

REVIEW

An approach to drug induced delirium in the elderly

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Postgrad Med J 2004;**80**:388–393. doi: 10.1136/pgmj.2003.017236

Drugs have been associated with the development of delirium in the elderly. Successful treatment of delirium depends on identifying the reversible contributing factors, and drugs are the most common reversible cause of delirium. Anticholinergic medications, benzodiazepines, and narcotics in high doses are common causes of drug induced delirium. This article provides an approach for clinicians to prevent, recognise, and manage drug induced delirium. It also reviews the mechanisms for this condition, especially the neurotransmitter imbalances involving acetylcholine, dopamine, and gamma aminobutyric acid and discusses the age related changes that may contribute to altered pharmacological effects which have a role in delirium. Specific interventions for high risk elderly with the goal of preventing drug induced delirium are discussed.

Drugs are one of the common risk factors for delirium and may be considered the most easily reversible trigger. Drug induced delirium is commonly seen in medical practice, especially in hospital settings. The risk of anticholinergic toxicity is greater in the elderly, and the risk of inducing delirium by medications is high in the frail elderly, and those with dementia. In addition to polypharmacy, altered pharmacokinetics and pharmacodynamics seen with aging, and associated co-morbid diseases, have an additive or synergistic role with drugs in causing delirium.

Many drugs have been associated with delirium, but certain classes of drugs (deliriants) (box 1) are more commonly viewed as causative agents for delirium.

The most common deliriants include high dose narcotics, benzodiazepines, and anticholinergic medications. Anticholinergic activity is also associated with the occurrence and severity of delirium.^{1,2} A number of studies have shown that anticholinergic medication use is a common precipitating risk factor.^{3,4} While delirium is a multifactorial process, it is estimated that medications alone may account for 12%–39% of all cases of delirium.^{5–7}

CLINICAL RECOGNITION OF DRUG INDUCED DELIRIUM

In the elderly who have acute confusion or acute on chronic confusion, delirium can be diagnosed by applying confusion assessment method criteria. Since delirium is often multifactorial, medications can be contributing in combination

with, for example, infections, structural, metabolic, or environmental causes. Sometimes drugs may be the sole cause of delirium. Clinicians should be aware of medications with a significant anticholinergic effect. They should also be cautioned that the addition of medications with mild to moderate anticholinergic levels to an already complicated medical regimen carries with it the potential risk of negatively affecting the patient's cognition. In patients who develop delirium a record of all medications and supplements given within the past few weeks should be carefully obtained. The most effective initial step is to review the medication list and attention should be given to the delirogenic drugs, the anticholinergic load of these medications, and possible drug interactions. Sometimes it is clear which drug is responsible for an episode of delirium because of a temporal relationship. If not, the clinician should carefully analyse the patient's history and look for a characteristic constellation of drug related findings. Any recent addition of a new medication or increase in dose should be verified. In situations where an elderly patient is likely to combat anticholinergic effects of multiple medications, the patient should often be examined for signs of anticholinergic toxicity.⁸ Specific syndromes such as serotonin syndrome and neuroleptic malignant syndrome caused by medications can also present as delirium with other features seen.

Drugs can cause any of the three types of delirium: hyperactive, hypoactive, and mixed delirium. Both hyperactive and mixed delirium are commonly seen in cholinergic toxicity, alcohol intoxication, certain illicit drug (stimulant) intoxication, serotonin syndrome, alcohol and benzodiazepine withdrawal. By contrast, hypoactive delirium is often due to benzodiazepines, narcotic overdose, or sedative hypnotic or alcohol intoxication.

