same

risk. There is a well reported syndrome of neonatal disturbance seen as a consequence of discontinuation or toxicity, most commonly described with paroxetine and fluoxetine. This is, in the majority, transient and self-limiting. The risk of Persistent Pulmonary Hypertension, again a rare but serious disorder, remains unclear. There is very little information on newer SSRIs or SNRIs.

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Chapter 7 Review of Australian Product Information (PI) documents

7.1 SSRI antidepressants and risk of clinical worsening and suicide

The Australian Product Information (PI) and Consumer medicine (CMI) documents for SSRIs have been updated several times in the last 5 years to reflect emerging data on the risks of increased suicidal thoughts and behaviours (suicidality) associated with use of those medicines for the treatment of depression and other psychiatric disorders.

In 2004-05, the TGA required updating of these documents to include warnings on suicidality for children and adolescents (7-17 years) following receipt of advice from the Adverse Drug Reactions Advisory Committee that was based its review of Australian ADR data and recent analyses of clinical trial data by other regulatory agencies which showed the use of these medicines increased suicidal thoughts and behaviours in children and adolescents but not suicides. The TGA also issued four health advisories on this issue on its website in 2004 and liaised with professional bodies including the National Health and Medical Research Council, the Royal Australian and New Zealand College of Psychiatrists and the Division of Paediatric and Child Health of the Royal Australian College of Physicians.

From mid-2007 to early 2008 the Australian PI and CMI documents for antidepressant medicines were further amended in response to emerging data in relation to increased suicidal thinking and behaviours in young adults (aged 18 to 24 years). The TGA's review of the emerging data and, consequently, the adequacy of the PI documents followed actions taken by the US FDA in May 2007 which were based on their own review of the literature. The FDA required sponsors to update existing black box warnings on product labels to include warnings about increased risks of suicidal thinking in persons aged 18 to 24 during the initial treatment period (generally the first one to two months). The FDA also required the labelling changes to include advice that the scientific data did not show an increased risk in adults older than 24 and that the data showed adults aged 65 and older have a decreased risk of suicidality. The proposed warning statements emphasized that depression and other serious psychiatric disorders are themselves the most important causes of suicide. The changes required by the TGA were essentially similar to those of the FDA.

As a combined result of these actions, the *Precautions* sections of the current approved PIs for antidepressants contain extensive information about the risks of clinical worsening and suicidality, as reflected in identical or near identical core safety information, excerpts of which are set out below.

Excerpts of core safety information contained under the Precautions subheading "Clinical Worsening and Suicide Risk"

1. The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients. *[Identical in all PIs except venlafaxine, which has alternative wording in place]*
2. Patients with depression may experience worsening of their depression symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of

treatment, patients should be closely monitored for clinical worsening and suicidality at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in those patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. *[Present in all PIs]*

3. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality. *[Present in all PIs]*

4. Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. *[Present in paroxetine, fluvoxamine, citalopram and escitalopram PIs. This specific wording is absent from the sertraline, fluoxetine, moclobemide, mirtazapine and venlafaxine PIs. The sponsors of the latter products have argued to the satisfaction of the TGA that similar warnings are contained elsewhere in the text pertaining to clinical worsening and suicide risk. In the case of reboxetine, the PI has alternative wording that the data are insufficient to quantify risk of increased suicidal thinking etc and urges this potential risk has to be balanced against clinical need, especially in young adults.]*

5. Pooled analyses of 24 short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the initial treatment period (generally the first one to two months) in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients treated with placebo. There was considerable variation in risk among the antidepressants, but there was a tendency toward an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazadone, venlafaxine). *[Present in all PIs. Note the venlafaxine and mirtazapine PIs contain alternative wording proposed by the FDA, in which there is no specific mention of the antidepressants included in the analyses.]*

6. A further pooled analysis of short-term placebo-controlled trials of antidepressant medicines (SSRIs and others) showed the increased risk of suicidal thinking and behaviour (suicidality) during the initial treatment period (generally the first one to two months) extends to young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. These studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there

was a reduction with antidepressants compared to placebo in adults aged 65 and older. *[Present in sertraline, fluvoxamine, citalopram, escitalopram, reboxetine, moclobemide, venlafaxine and mirtazapine PIs. The fluoxetine PI contains briefer, alternative wording and the paroxetine PI contains product-specific rather than pooled data on risk of suicidal behaviour in young adults and adults, with the same stated conclusions.]*

7. Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. *[Present in all PIs]*

8. Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non psychiatric), should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease. *[Present in all PIs]*

9. Prescriptions for [name of product] should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. *[Present in all PIs]*

Other information pertinent to risks of suicidality in children and adolescents

Two SSRI products – sertraline and fluvoxamine– are specifically approved for use in children (> 6 & 8 years, respectively) and adolescents for the treatment of obsessive compulsive disorder (OCD). The warnings of suicidality in the PIs of both these products are reinforced by the inclusion of specific information about the adverse event profiles observed in paediatric populations as follows:

Sertraline In the *Precautions* section of the PI there is an additional subheading ‘Children and adolescents (<18 yrs)’ in which it is noted that among 225 paediatric patients in OCD clinical trials, the safety profile was comparable to that in adult OCD studies and that sertraline should not be used in that age group for treatment of major depressive disorder. In the *Adverse Events* section there is also a specific subheading ‘Adverse Effects from Clinical Trials in Paediatric MDD’, which lists events that occurred with a frequency of at least 2% and at a rate of at least twice that of placebo, which included agitation (6.3% vs 1.1%). The subsection also lists the most common reasons for discontinuation due to adverse events and this includes aggressive reaction (1.6%), agitation (1.6%), suicidal ideation (1.6%), hyperkinesia (1.1%), suicide attempt (1.1%), aggravated depression (1.1%). Suicidal ideation was also noted to have been reported in three sertraline-treated patients.

Fluvoxamine In the *Adverse Reactions* section of the PI there is a subheading ‘Other Adverse Events in OCD Paediatric Population’, which notes the overall safety profile in 57 paediatric patients was similar to that in adult studies and cites abnormal thinking and emotional lability as having been reported in two or more paediatric patients and occurring more frequently than placebo.

All other SSRIs and other antidepressant ‘medicines of interest’ for this review are approved for use in adults only. The PIs of all these products contain a specific warning

statement in the *Precautions* section that the efficacy and safety of the product in children and adolescents <18 yrs has not been established and that these products are not indicated for use in those age groups. In some PIs this is repeated in the *Dosage and Administration* section. However, the PIs for venlafaxine and paroxetine also contain additional advice about the adverse event profile observed in clinical trials of paediatric populations:

Venlafaxine In the *Precautions* section of the PI there is a subheading 'Use in Children and Adolescents'. In addition to the warning that the product is not indicated in this age group, the subsection notes that in paediatric trials suicidal ideation was observed and there were increased reports of hostility and, especially in major depression, suicide-related events such as suicidal ideation and self harm. In the *Adverse Effects* section of the PI there is a subheading 'Paediatric Patients', in which the observations of increased reports of hostility and suicide-related events such as suicidal ideation and self harm are repeated.

Paroxetine In the *Precautions* section of the PI there is a subheading 'Children and Adolescents (<18 years)', in which it was noted that treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children with major depressive disorder and other psychiatric disorders, and that in clinical trials in children and adolescents adverse events related to suicidality (suicide attempts and suicidal thoughts) and hostility (aggression, oppositional behaviour and anger) were more frequently observed with paroxetine compared to placebo. In the *Adverse Events* section of the PI, under a subheading 'Adverse Events from Paediatric Clinical Trials' it is noted that the following events occurred with a frequency of at least 2% and at a rate of at least twice that of placebo – emotional lability, including self harm, suicidal thoughts, attempted suicide (noted to be mainly in adolescents with major depressive disorder), and hostility (mainly in children with obsessive compulsive disorder).

7.2 Antidepressants and the induction of mania/hypomania

Antidepressant monotherapy is not recommended in most guidelines for the treatment of bipolar depression. Furthermore, as approximately 50% of patients with bipolar disorder have an onset episode of depression and are treated predominantly with antidepressant monotherapy for varying periods of time prior to the onset of mania or hypomania, there is an important need to establish a bipolar diagnosis as early as possible.

All the PI documents mention hypomania/mania in context of emerging suicidality, viz: "Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non psychiatric." Otherwise, this issue is highlighted in the precautionary statements of most but not all the antidepressant PIs and with varying degrees of comprehensiveness:

Paroxetine Very clear warning and advice about considering depression being a presentation of Bipolar Disorder in the *Precautions* section under the subheading 'Mania and Bipolar disorder'. There is a general statement that it is believed that treating a major depressive disorder that is the initial presentation of BDP can increase the likelihood of precipitating a mixed/manic episode. Extensive advice is also given on need to screen patient to determine if at risk for bipolar disorder (e.g. detailed psychiatric history, including a family history of suicide & BPD). There is also a specific statement that paroxetine is not indicated in Bipolar Depression. Mentions mixed states.

