Update on recent case reports and reviews of serotonin toxicity

Abstract

In the last few decades experimental pharmacology, animal models, *in vitro* HCR receptor assays, *in silico* computer modelling, and detailed prospective studies in clinical toxicology, have all provided a comprehensive model of human serotonin toxicity (ST). This has enabled accurate predictions about the mechanism of action and the potency of various drugs with serotonin-mediated actions. The striking examples of this are the proof of the predicted MAOI activity of methylthioninium (methylene blue) and metaxalone. Continued publication, and analysis, of cases reports, that are usually of poor observational quality, completeness, and reliability is most unlikely to produce useful new knowledge; instead, it is producing confusion of the facts and issues for doctors by introducing spurious data. Recent examples of factually incorrect and misleading papers include (*inter tot alia*) Werneke et al., and reviews using data from the FDA FAERS system. These illustrate the chaos that can ensue from poor quality data, ignorance, and misapplied analyses. Werneke's summary of yet more published case reports from the last ten years highlights these serious problems, especially because it unjustifiably presents itself as a meta-analysis. Such misunderstanding has lessons for regulatory agencies, such as the FDA, that have issued several incorrect and misconceived warnings about ST that mirror the ignorance, misunderstandings, and poor scholarship encapsulated in the Werneke meta-analysis. There are also lessons for medical publishing because commercial considerations have facilitated this tsunami of poorly written and poorly refereed publications, which are obscuring that which is good and filling computerised drug interaction software with misinformation, which is being blindly followed by those who are insufficiently educated in science and pharmacology.

Introduction and background

I have long reasoned that the continued publication of case reports of supposed serotonin toxicity (ST — aka serotonin syndrome), is almost certain to be scientifically valueless [1]. This is because the reliability and information content of case reports is low compared to the validated and replicated data that we already have, and the firm scientific foundation on which that is based. I had been considering the task of updating my comments about case reports to confirm the above view — things seem to have become even worse since my reviews and editorial 10 years ago [1]. Then in July 2016 this so-called meta-analysis of case reports by Werneke et al. [2] appeared (one of the co-authors, Taylor, is an eminent professor at the Maudsley). It is an abysmal paper; it is astonishing that a professor at the Maudsley has put his name into it — *O tempora, o mores*!

The full quotation is even more apposite!

> *O tempora, o mores! Senatus haec intellegit, consul videt; hic tamen vivit. Vivit!*

Which can be translated as: Shame on our times and on our principles! The senate is aware of these things; the consuls see them; and yet this man lives. He lives!

Nevertheless, it has done the work of collating recent case reports for me and saved me the tedium of trawling through them — I confess I have ceased to 'log' the ST reports in my bibliography database for the last few years because it became such an unproductive use of time and energy.

Address for correspondence: ken.psychotropical@gmail.com
Website: https://psychotropical.com

The continuing stream of poor papers is also dispiriting — some good work has been published **(see here for a list of recommended papers),** but the good work has become lost in the tsunami of mediocrity; that is demonstrated by the fact that many of the poor papers have subsequently been cited more often than the seminal papers in the **field**[*]. That is the disaster of modern science publishing: thus, the good papers have a diminished effect on the collective knowledge-level and understanding, as evinced by the continuing misinformation and poor quality in case reports.

The other recent reviews noted below also reflect these problems.

The Werneke et al. 'meta-analysis' (it is a loose use of the word to call this a meta-analysis) seeks to use more recent case reports (2004 to 2014) to 'challenge' the 'textbook knowledge' about ST (more on their misuse of words below). However, this exercise merely demonstrates that applying 'meta-analysis' to case reports, all of which are of low observational quality, simply compounds the errors, of which there are many.

Bad data cannot negate good data. Or to put it more quaintly, like the country folk where I grew up, 'you cannot make a silk purse out of a sow's ear.'

Even properly done meta-analysis is not capable of transmuting base lead into gold. If everyone was adequately educated in the scientific method that would be the end of this discussion. Evidently they are not, and it isn't.

My concise advice to readers is do not waste your time reading the Werneke 'meta-analysis' — you will not learn anything useful from it: rather, you will be mis-informed and confused. Instead, read this excellent recent update on ST by a group of informed and experienced toxicologists [3], pdf is here, and the other recommended papers.

Other recent reviews

Racz et al. have used 'bioinformatics tools' (what a pathetic piece of meaningless jargon) to cover mechanisms and interactions producing ST with farci-tragical results [4]. They state, '*Bioinformatics tools can be used to detect drugs, drug pairs, and targets associated with adverse events.*' Perhaps they can detect ghosts as well. This paper is useless nonsense. They say:

> This study demonstrated that informatics tools and analyses can quickly identify drugs, targets, drug–drug interactions, and mechanisms that may be associated with adverse events. Computational analysis performed with FAERS and supporting pharmacokinetic data from the literature and case studies **show that second-generation antipsychotics are associated with serotonin syndrome**.

If the FAERS system data tell them that drugs (so-called 'second-generation antipsychotics') that are mostly 5-HT2A antagonists (which treat the symptoms of serotonin toxicity!) are associated with ST, then that tells us that FAERs data are useless and that their assumptions and methods are incorrect. The one drug that is definitely capable of causing severe ST (in combination with MAOIs) is Ziprasidone — which has significant SRI potency.

