REVIEW ARTICLE

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Drug-Induced Cognition Disorders in the Elderly

Incidence, Prevention and Management

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Abstract

The aetiology of cognitive impairment is multifactorial; however, drugs are an important cause of delirium and dementia. Several factors may increase the risk of drug-induced cognition disorders in the elderly including imbalances in

neurotransmitters (e.g. acetylcholine), age-related alterations in pharmacokinetics and pharmacodynamics, and high levels of medication use.

Nearly any drug can cause cognitive impairment in susceptible individuals; however, certain classes are more commonly implicated. Benzodiazepines, opioids, anticholinergics, and tricyclic antidepressants are probably the worst offenders. Older antihypertensive agents (reserpine, clonidine) have negative effects on cognition; however, large clinical trials in the elderly indicate that commonly used agents [e.g. thiazide diuretics, calcium antagonists (amiodipine, diltiazem) ACE inhibitors (captopril, enalapril) and β-blockers (atenolol)] have minimal effects on cognition. Newer antidepressants such as selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) and reversible inhibitors of monoamine oxidase A have not been shown to have negative effects on cognition. Although some drugs have shown low risk for causing cognition disorders in research studies, risk may be increased in frail older adults taking several medications and each case should be reviewed carefully.

Identification of drug-induced cognitive impairment is crucial to early detection and resolution of symptoms. Preventive strategies directed at avoiding high risk medications when possible, appropriately adjusting doses based on age-related changes and close follow-up may prevent these conditions.

Cognitive impairment in the elderly is a major public health problem, especially in light of the aging of the population. Although the aetiology of cognitive disorders is multifactorial, the adverse effects of drug therapy are an important cause of these disorders. This review will focus on 2 different drug-induced cognitive disorders observed in clinical practice in the elderly, delirium and dementia.

Delirium is a syndrome characterised by a disturbance in consciousness (reduced clarity of awareness of the environment) and a change in cognition or the development of perceptual disturbance.[1] The hallmark of delirium is an acute onset and a fluctuating course.[2] In contrast, the cognitive deficits in patients with dementia of the Alzheimer's type typically develop insidiously, are more chronic in nature and usually do not fluctuate throughout the day. Drugs may cause impairments in cognition that resemble those observed in dementia due to Alzheimer's disease. The concept of cognition refers to the information processing and psychomotor functions that allow organisms to adapt to and manipulate their surroundings. Cognition includes many processes such as perception, attention, memory, learning, thinking, verbal abilities, problem-solving and motor performance.[3] Drugs can affect one or many processes of cognition.

The traditional definitions of delirium and dementia (Alzheimer's disease) are used as a framework to discuss drug-induced cognition disorders, with the caveat that this is an oversimplification and substantial overlap between the 2 disorders may exist. This review primarily focuses on research examining drug-induced delirium or dementia in elderly patients receiving medication for treatment. However, since major gaps exist in the literature regarding adverse drug effects in the elderly, we will supplement with studies conducted in middle-aged and healthy volunteers, including single dose studies when necessary. It is beyond the scope of this article to review all literature relevant to drug-induced cognition disorders.

1. Epidemiology

1.1 Incidence and Prevalence

1.1.1 Delirium

The incidence of delirium is difficult to determine because of major differences among available

studies in the design, methodology (e.g. definition of delirium) and characteristics of the patient sample (e.g. age, medical versus surgical). It is estimated that 10 to 16% of elderly patients have delirium at time of hospital admission and 18 to 38% experience delirium during the hospital stay.[4-6] Delirium is associated with a mortality rate ranging from 10 to 65%.[4] Although not well characterised, medication use plays an important role in the development of delirium.[4] In 1 study, drug toxicity accounted for 25% of the delirium cases where a single definite or probable aetiology could be determined, representing the second leading cause after infections.[7]

1.1.2 Dementia

The prevalence of dementia increases significantly with age, affecting 25 to 48% of those older than 85 years of age.[8] Compared with delirium, even less is known about the prevalence of drug-induced dementia. Among 308 outpatients with dementia, 35 were found to have an adverse drug reaction that contributed to the cognitive impairment.[9] Discontinuation or modification of the drug(s) resulted in an improvement in cognition for all patients. For 29% of these individuals, the drug(s) was the sole cause of the cognitive impairment, indicating that additional causes of impairment were also present (e.g. Alzheimer's disease). The prevalence of drug-induced dementia in the general population is not known.

1.2 Risk Factors

Risk factors for delirium can be categorised as predisposing (baseline patient characteristics) and precipitating (acute insult).[4] Important predisposing risk factors that are consistent among studies include advanced age, pre-existing underlying cognitive impairment, cerebral damage, severe chronic illness and functional impairment.[4,6] Precipitating factors include drugs (including illicit drug use), as well as intercurrent illness, infections, metabolic disturbances, dehydration, acute urinary retention, malnutrition, alcohol withdrawal, and environmental and psychosocial factors.[4,5]

A patient admitted to the hospital with one or more predisposing risk factors is at greater risk of developing delirium with even a mild precipitating risk factor (e.g. addition of a drug) compared with patients with no baseline risk. Conversely, a patient with no predisposing risk factors may not develop delirium even in the presence of several noxious precipitating factors (e.g. drug added, severe infection).[5] This complex relationship makes it difficult to evaluate drugs as a cause of delirium in everyday practice.

2. The Elderly as a Risk Group

Age is a strong risk factor for the development of delirium and dementia. Several factors may increase the risk of drug-induced cognition disorders in the elderly including imbalances in neurotransmitters (e.g. acetylcholine), age-related alterations in pharmacokinetics and pharmacodynamics, and high levels of medication use.

Insight into the mechanism by which some medications contribute to delirium can be gained by understanding what is known of the aetiology of this syndrome. Delirium is marked by a global cerebral dysfunction resulting in a generalised reduction of cerebral oxidative metabolism and imbalance of several neurotransmitters.[10] Many lines of evidence support the hypothesis that delirium is mediated in part by a failure in central cholinergic transmission, a major system that regulates arousal, attention and memory processes.[6,10] First, clinical and experimental studies of anticholinergic intoxication have demonstrated the behavioural and electroencephalogram (EEC) manifestations of delirium; these effects are reversible upon administration of cholinesterase inhibitors.[11] Secondly, serum anticholinergic activity is associated with the presence of cognitive impairment in older medical[12] and presurgical patients.[13] Thirdly, deficits in cholinergic transmission contribute to the memory impairment observed in Alzheimer's disease. Age-related changes in cholinergic function are likely to be factors responsible for the increased sensitivity of older patients to the development of delirium.[10]

Anticholinergic medications are a well-known cause of cognitive impairment.[14-18] In the elderly, the majority of experimental studies with anticholinergic agents (e.g. scopolamine, trihexyphenidyl, oxybutynin) have been conducted in volunteers. Many medication classes have anticholinergic properties including tricyclic antidepressants, antipsychotics, histamine H_1 receptor antagonists (antihistamines) and antiarrhythmics. Some agents that are traditionally considered not to have anticholinergic effects do have serum anticholinergic activity as detected by assays[19] and their cognitive effects can be reversed with the administration of physostigmine.[20-23] Other neurotransmitters are likely to be involved in drug-induced cognition disorders. Dopaminergic, serotonergic and adrenergic transmission is altered in Alzheimer's disease and these transmitters are presumed to play a role in cognitive deficits.[24]

Age-associated changes in drug pharmacokinetics may predispose the elderly to adverse drug reactions.[25,26] Although several changes occur, reduced renal and hepatic elimination are of particular importance. Many drugs that undergo oxidative metabolism (e.g. benzodiazepines, tricyclic antidepressants, antipsychotics) may have reduced clearance in the elderly. The most predictable age-associated pharmacokinetic change is reduced renal clearance; thus many drugs that are primarily eliminated by the kidneys often have reduced clearance [e.g. lithium, digoxin, morphine, pethidine (meperidine), H_2 receptor antagonists]. If a medication is not adjusted appropriately for these age-related changes, increased serum concentrations and toxicity can occur.

