Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity

P. K. Gillman*

Pioneer Valley Private Hospital, Mackay, Queensland 4740, Australia

*E-mail: kg@matilda.net.au

Toxicity resulting from excessive intra-synaptic serotonin, historically referred to as serotonin syndrome, is now understood to be an intra-synaptic serotonin concentration-related phenomenon. Recent research more clearly delineates serotonin toxicity as a discreet toxidrome characterized by clonus, hyper-reflexia, hyperthermia and agitation. Serotonergic side-effects occur with serotonergic drugs, and overdoses of serotonin re-uptake inhibitors (SRIs) frequently produce marked serotonergic side-effects, and in 15% of cases, moderate serotonergic toxicity, but not to a severe degree, which produces hyperthermia and risk of death. It is only combinations of serotonergic drugs acting by different mechanisms that are capable of raising intra-synaptic serotonin to a level that is life threatening. The combination that most commonly does this is a monoamine oxidase inhibitor (MAOI) drug combined with any SRI. There are a number of lesser-known drugs that are MAOIs, such as linezolid and moclobemide; and some opioid analgesics have serotonergic activity. These properties when combined can precipitate life threatening serotonin toxicity. Possibly preventable deaths are still occurring. Knowledge of the properties of these drugs will therefore help to ensure that problems can be avoided in most clinical situations, and treated appropriately (with 5-HT2A antagonists for severe cases) if they occur. The phenylpiperidine series opioids, pethidine (meperidine), tramadol, methadone and dextromethorphan and propoxyphene, appear to be weak serotonin re-uptake inhibitors and have all been involved in serotonin toxicity reactions with MAOIs (including some fatalities). Morphine, codeine, oxycodone and buprenorphine are known not to be SRIs, and do not precipitate serotonin toxicity with MAOIs.

Keywords: analgesics, opioid; complications, serotonin toxicity syndrome; pharmacology, MAO inhibitors; serotonin re-uptake inhibitor

Advances in understanding the mechanism of action and receptor profile of drugs, and the features of serotonin toxicity, have led to increased ability to explain and predict drug interactions involving opioid analgesics and monoamine oxidase inhibitors (MAOIs). Ever since the discovery of the MAOI anti-tuberculous drug iproniazid, in the mid-1950s, there have been concerns about interactions between MAOI antidepressant drugs, including new reversible inhibitors of monoamine oxidase-A (RIMAs) typified by moclobemide, and analgesics used in anaesthesia. This topic continues to be confused by an incomplete understanding of the clinical picture of serotonin toxicity. This review aims to clarify the situation, through use of recent data concerning the nature of the interaction, its clinical characteristics and the properties of the drugs involved. The appropriate treatment using 5-HT2A antagonists for severe cases is highlighted.

Ever since the initial report by Oates in 1955 there have been periodic reviews in the literature concerning the safety, or otherwise, of opioid analgesics in patients who were taking MAOIs. The enduring difficulty in understanding the nature of the problem is related to several factors. First, the apparent serotonin re-uptake inhibitor (SRI) capacity of opioid analgesics is only partially documented even now, and it is possible they have other serotonergic effects. Also, until recently, there has been a lack of systematic data to accurately define the features of serotonin toxicity; and the spectrum concept of serotonin toxicity, that emphasizes it is a dose-related phenomenon not an idiosyncratic reaction, has only recently been formulated.

Definition and description

Recent ideas concerning serotonin syndrome, or serotonin toxicity as it is now termed by many authors, emphasize...
that there is a spectrum of serotonergic side-effects blending into more severe reactions that can be described as toxicity. This is the spectrum concept of serotonin toxicity and evidence supporting the existence of a clear dose–effect relationship has been described in detail elsewhere.

Serotonin toxicity has now been more clearly characterized as a triad of neuro-excitatory features.