They have conspicuously failed to detect that signal. They could hardly have got it more wrong.

Culbertson et al. [5] adopt a not dissimilar approach, again utilizing the poor quality FAERS data, with equally uninformative results: they too produce impressive jargon:

[*] Poor refereeing and failure to check references is the main cause.

> … Serotonergic Expanded Bioactivity Matrix (SEBM) employing a molecular bioinformatics, poly-pharmacologic approach for assessing the participation of individual 5-HT drugs in serotonin syndrome (SS) reports. The SEBM model suggests a possible poly-pharmacologic role in SS. Although further research is needed, off-target receptor activity may help explain differences in severity of toxicity and clinical presentation.

I detect a distinct rising aroma of bovine ordure.

Note that both these fancy sounding approaches conspicuously failed to identify the two drugs that have emerged in the last decade as being capable (in combination) of inducing serious or fatal serotonin toxicity, namely ziprasidone and metaxalone.

Other reviews (e.g. Uddin et al. [6] repeat the usual errors and seem oblivious of what has been learned from many different scientific disciplines in the last 20 years [6, 7].

More reviews 2021

Prakash et al. have just reviewed (2021) published cases of fatal 'serotonin syndrome' between1982 and 2020 [8]. They identified 56 deaths. In reviews such as this there is difficulty in assigning the diagnosis correctly due to the quality and incompleteness of the data in many cases — many experts would disagree with their diagnosis of ST in some of these cases, and there are clearly others in the literature (e.g. in my database [9-16] which are just as likely to be ST which are not included in their review, because their search strategy inevitably missed a number of cases. Obviously, of all the serious cases that were considered a sufficiently high risk of mortality to require treatment in 'intensive care units' they have only looked at fatal cases — fatal outcome may reflect the care given, rather than the severity of the condition itself. Some of their cases probably did not die of serotonin toxicity, but of some other cause. Also, these were only the reported deaths, not all deaths, and are probably inherently atypical because they were considered sufficiently interesting or unusual to warrant reporting in the literature. Since we already know a lot about this condition it is difficult to see how this atypical and selected cohort of deaths is likely to add anything much to our knowledge. Indeed, it does not. But it does perpetuate some inaccuracies and misconceptions.

When so much good work has been done, it is dispiriting to see how little it has achieved in raising standards of knowledge or understanding.

Optimistic note

I can now inject a more optimistic note by drawing attention to another excellent review by members of the Hunter group, in this case Professor Nick Buckley who is now in Sydney — these reviews are ones that should be read by anyone interested in ST, especially, special *The serotonin toxidrome: shortfalls of current diagnostic criteria for related syndromes* [17, 18].

They also draw attention to the problems with the Prakash paper, I quote from their summary:

> Shortfalls with diagnostic criteria can be illustrated by examining case fatalities. Of 55 fatal cases reviewed, 12 (22%) were unlikely to be serotonin toxicity. Sternbach and Radomski criteria were met by 25 (45%), 20 (36%) had insufficient data reported and 10 (18%) met an exclusion criterion. Few had sufficient information reported to determine whether Hunter Criteria were met, **with only 13 (24%) documented as meeting the criteria,** the remaining 42 (76%) had insufficient data.

More serious still is that this mis-reporting and mis-analysis of cases is the bedrock on which computerised drug interaction systems generate 'false' warnings that cause sensible treatment combinations to be blocked, even by pharmacists.

Essential context

The first thing for readers to be mindful of is that the Hunter criteria produced by Professor Whyte's research group — the only consequential target of Werneke's childish 'challenge' — have been developed from an enormous consecutive series of overdoses (of all sorts and causes) presenting to a regional toxicology service and **all examined by experts in toxicology**. Also note, they are research criteria, not clinical diagnosis criteria.

The initial setting up of Professor Whyte's prospective structured data collection project in a clinical toxicology service was informed by the initial observations, as represented by, *inter alia*, Sternbach's original sample of case reports [19]. That is what helped the hypothesis about ST which, when subsequently integrated with other areas of knowledge (pharmacology, experimental animal models, etc.), allowed me to propose the theory of the spectrum concept of ST [20]. The theory integrated all these findings and enabled useful predictions which were subsequently substantiated — that illustrates the difference between a hypothesis and a theory.

I played a part in helping Professor Whyte to decide on how to focus on the key observations that might be made in order to confirm, with systematic observations of a large number of consecutive cases, what the aetiology, features, and course of ST really were. It is only that sort of systematic observation of 'unselected' cases that is capable of progressing the subject beyond the selective and potentially misleading data generated by sporadic case reports, made by individuals of varying levels of expertise and awareness of what to look for.

Werneke et al. seem to think the opposite is true, and that by returning to analyze even more poor case reports they are, through the magic of 'M-A', going to reveal a hidden truth. Anyone versed in the methodology of science will recognize that is a naive and delusional notion — especially when it is divorced from all the other science involved: pharmacology, receptors affinity assays, experimental animal work etc.

Werneke: A masterclass in bad science

If you wish to understand more of how *not* to do science and wish to use Werneke et al. as an example of bad science if you are teaching, then do read on — otherwise, just read the papers that I have recommended and don't bother with the rest of this.

