RESEARCH ARTICLE

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Anticholinergic effect on cognition (AEC) of drugs commonly used in older people

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Objective: Use of anticholinergic drugs in older people is associated with increased risk of cognitive decline and of dementia and death.

Method: We identified drugs widely used in older people and attempted to classify their anticholinergic effect on cognition (AEC) according to our three-point scale which scored AEC according to *in vitro* anticholinergic potency, capacity to cross the blood–brain barrier and statements made in standard texts.

Results: In total, 165 drugs were examined. We identified 21 drugs with an AEC score of 3, 18 with a score of 2, 21 with a score of 1 and 62 with a score of 0. Owing to insufficient information, we were unable to classify 43 drugs.

Conclusions: A large number of drugs commonly used in older people are likely to be associated with cognitive impairment.

Key words: dementia; cognitive function; anticholinergic
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Introduction

'Anticholinergic' drugs block muscarinic receptors and impair cholinergic function. This action causes not only well-known peripheral effects but also central adverse effects including confusion, disorientation, memory impairment, hallucinations and delirium (Feinberg, 1993). Long-term use of anticholinergic drugs in older people is associated with an increased risk of cognitive decline, dementia and early death (Carriere *et al.*, 2009; Jessen *et al.*, 2010; Fox *et al.*, 2011; Gray *et al.*, 2015). Anticholinergic drugs also directly oppose the action of acetylcholinesterase inhibitors used in dementia. Despite this, up to half of the patients with Alzheimer's disease who are prescribed cholinesterase inhibitors are also taking drugs with anticholinergic activity (Carnahan *et al.*, 2004; Modi *et al.*, 2009). The concurrent use of the two drug classes predictably and demonstrably reduces the clinical efficacy of the cholinesterase inhibitor (Lu and Tune, 2003; Sink *et al.*, 2008). Anticholinergic agents may also be implicated in the time to onset of psychotic symptoms in patients with Alzheimer's disease (Cancelli *et al.*, 2009).

Five muscarinic receptor subtypes have been identified (M_1–M_5). The M_1 receptor is the most abundant subtype in the central nervous system (CNS) and is thought to have a primary role in mediating cholinergic effects on cognitive function. M_2 receptors are located throughout the brain and are involved in memory processes. M_4 receptors are abundant in the neostriatum and are thought to be involved in the regulation of acetylcholine levels (Volpicelli and Levey, 2004; Kay *et al.*, 2005). Thus, cognitive impairment, particularly memory dysfunction, can result from antagonism of M_1, and to some extent, M_2 or M_4 receptors in the CNS (Kay *et al.*, 2005). For an anticholinergic drug to cause cognitive impairment, it must also be able to penetrate the blood–brain barrier (BBB) and so act centrally.

Whilst some anticholinergic drugs are used specifically for the therapeutic effects of their anticholinergic action, other drugs have anticholinergic effects that are

secondary to their primary mode of action. To assist clinicians in minimising the use of drugs with anticholinergic action in people with cognitive impairment, various anticholinergic risk scales have been produced. These usually comprise a list of drugs with a classification of anticholinergic potency listed for each (Duran *et al.*, 2013). Scales have also been developed to calculate the total anticholinergic burden for an individual (Boustani *et al.*, 2008). There is considerable variation amongst these scales because of differences in scale development, selection of drugs and methods of evaluation of anticholinergic potency. In addition, factors such as the selectivity of drugs to specific muscarinic receptor subtypes and its ability to enter the brain have not always been considered.

The aim of this review was to produce a scale illustrating the negative anticholinergic effect of drugs on cognition using a clear, concise and systematic approach which takes into consideration the muscarinic binding affinity of drugs, their selectivity, their penetration into the brain and whether or not reports of cognitive impairment exist.

Method

Two authors (DH and DB) reviewed all British National Formulary categories in January 2014 and again in January 2015 to identify and agree upon the main drug classes and medicines commonly used in older people in the UK. We included the majority of categories of drugs, for example, those acting on the gastrointestinal, cardiovascular, genitourinary and central nervous systems, but excluded specialist drugs such as cytotoxics and hormone treatments (except those acting on insulin). Electronic searches using Pubmed, Medline and Embase were performed to identify which of these drugs had the potential to affect cognitive function using the search terms 'dementia', 'delirium' and 'cognition' or 'cognitive function' or 'cognitive impairment' and 'drugs' or 'medication', followed by the same searches using the same terms combined with the specific drug classes and individual drug names. In October 2014, searches using Pubmed and Embase were undertaken to identify drugs with known anticholinergic activity. From these searches, a list was made of the drugs which we deemed to merit further investigation. This list included those drugs noted in the literature as potentially affecting cognition and drugs listed in the literature as having anticholinergic activity. We also investigated any drug not in these two categories but which the authors agreed were commonly used by older people. We examined each individual drug to determine whether or not they had any reported anticholinergic properties and if so, the antimuscarinic potency and specificity to receptor subtypes, whether or not the drug penetrated the BBB and whether or not there were any reports of associated cognitive impairment.

All drugs generated by these reviews were individually:

(1) Entered into the National Institute of Mental Health Psychoactive Drug Screening Program (PDSP) Ki database (PDSP Ki Database, 2014) of published binding affinities (Ki) of drugs for muscarinic receptors and more specifically for M_1, M_2 and M_4 receptors. Data for muscarinic M_1 (linked to cognitive impaired) binding affinities were used in preference to other muscarinic receptor binding affinities where available. If drug specificity to the receptor subtypes was not available, general muscarinic binding affinity data were used. Anticholinergic activity is measured using competitive radioreceptor binding. The compound [3H]quinuclidinyl benzilate ([3H]QNB) is a specific muscarinic receptor antagonist often used as the radioligand. