Letter to the Editor

'Withdrawal neuroleptic malignant syndrome': a phantom explanatory cause for a fatality

I wish to draw your readers' attention to important issues concerning the report by Ball *et al.*,¹ using my perspective as one of the only researchers who has published reviews of both neuroleptic malignant syndrome (NMS) and serotonin toxicity (ST, a.k.a. serotonin syndrome).^{2,3} Ball *et al.* are not clear about what they mean by 'withdrawal NMS'. It is not an established term and no review I know of mentions it. They refer to at least two distinct ideas. However, the references they provide fail to substantiate their points, are outdated (only 2/7 are from this decade) and unrepresentative of the literature in the field, which has advanced usefully in that time. They confound different mechanisms, one which relates to withdrawal of drugs that increase dopamine (DA), i.e. agonists,⁴ the other relates to the opposite effects of either initiation, or withdrawal, of antagonists.^{5,6}

An NMS-like syndrome associated with withdrawal of DA agonists (L-dopa, etc.) has been extensively documented, although, as with NMS, a firm cause-effect relationship has not been established. The subject has been reviewed,^{2,7,8} but it is irrelevant to Ball's report because their patient never had such drugs. What remains is their apparent postulate of a cause-effect relationship between *withdrawal* of DA antagonist (anti-psychotic) drug and NMS, but there is not even evidence of an above-chance association between the two (as vaguely speculated by the poor references provided^{5,6}), never mind a cause-effect relationship.

An extraordinarily convoluted explanation, blatantly violating the law of parsimony, would be required to account for how two opposite mechanisms could both precipitate the same effect.

Also, it is still uncertain whether two related and widely held presumptions about NMS are in fact valid: (1) that there is a definite cause-effect relationship between antipsychotic drugs and NMS, and 2) that NMS represents a unitary and homogenous entity.^{2,9,10} There is no clear definition, convincing theory of aetiology or treatment for NMS after 50 years of study. The incidence across studies varies by an enormous two orders of magnitude.² Formal analysis demonstrates that the relationship between antipsychotic drugs and NMS fails to meet the scientific criteria for establishing cause-effect relationships,² developed by Hill,¹¹ which played the key role in the smoking/cancer debate.¹² That is principally because there is no clear relationship between the drugs, their dosage and the timing of onset of NMS; these things are almost a *sine qua non* for establishing cause and effect.

There is even less basis for their speculations relating to ST and serotonergic drugs, my special area of expertise, and no reference is made to substantive reviews germane to these topics. The cherry-picked reference given¹³ is only a poor-quality, barely relevant case report consisting of

scantly informed speculation by naïve authors with no track record of publication in the field. Ball *et al.* also vaguely refer to other mechanisms and toxidromes, which they fail to delineate or adequately reference.

Their report has other omissions and ambiguities, not all of which can be covered in a brief response. One example must suffice: three days after medication was ceased, under 'observation' in hospital, it is stated the patient 'suddenly collapsed'. That is neither compatible with a diagnosis of NMS (which does not have a 'sudden' onset, but invariably has an ingravescent course), nor is it a medically accurate or satisfactory description of any clinical state. It has no information content and it is almost certainly factually incorrect. There is no mention of preceding medical monitoring such as temperature, blood pressure, mental state, nor any laboratory tests. If such observations were unavailable, or not carried out, then that should be stated. Such absence would be unsatisfactory and would negate the purpose of having the patient in hospital. Indeed, the medical details provided are so vestigial that a diagnosis of NMS can only constitute speculation, and is not sustained by any reliable evidence. They state that a creatine kinase (CK, EC number 2.7.3.2, which is now the accepted nomenclature for this enzyme) of 19,000 U/L is 'extremely high'. That is not correct. Levels well above 20,000 U/L occur in exertional rhabdomyolysis. In a recent study, 25% (of 200 normal subjects) had a level > 10,000 U/L four days after moderate exercise.¹⁴ There is no discussion of the various more common (non-NMS) causes of elevated serum CK/rhabdomyolysis, which include, *inter alia*: exercise, physical trauma, intramuscular injections, and some foods and drugs, including antipsychotics.¹⁵⁻¹⁷

The accepted criteria for NMS, unsatisfactory as they may be, are simply not met. Their proposed entity of 'withdrawal-NMS' is ill-defined and its existence is unsubstantiated: failing to recognize a phantom is hardly an error. Speaking as an author in this field, I am sure this case report will confuse most readers, who will, I suggest, need to think and read further afield for enlightenment.^{8,11}

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P Ken Gillman MRC Psych

PO Box 86, Bucasia, Queensland 4750, Australia

Email: kg@matilda.net.au

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