1. Neuromuscular hyperactivity; tremor, clonus, myoclonus, hyper-reflexia and (in the advanced stage) pyramidal rigidity.
2. Autonomic hyperactivity; diaphoresis, fever, tachycardia and tachypnoea.
3. Altered mental status; agitation, excitement and (in the advanced stage) confusion.

The features that usually distinguish it from other states with which it might be confused are: myoclonus, clonus and hyperreflexia. Professor Whyte’s group at the Hunter Area Toxicology Service (HATS) have prospectively documented over 2000 cases of serotonergic drug overdose. Whyte has applied decision tree rules to their large data set and found . . . ‘only clonus (inducible, spontaneous or ocular), agitation, diaphoresis, tremor and hyperreflexia were needed for accurate prediction of serotonin toxicity as diagnosed by a clinical toxicologist’. The decision rules are detailed in their seminal paper, which should be studied. They demonstrate clearly that there is a spectrum of serotonergic side-effects blending into more severe reactions that can be described as toxicity.

A possible differential diagnosis is often stated to be neuroleptic malignant syndrome (NMS) where bradykinesia results in a state of immobilization, akinesia and stupor, lead pipe or cogwheel rigidity, fever and autonomic instability. However, in clinical practice, the following features invariably clearly differentiate the two.

- Serotonin toxicity is caused by serotonergic drugs (frequently and predictably, is dose-related). NMS occurs in association with neuroleptics (rarely and idiosyncratically, is not dose-related).
- Serotonin toxicity, rapid onset and progression (hours). NMS, slow onset and progression (days).
- Serotonin toxicity, hyperkinesia and hyperreflexia/clonus, pyramidal rigidity. NMS, bradykinesia and extrapyramidal rigidity.

NMS shares similarities with malignant hyperthermia (MH) and for the same reasons is unlikely to be confused with serotonin toxicity, except, perhaps, whilst a patient is under anaesthesia when hyperkinesia, hyperreflexia and clonus may be suppressed. Another possible differential diagnosis is anticholinergic delirium. Both anticholinergic delirium and serotonin toxicity can manifest with impairment of consciousness, tachycardia and pyrexia, but diaphoresis, clonus and hyperreflexia usually distinguish them and in anticholinergic toxicity the skin and mucous membranes are dry, and increased tone and hyper-reflexia are not present. Diaphoresis, clonus and hyperreflexia also make it difficult to confuse serotonin toxicity with drug withdrawal, for example alcohol or benzodiazepines.

Exclusion criteria for the diagnosis of serotonin toxicity have been suggested, including recent administration of a neuroleptic and substance withdrawal. There is no logical justification for those, or any other features, assuming a hierarchical precedence over signs of serotonin toxicity, as has been discussed elsewhere. In contrast to MH and NMS, serotonin toxicity is directly and frequently related to ingestion of serotonergic agents (i.e. it is poisoning). Conversely, NMS and MH are rare idiosyncratic reactions. NMS is not more common after over-doses.

**Implicated drugs**

The only therapeutic drugs implicated in severe reactions that are capable of precipitating fatalities is the combination of MAOIs with SRIs (Table 1). Illicit CNS stimulant drugs such as MDMA, ecstasy (3,4-methylenedioxymethamphetamine), if combined with MAOIs (including moclobemide) do also cause fatalities because they act as serotonin releasers (see Table 1). Serotonin releasers in combination with MAOIs are the only other combination able to cause serotonin toxicity of a severe and potentially fatal degree. Several unpublished cases (of MAOI/releaser combinations) are known to this author, and a recent case series of four deaths has been reported by Vuori.
none of the patients were treated with 5-HT_{2A} antagonists. Theoretically, a combination of amphetamine (but not methylphenidate) and an MAOI would precipitate serotonin toxicity;\textsuperscript{29} but this is rarely encountered in practice, and no fatalities are known. A comprehensive referenced list of drugs that possess MAOI or SRI properties, to a degree that is clinically significant, may be found in Gillman 1998.\textsuperscript{28} an abbreviated list is presented in Table 1 and an updated version is maintained on the author’s website (www.psychotropical.com).

Overall, there is a strong association between SRI potency and ability to precipitate fatalities in combination with MAOIs, such that binding affinities at the serotonin transporter (i.e. the serotonin re-uptake mechanism) of less than 1 nM are invariably associated with the ability to precipitate toxicity, and potencies in the 1–10 nM range are borderline (Table 2). Table 1 highlights the two anomalous and structurally related drugs venlafaxine and tramadol, because our current estimates of their SRI potency suggest they should not be a risk for toxicity. There is evidence they also act as serotonin releasers,\textsuperscript{23} not solely as re-uptake inhibitors, which may account for this discrepancy. What currently appears to be a large discrepancy in the case of pethidine, which is a very weak SRI (these new data only became available during the writing of this present paper), could possibly be accounted for by serotonin releasing properties, although as yet there is no direct evidence for this. For the structurally homologous tricyclic antidepressants (TCAs) the relationship between SRI potency and toxicity is robust, no TCA that is weaker than imipramine has ever been implicated in serotonin toxicity, and clomipramine which is significantly more potent, is much more prone to precipitate serotonin toxicity (Table 2).

Also, a recent review of the literature\textsuperscript{15} demonstrates that, of the releasers, amphetamine is relatively potent and a risk, whereas methylphenidate is a weak releaser\textsuperscript{67} and there is good evidence that there is no danger of serotonin toxicity with it and MAOIs.\textsuperscript{15,29} Familiarity with the drugs in Table 1 will ensure serious reactions are avoided. The old MAOIs are well-known, the most frequently encountered are phenelzine and tranylcypromine. The newer RIMA called moclobemide is an MAOI, as is linezolid, the new antibiotic. The standard SSRI antidepressants are also well-known, some other drugs with significant SRI potency are less familiar. These include the dual action antidepressants (SNRIs) venlafaxine, duloxetine, milnacipran and the weight reduction drug sibutramine. Some of the opioid analgesics are weak SRIs (see Table 2). The anti-histamine chlorpheniramine is available for the i.v. route of administration, and being an SRI might possibly provoke a reaction.

The early drugs that were involved in these interactions with MAOIs (pethidine and imipramine) are weak SRIs and, because there is a dose–effect relationship, they usually fail to produce a reaction. The practical consequences of this can be seen clearly from the work published by Evans-Prosser in