Even without changes in pharmacokinetics, the elderly are more sensitive to some medications, reflecting altered drug pharmacodynamics.[26] For example, memory is impaired to a greater extent with scopolamine in older patients compared with younger patients[14,15] and in patients with Alzheimer's disease compared with healthy age-matched controls.[27] This is likely to be because of reduced cholinergic transmission, making the elderly more sensitive to drug induced reductions in cholinergic transmission. Evidence exists for increased sensitivity to the effects of benzodiazepines and possibly opioids with aging.[26,28]

Lastly, many elderly use multiple long term medications. High drug use has been shown to increase the risk of general adverse drug reactions and cognition specific adverse drug reactions in the elderly. The risk of cognitive impairment increases with the number of prescription medications, especially if 4 or more are prescribed.[9]

3. Source of Data for Drug-Induced Cognitive Impairment

Information about drug-induced delirium and dementia has been generated from many sources including case reports, epidemiological evaluations and clinical trials. Case reports, although beneficial for discovering potential adverse drug reactions of newly marketed drugs, do not allow clinicians to determine whether the adverse drug reaction is rare or common. Almost every drug class has been implicated by case reports in causing cognitive impairment.[29,30]

A randomised controlled trial is the most reliable method to determine the cognitive effects of a medication. This design has been used primarily to evaluate the impairment of specific aspects of cognition for medications with known effects on the CNS (e.g. antidepressants, benzodiazepines). Many trials were conducted in healthy volunteers, after single or short term administration, which may provide insight into possible drug-induced cognitive effects, but may not provide information regarding the full extent of cognitive effects in individuals with chronic disease who take the medication as long term therapy.[31] Co-existing diseases and frail clinical status are risk factors for experiencing an adverse event. Lack of drug-induced cognitive effects in healthy volunteers or middle-aged adults should be interpreted cautiously, since these drugs may have different effects in an older, chronically ill individual.

Studies are often difficult to compare because of the several different types of instruments used to assess cognition. Furthermore, it is not known

Table I. Neuropsychological test classification[3,32]

1. Attention Examination of ability to focus attention (vigilance) or sustain behaviour while resisting distractions. Attention is needed for concentration and tracking
2. Perception Tests the acquisition or integration of sensory stimuli (visual, tactile, auditory). These tests require little or no physical manipulation of material and often test other aspects of cognition as well (attention, memory)
3. Memory Tests measuring the recall or recognition of newly learned information (visual, verbal, tactile). Immediate or long term memory can be tested. Memory involves separate process of encoding, storage and retrieval
4. Verbal functions and language skills Tests of language skills including reading, comprehension, writing and speaking
5. Construction These tests always have a spatial component and examine the integration of visual-perceptive skills and motor response. Concept encompasses drawing and building or assembling
6. Concept formation and reasoning Tests of complex mental abilities involving an available store of learned material, an intact system for organising perceptions, ability to process more than 2 mental events at a time, and diffuse cortical interconnections for 'thought'. Inability to think in generalisations is the most common sign of impairments in this area
7. Motor performance Tests evaluating motor response and coordination. Require relatively simple hand-eye coordination and direct motor responses

how subtle deficits on tests of cognition relate to ability to care for oneself in everyday life. Based on the categorisation by Lezak,[3] the tests in this review have been grouped by the primary effect on cognition (table I).[3,32] Some studies may use a brief screening instrument to assess overall cognition [e.g. Mini-Mental State Examination (MMSE)] which tends to be less sensitive in detecting changes due to drug effects.[13,33]

A randomised controlled trial is not feasible for studying the propensity of drugs to cause delirium, thus most information about drug-induced delirium comes from prospective cohort studies of hospitalised patients (table II).[5,7,34-41] Importantly, only 2 studies examined incident delirium cases and used criteria to ensure the medication exposure preceded the onset of delirium.[5,35] Rarely do epidemiological evaluations use standard criteria to assess the causality of implicated drug with cognitive disorder,[7,9] which is necessary when trying to determine if an adverse event is caused by drug therapy or other aetiologies.[42,43]

4. Adverse Effects of Specific Drug Classes

Nearly every drug class can cause delirium/dementia in susceptible individuals, but only a few agents are consistent risk factors in prospective studies (table III).[44,45] Importantly, cognitive changes may be associated with the disease the drug is used to treat (e.g. depression, epilepsy, hypertension) making it difficult to determine the full extent of drug-induced cognitive deficits. The most evidence exists for benzodiazepines, opioids, anticholinergic agents and tricyclic antidepressants but study results are discrepant.

4.1 Centrally Acting Agents

Eight prospective trials of hospitalised patients have evaluated specific drug classes as one of several potential risk factors for delirium (table II), with only 2 studies using rigorous methodology to examine drug effects.[5,35] Patients taking pethidine or benzodiazepines were approximately 3 times more likely to develop delirium after surgery.[35] Anticholinergic drug use was not a signif-

Table II. Summary of epidemiological studies that have evaluated medication as risk factors for delirium/dementia

