Abstract

This introductory commentary outlines this complex topic: the features of the condition, the drugs that are capable of inducing it (with a *genuinely* evidence-based table), the patho-physiology and medical management. The spectrum concept and the features associated with increasing degrees of severity are delineated with figures illustrating how, and to what extent, drugs capable of elevating serotonin via several different mechanisms may interact.

Preface

Even now, in 2021, more than three decades after key research and reviews that demonstrated the essentials of the interactions relevant to serotonin toxicity, there remains a great deal of misinformation and misunderstanding both in medical and non-medical texts. The latest dreadful example of misinformed writing from persons of minimal knowledge or experience (a supposed 'meta-analysis' of the last decades-worth of case reports) (1) illustrates the low-point in medical publishing that has been reached (2) and the poor refereeing standards now prevalent. For detailed comment on Werneke et al. see: Update on recent case reports of ST Such lack of knowledge and misunderstanding are reflected in advice and warnings concerning ST issued by 'official' agencies such as the World Health Organisation (WHO), the American FDA, the UK MHRA, Health Canada and the Australian TGA: their comments and advice have frequently been incorrect and misinformed. See, for detailed comment on the FDA, TGA etc. Serotonin Toxicity (Serotonin Syndrome) with 5-HT3 antagonists If you thinking 'who is this, who thinks his opinion is superior to the FDA?' the trite answer is, I am a widely recognized world expert on the topic. But suspend your judgment, read on, and learn the facts. I am not alone in my views or criticisms.

Most recently my criticisms have been reinforced by several Australian toxicologists, all professors, and all associated with the group here in Australia who have produced most of the quality prospectively gathered data relating to this subject (3-9). Indeed, these eminent Australian toxicologists recently stated (2014) in the British Medical Journal that:

> product information is a major impediment to sensible decision support in this area (4)

Product information is dictated largely by medico-legal defensiveness and the regulatory agencies, not practicing clinicians. The complex topic of ST requires an understanding of many aspects of medical science, including methodology and logic and especially pharmacology, drug interactions and toxicology. Evidently, not all commentators and writers have such an understanding.

Many of the publications about serotonin toxicity are published by younger and less experienced Doctors eager to get a few 'runs on the board' by publishing something. Unfortunately, in the last few years, there has been a burgeoning of the number of journals devoted to publishing case reports (from < 10 on 2005 to nearly 200 in 2016, see Akers (2)), most on an "author pays" publishing model, accompanied by little or no refereeing.

All but the most sophisticated of readers or researchers are probably unaware of this and how it has negatively affected the overall quality of medical publishing

Medical science has been seriously degraded in an insidious manner. To ascribe the same value to what non-experts write in such publications, as one should ascribe to the writings of experts, such as the professors referenced above, is mistaken and is wasteful of ones' intellectual energy. However, general readers are not usually able to assess the expertise and experience of the authors of

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published papers, or the quality of refereeing and cannot factor that into an assessment of a papers' possible value.

Caveat lector!

Recommended Recent Reviews

Enough of negatives. The following reviews are recommended.

1) Buckley et al. (3, 4). The authors of this paper are experienced toxicologists with special knowledge of serotonin toxicity. It does not get much better than this.

2) Gillman, 2011 (10). This is a review paper in which I set out the current understanding of ST which allows us to make accurate predictions about the properties of drugs. It summarises in diagrammatic form the severity of serotonin-mediated symptoms caused by therapeutic doses, and overdoses, of the various different drugs, and the interactions between them, that are capable of affecting the system to a clinically significant extent in humans. This paper draws on data provided by Prof Whyte from the 'HATS' database.

3) Gillman 2009 (11). Above I have alluded to the various misleading warnings about ST issued by the WHO, the FDA etc. implicating a range of different drugs. This paper is a detailed analysis of why their warning about the dangers of triptans is mistaken.

