BJA Advance Access published July 28, 2005

British Journal of Anaesthesia Page 1 of 8
doi:10.1093/bja/aei210

BJA

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-HT_{2A} 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.

Br J Anaesth 2005

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.[9 14 57 58 71 74] 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-HT_{2A} antagonists for severe cases is highlighted.

Ever since the initial report by Oates in 1955[55] there have been periodic reviews in the literature concerning the safety, or otherwise, of opioid analgesics in patients who were taking MAOIs.[9 13 36 47 54 61 68 78] 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.[20]

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.[23 28 39 83] 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.[20 39 81 83 84]

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.[12 20 27 28 80 83] 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,[12] which should be studied. They demonstrate clearly that if, *in the presence of a serotonergic agent*, spontaneous clonus is present serotonin toxicity may be reliably diagnosed; failing that, if inducible clonus is present with agitation or diaphoresis serotonin toxicity may be reliably diagnosed.

Clinically, the onset of frank toxicity is usually rapid, because it results from drug combinations and starts when the second drug reaches effective blood levels. The general clinical picture is often alarming, and rapidly progressive after the first or second dose of the second serotonergic drug in the patient's regimen. The serotonin toxic patient is often initially alert, even hypervigilant, with tremor and hyperreflexia. Ankle clonus and myoclonus may be demonstrable. Neuromuscular signs are initially greater in the lower limbs, then become more generalized as toxicity increases. Patients may exhibit such pronounced tremors as to cause concern that they may precipitate themselves from their bed to the floor. Then the autonomic features become more evident with fever, sweating, mydriasis, tachycardia and tachypnoea. These features fluctuate mildly, but are not usually severe, nor a management problem. Other symptoms may include shaking, shivering often including chattering of the teeth and sometimes trismus and even opisthotonous. Pyramidal rigidity is a late development in severe cases, and when it affects truncal muscles can impair ventilation. Rigidity, decreasing Pa_{CO_2}, and a fever of more than 38.5°C heralds life-threatening 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.[20 79 82–84]

- 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)[40 41 77] 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,[73] 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.[25 27 28] 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.[37]

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.[76] It may be noted that none of the patients were treated with $5\text{-}HT_{2A}$ antagonists. Theoretically, a combination of amphetamine (but not methylphenidate) and an MAOI would precipitate serotonin toxicity;[29] but this is rarely encountered in practice, and

Table 1 Drugs with clinically relevant serotonergic potency from reference[29] with permission. Fatalities from serotonin toxicity involving analgesics have been with pethidine, tramadol and dextromethorphan and, possibly, fentanyl. *Records in databases use alternative spellings of many drugs, for example fentanil as fentanyl; commonly encountered examples are indicated by, for example fentani(y)l

Serotonin re-uptake inhibitors (selective and non-selective)
Paroxetine sertraline fluoxetine fluvoxamine citalopram
Venlafaxine milnacipran duloxetine sibutramine
Clomipramine imipramine (but not other TCAs)
Tramadol pethidine fentani(y)l (and congeners) methadone
dextromethorphan dextropropoxyphene pentazocine
Chlorpheniramine brompheniramine (but not other anti-histamines)
Serotonin releasers
Amphetamine MDMA
Monoamine oxidase inhibitors
Tranylcypromine phenelzine nialamid(e)isoniazid
iproniazid(e)isocarboxazid(e)*
Pargyline selegiline clorgyline
Moclobemide toloxatone
Furazolidone procarbazine linezolid

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,[20] 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,[2 3] 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[15] demonstrates that, of the releasers, amphetamine is relatively potent and a risk, whereas methylphenidate is a weak releaser[67] and there is good evidence that there is no danger of serotonin toxicity with it and MAOIs.[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

Table 2 5-HT transporter affinity of narcotic analgesics and comparator drugs* from reference[29] with permission. **In vitro* receptor assays provide an estimate of the drugs potency as an SRI; a lower K_i indicates higher potency. Until replicated human cloned receptor data are available for all of these drugs no precise comparisons will be possible.[2 10 17 30] **There is evidence that venlafaxine might have some other serotonergic action as well as significant serotonin re-uptake inhibitor potency:[2 3] this might be related to the anomalous toxicity, it is much weaker as an SRI than any other antidepressant that is capable of inducing serotonin toxicity. It is important to note that these data cannot be compared directly drug to drug because it comes from different sources and species. It can only give a guide as to potency. The results from Codd[10] are presented separately because this is the only paper that has screened a group of drugs using the same methodology