Reference	Population	Drugs examined	Assessment of delirium or cognition	Results: adjusted RR/OR (95% CI)[a]	Comments
Dementia					
Larson et al.[9]	Outpatients with suspected dementia, >60y (n = 308)	All medications. Causality criteria used to assess association of drug with cognitive symptoms	Suspected drug was discontinued or reduced. Improved cognition defined by: MMSE ↑ 2 points, MDS ↑ 1.5 points and WAIS ↑ 10 points	Sedative/hypnotic: OR 5.89 (2.3-15.0) Antihypertensive: OR 4.26 (1.6-11.1)	BZD (n = 16) most common. Other medications: methyldopa, hydrochlorothiazide, reserpine, propranolol, major tranquillisers, pethidine (meperidine), aspirin (acetylsalicylic acid), cimetidine, insulin, amoxapine, amantadine
Delirium					
Inouye & Charpentier[5]	Medical patients, ≥70y (n = 196)	Anticonvulsants, major tranquillisers, antiemetics, opioids, >3 medications added	CAM every 48h	>3 medications added: RR 2.9 (1.6-5.4)	Advantages: drug had to be present at least 24h before onset of delirium
Rogers et al.[34]	Elective hip or knee surgical patients, ≥60y (n = 46)	Two drug categories: (i) propranolol/scopolamine/flurazepam; (ii) morphine equivalents: opioids, analgesic, hypnotic and tranquilliser	DSM-III on post-operative day 4	Scopolamine, propanolol/flurazepam significantly related to delirium (p = 0.0028)	Disadvantages: Grouping of medications. Unclear temporal relationship between exposure and delirium. Infrequent assessment of delirium
Marcantonio et al.[35]	Surgical patients, >50y (n = 91 cases, 154 control individuals)	Opioids, BZD, AC (antihistamines, TCAs, antiemetics and certain antipsychotics)	Daily ratings post-operative days 2-5 using CAM and Chart Medicus criteria	Pethidine: OR 2.7 (1.3-5.5) Pethidine epidural: OR 2.4 (1.3-4.4) Pethidine PCA: OR 2.1 (0.4-10.7) BZD: OR 3.0 (1.3-6.8) BZD long acting: OR 5.4 (1.0-29.2) BZD short acting: OR 2.6 (1.1-6.5)	Advantages: nested case control (matched on risk for delirium) – allows for better accounting for confounding by indication (e.g. preferential use of pethidine in the cognitively impaired). Drug had to be present 24h before delirium (eliminates exposure given in response to delirium)
Schor et al.[36]	Medical/surgical patients (included nursing home admissions), ≥65y (n = 291)	BZD, opioids, NSAIDs, antipsychotics, digoxin, H_2 antagonists, corticosteroids, AC (antihistamines, ipratropium, oxybutynin, atropine)	Daily ratings using DSI (based on DSM-III)[37]	Opioids: OR 2.5 (1.2-5.2) Antipsychotics: OR 4.5 (1.8-10.5)	Disadvantages: Antipsychotics may have been prescribed in response to delirium. Did not specify which exposure time point was used in analyses
Francis et al.[7]	Medical patients from community, ≥70y (n = 229)	Psychoactive (minor tranquillisers, sedatives/hypnotics, opioids), AC (not specified)	Evaluations every 48h using DSM-III-R[38]	Psychoactive agents: OR 3.9 (1.4-10.8)	Advantages: Assessed causality. Other drugs associated with delirium using causality criteria: opioids, BZD, AC, NSAIDs, methyldopa. Disadvantages: Only looked at baseline drug use. Did not separate prevalent and incident cases

icant risk factor perhaps because of limited power to detect an association. Interestingly, the second study did not find individual drug classes to increase the risk for delirium; however, the addition of 3 or more new medications during the 48 hours preceding the onset of delirium increased the risk almost 3-fold.[5] Unlike experimental studies, most epidemiological evaluations have not found an independent association between anticholinergic drugs and delirium.[7,35-40] One difficulty is that studies have used inconsistent definitions of anticholinergic drugs. For example, some studies included antipsychotics and tricyclic antidepressants as anticholinergic drugs,[35,36] whereas others do not specify which agents were included,[7,39,40] making interpretation of results difficult.

4.2 Hypnotics/Sedatives

Benzodiazepines have a wide range of CNS effects such as sedation, drowsiness, memory difficulties and lack of coordination. Single dose and short term studies indicate impaired learning of verbal and visual information, slowed psychomotor performance and impaired vigilance.[29,46-48] Anterograde amnesic effects are greater following use of higher potency and shorter-acting benzodiazepines. Little information is available describing the magnitude of cognitive effects in elderly patients taking benzodiazepines for therapeutic reasons. Tolerance appears to develop to some of these effects with multiple dose administration in healthy elderly patients; however, the elderly may develop tolerance more slowly when compared with younger individuals.[28,49] Some evidence exists for persistent cognitive and psychomotor impairments with long term benzodiazepine use.[50-55] The strongest evidence for benzodiazepine-related impaired cognition in the elderly is from a study that documented the improvement of cognitive deficits upon drug withdrawal.[9] The sedative properties of benzodiazepines do not fully explain these impairments.[56,57]

Use of benzodiazepines in hospitalised patients has been associated with increased risk of delirium in some,[35] but not all studies.[5,36] Users of long-

Foreman[39]	Medical patients, ≥60y (n = 71)	Sedative/hypnotics, analgesics, AC (not specified) = all grouped into one variable	Prospective daily. Confusion defined by MMSE and CAC	Number of drugs (p-value not specified)	Disadvantages: Grouping of medications. Unclear temporal relationship between exposure and delirium
Gustafson et al.[40]	Hip fracture surgical patients, ≥65y (n = 111)	Antidepressants, antipsychotics, BZD, AC (not specified), antiparkinsonians	Prospective daily assessment DSM-III	Drugs not associated [AC drugs (p = 0.09)]	Disadvantages: Only looked at baseline drug use. Did not separate prevalent and incident cases
Williams et al.[41]	Hip fracture surgical patients, ≥60y (n = 170)	Baseline – diuretics, tranquilliser; during hospital stay – opioids, tranquilliser, sedatives	Daily assessment of 4 symptoms post-operative days 1-5	Drugs not associated	

a Relative risks and odds ratios represent the increased risk of the specific drug class compared with no use of the agent. Results of most cohort studies are usually expressed as relative risks, whereas results of case control studies are expressed as odds ratios.

AC = anticholinergic; **BZD** = benzodiazepine; **CAC** = clinician assessment of confusion; **CAM** = confusion assessment method; **CI** = confidence intervals; **DSI** = delirium symptom interview; **DSM-III** = Diagnostic and Statistical Manual of Mental Disorders, 3rd ed; **DSM-III-R** = DSM-III revised version; **MDS** = modified dementia rating scale; **MMSE** = Mini-Mental State Examination; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **OR** = odds ratio; **PCA** = patient controlled analgesia; **RR** = relative risk; **TCA** = tricyclic antidepressant; **WAIS** = Wechsler Adult Intelligence Scale.