I have published similar papers about opioids (12), mirtazapine (13) etc. and I could write similar papers about several other drugs, but life is short, and I have other things I wish to do in my retirement.

4) Whyte, Buckley, Isbister, Dawson et al. (7-9, 14-16): Prof Whyte's group and other Australian toxicologists have done the lion's share of original research in this area. Any serious student will benefit from reading *all* their papers. These authors are experienced toxicologists who look after patients with ST and neuroleptic malignant syndrome etc. when they are sufficiently severe to be admitted to hospital.

5) Boyer 2005 (17): this is a good paper with useful pictures and diagrams, which draws extensively on Prof Whyte's, and my, work. The table of drugs causing serotonin toxicity is a little less reliable, for instance, it includes nefazodone: note that Boyer et al. agree (with Prof Whyte and me), that usually NMS and ST are clearly distinguishable, and not similar and easy to confuse, as is tediously and frequently repeated.

6) Gillman (12, 13, 18-24): I have published various other reviews on and around the subject of ST, particularly concerning the pharmacology and interactions of the main protagonist drugs, the '*dramatis personae*' as it were. Despite the clear evidence that mirtazapine is not an SRI, which I set out in this review (13) it is still stated to be a 'serotonergic' drug by most writers. Remember Santayana (25):

> 'Progress, far from consisting in change, depends on retentiveness. ...
> Those who cannot remember the past are condemned to repeat it'

Read also 'History and Risk' (26). That paper is a reminder of how psychiatry misunderstood these reactions for decades, despite clear evidence from the basic science literature. Students of history will not be surprised to learn that many writers continue to make these same mistakes today. The enduring confusion concerning TCAs is a case in point, with some writers still stating that *all* TCAs are contraindicated with MAOIs, whilst others, particularly on the European continent, contend that imipramine is safe.

7) Sternbach (27): this seminal paper was the first to attempt to describe and define (human) ST. It relied on case reports and was therefore only an initial step in delineating the problem. Its pharmacological basis was shaky. It is now of

mainly historical interest rather than being of scientific or clinical use or relevance. In my opinion this paper should now only be cited in the context of the history of serotonin syndrome. It no longer has clinical or pharmacological value.

Definition and Occurrence

ST can only occur after the ingestion of drugs that *substantially* increase brain serotonin levels. There is no other disease or a natural cause for this constellation of signs and symptoms. It is *poisoning* caused by drugs that have serotonin-mediated effects, so-called 'serotonergic' agents. The typical side effects caused by usual therapeutic doses of the SSRIs, which are the most widely known and used serotonin-elevating drugs, increase with increasing dose (7, 10, 21, 28). There is variation between individuals in the susceptibility to various typical side effects, and the actual blood level (and therefore 'end-effect') goes up more rapidly with some drugs than with others as the dose is increased. This is because some drugs have 'non-linear' pharmacokinetics (they inhibit their own metabolism, their blood level increases out of proportion to the increase in dose — not a desirable characteristic). NB. The notion of what constitutes side effects (especially for SSRIs) is 'context-dependant', because the effects being referred to are an inevitable consequence of the drugs main intended mechanism of action, i.e., reuptake inhibition of serotonin, resulting in increased intra-synaptic serotonin levels. These inevitably cause, for instance, tremor, diarrhoea, retarded orgasm etc. Whether retarded orgasm is regarded as a side-effect or a benefit depends on degree, gender and what effect was sought. The general pattern is that side effects gradually become worse with increasing dose, and some may reach a degree of severity which justifies calling them toxic effects. The meaning of the word toxicity is 'poisoning', and poisoning insinuates life threatening severity. If we are being precise and logical the term ST should be reserved for those cases where hospital admission and medical intervention is mandated. There will sometimes be dispute about whether a given clinical case is most appropriately described as 'severe' or 'atypical' side effects, or as 'toxic' effects. The most relevant and objective criterion of severe ST is body temperature. Excessively elevated temperature, hyperthermia, is the main change that mediates the severe life-threatening effects of ST ('pyrexia' refers to infection-mediated temperature elevation which is different — the terms pyrexia or hyperpyrexia and hyperthermia are *not* interchangeable). If core body temperature exceeds 39-40°c it is generally referred to as hyperthermia (NB the definition and use of this term is imprecise, see (29)). Regrettably, for such a categorical physical quantity, temperature is frequently not measured accurately and reliably. A separate commentary contains detailed comment about the unreliability of, for instance, aural temperature measurement devices.