Drug	K_i (nM)		Serotonin toxicity reports with MAOIs
	Other references	Codd	
All SSRIs	0.13–2.2 potent		Definite, and frequent fatalities
Clomipramine	0.14 potent		Definite, and frequent fatalities
Imipramine	1.3		Definite, and occasional fatalities
Amitriptyline	4.3 weak		None, no fatalities
Venlafaxine	8 anomalous**		Definite, and fatalities
Morphine	500 000	>100 000	None
Codeine	–	>100 000	None
Buprenorphine	–	>100 000	None
Oxycodone	–	>100 000	None
Tramadol	760	528	Definite, and possible fatalities
Dextromethorphan	–	23	Definite
Pethidine	413 weak, anomalous	–	Definite, and some fatalities
Pentazocine	–	–	No reports known
Fentanyl	–	–	Uncertain. One case of serotonin toxicity, and one possible death reported
Remifentanil	–	–	No case or death reported
Methadone	270	14.1	No reports known, but unlikely

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 1968. As a result of the uncertainty in this area Churchill-Davidson[9] 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, none 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 awareness 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 susceptible individuals, or with particularly large doses. The complete list of the references relating to serotonin toxicity and analgesics, located through a search of the listed papers and standard databases (approximately 40), are detailed at www.psychotropical.com. There are some cases detailed there that do not appear in any other review of the subject.[5 20 33] Pethidine has undoubtedly caused a number of severe reactions, and some fatalities;[48 57 58 60 63 70] the other SRI analgesics have also precipitated some fatalities.[31 53 59 60 64 69] Especially when considered in relation to the Evans-Prosser paper above, this is a clear illustration of how a small case series, using usual therapeutic doses, may lead to a false sense of security, because the dose–effect relationship is not sufficiently appreciated. This is especially important when phamacokinetic and pharmacodynamic interactions coincide, which can elevate blood levels above those found in the average patient. We now know that differences in cytochrome P450 enzymes produce 20–50-fold variations in serum levels between different patients.[34]

The limited available clinical and experimental data agree that morphine analogues are not SRIs, nor do any of them precipitate serotonin toxicity with MAOIs (morphine, codeine, oxycodone, buprenorphine). There are no reports of serotonin toxicity with those drugs. The phenylpiperidine series opioids, pethidine (meperidine), tramadol, methadone and fentanyl (and congeners), and dextromethorphan and propoxyphene, are probably all borderline, being weak serotonin re-uptake inhibitors.[10] These drugs have been implicated in multiple reports, which are almost certainly serotonin toxicity, as judged by a subjective interpretation of the old case reports[20] and informed by more accurate recent data concerning the characteristic features of serotonin toxicity.[12] More precise data about SRI potency from human cloned receptor assays would be valuable, because we can reliably predict that only those drugs that are potent SRIs or releasers will precipitate serotonin toxicity. Unfortunately, the only published data are from the paper by Codd,[10] which used older assay methods. The central internet accessible database maintained by Roth's group (called the 'PDSP Ki database' at http://pdsp.cwru.edu/pdsp.php)[65] contains no additional data (as of March 2005) on any of the drugs listed in Table 2.

Details of all cases involving analgesics (approximately 40) are contained in this author's updated review.[29] In summary, all the opioid analgesics with serotonergic effects have been involved in serotonin toxicity reports, but none of the drugs without SRI capacity have been. There remains a possibility that drugs with anomalous properties, like tramadol and pethidine, may yet be revealed to be working as serotonin releasers. Recently developed assays to estimate these properties may elucidate the situation in the near future.[66]