Fluoxetine In the *Precautions* section there is a subheading 'Activation of Mania/Hypomania'. The brief information is product-specific, citing results observed during pre-market testing. There is no advice about the need for careful psychiatric assessment prior to initiating therapy.

Sertraline In the *Precautions* section there is a subheading 'Activation of Mania/Hypomania'. The information is product-specific, citing results observed during pre-market testing. There is no advice about the need for careful psychiatric assessment prior to initiating therapy. Also mentions mania in post marketing adverse events

Fluvoxamine No other warnings in the PI. Mania included as a "rare" adverse event.

Citalopram Within the *Precautions* section there is a subheading 'Mania'. Contains a brief statement only that a change towards the manic phase may occur in patients with manic-depressive disease and to discontinue the drug if mania occurs. No advice about pre-treatment assessment of risks.

Escitalopram Within the *Precautions* section there is a subheading 'Mania'. Contains a brief statement only cautioning use in patients with a history of mania/hypomania and to discontinue the drug if mania occurs. No advice about pre-treatment assessment of risks.

Reboxetine In the *Precautions* section there is a very brief statement that as with all antidepressants, switches to mania/hypomania have occurred. Recommends close supervision of patients with BDP. There is no specific advice about the need for careful psychiatric assessment prior to initiating therapy.

Venlafaxine The *Precautions* section has a subheading 'Mania/Hypomania and Bipolar Disorder'. General statement that mania/hypomania may occur in patients with mood disorders who are treated with antidepressants. Advises caution in patients with history or family h/o BPD and to screen pt to determine if at risk for bipolar disorder (e.g. detailed psychiatric history, including a family history of suicide & BPD). Also notes the product is not approved for use in treating bipolar depression.

Mirtazapine Covered in a subsection of *Precautions*, titled 'Special warnings and special precautions for use'. Appears as a paragraph of minimal information imbedded amongst other warnings, without a heading to give it prominence.

Moclobemide No other statements are in the PI.

7.3 Serotonin syndrome and polypharmacy

The Australian PI documents of the antidepressants included in this review were assessed three important elements regarding serotonin syndrome:

- clear contraindication to use with MAOIs;
- recommendations for washout periods when switching from or to MAOIs; and
- advice regarding risk of developing serotonin syndrome with other serotonergic agents (including identification of likely agents)

All the PI documents contain specific statements contraindicating concomitant use with MAOIs (not applicable in the case of moclobemide) within the *Contraindications* section. In most PIs the contraindication statement(s) also contain advice regarding recommended washout periods, with the exception of citalopram (where the washout periods are given along with further advice under the *Precautions* section of the PI) and reboxetine (which does not contain any recommended washout periods). In the case of

moclobemide, data are presented from clinical trials (albeit limited) examining the safety of switching from SSRIs or TCAs to moclobemide along with suggested titration regimens.

In some PIs (fluoxetine, sertraline and escitalopram) serotonin syndrome is clearly identified as part of the text within the *Contraindications* section, whereas, in the remainder the link is implied through information contained elsewhere (within the *Precautions* section – sometimes under headings devoted to MAOIs and sometimes under a general discussion of interactions with serotonergic drugs). The resultant effect is that important information about serotonin syndrome is, in some instances (e.g. paroxetine), spread across three different sites within the PI, with cross referencing between those sections to maintain the thread of information. The Panel accepts that Australian PIs are required to conform to a standard format as set out in the Australian Regulatory Guidelines for Prescription Medicines, with each section having a different emphasis on the key messages therein. However, the net effect is that the information is disjointed and in many instances not immediately accessible to prescribers. This could dilute the key messages about this clinically significant pharmacodynamic interaction.

All but two of the PIs (moclobemide and reboxetine) also contain a brief description of the cardinal symptoms and signs of serotonin syndrome:

Paroxetine The *Contraindications* section includes contraindication to use with MAOIs, with recommended washout periods but without specific reference to serotonin syndrome. Within the *Precautions* section there is a subsection titled ‘Serotonin syndrome/Neuroleptic Malignant Syndrome’, with reference to combination with other serotonergic and/or neuroleptic drugs. Also mentions avoidance of serotonin precursors such as L-tryptophan and oxitriptan due to risk of serotonergic syndrome. There is a cross-reference to the *Interactions* section of the PI, where there is further discussion of the relevant drugs.

Fluoxetine In the *Contraindications* section there is specific contraindication for concomitant use of MAOIs, with reference to serotonin syndrome, which includes a description of the clinical features syndrome and recommended washout periods. In the *Precautions* section there is a minor reference to the fact that co-administration with serotonergic drugs (e.g. SNRIs, SSRIs, tramadol or triptans such as sumatriptan) may result in serotonin syndrome.

Sertraline In the *Contraindications* section there is specific contraindication for concomitant use of MAOIs, with reference to serotonin syndrome, which includes a description of the clinical features syndrome and recommended washout periods. Within the *Precautions* section, references are made to the fact that co-administration with serotonergic drugs such as tryptophan, phentermine, tramadol or 5-HT agonists should be undertaken only with caution and avoided wherever possible due to the potential for pharmacodynamic interaction.

Fluvoxamine The *Contraindications* section includes contraindication to use with MAOIs, with recommended washout periods but without specific reference to serotonin syndrome. In the *Precautions* section under the subheadings ‘Interactions with Other Drugs’ - ‘Pharmacodynamic interactions’ there is a description of the serotonin syndrome with mention of cautious use with other SSRIs, tricyclic antidepressants, tryptophan, sumatriptan, phentermine, tramadol, lithium and St Johns Wort because of possible potentiation of serotonergic effects.

Citalopram The *Contraindications* section includes contraindication to use with MAOIs, without specific reference to serotonin syndrome, but with a cross reference to the *Precautions* section. In the *Precautions* section there is a subheading “Monoamine Oxidase

Inhibitors', in which a description of the clinical features of the syndrome and recommended washout periods are given. Within the *Interactions* section, references are made to the fact that SSRIs may 'theoretically interact' with 5-HT agonists and that co-administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to enhanced serotonin effects. There is advice to not use the drug with 5-HT agonists and St Johns Wort.

Escitalopram The *Contraindications* section includes contraindication to use with MAOIs, with recommended washout periods with reference to serotonin syndrome (cross-referenced to the *Adverse Effects* section). Within the *Adverse Effects* section there is a brief description of serotonin syndrome under neurological disorders. Also, under *Interactions with other medicines*, it is noted that co-administration of the drug with MAOIs may cause serotonin syndrome and that co-administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to enhanced serotonin effects. There is also advice to not use the drug with St Johns Wort.

Reboxetine The *Contraindications* section includes contraindication to use with MAOIs without specific reference to serotonin syndrome. There is no reference to serotonin syndrome in the PI. Does not contain recommended washout periods.

Venlafaxine The *Contraindications* section includes contraindication to use with MAOIs, with recommended washout periods. There is no specific reference to serotonin syndrome within the contraindication but there is a cross reference to 'Interactions with other Medicines' which includes a specific heading 'Serotonin Syndrome' where there is an extensive list of serotonergic drugs (triptans, SSRIs, other SNRIs, lithium, sibutramine, tramadol, St John's Wort), drugs that impair the metabolism of serotonin (MAOIs, including linezolid) and serotonin precursors (tryptophan supplements) and a brief description of symptoms.

Mirtazapine The *Contraindications* section includes contraindication to use with MAOIs, with recommended washout periods. There is no specific reference to serotonin syndrome within the contraindication but there is a cross reference to 'Interactions with other Drugs' where the risk of development of serotonin syndrome with concomitant use with other serotonergic drugs (e.g. SSRIs and venlafaxine) is mentioned and additional information is given with regard to combination of MAOIs and antidepressants, including a description of clinical features.

Moclobemide In the *Contraindications* section serotonin syndrome is listed as a contraindication, with cross-reference to the 'Interactions with other Drugs' subheading in the *Precautions* section. Under 'Interactions with other Drugs', the possibility of development of serotonin syndrome with SSRIs and TCAs is noted. Advice given regarding safety of changing from SSRIs to moclobemide, with data presented from clinical trials (noted to be limited). Clinical features of the serotonin syndrome not presented.

7.4 Akathisia and atypical antipsychotic medicines

All the antipsychotics among the 'medicines of interest' for this review contain at least some information regarding the development of akathisia as a side effect of treatment.

