

136 Drugs That Can Cause Cognitive Impairment

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Drug-induced dementia and delirium are commonly misattributed to underlying medical illness or merely to "old age." But patients (and even their doctors!) might not know that by stopping or modifying the dosage of numerous, frequently prescribed drugs, most patients can be restored to a pre-drug state of mental function.

Fortunately, the drug safety experts at WorstPills.org have identified 136 drugs from published studies that can cause memory loss, confusion and other forms of cognitive impairment in older adults.

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PART 1

DRUG-INDUCED COGNITIVE IMPAIRMENT: ANTICHOLINERGIC EFFECTS

As you age, some degree of difficulty recalling memories is considered normal.

However, more pronounced memory loss could indicate a serious problem, such as dementia (which includes Alzheimer's disease). That's why the occurrence of memory loss or other forms of cognitive impairment — such as difficulty with attention, language or other brain function — can be so alarming.

Although most types of dementia cannot be reversed, there are several forms that can be undone. Importantly, a wide array of commonly prescribed medications, especially certain antidepressants and pain medications, can cause cognitive impairment which may be reversed by stopping the drug. Unfortunately, this reversible cause is often over-looked. But new evidence is emerging that shines additional light onto this important drug-induced adverse event.

While medications are known to cause many unwanted side effects, many doctors fail to identify the drug as the culprit. In the elderly, adverse effects of medications are generally more pronounced. This is due to a host of factors, including increased sensitivity to a drug's effects, slower rates of elimination from the body and consumption of multiple drugs at a time.

A well-known side effect of many drugs involves their effects (specifically interference) with one of the chemicals responsible for transmitting signals between nerve cells in our bodies, called "acetylcholine."

This "neurotransmitter" is vital for diverse array of nervous system functions from muscle movement to sweating to memory, so it is no surprise that interference with it, or drugs with "anticholinergic" properties, can cause a host of symptoms (see Box).

Anticholinergic effects confused with early signs of dementia

Drugs with anticholinergic properties can cause delirium, but longer-term effects, which may be mistaken as the early signs of dementia, have not been studied as well for this class of drugs.

However, a recently published study specifically looked at this problem. The authors created a tool in which they rated many medications according to their anticholinergic properties on a scale of zero (no anticholinergic properties) to three (extremely anticholinergic; see Table). After adjusting for other factors that may account for cognitive decline, the authors noted a decrease on two measures of cognitive performance in men aged 65 and older. For each point on their scale, patients had a decrease of 0.8-percent

on a cognitive test and 1.1-percent on a measure of routine activities one can perform for themselves (another measure of intact cognition).

Unfortunately, cognitive decline that is due to anticholinergic medications is often overlooked because most medications listed in the accompanying Table would not necessarily, alone, account for a striking decline in memory or other cognitive function. But, the cumulative impact of consuming multiple medications with anticholinergic effects may be significant, resulting in unnecessary distress among patients, families and physicians alike.

While these findings are only preliminary, they permit physicians and patients to semi-quantitatively account for the anticholinergic effects of a patient's medications when the patient complains of memory and other cognitive problems.

If you are suffering from a troubling decline in one of your cognitive functions, the first thing you and your physician should do is take a look at your medication list. The answer may be as simple as changing to an alternative or stopping an offending drug or multiple drugs.

Box. Full List of Anticholinergic Effects

Cognitive impairment
Delirium
Hallucinations
Rapid heart rate
Dry mouth
Constipation
Urinary retention(inability to urinate)
Decreased sweating/fever/overheating
Skin flushing & inability to sweat
Pupil dilation & difficulty with vision

Table. Anticholinergic properties

Drugs with a score of 0 are not shown; a score of 3 indicates the strongest side effects.

Drug (BRAND NAME): Anticholinergic Score

Alprazolam (XANAX)*: 1

Amitriptyline (ELAVIL)*: 3

Atenolol (TENORMIN): 1

Atropine*: 3

Baclofen (LIORESAL): 2

Belladonna: 3

Benazepril (ETHEX, LOTENSIN)**: 1

Betaxolol (KERLONE): 1

Bupropion (WELLBUTRIN)**: 1

Carbamazepine (CARBATROL, TEGRETOL): 1

Carbidopa (SINEMET): 1

Cetirizine (ZYRTEC)**: 2

Chlordiazepoxide (LIBRIUM)*: 1

Chlorpheniramine (ALERMINE, CHLOR-TRIMETON): 3

Chlorpromazine (THORAZINE)**: 3

Codeine: 1

Cyclobenzaprine (FLEXERIL)*: 1

Desipramine (NORPRAMIN): 2

Dextromethorphan (BENYLIN, DELSYM)*: 1

Diazepam (VALIUM)*: 1

Diphenhydramine (BENADRYL, DYTAN SUSPENSION, DYTAN-D SUSPENSION, SOMINEX FORMULA): 3