There are a few individual case reports worthy of particular comment. In my opinion the Noble case report fatality[53] was probably a result of serotonin toxicity. This patient was on MAOIs before cardiac surgery and was administered fentanyl. In the postoperative recovery phase the patient exhibited shivering and hyperpyrexia. The authors considered the possibility of serotonin toxicity and reached the conclusion that fentanyl cannot be assumed to be safe. A more recent report by Roy and colleagues, although not considered by its authors to be serotonin toxicity, may represent a hitherto unrecognized report of serotonin toxicity with fentanyl.[68] Therefore, as predicted from the SRI potency data, there is a question mark over fentanyl, despite opinions in previous reviews that it is safe.[1 8 72] However, its potency as an SRI is low, so as expected (and like pethidine) it has been reported to have been used with impunity.[13 16 36 47 53 68 72 78] It is appropriate to note that it is probable that fentanyl has been used in a many cases in combination with MAOIs that have not been reported in the literature because there has been no problem. There is insufficient basis for an accurate estimate of the risk, which would seem to be so low that one could not suggest use of fentanyl (or its congeners) is strongly contra-indicated if there is no appropriate alternative. Although there are no SRI data concerning remifentanil, all fentanyl congeners have short half-lives and would be expected to be more safe because they are quickly reversible. Remifentanil's safe use in conjunction with MAOIs has been reported.[75] It is to be expected that pharmacogenetics may enable advanced prediction of those cases likely to develop high blood levels and thus be at higher risk, and in the future such patients may be genetically screened before operation if they are on MAOIs.[35]

There are a number of lesser known drugs, such as the MAOIs linezolid and moclobemide, and the SRIs tramadol and sibutramine, which possess these properties and can therefore precipitate life threatening serotonin toxicity.[23 26] 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.[22 24] Deaths that might have been prevented are still occurring.[4 56 76] 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[20 56 62] 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[83 84] for 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.[38] Even therapeutic doses of moclobemide have been associated with severe toxicity when combined with SRIs, especially venlafaxine,[23 32] despite opinion expressed in recent reviews[7 11] 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-HT_{2A} antagonists and possibly neuromuscular paralysis with trachael 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 Pa_{CO_2}, which precipitates the need for intubation and neuromuscular paralysis.

The 'HATS' treatment protocol builds on the data and recommendations reviewed previously by Gillman.[20 21] Cyproheptadine (see Table 3), only available as tablets, is effective for the milder cases; current experience suggests doses of 12 mg orally (or crushed via nasogastric tube) initially, followed by 4–8 mg every 6 h. However, if charcoal has already been given, or the urgency of the situation requires rapid intervention, then chlorpromazine may be used via the i.v. route. At present there is no widely available 5-HT_{2A} antagonist for i.v. use in humans except chlorpromazine. In severe toxicity (life-threatening cases) it has been used in more than 20 instances (in the 'HATS' experience) with good effect and no fatalities: see also reference[21] for a review of all other reported 'non-HATs' cases. Fluid loading is advised before giving chlorpromazine (because of hypotension via adrenergic α2 receptor antagonism). HATS experience suggests dosing in the range of 12.5–25 mg i.v. initially, followed by 25 mg orally or i.v. every 6 h. Higher doses have also been used with apparent safety and effectiveness, all reported cases in the literature from 1955 have been systematically reviewed in detail.[18 19 21] Chlorpromazine might possibly aggravate cardiotoxic or epileptogenic properties of other drugs (e.g. venlafaxine and TCAs). Further details of treatment with 5-HT_{2A} antagonists are contained in recent toxicology texts.[83] Benzodiazepines have recently been demonstrated to reduce pyrexia in serotonin toxic rats and may be a reasonable adjunctive treatment with 5-HT_{2A} antagonists.[49–52] These recent developments strongly support the early work, reviewed by Gillman,[20] concerning the effectiveness of 5-HT_{2A} antagonists in preventing hyperpyrexia and death in an animal model of serotonin toxicity, and also for the treatment of serious serotonin toxicity in humans.[21 28 83]

Extensive details analysing the history and evidence relating to drugs that have been tested in animal models of serotonin toxicity are contained in two major reviews.[20 21] However, it may be noted that no expert animal pharmacologist has yet reviewed this subject in detail, and there remains much work to be done in relation to testing drugs in

Table 3 Affinity of 5-HT_{2A} and 5-HT_{1A} receptor antagonists, effectiveness for serotonin toxicity. Abbreviated from reference[29] with permission, originally compiled from http://pdsp.cwru.edu/pdsp.php (reference[65]). 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.[21] See reference[29] for a full list of all 5-$HT_{2A/1A}$ antagonists. As for SRIs, it appears single figure nanomolar potencies are required for efficacy, note the ineffectiveness of haloperidol