However, the prominence given to this information is quite variable. Only the PI for amisulpride contains the information as part of a warning statement in the *Precautions* section of the PI – the documents of the other medicines refer to the development of tardive dyskinesia. In these documents specific information about akathisia appears within the adverse effects sections, although with a considerable variation of detail. Overall, the documents recognise that akathisia is a common adverse effect of these medicines. Key findings on review of the PIs were:

Amisulpride The *Precautions* section states that extrapyramidal symptoms, including akathisia may occur, noting the symptoms are generally mild at optimal doses and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. Also notes the incidence of EPS is dose related and is low in treatment of patients with mainly negative symptoms with doses of 50-300mg/day.

Aripiprazole No specific mention of akathisia or, more generally, EPS in the *Precautions* section. There is, however, a warning regarding the risk of tardive dyskinesia. The *Adverse Reactions* section of the PI includes rates of treatment-emergent akathisia and extrapyramidal disorder for aripiprazole vs placebo in short term studies of 7.4% vs 4.4% and 5.4% vs 5.1%, respectively. There is also text specifically dedicated to extrapyramidal symptoms within the discussion of events occurring in long term clinical trials – it was noted the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs 5% for placebo, with the a difference on the Barnes Akathisia Scale of 0.08 for aripiprazole and -0.05 for placebo. It was stated no difference between aripiprazole and placebo exists with respect to EPS and dyskinesias.

Risperidone No specific mention of akathisia or, more generally, EPS in the *Precautions* section. There is however a warning regarding the risk of tardive dyskinesia. The *Adverse Effects* section of the PI notes Parkinsonism occurs with a frequency of $\geq 10\%$. Akathisia is listed in a tabulation of ADRs as being common ($\geq 1/100$ to $<1/10$).

Quetiapine No specific mention of akathisia in the *Precautions* section. There are, however, separate statements regarding tardive dyskinesia (essentially advice to reduce or cease the drug if signs and symptoms appear) and EPS (noting that rates in placebo controlled trials in schizophrenia and bipolar mania showed no difference between quetiapine and placebo). The *Adverse Reactions* section of the PI repeats the advice regarding EPS and provides actual rates from the trials. This section also stated the incidence of EPS in treatment of bipolar depression was double that of placebo but the incidence of individual symptoms, including akathisia was generally low and did not exceed 4% in any group (noting that the product is not approved for that indication).

Olanzapine No specific mention of akathisia or, more generally, EPS in the *Precautions* section. There is however a warning regarding the risk of tardive dyskinesia. Akathisia is listed as a common adverse event ($\geq 1/100$ to $<1/10$) in the *Adverse Effects* section of the PI.

7.5 Weight gain, obesity and diabetes

The current approved Australian PIs for the ‘medicines of interest’ were reviewed, in turn, with respect to the comprehensiveness of information about risks of weight gain/loss; development of hyperglycaemia and diabetes mellitus; and effect on lipid profile.

7.5.1 Atypical antipsychotics

Weight gain/obesity

The olanzapine PI contains text dedicated specifically to weight gain within the *Precautions* section of the PI, which highlights potential for significant weight gain and the need for monitoring. This is appropriate and in keeping with findings in the published literature. The information across the remaining atypical antipsychotics is less prominent, being either positioned within the *Adverse Reactions/Effects* sections of the PIs (e.g. quetiapine, aripiprazole, risperidone) or not mentioned (amisulpride). This ‘positioning’ reflects the literature findings that quetiapine and risperidone are associated with somewhat smaller effects on weight and less deserving of specific

warning statements, and that there appears to be little or no information available currently about the effects of amisulpride.

Hyperglycaemia/risk of diabetes

All the atypical antipsychotic PIs contain text specifically dedicated to warnings within the *Precautions* section about diabetes mellitus (DM) and need to monitor glycaemic control in those with established DM and those at risk of developing DM. This is appropriate. However, none of the PIs outline a recommended monitoring regime.

Effects on lipid profile

Information is presented only with respect to olanzapine and quetiapine, based on results obtained from the premarket clinical trial program. There is relatively limited data available within the published literature for the lipid effects of atypical antipsychotics other than for olanzapine and clozapine (which have been associated with hypertriglyceridemia).

- Amisulpride** - No information about weight gain.
 - *Precautions* section contains warning about development of hyperglycaemia and recommends monitoring in patients with established diabetes mellitus or risk factors for DM. In the *Adverse Effects* section it is noted hyperglycaemia was uncommonly reported in clinical trials.
 - No information about effects on lipid profile.
- Aripiprazole** - Dedicated subheading for 'Weight Gain' in the *Adverse Reactions* section - presents results from placebo-controlled and long term double-blind olanzapine- and haloperidol-controlled clinical trials. The latter pointed to higher incidence of significant weight gain ($\geq 7\%$ above baseline) compared to haloperidol (20% vs 13%, $p \leq 0.01$) and lower incidence compared to olanzapine (13% vs 33%, $p < 0.001$).
 - Dedicated subheading for 'Hyperglycaemia and DM' in the *Precautions* section. Cites results from pre-marketing clinical trial program that found no statistically significant differences compared to placebo. Refers to potential for hyperglycaemia and in some cases ketoacidosis or hyperosmolar coma. Advises monitoring for symptoms and signs of hyperglycaemia in all patients plus blood glucose levels in patients with established DM or risk factors for DM.
 - No information about effects on lipid profile.
- Risperidone** - Little text specifically dedicated to weight gain - *Pharmacodynamics* section states antagonism of serotonergic and histaminergic receptors may induce weight gain. *Adverse Effects* section - 'weight increased' is a common ADR (incidence $\geq 1/100$ to $< 1/10$).
 - Dedicated subheading for 'Hyperglycaemia and DM' in the *Precautions* section. Relatively more detailed than for other atypical antipsychotics – cites increased background risk for schizophrenic and epidemiological studies that also suggest increased risk of treatment-emergent DM, noting precise estimates not available. Monitoring recommended
 - No information about effects on lipid profile.

- Quetiapine**
- No text specifically dedicated to weight gain - *Adverse Reactions* section states incidence of weight gain is common ($\geq 1/100$ to $<1/10$).
 - Dedicated subheading for 'Hyperglycaemia and DM' in the *Precautions* section. Relatively more detailed than for other atypical antipsychotics – cites increased background risk for schizophrenic and epidemiological studies that also suggest increased risk of treatment-emergent DM, noting precise estimates not available. Blood glucose level increased to hyperglycaemic level noted to be common ($\geq 1/100$ to $<1/10$). Exacerbation of pre-existing diabetes mellitus noted to be very rare ($<1/10,000$). Monitoring recommended
 - Dedicated subheading within the *Precautions* section, with advice that increases in triglycerides and cholesterol have been observed in clinical trials, with cross reference to the *Adverse Reactions* section where elevations in serum triglyceride levels, total cholesterol (predominantly LDL cholesterol) noted to be very common ($\geq 1/10$)
- Olanzapine**
- Dedicated subheading for 'weight gain' in both the *Precautions* section and *Adverse effects* section. Results of olanzapine studies cited, in which significant weight gain was observed across all baseline BMI categories in olanzapine-treated patients. Notes that there should be regular monitoring of weight.
 - Dedicated subheading for 'Hyperglycaemia and DM' in the *Precautions* section. Relatively more detailed than for other atypical antipsychotics – cites increased background risk for schizophrenic and epidemiological studies that also suggest increased risk of treatment-emergent DM, noting precise estimates not available. Also information specifically in relation to adolescents. Advice given about monitoring.
 - Dedicated subheading for 'lipid alterations' in the *Precautions* section, noting olanzapine-treated patients had greater mean increase in fasting total cholesterol, LDL cholesterol and TGs compared to placebo, particularly in patients without evidence of lipid dysfunction at baseline. Repeated in *Adverse effects* section, with specific information for adolescents as well.

7.5.2 SSRI and SNRI Antidepressants

Effects on Weight

As a group, the SSRI and SNRI PIs present quite comprehensive information about their effects on weight that is generally consistent with findings reported in the literature and that observed through adverse event reporting. There is, however, a lack of consistency in how the information is presented across the PIs (some contain specifically dedicated text with the *Precautions* section, whilst in others the information is located under *Adverse Effects*). The PIs of those medicines with specific paediatric indications (i.e. sertraline and fluvoxamine) include information about effects on growth and weight in the *Precautions* section that, appropriately, recommend monitoring in paediatric patients on long-term treatment.

Hyperglycaemia/risk of diabetes

The PIs of older SSRI antidepressants do not contain specifically dedicated information about hyperglycaemia and diabetic risks and rely on the presentation of adverse event data from their premarketing clinical trial programs. However, the newer SSRIs, such as citalopram and escitalopram include specific precautionary statements about the need

to monitor diabetic patients, pointing to a more general antidepressant effect rather than SSRI class effect.

Effects on lipid profile

With the exception of venlafaxine, none of the PIs contain information specifically dedicated to effects on lipids. They rely solely on adverse event data reported in premarketing clinical trials. In the absence of an established link with any undesirable effects on lipid profile in the published literature, this is appropriate. In the case of venlafaxine, reference is made to data from short term (up to 12 week) studies in depression and social anxiety disorder, showing cholesterol elevation occurred commonly. There is a recommendation for measuring serum cholesterol levels during long term treatment.