There is sufficient to criticise in Werneke's paper to keep a tutorial group of honours students busy for a whole semester.

It is the worst paper that I can remember seeing for a long time.

The very fact that they have used the term 'serotonin syndrome', rather than 'serotonin toxicity', is the first clue to their lack of overall understanding of this subject. It is a toxidrome, not a syndrome. A basic but essential point to grasp.

Not only is the Werneke paper pointless, but worse, it adds to the errors and confusion in the literature, that in turn has adverse consequences for other researchers (see how relying on Werneke has confused Racz et al., above) and ordinary doctors trying to engage in sensible patient management of cases that they encounter. This paper just adds to the mass of erroneous facts and misinformed opinion and makes it more difficult to find that which is good.

There are so many misconceived and incorrect presumptions and statements in this report that there is an embarrassment of choice about where to start one's comments in order to help general readers understand how deeply flawed it is.

A selection of their errors

Werneke et al. repeatedly fail to cite primary sources of key data (e.g. citing, the references from Sun-Edlestein and Boyer [21, 22], which are themselves reviews, not original research, instead of the original sources relied on by those two papers [23, 24]. Writing a review that relies on other reviews is largely pointless: it can be regarded as a kind of plagiarism — if you are not critiquing the original data, you are not really writing a review at all.

They use incorrect ideas and references about hyperthermia (and fail to make the important distinction between fever and hyperthermia), which is crucial to the validity of their paper (see below). Remember, if people die from ST, it is essentially because of hyperthermia, so it is a key issue.

They describe their objectives:

> … to test 'four **commonly held hypotheses** regarding about [sic] the clinical features and aetiology of SS [1, 11], which have become established "textbook knowledge" despite their limited or partially biased evidence base'.
> 1: HC performs clinically better than SC and RC.
> 2: In contrast to neuroleptic malignant syndrome (NMS), the onset of SS syndrome is usually rapid.
> 3: Hyperthermia is a hallmark of severe SS.
> 4: SS can readily be distinguished from NMS on clinical grounds and on the basis of medication history.

Well, '**commonly held hypotheses'**. Right at the start, here is an illustration of their lack of grasp and science and its methods. In essence, we are not talking about hypotheses, we are talking about theories: theories are formed from established scientific observations providing an explanatory framework and making testable predictions. That is different to a hypothesis, or something that is just a supposition or claim (cf. 1). The whole basis of ST, to which their four points above relate, is founded on a mass of observations from various fields of science (which they do not review or consider) which are all confluent. To suppose that a few case reports can overthrow all that is to completely fail to understand scientific theory and methodology.

> … which have become established "textbook knowledge" despite their limited or partially biased evidence base

This is one example of several sweeping unreferenced generalisations which no good referee should have allowed them to make — I will say more about the deteriorating standards of refereeing of the scientific literature below. It is not accurate to use the term '*established textbook knowledge*', because most textbooks are still out of date and muddled when it comes to ST (indeed, they mostly make the same mistakes as these authors do), and the description of the '*limited or partially biased evidence base'* would seem to indicate either a complete ignorance of a vast body of scientific work, or an attempt to denigrate that work with a dismissive description — '*limited or partially biased evidence base'* is more a description of their own work.

Given their paper is such a trivial piece of scholarship, if one can call it scholarship at all, this constitutes both irony and hubris.

This so-called 'meta-analysis' audaciously claims to contradict much of what has become established through many fields of science: experimental pharmacology, animal models, *in vitro* receptor assays, *in silico* computer modelling, drug side effect data, drug interaction data, and drug overdose data (detailed prospective

studies in clinical toxicology). These studies have all been undertaken over the last fifty years, and they all point in the same direction and support the explanatory model (theory) of the spectrum concept serotonin toxicity.

The Werneke paper seeks, however naïvely, to contradict this massive body of scientific evidence: it must, perforce, receive some attention beyond insouciant dismissal, which is all it warrants — **unfortunately, it has received citations, approximately 60 to date (2021).**

Werneke et al. make various key errors in both their reporting and understanding of the Hunter research data — this research group have published a number of papers not cited, and presumably not read, by Werneke.

These errors invalidate their criticisms. I will start with these examples:

> 'Yet, the purported HC superiority is based on one study only.'
> 'One concern regarding validity is that HC was derived exclusively from SSRI overdoses'.
> … a proportion of the cases used to derive HC was then also used to validate HC.

These statements are all erroneous: one can hardly suppose Werneke et al. actually studied the paper they cite [23], because it states perfectly clearly:

> 'A learning dataset of 473 selective serotonin reuptake inhibitor (SSRI)–alone overdoses was used to determine individual clinical features predictive of serotonin toxicity by univariate analysis. Decision rules using CART analysis were developed, and tested on the dataset of **all serotonergic overdose admissions**.'

'All serotonergic overdose admissions' does not mean '*derived exclusively from SSRI overdoses*'. This indicates they gave this paper only cursory attention, even though it is at the centre of their criticism.

In fact, the HATS data was derived from all different classes of drugs in small and large doses and all degrees of severity of ST starting from the odd shake and twitch through to near-fatal cases requiring IC admission and care. This discrepancy between Whyte's publication, and the impression and account that Werneke et al. give of it, is sufficiently pronounced for one to conclude that they did not study this paper properly. If these mistakes are solely due to careless scholarship, then it is careless scholarship writ large. The only other explanation is incompetence, plain incompetence.

