Neuroscience-based criteria for assessing serotonin-mediated effects of drugs: defining and predicting which drugs cause serotonin toxicity

Setting the record straight

There continues to be a great deal of confusion and misunderstanding concerning which drugs may be capable of precipitating serotonin toxicity (ST). This has been fuelled by lack of knowledge about pharmacology and particularly by over-extrapolation from unreliable case reports (many published by predatory journals and journals incapable of quality peer review —- to the extent that quality peer review still exists). There are myriad case reports of supposed ST by drugs that have no capacity to elevate 5-HT — that is a clear indication that case reports are generally misleading and best ignored, unless strongly supported by other data (cf. the emblematic methylene blue story [1-3]).

This commentary contains the table that I have compiled setting out the candidate drugs, and their properties (see below); these guide us in making confident judgements about what combinations are likely to have potential to dangerously elevate serotonin.

As I have discussed elsewhere, this is a consequential issue because much ill-informed comment has led to misconceived and misdirected patient-care decisions and considerable cost in delivery of sensible healthcare, as well as some fatalities — such decisions have been made as a result of inadequate knowledge of pharmacology exhibited by many authors (and not corrected by the refereeing process) and a widespread failure to understand **neuroscience-based nomenclature of drugs [4-8]**.

Indeed, the ill-informed comment includes several 'warnings' issued by drug regulatory authorities, both in the USA and Europe — see especially statements issued about 'setrons', 'tryptans', and methylene blue, all of which are beset by misunderstandings and errors of various sorts, some serious; I will not reference them all here, there are too many, but searches of the relevant agency websites will locate them readily. These misconceived warnings have clearly been formulated by people who are taking an unrealistically precautionary 'risk-averse' stance about these matters and who do not adequately understand toxicology, pharmacology, and drug interactions. Even more unfortunately, these **misguided warnings are replicated in the product information sheets and the electronic databases** that pharmacists and doctors rely on.

What matters, and why does it matter?

What matters is identifying those cases of ST that are likely to become severe and life-threatening. That is straightforward, because these are the cases that involve a combination of an MAOI and an SRI*. The signs in such cases — the harbingers of imminent danger of a fatal outcome — are increasing core body temperature (>39°C) and spontaneous sustained clonus, muscle rigidity — truncal rigidity causes impairment of respiration (> $PaCO_2$). That necessitates intubation/paralysis and active cooling.

*Incidentally, the research from HATS has demonstrated more than once that the history obtained about the drugs and the amounts taken in overdoses is generally quite accurate and usually obviates the need to do toxicology screening, which is expensive.

Why does it matter? It matters because cases involving drugs other than MAOIs, drugs posited, in many erroneous reports, to have SRI potency, or other serotonin-mediated effects, do not cause potentially fatal ST. Many drugs are reported (falsely) to cause 'SS' or 'ST', but they will not be, and cannot be, severe (at least, not as a result of ST). These cases only require observation and withdrawal of offending drugs, or just reduction of dosage, as described below.

Understanding and recognising this essential distinction will avoid a great deal of consternation, panic, and expensively misdirected care, some of which is unnecessarily invasive (and thus may add to risks, rather than reducing them). Indeed, Professor Isbister once said something to the effect of '[informed] masterly inactivity is usually all that is required'. If you study this commentary, you will be informed!

Confused terminology: 'serotonin syndrome' or 'serotonin toxicity'

When Professor Whyte and I first advocated the use of the term ST, to replace the previous term of SS, it was not only for semantic and nosological reasons. We were intending ST to delineate only those serious cases (MAOI+SRI) that engendered a risk of morbidity and potential fatality, as opposed to less serious adverse reactions and side-effects, which is all that most reports of 'SS' represent. Our attempt to draw a clear distinction between toxicity and side-effects appears to have been only partially successful because people frequently refer to 'mild toxicity' — that is oxymoronic. It is not unlike saying somebody is 'a little bit dead'.

