# Serotonin toxicity contrasted with neuroleptic malignant syndrome

## Abstract

The distinction between NMS and ST continues to generate much poorly informed and confused debate in the literature. Why this is so is a puzzle, because the evidence is clear that they are quite different in aetiology, presentation, course, signs and symptoms, and straightforward to distinguish between.

## Fundamental differences

Before discussing the controversies and misconceptions surrounding this subject it may be best to start by stating what one would consider to be the basics which make it obvious that the two conditions are different.

**ST** has a rapid onset (hours) and progression, it happens **exclusively** and **predictably** in association with potently serotonergic drugs, but **not** with DA antagonists.

**NMS** has a slow onset and progression (hours to days), **non-predictably,** and **only rarely** in association with neuroleptics: it also happens in the **complete absence** of neuroleptics, but **not** with typical 'serotonergic' drugs like SSRIs.

**ST** is a well delineated and clearly recognisable condition (best called a 'toxidrome') showing the signs and symptoms of hyperkinesia (increased physical activity) and increased mood/mental activity with hyperreflexia and marked clonus.

**NMS**, conversely, is defined by bradykinesia (decreased physical activity) and bradyphrenia (slowed mentation) in the absence of clonus, but with fever (i.e., with an APR, acute phase reaction), or hyperpyrexia, and extrapyramidal rigidity.

**ST** is clearly a manifestation of toxicity (it is predictable and common with specific drug combinations)

**NMS** is a **rare** idiosyncratic reaction to **normal doses** and very rarely occurs after over-doses. That strongly indicates that the underlying patho-physiology of the two conditions is dissimilar. This is because ST is clearly linked to the known mechanism of action of the precipitating drugs, whereas NMS is not, and there is no known or established mechanism to explain the possible connection.

ST typically resolves rapidly within hours after the cessation of the relevant drugs, depending on their respective half-lives, whereas NMS resolves slowly over some/many days. Also, there is a specific effective antidote for ST, 5-HT2A receptor antagonists, whereas NMS tends to improve with dopamine agonists such as bromocriptine and apomorphine.

There is doubt that NMS is unitary syndrome, rather it seems to be a heterogenous collection of symptoms with variable contributing factors and causes, see [1]. Indeed, the fact that after 50 years there are still no generally accepted diagnostic criteria [2, 3] probably tells us something important.

Furthermore, the course of hyperthermia may be different in the two conditions. In hyperthermic (i.e., > 39°C) serotonin toxicity (which is usually only seen with combinations of MAOI+SRI) body temperature increases rapidly and reaches levels in excess of 40°C and, without aggressive treatment, death from the consequences of hyperthermia is frequent within a few hours. In NMS the temperature increases slowly and infrequently exceeds 39°C [1] and also **morbidity and mortality are significant in the absence of serious hyperthermia** [1, 4].

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The usually clinical picture is typically very different. NMS is preceded by increasingly severe Parkinsonian symptoms, often with a severe degree of bradykinesia amounting to immobility, stupor and mutism. Typically, sufferers are delirious, fearful, prostrate and mute [5]. Contrary-wise, the early stages of ST involve excitability, overactivity and can resemble a manic state. In other words, although the vague term 'changes in mental state' is used for both conditions, the reality is that the characteristics of these mental state changes are completely different.

The excitability of ST often precedes the development of overt neurological symptoms like hyperreflexia and clonus. It is only if, and when, ST reaches the severe state that clonus shades into rigidity, which paralyses chest wall muscles leading to > $PaCO_2$ & the complications that may bring on confusion and coma.

Various other symptoms are often recognisably different. For instance, shivering is quite frequent in ST but never occurs in NMS. The tremor in ST tends to be more marked and of the intention type, whereas in NMS it is extra-pyramidal like a typical Parkinsonian tremor. Autonomic instability tends to be rather worse in NMS as does diaphoresis. Tachycardia, flushing, and diarrhoea are usually more prominent in ST.

Thus, in NMS, bradykinesia and rigidity are prodromal symptoms but in ST bradykinesia does not occur and rigidity (when it occurs in severe cases), is a terminal development.

The aetiology, progression, symptoms, signs, patho-physiology and treatment response are all quite different and thus we can say confidently that the two conditions are usually clearly distinguishable.