Drug name	K_i (nM)		Notes, and effectiveness for treating serotonin toxicity
	2A	1A	
Chlorpromazine	2.75	3000	I.M./i.v. injection, effective in animals and humans
Cyproheptadine	1.67	50	Tablet only, no i.m./i.v. injection, effective in animals and humans
Haloperidol	30	3500	Ineffective in animals
Ketanserin	2	1044	Effective in animals
Methysergide	3.25	25	Effective in animals and humans
Risperidone*	0.2	427	Effective in animals, depot i.m. only
Propranolol**	2260	78	Ineffective in animals and humans
Bromocriptine	107	12.9	Worsens serotonin toxicity in humans

animal models of serotonin toxicity using more up-to-date techniques. The only systematic recent work since Marley's seminal papers[42–46] in the early 1980s has been done by Nisijima. In brief, from the very earliest experiments in 1958,[6 58] through to Nisijima's work, a wide variety of structurally different agents have been tested in animal models. In many cases the receptor properties of the drugs were not known at the time the experiments were done, accurate receptor potency estimations have only been available in the last two decades, and much of the work preceded that. All the agents that have appeared to be effective have turned out to be 5-HT_{2A} antagonists. None of the 5-HT_{1A} antagonists tested has appeared to exhibit efficacy, either in animal models or very limited human test cases, indeed bromocriptine (see Table 3) seems to worsen serotonin toxicity.[20] However, recognition of the limited amount of accurate comparative data for most of these drugs at 5-HT receptor subtypes needs to be taken into account before reaching firm conclusions. In practice, the only drugs with some specificity at 5-HT receptor subtypes, that are available for use in humans, are listed in Table 3, where it can be seen that the evidence for efficacy is strongly in favour of those drugs which appear to be potent and specific 5-HT_{2A} antagonists. It remains possible that more sophisticated understanding of the effects of these drugs will in future modify our understanding of the precise 5-HT receptor subtypes involved. For instance, there are almost no data at all concerning the relative potency of any of these drugs at the 5-HT_2 A, B, C, D receptor subtypes. It is clear that GABA agents like benzodiazepines are less effective than 5-HT_{2A} antagonists, but do attenuate elevation of temperature in rat models of serotonin toxicity. Dopamine antagonists are ineffective.[21]

Conclusion

In summary, morphine, codeine, oxycodone and buprenorphine 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-dependant 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 compromised by a lack of systematically recorded data on the clinical toxicity of these drugs, and also by the lack of pharmacological data concerning their precise potency, as SRIs or releasers, using the latest assay techniques. For some drugs (propoxyphene, 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 judgments 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-HT_{2A} 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.

References

1 Baele P, Kestens-Servaye Y, Goenen M. MAOI and cardiac surgery. *Can J Anaesth* 1993; **40**: 579–80
2 Bamigbade TA, Davidson C, Langford RM, Stamford JA. Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus. *Br J Anaesth* 1997; **79**: 352–6
3 Beique JC, Lavoie N, de Montigny C, Debonnel G. Affinities of venlafaxine and various reuptake inhibitors for the serotonin and norepinephrine transporters. *Eur J Pharmacol* 1998; **349**: 129–32
4 Bilbao Garay J, Mesa Plaza N, Castilla Castellano V, Dhimes Tejada P. [Serotonin syndrome: report of a fatal case and review of the literature]. *Rev Clin Esp* 2002; **202**: 209–11
5 Bodner RA, Lynch T, Lewis L, Kahn D. Serotonin syndrome. *Neurology* 1995; **45**: 219–23
6 Bogdanski DF, Weissbach H, Udenfriend S. Pharmacological studies with the serotonin precursor 5-hydroxytryptophan. *J Pharmacol Exp Ther* 1958; **122**: 182–94
7 Bonnet U. Moclobemide: therapeutic use and clinical studies. *CNS Drug Rev* 2003; **9**: 97–140
8 Bowdle TA. Adverse effects of opioid agonists and agonist-antagonists in anaesthesia. *Drug Saf* 1998; **19**: 173–89
9 Churchill-Davidson HC. Anesthesia and monoamine-oxidase inhibitors. *Br Med J* 1965; **5433**: 520
10 Codd EE, Shank RP, Schupsky JJ, Raffa RB. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: structural determinants and role in antinociception. *J Pharmacol Exp Ther* 1995; **274**: 1263–70
11 DeBattista C, Sofuoglu M, Schatzberg AF. Serotonergic synergism: the risks and benefits of combining the selective serotonin reuptake inhibitors with other serotonergic drugs. *Biol Psychiatry* 1998; **44**: 341–7
12 Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. Hunter Serotonin Toxicity Criteria: a simple and accurate diagnostic decision rule for serotonin toxicity. *Q J Med* 2003; **96**: 635–42

