Anticholinergic side-effects of drugs in elderly people

Jacobo Mintzer MD Alistair Burns MD FRCPsych

J R Soc Med 2000;**93**:457–462

Old age is accompanied by an increased likelihood of illness, and old people take a disproportionate amount of self-administered and prescribed medications. In the USA, people over 65 consume 30% of prescriptions and 40% of over-the-counter remedies, despite making up only 13% of the population[1]. In the UK, elderly people comprise only 18% of the population but use 45% of all prescription drugs, some of which are prescribed inappropriately and without proper attention to side-effects[2]. Elderly people living in nursing homes are even more likely to receive medications and to experience side-effects[3]. Thus, in one year, 97% of elderly nursing home residents received a prescription drug, compared with 71% of patients living in the community[4]. Failure to identify side-effects can lead to use of other drugs to treat the symptoms, rather than adjustment of the dose of the drug responsible.

Why do side-effects go unnoticed in elderly people? Older people often have low health expectations and are less likely to complain. Patients with cognitive impairment have difficulties in communicating their discomfort; those living in nursing homes may rely on care staff to alert the physician to possible side-effects. Some side-effects can be mistaken for the effects of old age and age-related illness. This is particularly the case for anticholinergic side-effects, which are among the most common drug-related effects experienced by elderly people living in nursing and residential homes[5,6]. This review highlights the need for better understanding, assessment and management of anticholinergic side-effects in elderly people.

DRUGS WITH ANTICHOLINERGIC ACTIVITY

Blazer *et al.*[4] reported that, during one year, nearly 60% of nursing home residents had received drugs with anticholinergic (antimuscarinic) activity, compared with 23% of elderly people living in the community. The most frequently prescribed of these drugs were thioridazine, chlorpromazine and diphenoxylate/atropine. Several types of drug can cause anticholinergic side-effects (Box 1). Peters[5] identified 22 categories with significant anticholinergic activity, including those with an anticholinergic

Box 1 **Drugs with anticholinergic adverse effects used in the elderly**
(Adapted from Refs 5 and 6)

Anticholinergic drugs	
Antiemetics/anti-vertigo	Hyoscine, cyclizine, dimenhydrinate, meclozine, trimethobenzamide, promethazine, prochlorperazine
Antiparkinson	Benztropine, biperiden, procyclidine, trihexyphenidyl, ethopropazine
Antispasmodics (gastrointestinal)	Belladonna alkaloids, clidinium bromide, dicycloverine, hyoscyamine, methscopolamine bromide, propantheline
Antispasmodics (genitourinary)	Oxybutynin, flavoxate, dicyclomine
Anti-migraine drugs	Belladonna alkaloids
Bronchodilators	Atropine solution, ipratropium
Pre-anaesthetics	Hyoscine, atropine
Mydriatics/cycloplegics	Atropine solution, cyclopentolate, homatropine, tropicamide
Drugs with anticholinergic side-effects	
Antiarryhthmics	Disopyramide, procainamide, quinidine
Antidiarrhoeals	Diphenoxylate/atropine, tincture of belladonna
Antihistamines	Diphenhydramine, chlorphenamine, clemastine, dexchlorpheniramine, hydroxine, mepyramine (pyrilamine), promethazine
Skeletal muscle relaxants	Cyclobenzaprine, orphenadrine
Anti-ulcer drugs	Propantheline
Antidepressants	Amitriptyline, imipramine, doxepin, trimipramine, nortriptyline, protriptyline, amoxapine, maprotiline, clomipramine
Antipsychotics	Chlorpromazine, thioridazine, clozapine, fluphenazine, prochlorperazine, thiothixene
Miscellaneous	Glutethimide, pethidine
Herbal medicines	Henbane, deadly nightshade

Medical University of South Carolina, Department of Psychiatry (PH-141), 67 President Street, PO Box 250861, Charleston, South Carolina, 29425, USA; [1]School of Psychiatry and Behavioural Sciences, University Hospital of South Manchester, Manchester, UK

Correspondence to: Professor Jacobo Mintzer
E-mail: mintzerj@musc.edu

Table 1 ***In-vitro*** **anticholinergic activity (at 10 nmol/L) of the 25 medications most commonly prescribed to elderly people in the USA** (Adapted from Ref. 7)

Detectable atropine-like activity (ranked from high to low)	*No detectable atropine-like activity*
Cimetidine	Hydrochlorothiazide
Prednisolone	Propranolol
Theophylline	Salicyclic acid
Digoxin	Nitroglycerin
Nifedipine	Insulin
Frusemide	Methyldopa
Ranitidine	Ibuprofen
Isosorbide dinitrate	Diltiazem
Warfarin	Atenolol
Dipyridamole	Metoprolol
Codeine	Timolol
Dyazide	
Captopril	

mode of action (e.g. drugs for parkinsonism, irritable bowel syndrome, urinary incontinence) and others with unwanted anticholinergic effects. Tune *et al.*[7] looked for *in-vitro* anticholinergic activity in the 25 drugs most commonly prescribed for elderly people and found such activity in 14 (Table 1). Often, elderly patients receive several such drugs simultaneously.