The Hunter toxicology group, formed by Professor Whyte, has been keeping a detailed **prospective** database of all toxicology cases for over 20 years. This has enabled a series of seminal papers on many aspects of toxicology, not just psychotropic drugs and ST. For Werneke et al. to appear to diminish or dismiss this massive achievement with the ill-informed comment that it is '*one study only*' is highly inaccurate and insulting. It is also breath-taking hubris.

The Hunter publications about ST (there are a number that Werneke et al. do not cite and have presumably not read) encompass all ranges of severity of ST, including potentially fatal toxicity from combinations of MAOIs and SRIs. Werneke et al. have obviously not read and understood the oeuvre of Professor Whyte's 'Hunter' group — nor indeed much of the other seminal work in this field.

Their scholarship is lamentably deficient for those who make such presumptuous refutations.

Whyte's paper [23] also clearly states:

> Six patients were intubated solely for worsening serotonin **toxicity**[*]. All of these patients had a high fever [>38.5_] and multiple features of serotonin toxicity. Review of these life-threatening cases showed that progressive rigidity compromising respiratory function was the precipitating event for intervention in these patients. The preceding signs were a high fever (>38.5) and increasing (particularly truncal) rigidity and peripheral hypertonicity [25].

Some scholarship. Some understanding.

That paper [25] reports in more detail on those severe cases, and others, in a larger series of severe cases of ST specifically caused by an MAOI/SRI interaction.

So, it is assuredly not the case, as these authors carelessly and mistakenly contend, that the Hunter criteria have been derived from a specialised subset of patients ('*derived exclusively from SSRI overdoses*') and that they therefore do not represent the drugs, combinations, and degrees of severity, that have been shown to precipitate ST.

These points are crucial in understanding ST, and for their argument: but they have got it badly wrong.

My 'MB exemplar' review [26] contains a summary of Hunter data illustrating degrees of severity of ST seen with different drug classes and combinations. That illustrates the key concept of the spectrum concept of severity, and highlights that SSRIs-alone do not cause serious or life-threatening toxicity: see especially Fig. 3 [26].

Also note, the toxicologists who developed the Hunter criteria have seen and cared-for many other cases of ST caused by MAOIs and SRIs and also many cases of neuroleptic malignant syndrome. They are experts who are fully conversant the whole range of severity of presentation of both these conditions, so their opinions are to be taken seriously.

You might well wonder how the clinical experience of 'Werneke et al.' stacks up in comparison?

Few scientists who understand clinical medicine will give weight to case reports (authored by doctors, and even non-medical people, of 'uncertain' expertise and experience), and the conclusions drawn from them by persons inexperienced in the field. Such opinions are of little value in comparison to the Hunter groups' data and expert experience.

Bad data cannot negate good data

Severe life-threatening cases of ST are caused (almost exclusively) by the co-ingestion of an SRI in conjunction with a monoamine oxidise inhibitor. That fact has been exhaustively documented over four decades [20, 26-28], yet these authors — **shoddier still, the referees** — appear quite oblivious to all that. Such cases of MAOI/SRI interaction are now rare (cf. the MB story): but they are *predictably* severe and life-threatening. That is precisely because ST is, without doubt, a synaptic serotonin-concentration-dependent phenomenon which is dose-related and predictable.

It may be noted that the discovery of the MAOI properties of methylene blue (MB) was entirely due to my confidence in the *predictive validity* of the spectrum concept of ST that allowed me to persuade the biochemists to find the research money to assay MB in order to establish that it had MAOI potency [29]. And indeed, the same process of logic has more recently established the MAOI

[*] Needless to say, these were all MAOI/SRI interactions, but Werneke et al. clearly did not understand that point and did not look at the reference [25] to the other publication of Whyte et al.

properties of metaxalone, this time using *in silico* methods: see here for that interesting story.

Contrary-wise, overdoses of SRIs (combined with almost any drug, other than an MAOI) causing ST are only of mild to moderate severity and are not life-threatening.

> 'Our findings challenge four commonly made assumptions about SS'

I think not.

The following paragraph from Werneke et al. can be seen to exemplify a profound failure of understanding:

> 'Clinically, particularly when a condition is life threatening, it may be better to err on the side of caution and temporarily withdraw a purported offending agent, until the differential diagnosis is clarified and appropriate action can be taken. The alternative of **refusing*** to take into account symptoms because they do not meet HC and continuing a potentially harmful agent seems less safe.'

Research diagnostic criteria are, obviously, intended for research — not for clinical practice

The idea that less severe cases of ST, precipitated by drugs such as SRIs, can somehow mysteriously progress to life-threatening ST is a misunderstanding emanating from their obvious ignorance of basic facts, also exhibited by other authors. Severe ST (i.e., toxicity) precipitated by SRIs-alone **does not occur and has not been reliably documented** (very few case reports can be reasonably typified as reliable documentation). Hence becoming concerned that mild-to-moderate ST cases (precipitated, typically, by SRIs) represent some kind of incipient danger demonstrates a fundamental misunderstanding of the whole 'spectrum concept' of ST [26, 30] and of the 'ceiling' effect exhibited by each drug class (see 'MB exemplar' paper [26]). This is another reason why it is useful to understand that the consequences of serotonin elevation by drugs are more correctly, and more usefully, considered as a toxidrome, not a syndrome.