13 el-Ganzouri AR, Ivankovich AD, Braverman B, McCarthy R. Monoamine oxidase inhibitors: should they be discontinued preoperatively? *Anesth Analg* 1985; **64**: 592–6

14 Evans-Prosser A. The use of pethidine and morphine in the presence of monoamine oxidase inhibitors. *Br J Anaesth* 1968; **40**: 279

15 Feinberg SS. Combining stimulants with monoamine oxidase inhibitors: a review of uses and one possible additional indication. *J Clin Psychiatry* 2004; **65**: 1520–4

16 Fobe F, Kestens-Servaye Y, Baele P, Goenen M. Heart-transplant and mono-amine oxidase inhibitors. *Acta Anaesthesiol Belg* 1989; **40**: 131–8

17 Frink MC, Hennies HH, Englberger W, Haurand M, Wilffert B. Influence of tramadol on neurotransmitter systems of the rat brain. *Arzneimittelforschung* 1996; **46**: 1029–36

18 Gillman PK. Successful treatment of serotonin syndrome with chlorpromazine. *Med J Aust* 1996; **165**: 345

19 Gillman PK. Serotonin syndrome treated with chlorpromazine. *J Clin Psychopharmacol* 1997; **17**: 128–9

20 Gillman PK. Serotonin syndrome: history and risk. *Fundam Clin Pharmacol* 1998; **12**: 482–91

21 Gillman PK. The serotonin syndrome and its treatment. *J Psychopharmacol (Oxf)* 1999; **13**: 100–9

22 Gillman PK. Linezolid and serotonin toxicity. *Clin Infect Dis* 2003; **37**: 1274–5

23 Gillman PK. Moclobemide and the risk of serotonin toxicity (or serotonin syndrome). *CNS Drug Rev* 2004; **10**: 83–5

24 Gillman PK. The spectrum concept of serotonin toxicity. *Pain Med* 2004; **5**: 231–2

25 Gillman PK. Making sense of serotonin toxicity reports, a comment on Chopra *et al.* (*World J Biol Psychiatry* 2004; 5: 114–115). *World J Biol Psychiatry* 2004; **5**: 167–8

26 Gillman PK. Comment on: serotonin syndrome due to co-administration of linezolid and venlafaxine. *J Antimicrob Chemother* 2004; **54**: 844–5

27 Gillman PK. Defining toxidromes: serotonin toxicity and neuroleptic malignant syndrome: a comment on Kontaxakis *et al. Arch Gen Hosp Psychiatry* 2004; http://www.general-hospital-psychiatry.com/content/2/1/10/comments#41454

28 Gillman PK, Whyte IM. Serotonin syndrome. In: Haddad P, Dursun S, Deakin B, eds. *Adverse Syndromes and Psychiatric Drugs*. Oxford: Oxford University Press, 2004; 37–49

29 Gillman PK. Serotonin toxicity, serotonin syndrome: 2005 update, overview and analysis. www.psychotropical.com/SerotoninToxicity.doc 2005

30 Giusti P, Buriani A, Cima L, Lipartiti M. Effect of acute and chronic tramadol on [3H]-5-HT uptake in rat cortical synaptosomes. *Br J Pharmacol* 1997; **122**: 302–6

31 Gong SN, Rogers KJ. Role of brain monoamines in the fatal hyperthermia induced by pethidine or imipramine in rabbits pretreated with pargyline. *Br J Pharmacol* 1971; **42**: 646P

32 Hawley CJ, Quick SJ, Ratnam S, Pattinson HA, Mcphee S. Safety and tolerability of combined treatment with moclobemide and SSRIs—a systematic study of 50 patients. *Int Clin Psychopharmacol* 1996; **11**: 187–91

33 Hilton SE, Maradit H, Moller HJ. Serotonin syndrome and drug combinations: focus on MAOI and RIMA. *Eur Arch Psychiatry Clin Neurosci* 1997; **247**: 113–9

34 Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. *Trends Pharmacol Sci* 2004; **25**: 193–200

