

DRUG-INDUCED DELIRIUM

Delirium is acute cognitive dysfunction, with inattention and altered level of consciousness, that often fluctuates in severity. It is common (affecting about one third of elderly medical inpatients), and is associated with increased morbidity and mortality, prolonged hospital stay and increased likelihood of rest home placement. The pathophysiology is not clearly defined, but impaired central cholinergic transmission and cholinergic/dopaminergic imbalance are thought to be involved. The aetiology is usually multifactorial and a full medical workup is required. Drugs have been implicated in around 30% of all cases, making them the most common 'reversible' cause.

Risk Factors

- *Age* – the risk of delirium from all causes increases with age. Altered pharmacokinetics (eg reduced clearance) and pharmacodynamics (eg increased CNS sensitivity) predispose the elderly to adverse drug effects including delirium
- *Underlying brain disease* – eg dementia, cerebrovascular disease, Parkinson's disease
- *Polypharmacy* - see below
- *Comorbidities* - medical illness (particularly infection), surgery, pain, poor functional status

Drugs

Virtually any drug can be associated with delirium, however drugs with anticholinergic effects have the highest potential, in a dose-related fashion.

Highly lipid soluble drugs cross the blood-brain barrier readily and are more likely to cause central nervous system effects than more water soluble drugs.

The initiation of three or more drugs over a 24-hour period is an independent predictor of delirium.

Specific drugs that have been strongly associated with delirium include:

- *tricyclic antidepressants (TCAs)* – amitriptyline (strongly anticholinergic) more so than nortriptyline
- *hypnotics* eg zopiclone, benzodiazepines (particularly long-acting agents such as diazepam)
- *opioid analgesics* – pethidine more than morphine
- *phenothiazines* eg chlorpromazine, prochlorperazine
- *sedating antihistamines* eg promethazine, cyclizine
- *antispasmodics* eg oxybutinin, hyoscine
- *antiparkinsonian agents* including levodopa, anticholinergics (eg benztropine), dopamine agonists (eg pergolide)
- *other* – corticosteroids, digoxin, anticonvulsants (especially phenytoin and carbamazepine), lithium, lipophilic beta blockers (eg metoprolol), metoclopramide, ciprofloxacin, selective serotonin reuptake inhibitors (SSRIs, eg fluoxetine), nonsteroidal anti-inflammatories, H₂-receptor antagonists

Assessment

Delirium tends to be underdiagnosed - maintain a high index of clinical suspicion. A careful drug history is important - use family/GP/pharmacist for collateral history. Remember to consider alcohol, benzodiazepines, drugs of abuse, over-the-counter, herbal and 'prn' medications. Therapeutic drug monitoring may be helpful, but in the elderly toxic effects may occur within the normal therapeutic range (eg digoxin, phenytoin).

Management

Prevention - when possible, avoid polypharmacy and anticholinergic drugs in at-risk individuals.

Treatment - offending drugs should be withdrawn. Delirium may take weeks/months to subside completely after removal of an underlying precipitant. The dopamine antagonist haloperidol is the drug of choice if pharmacotherapy is needed, as it has minimal anticholinergic, sedating or autonomic effects. Akathisia (severe motor restlessness) is an extrapyramidal side effect of haloperidol that should not be mistaken for worsening delirium. Benzodiazepines may aggravate delirium and should be avoided if possible. Non-pharmacologic management is important. Refer to 'Blue Book 2003' for more detailed information on the management of delirium. Consider referral to the Delirium Service if management is problematic.

Specific Situations

- *Drug/alcohol withdrawal*: usually an agitated delirium. Re-instate the medication (eg benzodiazepines, opioids, SSRIs) and withdraw more slowly in the future if drug cessation is planned. For alcohol withdrawal use benzodiazepines eg diazepam.
- *Serotonin syndrome*: can occur when pro-serotonergic drugs are combined (eg SSRIs, monoamine oxidase inhibitors, TCAs, tramadol, pethidine, sumatriptan, St John's wort). Features include delirium, myoclonus, fever/sweats, diarrhoea and tachycardia.
- *Neuroleptic malignant syndrome*: may occur with any antipsychotic/dopamine antagonist, and presents as delirium, fever, extrapyramidal signs, raised plasma CK and leukocytosis.