In my view the HATS papers reporting 'ST' with approximately 15% of overdoses of SSRIs have confused this issue. Although the HATS team are clear these cases are not severe, never can be severe, never require 'ICU' care, and are different from the severe cases alluded to above, the fact that they use that terminology (ST) to describe those cases continues to confuse those readers who are less familiar with the subject. Professor Isbister has suggested '5-HT storm' or '5-HT crisis' to differentiate it from mild to moderate toxicity. I argue that toxicity, is toxicity, is toxicity*. Thus, we should stick to using that word in its proper 'OED' sense. If we introduce the term 'serotonin crisis', in no time at all people will be saying 'mild serotonin crisis'! It is like the common nonsensical usage of the term 'severe hypomania' which, etymologically speaking is 'severe not-severe mania'. Psychiatry has an appalling history of poorly defined and poorly applied terminology.

> * The words toxin and poison both carry the clear connotation (OED) of causing serious illness, serious harm, and death. That describes serotonin toxicity — therefore, it is not necessary to invent any other terminology.

Professor Isbister now leads the research group that is continuing the work of the HATS database, started back in the 1990s by Professor Whyte (now retired) — it is now referred to as the 'Clinical Toxicology Research Group' (Department of Clinical Toxicology and Pharmacology, Newcastle Mater Misericordiae Hospital and University of Newcastle, Australia).

In a review which summarises the views and experience of that expert group of toxicologists and pharmacologists Professor Isbister makes several key points [9].

> *1) Most patients with serotonin-related adverse effects can be treated simply by cessation of the suspected drug and symptomatic treatment*
>
> *2) more aggressive treatment of mild to moderate toxicity needs to be justified by clinical trials [which do not, and probably never will, exist]*
>
> *3) those with the most severe serotonin toxicity (usually MAOI + SRI*) clearly warrant a more active approach.*
>
> *4) Any suggestion for a specific treatment of serotonin toxicity (i.e. 5HT2A antagonist) must be preceded by considering the therapeutic goals of treatment.*
>
> *5) Isbister also states [9] that with such drugs which are 'highly unlikely to cause a generalized increase in serotonin it should be self-evident that the diagnosis of serotonin syndrome will become clinically meaningless if there is no requirement for excessive serotonin activity accompanied by specific signs of serotonin toxicity' [severe clonus, rigidity, and hyperthermia].*
>
> * MAOI plus MDMA might also be involved, but other combinations causing serious ST are almost unheard of.

The severity of ST manifestations primarily depends on the degree of elevation of intrasynaptic 5-HT*. **Therapeutic degrees** of elevation are **<10 times physiological levels***, thus resulting symptoms are better referred to as **'serotonin-mediated (side-)effects' (SM(S)Es).** By contrast, **severe or life-threatening ST results from elevations 100s to 1000s of times above physiological levels**** (requiring active intervention and intensive care admission due to rigidity and hyperthermia). Such levels, and effects, cannot be achieved by SRIs alone, even when taken in large overdoses, but only by combinations of drugs which act via different mechanisms, viz. MAOIs and SRIs.

> * note that physiological levels, often referred to as 'baseline' in reports, vary considerably and should be interpreted with a degree of latitude
>
> ** there may be some degree of variability in the susceptibility to get symptoms at various different degrees of elevation of serotonin, which could be partly genetic, but that is beyond the scope of this discussion and probably not of great clinical relevance.

The scientific foundations of our knowledge

Our basic science and pharmacological knowledge relevant to ST is derived from multiple converging lines of research:

(a) In vitro and in silico estimations of the effect of drugs on hSERT (and MAO, cf. MB and metaxalone)

(b) Experimental animal studies of several different sorts

(c) Observations in humans concerning the therapeutic effects; e.g., that clomipramine treats cataplexy and OCD—reflecting its hSERT affinity—but amitriptyline does not)

(d) Observations of SMEs in therapeutic use (e.g., amitriptyline does not cause retarded orgasm; clomipramine does)

(e) Whether single-drug overdoses cause SMEs; e.g., no for amitriptyline; yes for clomipramine and SSRIs

(f) Whether there are SM(S)Es or ST when these drugs are combined with an MAOI; e.g., no for amitriptyline; yes for clomipramine

(g) Whether the drug concerned has innate activity as a 5-HT2A antagonist, which reduces ST manifestations, e.g., clomipramine

These are the various measures by which proposed SMEs may be assessed and they are tabulated below to illustrate how different drugs 'score' according to these criteria. These data come from several different experimental methods and paradigms, and have been replicated many times, and are congruent. They must therefore be regarded as reliable. They correspond in the potencies and outcomes they indicate, thus they must be considered as infinitely more reliable than poorly informed, incomplete, and unreliable case reports. I should also add here that an overwhelming majority of the 'ST' reviews (>100, almost all unnecessary, unoriginal, and unedifying) and comments that have been published in the supposedly peer-reviewed literature take little or no notice of this mass of evidence from basic science research. In this way they are similar to RCTs, which exist in their own little bubble, divorced from basic science, mechanistic explanation, and causality. As I find myself repeating frequently, 'science is nothing without causality'.