35 Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J* 2005; **5**: 6–13

36 Insler SR, Kraenzler EJ, Licina MG, Savage RM, Starr NJ. Cardiac surgery in a patient taking monoamine oxidase inhibitors: an adverse fentanyl reaction. *Anesth Analg* 1994; **78**: 593–7

37 Isbister GK, Downes F, Whyte IM. Olanzapine and serotonin toxicity. *Psychiatry Clin Neurosci* 2003; **57**: 241–2

38 Isbister GK, Hackett LP, Dawson AH, Whyte IM, Smith AJ. Moclobemide poisoning: toxicokinetics and occurrence of serotonin toxicity. *Br J Clin Pharmacol* 2003; **56**: 441–50

39 Isbister GK, Bowe SJ, Dawson A, Whyte IM. Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol* 2004; **42**: 277–85

40 Jurkat-Rott K, Lerche H, Lehmann-Horn F. Skeletal muscle channelopathies. *J Neurol* 2002; **249**: 1493–502

41 Keck PE jr, Caroff SN, McElroy SL. Neuroleptic malignant syndrome and malignant hyperthermia: end of a controversy? *J Neuropsychiatry Clin Neurosci* 1995; **7**: 135–44

42 Marley E, Wozniak KM. Clinical and experimental aspects of interactions between amine oxidase inhibitors and amine re-uptake inhibitors. *Psychol Med* 1983; **13**: 735–49

43 Marley E, Wozniak KM. Interactions between non-selective amine oxidase inhibitors (MAOI) and other antidepressants. *Br J Pharmacol* 1983; **78**: 20p

44 Marley E, Wozniak KM. Interactions between relatively selective amine oxidase (MAOI) inhibitors and clomipramine. *Br J Pharmacol* 1983; **78**: 21p

45 Marley E, Wozniak KM. Interactions of a non-selective monoamine oxidase inhibitor, phenelzine, with inhibitors of 5-hydroxytryptamine, dopamine or noradrenaline re-uptake. *J Psychiatr Res* 1984; **18**: 173–89

46 Marley E, Wozniak KM. Interactions of non-selective monoamine oxidase inhibitors, tranylcypromine and nialamide, with inhibitors of 5-hydroxytryptamine, dopamine and noradrenaline re-uptake. *J Psychiatr Res* 1984; **18**: 191–203

47 Michaels I, Serrins M, Shier NQ, Barash PG. Anesthesia for cardiac surgery in patients receiving monoamine oxidase inhibitors. *Anesth Analg* 1984; **63**: 1041–4

48 Mitchell RS. Fatal toxic encephalitis occurring during iproniazid therapy in pulmonary tuberculosis. *Ann Intern Med* 1955; **42**: 417–24

49 Nisijima K, Yoshino T, Ishiguro T. Risperidone counteracts lethality in an animal model of the serotonin syndrome. *Psychopharmacology (Berl)* 2000; **150**: 9–14

50 Nisijima K, Yoshino T, Yui K, Katoh S. Potent serotonin (5-HT)(2A) receptor antagonists completely prevent the development of hyperthermia in an animal model of the 5-HT syndrome. *Brain Res* 2001; **890**: 23–31

51 Nisijima K, Shioda K, Yoshino T, Takano K, Kato S. Diazepam and chlormethiazole attenuate the development of hyperthermia in an animal model of the serotonin syndrome. *Neurochem Int* 2003; **43**: 155–64

52 Nisijima K, Shioda K, Yoshino T, Takano K, Kato S. Memantine, an NMDA antagonist, prevents the development of hyperthermia in an animal model for serotonin syndrome. *Pharmacopsychiatry* 2004; **37**: 57–62

53 Noble WH, Baker A. MAO inhibitors and coronary artery surgery: a patient death. *Can J Anaesth* 1992; **39**: 1061–6

54 Noorily SH, Hantler CB, Sako EY. Monoamine oxidase inhibitors and cardiac anesthesia revisited. *South Med J* 1997; **90**: 836–8

55 Oates JA, Sjoerdsma A. Neurologic effects of tryptophan in patients receiving a monoamine oxidase inhibitor. *Neurology* 1960; **10**: 1076–8