It is not idiosyncratic; it is a predictable dose-related phenomenon

A further key point is that the whole concept of ST, and the relationship between severity of signs, degree of elevation of serotonin and the potency and interactions of the drugs causing that, has been well-established in a large number of experiments using *in vitro* Human Cloned Receptor (HCR) assays, animal models, as well as human data (of various kinds). This enables very confident and clear statements concerning those drugs which can, and cannot, raise levels of serotonin in the brain and therefore which drugs are, or are not, capable of inducing *substantial* serotonin elevation, or even toxicity. This is what gives the construct of ST an almost unassailable level of external and predictive validity.

The comparison Werneke et al. make to a psychometric rating scale is ridiculous, incomprehensible, and speaks to their extremely poor understanding of science

We are talking about science, not ghost hunting, which is what these authors appear to be engaged in with their spotting of supposed ST cases detailed in their supplementary list of references. The diagnostic reliability of those is exceedingly

* This passage has a kind of petulant childish element to it, 'refusing to take into account symptoms'. Who do they suppose is doing this refusing? This is specious and a classic straw man argument, albeit a pathetic

low (no matter what 'criteria' one *retrospectively* applies). This comment applies even more forcefully to the Rasz review commented on above.

A substantial proportion of the cases in their supplementary list do not meet the criteria for ST, because they do not even involve drugs with serotonin elevating properties (e.g., triptans, 'setrons', trazodone, mirtazapine etc.). Those are, without question, false positives — ingestion of a drug *known* to produce substantial elevation of 5-HT is a *sine qua non*. So much for pharmacology, which might as well be a foreign land to **Werneke et al.***

Werneke et al. also (mis)cite a paper that is a good example of how common false positives are: the example involves the old drug nefazodone [31]. Like trazodone, it has no SERT potency and has never caused ST, or even serotonin-mediated side effects, even in overdose. Yet, in this paper it was 'shown' to cause more 'SS' than venlafaxine, and several SSRIs — clearly utterly nonsensical.

Only a fraction of these cases could be rated as 'definite' ST. The methylene blue story illustrates many of these points well and I strongly recommend to those who wish to learn about ST that they read Gillman 2011 [26], and or the introduction to ST here.

The whole scientific basis of ST, from the pharmacology of the drugs involved, the magnitude of their effect on SERT *in vitro*, serotonin levels in the animal brain, and the symptoms associated with that in both animals and humans, are all firmly scientifically established [26, 32]. To imagine that a series of uncontrolled case reports, that by their nature are selective, retrospective and of variable, usually poor, reliability, can possibly contradict all of this is illogical and unscientific.

It is difficult to comment on the effort of these authors, the referees, or the journal, without provoking discombobulation (see addendum).

> There are too many journals publishing too much third-rate material, such that it is now difficult to see the forest for the trees

Papers are often refereed by people who are not adequately expert in the fields concerned. That is turning much of the scientific publishing enterprise into a farce — but it is generating ever increasing profits for publishing companies and forcing University libraries to pay more and more money for less and less quality.

> Science publishing must be one of the only businesses where one can reliably generate more money by producing a worse product

Errors about temperature and hyperthermia

These authors repeat mistakes made in the body of their text in their conclusions. I will pick just one example of their careless and faulty thinking to illustrate my point — the text below is not a mistake, it is exactly as rendered in their paper:

> 'Fever is considered a hallmark of SS and hyperthermia. To be more precise, a temperature > 41.1 °C, a hallmark of severe SS [22].'

This is confused English and confused thinking, to the point of being devoid of useful meaning.

Fever (pyrexia) and hyper-thermia are different. A similar confusion appears earlier in their text, so this cannot be put down to a typo. A more detailed

* The poor pharmacology in the paper proves that Professor Taylor had a little to do with the paper, since he is a competent clinical pharmacologist — so it is unethical, and a disgrace, that he put his name to the paper.

examination of elevated temperature, and the distinction between fever and hyper-thermia is in various sources, e.g. Gillman 2010 [33]. At a *true* core temperature of about 41°C irreversible cell damage is in well progress and death is imminent [33].

Their figure of 41.1°C has an absurd false degree of precision.

Serious hyper-thermia does not have a universally accepted definition, but it has been argued that 39°C or higher is an appropriate cut-off. Here is what they say earlier in their text:

> We defined fever as a temperature >38 °C (100.4 °F) [34] and hyperthermia as a temperature >41.1 °C (106.0 °F) [19].

One cannot ignore this odd statement, so I must give some space to explaining temperature measurement, since elevated temperature is such a vital defining feature of ST and is the ultimate cause of death. Yet it is measured in the most casual and unscientific way in almost all reports, except those that involve patients in intensive care units. The site, type of instrument used, and the number of elevated measurements (and over what time) are rarely presented [35], which of course they should be. So much for science.

These authors take the abuse of temperature considerations to a new level by *inventing* their own definitions of fever and hyper-thermia and **justifying them with altogether inappropriate references** from Sclar and Sternbach [19, 34]. Sternbach is a misplaced reference because it says nothing at all about hyperthermia being >41.1°C (106°F); even if it did, that would not be relevant, because it is not a paper that considers that question. The Sclar reference does not even mention temperature! Gillman [33] discusses temperature measurement in detail, and what constitutes hyperthermia, with *appropriate* references.