- Paroxetine**
- No specifically dedicated section on effects on weight. In *Adverse Effects* section, both weight gain and weight loss are listed as common events from OCD clinical trials and, in the case of weight gain from panic disorder clinical trials. Obesity was also listed as an uncommon event from clinical trials generally. Decreased appetite was noted to be one of the most commonly observed events in clinical trials and at higher rates than seen in subjects receiving placebo.
 - No specifically dedicated information about effects on glucose levels. Under *Adverse Effects*, hyperglycaemia and hypoglycaemia are both listed as uncommon clinical trial events and diabetes mellitus is listed as a rare event
 - No specifically dedicated information about effects on lipid profile. In *Adverse Effects* section, increased serum cholesterol is listed as a rare post marketing event and appetite increased listed as a common event in clinical trials.
- Fluoxetine**
- Dedicated subheading for 'Altered Appetite and Weight' in the *Precautions* section - presents results from controlled trials, noting approximately 9% patients treated with fluoxetine experienced anorexia (6 times rate with placebo. Also weight loss of >5% noted to have occurred in 13% subjects treated with fluoxetine, compared to 4% treated with placebo and 3% treated with TCAs, although rarely has fluoxetine been discontinued for weight loss. Within the *Adverse Reactions* section, anorexia and weight loss are both listed as common events from clinical trials. There is also information specifically on effects on weight and height of children and adolescents, viz, as with other SSRIs decreased weight gain has been observed in association with use of fluoxetine. Cites results of 19 week trial where fluoxetine subjects gained 1.1kg less in weight (p=0.008) than those treated with placebo. Notes absence of long term data and recommends periodic monitoring of growth and weight in paediatric patients.
 - No information about effects on glucose levels or diabetes mellitus.
 - No information about effects on lipid profile.
- Sertraline**
- Dedicated subheading for 'Weight Loss' in the *Precautions* section - presents results from placebo controlled trials and compares weight loss by age strata. Recommends monitoring of growth and weight in paediatric patients on long-term treatment. In *Adverse Effects* section, weight gain and weight loss are both listed as common events from placebo-controlled trials and appetite increased listed as an uncommon post marketing event.
 - No specifically dedicated information about effects on glucose levels. Under *Adverse Effects*, hyperglycaemia is listed as a rare post marketing event.

- No specifically dedicated information about effects on lipid profile. In *Adverse Effects* section, increased serum cholesterol is listed as a rare post marketing event.
- Fluvoxamine**
- Under the subheading 'Use in Children and Adolescents (age <18 years)' within the *Precautions* section, there is a warning that decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs and recommends monitoring of growth and weight in paediatric patients on long-term treatment. In *Adverse Effects* section, both weight gain and weight loss were noted to have been reported as post marketing events.
 - *Precautions* section includes warning that glycaemic control may be disturbed in early stages of treatment and dose of anti-diabetic drugs may need to be adjusted.
 - No information about effects on lipid profile
- Citalopram**
- In *Adverse Effects* section, a tabulation of AEs occurring with frequency of >1% in clinical trials shows weight loss was reported in 1.5% citalopram recipients compared to 0.6% placebo recipients. It was also noted under a subheading 'Weight Changes' that citalopram treated patients lost an average of 0.5kg compared to no change for placebo. In the general summary of all AEs reported in premarketing clinical trials, both weight gain and weight loss are listed as common events. Obesity was also listed as a rare event.
 - *Precautions* section includes a warning under the subheading 'Diabetes' which states that, as with other psychotropics, citalopram may modify insulin and glucose responses in early stages of treatment and dose of anti-diabetic drugs may need to be adjusted. In the *Adverse Effects* section, abnormal glucose tolerance listed as uncommon clinical trial event and hypoglycaemia is listed as a rare event.
 - No information about effects on lipid profile
- Escitalopram**
- In *Adverse Effects* section, a tabulation of AEs occurring with frequency of $\geq 1\%$ in clinical trials shows weight increase was reported in 1.7% escitalopram recipients compared to 1.1% placebo recipients. It was also noted under a subheading 'Weight Changes' that there was no difference between escitalopram and placebo with respect to patients with clinically important changes in body weight. In the general summary of all AEs reported in premarketing clinical trials, weight loss is listed as an uncommon event.
 - *Precautions* section includes a warning under the subheading 'Diabetes' which states that treatment with an SSRI may alter glycaemic control possibly due to improvement of depressive symptoms and insulin and/or oral hypoglycaemic doses may need to be adjusted. In the *Adverse Effects* section, abnormal glucose tolerance, diabetes mellitus and hyperglycaemia are listed as uncommon clinical trial events.
 - No specifically dedicated information about effects on lipid profile. In *Adverse Effects* section, hypercholesterolaemia and hyperlipidaemia are listed as uncommon clinical trial events.
- Reboxetine**
- No specifically dedicated section on effects on weight. In *Adverse Effects* section, rate of weight increase or decrease was stated to be uncommon ($\geq 0.1\%$ to <1%). Rate of anorexia with reboxetine in short term trials was noted to be 3.9% (compared to 3.0% for placebo) and 1.5% in long term studies (placebo).
 - No information about effects on glucose levels or diabetes mellitus

- No specifically dedicated information about effects on lipid profile. In *Adverse Effects* section, rates of hyperlipidaemia and hypercholesterolaemia with short (≤ 6 mo) and long term (>6 mo) treatment in clinical trials were cited.

Venlafaxine - Dedicated subheading 'Altered Weight' in *Precautions* section – notes weight changes do not appear to be a clinically important feature, presents summary of results from clinical trials, including absence of data from use in combination with weight loss agents. Recommends against co-administration with weight loss agents or for weight loss alone. The *Adverse Effects* section lists appetite decreased and weight loss as common adverse reactions and weight gain as an uncommon adverse reaction.

- No information about effects on glucose levels or diabetes mellitus
- Dedicated subheading 'Increase in Serum Cholesterol' in *Precautions* section – includes results from short term (up to 12 week) studies in depression and social anxiety disorder, with recommendation for measuring serum cholesterol levels during long term treatment. The *Adverse Effects* section lists serum cholesterol increased (particularly with prolonged administration) as a common adverse reaction.

Note: venlafaxine PI also has a 'Paediatric patients' subheading within the *Adverse Effects* section which notes that decreased appetite, weight loss and increased serum cholesterol were also observed in clinical trials in children and adolescents. This is cross referenced to the *Precautions* section which warns that venlafaxine is not indicated for use in these patient groups. It also has a 'Use in patients with pre-existing heart disease' subheading within the *Precautions* section.

Mirtazapine - No specifically dedicated section on effects on weight. In *Adverse Reactions* section, weight gain and appetite increased are listed as common events reported in both clinical trials and post marketing.

- In the *Precautions* section there is a statement under the subheading 'Special warnings and special precautions for use', there is a warning that, as for antidepressants in general, care should be taken in patients with diabetes mellitus without any specific advice regarding monitoring etc.
- No specifically dedicated information about effects on lipid profile. In *Adverse Reactions* section, it is noted that there have been rare cases of hypercholesterolaemia and hyperlipidaemia.

Moclobemide - No information about effects on weight.

- No information about effects on glucose levels or diabetes mellitus.
- No information about effects on lipid profile.

7.6 Interactions between antipsychotic and antidepressant medications

Australian PI documents are required to include, within the *Precautions* section, information about known clinically relevant interactions and other potentially serious interactions based on the pharmacology of the medicine. This is presented under the subheading 'Interactions with other medicines'. Within the PI there is also pharmacodynamic and pharmacokinetic information, including metabolic pathways and the potential for CYP2C19 and CYP2D6 polymorphism, where relevant.

The clinically significant antidepressant-antipsychotic interactions identified in section 7.6 of this report are covered in the relevant Australian PIs. Some of these interactions are, appropriately, included within the *Contraindications* section as well as the *Precautions* section of the PI.

However, in many of the PIs the information contained under the 'Interactions with other medicines' subheading is presented in a haphazard fashion with no apparent logic to the sequence of the medicines and no distinction between pharmacodynamic interactions (which can be predicted from knowledge of pharmacologic action of the medicines concerned) and pharmacokinetic interactions (which cannot always be readily predicted or their significance understood from knowledge of the pharmacokinetics of the individual agents). The accessibility and understanding of this information would be assisted by a well structured format.

7.7 Antidepressants and Pregnancy

All PI documents are required to contain information for *Use in Pregnancy*, including:

- a proposed or approved Australian Pregnancy Categorisation (A, C, B1, B2, B3, D or X);
- any relevant standard text or other information consistent with the pregnancy categorisation; and
- effects on labour and delivery.