56 Otte W, Birkenhager TK, van den Broek WW. Fatal interaction between tranylcypromine and imipramine. *Eur Psych* 2003; **18**: 264–5
57 Palmer H. Potentiation of pethidine. *Br Med J* 1960; **2**: 944
58 Papp C, Benaim S. Toxic effects of iproniazid in a patient with angina. *Br Med J* 1958; **2**: 1070–2
59 Peeters-Asdourian C. [Fatal drug interactions]. *Rev Med Brux* 1986; **7**: 570
60 Pollock RA, Watson RL. Malignant hyperthermia associated with hypocalcaemia. *Anesthesiology* 1971; **34**: 188
61 Powell H. Use of alfentanil in a patient receiving monoamine oxidase inhibitor therapy. *Br J Anaesth* 1990; **64**: 528
62 Power BM, Pinder M, Hackett LP, Ilett KF. Fatal serotonin syndrome following a combined overdose of moclobemide, clomipramine and fluoxetine. *Anaesth Intensive Care* 1995; **23**: 499–502
63 Reid NCRW, Jones D. Pethidine and phenelzine. *Br Med J* 1962; **1**: 408
64 Rivers N, Horner B. Possible lethal interaction between Nardil and dextromethorphan. *Can Med Assoc J* 1970; **103**: 85
65 Roth B, Kroeze W, Patel S, Lopez E. The multiplicity of serotonin receptors: uselessly diverse molecules or an embarrasment of riches? *Neuroscientist* 2000; **6**: 252–62 http://kidb.cwru.edu/pdsp.php
66 Rothman RB, Baumann MH, Dersch CM, *et al*. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse* 2001; **39**: 32–41
67 Rothman RB, Baumann MH. Monoamine transporters and psychostimulant drugs. *Eur J Pharmacol* 2003; **479**: 23–40
68 Roy S, Fortier LP. Fentanyl-induced rigidity during emergence from general anesthesia potentiated by venlafexine. *Can J Anaesth* 2003; **50**: 32–5
69 Shamsie SJ, Barriga C. The hazards of monoamine oxidase inhibitors in disturbed adolescents. *Can Med Assoc J* 1971; **104**: 715
70 Shee JC. Dangerous potentiation of pethidine by iproniazid and its treatment. *Br Med J* 1960; **2**: 507–9
71 Spencer GT, Smith SE. Dangers of monoamine oxidase inhibitors. *Br Med J* 1963; **5332**: 750
72 Stack CG, Rogers P, Linter SPK. Monoamine oxidase inhibitors and anaesthesia. *Br J Anaesth* 1988; **60**: 222–7
73 Sternbach H. The serotonin syndrome. *Am J Psychiatry* 1991; **148**: 705–13
74 Taylor DC. Alarming reaction to pethidine in patients on phenelzine. *Lancet* 1962; **2**: 401–2
75 Ure DS, Gillies MA, James KS. Safe use of remifentanil in a patient treated with the monoamine oxidase inhibitor phenelzine. *Br J Anaesth* 2000; **84**: 414–6
76 Vuori E, Henry JA, Ojanpera I, *et al*. Death following ingestion of MDMA (ecstasy) and moclobemide. *Addiction* 2003; **98**: 365–8
77 Wappler F. Malignant hyperthermia. *Eur J Anaesthesiol* 2001; **18**: 632–52
78 Wells DG, Bjorksten AR. Monoamine oxidase inhibitors revisited. *Can J Anaesth* 1989; **36**: 64–74
79 Whyte IM. Serotonin syndrome complicating the treatment of recurrent depression. *Curr Ther* 1999; **40**: 6–7
80 Whyte IM, Dawson AH. Redefining the serotonin syndrome. *J Toxicol Clin Toxicol* 2002; **40**: 668–9
81 Whyte IM, Dawson AH, Buckley NA. Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. *Q J Med* 2003; **96**: 369–74
82 Whyte IM. Neuroleptic malignant syndrome. In: Dart RC, ed. *Medical Toxicology*, 3rd edn. Baltimore: Lippincott Williams & Wilkins, 2004; 101–3
83 Whyte IM. Serotonin toxicity (Syndrome). In: Dart RC, ed. *Medical Toxicology*, 3rd edn. Baltimore: Lippincott Williams & Wilkins, 2004; 103–6
84 Whyte IM. Serotonin uptake inhibitors. In: Dart RC, ed. *Medical Toxicology*, 3rd edn. Baltimore: Lippincott Williams & Wilkins, 2004; 843–51