<table>
<thead>
<tr>
<th>Study</th>
<th>Sources Summary</th>
<th>Summary (continued)</th>
<th>Summary (continued)</th>
</tr>
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<tbody>
<tr>
<td>Moore 1999</td>
<td>Search methodology / Databases searched</td>
<td>Delirium (continued)</td>
<td>CNS toxicity may develop</td>
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<tr>
<td></td>
<td>Not described</td>
<td>Other associations</td>
<td>- dose dependent manner</td>
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<tr>
<td>Clinical Review</td>
<td>Delirium</td>
<td>- high mortality rate</td>
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<tr>
<td>Purpose</td>
<td>Definition: an acute organic disturbance of higher cerebral function associated with impaired ability to attend to the environment</td>
<td>- prolonged duration of hospital stay</td>
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<td></td>
<td>- rapid onset</td>
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<td>- cognitive disturbance fluctuates over the day</td>
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<td>- disorientation</td>
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<td>- poor short term memory</td>
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<td>- altered level of consciousness</td>
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<td></td>
<td>- possible disturbance of the sleep/wake cycle</td>
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<td>- possible development of hallucinations or delusions</td>
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<td>- possible psychomotor disturbance (hyper- or hypo-activity)</td>
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<td></td>
<td>This cognitive disturbance is most clearly associated with drug toxicity</td>
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<td></td>
<td>Pathophysiology</td>
<td>Dementia due to drug toxicity</td>
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<td></td>
<td>Most widely accepted theory = the clinical manifestation of diffuse, reversible impairment of cerebral oxidative metabolism and neurotransmission</td>
<td>Medication toxicity accounts for between 2% and 12% of cases</td>
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<td></td>
<td>- any drug interfering with neurotransmitter function or with the supply or use of substrates for metabolism can cause delirium</td>
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<td></td>
<td>Central cholinergic pathways are highly sensitive to metabolic and toxic insults</td>
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<td>- involved in the regulation of attention, memory and sleep</td>
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<td>- impaired cholinergic neurotransmission may represent the final common pathway for the development of delirium</td>
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<td>- other neurotransmitters implicated in pathogenesis</td>
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<td>- serotonin</td>
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<td>- noradrenaline</td>
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<td>- dopamine</td>
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<td>- GABA</td>
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<td></td>
<td>Clinical significance</td>
<td>Drugs more commonly have an additive effect on cognitive impairment due to underlying brain pathology</td>
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<td>Prevalence in older people</td>
<td>Withdrawal may lead to temporary improvement rather than resolution</td>
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<td>- range = 10-24% on hospital admission</td>
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<td>- range = additional 5-32% develop after admission</td>
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<td></td>
<td>Predisposing factors</td>
<td>Cognitive impairment due to anticholinergic drugs</td>
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<td></td>
<td>- advanced age</td>
<td>Aging and the risk of anticholinergic toxicity</td>
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<td></td>
<td>- existing dementia</td>
<td>Healthy elderly individuals are more sensitive to the cognitive effects of anticholinergic agents than younger individuals</td>
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<td>- severe illness</td>
<td>Elderly individuals are at particular risk for developing cerebral complications of anticholinergic drugs</td>
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<td>Anticholinergic delirium is most common in patients with Alzheimer’s disease (AD)</td>
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<td>Polypharmacy with anticholinergic compounds is common in nursing home residents</td>
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<td>Clinical features of anticholinergic toxicity</td>
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<td>Subtle neuropsychological deficits</td>
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<td>- memory</td>
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<td>- attention</td>
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<td>- delirium</td>
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<td>Peripheral autonomic anticholinergic toxicity</td>
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<td>- may or may not be present</td>
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<td>Chronic cognitive deficits may mimic AD</td>
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**Cognitive impairment due to anticholinergic drugs**

Drugs causing anticholinergic toxicity
- scopolamine
- atropine
- midriatics (atropine eyedrops)
- drugs used in Parkinson’s disease (trihexyphenidyl, penzatropine, oxybutynin

Importance of total anticholinergic load
Whether a patient will develop cognitive impairment or not when prescribed a particular drug with anticholinergic properties is unpredictable; depends on
- co-medications with anticholinergic effects (including OTC)
- baseline cognitive status
- individual pharmacokinetic variations
- pharmacodynamic changes that may accompany disease states

Endogenous anticholinergic activity may lower the threshold for anticholinergic toxicity

Studies suggest it is often the total burden of anticholinergic drugs that determines the development of delirium rather than any single agent

Serum radioreceptor assay can predict delirium in surgical and medical patients
- reduction in serum anticholinergic activity is associated with improvement in cognitive function

**Cognitive impairment due to psychoactive drugs**

**Hypnotics/sedatives**
- Benzodiazepines
  - longer acting (flurazepam, diazepam)
  - high dose
  - chronic treatment
  - sudden withdrawal of short acting benzodiazepines a common cause of delirium in hospitalized patients

- Barbiturates
  - chronic cognitive impairment may mimic AD
  - excessive sedation lowers threshold for developing delirium or dementia
  - withdrawal syndrome from long term barbiturates

**Opioid analgesics**
- Among the most important causes of delirium in postoperative patients
- postoperative pain also predisposes to delirium

- Meperidine seems to be the most deliriogenic narcotic

**Antipsychotics**
- Phenothiazines
  - risk greatest in patients taking several medications and older patients

- Atypical antipsychotics with considerable anticholinergic activity
  - clozapine
  - thiothixene
  - chlorpromazine

**Neuroleptic malignant syndrome**
- clinical features = muscle rigidity; autonomic instability; fluctuating consciousness
- predisposing factors
  - dehydration
  - use of long-acting or high doses
  - rapid dose increases
  - abrupt discontinuation of antiparkinsonian agents or antipsychotics
  - concurrent lithium therapy