Misquoted and misinterpreted references

Werneke et al. contains a number of other instances, similar to the above paragraph, of misquoted or misinterpreted references — **that is a very serious academic failing**. Repeatedly citing papers that do not support the material they relate to, or are irrelevant, or are completely misrepresented, as Werneke et al. do, **shades, at some point, from carelessness into deceit and fraud.** Some might say '*J'accuse'*.

However, I will simply note that these errors obviously reflect on their general level of deficient scholarship.

In conclusion

Incidentally, the Hunter database now has more than 5,000 (five thousand) SRI-alone overdoses documented in it, the last published update (not cited by Werneke) was in 2015 [36]. None of these cases have developed a temperature greater than 38.5°C, or been rated as more than mild, or occasionally moderate, severity [Professor Whyte, personal communication: 27/7/2016].

There are few paragraphs of their manuscript that do not invite significant criticism. I will just add one last comment (I have to stop somewhere) on the section sub-titled '*Is there a gold standard for diagnosing SS*?' which opens:

> Rather than being a tangible physical quantity such as body temperature or blood glucose, SS is an abstract construct made up of various conceptual, elements (items). In this way, the three classification systems are similar to a psychometric scale that might measure a construct such as quality of life. … In the case of SS, we measure CNS hyper-excitability and try to relate this to a **purported** drug-induced serotonin excess.

An 'abstract construct', a **'purported'*** drug-induced serotonin excess?

This statement surely takes the prize is being the most outrageously incorrect in the whole paper — there is nothing 'abstract' or 'purported' about it — the fact of elevated serotonin and its consequences is reliably established by much good and replicated science (as outlined above). It is nothing remotely like a psychometric rating scale: it has massive and indestructible external validity, predictive validity and objective signs and… . What Werneke et al. state is complete and utter nonsense. The fact that it has found its way into a supposedly scientific journal is almost beyond belief, or at least it should be beyond belief. However, it now seems to be the norm, now that much refereeing has become a little more than a joke.

Then they say, '*Rather than being a tangible physical quantity such as body temperature …*'.

That is exactly what severe ST is — a potentially fatal hyper-thermic state

I cannot comprehend how anyone could describe or typify their statement as anything other than extremely stupid. These authors exist in an alternative post-modern fantasy world quite unrelated to science.

One specific comment, on the summation they make about establishing their four criticisms, must be of the 'challenge' they make to the 'assumption' that hyperthermia is a hallmark of severe ST (hypothesis 3). They make a fundamental error by dichotomizing the continuous variable of temperature using a totally inappropriate cut-off of 41.1c for 'hyperthermia' (I am sure any statistician reading this will be aghast). I trust there is no one who was read my work will not realize immediately how mind-numbingly absurd this notion is. Never mind the animal work that shows conclusively that it is progressively increasing core body temperature that causes death. It is also the case that no human patient has died of ST without having progressively increasing core body temperature >~ 39c, and that no case of SSRI caused ST has died or had hyperthermia in excess of 38.5 — that data is from the Hunter toxicology series of more than five thousand patients.

Their comment in relation to this is yet another spectacular example of their ignorance and scientific ineptitude.

These authors do a very different kind of science to me, and I hope, most of my readers.

I suggest you remember this paper as a supreme example of ultracrepidarian bloviation, editorial laxity, and incompetent refereeing.

Remember the admonition '*caveat lector*'.

Addendum

First, note that this paper has been published in one of the most insignificant neurology journals imaginable (a pay-to-publish journal). Among the many journals in the field of neurology, this one ranks below 150 others, you cannot get much more insignificant than that.

I am emphasising these points, some people may think I am belabouring them, because many general readers, and younger researchers and doctors, will not yet have gained an appreciation of just how much academic standards, editorial standards, and refereeing standards have fallen below acceptable levels. This has created the absurd situation where there is massive duplication of papers covering

* One must observe that in their paper they repeatedly use words in a value-laden or misleading way — 'assumptions about SS' (six occurrences), to mis-describe observations, deductions and conclusions based on good evidence. Likewise, their use of 'purported' (six occurrences), 'claim', 'refusing'. I will leave the examples there, but check them out, you may get the impression of low objectivity and immature attitudes, as I do.

the same material, each one worse than its predecessors, partly because any competent referees have become exhausted by the avalanche of requests to referee nonsense for insignificant poor-quality journals. See my commentary on medical science publishing for a lengthy exposition of this extremely serious problem.

Perhaps worst of all are the referees' poor and perfunctory reviews of the **paper*** which reveal the deficiencies in their own understanding, and in their degree of application to the task they voluntarily undertook. They should be ashamed of themselves because they have not picked up on any of the above gross errors, nor indeed on the many other major problems with this paper.

I communicated with the referees to ask them how they came to overlook the gross errors this paper contains and received an extraordinary reply from Prakash that, 'you didn't need to be an expert to comment on the paper' and 'all comments about SS deserve to be published'. He finished with the statement 'Every patient with mild SS is a potential candidate for developing life-threatening, severe SS'. That statement alone proves that he has no idea what he is talking about.