### Table 1

<table>
<thead>
<tr>
<th>Drugs with clinically relevant serotonergic potency from reference\textsuperscript{29}</th>
<th>Other references</th>
<th>Codd</th>
<th>Serotonin toxicity reports with MAOIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine MDMA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Monoamine oxidase inhibitors</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tranylcypromine phenelzine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>iproniazid/eisosonilamide</td>
<td></td>
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<tr>
<td>Pargyline selegiline</td>
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<tr>
<td>Clorgyline toloxatone</td>
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<td></td>
</tr>
<tr>
<td>Furoxone procarbazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iproniazid(e)isocarboxazid(e)*</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>iproniazid(e)isocarboxazid(e)*</td>
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</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>$K_i$ (nM)</th>
<th>Other references</th>
<th>Codd</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SSRI</td>
<td>0.13–2.2 potent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>0.14 potent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>4.3 weak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>8 (anomalous)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>500 000 None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>– ($&gt;100 000$) None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>– ($&gt;100 000$) None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>– ($&gt;100 000$) None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>760 528</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>– 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pethidine</td>
<td>413 weak, (anomalous)</td>
<td>Definite, and some fatalities</td>
<td></td>
</tr>
<tr>
<td>Pentazocine</td>
<td>– No report known</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>–</td>
<td>Uncertain. One case of serotonin toxicity, and one possible death reported</td>
<td></td>
</tr>
<tr>
<td>Remifentanil</td>
<td>–</td>
<td>No case or death reported</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>270 14.1</td>
<td>No reports known, but unlikely</td>
<td></td>
</tr>
</tbody>
</table>
1968. As a result of the uncertainty in this area Churchill-
Davidson9 developed a testing procedure for checking
whether patients on MAOIs were going to exhibit a reaction
to analgesics. Evans-Prosser modified this procedure in
1968 and described an experiment in which they gave
15 patients injections of pethidine, morphine or water, in
graduated doses, under controlled conditions in hospital.
The maximum dose of pethidine was 75 mg and morphine
7.5 mg. All of the 15 patients received, in blind random
order, each of these three treatments. They administered a
maximum single dose of 75 mg pethidine to 15 subjects,
one of whom experienced any serotonergic symptoms.
Serotonin toxicity was not then well defined or understood,
so they could not have known the key symptoms to elicit, so
did not examine patients for hyperreflexia or clonus, they
measured the pulse and arterial pressure. A lack of aware-
ness of what specific symptoms to look for continues, even
now, to inhibit detection of these reactions. Evans-Prosser’s
group of patients represents the only case series of this sort,
and even now constitutes valuable data. This confirms the
predictions of the spectrum concept of serotonin toxicity,
which is that weak SRIs like pethidine are sometimes
capable of precipitating serotonin toxicity, but only in sus-
ceptible individuals, or with particularly large doses. The
complete list of the references relating to serotonin toxicity,
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complete list of the references relating to serotonin toxicity,
We can therefore predict that combinations of linezolid with various lesser known SRIs, like sibutramine or even fentanyl, might possibly precipitate serious serotonin toxicity, or even cause fatalities. Deaths that might have been prevented are still occurring. The Ottey case is a salutary example of the clinical consequences that can result from a single dose of an SRI; this occurred in a European university hospital recently when imipramine 225 mg was administered to a patient already stabilized on 50 mg daily of tranylcypromine. The error was recognized and the patient was transferred to ITU. Rapid deterioration occurred with rigidity and hyperthermia of 40 °C, the patient died within 24 h. No serotonin antagonists were used; neither does the report contain references indicating post hoc recognition of their possible benefit. A knowledge of the properties of these drugs may help to ensure that problems can avoided in most clinical situations, and treated appropriately if they occur.

**Treatment**

Careful consideration of the need for treatment is important, especially because the inappropriate generalization has often been repeated, that ‘cessation of drugs and non-specific treatment is all that is necessary in a majority of cases’. To state that without understanding the spectrum concept is a risky over-simplification of the issues, because some patients will die before the effects of ingested drugs wear off: when both an MAOI and an SRI have been co-ingested (even in low doses) rapid deterioration and death is well documented if appropriate intervention is not promptly initiated. Early transfer to a medical ICU and consultation with a toxicologist is strongly recommended. An overdose of an SSRI alone only produces a moderate degree of serotonin toxicity at worst (in ~15% of cases it is sufficient for admission and active medical treatment), but with no serious sequelae or fatalities (see details). However, if an MAOI or RIMA+SRI have been co-ingested (as an ‘over-dose’) then more than 50% of such cases experience severe serotonin toxicity. Even therapeutic doses of moclobemide have been associated with severe toxicity when combined with SRIs, especially venlafaxine, despite opinion expressed in recent reviews suggesting that such combined treatment for depression might be safe. It is these combinations of MAOI or RIMA+SRI that are most likely to require active medical intervention including, cooling, 5-HT2A antagonists and possibly neuromuscular paralysis with tracheal intubation and mechanical ventilation of the lungs. Severe late stage serotonin toxicity progresses from clonus and hyper-reflexia to rigidity, of first the lower limbs, and then the truncal muscles. This may produce impairment of breathing and a rise in PaCO₂, which precipitates the need for intubation and neuromuscular paralysis.

The ‘HATS’ treatment protocol builds on the data and recommendations reviewed previously by Gillman. 

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Ki (nM)</th>
<th>Notes, and effectiveness for treating serotonin toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>2.75</td>
<td>I.M./i.v. injection, effective in animals and humans</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>1.67</td>
<td>Tablet only, no i.m./i.v. injection, effective in animals and humans</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>30</td>
<td>Ineffective in animals and humans</td>
</tr>
<tr>
<td>Ketanserin</td>
<td>2</td>
<td>Effective in animals</td>
</tr>
<tr>
<td>Methysergide</td>
<td>3.25</td>
<td>Effective in animals and humans</td>
</tr>
<tr>
<td>Risperidone*</td>
<td>0.2</td>
<td>Effective in animals, depot i.m. only</td>
</tr>
<tr>
<td>Propranolol**</td>
<td>2260</td>
<td>Ineffective in animals and humans</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>107</td>
<td>Worsens serotonin toxicity in humans</td>
</tr>
</tbody>
</table>

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### Table 3

Affinity of 5-HT₂A and 5-HT₁A receptor antagonists, effectiveness for serotonin toxicity. Abbreviated from reference with permission, originally compiled from http://pdsp.cwru.edu/pdsp.php (reference). Drugs currently available for use in humans. Only available as long acting slow release injection for schizophrenia included for comparison because it has been demonstrated to be ineffective in animal models of serotonin toxicity and human cases. See reference for a full list of all 5-HT₂A/₁A antagonists. As for SRIs, it appears single figure nanomolar potencies are required for efficacy, note the ineffectiveness of haloperidol.
agents like benzodiazepines are less effective than 5-HT2A drugs (propoxyphene, pentazocine, fentanyl, remifentanil releasers, using the latest assay techniques. For some toxicity of these drugs, and also by the lack of pharmaco-ised by a lack of systematically recorded data on the clinical large doses or susceptible individuals. Our ability to estimate conjunction with any type of MAOI), but perhaps only in dose-dependant serotonin toxicity (when administered in weak SRIs (see Table 2), and may infrequently precipitate reactions may be tempered by the knowledge that any reaction is dose-dependent and that we are now confident that reactions can be successfully treated, if severe, with 5-HT2A antagonists.

Conclusion

In summary, morphine, codeine, oxycodone and bupren-orphine are now known not to be SRIs and they do not precipitate serotonin toxicity with MAOIs. Pethidine, tramadol, dextromethorphan and methadone definitely are weak SRIs (see Table 2), and may infrequently precipitate dose-dependent serotonin toxicity (when administered in conjunction with any type of MAOI), but perhaps only in large doses or susceptible individuals. Our ability to estimate the risk with particular drugs with any precision is comprom-ised by a lack of systematically recorded data on the clinical toxicity of these drugs, and also by the lack of pharmaco-logical data concerning their precise potency, as SRIs or releasers, using the latest assay techniques. For some drugs (proproxyphene, pentazocine, fentanyl, remifentanil and congeners) there is no SRI affinity data at all, and we have to rely on interpolations and the presence or absence of clinical reports (Table 2). It is to be hoped that increasing understanding and awareness of this situation will stimulate further research that will answer these remaining questions. However, the clinical situation and the risks are now more clearly defined and understood and the information herein will enable many clinicians to be more confident when making decisions about patient management. Choices involving the known serotonergic opioids can now be made in particular clinical situations by balancing the advantages and disadvantages that there may be for individual patients with respect to particular drugs. The level of risk with known serotonergic opioids is probably low, but its unpredictable and serious nature makes it difficult to form judgments. All other factors being equal, it would seem prudent to use the drugs known not to be SRIs where possible. These judg-ments may be tempered by the knowledge that any reaction is dose-dependent and that we are now confident that reactions can be successfully treated, if severe, with 5-HT2A antagonists.

Acknowledgements

I gratefully acknowledge the expertise and time of my wife Isobel, for maintaining the computers and programs necessary to achieve this review, as well as for her support and patience. We will always remember the special part played by Tess Gillman (1984–2002). Vale, to a noble heart that seemed to rise above the beast.

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