Understanding Medical Management

A key goal of medical management is to predict those small proportion of cases that may become sufficiently severe to necessitate decisive active intervention (intensive supportive care, active cooling and drugs).

> It is now beyond reasonable argument that the degree of ST exhibited in experimental animals, given combinations of drugs that elevate serotonin levels, gradually increases, eventually causing hyperthermia and death as a result: this is a 'dose-related' phenomenon

When pharmacologists say 'dose-related' what they mean that it is related to the end effect of the drug. In human beings there are intervening variables relating to metabolism that cause large variations in the actual level of the drug at the

sight of action. This means that the direct relationship between dose and effect is less precise than it is in inbred laboratory (i.e., genetically similar) animals. Serotonin toxicity illustrates this point further because there are (usually) cumulative effects caused by the interaction of two drugs, *with different mechanisms of action*, producing an effect which is much larger than either individual drug can produce by itself. For these reasons the term 'dose-effect' relationship needs to be understood as the cumulative effect of all drugs taken on the relevant measure, which in this case is the intra-synaptic serotonin level (see figure STT below).

It is also now clearly established that drugs that block 5-HT2A post-synaptic receptors prevent deaths from hyperthermia in animals and almost certainly do the same in Humans

Although it is frequently suggested that 5-HT1A receptors may be important for mediation of ST, 1A antagonists (blockers) have little effect, possibly making ST a little worse, not better. This leads to the conclusion that the important consequences of ST are mediated by 2A receptors. That conclusion is cemented by the confirmatory animal experimental evidence. If this were more widely known and appreciated some of the recently reported deaths and serious cases may have been avoided by more timely use of 5-HT2A antagonists viz. chlorpromazine (7, 19) and cyproheptadine (e.g., see (30)). Recent papers, particularly those from Professor Whyte's HATS research group and associates, have now clearly established the typical clinical picture, the diagnostic features, and also validated clear research diagnostic decision rules for serotonin toxicity (7, 9, 16, 31-34).

It is important to understand that diagnostic decision rules cannot replace clinical experience and judgment

There are many case reports which have applied these rules without sufficient understanding of what constitutes a 'serotonergic' drug and what constitutes significant signs and symptoms, especially clonus. Indeed, many reports appear to confuse clonus with myoclonus. There is no substitute for clinical experience and an understanding of the time-course of progression of the signs and symptoms. It is often stated that serotonin toxicity is difficult to diagnose and has no clear diagnostic features: that is wrong. One of the main reasons for using the term ST, not serotonin syndrome, is because this clarifies that it is a form of poisoning, as Lithium toxicity is a form of poisoning. It not an idiosyncratic syndrome: a syndrome is often understood to imply something that occurs in some people, but not in others. Neuroleptic malignant syndrome is such a condition, it is idiosyncratic and rarely occurs after an over-dose of neuroleptics: it occurs in a small proportion of patients who are taking therapeutic doses. No-one would suggest using the term 'lithium syndrome', why the term 'serotonin syndrome' persists is hard to see.

ST & NMS

It is often stated that ST & NMS are similar and that it is hard to distinguish between: that is wrong.