MEDICATIONS ASSOCIATED WITH DELIRIUM

Many groups of drugs can cause delirium. This includes prescription, over the counter, complementary/alternative, or illicit products. Observational studies show that the most common drugs associated with delirium are sedative hypnotics (benzodiazepines), analgesics (narcotics), and medications with an anticholinergic effect. Other medications in toxic doses can also cause delirium. Drugs may indirectly contribute

Abbreviations: GABA, gamma aminobutyric acid; NMDA, N-methyl-D-aspartate; NSAIDs, non-steroidal anti-inflammatory drugs

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Submitted
16 November 2003
Accepted 16 January 2004

Box 1: Deliriant (drugs causing delirium)**Prescription drugs**

- Central acting agents:
 - Sedative hypnotics (for example, benzodiazepines).
 - Anticonvulsants (for example, barbiturates).
 - Antiparkinsonian agents (for example, benzotropine, trihexyphenidyl).
- Analgesics:
 - Narcotics (NB. meperidine*).
 - Non-steroidal anti-inflammatory drugs*.
- Antihistamines (first generation—for example, hydroxyzine).
- Gastrointestinal agents:
 - Antispasmodics.
 - H₂-blockers*.
- Antinauseants:
 - Scopolamine.
 - Dimenhydrinate.
- Antibiotics:
 - Fluoroquinolones*.
- Psychotropic medications:
 - Tricyclic antidepressants.
 - Lithium*.
- Cardiac medications:
 - Antiarrhythmics.
 - Digitalis*.
 - Antihypertensives (β-blockers, methyldopa)
- Miscellaneous:
 - Skeletal muscle relaxants.
 - Steroids.

Over the counter medications and complementary/alternative medications

- Antihistamines (NB. first generation— for example, diphenhydramine, chlorpheniramine).
- Antinauseants (for example, dimenhydrinate, scopolamine).
- Liquid medications containing alcohol.
- Mandrake.
- Henbane.
- Jimson weed.
- Atropa belladonna extract.

* Requires adjustment in renal impairment.

to delirium by causing syndromes such as serotonin syndrome, neuroleptic malignant syndrome, or secretion of inappropriate antidiuretic hormone.

(A) Cardiovascular drugs

The antiarrhythmic drug disopyramide has strong anticholinergic effects and can induce delirium. In the elderly, because of the decreased renal clearance, even normal doses

of digoxin can accumulate and cause toxicity and delirium. Beta-blockers, especially propranolol, have been reported to cause delirium.⁹ Diuretics can induce delirium by dehydration and electrolyte disturbances.

(B) Pulmonary drugs

Theophylline and steroids in high doses may be contributors to delirium. Often these medications are used in patients with poor oxygenation, which in itself can increase the risk of delirium.

(C) Central nervous system drugs

Benzodiazepines are lipid soluble medications that have a prolonged half life in the elderly because of accumulation in lipid tissue. Because of the extended duration of action and increased sensitivity to sedative hypnotics in the elderly, benzodiazepines can cause delirium. Benzodiazepines are independently associated as a risk factor for delirium.¹⁰

All antidepressants can contribute to delirium. The tricyclic antidepressants have an anticholinergic effect and can induce delirium. Of the selective serotonin uptake inhibitors, paroxetine has the greatest affinity for muscarinic receptors, similar to nortriptyline.¹¹ Dopaminergic medications such as levodopa or dopamine agonists can contribute to delirium in a dose related manner. For these necessary medications, a dosage reduction or adjusting the dosage schedule may be helpful. If antiparkinsonism medications are suspected of causing confusion, anticholinergic medications (for example, trihexyphenidyl) should be the first to be discontinued, followed by selegiline, dopamine agonists and finally by tapering levodopa. Delirium occurs usually with end stage Parkinson's disease and with high doses of medications. In elderly patients with dementia, lithium can cause delirium even at therapeutic serum levels.¹² Narcotics are also independent risk factors for delirium. Meperidine (demerol, pethidine) is often avoided in seniors due to accumulation in decreased renal function. Meperidine is converted to an anticholinergic metabolite that can cross the blood-brain barrier and lead to delirium. All other opioids can cause delirium if excessive doses are used.

