

## Update on recent serotonin toxicity publications including comment on, ‘Conundrums in neurology: Diagnosing serotonin syndrome – a meta-analysis of cases’

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### Abstract

In the last decade 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) which has enabled accurate predictions about the mechanism of action and the potency of various drugs. The striking examples of this are the proof of the predicted MAOI activity of methylthionium (methylene blue) and metaxalone. Continued publication of cases reports that are usually of poor observational quality, completeness, and reliability is unlikely to be productive and is confusing the picture for doctors by introducing spurious data. Recent reviews using data from the FDA FAERS system illustrate the chaos that can ensue from misapplied analyses, and a recent summary of more published case reports from the last ten years illustrates these problems, especially because it unjustifiably presents itself as a ‘meta-analysis’. This confusion has lessons for regulatory agencies, such as the FDA, that have issued a number of incorrect and misconceived warnings about ST that mirror the misunderstandings and poor scholarship encapsulated in the Werneke ‘meta-analysis’. There are also lessons for medical publishing where commercial considerations have resulted in an excessive number of poorly refereed publications which have swamped the literature, obscuring that which is good.

### 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. 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) — when this (July 2016) so-called meta-analysis of case reports by Werneke et al. (2) appeared. One cannot recommend this paper, but at least it has done some of the work of collating recent reports for me and saved me the tedium of trawling through them all — I confess I have ceased to ‘log’ all the ST reports in my bibliography database for the last few years because it became such an unproductive use of time and energy. It is also

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dispiriting — some good work has been published ([see here](#) for a list of recommended papers), but the good work becomes lost in the tsunami of mediocrity that is modern science publishing, and has little effect on the collective knowledge-level and understanding, as evinced in most case reports. The other recent ‘reviews’ noted below also reflect these problems.

The Werneke et al. ‘meta-analysis’ (it is meaningless 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. 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 the discussion. Evidently, they are not.

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). The full free pdf of this paper is [here](#)

### Other recent ‘reviews’

Racz et al. have used ‘bioinformatics tools’ (what a splendid 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 it can detect ghosts as well. This paper is utter nonsense.

“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-HT<sub>2A</sub> antagonists 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 combo with MAOIs) is Ziprasidone (which has significant SRI potency) — needless to say they have failed to detect that ‘signal’.

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 ‘... *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 of inducing 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 so many different scientific disciplines in the last 20 years (6, 7).

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

### Essential context

The first thing for readers to be mindful of is that the Hunter criteria produced by Prof Whytes research group — the only consequential target of Werneke's '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**.

The initial setting up of Prof White'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. That is what helped the hypothesis about ST which when subsequently integrated with other areas of knowledge (pharmacology, experimental animal models, etc. allowed the theory of the spectrum concept of ST to be proposed (8). The theory of the spectrum concept of ST, first enumerated by Gillman, integrated all these findings and enabled useful predictions which were subsequently substantiated — and that illustrates the difference between a hypothesis and a theory.

I played a small part in helping Prof 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: an object lesson in bad science

If you wish to understand more of how *not* to do science, and maybe use Werneke et al. as an example of bad science if you are teaching, then do read on. There is sufficient to criticise in this to keep a tutorial group of honours students busy for a whole semester. It is the worst paper on this, or any other subject 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 et al. paper pointless, but worse, it adds to the errors and confusion in the literature that in turn has adverse consequences for 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

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where to start one's comments in order to help general readers understand how deeply flawed it is.

### List of points

Werneke et al. repeatedly fail to cite primary sources of key data (e.g. citing, in their introduction the references from Sun-Edlestein and Boyer (9, 10), which are themselves reviews, not original research, instead of the original sources relied on by those two papers (11, 12). NB I should know: I corresponded & spoke with & advised Boyer as he was preparing his paper. The same applies to references about hyperthermia, which are crucial to the validity of their paper (see below)

They describe their objective:

... 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 repeatable scientific observations providing an exclamatory framework and making testable predictions. That is quite different to a hypothesis. 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 are all confluent. To suppose that a few case reports can overthrow all that is to fail to understand the scientific theory and methodology.