NMS is different to ST (26, 29, 35, 36). The usefulness of conceptualising the condition as ST, not SS, is made evident in a variety of ways. For instance, consider the frequent comment one sees that 'serotonin syndrome is rare….' and now the statement 'poisoning is rare': it is true that poisoning is rare, except in those who take poisons. However, neither statement is more helpful, nor more revealing than saying 'it never rains if the sky is blue'. This point is consonant with Bayesian theory: this states that the probability of an 'experiment' cannot be properly calculated without factoring in our estimate of the prior probability. If you feel something like rain falling on you when the sky is clear and blue 'natural

common sense' (a form of Bayesian reasoning) tells you it may be your neighbour with an over exuberant garden sprinkler, not a miracle. This important logical principle was emphasised more recently by the astronomer Carl Sagan as, 'extraordinary claims require extraordinary evidence'. This line of thought originates from the Scottish philosopher David Hume (1711-1776) who launched an effective critique of miraculous claims. This sceptical rationalism was (and still is) a major challenge to religious belief (37, 38). Those who enjoy a good chortle might care to read the splendid essay on miracles by Darwin's cousin, Sir Francis Galton (the extraordinary Victorian polymath) on the effect of prayers on missionary ships vs. merchant ships: see http://galton.org/essays/1870-1879/galton-1872-fortnightly-review-efficacy-prayer.html

It is difficult to suffer from poisoning if you have not taken a poison. Therefore, an important piece of information for doctors to know if they are dealing with a possible case of ST is: what drugs have been ingested? The ingested drugs determine the form of poisoning and large enough doses will produce poisoning in all people, even if there is some inter-individual variation in susceptibility. This is what has led to the first diagnostic decision rule from the HATS data which is: a definite prediction of impending ST can be confidently made if, but only if, a **known** potently serotonergic drug has been ingested and the single physical sign of clonus is present. See link for discussion on how to elicit and assess clonus:

Conversely one can state that if an overdose of a mixture of MAOIs and SSRIs is known to have been ingested there is a high probability of life-threatening ST: even if the patient currently appears symptom-free, one would be well-advised to observe them in an intensive care unit.

In order to understand the complexities of this issue it is necessary first to remember that ST is mediated by an increase in the level of serotonin in synapses in the central nervous system, which then excessively stimulates all types of serotonin receptors. Because there are several types of drugs with different mechanisms of action, each of which can increase serotonin levels to differing degrees, there is a characteristic degree of severity of serotonin-mediated effects, or toxicity, associated with each type of drug when taken by itself, either in normal therapeutic doses, or in over-dose (21). For instance, over-doses of selective serotonin reuptake inhibitors (SSRIs) alone do not produce dangerous toxicity or temperatures in excess of 38.5°C; however, an overdose of an MAOI like tranylcypromine-alone will produce hyperthermia, and even death, but over-dose of the RIMA moclobemide does nothing. This demonstrates that the maximum elevation of serotonin produced by these mechanisms is significantly different, being greater with the old irreversible MAOIs (see figure ST triangle below and ref. (10). NB Because serotonin is unable to cross the blood brain barrier conditions such as carcinoid syndrome that involve considerable increases in peripheral serotonin do not cause CNS symptoms. The bodies capacity to break down serotonin is sufficiently rapid that it seems to be difficult to raise levels sufficiently high to cause death (from serotonin toxicity) by taking only one type of drug (e.g., MDMA, ecstasy (3,4-methylenedioxymethamphetamine)). It is almost always the case that serious toxicity and death is associated with combining two different types of drugs with a different mechanism of action. The great majority of human fatalities have been associated with a combination of MAOIs and (S)SRIs. About the only other combination capable of causing fatalities is MAOIs with serotonin releasers ('indirect agonists') e.g., MDMA (but not methylphenidate) (39-41). Over-doses of SSRIs-alone cause a marked increase in serotonin-mediated side effects which, in about 15 per cent of typical over-dose cases, leads to a degree of symptoms sufficient to cross an arbitrary threshold of severity which is now commonly referred to as ST. It is more helpful to understand that there is a gradually increasing degree of severity of serotonin-mediated effects, which, at some point on the severity spectrum, it is appropriate to call 'toxicity': the spectrum concept.

