

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome is one of a number of complications of treatment with neuroleptic medication. While common side effects include sedation, irritability, and apathy, the most worrying disorders are the extrapyramidal dystonic reactions. These reactions may broadly be classified as acute, late onset, and withdrawal emergent.¹

There are two common acute reactions: parkinsonism and akathisia. Parkinsonism is produced by neuroleptic action on nigrostriatal dopamine receptors with characteristic involuntary tremor, skeletal muscle rigidity, and bradykinesia. Features are similar to those of Parkinson's disease, where depletion of pigmented cells in the substantia nigra results in reduced dopaminergic activity, and imbalance between dopaminergic and cholinergic neuronal systems. Benztropine, and to a lesser extent benzhexol and orphenadrine, inhibit neuronal reuptake of dopamine and block cholinergic muscarinic receptors, thereby alleviating these parkinsonian symptoms.

Akathisia is the other common and troublesome acute extrapyramidal side effect. It consists of a subjective sensation of overwhelming restlessness that frequently manifests as repeated pacing about.²

The main late onset reaction to neuroleptic medication, tardive dyskinesia, consists of rhythmic spontaneous movements of mouth and tongue, occasionally with choreiform movements in the limbs. It is irreversible once established. Risk of this complication is related to the patient's age, duration of treatment and dose, presence of brain damage, and the chronic use of antiparkinsonian drugs. The mechanism is not fully understood, but may be due to dopaminergic hypersensitivity in the nigrostriatal system with relative reduction in cholinergic functioning. Medication should be stopped if possible. Increased dosage will decrease dopaminergic activity but is more harmful in the long term.³

Withdrawal emergent symptoms are adverse drug reactions which manifest only when medication has been withdrawn. Clinical presentation is characterised by involuntary movements and ataxia that may only remit once medication has been reintroduced.⁴

Neuroleptic malignant syndrome

The most serious of the adverse reactions to neuroleptic medication is the neuroleptic malignant syndrome. This comprises an idiosyncratic reaction to the neuroleptic recognised by its characteristic clinical features of altered sensorium, muscular rigidity, hyperpyrexia of unknown origin, and autonomic dysfunction.⁵ The extreme peripheral muscle spasm had once been considered sufficient to generate the dramatic rise in body temperature. This view was supported by *in vitro* muscle biopsy studies and beneficial effects of dantrolene. However it is now thought more likely that, at least in the early stages, the hyperpyrexia has a central origin arising from sudden disturbance of dopaminergic pathways within hypothalamic thermoregulatory centres. In support of this view is work demonstrating prolonged hyperthermia following phenothiazine injection into animal rostral hypothalamus, and the usefulness of centrally

acting drugs such as bromocriptine and curare. Laboratory investigation often demonstrates raised creatine phosphokinase and serum potassium concentrations indicative of skeletal muscle necrosis, although absence of positive laboratory indices is compatible with the diagnosis, as these are secondary or non-specific.⁶

Neuroleptic malignant syndrome occurs in 0.5-1% of patients on antipsychotic treatment, can strike at any age, and can be rapidly fatal.⁷ Such reactions have been reported as being commoner in infants, particularly with associated exhaustion, dehydration, or fever.⁸ Brain damaged individuals are thought to be more susceptible to the syndrome.⁹ Anticholinergics are of little use.⁶ The syndrome's development is unrelated to dosage or duration of medication.⁷ Piperazine and butyrophenone are major tranquillisers that are particularly associated with the neuroleptic malignant syndrome in childhood, although any antipsychotic medication may precipitate the condition.⁷ Symptoms of neuroleptic malignant syndrome may spontaneously remit despite continued neuroleptic medication, with later fatal recurrence.¹⁰ It is particularly important to differentiate between commoner extrapyramidal side effects, which characteristically respond to anticholinergic medication, and neuroleptic malignant syndrome which may be worsened by antiparkinsonian agents but is helped by dopamine-2 agonists like bromocriptine.

Treatment consists of stopping medication, rehydration, measures to reduce fever, adequate monitoring, and support of cardiovascular, respiratory, renal and other vital functions, and specific antidote medications—for example, dantrolene or bromocriptine.¹¹

Successful simultaneous administration of the neuroleptic and bromocriptine has been undertaken, thereby circumventing the 'catch 22' situation of an individual with incapacitating psychosis as well as neuroleptic malignant syndrome.¹²

Conclusion

Clinicians must be alert to the possibility of rare but serious side effects to neuroleptic medication in childhood and adolescence. Certain factors, including the individual's age and coexisting brain damage, may predispose to the conditions. Clinical presentation is similar to adulthood, but may more readily be misattributed to non-organic or other physical causes.

Early accurate diagnosis is essential in order to ensure appropriate treatment and the individual's physical safety.

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