The fact that the journal editor — who needs to think more about ethics and perspicacity — selected such referees for this paper illustrates that many journals have descended into a parody of the refereeing system where the blind are leading the blind. It is very clear that many, most, journal editors make little or no effort to ensure the referees who they recruit to review papers have appropriate expertise in the field.

Editorial and refereeing standards have been massacred by the maw of commercialism

It is particularly lamentable that this paper was published under the imprimatur of a professor at one of the top-ranked UK tertiary education institutes in psychiatry, the Maudsley in London. It is there that Professor Taylor holds his chair (in Psychopharmacology). It verifies what I have opined repeatedly, about the declined state of academia and scientific publishing. I wrote to Professor Taylor offering him a chance to respond to this article: he chose not to. He clearly put his name to the paper having given it scant attention, not even troubling to correct the obvious 'non-standard' English usage — no wonder some senior academics manage to publish so many papers every year. Whatever his degree of involvement in the writing of this paper might have been, it reflects little credit on him, or the Maudsley.

Any competent scientist will immediately understand what a farce all this is, and what a disastrous approach to science and scientific publishing it represents.

---

* It is relevant to be aware of the background (scientific and medical) of doctors and referees involved in publishing scientific papers, in order to evaluate their likely quality (to do so is not ad hominem). I will therefore make two brief comments: the main author of the paper is a young doctor who has no apparent experience of seeing or caring for ST/NMS cases in a hospital or ICU setting, is not a toxicologist, and who has no expertise in the area of pharmacology or ST. Also, the lowly-ranked journal publishing the Werneke et al. paper engages in open peer-review, so one can see the comments of the reviewers. One of them (Prakash), whose comments are far from perspicacious, is the author of the paper below concerning ST. Anyone with a simple understanding of scientific method can see from the link that his paper is of minimal value and certainly does not qualify Prakash to referee other works on this subject as an 'expert'.

Here is the reference to Prakash's paper about ST [37]. The other referee, Adam Kaye, is a pharmacist, who is obviously not qualified to review a paper such as this covering 'clinical neurology', yet the editor selected him because he was scraping the bottom of the barrel to find anyone who would agree to referee in such a third-rate journal. He is a co-author of yet another poor and unnecessary paper on 'serotonin syndrome' [38] in the house Journal of an institute in the USA (Ochsner Journal) that has an extremely low impact factor and insignificant circulation. You can see his ultra-brief comments which are limited to the appropriate suggestion that the paper is not fit for publication because of its poor English! He appears not to have been asked for an opinion on the revised manuscript.

As I observed in the opening section, this mis-reporting and mis-analysis of case reports is the bedrock on which computerised drug interaction systems cause sensible treatment combinations to be blocked, including by pharmacists. Many doctors will consider that outcome to be undesirable and inappropriate. If a pharmacist did that to me, I would try to educate them first, but then if they were obdurate, suggest they were exposing themselves to a risk of a lawsuit for either slander or libel, which ever was appropriate, since they are essentially maligning my opinion as an expert.

References

1. Gillman, P.K., *Extracting value from case reports: lessons from serotonin toxicity.* Anaesthesia, 2006. **61**: p. 419-422.

2. Werneke, U., et al., *Conundrums in neurology: diagnosing serotonin syndrome-a meta-analysis of cases.* BMC Neurology, 2016. **16**(1): p. https://doi.org/10.1186/s12883-016-0616-1.

3. Buckley, N.A., A.H. Dawson, and G.K. Isbister, *Serotonin syndrome.* BMJ, 2014. **348**: p. 10.1136/bmj.g1626.

4. Racz, R., et al., *Association Between Serotonin Syndrome and Second - Generation Antipsychotics via Pharmacological Target - Adverse Event Analysis.* Clinical and translational science, 2018. **11**(3): p. 322-329.

5. Culbertson, V.L., et al., *Implications of Off-Target Serotoninergic Drug Activity - An Analysis of Serotonin Syndrome Reports using a Systematic Bioinformatics Approach.* Pharmacotherapy, 2018.

6. Uddin, M.F., et al., *Controversies in serotonin syndrome diagnosis and management: A review.* Journal of clinical and diagnostic research: JCDR, 2017. **11**(9): p. OE05.

7. Preve, M., et al., *Serotonin syndrome with SSRIs augmentation of amisulpride: Two case report and literature review.* European Psychiatry, 2017. **41**: p. S700.

8. Prakash, S., et al., *Fatal serotonin syndrome: a systematic review of 56 cases in the literature.* Clin Toxicol (Phila), 2021. **59**(2): p. 89-100.

9. Brennan, D., et al., *Neuroleptic malignant syndrome without neuroleptics.* British Journal of Psychiatry, 1988. **152**([letter]): p. 578-579.

10. Beasley, C.M., et al., *Possible monoamine oxidase inhibitor-serotonin uptake inhibitor interaction: fluoxetine clinical data and preclinical findings.* Journal of Clinical Psychopharmacology, 1993. **13**: p. 312-320.

11. Braitberg, G., *Serotonin syndrome.* Medical Journal of Australia, 1994. **160**(8): p. 527-528.

12. Noble, W.H. and A. Baker, *MAO inhibitors and coronary artery surgery: a patient death.* Canadian Journal of Anaesthesia, 1992. **39**(10): p. 1061-1066.