The Spectrum Concept

One important reason for trying to understand this is because some patients die. The question is, can we predict which patients are likely to die without treatment? The answer is unequivocally yes, as a result of the information and concepts above. We know that even large over-doses of SSRIs-alone rarely or never cause life threatening ST. The dramatic illustration of the usefulness of the 'dose-effect' idea (the spectrum concept) is contained in the story of methylene blue (MB).

In 2006 I noticed that there were several reports that appeared to be severe serotonin toxicity following surgery for parathyroid conditions (42, 43). It was soon apparent that it was only patients who had previously been taking SRIs who were getting this reaction. The only common link in terms of drugs was methylene blue, this suggested that it must be a monoamine oxidase inhibitor, although this had not previously been recognised, despite the fact that it has been in use for 50 years. I initiated research that provided strong evidence that this was indeed the case (24, 44, 45): other details are contained in the MB commentaries [see left-hand menu]. Similar reasoning led to the identification of metaxalone as a weak MAOI, see: https://psychotropical.com/metaxalone-skelaxin-potential-serotonin-toxicity/

Diagnostic Features

- ST has now been clearly characterized as a triad of neuro-excitatory features. 1) Neuromuscular hyperactivity (hyperkinesia, the opposite of NMS which shows bradykinesia); tremor, clonus, hyperreflexia, and (in the advanced severe stage) pyramidal rigidity.
- 2) Autonomic hyperactivity; diaphoresis, hyperthermia, tachycardia and tachypnoea.
- 3) Altered mental status; characterised by 'over-arousal' typified by agitation, excitement, 'mania' and (usually only in the advanced stage) confusion.

Professor Whyte's group have applied decision tree rules (CART) to their large data set and shown that only the symptoms of clonus (inducible, spontaneous or ocular), agitation, diaphoresis, tremor and hyperreflexia are needed for accurate diagnosis of serotonin toxicity. Their diagnostic rules are in their various papers, in my opinion these are the key ones (4, 7, 9, 16, 20, 32, 34, 46-48).

They demonstrate, for instance, that if in the presence of a drug known to produce potent serotonin-mediated effects (see table for what is a clinically relevant drugs), the sole sign of spontaneous clonus is present, then ST may be reliably diagnosed. Clinically, the onset of toxicity is usually rapid, because it results from drug combinations and starts when the second drug reaches effective blood levels. The clinical picture is often alarming and rapidly progressive after the first or second dose of the second serotonergic drug in the patient's regime. The patient is often alert, with tremor and hyperreflexia. Ankle clonus is usually demonstrable, progressing to generalised repetitive spontaneous clonus.

Neuromuscular signs are initially greater in the lower limbs, then become more generalized as toxicity increases. Patients may exhibit pronounced tremors. Other symptoms may include shaking, shivering often including chattering of the teeth and sometimes trismus. Pyramidal rigidity is a late development in severe cases, and when it affects truncal muscles, the rigidity impairs respiration. Rigidity, increasing PaCO2, and a temperature of >38.5ºC heralds life-threatening toxicity (14, 17).

Diagnostic decision rules cannot replace clinical experience and judgment. There is no substitute for clinical experience and an understanding of pharmacology and the time-course of progression of symptoms

The above information indicates that it is important to have an accurate validated list of drugs that possess significant clinical potency for elevating serotonin in humans. A definitive table of the relevant drugs is below, the justification for why particular drugs are included, or excluded, is based on *in vitro* HCR data, *in silico* data, animal experiments and human toxicology data. Understanding it requires extensive and detailed study (see my published papers and other commentaries). Many published tables of 'serotonergic' drugs contain errors and misinformation. The term 'serotonergic' is generally misused because, strictly speaking, it means a drug affecting the serotonin system, which may therefore be either pro- or anti- serotonergic. That is why I try to use the terms 'serotonin-mediated', and 'serotonin-elevating' in preference.