(D) Role of anaesthetic agents in postoperative delirium

The incidence of postoperative delirium varies from 10%–26%. Ketamine is an intravenous anaesthetic agent and has been associated with excitability, vivid unpleasant dreams, and delirium. Delirium has also been associated with inhalational anaesthetics.¹³

(E) Miscellaneous drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to induce delirium. Some NSAIDs can cross the blood-brain barrier. In addition, older antihistamines (for example, diphenhydramine, dimenhydrinate, chlorpheniramine) have potent anticholinergic effects and are associated with delirium.

H₂-blockers, such as cimetidine, ranitidine, and famotidine can cause delirium but there is more evidence with cimetidine. Antispasmodics used for gastrointestinal motility or bladder urgency do have some anticholinergic effects, which can increase the risk of delirium.

(F) Complementary/alternative medicine products

The use of complementary medicine is increasing in North America. While these products are considered to be “natural”, they may contain ingredients or contaminants that can contribute to delirium. Some examples of herbal products that have anticholinergic effects are henbane, jimson weed, and mandrake.^{14 15} Numerous other products and teas have also been associated with delirium. Unfortunately there has

been limited research on the adverse cognitive effects of complementary and alternative medicine products, so the clinical effects may be greater than perceived.

(G) Drug abuse/withdrawal

Use of alcohol or sedative hypnotics is quite common in the elderly. Busto *et al* found that 53% of seniors had used a sedative hypnotic in the past year. Seventeen percent of them used over the counter sedatives, while 83% were using prescription medications.¹⁶ Abrupt withdrawal of drugs such as benzodiazepines can trigger delirium, which is a common situation in hospitalised patients. Chronic alcoholics may have delirium complicated by ataxia and ophthalmoplegia, a condition known as Wernicke's encephalopathy. Alcohol withdrawal may present with prominent anxiety, autonomic hyperactivity, seizures, and delirium tremens.

(H) Poisoning/intoxication

Drug poisoning can cause delirium. Commonly used medications, such as lithium, salicylates, or anticholinergics, can present as delirium if excessive doses are consumed. Environmental exposures to carbon monoxide poisoning, mushroom toxins, and organophosphorus insecticides can present as delirium.

(I) Polypharmacy

Inouye *et al* has observed that the number of medications added before the delirium episode is a risk factor for delirium.¹⁷ Martin *et al* also found an independent association between the number of medications and delirium.¹⁸ This may be because patients using a large number of medications have a significant number of co-morbidities or it may be due to pharmacokinetic or pharmacodynamic drug interactions.

MECHANISMS OF DRUGS CAUSING DELIRIUM

Neurotransmitter imbalances involving acetylcholine, dopamine, and gamma aminobutyric acid (GABA) traversing cortical and subcortical nervous system pathways are seen in delirium.¹⁹ The chemical basis of delirium remains either a diffuse excess of brain dopaminergic activity, a diffuse deficit in brain cholinergic activity, or both.²⁰⁻²¹ Most commonly, a relative excess of dopamine is implicated in the aetiology of the disorder and this may explain why dopamine blockers are helpful in providing symptomatic relief of delirium.

Evidence supports a major role for cholinergic failure in delirium. Anticholinergic intoxication causes a classical delirium syndrome that may be reversible with cholinesterase inhibitors such as physostigmine. Drugs which can cause a muscarinic blockade can lead to delirium. Some of the drugs causing delirium, such as digoxin, lithium, and histamine (H₂)-antagonists show measurable cholinergic receptor binding, even though they are not traditionally classified as anticholinergic.

The mechanisms of drug induced delirium are not well defined. Some hypothesis have been supported by *in vitro* or animal studies. For example, in benzodiazepine withdrawal, a rebound decline in GABAergic function may precipitate delirium. GABA acting at GABA-A receptors inhibits the release of dopamine.²² GABA antagonist or sudden withdrawal from a GABA agonist may increase the risk of a hyperdopaminergic state, which in turn facilitates the action of glutamate at *N*-methyl-D-aspartate (NMDA) receptors.²³ Digoxin, in addition to muscarinic antagonist activity, also inhibits membrane Na⁺K⁺ATPase, which can cause profound disruption of neuronal activity.²⁴ Quinolone antibiotics are NMDA receptor agonists, GABA-A receptor antagonists, and have weak dopaminergic activity.²⁵⁻²⁶ Morphine has been shown to increase the release of dopamine and inhibit neuronal Na⁺ K⁺ATPase.²⁷⁻²⁸ Both codeine and diphenhydramine are muscarinic antagonists, while diphenhydramine

also blocks reuptake of dopamine. Histamine (H₂)-receptor blockers such as ranitidine increase the release of dopamine in addition to muscarinic antagonist activity.²⁹