**Antiparkinsonian drugs**
- Levodopa (incidence = about 5%)
- Pergolide (incidence = 11 to 33%)
- Bromocriptine (incidence = about 12%)

- Delirium must be distinguished from isolated hallucinations which is also common during treatment with levodopa or other dopaminergic agents (incidence = 20 to 35%)

**Antidepressants**
- Tricyclic antidepressants (TCAs)
  - significant anticholinergic actions
  - TCA induced delirium incidence = about 1.2%
  - TCA CSN toxicity incidence = about 6%

  - risk factors
    - TCA plasma concentration
    - advanced age
    - female gender
    - amitriptyline or imipramine risk = about 5%
    - less risk with desipramine and nortriptyline

**SSRIs and MAIOs rarely cause major cognitive impairment of delirium**
- SSRI + MAOI
- SSRI + clomipramine
- SSRI + selegiline

- SSRI induced hyponatremia also associated with delirium

Delirium is a recognized feature of lithium toxicity

**Anticonvulsants**
- All anticonvulsant drugs can impair cognitive function
- Maximal cognitive deficits seen with
  - phenytoin
  - primidone
  - phenobarbital

- Maximal impairment seen in patients with polypharmacy
- Mild deficits with
  - carbamazepine
  - valproic acid
  - newer anticonvulsants

- There is high prevalence of underlying brain disease, especially in elderly people with seizures, the occurrence of delirium and psychosis during and after seizures and the propensity of anticonvulsants to be involved in drug interactions makes it difficult to determine the cognitive effects of anticonvulsants independent of other factors

- CNS toxicity can occur within the “normal” therapeutic range of anticonvulsant drugs in older people
### Cognitive impairment due to nonpsychoactive drugs

**Histamine H₂ receptor antagonists**
- Cimetidine has been involved in most reports of CNS toxicity
  - no evidence for differences in the incidence of CNS reactions to different H₂ antagonists
- CNS toxicity rare in outpatients, incidence is approximately 1 to 2% of all hospital patients and 15 to 80% of intensive care patients treated with these drugs
- Most toxicity occurs in elderly patients
- Patients with renal dysfunction may be at greater risk
- CNS toxicity not usual with H₂ antagonist overdose; many episodes of H₂ antagonist-induced delirium have developed with standard drug doses and normal organ function

**Cardiac drugs**
- CNS symptoms may be the first and only manifestation of digoxin toxicity and are most common in the elderly
- Cognitive impairment due to digoxin can occur with normal serum digoxin concentrations as well as overdose
- Class IA antiarrhythmic agents with significant anticholinergic effects
  - disopyramide
  - quinidine
  - procainamide
- Idiosyncratic reports of delirium
  - calcium antagonists
  - ACE inhibitors
  - amiodarone
  - lignocaine
- Beta blockers
  - chronic cognitive impairment and “pseudodementia” reported
  - topical Timolol
- Metyldopa
  - reported to cause impaired mental function and to produce delirium and dementia

### Summary (continued)

### Cognitive impairment due to nonpsychoactive drugs

**Corticosteroids**
- Hospitalized patients treated with prednisone
  - 1.6% = <40 mg/d
  - 4.6% = 40-80 mg/d
  - 18.4% = >80 mg/d
- Chronic cognitive deficits in attention, concentration and memory have also been reported
- Hypercortisolemia, as part of the stress response, has been implicated in the pathogenesis of non-medication related delirium and dementia and of age-associated cognitive decline
- Brief exposure to high levels of corticosteroids cause reversible dysfunction in neurons in the hippocampus; prolonged exposure can cause permanent hippocampal damage

**Nonsteroidal anti-inflammatory drugs (NSAIDs)**
- The elderly are more prone to develop salicylate toxicity; delirium is one manifestation of this disturbance
- More commonly, delirium due to NSAIDs is an idiosyncratic phenomenon
- Indomethacin and sulindac have been reported to cause paranoid psychosis and delirium
- Acute, clinically significant disturbance of memory and concentration have been reported in elderly patients following treatment with naproxen or ibuprofen

### Antibiotics

**Risk factors**
- prior psychiatric illness
- severe medical illness
- slow acetylator status
- advanced age
- renal impairment
- increased permeability of the blood-brain barri
- high dosage
- intrathecal or intravenous administration

### Prevention of drug induced cognitive impairment

- The risk of drug induced confusion increases with the number of drugs prescribed
- Nonessential drugs should be kept to a minimum in elderly people
- Special care is needed for people with pre-existing cognitive impairment
- Psychoactive and those drugs with anticholinergic activity should be avoided whenever possible
- Routine use of brief mental test scores not only improves detection of cognitive deficits, but provides a baseline against which possible changes can be measured
- Serum concentrations of medications can be useful as a guide to safe prescribing for agents with a narrow therapeutic index such as digoxin, theophylline, anticonvulsants and lithium

### Management of drug induced cognitive impairment

- The management of patients with cognitive impairment requires a critical review of all medications which together or singly might be contributing to or have led to the impairment
- Anticholinergic and antipsychotic drugs should be the first for consideration of discontinuation.
- In patients with delirium, it is often appropriate to stop as many medications as possible, although this may give rise to difficulty in determining which drug had been causing the problem.

### Conclusion:

- Usually the main suspects for causing drug induced cognitive impairment are the anticholinergic and antipsychotic drugs.
- In the case of anticholinergic drugs, there is good evidence that it is the combination of multiple drugs which is most likely to precipitate or predispose to cognitive impairment.