Table III. Drugs implicated in causing delirium or dementia

Drug/drug class	Strength of data to support association[a]	Clinical implications
Benzodiazepines	S (+)	Avoid use if possible. If use is warranted, use short-acting agents at low doses
Antidepressants:		SSRIs and RIMAs are preferred over high anticholinergic antidepressants (tertiary TCAs). TCAs may be okay in low doses
TCAs, trazodone	M to S (+)	
SSRIs, RIMAs	M to S (0)	
Anticholinergics	M to S (0/+)	Within a class of medications, select an agent with the least anticholinergic properties. Look for additive effects; multiple medication classes have anticholinergic properties
Antipsychotics	M (+)	Potential to cause cognitive effects may be related to anticholinergic properties, but even low anticholinergic antipsychotics have caused impaired cognition. Risperidone or olanzapine may be preferable, but selection should be patient-specific
Lithium	M (+)	Many drugs used by the elderly interact with lithium and can increase risk of toxicity (thiazide diuretics, NSAIDs)
Analgesics:		Use opioids judiciously, after non-opioid alternatives. Avoid pethidine (meperidine), which may be the worst offender. Adequate pain relief is important, as this can be related to delirium
opioids	M to S (+)	
non-opioid [paracetamol (acetaminophen), NSAIDs]	M to S (0)	
Antiparkinsonian agents	M to S (+)	If patient is experiencing cognitive effects, discontinue or reduce antiparkinsonian therapy one agent at a time. First adjust adjunctive therapy [anticholinergics, selegiline (deprenyl), amantadine] as patient condition allows
Anticonvulsants:		Minimal impairment with monotherapy and serum concentrations within therapeutic range. Phenobarbital and primidone appear to have more effects on cognition
phenobarbital (phenobarbitone), primidone	M (+)	
others	M (0)	
Antihypertensive agents:		Group A antihypertensive agents have been well studied and rarely cause cognitive impairment. Preferable to avoid reserpine, clonidine, methyldopa in the elderly
group A: thiazides, calcium antagonists (amlodipine, diltiazem), ACE inhibitors (captopril, enalapril) and β-blockers (atenolol)	M to S (0)	
group B: reserpine, clonidine, methyldopa	L to M (+)	
Digoxin	L (+)	
Histamine H_2 receptor antagonists	L (+/0)	All have similar propensity to cause effects on cognition. Incidence is rare; more likely in elderly hospitalised patients. Reduce dose in patients with renal impairment
Histamine H_1 receptor antagonists		Second generation antihistamines (loratadine, astemizole) preferred, provided no contraindications exist (drug interactions). Certrizine has intermediate sedative effects
diphenhydramine	M (+)	
Corticosteroids	M (+)	
Pulmonary agents[b]	L (0)	Theophylline or ipratropium not likely to produce cognitive and psychomotor impairment with usual doses

a Represents strongest evidence available. All classes have been implicated in causing cognition disorders from case reports.

b See Ramsdell et al.[44] and Newman et al.[45] for discussion of the effects of these agents.

L = low; evidence based on case reports/case series; **M** = moderate; evidence based on 1 or more study, may be conflicting reports; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **RIMA** = reversible inhibitors of monoamine oxidase; **S** = strong evidence based on > 1 well controlled study; **SSRI** = selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor; **TCA** = tricyclic antidepressant; **+** signifies associated with drug-induced cognition disorders; **0** signifies minimal risk for drug-induced cognition disorders.

acting benzodiazepines were significantly more likely to experience delirium compared with users of short-acting agents or non-users ($p = 0.02$).[35] Importantly, the risk of delirium was higher in those taking higher doses of benzodiazepines.[35]

Zolpidem, a nonbenzodiazepine short-acting hypnotic, is perceived to be a safer alternative to benzodiazepines.[58,59] Few studies have examined the effect of zolpidem on cognition in the elderly. In a 3-way, double-blind crossover study in 24 healthy elderly, zolpidem 5 or 10mg did not produce impairments on tests of attention, memory and perception after 7 days of therapy when compared with placebo.[60] In another study, zolpidem 5 to 20mg reduced performance on a measure of attention after 2 nights of therapy when compared with placebo.[61] Zolpidem appears to produce impairments that resemble those seen with triazolam with reductions in memory that correspond with peak concentration.[62] The scarcity of long term trials and past experience with new hypnotics initially believed to be safer suggests that clinicians should remain concerned about possible adverse effects on cognition, especially in frail elderly patients.

4.3 Antidepressants

Several clinical studies have assessed the effects of antidepressants on global cognition[63-67] or specific aspects of cognition[33,68-71] in the elderly (table IV).[72] Depression can cause impairment in cognitive processes as part of the disease, as well as coexist with dementia, which may make it difficult to assess the cognitive effects of antidepressants. The treatment of depression often results in improvement in cognitive abilities; adverse effects of antidepressants may mask or blunt this improvement.

Tricyclic antidepressants are often considered to be the most troublesome agents, especially amitriptyline.[69,72,73] Amitriptyline is associated with reduced reaction time, impaired retrieval from secondary memory,[69] and impaired information processing.[68] However, even tricyclic antidepressants with lower anticholinergic properties can cause deficits in cognition. Nortriptyline was found to impair immediate recall in formerly depressed patients undergoing single-blind withdrawal of nortriptyline (switched to placebo).[33] Medications with anticholinergic actions are a special concern for patients with Alzheimer's disease. Low dose imipramine (i.e. 25 mg/day),[67] but not amitriptyline 25 mg/day,[63] was well tolerated in patients with depression and Alzheimer's disease. Patients with Alzheimer's disease have shown significant improvements in MMSE score with placebo.[64,67]

The effects of trazodone on cognition in the elderly have mainly been investigated in single dose healthy volunteer studies. Amitriptyline 50mg impaired attention, vigilance and tracking performance, while trazodone 100mg only impaired the most difficult tracking test compared with placebo in 15 older volunteers (>60 years).[74] Trazodone 100mg impaired immediate memory, while amitriptyline impaired retrieval from secondary memory and reduced psychomotor speed compared with placebo.[75]

Evidence exists for minimal or even improved effects on specific measurements of cognition with the SSRIs and reversible inhibitors of monoamine oxidase A (RIMAs) [e.g. moclobemide, brofaromine].[64,68,71,73,76] Performance on tests of perceptual function improved with fluoxetine treatment and was maintained throughout the 6-week study period. In contrast, performance declined significantly from baseline at 1 week and returned to baseline within 3 weeks in the group receiving amitriptyline. At all time points, performance was significantly better in participants receiving fluoxetine than amitriptyline.[68] SSRIs appear to be well tolerated in patients with cognitive decline/dementia.[63,77] SSRIs and RIMAs may improve cognitive function by mechanisms separate from their antidepressant effects.[73] Little is known about newer antidepressants (e.g. nefazodone, venlafaxine).