Many non-prescription drugs have anticholinergic potential; this is true of the antihistamines in cold/flu and hayfever treatments—e.g. diphenhydramine (Benylin Four Flu); triprolidine (Actifed); chlorpheniramine (Piriton/Contact 400); and promethazine (Night Nurse/Phenergan). Skin creams and lotions also contain antihistamines—e.g. diphenhydramine (Allereze cream) or mepyramine (Anthisan)—and treatments for sleep disturbance include diphenhydramine (Nightcalm/Nytol) and promethazine (Sominex/Phenergan). Some hayfever medications contain theophylline (e.g. Chest-Eze), antidiarrhoeals include extract of belladonna (Enterosan, Opazimes) and some treatments for irritable bowel syndrome contain hyoscine (Buscopan).

The number of drugs with anticholinergic potential available without prescription is increasing[6], so that the use of such medications is becoming more difficult to monitor. For example, histamine H_2 antagonists can be had over the counter for indigestion—cimetidine (Tagamet/Acid-eze); ranitidine (Zantac); famotidine (Pepcid AC). Of those drugs examined by Tune *et al.*[7], cimetidine had the highest anticholinergic activity *in vitro*, although side-effects attributed to this activity do not feature in the labelling of cimetidine. One interpretation is that *in-vitro* pharmacological activity does not always predict clinical effects; alternatively, the activity reported by Tune *et al.*, though insufficient to cause obvious side-effects with cimetidine monotherapy in young adults, might be troublesome in those already receiving anticholinergic medications or otherwise vulnerable. High doses of cimetidine in elderly patients have occasionally been associated with reversible confusional states (confusion, delirium, slurred speech, hallucinations, coma[8]).

RECOGNIZING ANTICHOLINERGIC SIDE-EFFECTS

Symptoms which may be caused by drugs with anticholinergic activity include:

- Dry or sticky lips; difficulty beginning to speak (need to lick lips first)
- Urinary disorders, necessitating use of catheter
- Skin dry, pale and cool
- Insecure movement; falls without obvious reason, blurred vision
- Increased anxiety, with rapid, shallow breathing, tachycardia, cardiac arrhythmias.

Anticholinergic actions affect multiple systems, causing a range of peripheral and central side-effects and symptoms (Table 2). Central anticholinergic effects include memory deficits, confusion and disorientation, agitation, hallucinations and delirium[4,6]. In the extreme, anticholinergic toxicity depresses brain function, with coma and circulatory collapse.

IMPACT OF ANTICHOLINERGIC SIDE-EFFECTS

Why should old people be at increased risk of anticholinergic side-effects[4,9]? Part of the reason may lie in deficient drug metabolism and elimination, as well as age-related deficits in cholinergic neurotransmission[6]. For people living in nursing homes, with little to distract them, side-effects can be particularly distressing and difficult to cope with. For example, dry mouth, while apparently trivial, can cause speech difficulties, dental decay or trouble with dentures. Chewing and swallowing may become painful, and the patient may refuse solid food. The pain of dry mouth can be extremely distressing for older patients, who may become frustrated and agitated by an inability to communicate their distress.

Older people often have multiple illnesses. In the USA as many as five chronic conditions in one person is not unusual[10], and conditions such as angina, congestive heart failure, constipation, diabetes mellitus, glaucoma, urinary dysfunction, sleep disturbance and dementia are all worsened by drugs with anticholinergic activity[6]. Pupillary dilatation and the inability to accommodate will impair near vision, thus increasing the risk of accidents, including falls,

Table 2 **Spectrum of anticholinergic side-effects** (Adapted from Ref. 6)