FACTORS THAT MAY HAVE A ROLE IN THE SUSCEPTIBILITY OF AN INDIVIDUAL TO DRUG INDUCED DELIRIUM

In addition to physiological changes with aging, there are pharmacokinetic and pharmacodynamic changes as well as medical co-morbidities that can increase the susceptibility to a drug induced delirium.

Physiological changes due to aging

In the elderly, response to drugs may be accentuated or modified by age related changes. Among those which may have a role in inducing delirium are an increase in total body fat, decrease in lean body mass and water, decrease in albumin, and decrease in glomerular filtration rate.

Medical co-morbidities

Concurrent medical problems may also contribute to "drug induced delirium". For example, in heart failure, patients have reduced metabolism due to hepatic congestion and reduced elimination of drugs due to renal insufficiency. Hepatic insufficiency leads to reduced synthesis of albumin that can lead to decreased protein binding and a transient larger volume of distribution for some drugs. Renal failure can cause decreased elimination of drugs. The above mentioned conditions may increase the free concentration of certain drugs, thus enhancing their effect, and increasing the risk of delirium. In addition, conditions that lead to hepatic or renal insufficiency cause an accumulation of metabolic by-products that can be toxic.

In stroke and dementia, there is impaired integrity of the blood-brain barrier function, which allows more of a potentially toxic drug to reach the brain. Reduced integrity of blood-brain barrier function is strongly associated with susceptibility to delirium and so many agents are more likely to move into the highly lipophilic brain.³⁰ Because of the relative increase in fat mass with aging, lipophilic agents have an increased volume of distribution, thereby extending the half life of these agents.

Contribution of pharmacokinetic changes to delirium

One of the basic principles in the management of drugs in delirium is to individualise dosage according to patient characteristics. Pharmacokinetic parameters that change with age generally include an extension of the half life, due to reduced metabolic capacity or decreased renal elimination, and volume of distribution, which expands for lipid soluble medications. For water soluble drugs the serum concentration is often much higher because there is reduced volume of distribution. Water soluble drugs that are affected include lithium and ethanol. Digoxin is stored in muscle tissue. In an elderly patient with decreased muscle mass the digoxin reaches a much higher level than expected because the volume of distribution is much smaller.

Metabolism is broken down into two phases. Phase I metabolism refers to oxidation/reduction reactions, where the medications may be transformed into active metabolites. Phase II metabolism involves conjugation, and this tends to produce inactive metabolites. In the elderly, phase I metabolism declines or have reduced activity, while phase II metabolism remains relatively intact. Medications that undergo phase I metabolism may have extended half lives, in addition to having a more unpredictable elimination pattern.³¹ In addition to metabolic changes due to age, medical illness can reduce metabolising capacity. Acute illness such as pneumonia, hip fracture, and inflammatory

conditions can abruptly reduce the cytochrome P450 microsomal enzyme system.³²

Reduced renal function can also contribute to extended high levels of medication. Renal elimination is decreased due to reduced renal blood flow (2% per year after 40), renal mass (10%–20% between 40 and 80 years), and glomerular filtration rate (50% between 50 and 90 years). Calculation of renal function is less accurate in the elderly and often overestimates the actual renal function, due to age related reduction in creatinine, which is secondary to reduced lean body mass.³³

Protein binding also determines volume of distribution. Plasma protein, particularly albumin, is altered with aging. Albumin is often decreased, and α_1 -acid glycoprotein is increased, especially during an inflammatory illness.³⁴ In delirium plasma albumin drops precipitously; conversely α_1 -acid glycoproteins, being acute phase reactants, increase. Thus, by changing the amount of free drug available, protein binding drug interactions may affect mental status by allowing a larger free fraction to cross the blood-brain barrier. Dosage adjustments are generally well defined for renally eliminated medications. Depending on the pharmacodynamics, the dose can be reduced, or the administration interval extended. Adjustments for low albumin are not well established, but it is prudent to administer all drugs, especially highly albumin bound medications in conservative doses during a delirium.