## Causation

In my 2010 review of neuroleptic malignant syndrome [1] I compared ST, NMS and malignant hyperthermia (MH), using the Hill criteria for causality. That exercise underlined the tenuous causal connection between neuroleptics and the presumed syndrome of NMS. This is thus an appropriate point at which to observe that NMS is a misnomer, a miss-named entity, because it is:

a) not exclusively related to neuroleptics,

b) it is not 'malignant', and

c) it is doubtful that it is valid to regard it as a meaningful syndrome

From Gillman 2010:

> Criteria for establishing cause–effect relationships in medical science, established by Sir Austin Bradford Hill [6] have recently been applied in several situations similar to NMS [7, 8] and refinements have been discussed [9, 10]. These criteria or considerations are, as initially enumerated by Hill [6]: "1) Strength, 2) consistency, 3) specificity, 4) temporality, 5) biological gradient (dose–effect), 6) plausibility, 7) coherence, 8) experiment and 9) analogy" (see references for a more detailed expositions of these points).

## Table 1 Hill criteria applied to MH, NMS and ST

**Legend Table 1***

| Hill Criterion | MH | NMS | ST |
|---|---|---|---|
| Strength | Strong | Weak | Strong |
| Consistency | Strong | Equivocal | Strong |
| Specificity | Strong | Absent | Strong |
| Temporality | Strong | Weak | Strong |
| Biological gradient | Strong | Equivocal | Strong |
| Plausibility | Strong | Equivocal | Strong |
| Coherence | Strong | Weak | Strong |
| Experiment | Strong | Absent | Strong |
| Analogy | Strong | Absent | Strong |

## Case reports and other publications

Profs Whyte and Buckley and Isbister (professors of toxicology, who look after these kinds of patients regularly in intensive care units), and I, are among the few experts who have published reviews on the subject of both serotonin toxicity and neuroleptic malignant syndrome. We all agree about the clear distinction between these two conditions [11-15]. It is probably fair to say that confusion is more prominent among psychiatrists and in psychiatric journals than it is in journals covering neurology or medicine.

Over the years various authors have put forward a view that these two conditions are 'similar', 'alike', share 'a common [final] pathway', or are 'indistinguishable'. However, ignorance of some established facts (as above) and the fallaciousness of the 'evidence' on which such propositions are based (poor single cases reports) render these arguments ill-founded and weak.

I would say that clinicians who state that ST and NMS are usually 'indistinguishable' probably have little or no practical experience of these conditions.

Only recently I had a brief correspondence with Steele & Keltner, the authors of a recent paper that suggested ST and NMS are similar [16]. Do not forget, this is a complex topic which requires more than a nodding acquaintance with advanced psycho-pharmacology, toxicology etc. as well as significant background clinical experience in medicine, neurology and intensive care medicine. This sort of expertise is usually only accumulated by quite experienced doctors in relevant disciplines. The main author of this particular contribution is Keltner, a professor, not of medicine but of **nursing**, in the United States of America. I do not intend to deride or belittle Professor Keltner when I suggest that his knowledge and experience in these matters cannot be weighed equally with persons such as Professors Whyte and Buckley, nor indeed myself. However, many people reading this kind of material will not be aware of this distinction, nor of the modest status of the journal in question, nor of the fact that many key references are missing from the paper and that some of the references quoted have been rebutted (although he does not appear to recognise this). The paper

* The evidence for criteria is rated as: Strong, Equivocal, Weak, or Absent (see Gillman [1] for explanation of ratings).
Abbreviations: MH malignant hyperthermia, NMS neuroleptic malignant syndrome, ST serotonin toxicity

contains a number of misconceptions and superficial over-simplifications and I will not unnecessarily expand this commentary by going into them in detail. It is merely sufficient to illustrate the justification for my points above with one example from their table 1 (p. 59) and associated text. Here they compare the features of the two conditions. They highlight that hyperthermia, altered consciousness, motor symptoms, and autonomic instability are shared by both. However, that does not indicate there is any meaningful commonality between them, and to imagine so is unscientific. Their term 'motor symptoms' is not a precise medical term but a general category covering many different specific symptoms that may occur in many different conditions (e.g., clonus is a 'motor' sign, it is highly characteristic of ST but does not occur in NMS). This specific 'motor' symptom of clonus that is characteristic of ST is completely different to the motor symptoms that occur in NMS and Parkinson's disease. To offer this comparison as a justification that they are similar is either naïve, ignorant or a disingenuous obfuscation of the issues. It is a bit like saying it is difficult to tell the difference between cars and trucks because they both have an engine, four wheels and a steering wheel. Their assumptions and logic are patently absurd. Enough said, let us move on.