All the antidepressants of interest have PI documents that satisfy these criteria to varying degrees. All of the PI documents contain reasonably detailed and good discussion of data (teratogenic and non-teratogenic) from animal studies, mostly accompanied by mention of the fact that experience with the use of the medicine in pregnancy was limited and/or there were no adequate and well controlled studies in pregnant women. The PI for paroxetine, however, also contained a very clear and detailed summary of the risk of congenital malformations, citing several key human epidemiological studies from the US and the Swedish Medical Birth Register. Specific issues raised by the literature review are addressed further below.

General statements regarding use in pregnancy and risk of congenital malformations

All of the PIs of the antidepressants reviewed contain a cautionary statement about use in pregnancy, albeit with some variability. The statements include:

- “do not use in pregnancy” [paroxetine] and “avoid use in pregnancy” [sertraline];
- “caution should...be exercised when prescribing to pregnant women” [fluvoxamine];
- “use only if benefits outweigh the risks” (or words to that effect) [sertraline, fluoxetine, moclobemide, reboxetine, venlafaxine, citalopram, escitalopram, mirtazapine and]; and
- “women of child-bearing potential should employ an adequate method of contraception: [mirtazapine].

Advice regarding neonatal effects

The PIs for all the SSRIs and venlafaxine contain a statement on the potential for neonatal withdrawal. Most of them have the following standard passage of text (with some minor editorial variation).

“Neonates exposed to [name of drug], other SSRIs and SNRIs, late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizure, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, constant crying, [somnolence] and [difficulty sleeping]. These features are consistent with either a direct effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome”

However, there is no statement in the PI about the potential for neonatal withdrawal for reboxetine, which is surprising considering the reference to SNRIs.

Risk of Persistent Pulmonary Hypertension in the newborn

The potential for PPHN is mentioned only in the paroxetine and sertraline PIs.

Part C Conclusions and Recommendations

Chapter 8 Are changes to Product Information documents warranted or are broader educational initiatives required?

- 8.1 What is the role of the Product Information document?**
- 8.2 The broader prescribing environment and implications for quality use of psychotropic medicines**
- 8.3 How to move forward with respect to the issue of polypharmacy – improving medicine usage**
- 8.4 Recommended changes to the Australian PI documents**
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Chapter 9 Pharmacosurveillance

- 9.1 Background**
- 9.2 Overseas initiatives**
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- 9.4 Developments in Australia**
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Chapter 8 Are changes to Product Information documents warranted or are broader educational initiatives required?

The case reports have highlighted a number of issues associated with the use of psychotropic medicines. In particular, the Panel has noted the extent of and problems associated with polypharmacy set out in the reports; the difficulties for clinicians in distinguishing some side effects, such as akathisia, from underlying psychiatric disorders; and inconsistencies between current Australian Product Information documents and international monographs for some of these medicines. Understandably, it is prudent to ask whether, as a result, changes to the Australian Product Information documents over which the TGA has jurisdiction are required. However, it must be appreciated that some of the issues highlighted in the case reports go beyond the safety of the medicines *per se* and into the realm of therapeutic decision-making and decision-taking (i.e. the quality use of medicines) of which the availability of accurate Product Information is one small part.

8.1 What is the role of the Product Information document?

The Product Information (PI) is required to contain information that is sufficient to ensure safe and effective use of the medicine under nearly all circumstances. It is meant to present a scientific, objective account of the medicine's usefulness and limitations as shown by the data supporting the marketing of the product and is required by the TGA to be devoid of any promotional material ¹.

Importantly, the PI is not meant to be a source of information that the reasonable prescriber ought to know about the practice of medicine (including the epidemiology, pathogenesis, differential diagnosis, investigation or possible treatments of the condition for which the medicine is indicated as well as conditions that could arise as side effects) or to provide a comparison with other available treatments. The indiscriminate inclusion of such information in product information documents would make them unwieldy and serve to dilute the impact of clinically important information about the safe and effective use of the medicine. However, as part of the safety information, the PI would be expected to contain information about monitoring of the condition during treatment with the particular medicine concerned, especially with regard to monitoring of important adverse reactions/outcomes in high risk populations.

Australian sponsors of prescription medicines such as antidepressants and antipsychotics are required to produce a PI for each registered product as a condition of its registration. The TGA ensures the PI provides an accurate and concise summary of the efficacy and safety of the medicine and how it should be used (i.e. dosage, administration and monitoring information). Sponsors of products are expected to ensure their PI documents remain current and include all identified clinically significant safety issues. The therapeutic goods legislation allows for the readily incorporation (by way of so-called safety related notifications to the TGA) of certain types of important safety information that reduces the class of persons for whom the medicines are suitable or adds a warning, or precaution, that does not include any comparison with any other medicines.

8.2 The broader prescribing environment and implications for quality use of psychotropic medicines

In addition to the TGA-approved PI, the major independent Australian sources of information available to clinicians to assist with understanding of the medicine, its indication and its use include independent drug bulletins, *Australian Prescriber*, therapeutic guidelines (generally available, published guidelines as well as those developed and used at an institutional or practice level), the *Australian Medicines Handbook* and regular publications from the National Prescribing Service.

Despite the existence of these various sources of information, suboptimal prescribing, such as potentially life-threatening polypharmacy still occurs ². Clearly, it is not simply due to a lack of access to drug information. A complex array of factors impact on prescribing and since therapeutic decision-making is loaded with uncertainties, the environment in which prescribing occurs has a powerful influence. Time pressures on the prescriber are great, often resulting in hasty decision-making. Prescribers have expectations of a drug's efficacy and adverse effects moulded by experience, peers and advertising, but these expectations may not be consistent with the evidence ³. Furthermore, increasingly clinicians are faced with an imposing and evolving body of information about new medicines and their potential drug-drug interactions. The amount of information can be so great as to overwhelm clinicians causing them to overlook important information ⁴.

The use of computers in medical practice has grown dramatically since the turn of this century, coupled with a dramatic improvement in the quality of prescribing software. This has seen many benefits in the form of allergy warnings, greater legibility of prescriptions and an improved medication history. However, concern has been raised about the potential to overload doctors with large amounts of indiscriminate information, such as rare and clinically unimportant drug interactions, thereby potentially diluting expected benefits associated from decision support with drug interactions, especially if that information can be readily overridden. Furthermore, the development and integration of decision support in prescribing software in Australia has happened in an ad hoc and uncoordinated fashion, with different products evolving in different ways. There is no established framework of standards for quality and safety within which software developers are required to work ⁵.

8.3 How to move forward with respect to the problem of polypharmacy – improving medicine usage

Optimising quality use of medicines is not easy. Multifaceted interventions aimed at the different barriers to change probably have the greatest chance of improving medicines use although they usually require repetition to maintain their impact. The nature of the intervention will largely be dependent on the setting. For example, within an institution it may be possible to include quality use of medicines activities within induction programs, regular in-service programs and continuing education seminars. Formal drug usage evaluation programs in such settings can identify, observe and explain patterns of practice and then implement activities to improve drug use, and then evaluate the effects of the interventions. To work, these programs need clinicians' involvement, individual practitioner feedback and a supportive organisational culture, in particular

an authoritative and credible drug and therapeutics committee ³. The importance of hospital based programs cannot be underestimated as doctors learn how to prescribe in hospitals and this has the greatest bearing on how they prescribe thereafter. The hospital setting, therefore, provides an excellent opportunity to combine the methods of educational outreach with audit and feedback to deliver concurrent prescriber feedback. Activities within a private practice setting, on the other hand, may be more self-directed or undertaken as part of accreditation for continuing education requirements of colleges or professional bodies, such as on-line CME activities.

A key element of quality use of medicines is the availability and use of therapeutic guidelines, but guidelines alone are unlikely to lead to lasting behaviour change. The effective implementation of guidelines requires support with strategies such as systematic audit and feedback and active educational measures. Feedback is a potentially powerful intervention, whereby clinicians in a variety of settings are given information comparing their practices or patient outcomes with other clinicians' or an external standard (e.g. a practice guideline). The advantages of such an approach is that it is immediate, specific, able to identify those to whom it is directed, and uses the power of the face-to-face encounter of educational outreach. Academic detailing can support the implementation of guidelines, whereby independent drug information pharmacists visit doctors in the same manner as pharmaceutical company representatives. It can focus on specific therapeutic issues or specific medicines. To be most effective, guidelines need to be accessible at the point of decision making ³.