Table IV. Summary of studies evaluating the cognitive effects of antidepressants

Reference	Population	Study design	Treatments	Duration	Aspects of cognition tested	Results
Meyers et al.[33]	Recovered depressed patients taking nortriptyline; >60y (n = 9)	sb (withdrawal to placebo)	Placebo	Assessed 2-4wk before and 2wk after withdrawal	List-learning test (M) MMSE (G)	MMSE: no significant change in MMSE, nortriptyline (27.0 ± 3.0) versus placebo (28.4 ± 3) Immediate recall was improved with placebo versus nortriptyline for trial 2 and trial 3 ($p < 0.05$) Delayed free recall: no difference
Taragano et al.[63]	Patients with depression and Alzheimer's disease; mean age 72y (n = 37)	db, r	Fluoxetine 10 mg/day Amitriptyline 25 mg/day	45 day	MMSE (G)	MMSE improved significantly compared with baseline for patients in both treatment groups, overall mean increase of 2.4 points. No difference between treatments. However, more patients withdrew from treatment with amitriptyline versus fluoxetine (11 *vs* 4). 10 patients in the amitriptyline group withdrew from treatment because of confusion or disorientation
Roth et al.[64]	Two groups: 60-90y: (i) dementia with depressive symptoms (n = 511); (ii) depression with cognitive decline (n = 183)	db, r, pc, mc	Moclobemide 400 mg/day. Placebo	42 day	SCAG-factor 1 (G) MMSE (G)	Intention-to-treat analysis A. Dementia/depressive symptoms MMSE: patients receiving moclobemide had a mean higher difference from baseline compared with placebo recipients (2.6 *vs* 1.9; $p < 0.05$) SCAG: mean increase 3.2 (moclobemide) *vs* 2.5 (placebo); $p < 0.05$ B. Depression/cognitive decline MMSE: mean change from baseline improved for both groups, 2.4 (moclobemide) *vs* 2.1 (placebo); p = NS SCAG : mean change from baseline significantly higher with moclobemide (3.3) versus placebo (2.4); $p < 0.005$
Hoyberg et al.[65]	In- and out-patients with no cognitive impairment; 60-85y (n = 115)	db, r, mc	Mirtazapine 15-45 mg/day Amitriptyline 30-90 mg/day	6wk	Brief Cognitive Rating Scale (G)	Intention-to-treat analysis Nonsignificant improvements in global cognition were observed for patients receiving both treatments (mean change ± SD): mirtazapine (3.7 ± 4.5), amitriptyline (4.0 ± 3.9), p = NS
Geretsegger et al.[66]	In- and out-patients with no dementia; 61-85y (n = 106)	db, r, mc	Fluoxetine 20-40 mg/day Paroxetine 20-60 mg/day	6wk	SCAG – cognitive subscale (G) MMSE (G)	Intention-to-treat analysis SCAG: paroxetine group had a higher mean change (improvement) from baseline at week 3 ($p = 0.03$) and week 6 ($p < 0.01$) compared with fluoxetine group MMSE: paroxetine group had a higher mean change (improvement) from baseline at week 3 (2.6 *vs* 1.2, $p = 0.02$) and week 6 (2.3 *vs* 1.1, p = NS) compared with fluoxetine group

Kerr et al.[68]	Elderly, selection criteria not specified (n = 66)	db, r	Amitriptyline 75 mg/day Fluoxetine 20 mg/day	42 day	Critical Fusion Flicker Test (P), Choice Reaction Time (ATN), Word Recognition Task (M), Sternberg Memory Scanning Task (M)	Critical Fusion Flicker Test: patients receiving fluoxetine had improved scores at all time points when compared with amitriptyline recipients ($p < 0.005$). For patients receiving amitriptyline, performance declined significantly at 1 week but improved (close to baseline level) from week 1 to week 3 Reaction Time: patients receiving fluoxetine had improved reaction time at week 1 ($p < 0.005$) compared with amitriptyline recipients. Patients in both treatment groups improved by week 6 Tests of memory: no data presented. Authors state performance improved over time with both drugs, more slowly with amitriptyline
Branconnier et al.[69]	Outpatients with depression and cognitive impairment; ≥60y (n = 75)	db, r, pc, sb (placebo run-in)	Mianserin 30-60 mg/day Amitriptyline 75-150 mg/day Placebo	35 day	Hands Test (ATN), Bender Visual Motor Gestalt Test (C), Yerkes Test (CR), Analogies Test (CR), Digit-Digit Coding (ATN), Sperling's Perceptual Trace (M), Guild Memory Test (M), Gottschaldt Hidden Figures Test (P), Reaction Time Test (ATN)	63 completed study Bender Visual Motor Gestalt Test: amitriptyline recipients worse than placebo recipients ($p < 0.01$) Guild Memory Test: no significant differences between groups Digit-Digit Coding: patients receiving amitriptyline had worse performance Impairment Index (composite score of 9 tests): patients receiving amitriptyline were worse on day 35, other groups had improved ($p < 0.005$)
Siegfried & O'Connolly[70]	Patients with depression, but no dementia; ≥65y (n = 75)	db, r	Maprotiline 100 mg/day Mianserin 40 mg/day Nomifensine 100 mg/day	4wk	Critical Fusion Flicker Test (P), Digit span (ATN), Cancellation test (ATN), Choice reaction time (ATN), Paired associate learning (M)	Critical Fusion Flicker Test: all groups improved, no differences. Improvements were faster with nomifensine > mianserin >maprotiline Cancellation Test: recipients receiving nomifensine were significantly better than maprotiline and mianserin recipients Tests of memory: all drugs improved performance, no significant differences Reaction time improved for all groups (nomifensine, mianserin > maprotiline)
Pancheri et al.[71]	Outpatients; 60-85y (n = 30)	db, r	Moclobemide 400-600 mg/day Imipramine 75-100 mg/day	60 day	Benton Visual Renton Test (M), Digit Substitution Test (ATN)	In the moclobemide group 5 patients withdrew from treatment; however, none related to cognitive effects Benton Visual Renton Test: moclobemide group improved significantly at day 60 compared with baseline ($p < 0.05$) Digit Substitution Test: moclobemide group improved significantly at days 30, 45, 60 compared with baseline ($p < 0.01$) No significant changes in any tests for imipramine group

ATN = attention; **C** = construct; **co** = crossover; **CR** = concept formation and reasoning; **db** = double-blind; **G** = global assessment; **M** = memory; **mc** = multicentre study; **MMSE** = Mini-Mental State Examination; **NS** = not significant; **P** = perceptual tests; **pc** = placebo-controlled; **r** = randomised; **sb** = single-blind; **SCAG** = Sandoz Clinical Assessment Geriatric Scale.

4.4 Antipsychotics

Antipsychotic drugs are often used to treat behavioural problems associated with dementia. Few studies have examined whether antipsychotic drug use impairs cognition in the elderly. In healthy volunteer (non-elderly) studies, haloperidol resulted in impairment in various aspects of cognition.[78-80] Based on anticholinergic effects, it is often assumed that low potency agents which have high anticholinergic activity (e.g. thioridazine) are more likely to worsen cognition than high potency agents (e.g. haloperidol); however, this assumption has not been carefully studied.[81] Furthermore, antipsychotics affect many neurotransmitters, thus other mechanisms are likely to mediate the effects on cognition. A single-blind study in patients with Alzheimer's disease found a decline in MMSE scores with use of haloperidol 1 to 5 mg/day, an agent with lower anticholinergic effects relative to comparable doses of low-potency agents.[82] However, a double-blind placebo-controlled trial did not find a detrimental effect on MMSE after 6 weeks of haloperidol 2 to 3 mg/day.[83] One epidemiological study reported that the initiation of a antipsychotic coincided with a more rapid decline in global cognition of dementia participants after controlling for several factors.[84]

A few studies have evaluated the cognitive effects of newer atypical antipsychotics (e.g. risperidone, clozapine). Clozapine was evaluated in a double-blind, placebo-controlled trial to determine whether it was effective in treating drug-induced psychosis in patients with Parkinson's disease. Low dose treatment (average dose 24.7mg) did not have a negative effect on MMSE scores over a 4-week period.[85] Clozapine has strong anticholinergic effects, so higher doses may be problematic in the elderly. Use of risperidone (1 or 2 mg/day) in patients with Alzheimer's disease did not result in a significant reduction in MMSE score over a 12-week period compared with placebo.[86] Although these agents deserve further study, atypical agents may be preferable in the elderly because of a lower risk for other adverse events.