13. Tackley, R.M. and B. Tregaskis, *Fatal disseminated intravascular coagulation following a monoamine oxidase inhibitor / tricyclic interaction.* Anaesthesia, 1987. **42**: p. 760-763.

14. Stern, T.A., J.H. Schwartz, and J.L. Schuster, *Catastrophic illness associated with the combination of clomipramine, phenelzine, and chlorpromazine.* Annals of Clinical Psychiatry, 1992. **4**: p. 81-85.

15. Azoyan, P., et al., *[Acute toloxatone poisoning. Apropos of 122 cases].* Therapie, 1990. **45**(2): p. 139-144.

16. Serkan, S., Y. Yamanel Levent, and C. Bilgin, *A fatal case of severe serotonin syndrome accompanied by moclobemide and paroxetine overdose.* Indian J Crit Care Med, 2005. **9**: p. 173-175.

17. Perananthan, V. and N. Buckley, *Opioids and antidepressants: which combinations to avoid.* Australian Prescriber, 2021. **44**(2): p. 41-44.

18. Chiew, A.L. and N.A. Buckley, *The serotonin toxidrome: shortfalls of current diagnostic criteria for related syndromes.* Clin Toxicol (Phila), 2021: p. 1-16.

19. Sternbach, H., *The serotonin syndrome.* American Journal of Psychiatry, 1991. **148**: p. 705-713.

20. Gillman, P.K., *Serotonin Syndrome: History and Risk.* Fundamental and Clinical Pharmacology, 1998. **12**(5): p. 482-491.

21. Sun-Edelstein, C., S.J. Tepper, and R.E. Shapiro, *Drug-induced serotonin syndrome: a review.* Expert Opinion on Drug Safety, 2008. **7**(5): p. 587-96.

22. Boyer, E.W. and M. Shannon, *The serotonin syndrome.* New England Journal of Medicine, 2005. **352**(11): p. 1112-20.

23. Dunkley, E.J.C., et al., *Hunter Serotonin Toxicity Criteria: a simple and accurate diagnostic decision rule for serotonin toxicity.* Quarterly Journal of Medicine, 2003. **96**: p. 635-642.

24. Whyte, I.M. and A.H. Dawson, *Relative toxicity of venlafaxine and serotonin specific reuptake inhibitors in overdose.* Journal of Toxicology. Clinical Toxicology, 2001. **39**: p. 255.

25. Isbister, G.K., et al., *Moclobemide poisoning: toxicokinetics and occurrence of serotonin toxicity.* British Journal of Clinical Pharmacology, 2003. **56**: p. 441-450.

26. Gillman, P.K., *CNS toxicity involving methylene blue: the exemplar for understanding and predicting drug interactions that precipitate serotonin toxicity.* Journal of Psychopharmacology, 2011. **25**(3): p. 429-3.

27. Gillman, P.K., *The serotonin syndrome and its treatment.* Journal of Psychopharmacology, 1999. **13**(1): p. 100-9.

28. Bodner, R.A., et al., *Serotonin syndrome.* Neurology, 1995. **45**: p. 219-223.

29. Ramsay, R.R., C. Dunford, and P.K. Gillman, *Methylene blue and serotonin toxicity: inhibition of monoamine oxidase A (MAO A) confirms a theoretical prediction.* Br J Pharmacol, 2007. **152**(6): p. 946-51.

30. Gillman, P.K. and S. Hodgens, *Serotonin syndrome following SSRI mono-therapy.* Human Psychopharmacology. Clinical and Experimental, 1998. **13**: p. 525-526.

31. Mackay, F.J., N.R. Dunn, and R.D. Mann, *Antidepressants and the serotonin syndrome in general practice.* British Journal of General Practice, 1999. **49**(448): p. 871-4.

32. Gillman, P.K., *A review of serotonin toxicity data: implications for the mechanisms of antidepressant drug action.* Biological Psychiatry, 2006. **59**(11): p. 1046-51.

33. Gillman, P.K., *Neuroleptic Malignant Syndrome: Mechanisms, Interactions and Causality.* Movement Disorders, 2010. **25**(12): p. 1780-1790.

34. Sclar, D.A., et al., *Concomitant Use of Triptan, and SSRI or SNRI After the US Food and Drug Administration Alert on Serotonin Syndrome.* Headache, 2012. **52**(2): p. 198-203.

35. Gillman, P.K., *Neuroleptic malignant syndrome, poor science and inaccurate measurements.* Journal of Psychopharmacology, 2010: p. 20 May 2010, 10.1177/0269881110367461.

36. Buckley, N.A., et al., *A prospective cohort study of trends in selfpoisoning, Newcastle, Australia, 1987-2012: plus ça change, plus c'est la même chose.* Medical Journal of Australia, 2015: p. https://www.mja.com.au/journal/2015/202/8/prospective-cohort-study-trends-self-poisoning-newcastle-australia-1987-2012-plus.

37. Prakash, S., et al., *Mild serotonin syndrome: A report of 12 cases.* Ann Indian Acad Neurol, 2015. **18**(2): p. 226-30.

38. Volpi-Abadie, J., A.M. Kaye, and A.D. Kaye, *Serotonin Syndrome.* Ochsner, 2013. **13**: p. 533-540.