Doxepin (SINEQUAN)** : 3

Fexofenadine (ALLEGRA)** : 2

Fluoxetine (PROZAC)**: 1

Guaifenesin (MUCINEX, ROBITUSSIN)*: 1

Homatropine (ISOPTO HOMATROPINE) : 3

Hydrocodone: 2

Imipramine (TOFRANIL, TOFRANIL PM)** : 3

Ketorolac (TORADOL)*: 1

Loperamide (IMODIUM)** : 1

Loratadine (CLARITIN)**: 1

Metoclopramide (REGLAN)** : 3

Methadone (DOLOPHINE, METHADOSE)**: 2

Methocarbamol (ROBAXIN)*: 1

Metoprolol (LOPRESSOR, TOPROL XL) : 1

Morphine (AVINZA, KADIAN, MS CONTIN): 1

Nefazodone (SERZONE)*: 1

Nortriptyline (AVENTYL, PAMELOR) : 3

Olanzapine (ZYPREXA)**: 1

Oxycodone (OXYCONTIN)**: 1

Paroxetine (PAXIL, PEXEVA)** : 2

Perphenazine (TRILAFON): 2

Phenobarbital (LUMINAL, SOLFOTON)**: 1

Prochlorperazine (COMPAZINE)**: 2

Propantheline (PRO-BANTHINE) : 2

Propoxyphene (DARVON)*: 2

Quetiapine (SEROQUEL)** : 2

Ranitidine (ZANTAC): 2

Risperidone (RISPERDAL)** : 1

Scopolamine (TRANSDERM-SCOP) : 3

Sertraline (ZOLOFT)** : 1

Thioridazine (MELLARIL)* : 3

Tolterodine (DETROL, DETROL LA)**: 3

Tramadol (ULTRAM)*: 2

Trandolapril (MAVIK)** : 1

Trazodone (DESYREL)** : 1

Triazolam (HALCION)* : 1

Trihexyphenidyl (ARTANE)* : 3

Venlafaxine (EFFEXOR, EFFEXOR XR)**: 1

* Do Not Use

** Limited Use

PART 2

DRUG-INDUCED COGNITIVE IMPAIRMENT: DELIRIUM AND DEMENTIA

As people age, they become more susceptible to delirium and dementia caused by drugs. This is known as drug-induced cognitive impairment, and it is an important syndrome to recognize, because in almost all cases it can be reversed or returned to the pre-drug state (in the case of people whose cognitive impairment was worsened by drugs) by stopping the offending drug.

Both in the hospital and office settings, drug-induced cognitive impairment is often overlooked and attributed to an underlying medical illness or merely to "old age," when it is actually a side-effect of a drug. In many cases, the reason for prescribing the culprit drug is questionable, or the cognitive impairment is related to taking multiple drugs at once.

As discussed in Part I of this series, there are many drugs that cause delirium and dementia (see Box 2 for definitions of delirium and dementia) through their anticholinergic effects. Most of these drugs have important functions other than blocking the neurotransmitter acetylcholine. In addition, there are several other classes of drugs that can cause cognitive impairment in susceptible individuals.

Drugs that can cause cognitive impairment

Drug-induced cognitive impairment is most commonly linked to benzodiazepines, opiates, tricyclic antidepressants and anticonvulsants (drugs used to treat and prevent seizures). These, and a few other drugs, are listed in the Table and described below. This is not an exhaustive list, but includes many of the most commonly implicated drugs and ones for which we have the most evidence. Some of the drugs discussed and listed below were also mentioned in Part 1 because they had anticholinergic effects.

Benzodiazepines

Benzodiazepines — which include tranquilizers and sleeping pills — have a wide range of effects on the central nervous system. They are commonly used to treat anxiety in the short-term, and also to sedate critically ill patients or those undergoing surgery.

People who take benzodiazepines chronically for anxiety, which is not recommended, can also develop more chronic cognitive impairment. Furthermore, because addiction to benzodiazepines is common, stopping them abruptly can result in a withdrawal syndrome similar to what is seen with alcohol withdrawal, including sweating, agitation, confusion, hallucinations and even seizures.

Patients on benzodiazepines are at greater risk for developing delirium while hospitalized, and when benzodiazepines are used to treat agitation associated with delirium from other causes, they often make it worse.

Sedatives that have similar central nervous system effects as benzodiazepines, such as the commonly used sleep agents zolpidem (AMBIEN), zaleplon (SONATA) and eszopiclone (LUNESTA) can also induce delirium. As with benzodiazepines, stopping these agents abruptly after chronic use can result in a withdrawal syndrome.