## *Accumulated reports*

Here is my collection, over the years, of case reports (mostly dubious) relevant to this discussion, along with published comments, associated material and rebuttals etc. [1, 12, 14-55].

This does not claim to be a definitive or all-inclusive list, but it is extensive and will assist any researchers who wish to locate relevant reports, comment and material. Below I will use one or two of them to illustrate what I think are some relevant or important points.

## *Reports illustrating salient points*

Professor Max Fink of catatonia fame [56, 57] proposed a general neurotoxic syndrome encompassing both ST and MMS. This was on the basis of one highly unsatisfactory case report [32] which was stated to involve serotonergic drugs and appeared (at least to them) to be indistinguishable from NMS (but reported no proper description of a medical examination of the patient and seemed to be a second-hand report). The drugs being administered were nortriptyline and trazodone and the patient had recently ceased l-Dopa. The data in this report are unreliable and neither nortriptyline nor trazodone are 'serotonergic' drugs. It is difficult to understand the rationale of this report and the whole basis and idea is groundless and illogical. They did not even discuss l-dopa withdrawal as a possible precipitator of this NMS-like state, which would be the most parsimonious explanation. This is not competent science and did not deserve publication in a scientific journal.

Other authors have picked up this and similar notions and run with them. Fink resurrected his argument [58] in response to a report by Haddow in the BMJ years later [59].

This Haddow case is one of the few interesting case reports and illustrates one important and fundamental observation: it is neither logical nor wise to generalize or extrapolate in the case of adverse drug reactions occurring with CNS-active drugs in patients who are known to have significant brain disease, frequently some kind of dementia or brain damage. This is because it is recognised that such patients frequently exhibit exaggerated, atypical and paradoxical responses to CNS drugs. In my research as an expert in serotonin toxicity I have read, reviewed and refereed many hundreds of reports concerning CNS drug reactions and in my opinion it is striking that nearly all the genuinely anomalous and atypical cases occur in patients with cerebral pathology. The other key consideration is this: it has not been established that NMS is in fact a unitary

homogenous syndrome. Indeed, much evidence indicates that it is not. Thus, it is obviously even more risky to generalize and extrapolate about cases that are labeled as, or proposed to be, NMS.

Some suggest that serotonin toxicity occurs with olanzapine and other 'atypical' neuroleptics. Kontaxakis argued (from a selective review of 17 case reports, always a dubious enterprise) that neuroleptic malignant syndrome cases with olanzapine exhibit serotonin toxicity-like symptoms [60-62]. Like Fink, they suggest that NMS and ST share a common patho-physiology and represent some sort of generic non-specific neuro-toxic syndrome.

There are so many basic flaws in the assumptions and logic of this report that it is difficult to know where to start any criticism of it. Firstly, picking on olanzapine because it has significant activity at 5-HT2A receptors, as if that was some special property, is mistaken and absurd. Many neuroleptics, including many of the older neuroleptics like chlorpromazine, have this property. It is not special to the so-called second-generation, or atypical, drugs. Nevertheless, it appears to be the reason they have chosen this drug, although that is not clearly and explicitly stated:

> "Olanzapine is an atypical antipsychotic, which exhibits greater affinity to serotonin (5-HT2A) receptors than to dopamine (D2) receptors [9]."

I also note that this reference [9] that they give contains no original data relevant to the claim they make (re receptor affinity), which is poor scholarship. To cite references which do not provide the data claimed is only one step away from scientific fraud. There is no more delicate way of stating that. Their report uses the non-specific and out-dated Sternbach **criteria*** for serotonin toxicity which automatically makes it of limited validity.

Whyte, Buckley, Isbister and I have pointed out the strong evidence that contradicts these ideas in various publications (see refs above). The idiosyncratic nature of NMS precludes patho-physiological comparison with ST in relation to the mechanism of action of the precipitating drugs even if the symptoms were like ST (as is proposed by Kontaxakis). They are not similar — see above, and especially my published response 'Defining toxidromes: serotonin toxicity and neuroleptic malignant syndrome: A comment on Kontaxakis et al' [38] — so the proposal is doubly flawed.

Consider also that neither olanzapine, nor any other 'atypical' neuroleptics show evidence of 'serotonergic' effects, they neither produce serotonin-mediated side effects in therapeutic trials, nor do they produce serotonin-mediated effects, nor symptoms of ST, when taken by themselves in over-dose.