4.5 Lithium

Several case reports indicate that lithium has effects on cognition (delirium, impaired memory and psychomotor performance),[87,88] but controlled studies in the elderly are lacking. In a study of 46 long term lithium users undergoing blinded discontinuation and resumption of lithium therapy, scores on tests of memory, tapping speed and associative productivity improved significantly during the time off lithium.[89] Impairments can be present with therapeutic serum concentrations.

4.6 Analgesics

Opioid use was associated with delirium in 3 of 5 large prospective studies of hospitalised patients (table II);[7,35,36] however, one study grouped opioids with other psychoactive agents which makes interpretation difficult for this study.[7] In one evaluation, the only opioid considered to be a risk factor for delirium was pethidine. The association of morphine, fentanyl, oxycodone and codeine with delirium did not reach statistical significance, although these agents were used less frequently than pethidine.[35] Pethidine has an active metabolite, norpethidine (half-life of 15 to 30 hours), which can accumulate in elderly patients with renal insufficiency and is associated with CNS toxicity. Pethidine also has weak anticholinergic activity.[23] Route of administration may play a role in risk for delirium. Epidural[35] and intramuscular administration[90] of opioids resulted in higher risk of confusion/delirium when compared with patient controlled analgesia.

Non-opioid analgesics may also cause cognitive changes. Paracetamol (acetaminophen) does not cause delirium at usual dosages but may in an overdose situation. Delirium or confusion may be present with acute or chronic salicylate intoxication.[91] The elderly may experience confusion with chronic salicylate intoxication with therapeutic doses of aspirin (acetylsalicylic acid).[91]

Disparate effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the CNS have been reported. Various NSAIDs have been implicated in

causing delirium, psychosis and cognitive impairment in case reports.[92-94] Clinical trials have not demonstrated significant adverse effects on cognition after 3 weeks of naproxen[95] or 1 week of indomethacin treatment.[96] More recently, NSAIDs have been hypothesised to be protective against the development of cognitive impairment. Results from epidemiological evaluations have been mixed, indicating that NSAIDs have a beneficial,[97] detrimental[98,99] or no effect[100,101] on tests of cognition. However, it appears high dose NSAIDs may be associated with a decline in memory.[98,99] The summary of 3 case control studies indicated a 50% reduction in prevalence of Alzheimer's disease in participants reporting NSAID use.[102] It is likely that NSAIDs cause subtle cognitive impairment especially in high doses in susceptible individuals, but the overall incidence is rare.

4.7 Antiparkinsonian Agents

Confusion is relatively rare in the early stages of Parkinson's disease. As the disease progresses, patients frequently experience neuropsychiatric complications (e.g. visual hallucinations, delusions, confusion, delirium).[103] The aetiologies of these complications are often difficult to determine in that they can be related to the progression of the disease, co-existing dementia or antiparkisonian therapy. The prevalence of coexisting dementia is 20 to 30%. Risk factors for drug-induced confusion include increasing age, presence of dementia, and high doses of antiparkinsonian agents.[103]

All medications used to treat Parkinson's disease have been implicated in causing confusion/delirium (anticholinergics, amantadine, levodopa, dopamine agonists, monoamine oxidase inhibitors).[103] These agents may produce minimal problems early in the disease,[104] but confusion/delirium is more common with advanced disease especially in the patient who is taking several antiparkinsonian agents. Patients with mild to moderate Parkinson's disease taking levodopa for up to 6 months had no change on a test of memory.[104] Small improvements occurred in tests of frontal lobe function (verbal fluency) and one test of attention.[104] However, long term therapy with levodopa may have different effects on aspects of cognition.[105] Increased confusion and hallucinations were reported in a small case series of elderly patients that were switched from standard to the controlled release formulation of levodopa-carbidopa.[106] The dopamine agonists differ in their affinity for the dopamine subreceptors, and it is not clear if this translates into differences in propensity to cause neuropsychiatric adverse effects. For patients experiencing cognitive effects, adjunctive therapy [e.g. anticholinergics, amantadine, selegiline (deprenyl)] should be tapered slowly to the lowest effective dose or discontinued as patient condition allows.[103,107]

4.8 Anticonvulsants

While considerable research has evaluated the cognitive effects of anticonvulsants in children and middle age adults,[108,109] only 1 study could be found that was conducted in the elderly.[110] The effects of phenytoin and valproic acid (sodium valproate) on tests of attention, concentration and memory were evaluated in 47 older patients with new onset epilepsy. 38 study participants completed 6 weeks of therapy and both treatments had minimal effects on cognition; however, phenytoin produced less detriment on tests of attention. Findings at 1 year were similar; however, there were high rates of treatment discontinuation in this study.[110]

Despite limited information in the elderly, several large trials have been conducted in middle age adults. In the Veteran's Affairs Cooperative study, participants (n = 622) with well-defined seizure types, were randomised to receive carbamazepine, phenytoin, primidone or phenobarbital (phenobarbitone).[111,112] The overall behavioural toxicity score, based on transformed data of several subscales, indicated that carbamazepine had fewer effects on cognition than the other treatments at 3 months. However, results on individual subscales varied with no consistent pattern of one drug being superior.[111] When the authors tabulated the num-

Table V. Summary of studies evaluating the cognitive effects of antihypertensive agents

Reference	No. of patients [age range (y)]	Study design	Treatments	Duration	Aspects of cognition tested	Results
Prince et al.[119]	2584 [65-74]	sb, r, pc, mc	Atenolol 50 mg/day Hydrochlorothiazide 25 mg/day plus amiloride 2.5 mg/day Placebo	54mo	Paired associate learning test (M), Trail Making test A (ATN)	Intention-to-treat analysis No difference between groups on either test. Memory tended to decline in all groups over time. Time to take trailmaking improved over time
Starr et al.[123]	81 [70-85][a]	db, r	Captopril 12.5-25mg bid Bendrofluazide 2.5-5 mg/day	24wk	Logical Memory Immediate & Delayed (M), Paired Associates Recall (M), Raven's Progressive Matrices (CR), Trail Making A (ATN), Anomalous Sentences Repetition Test (M, ATN)	Intention-to-treat analysis No differences between treatment groups for any tests. Patients with highest DBP reduction (highest quartile) had improved scores on Anomalous Sentence Repetition Test ($p = 0.012$) and Paired Associates Recall ($p = 0.044$) compared with patients in lowest quartile Type II error possible
Applegate et al.[121]	242 [≥65][b]	db, r, mc	Atenolol 50-100 mg/day Enalapril 5 -20 mg/day Diltiazem SR 60-180mg bid	16wk	Digit Symbol Substitution Test (ATN), Rey Auditory Verbal Learning Test (M),Taylor Complex Figure Tests (M), Rey-Osterreith test	No difference in change from baseline between treatments at week 16 Digit Symbol Substitution Test: treatment with atenolol was associated with a significant decline from baseline compared with treatment with diltiazem and enalapril at week 8 only ($p = 0.03$)
Applegate et al.[122]	1993 [≥60y][c]	db, r, mc	Step 1: chlorthalidone 12.5-25 mg/day Step 2: addition of atenolol 25-50 mg/day or reserpine 0.05-0.10 mg/day	5y	Digit Symbol Substitution Test (ATN), Letter Sets Test (CR), Addition Test (ATN), Finding A's Test (ATN), Boston Naming Test (VER), Delayed Recognition Span Test (M)	Intention-to-treat analysis No difference on any test of cognitive function between treatment and placebo group. Unable to evaluate differences between Step 1 and Step 2 treatment
Skinner et al.[120]	31 [60-81]	db, r, co	Atenolol 50-100 mg/day Nifedipine 30-90 mg/day	6-10wk per drug	Buschke Selective Reminding Test (M), Raven Progressive Matrices (CR), Stroop Test (ATN), Trail Making B (ATN), Finger-Tapping Test (MP), Digit Symbol Test (ATN), Vocabulary Test (VER), Block Design Test (C)	Period effect observed for Bushke Selective Reminding Test and Digit Symbol Test – only the first period was analysed Buschke Selective Reminding Test: patients treated with nifedipine recalled fewer words (9% decrease) compared with placebo recipients ($p = 0.03$); 16% decrease compared with atenolol group ($p = 0.03$) Digit Symbol Test: performance in patients receiving nifidepine tended to decline whereas performance in patients receiving atenolol tended to improve. The difference between nifedipine and atenolol (change in scores from placebo) was 4.3 codings ($p = 0.04$) in favour of atenolol No differences on other tests were found.