Box 1. Three Reasons Older People Are More Susceptible to Drug-Induced Delirium and Dementia

1. The body's ability to clear drugs decreases with age, often because of a normal age-related decrease in kidney and liver function. This results in a greater accumulation of drugs in the body.
2. Older patients are often prescribed multiple drugs at the same time. Due to complicated interactions between different drugs, side effects can become more prominent.
3. Some research suggests that neurotransmitters become naturally imbalanced as people age, increasing

the brain's sensitivity to drugs that have activity in the central nervous system.

Opiates

Opiates, also called narcotics, are a class of highly effective pain medication that act on the opioid receptor in the brain. Opiates can cause delirium and the more chronic cognitive changes seen in dementia.

Like benzodiazepines, chronic use of opiates has been linked to increased tolerance (in which case the patient requires increasing amounts of the medication to achieve the same therapeutic result), and abrupt cessation causes a withdrawal syndrome that includes agitation, sweating, chills, diarrhea, and severe discomfort.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are an older class of antidepressants that are known to cause cognitive impairment. Although TCAs are still used to treat severe depression in some patients, they are also used to treat pain syndromes, especially pain caused by a neuropathy (damaged or diseased nerves). The TCAs with the greatest anticholinergic properties are the ones most strongly linked to cognitive impairment, but even TCAs with weak anticholinergic effects can cause problems with thinking, possibly via other mechanisms.

Selective-serotonin release inhibitors (SSRIs), a newer and more commonly prescribed generation of antidepressants, have not been linked with cognitive impairment. Severe depression itself can be associated with difficulty thinking and concentrating, as well as with more serious consequences. Thus, if you think that your antidepressant may be causing problems with your thinking, it is very important that you consult with your physician to determine if you should stop taking the drug.

Others

A few other notable classes of drugs to mention include corticosteroids, fluoroquinolone antibiotics, H₂-receptor antagonists, anticonvulsants and drugs used to treat Parkinson's disease.

Corticosteroids are a type of hormone commonly used to treat severe asthma attacks and to suppress the immune system including the treatment of so-called auto-immune diseases such as rheumatoid arthritis, but an excess can cause agitation and even actual psychoses.

Fluoroquinolone antibiotics are increasingly used to treat a variety of infections and have been linked with delirium in elderly patients.

H₂-receptor antagonists are an older class of drug used to decrease stomach acid production. They, too, can cause delirium in elderly patients.

There are many different classes of anticonvulsants, which act on brain through different mechanisms. Nearly all of them have been associated with drowsiness and difficulty thinking, some more commonly than others.

What You Can Do

Because cognitive impairment caused by drugs is so frequently overlooked, it is important that when symptoms of confusion, altered concentration or difficulty thinking occur that you and your physician review any medications you are taking to determine if any of them might be the cause.

This is in accordance with our Rule # 7 for safer drug use: "Assume that any new symptom you develop after starting a new drug may be caused by the drug."

Fortunately, if the cause is a medication, your symptoms should go away or become less severe after stopping the drug, even if it takes weeks or months.

Box 2. The Difference Between Delirium and Dementia

Delirium is a syndrome of changes in attention perception (i.e., vision and hearing), and thinking that is commonly seen in the hospital setting or during an acute illness. Delirium usually starts abruptly, over the course of hours or a few days, and has a fluctuating course. There are many causes of delirium, but the most common are acute medical illnesses (such as a serious infection) and medications.

Older individuals are the most susceptible to delirium, which can result from problems as simple as constipation or urinary blockage in these patients. Almost all cases of delirium improve when the cause is treated or removed.

Dementia, on the other hand, is a chronic alteration in thinking that begins more insidiously, sometimes progressing over a course of months or years. It is more common the older you get. However, this does not mean that dementia is simply due to "old age."

Alzheimer's disease is the most common cause of dementia, but other neurologic conditions, including strokes, can cause it. So can drugs which can cause or worsen dementia. Unlike most of the medical causes for dementia, which are irreversible, stopping a drug that has caused dementia can lead to improvement.