One of the keys to moving forward in improving quality use of medicines is obtaining a more complete understanding of the barriers to implementing lasting change in prescriber behaviour. To this end, the National Prescribing Service currently has a number of research projects that should shed light on this issue and ultimately improve the outcome of existing educational activities. These include ⁶:

- *Uptake of evidence-based drug information and decision support* - this project is aimed at understanding factors influencing clinicians' decisions to access and use evidence-based drug information and decision support in paper and electronic format and identifying interventions (made available in paper or electronic form) that improve access and uptake of evidence-based drug information by clinicians. It includes pilot testing of interventions to improve uptake of evidence-based drug information using information communication and technologies.
- *Prescribing practice research project* - this project is examining the influences affecting prescribers, including factors affecting the awareness and uptake of new drugs and identifying interventions/strategies to increase appropriate, evidence-based, safe and cost-effective prescription of medicines. It is investigating patterns of drug adoption and displacement by practitioners and will pilot test interventions to improve evidence-based drug prescribing.
- *Evaluation of the safety, quality and usefulness of electronic prescribing systems in general practice* - the aims of the project are to determine the most important functional features provided by electronic prescribing systems in general practice which promote patient safety, quality of care and usefulness to the clinician and the consumer. The project will also evaluate seven software systems currently used by Australian GPs to determine how well these features are currently implemented.

Perhaps at a most simplistic level there is the need to teach and reinforce, at all stages from undergraduate to postgraduate activities, irrespective of setting, some

fundamental principles of *good prescribing practice* such as (based on the sentiments of Sandson et al ⁴):

- use a limited range of medicines in your day to day practice;
- become an expert on medicines that you prescribe most frequently – this should make it more practical to acquire a solid knowledge of the safe and effective use of these medicines and of the drug-drug interactions;
- select agents that minimise safety risks and risk of clinically significant drug-drug interactions;
- pay special attention to agents with a lower therapeutic index and have standard approach to monitoring the use of such agents;
- regularly read and re-read standard reference material, such as Product Information, and emerging literature, especially drug safety reviews; and
- educate patients about their medication and about the important symptoms and signs to report when taking their medication; for example, providing clear written information about its uses and side effects when prescribing.

8.4 Recommended changes to the Australian PI documents

In Chapters 6 and 7 the Panel has undertaken an extensive review of the published literature that exists for 6 key issues identified by the psychiatrist who submitted reports to the TGA and reconciled the findings of these reviews with the current approved Product Information documents. Each of the issues is addressed below as to whether any changes to the PI are required in the view of the Panel. Of course, it follows that the Consumer Medicine Information documents will also require amendment as necessary by the Australian sponsors to maintain consistency of information with the respective amended PI document.

8.4.1 SSRIs and risk of clinical worsening and suicidality

The Panel found (section 7.1 of this report) the *Precautions* sections of the current approved PIs for antidepressants contain extensive information about the risks of clinical worsening and suicidality, with identical or near identical core safety information. The information is consistent with FDA warning statements (with the exception of the inclusion of information in a box warning in the US documents). In the view of the Panel, inclusion of the information in a boxed warning is not necessary as an additional requirement in Australia given the prominence of the information currently within the Australian PI documents. Overall, no change is required to the PIs of the SSRIs and SNRIs regarding risks of clinical worsening and suicidality.

8.4.2 Induction of mania/hypomania

In section 7.2 of this report, the Panel found the Australian PI documents of the newer antidepressants are generally inconsistent with respect to advice about the risk of the induction of mania/hypomania. In particular, a number of the documents are deficient with regard to advice about pre-treatment assessment and screening for bipolar depression (fluoxetine, sertraline, fluvoxamine, citalopram, escitalopram, reboxetine, mirtazapine and moclobemide).

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.”

8.4.3 Serotonin syndrome arising from polypharmacy

In section 7.3 of this report, the Panel found that the PI documents of the newer antidepressants, by and large, contained appropriate information regarding the risk of development of serotonin syndrome, including contraindication with MAOIs, recommended washout periods with MAOIs, and potential to develop serotonin syndrome with other serotonergic agents. However, there was considerable variation as to how this information was presented. In most cases the information relevant to this condition was spread across multiple locations within the PI, with cross referencing between those sections to maintain the thread of information.

The Panel accepts that Australian PIs are required to conform to a standard format as set out in the Australian Regulatory Guidelines for Prescription Medicines, with each section having a different emphasis on the key messages therein. However, the net effect is that the information is disjointed and in many instances not immediately accessible to prescribers. This can dilute the key messages about this clinically significant pharmacodynamic interaction.

The Panel also noted that most but not all PIs also contained information about the cardinal symptoms and signs of serotonin syndrome. Whilst it is not the intention that PI documents contain information that a clinician ought to know as part of their general medical knowledge, inclusion of the cardinal features of serotonin syndrome is appropriate given the potentially life-threatening nature of the interaction and, thus, the importance of monitoring for appropriate symptoms and signs, as well as the fact that many clinicians are unaware of serotonin syndrome as a clinical diagnosis⁷. (See also Recommendations for prescriber education and quality use of medicines.)

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.”

With respect to the occurrence of serotonin syndrome with atypical antipsychotics, the Panel found there had been rare reports of somewhat dubious veracity, with possible confusion with neuroleptic malignant syndrome. Given the paucity of reports and the lack of clearly definitive evidence the Panel found insufficient evidence to support a requirement for information about serotonin syndrome to be included in the PIs of these products. It was noted that the PIs for the atypical antipsychotics all have appropriate warning statements about neuroleptic malignant syndrome, including a description of its cardinal features.

8.4.4 Akathisia and atypical antipsychotics

The Panel found (section 7.4 of this report) that the PIs of the atypical antipsychotics collectively recognise akathisia is a common adverse event with this group of drugs (albeit lower than with typical antipsychotics). However, the prominence given to this information in the PIs is quite variable. Given the diagnostic difficulties with akathisia and the fact that it is, potentially, a very disabling side effect which is associated with poor compliance and poorer treatment outcomes if unrecognised/untreated, it would

be prudent to improve the quality and prominence of information about this side effect across all the PIs of the atypical antipsychotic medicines. This should include information about clinical presentation to aid in its recognition. (See also Recommendations for prescriber education and quality use of medicines.)

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.”

8.4.5 Psychotropic medication and obesity

The Panel found (section 7.5 of this report) the PIs of the atypical antipsychotics and antidepressants were generally consistent with the published findings with respect to comprehensiveness of information about risks of weight gain/loss, development of hyperglycaemia and diabetes mellitus, and effect on lipid profile, whilst noting there was a paucity of data on the effects of SSRI medicines on weight- and obesity-related diseases such as diabetes and dyslipidaemia. The issues identified were:

- The absence of recommended glycaemic monitoring regimes for application in conjunction with use of atypical antipsychotic medicines

It could be argued this is something the reasonable practitioner ought to know. However, norms for monitoring of the general population may not be readily transferable to schizophrenic patients who appear to have a higher incidence of diabetes than the general population. Also a US study concluded that the risk of developing type II diabetes was approximately 1.5 times greater in patients taking olanzapine, risperidone, or quetiapine than in those taking conventional antipsychotics⁸. Furthermore, hyperglycaemia and diabetes have been reported in the absence of weight gain in these patients. In 2004 a consensus conference suggested BSL measurement at 3 months and annually thereafter. It was also suggested that a weight gain of more than 5% should prompt consideration of a change of drug⁹.

- An inconsistency in the way in which information about diabetic risks with SSRI treatment are presented across the class as a whole.

The PIs of older SSRI antidepressants do not contain specifically dedicated information about hyperglycaemia and diabetic risks or monitoring and rely on the presentation of adverse event data from their premarketing clinical trial programs. However, the newer SSRIs, such as citalopram and escitalopram include specific precautionary statements about the need to monitor diabetic patients, stating that treatment with an SSRI may alter glycaemic control possibly due to improvement of

depressive symptoms. The reason for the inconsistency across the SSRI class is not immediately apparent to the Panel from its review of the literature.

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.

8.4.6 Interactions between antipsychotic and antidepressant medications

In section 7.6 of this report, the Panel found that many of the PIs the information contained under the 'Interactions with other medicines' subheading is presented in a haphazard fashion with no apparent logic to the sequence of the medicines and no distinction between pharmacodynamic interactions (which can be predicted from knowledge of pharmacologic action of the medicines concerned) and pharmacokinetic interactions (which cannot always be readily predicted or their significance understood from knowledge of the pharmacokinetics of the individual agents). The accessibility and understanding of this information would be assisted by a well structured format.

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

8.4.7 Other required changes

Consistency of Australian PIs with international monographs

In section 5.1 of this report, the Panel found variation in the information on adverse effects in product monographs between jurisdictions, the reason for which is unclear. For instance in the case of olanzapine, the product monograph for the United States contained more information on potential adverse effects than the one for Australia. This included important adverse effects such as the possibility of withdrawal symptoms

(which would be considered to be ‘core safety information’), which was missing from the Australian document.