The therapeutic index is a description of how close the therapeutic or effective level of a medication is relative to the toxic level. Digoxin, for example, is viewed as a narrow therapeutic index medication. The effective level is very close to the toxic level, and dosage changes must be made cautiously and with continued monitoring. It is particularly important to monitor narrow therapeutic index medications during acute illness. Decisions on drug adjustments can be made in the context of serum or plasma levels. Because of acute changes in illness, a medication level may be less predictable. However, monitoring drug levels can provide assistance in predicting toxicity.

Drug-drug interactions are also significant. One medication may alter the rate of metabolism, the free fraction, and the volume of distribution of another medication. Monitoring the drug profile in seniors is particularly important, particularly during acute illness.

Contribution of pharmacodynamic changes to delirium

In addition to pharmacokinetic interactions, drugs may interact pharmacodynamically, leading to an enhanced toxic effect. For example, multiple anticholinergic medications, or too many sedating drugs, can lead to an excess toxic effect and can trigger a delirium. It is important to evaluate the total anticholinergic or dopaminergic burden of a patient's drug regimen, which may be important in determining the development of delirium. Knowledge of these interactions can help clinicians predict the risk of two drugs pharmacodynamically interacting to increase the likelihood of delirium.

Seniors experience many receptor changes due to aging. For example, cholinergic receptors appear to be more sensitive.³⁵ Pharmacodynamic changes can therefore produce a more pronounced drug effect for a given serum drug level. Anticholinergic medications also appear to have exaggerated adverse effects secondary to receptor site changes. Increased drug sensitivity to anticholinergic, narcotic, or sedating medications, can lead to delirium. In the elderly, changes in receptor function occurs across organs. The net effect of these changes is heightened sensitivity of the brain to adverse drug effects.³⁶

Pharmacodynamic interactions can also occur between a drug and a disease state. For example, a patient with Alzheimer's disease has a decrease in cholinergic reserve. By adding an anticholinergic medication, the effect is far more pronounced than in a person without Alzheimer's disease. It is important to review medications in the elderly for both pharmacokinetic and pharmacodynamic effects, as drug-drug or drug-disease interactions can contribute to delirium.

INVESTIGATIONS

In all cases of delirium the clinician should order standard, relevant investigations to rule out non-drug causes of delirium. Particular attention should be given to serum creatinine in order to calculate creatinine clearance and adjust renally eliminated medications appropriately. Serum and urine drug screens for illicit drugs and other deliriogenic medications should be done (for example, salicylate, digoxin, theophylline, lithium). Since delirium is commonly a multifactorial disorder, look for other reversible medical causes such as hypoxia, fluid and electrolyte imbalance, infections, constipation, and sensory deprivation such as hearing and vision impairment.

MANAGEMENT

Non-pharmacological measures and treatment of the underlying cause is the most important step in the management. Medications are the most common reversible cause of delirium and review is therefore required in all delirious patients. Clinicians should review the medication list and look for a temporal relationship between the drug and the onset of signs and symptoms of delirium. Any recent change to the medications or increase in dose should be reviewed. Over the counter medications and alcohol should not be overlooked. Clinicians should also ask about illicit drug use in the elderly.

Creatinine clearance should be measured routinely in the elderly and dosage should be adjusted for medications that are more prone to cause delirium. If possible, medications with anticholinergic properties should be avoided, or doses of necessary medications with anticholinergic properties should be minimised. Alternatively, a drug with lower anticholinergic potency could be substituted (for example, by using a tricyclic antidepressant that is a secondary amine, such as desipramine or nortriptyline, instead of a tertiary amine, such as amitriptyline) (table 1). While evaluating the risk: benefit ratio of medications causing delirium, tapering or discontinuing non-urgent medications may be an option. A medication that is suspected of triggering the delirium should be discontinued as quickly as possible (box 2).