Mild	*Moderate*	*Severe*
Dryness of mouth (modest)	Moderately disturbing dry mouth/thirst Speech problems Reduced appetite	Difficulty chewing, swallowing, speaking Impaired perception of taste and texture of food Mucosal damage Dental decay, periodontal disease, denture misfit Malnutrition Respiratory infection
Mild dilatation of pupils	Inability to accommodate Vision disturbances Dizziness	Increased risk of accidents and falls, leading to decreased function Exacerbation/precipitation of acute angle closure glaucoma
	Oesophagitis Reduced gastric secretions, gastric emptying (atony) Reduced peristalsis, constipation	Faecal impaction (in patients with constipation) Altered absorption of concomitant medications Paralytic ileus, pseudo-obstruction
Urinary hesitancy		Urinary retention, urinary tract infection (in patients with urinary hesitancy)
	Increased heart rate	Conduction disturbances, supraventricular tachyarrhythmias Exacerbation of angina Congestive heart failure
Decreased sweating		Thermoregulatory impairment leading to hyperthermia (heatstroke)
Drowsiness Fatigue Mild amnesia Inability to concentrate	Excitement Restlessness Confusion Memory impairment	Profound restlessness and disorientation, agitation Hallucinations, delirium Ataxia, muscle twitching, hyperreflexia, seizures Exacerbation of cognitive impairment (in patients with dementia)

and may precipitate narrow-angle glaucoma in predisposed patients. In patients with constipation, anticholinergic effects may lead to stomatitis, paralytic ileus or faecal impaction. Drug-induced increases in heart rate may worsen symptoms of angina, and inhibition of sweating may cause life-threatening hyperthermia. Patients with urinary hesitancy may experience urinary retention and urinary tract infection, a common cause of delirium. Men with prostatism are at high risk of acute urinary retention as an anticholinergic side-effect.

Delirium can be caused by blockade of brain muscarinic receptors; drugs with anticholinergic activity are the most common cause of drug-induced delirium[7,11]. More than one-fifth of elderly patients admitted to hospital develop delirium, particularly those with dementia and multiple illnesses. In patients with dementia, anticholinergic drugs further inhibit cognitive performance and counteract the beneficial effects of cholinergic enhancers used to treat cognitive impairment.

Williamson *et al.*[9] examined the use of psychotropics and antiparkinsonian drugs (both have marked anticholinergic effects) in nearly 2000 patients admitted to geriatric units. More than a quarter were receiving one such drug, and 13% of those patients had significant adverse events[6]. Nevertheless, physicians often attribute anticholinergic symptoms in elderly people to ageing or age-related illness rather than the effects of drugs[6]. Even physicians and carers who appreciate that such symptoms can be drug-induced may regard them as inevitable, simply because they are so common.

UNDERSTANDING THE RISK: POLYPHARMACY AND 'ANTICHOLINERGIC LOAD'

In their nursing home study, Blazer *et al.*[4] calculated that between 21% and 32% of residents could have been taking two or more drugs with anticholinergic activity (three or more drugs 10–17% of patients; five or more drugs, up to 5%). The most common combinations were thioridazine/benzhexol and thioridazine/chlorpromazine (benzhexol is now seldom used). However, combined use of thioridazine and amitriptyline (each with marked anticholinergic activity) was also very common, demonstrating a lack of concern about combined anticholinergic effects.

Partly through legislation, there have been reductions in the use in US nursing homes of psychotropic drugs, many of which have marked anticholinergic activity[12]. The availability of newer psychotropic drugs has also had an impact on prescribing by primary care physicians

treating patients in nursing homes[13]. With increasing use of newer psychotropics anticholinergic side-effects in elderly people may be declining, but many different drugs have some anticholinergic activity and elderly patients receiving multiple drugs are still at risk of 'anticholinergic load'[14]. In theory the physician can predict the anticholinergic load and the risk of side-effects associated with any combination of drugs. In practice, the information available from the product label and from the published work focuses on side-effects of drugs used as monotherapy. The concept of anticholinergic load illustrates that side-effects can be caused by combinations of drugs, even if the individual drugs do not cause obvious side-effects.

PSYCHOTROPIC DRUGS: THE MAJOR BURDEN

These are among the most common medications taken by elderly people living in nursing homes (mainly anti-psychotics, antidepressants and anxiolytics/sedatives). Spore *et al.*[15] found that 43% of elderly patients in residential care were receiving psychotropic drugs. Antidepressants and antipsychotics have been linked most often with disorders due to anticholinergic activity.

Antidepressants

The use of antidepressants in elderly people requires particular care[16,17]. Tricyclic antidepressants (TCAs) have been in use for over 30 years, and imipramine and amitriptyline are the standard against which new drugs are evaluated. Old patients are more likely than young adults to experience side-effects with TCAs (see Box 1 for examples). Apart from the postural hypotension and sedation associated with the TCAs, anticholinergic side-effects such as constipation, urinary retention and confusion are particular causes for concern. Some authorities have advised against the use of TCAs such as imipramine, amitriptyline and doxepin in the elderly because of their side-effects, not least their anticholinergic effects[18–20]. Nortriptyline, lofepramine and desipramine (the least anticholinergic of the TCAs) tend to be better tolerated.