The Panel recognises the TGA has a requirement for sponsors to submit Periodic Safety Update Reports (PSURs) for three years from the time of marketing approval in Australia and that as part of its evaluation of these reports the TGA reviews any amendments to core safety information undertaken in overseas jurisdictions (and the basis for such amendments) when considering if any action is needed in Australia. However, consideration needs to be given to instituting a mechanism whereby the consistency of PI documents is monitored routinely beyond the initial three year period and therefore maintained throughout the lifecycle of the medicine to prevent major discrepancies with international monographs developing.

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.

Antidepressants and pregnancy

The Panel has also reviewed the use of SSRIs in pregnancy as it remains of current interest to prescribers and consumers. Of most note, there is a well reported syndrome of neonatal disturbance seen as a consequence of discontinuation or toxicity, most commonly described with paroxetine and fluoxetine. The PI documents of all the SSRIs and venlafaxine as well have been amended to include a standardised text that refers to the risk of such an occurrence with SSRI and SNRI medicines. However, the PI for reboxetine, an SNRI, does not include such a statement.

Persistent Pulmonary Hypertension in the newborn has also been identified as a rare but serious risk occurring when SSRIs are taken after the 20th week of gestation. The FDA has required sponsors of all SSRIs to include warning statement about PPHN in their PIs. In Australia, this has occurred only for paroxetine and sertraline.

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.

8.5 Recommendations regarding prescriber education and quality use of psychotropic medicines

There are three main areas where prescriber education is particularly warranted to complement recommended changes to the PI documents of antidepressant and antipsychotic medicines – serotonin syndrome, akathisia and good prescribing practice.

The Panel recognises that broader educational initiatives about the quality use of medicines are not within the remit of the TGA. Nevertheless, given the significant role that the TGA plays within the National Medicines Policy and its regular interaction with other key contributors to the realisation of the objectives of that policy, the Panel is of the view that the TGA should facilitate the promulgation of such educational initiatives.

For example, the TGA could work with the National Prescribing Service and Australian Prescriber to develop and disseminate good prescribing practice guidelines. As part of a more general outreach program, the TGA (through its Principal Medical Adviser), and in concert with the National Prescribing Service, could also liaise regularly with the drugs and therapeutics committees (or committees performing that function) within the various professional colleges to highlight medicines safety and quality use issues of concern. Specifically, with regard to serotonin syndrome and akathisia, the TGA could supplement these proposed outreach activities by including items on these topics in future issues of its Adverse Drug Reactions Bulletin. Such items are often picked up by and highlighted in the medical media such as Medical Observer and Australian Doctor which serve to reinforce key messages.

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.

It is also timely to consider whether the TGA should develop the capacity to commission epidemiological studies, through the use of linked databases, to more effectively identify and quantify safety issues related to the use of therapeutic products, including safety issues arising from polypharmacy. For example it would be useful to examine the current extent of polypharmacy of serotonergic medicines following on from the study conducted by Ringland et al in 2004¹⁰.

Whilst the TGA currently has no ability to commission or undertake research activities, the Panel is aware that TGA staff within the former Adverse Drug Reactions Unit (now the Office of Medicines Safety Monitoring) have previously undertaken complex analyses of the association between adverse drug reaction incidences and the extent of drug utilisation, including concurrent use of two or more drugs^{11,12}. The Pharmaceutical Benefits Branch (PBB) within the Department of Health and Ageing has developed the capacity and necessary analytical skills to undertake similar analyses, frequently to assist the work of the Drug Utilization Subcommittee of the Pharmaceutical Benefits Advisory Committee (PBAC). Thus, the TGA could explore with the Pharmaceutical Benefits Division a closer liaison, with a view to a shared capability to undertake such studies. (See also Chapter 9 - Pharmacosurveillance)

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

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Chapter 9 Pharmacosurveillance

9.1 Background

Drugs currently account for the second largest share of total health expenditures (after hospitals), and these costs are expected to continue to rise. However, there is a lack of surveillance of health outcomes related to the increasing use of drugs, including the impact of drug interactions and side effects at the population level.

Concerns about safety have led to a growing international interest in post market surveillance of pharmaceuticals to better understand risks and benefits changes throughout a drug's life cycle. This is because Phase 3 clinical trials are based on limited numbers of fairly homogenous patients who do not necessarily reflect the drug's use in the real world ¹.

Conventional clinical trials generally enrol small numbers of patients who may not represent the general population, and the trials are often short-term, employ surrogate outcomes, and use placebo as a comparator. These studies usually explicitly exclude patients with co-morbidities, including alcohol or substance use, and fail to consider the influence of socio-economic or environmental factors in determining response. As a result, there is little information on long term use, drug interactions, and use of the drug in possible target populations such as high risk, complex patients who may be more susceptible to adverse events once a drug is released onto the market ¹.

Long term safety and effectiveness therefore require continuous surveillance after a drug has entered the market to establish real world safety and effectiveness, and to collect information on rare, but serious, adverse events. The detection of an increased incidence of a common event secondary to medication, such as heart attack or stroke, is even more difficult. The recent case of COX 2 inhibitors is a notable example.

Surveillance is defined as the ongoing, systematic use of routinely collected population-based health data to identify associations and predictors of health outcomes ^{2, 3}. Surveillance systems can also help decision-makers assess need, as well as plan, implement and evaluate interventions. Post-market surveillance of medication is the continued monitoring for, and the study of effects and other safety and effectiveness related aspects of, health products that have been marketed to the public ⁴.

Australia is well placed to introduce such a surveillance system given that a national authority funds medicines for the whole population and the panel believes that the TGA should investigate examples of good practice from other countries.

9.2 Overseas initiatives

Regulatory agencies in France, New Zealand, the United Kingdom and the United States have arrangements with one or more research networks for research into drug safety and effectiveness ¹. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance provide a network spanning the European Union. There are several approaches to pharmacosurveillance ¹.

Active surveillance includes tracking patients who are prescribed a targeted drug (prescription event monitoring); setting up cohort studies for those using new drugs; regular surveys of prescribers and pharmacists; disease registries (especially for drugs that present particular risks); database mining (such as that done on the UK General

Practice Research Database and the Scottish Medicines Monitoring Unit); and electronic surveillance of emergency ward charts (such as an existing US initiative encompassing 64 hospitals and plans for a database of 25 million patients) ¹.

Passive approaches include adverse drug reaction (ADR) reporting and monitoring (levels vary internationally, with New Zealand having one of the highest rates); requirement for risk management plans as a condition of market authorization (as required in the European Union, though there are no legal controls for plan completion); requirements for, and monitoring of, phase 4 trials; networks of pharmacovigilance centres; five year renewals for market authorization and commissioning of post market research projects ¹.

Passive and active approaches are complementary. Passive ADRs can signal potential safety issues but can generally only generate hypotheses. Signals from passive ADRs must therefore be confirmed by hypothesis testing through active pharmacovigilance. The US, France and New Zealand take passive reports of ADRs and subject them to a process of formal confirmatory investigation such as prescription event monitoring (PEM) and data mining of healthcare databases.

Pharmacosurveillance frameworks may use many types of information ^{1,5}:

- Administrative databases;
- Results from pragmatic trials;
- Patient registries;
- Surveys; and
- Reporting of adverse events by clinicians or patients, whether reporting is spontaneous or mandatory.

Canada provides one example of pharmacosurveillance using administrative databases⁵. Several academic/research units provide post-market surveillance expertise to provincial drug plans on a contract basis or with year-to-year funding. Some, like the Institute for Clinical Evaluative Sciences (ICES) in Toronto, the Population Health Research Unit (PHRU) at Dalhousie University, and the Manitoba Centre for Health Policy (MCHP), have a group of researchers who focus on prescription drug issues within a larger research unit. Others, like the Therapeutics Initiative (TI) at the University of British Columbia (UBC), concentrate solely on the evaluation of drugs. These post-market surveillance projects are seldom clinical trials; they most often rely on administrative data for utilization and observational/cohort studies.

9.3 Advantages & disadvantages of pharmacosurveillance using administrative data.

Carleton and colleagues have reviewed the strengths and limitations of using administrative data for pharmacosurveillance ⁵.

Advantages

- They cover full populations and real world safety and effectiveness (e.g., less selected populations).
- Analyses are relevant to policy decisions.
- Cross-jurisdictional pooling of large datasets may allow for earlier analyses of rare events than waiting for them to accumulate over time in one area.

Limitations

- Randomization is seldom possible and statistical adjustments for bias are not always adequate
- There is uncertainty as to how differences between randomized controlled trial (RCT) evidence and real world safety and effectiveness (RWSE) evidence should be interpreted. RWSE may be most useful for detecting early signals that need to be confirmed by RCTs.
- Administrative data can be limited in scope of variables and may not include the entire population
- Such analyses involve retrospective review versus prospective study to determine drug effectiveness.
- There can be long delays in data access under some privacy legislation/review processes.