Table: Neuroscience-based criteria for properties of drugs in relation to serotonin-mediated effects and toxicity

The columns in the table, (a) to (g), from left to right, represent the diverse types of data and are briefly elaborated:

(a) In vitro (and in silico) estimations of the effect of drugs on hSERT

This is the most important and relevant data, and probably gives the definitive initial guide as to whether the drug might be a clinically relevant SRI. 'In silico' refers to the computer-generated models of how drugs interact, which are now sufficiently sophisticated and accurate to give a useful indication about a drug's putative potency — for instance, that is how I established that metaxalone is likely to bne a clinically significant MAOI (Professor Yelekci in Turkey kindly ran the simulations for us).

(b) Experimental animal studies

Various kinds of studies are possible, including on isolated neural tissue and on living animals.

(c) Observations in humans concerning therapeutic effects in serotonin-infuenced illnesses

Viz. clomipramine treats cataplexy, OCD, and trichillomania, but amitriptyline and imipramine do not. Because manipulating serotonin has an important effect on these and other illnesses it is reasonable to infer that this reflects a difference in their actual ability to alter serotonin in humans with illness to a degree that alters symptoms

(d) Observations of serotonin-mediated side effects in therapeutic use

Amitriptyline does not cause retarded orgasm; clomipramine, and all SRIs, do. The same is true of other side-effects which are generally regarded as serotonin-mediated

(e) Whether overdoses cause serotonin-mediated effects or toxicity

Amitriptyline does not cause clonus or ST; clomipramine does cause clonus and moderate ST

(f) Whether there are serotonin-mediated effects, or toxicity, when combined with an MAOI

Amitriptyline, none; clomipramine, fatal ST

(g) Receptor antagonism

Strong evidence indicates 5-HT2A receptors are responsible for rigidity and hyperthermia which are the mechanisms underlying potentially fatality. It is also the case that patients who ingest overdoses which include drugs with potent 2A antagonism are less likely to exhibit toxicity [10] – further buttressing the conclusion that these receptors are central to those potentially fatal effects.

	a	b	c	d	e	f	g
Drug	**hSERT Ki[c]**	5HT animal studies	Therap-eutic SEs	Therap-eutic effects	Overdose effects	Combined with MAOI	Post-synaptic 2A antagonism
CMI	**0.1**	+++	++	+++	+[a]	+++	++
IMI	**10**	++	+	+	**0**	+++	+
AMI	**20**	**0**	**0**	**0**	**0**	**0**	++
NTP	**100**	**0**	**0**	**0**	**0**	**0**	++
Other TCAs	**>50**	**0**	**0**	**0**	**0**	**0**	+/++
SSRIs	**<10[d]**	**0**	++	+++	++	+++	**0**
SNRIs	**<10**	++	++	++	++	+++	**0**
Venlafxine[g]	**7-80**	+	+	++	++	+++	**0**
Mirt/Mian	**>10,000**	**0**	**0**	**0**	**0**	**0**	+++
Traz/nef	**>10,000** [R2]	**0**	**0**	**0**	**0**	**0**	++
Lithium	**>10,000**	**0**	**0**	+	**0**	+	**0**
L-TP	**500**	+	+	+	-	+	**0**
Busp	-	**0**	**0**	**0**	**0**	**0**	**0**
Pethidine	**100**	+	**0**	**0**	**0**	++	**0**
Dextrometh	**20**					+	-
Methadone	**14**					**0/+**	**0**
Tramadol	**500**					++	-
Oxycod etc.	**>100,000**	**0**	**0**	**0**	**0**	**0**	**0**
Fent	**70,000**	**0**	**0**	**0**	**0**	**0**	**0**
Buprenorph	**>100,000**	**0**	**0**	**0**	**0**	**0**	**0**
Morph	**78,000**	**0**	**0**	**0**	**0**	**0**	**0**
Setrons	**>100,000**[R]	**0**	**0**	**0**	**0**	**0**	**0**
APs, typical[b]	**>10,000**	**0**	**0**	**0**	**0**	**0**[a]	+/++
Atyp, Zip	**53 (rat)**	-	-	-	**0**	++	+
Drug	**hSERT Ki**	ST animal studies	therap eutic SEs	Therapeut ic effects	Single-drug overdose	Combined with MAOI	Receptor effects
Atyp APs[b]	**>10,000**	**0**	**0**	**0**	**0**	**0**[a]	+++[b]
Classic MAOIs	**>10,000**	+	+	++	++	**N/A**	**0**