## Can Previous Neuroleptic Administration 'Trump' ST

There is also a widespread perception that neuroleptic malignant syndrome symptoms somehow 'trump' or override symptoms of serotonin toxicity, and that serotonin toxicity cannot be diagnosed in the presence of neuroleptics. The origin and logic for this *ipse dixit* ('because I say so') assertion is unclear and has never been adequately articulated, yet it has become widely and uncritically accepted. This may be because of the misinformation perpetuated by poor case reports: readers who wish to learn about NMS and ST are advised, in additional to information on this web site, to start with the major recent reviews by Caroff, Whyte et al and Gillman [1, 39, 64-70].

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* Sternbach made suggestions [63], long ago, about diagnostic criteria, which were reasonable initially, but were non-validated proposals derived from a selected (non-random) sample. Sternbach's review was superseded many years ago by the more reliable data from Professor Whyte's HATS data published in a series of seminal papers. Sternbach noted the likelihood of reporting bias in his series, but that qualification has received insufficient subsequent attention.

Special evidence is required to logically justify assigning one illness or toxidrome a hierarchical precedence over another; one cannot claim that previous intake of neuroleptics goes against or negates a diagnosis of ST without such special evidence. No-one has ever advanced such evidence.

There are good reasons for rejecting that supposition and assuming the exact opposite. That is because ST is much more strongly and predictably associated with serotonergic drugs than NMS is with neuroleptics. NMS is unpredictable and rare (i.e., idiosyncratic).

## ST and NMS: Chalk and Cheese

As alike as chalk and cheese is how I summarised it [14] and Professor Whyte wrote some time ago re NMS and ST: (43, 46)

> "In my capacity as a general physician to the local psychiatric hospital and as a clinical pharmacologist who takes referrals of drug related problems, I have managed over 50 patients with Neuroleptic Malignant Syndrome over the last 12 years. From this clinical experience and the literature, I have compiled a table comparing the clinical features of Serotonin Syndrome with those of Neuroleptic Malignant Syndrome.....
> "From this comparison it can be seen that while there are several features in common, a full physical examination and clinical assessment makes it almost impossible to confuse the two diagnoses. A similar table and conclusions have been recently published by Gillman (Gillman, PK., The Serotonin Syndrome at its treatment. Journal of Psychopharmacology. Vol 13 (1): 1999, pp 100-109)".

NB. From more recent conversations with Prof Whyte I would estimate that the numbers referred to above are much higher and his confidence in his opinion remains the same.

It seems that it is mostly psychiatrists who subscribe to the opinion that NMS and ST are 'virtually indistinguishable' and this may be because they do not usually have involvement in the care of these seriously ill patients in the intensive care units where they are treated by physicians and toxicologists. Thus, their opinions are essentially ultracrepidarian, i.e., those opinions go well beyond their level of expertise.

### *Postscript: Why is There so Much Misinformation in the Medical Literature?*

A brief diversion may be educative. Although the peer review system in scientific publishing is an excellent and laudable idea in principle, in practice it is far from perfect. There are many journals that are not in the top division who are unable to get quality reviewing of their material and often accept and publish papers with meretricious, rather than meritorious, content. Many of them are just substandard scholarship.

Much of this kind of material gets published as case reports which are inherently of lesser scientific standard and are often very misleading. There has been much debate about whether journals should publish case reports at all and many more eminent journals elect not to do so.

Such short reports and mini reviews usually require the authors to make a stab at reviewing the literature on the subject in question. For complex topics like ST and NMS that is a nearly impossible exercise (due to the constraints of time and space and the inexperience of most authors) and frequently leads to pointless and erroneous publications that are then inadequately refereed). There are various other comments on my website in relation to the whole business of substandard and biased publications, for those with the time and interest to read about it.

Most people are aware of the importance of the old expression 'buyer beware' (caveat emptor) and it is also helpful to realise that even in the scientific literature one should remember the sister phrase 'caveat lector', that is, 'reader beware'.

**References**


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

2. Gurrera, R.J., et al., *An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the delphi method.* J Clin Psychiatry, 2011.

3. Gurrera, R.J., et al., *A Validation Study of the International Consensus Diagnostic Criteria for Neuroleptic Malignant Syndrome.* J Clin Psychopharmacol, 2017. **37**(1): p. 67-71.