Medication use in delirium

While medications may cause delirium, they can also be used to manage symptoms of delirium, including agitation and aggression. Antipsychotics are the cornerstone of treatment. Haloperidol is the drug of choice, as it has the least side effects for short term use in delirious patients.³⁷ Haloperidol has low anticholinergic effect and is used for a brief period for most cases of delirium. There is weaker evidence with newer agents. Atypical antipsychotics may be associated with greater anticholinergic effect, have not been adequately studied for delirium, do not come in parenteral formulations, and the pharmaceutical preparations are not easily broken down into the smaller doses that are often used in delirium. However, Sipahimalani *et al* in a case series demonstrated that risperidone was effective and reasonably safe in treating delirious patients with agitation.³⁸ While antipsychotics are not labelled for use in delirium, there is evidence that they may reduce the agitation and combativeness.

Table 1 Some commonly used medications with moderate to high anticholinergic properties and alternative suggestions

Type of medication	Alternatives with less delirogenic risk
Antidepressant (for example, TCA, tertiary)	Trazodone, SSRI, TCA (secondary amine)
Antihistamine (for example, diphenhydramine)	Second generation antihistamine (for example, loratadine)
Antiparkinsonian (for example, benztropine, trihexyphenidyl)	Levodopa
Gastrointestinal agents, for example:	
(A) Cimetidine, ranitidine	Proton pump inhibitor
(B) Dimenhydrinate	Domperidone
Antispasmodic (for example, oxybutynin)	Tolterodine
Low potency antipsychotic (for example, chlorpromazine, thioridazone)	Haloperidol, atypical antipsychotic

SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Benzodiazepines may be useful in treating delirium due to benzodiazepine withdrawal, alcohol withdrawal, and seizures. In syndromes causing delirium, sometimes using specific antidotes may be helpful (for example, physostigmine), in addition to withdrawing the causative medication.

CONCLUSION

Drug induced delirium is often seen in clinical practice. The risk of inducing delirium in elderly subjects who are frail or having dementia is high. Clinical activities aimed at improved recognition and management of drug induced delirium is important. All clinicians should be aware of the signs and symptoms of delirium, in order to rapidly detect any cases. Drugs that might induce delirium should be avoided.

Adjusting drug dosing for any pharmacokinetic changes or interactions will reduce the risk of drug induced delirium in the elderly. Better management of this condition is possible if clinicians are aware of the age related changes that may contribute to altered pharmacological effects and their role in delirium. Heightened awareness of drug induced delirium will encourage the clinicians to use more conservatively the high risk medications and also closely monitor in high risk elderly patients.

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Box 2: Suggested approach to drug induced delirium

1. Implement non-pharmacological intervention for support.
2. Review all the medications and look for a temporal relationship.
3. Review medications for a recent addition of a new drug or an increase in dosage of medication.
4. Stop/taper the medication causing delirium.
5. If many medications can contribute to delirium:
 - Discontinue all anticholinergic medicines, if possible.
 - Reassess pain; adding analgesic may be necessary, or reduce the dose or discontinue narcotics if high doses have been used.
 - Discontinue all benzodiazepines if use <1 week; if >1 week taper slowly as tolerated and use non-pharmacological management for sleep.
 - Reduce the dose of other delirogenic medication as appropriate.
6. Calculate creatinine clearance and adjust the dosage of renally eliminated medications.
7. Specific antidotes in poisoning or toxic conditions.
8. If necessary use antipsychotics (haloperidol is the drug of choice) to control the behavioural problems of delirium.
9. Minimise polypharmacy and use non-delirogenic drugs when possible. If drugs with known risk of inducing delirium is used close observation and monitoring is essential.

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doi: 10.1136/pgmj.2003.017236

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