Partial List of Drugs Associated with Drug-Induced Cognitive Impairment

Anticonvulsants

- Carbamazepine (CARBATROL, TEGRETOL)
- Clonazepam (KLONOPIN)
- Ethosuximide (ZARONTIN)
- Felbamate (FELBATOL)
- Fosphenytoin (CEREBYX)
- Gabapentin (NEURONTIN)**
- Lamotrigine (LAMICTAL)
- Levetiracetam (KEPPRA)
- Lorazepam (ATIVAN)*
- Oxcarbazepine (TRILEPTAL)
- Phenytoin (DILANTIN)
- Pregabalin (LYRICA)*
- Primidone (MYSOLINE)
- Tiagabine (GABITRIL)
- Topiramate (TOPAMAX)
- Valproic acid (DEPAKENE)
- Zonisamide (ZONEGRAN)

Antihistamines (these are OTC meds, and too numerous to list)

- Azelastine (ASTELIN)*
- Chlorpheniramine injection
- Cyproheptadine (PERIACTIN)
- Desloratadine (CLARINEX)*

- Diphenhydramine injection
- Hydroxyzine (ATARAX, HY-PAM, VISTARIL)
- Olopatadine (PATANOL)

Benzodiazepines

- Amitriptyline and chlordiazepoxide (LIMBITROL)*
- Chlordiazepoxide and clidinium (LIBRAX)**
- Clonazepam (KLONOPIN)
- Clorazepate (TRANXENE)*
- Estazolam (PROSOM)*
- Flurazepam (DALMANE)*
- Halazepam (PAXIPAM)*
- Lorazepam (ATIVAN)*
- Oxazepam (SERAX)**
- Prazepam (CENTRAX)*
- Quazepam (DORAL)*
- Temazepam (RESTORIL)*

Benzodiazepine-like Sedatives

- Eszopiclone (LUNESTA)
- Zaleplon (SONATA)
- Zolpidem (AMBIEN)

Corticosteroids

- Betamethasone (ALPHATREX, DIPROLENE, DIPROSONE)
- Cortisone (CORTONE)
- Dexamethasone (DECADRON, HEXADROL, MYMETHASONE)
- Fludrocortisone (FLORINEF)
- Hydrocortisone (ALA-CORT, HI-COR, HYTONE, NEACLEAR LIQUID OXYGEN SCAR ADVANTAGE, PENECORT, SYNACORT, CORTEF, HYDROCORTONE)
- Methylprednisolone (MEDROL)
- Prednisolone (PRELONE)
- Prednisone (DELTASONE)
- Triamcinolone (ARISTOCORT, KENALOG, TRIACET, TRIDERM)

Drugs with Anticholinergic Properties

- See Part 1

Drugs Used to Treat Parkinson's Disease

- Benztropine (COGENTIN)*
- Bromocriptine (PARLODEL)**
- Entacapone (COMTAN)**
- Entacapone with levodopa and carbidopa (STALEVO)**
- Selegiline/deprenyl [oral] (ELDEPRYL)**
- Tolcapone (TASMAR)*

Fluoroquinolone Antibiotics

- Ciprofloxacin (CILOXAN, CIPRO)**
- Gatifloxacin (TEQUIN)*
- Gemifloxacin (FACTIVE)*
- Levofloxacin (LEVAQUIN)**
- Lomefloxacin (MAXAQUIN)**
- Moxifloxacin (AVELOX)*
- Moxifloxacin [eye drops] (VIGAMOX)
- Norfloxacin (CHIBROXIN, NOROXIN)**
- Ofloxacin (FLOXIN)**

- Ofloxacin [eye] (OCUFLOX)
- Sparfloxacin (ZAGAM)*
- Trovafloxacin (TROVAN)*

H2-antagonists (Typically associated with delirium only)

- Cimetidine (TAGAMET)
- Famotidine (PEPCID)
- Nizatidine (AXID)

Opiates (Typically associated with delirium only)

- Acetaminophen and codeine (APAP, TYLENOL WITH CODEINE)
- Acetaminophen and hydrocodone (BANCAP-HC, LORTAB, VICODIN)
- Acetaminophen and oxycodone (PERCOCET, ROXICET, TYLOX)**
- Aspirin and oxycodone (PERCODAN)**
- Butalbital, acetaminophen and caffeine (ESGIC PLUS, FIORICET)*
- Butalbital, caffeine and aspirin (FIORINAL)*
- Butalbital, caffeine, aspirin and codeine (FIORINAL WITH CODEINE)*
- Butorphanol (STADOL)*
- Fentanyl [patch] (DURAGESIC)**
- Hydrocodone and ibuprofen (VICOPROFEN)
- Hydromorphone (DILAUDID)
- Meperidine (DEMEROL)
- Pentazocine (TALWIN)*
- Pentazocine and naloxone (TALWIN-NX)*
- Tramadol and acetaminophen (ULTRACET)*

Tricyclic Antidepressants

- Amitriptyline and chlordiazepoxide (LIMBITROL)*
- Amitriptyline and perphenazine (TRIAVIL)*
- Amoxapine (ASENDIN)**

Other

- Digoxin (DIGITEK, LANOXICAPS, LANOXIN)
- Lithium (ESKALITH, LITHOBID, LITHONATE)**