4. Gillman, P.K., *The Nature of Hyperthermia in Neuroleptic Malignant Syndrome and the Use of Bromocriptine.* J Med Toxicol, 2010. **6**: p. 272-273.

5. Rosebush, P. and T. Stewart, *A prospective analysis of 24 episodes of neuroleptic malignant syndrome.* American Journal of Psychiatry, 1989. **149**: p. 717-725.

6. Hill, A.B., *The Environment and Disease: Association or Causation?* Proc R Soc Med, 1965. **58**: p. 295-300.

7. Perrio, M., S. Voss, and S.A. Shakir, *Application of the bradford hill criteria to assess the causality of cisapride-induced arrhythmia: a model for assessing causal association in pharmacovigilance.* Drug Safety, 2007. **30**(4): p. 333-46.

8. Licht, R.W., et al., *Are antidepressants safe in the treatment of bipolar depression? A critical evaluation of their potential risk to induce switch into mania or cycle acceleration.* Acta Psychiatrica Scandinavica, 2008. **118**(5): p. 337-46.

9. Shakir, S.A. and D. Layton, *Causal association in pharmacovigilance and pharmacoepidemiology: thoughts on the application of the Austin Bradford-Hill criteria.* Drug Safety, 2002. **25**(6): p. 467-71.

10. van Reekum, R., D.L. Streiner, and D.K. Conn, *Applying Bradford Hill's criteria for causation to neuropsychiatry: challenges and opportunities.* Journal of Neuropsychiatry and Clinical Neurosciences, 2001. **13**(3): p. 318-25.

11. Whyte, I.M., *Serotonin Toxicity (Syndrome).* in *Medical Toxicology*, R.C. Dart, Editor. 2004, Lippincott Williams & Wilkins: Baltimore. p. 103-106.

12. Whyte, I.M., *Serotonin syndrome complicating the treatment of recurrent depression.* Current Therapeutics, 1999. **40**: p. 6-7.

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

14. Gillman, P.K., *NMS and ST: chalk and cheese.* British Medical Journal, 2005: p. http://bmj.bmjjournals.com/cgi/eletters/329/7478/1333.

15. Isbister, G.K. and N. Buckley, *Adverse reactions to psychotropic medication: the literature continues to confuse.* British Medical Journal, 2005: p. http://bmj.bmjjournals.com/cgi/eletters/329/7478/1333.

16. Steele, D., N.L. Keltner, and T.M. McGuiness, *Are neuroleptic malignant syndrome and serotonin syndrome the same syndrome?* Perspect Psychiatr Care, 2011. **47**(1): p. 58-62.

17. Slettedal, J.K., et al., *Brain pathology in fatal serotonin syndrome: Presentation of two cases.* Neuropathology, 2010: p. DOI: 10.1111/j.1440-1789.2010.01153.x.

18. Gillman, P.K., *Hyperthermic Fatalities of Uncertain Cause.* Neuropathology, 2010. **31**: p. 306-307 (published online: 14 Mar 2011).

19. Odagaki, Y., *Atypical neuroleptic malignant syndrome or serotonin toxicity associated with atypical antipsychotics?* Curr Drug Saf, 2009. **4**(1): p. 84-93.

20. Gomez-Esteban, J.C., et al., *Neuroleptic malignant syndrome and serotonin syndrome in a female patient: a clinicopathologic case.* Clin Neuropharmacol, 2009. **32**(5): p. 299-300.

21. Bruscas Alijarde, M.J., et al., *[Malignant neuroleptic syndrome and serotoninergic syndrome: two cases].* Revista Clinica Espanola, 2007. **207**(7): p. 374-5.

22. Christensen, V. and B.Y. Glenthoj, *[Malignant neuroleptic syndrome or serotonergic syndrome].* Ugeskrift for Laeger, 2001. **163**(3): p. 301-2.

23. Nimmagadda, S.R., D.H. Ryan, and S.L. Atkin, *Neuroleptic malignant syndrome after venlafaxine.* Lancet, 2000. **355**(9200): p. 289-90.

24. Cassidy, E.M. and V. O'Kearne, *Neuroleptic malignant syndrome after venlafaxine.* Lancet, 2000. **355**(9221): p. 2164-5 comment on nimmagadda.

25. Carbone, J.R., *The neuroleptic malignant and serotonin syndromes.* Emergency Medicine Clinics of North America, 2000. **18**(2): p. 317-25.