Some newer antidepressants may be useful alternatives to TCAs in elderly people[21]. The selective serotonin reuptake inhibitors such as fluoxetine and sertraline have been recommended, partly because of their relative freedom from anticholinergic side-effects[19,20]. Nefazodone, bupropion, venlafaxine and mirtazapine also have less anticholinergic potential than the older drugs[22].

Antipsychotics

Conventional neuroleptic drugs are widely used in the treatment of behavioural and psychological symptoms of dementia[23–25], despite a lack of prospective placebo-controlled studies on their use in these circumstances[26]. Substantial differences exist between conventional neuroleptic drugs with respect to anticholinergic activity; chlorpromazine and thioridazine have the highest activity[27,28] with considerable side-effects[29] (see Box 1). Haloperidol has lower muscarinic affinity and the risk of anticholinergic side-effects is lower, but extrapyramidal symptoms are more troublesome[29]. Conventional neuroleptic drugs can also cause other side-effects. Low doses have been recommended for elderly patients, although this may limit the efficacy of these agents[26].

Novel antipsychotic drugs have been widely studied in younger patients (particularly those with schizophrenia), but for most drugs no controlled trials have been reported in elderly patients[26]. An exception is risperidone, which has been compared with placebo in two trials in elderly nursing home patients with dementia[30,31]. Risperidone is the only novel antipsychotic so far registered for this indication in certain countries (though not in the UK). It has no measurable anticholinergic activity[28] and has not been reported to cause anticholinergic side-effects in elderly patients[30,31]. By contrast, clozapine has marked anticholinergic activity and is associated with profound anticholinergic side-effects[32–34]. When clozapine (and other antipsychotics with high anticholinergic activity) are withdrawn, two types of withdrawal reaction are seen—'cholinergic rebound', with nausea, vomiting, loss of appetite, malaise, diarrhoea, rhinorrhoea, sweating, anxiety, agitation and insomnia[35,36]; and movement disorders such as dyskinesia, akathisia and parkinsonism[37]. When switching patients to a drug with low anticholinergic potential, physicians sometimes mistake withdrawal symptoms for the side-effects of the new drug.

CHANGING PRESCRIBING PRACTICE

Physicians should be alert to the possibility that dry mouth, constipation and blurred vision may be caused by medication. Changes in intellectual function should also be investigated, especially in patients who already have cognitive impairment. For patients in whom side-effects can have particularly unpleasant consequences (e.g. those with gastrointestinal disease, bladder neck obstruction, glaucoma, cardiac disease or cognitive impairment), serious consideration should be given to switching to a drug that lacks anticholinergic side-effects.

For most drugs with anticholinergic potential an alternative is available. Combinations of drugs with strong anticholinergic activity, such as thioridazine and amitriptyline, should obviously be avoided. The use of drugs with minimal anticholinergic activity from the outset should avoid the need to switch medication (and the risk of

cholinergic rebound). If switching is necessary, the hazard of rebound can be lessened by slowly tapering the doses, with additional anticholinergic medication if necessary[38].

For patients already receiving treatment, the current anticholinergic load should always be considered before another drug is introduced. If the current load is high, even drugs with moderate or low anticholinergic activity may precipitate side-effects. No drug should be introduced without careful assessment of existing medications and symptoms. Often, there is little published information on the complex combinations of drugs used in elderly people. *In-vitro* activity can only be a broad predictor of clinical effects, and information from clinical trials may likewise be of limited value; for example, so far, trials of antipsychotic drugs in elderly people have not specifically inquired about anticholinergic side-effects but have relied on spontaneous reporting by patients or carers. The range and severity of side-effects may therefore have been underestimated.

INFORMING PATIENTS AND CARERS

Informing patients and carers about potential side-effects is of great importance. Difficulties with side-effects are likely to result in poorer treatment outcomes and are a major cause of non-compliance. If patients and carers are sensitively informed about unwanted effects, this will help to reduce the anxiety and distress that side-effects may cause.

PHYSICAL MEASURES

When anticholinergic side-effects do occur and the drug cannot be stopped, some steps can be taken to reduce their impact on the patient. The discomfort of dry mouth can be reduced by taking sips of water, or by chewing sugarless gum or soft sweets, while artificial tears are useful for dry eyes. Pilocarpine solution has been used as a mouthwash for dry mouth or as eye drops for blurred vision[39,40]. Constipation can be reduced by high-fibre diets, fibre supplements, increased fluid intake or greater patient mobility (e.g. walking down the ward to meals). Oral bethanechol, a cholinergic agonist, has been used to treat anticholinergic effects but can itself cause tremor, diarrhoea and abdominal cramps[39]. Furthermore, treatment of drug side-effects with another drug is not good practice; a much better strategy is to prescribe a medication relatively free from side-effects.

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