bers of 'best' and 'worst' scores for individual subscales, the phenobarbital and primidone groups received the 'worst' scores more than the other groups. Some have questioned the validity of these conclusions based on statistical issues.[108,113] Other studies have reported no significant differences between carbamazepine and phenytoin, after controlling for seizure frequency and serum concentrations.[108,109] Carbamazepine and valproic acid had minimal effects after 1 year of therapy.[114]

In general, use of monotherapy and maintaining serum concentrations within the therapeutic range will minimise cognitive problems in most patients.[108,109] Nonetheless, all anticonvulsants have dose-related adverse effects. Based on non-elderly studies, phenobarbital and primidone appear to have more cognitive effects than carbamazepine, phenytoin or valproic acid.[108,113] Additional study is needed to assess the cognitive effects of newer agents (vigabatrin, gabapentin, tiagabine, topiramate) in the elderly; however these agents appear to have minimal effects on cognition in non-elderly populations.

4.9 Antihypertensive Agents

In longitudinal studies, higher blood pressure in mid-life was associated with impaired cognitive function in later years.[115] Concerns have been raised that antihypertensive therapy itself may adversely affect cognition. Agents that affect the catecholamine system (methyldopa, clonidine, reserpine) are most commonly cited as having an adverse effect on cognition; however, there has been no rigorous testing of the effects of the drugs on cognitive function.[29,32,116,117] In any case, these medications are not typically used in the elderly. Initial reports suggested that lipophilic β-blockers (e.g. propranolol) had a greater risk of CNS effects than hydrophilic agents (e.g. atenolol); however, many studies have disputed these findings.[32,118] The overall incidence of β-blocker-induced cognitive impairment is rare.[117,119-121]

With the availability of many effective hypertensive agents, studies have focused on differentiating the effects of therapy on quality of life, with

Goldstein et al.[117]	690 [≥60][d]	db, r	Hydrochlorothiazide: low dosage (25 mg/day once to twice daily) or high dosage (50mg once to twice daily). If BP not controlled, randomised to: hydralazine 50-200 mg/day or methyldopa 500-2000 mg/day or metoprolol 100-400 mg/day or reserpine 0.05-0.25 mg/day	12mo	Intellectual Process Scale-Luria-Nebraska, Trail Making Test (ATN), Smith Symbol Digit Modalities Test (ATN), Hooper Visual Organization Test (P), Benton Visual Retention Test (M), Finger Tapping Test (MP), Token Test (VER), Controlled Word Production (VER)	Performance improved in treatment and placebo control group (practice effect). In patients receiving only hydrochlorothiazide there was no deterioration on any test from baseline in the low and high dosage groups. For combination therapy there was no deterioration among treatments. There were differences in the number of tests that showed improvement (practice effect): reserpine (1 test) versus metoprolol (5 tests); versus methyldopa (8 tests); versus hydralazine (9 tests)

a Mini-Mental state examination between 20 to 28.

b Women; Mini-Mental state examination ≥24.

c Subset with isolated systolic hypertension.

d Men.

ATN = attention; **bid** = twice daily; **BP** = blood pressure; **C** = construct; **co** = crossover; **CR** = concept formation and reasoning; **db** = double-blind; **DBP** = diastolic blood pressure; **G** = global assessment; **M** = memory; **mc** = multicentre study; **MP** = motor performance; **P** = perceptual tests; **pc** = placebo-controlled; **r** = randomised; **sb** = single-blind; **SR** = slow release; **VER** = verbal function.

cognition being one important aspect (table V). Data are available from 2 large randomised, long term, controlled trials, which indicate minimal negative effects on cognition of commonly used antihypertensive agents.[119,122] The Medical Research Council trial found no difference between atenolol, hydrochlorothiazide and amiloride and placebo after 54 months of treatment in 2584 patients with moderate hypertension.[119] Investigators of the Systolic Hypertension in the Elderly Program (SHEP) reported no differences on various tests between active treatment (chlorthalidone with or without atenolol or reserpine) versus placebo after 5 years of therapy.[122] It was not possible to examine if differences existed between Step 1 (chlorthalidone alone) and Step 2 (need for addition of atenolol or reserpine) subgroups of active treatment.

Several shorter term studies have also been conducted.[120,121,123] In a comparison of atenolol, enalapril and diltiazem, no differences were found in tests of cognitive function after 16 weeks.[121] However, in a crossover trial, nifedipine but not atenolol, significantly reduced verbal learning and memory.[120] Other dihydropyridine calcium antagonists (e.g. nimodipine) have resulted in improved cognition in dementia patients,[124] thus it is not clear why nifedipine was found to have detrimental effects.[120] A randomised study in previously untreated hypertensive patients found no detrimental effects on various aspects of cognition for captopril and bendrofluazide (no placebo group) after 24 weeks of treatment.[123] Patients with the greatest decrease in diastolic blood pressure had the greatest improvements in a few of the cognitive tests compared with persons with lower levels of blood pressure reduction. This study is of particular interest because it included patients with cognitive impairment who may be more susceptible to adverse effects, a group often excluded from previous trials.

In large clinical trials, the use of thiazide diuretics, calcium antagonists (amlodipine, diltiazem), ACE inhibitors (captopril, enalapril) and β-blockers (atenolol) rarely caused cognitive impairment. Large clinical trials spanning 4 to 5 years have not demonstrated that lowering blood pressure with drug therapy in older individuals improves cognition,[119,122] which might have been expected with the prevention of ischaemic events.