26. Demirkiran, M., J. Jankovic, and J.M. Dean, *Ecstasy intoxication: an overlap between serotonin syndrome and neuroleptic malignant syndrome.* Clinical Neuropharmacology, 1996. **19**(2): p. 157-164.

27. Hund, E. and B. Wildemann, *Neuroleptic malignant syndrome following tricyclic antidepressant overdose.* Intensive Care Medicine, 1994. **23**: p. 480-481.

28. Heyland, D. and M. Sauve, *Neuroleptic malignant syndrome without the use of neuroleptics.* Canadian Medical Association Journal, 1991. **145**: p. 817-819.

29. Parsa, M.A., et al., *Neuroleptic malignant syndrome without neuroleptics.* Journal of Clinical Psychopharmacology, 1990. **10**: p. 437-438.

30. Kline, S.S., et al., *Serotonin syndrome versus neuroleptic malignant syndrome as a cause of death.* Clinical Pharmacy, 1989. **8**([letter]): p. 510-514.

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

32. Fink, M., *Toxic serotonin syndrome or neuroleptic malignant syndrome.* Pharmacopsychiatry, 1996. **29**: p. 159-161.

33. Dosi, R., et al., *Serotonin syndrome versus neuroleptic malignant syndrome: a challenging clinical quandary.* BMJ Case Rep, 2014. **2014**.

34. Perry, P.J. and C.A. Wilborn, *Serotonin syndrome vs neuroleptic malignant syndrome: A contrast of causes, diagnoses, and management.* Ann Clin Psychiatry, 2012. **24**(2): p. 155-62.

35. Sokoro, A.A., J. Zivot, and R.E. Ariano, *Neuroleptic malignant syndrome versus serotonin syndrome: the search for a diagnostic tool.* Ann Pharmacother, 2011. **45**(9): p. e50.

36. Nisijima, K., K. Shioda, and T. Iwamura, *Neuroleptic malignant syndrome and serotonin syndrome.* Progress in Brain Research, 2007. **162**: p. 81-104.

37. Kaufman, K.R., et al., *Neuroleptic malignant syndrome and serotonin syndrome in the critical care setting: case analysis.* Annals of Clinical Psychiatry, 2006. **18**(3): p. 201-4.

38. Gillman, P.K., *Defining toxidromes: serotonin toxicity and neuroleptic malignant syndrome: A comment on Kontaxakis et al.* Archives of General Hospital Psychiatry, 2004: p. http://www.general-hospital-psychiatry.com/content/2/1/10/comments#41454.

39. Whyte, I.M., *Neuroleptic malignant syndrome.*, in *Medical Toxicology*, R.C. Dart, Editor. 2004, Lippincott Williams & Wilkins: Baltimore. p. 101-103.

40. Gillman, P.K., *Neuroleptic malignant syndrome: half a century of uncertainty suggests a Chimera.* Pharmacoepidemiology and Drug Safety, 2010. **19**(8): p. 876-7.

41. Isbister, G.K., F. Downes, and I.M. Whyte, *Olanzapine and serotonin toxicity.* Psychiatry Clin Neurosci, 2003. **57**(2): p. 241-2.

42. Isbister, G.K. and I.M. Whyte, *Atypical presentation of risperidone toxicity.* Veterinary and Human Toxicology, 2002. **44**(2): p. 118-9.

43. Isbister, G.K., A.H. Dawson, and I.M. Whyte, *Comment: neuroleptic malignant syndrome associated with risperidone and fluvoxamine.* Ann Pharmacother, 2002. **36**(7): p. 1294.

44. Whyte, I.M. and G.K. Isbister, *Misdiagnosis of myoclonus in antidepressant induced serotonin excess.* Vet Hum Toxicol, 2001. **43**(6): p. 375-6.

45. Reeves, R. and J. Bullen, *Serotonin syndrome produced by paroxetine and low-dose trazodone.* Psychosomatics, 1995. **36**(2): p. 159-160.

46. Miyaoka, H. and K. Kamijima, *Encephalopathy during amitriptyline therapy - are neuroleptic malignant syndrome and serotonin syndrome spectrum disorders.* International Clinical Psychopharmacology, 1995. **10**(4): p. 265-267.

47. Godinho, E.M., A.E. Thompson, and D.J. Bramble, *Neuroleptic withdrawal versus serotonergic syndrome in an 8-year-old child.* Journal of Child and Adolescent Psychopharmacology, 2002. **12**(3): p. 265-70.