MOC (RIMA)	**>10,000**	**+**	**+**	**+**	**0**	**N/A**	**0**
MAOI, metaxalone[d]	**-**					**N/A**	**0**
MAOI, MB	**-**	**+**				**N/A**	**0**
MAO-B[e] Rasagiline, selegiline	**>10,000**	**0**	**0**	**0**	**0**	**N/A**	**0**
MAOI, Linezolid, tedizolid	**0**	**0**	**0**	**0**	**0**	**0/+**	**0**
MDMA	**-**	**++**	**-**	**-**	**++**	**+++**	**0**
LSD	**-**	**0**		**0**	**0**	**0**	**Lig dir Sig[f]**
Psilocibin (psilocin)	**-**					**0**	**Lig dir Sig[f]**

Legend & notes

+/++/+++ weak/medium/strong; no/little/definite effect

- Indicates no data available

a) Those drugs with 5-HT2A antagonistic activity, in the single digit nanomolar range, reduce ST. Thus, for instance CMI induces only modest ST symptoms in overdose and significantly less frequently than SRI drugs. Likewise, combined overdoses of SSRI with an antipsychotic that has substantial 5-HT2A antagonist potency show a lower incidence of ST compared to single drug overdoses with SRIs.

b) Many typical and atypical antipsychotics are medium/strong 2A antagonists

c) most hSERT data is taken from the PDSP database

d) metaxalone, when taken in overdose appears to be capable of interacting with SRIs to cause severe ST and in this respect is similar to moclobemide (the same applies to Linezolid)

e) selective MAOB inhibitors do not cause ST when combined with SRIs

f) Although these are potent 5-HT2A agonists they do not appear to provoke hyperthermia or ST symptoms, which may reflect the phenomenon of ligand directed signalling

(g) Note the unusually large variation in results from affinity studies, and it's rather low affinity at the NAT (~2000, PDSP data)). There are several measures which suggest the drug is more than just an SNRI. It has noticeably greater withdrawal effects than all of the similar drugs and is structurally closely related to tramadol. It seems to have a slightly greater propensity to trigger ST and has even been reported to cause ST in combination with amphetamines [11]. It is also more toxic in overdose by itself than any other similar antidepressant. These facts have made me wary of this drug, despite these potential difficulties it has for years been the most popular SNRI. That exemplifies the irrationality of clinical psychiatry!

Affinity data are valuable, but must not be over-interpreted. Values from different laboratories routinely vary by a factor of 10, and sometimes more, e.g. see (g). Comparison of one set of data to another is therefore to be interpreted with caution, unless the differences are large and the inferences drawn from them are congruent with other data. It is more accurate to compare the ratio of potency at one receptor versus another, e.g. hSERT versus 5-HT2A, within the same set of data, and those ratios are more precisely comparable when

compared with similar ratios from a different laboratory, whereas the absolute K_i values between different laboratories are less precisely comparable.

Note that hSERT values of other types or classes of drugs cannot be compared directly with TCAs for various reasons, e.g., unknown tissue concentrations in the brain.

Case reports presuming to describe SS or ST are highly unreliable, as evidenced by the fact that many drugs with no significant capacity to elevate 5-HT have generated hundreds of spurious reports; examples are trazodone, nefazodone, mirtazapine, olanzapine (and other SGAs), setrons, and triptans [12]. More recently, second-generation antipsychotics (SGAs) have been claimed to be associated with ST by, among others, Racz et al. [13], who erroneously stated that 'SGAs may induce SS', but there are no credible case reports (bar ziprasidone)— most SGAs are 5-HT2A antagonists, which have been clearly demonstrated to reduce the propensity for ST [14].

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