'... which have become established "textbook knowledge" despite their limited or partially biased evidence base', is an example of one of a number of sweeping unreferenced generalisations which no good referee should have allowed them to make — I will say more about the deteriorating standards of refereeing in 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 make all the same mistakes as these authors do), and the description of the '*limited or partially biased evidence base*' would seem to indicate 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 own paper is such a trivial piece of scholarship, if one can call it scholarship at all, this constitutes both irony and hypocrisy.

This so-called 'meta-analysis' audaciously claims to contradict much of what has become established through the various fields of experimental pharmacology, animal models, *in vitro* receptor assays, *in silico* computer modelling, drug interaction data, and detailed prospective studies in clinical toxicology etc., over the last twenty years. It must perforce receive some attention beyond insouciant dismissal, which is all it warrants.

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

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

‘Yet, the purported HC superiority is based on one study only.’

and

‘One concern regarding validity is that HC was derived exclusively from SSRI overdoses’.

and

... a proportion of the cases used to derive HC was then also used to validate HC.

These statements are erroneous: one can hardly suppose Werneke et al. actually studied the paper they cite (11), because it states 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**.’

So, not ‘*derived exclusively from SSRI overdoses*’.

In fact, 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 extensive. Can it possibly be due solely to careless scholarship?

The Hunter toxicology group, formed by Prof Whyte, has been keeping a detailed **prospective** database of all toxicology cases for some 20 years. This has enabled a series of seminal papers on many aspects of toxicology, not just 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 not only highly inaccurate, but is 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 Prof Whyte’s ‘Hunter’ group. Their scholarship is lamentably deficient for those who make such presumptuous refutations.

Whyte’s paper (11) 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 (13)\*\*\*.

\*\*\* 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 (13) to the other publication of Whyte et al. Some scholarship. Some understanding.

That paper, Isbister 2003 (13), 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: they have got it badly wrong.

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My 'MB exemplar' review also contains a summary of Hunter data illustrating degrees of severity of ST seen with different drug classes and combinations, which illustrates the key concept of the spectrum of severity, and highlights that SSRIs-alone do not cause serious or like-threatening toxicity: see especially Fig. 3 (14).

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 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, 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 SRIs in conjunction with a monoamine oxidase inhibitor. That fact has been exhaustively documented over four decades (8, 14-16), yet these authors (and, worst still, the referees) appear quite oblivious to all that. Such cases are now rare (cf. the MB story): but they are *predictably* severe and life-threatening.

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 (17). And indeed, the same process of logic has more recently established the MAOI properties of metaxalone, this time using *in silico* methods: see [here](#) for that 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.'

NB \*\*\* 'refusing ...' Who do they suppose is doing this refusing? This is specious and a classic straw man argument, albeit a rather pathetic one. And the 'gold standard' is the diagnosis of a clinical toxicologist, no-one is a slave to research diagnostic criteria.

If any readers thought these authors were serious intellectual disputants, I hope I have disabused them of that idea by now.

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 ignorance of basic facts, exhibited by many authors. Severe ST 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

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cases (precipitated, typically, by SRIs) represent some kind of incipient danger demonstrates a fundamental misunderstanding of the whole ‘spectrum concept’ of ST (14, 18) and of the ‘ceiling’ effect exhibited by each drug class (see ‘MB exemplar’ paper). This is why it is useful to understand that the consequences of serotonin elevation by drugs are more usefully considered as a toxidrome, not a syndrome (i.e. 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 & 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 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 which is exceedingly 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 do not even involve drugs with serotonin elevating properties (e.g. triptans, ‘setrons’, trazodone, mirtazapine etc.) so these 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 them.

Werneke et al. cite a paper that is a good example of how common false positives are: the example involves the old drug nefazodone (19). Like trazodone, it has no SERT potency and has never caused ST, or even serotonin-mediated side effects, in overdose. Yet, in this paper it was ‘shown’ to cause more ‘SS’ than venlafaxine or several SSRIs — clearly utterly nonsensical.