48. Haslett, C.D. and S. Kumar, *Can olanzapine be implicated in causing serotonin syndrome?* Psychiatry Clin Neurosci, 2002. **56**(5): p. 533-5.

49. Chopra, P., C. Ng, and I. Schweitzer, *Serotonin syndrome associated with fluoxetine and olanzapine.* World Journal of Biological Psychiatry, 2004. **5**(2): p. 114-5.

50. Suchard, J. and R. Erickson, *Serotonin Syndrome from Acute Olanzapine Overdose.* Journal of Toxicology. Clinical Toxicology, 2004. **42**: p. 718.

51. Gillman, P.K., *Misleading cases.* Journal of the American Medical Directors Association, 2005. **6**: p. 422-3.

52. Gillman, P.K., *More misleading case reports.* Anaesthesia, 2005: p. http://www.anaesthesiacorrespondence.com/Correspond3.asp?articleid=4345&archive=.

53. Isbister, G.K. and N.A. Buckley, *Clomipramine and neuroleptic malignant syndrome: literature on adverse reactions to psychotropic drugs continues to confuse.* British Medical Journal, 2005. **330**(7494): p. 790-1.

54. Lu, T.C., et al., *Neuroleptic malignant syndrome after the use of venlafaxine in a patient with generalized anxiety disorder.* Journal of the Formosan Medical Association, 2006. **105**(1): p. 90-3.

55. Uguz, F. and E. Sonmez, *Neuroleptic malignant syndrome following combination of sertraline and paroxetine: a case report.* General hospital psychiatry, 2013. **35**(3): p. 327. e7-327. e8.

56. Fink, M. and M.A. Taylor, *The many varieties of catatonia.* European Archives of Psychiatry and Clinical Neuroscience, 2001. **251 Suppl 1**: p. I8-13.

57. Taylor, M.A. and M. Fink, *Catatonia in psychiatric classification: a home of its own.* American Journal of Psychiatry, 2003. **160**(7): p. 1233-41.

58. Fink, M. and M.A. Taylor, *Treat TSS and NMS as Maligant Catatonia.* British Medical Journal, 2005: p. http://www.bmj.com/rapid-response/2011/10/30/treat-tss-and-nms-maligant-catatonia

http://www.bmj.com/rapid-response/2011/10/30/nms-tss-or-mc.

59. Haddow, A.M., et al., *Clomipramine induced neuroleptic malignant syndrome and pyrexia of unknown origin.* British Medical Journal, 2004. **329**(7478): p. 1333-5.

60. Kontaxakis, V.P., et al., *Olanzapine-associated neuroleptic malignant syndrome: Is there an overlap with the serotonin syndrome?* Archives of General Hospital Psychiatry, 2003. **2**(1): p. 10.

61. Kontaxakis, V.P., et al., *Neuroleptic malignant syndrome after addition of paroxetine to olanzapine.* Journal of Clinical Psychopharmacology, 2003. **23**(6): p. 671-2.

62. Kontaxakis, V.P., et al., *Neuroleptic-induced catatonia or a mild form of neuroleptic malignant syndrome?* Neuropsychobiology, 1990. **23**(1): p. 38-40.

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

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

65. Strawn, J.R., P.E. Keck, Jr., and S.N. Caroff, *Neuroleptic malignant syndrome.* American Journal of Psychiatry, 2007. **164**(6): p. 870-6.

66. Caroff, S., et al., *Neuroleptic malignant syndrome*, in *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*, S.J. Frucht and S. Fahn, Editors. 2005, Humana Press Inc.: Totowa, NJ. p. 41-51.

67. Hasan, S. and P. Buckley, *Novel antipsychotics and the neuroleptic malignant syndrome: a review and critique.* American Journal of Psychiatry, 1998. **155**(8): p. 1113-6.

68. Trollor, J.N., et al., *Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics.* BJP, 2012.

69. Nakamura, M., et al., *Mortality of neuroleptic malignant syndrome induced by typical and atypical antipsychotic drugs: a propensity-matched analysis from the Japanese Diagnosis Procedure Combination database.* J Clin Psychiatry, 2012. **73**(4): p. 427-30.

70. Gurrera, R., *Neuroleptic malignant syndrome controversies revisited-what is the incidence of neuroleptic malignant syndrome?* Pharmacoepidemiol Drug Saf, 2011. **20**(6): p. 659.