4.10 Other Cardiovascular Agents

Digoxin toxicity can present with various neuropsychiatric symptoms including delirium, confusion, hallucinations and delusions,[125-127] but the overall incidence is rare.[128,129] Confusion has also been reported in patients with therapeutic plasma digoxin concentrations.[130,131] Case reports of confusion and other neuropsychiatric symptoms have been reported with various cardiovascular agents including quinidine,[132] tocainide,[133] and lidocaine (lignocaine).[29,134]

4.11 Histamine Receptor Antagonists

4.11.1 H_2 Antagonists

Delirium has been reported with all H_2 antagonists but is relatively rare.[135-142] A large prospective study did not find an increased risk of delirium with H_2 antagonists;[36] however, a relationship may have been obscured if only a subset of patients are at increased risk. Cimetidine has received the most attention which is likely to be because of its widespread use as the first available agent in this class.[142] H_2 antagonist–induced delirium has reoccurred with rechallenge.[139,143] Some patients can tolerate a different H_2 antagonist without reemergence of symptoms, whereas cross-sensitivity between agents has also been described.[136,142] Evidence exists for full or partial reversal of symptoms with physostigmine administration, suggesting that an indirect effect on cholinergic transmission may be involved in mediating drug-induced effects on cognition.[20-22]

4.11.2 H_1 Receptor Antagonists

Diphenhydramine has been found to impair attention, short term verbal memory, and concentration and reaction time in older volunteers[16] and cause delirium in patients.[144] In healthy nonelderly patients, second generation antihistamines (loratadine, astemizole) cause less sedation and

cognitive impairment,[145,146] and therefore are preferable choices for the elderly, provided no contraindications exist. Certrizine, also a second generation agent, may have intermediate sedative effects.[145]

4.12 Corticosteroids

Glucocorticoids have been associated with reversible memory impairment, psychosis and dementia.[147] A cross-sectional study was conducted in 25 patients between the ages of 22 and 72 years (median age 55 years) and 25 matched clinic control participants.[148] Treated patients were taking prednisone in dosages of 5 to 40 mg/day for at least a year and demonstrated poorer paragraph recall ('explicit memory') but were equivalent on tests of implicit memory when compared with the matched controls.

4.13 Other Agents

Delirium has been documented with cytokines and antineoplastic agents;[149-151] however, the use of multiagent chemotherapy and adjunctive medications makes it difficult to determine the causative agent. There have been case reports of cognitive impairment and other psychiatric symptoms with antibacterials, antimalarials and antifungals.[29,30] Although often overlooked, metoclopramide has been associated with confusion and extrapyramidal symptoms in the elderly.[152]

5. Detection and Management/Prevention

Drug-induced delirium and dementia are usually encountered in different clinical settings (inpatient versus outpatient); therefore, the discussion of detection and management will be treated separately. General principles for preventing drug-induced cognitive disorders are listed in table VI.

5.1 Drug-Induced Delirium

The ultimate goal is to prevent delirium; however, this will be difficult in many clinical situations. Since delirium is common in the hospitalised older patient, we advocate assessment of cognition in most older patients upon admission using a brief screening instrument.[4] General principles to minimise delirium include the avoidance of medication likely to cause delirium if alternative medications exist and using the lowest effective dose. Patients should be monitored carefully when multiple agents with CNS effects are required. These principles are especially important for patients with baseline cognitive impairment, who are at an increased risk for delirium.

Early resolution of delirium hinges on accurate and prompt identification of the syndrome. Delirium is under-recognised by clinicians; studies indicate that 32 to 67% of delirious patients went unrecognised by the clinicians who were caring for them.[4] Furthermore, delirium is often misdiagnosed as dementia or psychiatric illness or misattributed to the normal aging process.[4] Thus, increased clinician awareness is important to identify changes in cognitive status during the hospital

Table VI. Prevention and detection of drug-induced delirium/dementia

Take a thorough medication history, including over-the-counter medications
Assess cognition of elderly patients upon hospital admission and at times when clinical status changes
Minimise medication use:
treat conditions with nonpharmacological measures when possible
review drug list periodically, attempt discontinuation of medications when feasible
Adjust medication doses appropriately for age-related changes in pharmacokinetics and pharmacodynamics (START LOW, GO SLOW)
Assess for potential subtle cognitive changes whenever new drugs are initiated or doses increased
Consider trials of sequentially eliminating drugs suspected of impairing cognition. Assess cognition and desired therapeutic effect after discontinuation

course. Important to note is that not all delirious patients exhibit agitation, hallucinations and inappropriate behaviour. Many older patients may exhibit a hypoactive form of delirium that may manifest as lethargy and decreased activity.[2,4]

If delirium is suspected, a comprehensive history and physical examination should be conducted to identify all precipitating factors. As part of this work up, reviewing medication use will assist in determining if the delirium is drug-related. First, new medications or dosage increases should be identified and then a temporal relationship should be established between these changes and onset of symptoms.

Delirium may be caused by many concurrent factors and management should address each suspected factor. In terms of drug-related delirium, the implicated medication should be discontinued, if warranted, or the dose should be reduced. Supportive care such as ensuring adequate sleep, nutrition, hydration and providing emotional reassurance is important for managing the patient with delirium.[2] If symptoms cannot be managed with supportive care, pharmacological strategies may be needed to control severe agitation and psychosis.[153] Management of drug-induced delirium has recently been reviewed.[153]

5.2 Drug-Induced Dementia

Almost any drug can cause subtle changes in cognition, therefore prevention may be difficult. It is important for clinicians to have an awareness that subtle changes in cognition in their elderly patients may be caused by drug therapy. Good provider prescribing may avoid some cases of drug-induced dementia (table VI). A complete accounting of all medications a patient is using is important. Patients often receive medications from multiple prescribers or take over-the-counter medications, therefore it may be difficult for providers to be aware of all medication use. Medication use not accounted for may make it difficult to identify drug-related cognitive decline. For example, a person may have a recent worsening of dementia caused by an over-the-counter antihistamine; this drug-related cause of worsening symptoms may be overlooked if the clinician is unaware of the antihistamine use. Thus, we recommend that patients bring a list of medications they are taking or the actual medications to each clinic visit.

Recognition of drug-induced cognitive impairment, especially if deficits are subtle, may be difficult in the older adult. Symptoms often appear insidiously and patients may not bring the deficits to the attention of their provider.[94] Thus, patients should be assessed for subtle changes in cognition with the addition or increase in medication dosages. If a change in cognition is suspected, elimination (one at a time) of the suspected drug(s) and follow-up evaluation may be the only way to detect drug-induced cognitive impairment.

6. Conclusion

Drug-induced delirium and dementia are relatively common disorders that are under-recognised. Individuals at greatest risk are the elderly with baseline cognitive impairment. Medications should always be considered a potential cause when a patient presents with cognitive changes. Although evidence from research studies indicates that the incidence of cognitive impairment is rare for many commonly used agents, frail elderly patients may be more susceptible. Preventive strategies directed at avoiding high risk medications, appropriately adjusting doses based on age-related changes and close follow-up may prevent these conditions.

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