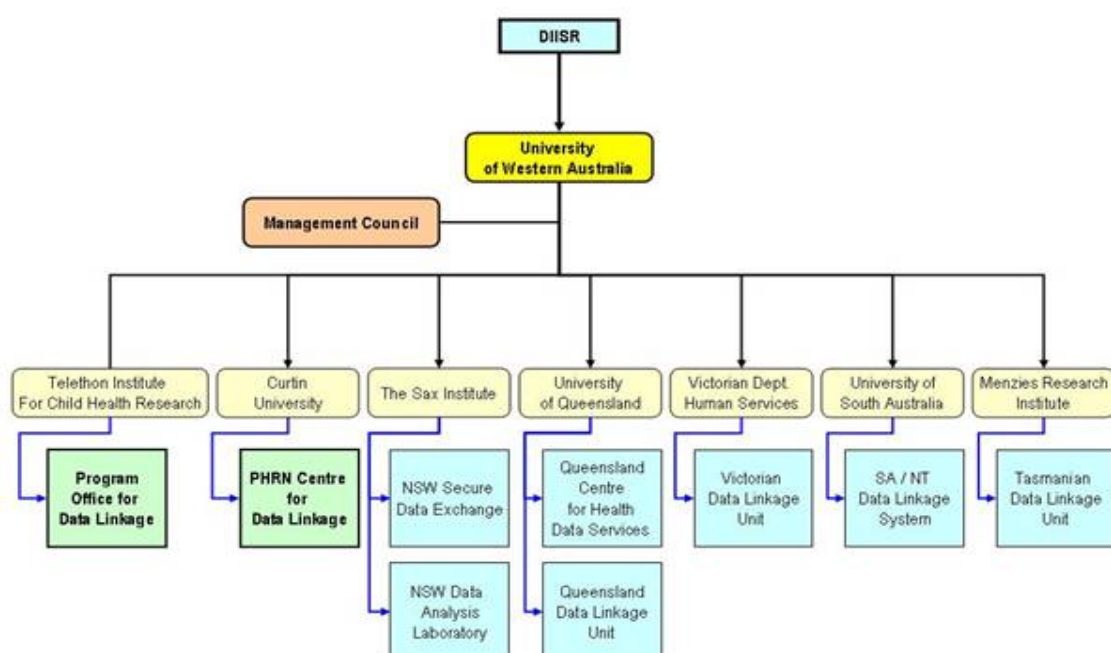
On balance, administrative data can be a valuable source of information for pharmaco-surveillance especially if complemented by other data sources.

9.4 Developments in Australia

Australia is one of few countries that have comprehensive, high-quality, population data on many aspects of health and health care. With data linkage, much information could be drawn from routine data collections and research datasets without the intrusion and cost of additional data collection.

In recognition of this the Australian Government has provided \$20 million for a National Collaborative Research Infrastructure Support (NCRIS) initiative to establish the Population Health Research Network (PHRN). This is a national network with representation from all States and Territories that will use Australia's extensive health data to provide linkage across data sets to facilitate population health research. (Figure 9.1)

Figure 9.1 Australia's Population Health Research Network



The PHRN infrastructure comprises a set of processes, methodologies, technologies and expertise. The infrastructure will include the following: 1) information and communication technology (ICT) and support; 2) acquisition and maintenance of research equipment; 3) workforce training and development; 4) data management and custodianship; 5) analytical capacity; 6) coordination among interested parties; and 7) governance.

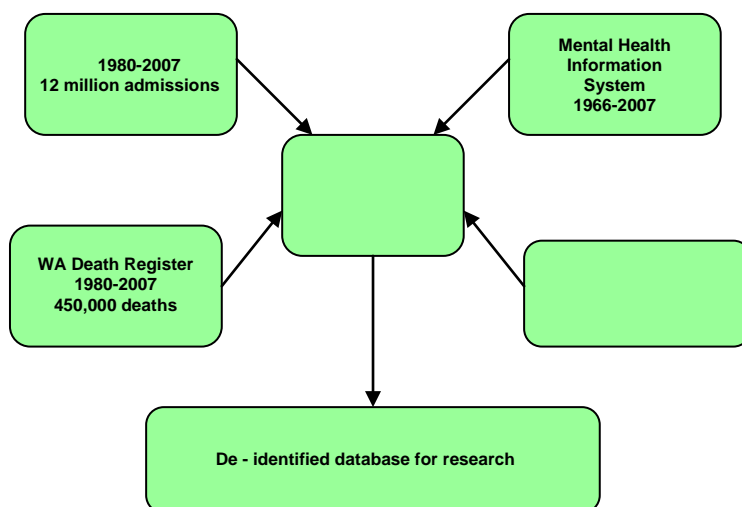
NCRIS Funding will be used entirely for expanding, building and/or evaluating infrastructure for the probabilistic linkage of datasets relevant to the health and wellbeing of the Australian population. The funding will expand the capacity of existing units, including capacity for the future linkage of national datasets.

The project will develop research infrastructure that will have benefits across Australia. The PHRN will enable researchers in universities, research institutes, government agencies and other organisations to access new and existing research datasets, ad hoc survey datasets and routine administrative datasets. The ultimate purpose is to improve health and wellbeing and enhance the effectiveness and efficiency of health services.

The PHRN became operational at the beginning of 2009. The major initial focus will be on State-held data such hospital separations, perinatal (midwives) records, community psychiatric contacts and vital statistics ⁶. These will be expanded to cancer registries, and in the longer term, to commonwealth data such as Medicare and PBS. In some jurisdictions such as Western Australia the expansion into these other databases is already advanced (Figure 2, page 99). Links between commonwealth and state data will prove the opportunity to institute a country wide pharmacosurveillance system in the near future.

The PHRN will consist of three layers⁶. The first layer includes existing local linkage programs such as the cancer registries which are common to all jurisdictions. The next layer includes jurisdictional linkage units (such as already exist in Western Australia and New South Wales) which link together information on a much broader scale. This includes numbers of health-related databases holding information on all individuals within the jurisdiction. At this level, linkages are made to single episodes in most databases (e.g. hospital discharges, perinatal forms, death records) and also to groups of pre-linked records (each group representing one individual) in pre-existing linkage programs such as disease registries and longitudinal studies of specific population groups. The third layer will be performed at a national centre for data linkage to construct a national linkage map covering the Australian population through cross-links between the jurisdictional units. Linkage results will be stored as linkage maps. As in the current Western Australian Data Linkage System, these do not contain any personal identifying information but rather references to the origin of the information and to other records that may refer to the same person. Similarly, the national map will contain encrypted references to the original location of jurisdictional information included in the PHRN system, together with group or person identifier, often referred to as a chain identifier.

Figure 9.2 Schema of the WA Health Services Research Linked Database



9.5 Conclusions and recommendation

The Panel endorses the views of experts from elsewhere for a post market surveillance system with the following elements^{1,5,7}:

- **Research networks** that:
 - § ensure studies are conducted in areas in which manufacturers have a disincentive to investigate (e.g., analyses of whole drug classes for specific indications, head-to-head comparisons)
 - § conduct directed research into unanticipated safety problems and report in a timely fashion (such as the Regional Pharmacovigilance Centres in France or the National Pharmacovigilance Centre in New Zealand)
- **Strengthened relationships** between regulatory authorities and academic research networks to enhance regulators' capacity to investigate safety and effectiveness issues
- **Public oversight of independently conducted post-market research** that permits third party review of study protocols, avoids proprietary data conflicts, and allows vetting of industry suggestions to alleviate doubts about the validity of research results
- **Phased introduction of new drugs with potential for large scale use.** An Only in Research (OIR) assessment can limit the use of publicly funded medicines until 'real-world' safety and effectiveness is determined
- **Adoption of risk management plans (RMPs)** and post-authorization safety studies as a condition of on-going market authorization could increase industry compliance. The Panel noted that in April 2009 the TGA formally adopted the *EU Guideline on Risk Management Systems for Medicinal Products for Human Use* (EMA/CHMP/ 96268/2005). Adoption of this guideline means that applications for the registration of certain higher risk prescription medicines ((new chemical entities, applications for paediatric use, new dosage forms, new routes of

administration and significant extensions of indication) are now required to include a Risk Management Plan (RMP) as part of the application.

- **A flexible and enforceable "tool kit"** of regulatory options that may be applied at or after approval, e.g., conditions and restrictions on promotion and distribution, postmarketing studies
- **Adequate funding** to facilitate long-term planning to address emergent issues and threatened access to needed expertise
- **Active surveillance** to identify and verify the cause of ADRs and unexpected problems. (For example, in the United States, the Food and Drug Administration and Veterans Affairs Memoranda of Understanding to share information attained from VA database mining will enable better targeting of potential safety issues, and responsive feedback to FDA.)
- **Regional Pharmacovigilance Centres** such as those in France, which offer an important link to clinical care that facilitates prospective observations studies and 'real world' RCTs.

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

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