Drugs with clinically relevant serotonin-elevating effects

Serotonin reuptake inhibitors (selective and non-selective)

Paroxetine sertraline fluoxetine fluvoxamine (es)citalopram and vortioxetine, vilazodone

. (des)venlafaxine (levo)milnacipran duloxetine sibutramine. clomipramine imipramine (but not other TCAs).

Tramadol pethidine dextromethorphan dextropropoxyphene pentazocine, (we can now be confident fentanil (and congeners) are not significant elevators of serotonin). Chlorpheniramine brompheniramine (but not other anti-histamines). Ziprasidone (an anti-psychotic with some SRI action)

Serotonin releasers

MDMA (not Methylphenidate), fenfluramine (withdrawn)

Monoamine oxidase inhibitors Tranylcypromine phenelzine isocarboxazid (nialamid, iproniazid generally unavailable, isoniazid is too weak as MAOI) MAO-B selective drugs do not precipitate ST: viz. selegiline, rasagiline ladostigil

MAO-A selective drugs do ppt. ST methylene blue, clorgyline Moclobemide (befloxatone & toloxatone, if re-introduced)

Weak MAOIs: possibly rarely a risk with high/IV dosing: linezolid, metaxalone (not furazolidone or procarbazine).

Table notes

Although clomipramine and imipramine do precipitate ST, none of the other TCAs are able to because they are too weak as SRIs. Trazodone, nefazodone, mianserin, mirtazapine are not significant SRIs. Fatalities from ST involving opioids have been with pethidine, tramadol and dextromethorphan, but not fentanil. Methylphenidate is not a serotonin releaser. See other commentaries for detailed information about other drugs of interest.

