In Response to Morris et al.'s "Neuroleptic Malignant Syndrome Developing after Acute Overdose with Olanzapine and Chlorpromazine"

Dear Editor,

Morris et al.'s interesting and valuable case report [1] invites further observations and speculations about this mysterious syndrome: we still do not know if neuroleptic malignant syndrome (NMS) involves an abnormal degree of heat generation (and if so from where), or if there is a failure of heat dissipation. It is not even clear that NMS is a primarily hyperthermic syndrome, and this report supports the idea it may not be. The term hyperthermia is not usually precisely defined: elevated temperature is not a significant problem until it reaches ~40°C and, as in this case, many patients with diagnosed NMS do not exceed 39°C, even with only conservative treatment [2]. Therefore, NMS is a misleading term: it is hardly justified to call the syndrome malignant, it occurs frequently without dopamine antagonist drugs of any sort [3], and it is often not hyperthermic.

This report is especially interesting because it documents the deterioration of the mental and neurological state in the absence of significant hyperthermia (maximum 39°C); and it shows how changes unrelated to hyperthermia become life threatening early in development of the syndrome.

The usefulness of bromocriptine is unclear, and in this case seemingly of no benefit, despite early initiation. Bromocriptine is not only a dopamine agonist but also a serotonin 5-HT_{2A} agonist [4]. This property promotes hyperthermia, because 5-HT_{2A} receptor activation mediates hyperthermia in serotonin toxicity, and worsens the outcome in other models of hyperthermia like malignant hypothermia (MH) and heatstroke [5]; conversely, 2A antagonism improves such states. A DA agonist that is also a 5-HT_{2A} antagonist, like apomorphine [6], may be preferable, the theoretical rationale being that D₂ agonism promotes heat loss [7]. This has been reported as an efficacious strategy in the NMS-like condition, Parkinsonism-hyperpyrexia syndrome (PHS) [8].

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