Only a fraction of these cases could be rated as ‘definite’ ST. The methylene blue story illustrates all these points very well and I strongly recommend to those who wish to learn about ST that they read Gillman 2011 (14), 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 (14, 20). To imagine that a series of uncontrolled case reports, that by their nature are selected, 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 without provoking discombobulation. The referees’ poor and perfunctory reviews of the paper\*\*\* reveal the deficiencies in their own understanding, and in their degree of application to the task they voluntarily undertook.

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\*\*\* It is relevant to be aware of the background (scientific and medical) of doctors who publish scientific papers. I will therefore make two brief comments: the main author of the paper is a 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 journal publishing the Werneke et al. paper engages in open peer-review and 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'.

Referee 1— Prakash. Here is the reference to this referee's paper about ST (21); txt at:

<http://www.annalsofian.org/article.asp?issn=0972-2327;year=2015;volume=18;issue=2;spage=226;epage=230;aulast=Prakash>

The fact that the journal editor — who needs to think more about ethics and perspicacity — selected such an author to referee 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 journal editors make little effort to ensure the referees who they recruit to review papers have appropriate expertise in the field (you really should see the many ridiculously inappropriate requests that I get). Editorial & refereeing standards have been massacred by the maw of commercialism.

There are too many journals publishing too much third-rate material 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 is generating increasing profits for publishing companies and forcing libraries to pay more money for less quality].

## Errors concerning 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 (10).'

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

Fever (pyrexia) and hyper-thermia are different (other people confuse them too, but that is no excuse). A similar confusion appears earlier in their text, so this cannot be put down to a typo. A more detailed examination of elevated temperature, and the distinction between fever and hyper-thermia is in various sources e.g. Gillman 2010 (22). At a *true* core temperature of 41°C irreversible cell damage is in well progress and death is imminent (22): their figure of 41.1°C has, in this context, an absurdly 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 appropriate. Here is what they say earlier in their text:

We defined fever as a temperature > 38 °C (100.4 °F) (23) and hyperthermia as a temperature > 41.1 °C (106.0 °F) (24).

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

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time period) are rarely presented (25), 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 & Sternbach (23, 24). Sternbach is a misplaced reference, it says nothing about hyperthermia being  $>41.1^{\circ}\text{C}$  ( $106^{\circ}\text{F}$ ), even if it did that would not be relevant, because it is not a paper that considers that question in any depth. The Sclar reference does not even mention temperature! Gillman 2010 discusses this, with *appropriate* references (22).

Werneke et al. contains a number of other instances 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, as they do, shades, at some point, from carelessness to deceit and fraud. Some might say ‘*J’accuse*’.

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

Incidentally, the Hunter database now has more than 5,000 (five thousand) SRI overdoses documented in it, the last published update (not cited by Werneke) was in 2015 (26). None of these cases have developed a temperature greater than  $38.5^{\circ}\text{C}$ , or been rated as more than mild, or occasionally moderate, severity [Prof 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.

A ‘purported’\*\*\* drug-induced serotonin excess? Have we slipped into an alternative post-modernist reality?

There is nothing purported about it. The fact of elevated serotonin and its consequences is reliably established by a lot of good replicated science (as outlined above), so it is nothing remotely like a psychometric rating scale: it has massive and indestructible external validity, predictive validity and objective signs and ...). Werneke et al.’s above paragraph is complete and utter nonsense. ‘*Rather than being a tangible physical quantity such as body temperature ...*’. That is exactly what severe ST is — a potentially fatal hyper-thermic state.

\*\*\* 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. Like-wise 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.

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 an inappropriate cut-off of  $41.1^{\circ}\text{C}$  for ‘hyperthermia’ (I am sure any statistician reading this will be aghast). I trust there is no one who was read

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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  $> \sim 39^{\circ}\text{C}$  (with the typical consequences of DIC etc.), 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 five thousand patients. Their comment in relation to this is the most spectacular example of their complete and utter ignorance and ineptitude.

I can only suppose that these authors do a different kind of science to me, and I hope, most of my readers.

And, perhaps worst of all, the referees, who should be ashamed of themselves, have not picked up on any of the above, nor indeed on the many other problems with this paper.

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

Remember the admonition '*caveat lector*'.

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