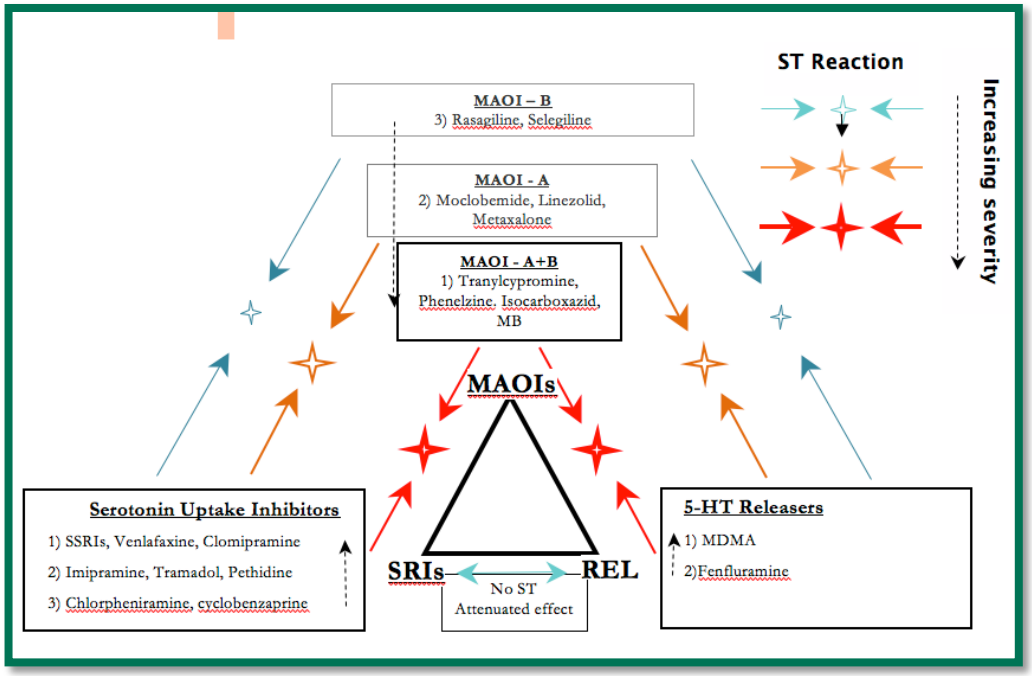

Figure 1: The Serotonin Toxicity Triangle STT

The figure illustrates the severity of drug interactions between the three important classes of drugs that precipitate ST: MAOIs, SRIs, and 'releasers' like MDMA, as represented by the small centre triangle, the corners of which represent the three classes. ST is a concentration related phenomenon that increases with dose (and mixtures of different types of serotonergic drugs), Each class of drug has a maximum level to which it can elevate 5-HT. Numbers in boxes indicate potency: e.g. 1) Tranylcypromine, Phenelzine 2) Methylene Blue, 3) RIMAs, indicates that, in a given situation, TCP is a more potent precipitator of ST than is a RIMA *amphetamines: serious reactions and deaths do occur from hypertension, but probably not from ST, because they are DA releasers much more than 5-HT releasers.

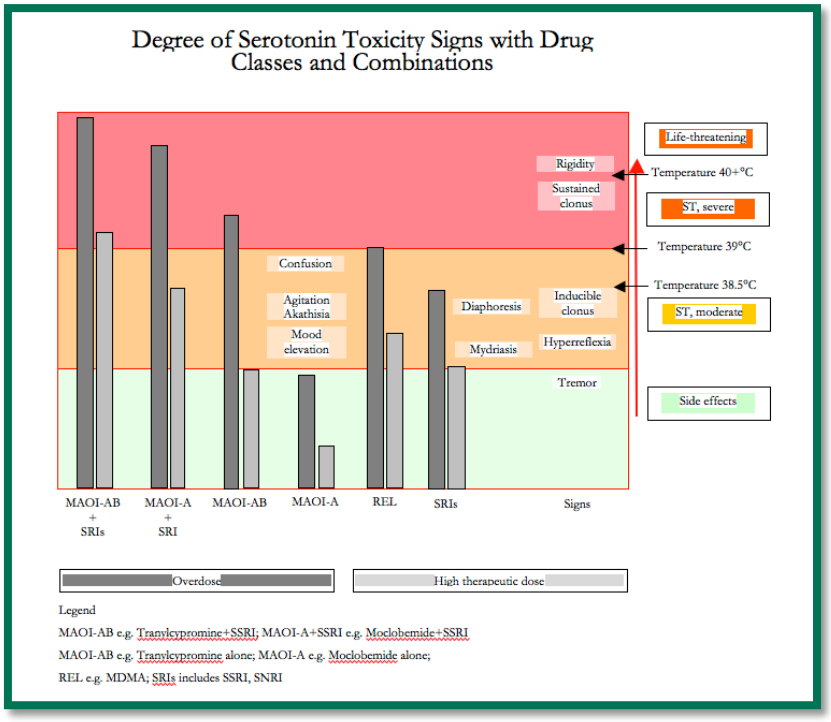

Figure 2 Degree of Serotonin Toxicity Typical with Drug Classes

The bars depict 'overdose' and 'high therapeutic dose', which reflects the full effect of the drug as used for refractory illness. MAO-AB = non-selective irreversible inhibitors e.g. tranylcypromine and phenelzine; MAO-A = moclobemide; REL = 5-HT releasers like MDMA (the only one in therapeutic use, fenfluramine, has been withdrawn); SRI = all serotonin reuptake inhibitors, selective and non-selective and SNRIs. Amphetamine is a releaser, but mainly of dopamine more than 5-HT. The typical sequence of signs at their approximate initial appearance is shown. Note the clear 'ceiling' effects: e.g. SRIs alone rarely or never induce severe signs or temperatures of > 38.5°C Moclobemide overdose does not induce ST of even moderate degree, mirtazapine has no serotonergic side effects, and no serotonergic toxicity.

The data on which this figure is based were checked and verified with the signs documented in the HATS database of thousands of overdoses (last checked March 2012), with the assistance of Professor Ian Whyte.

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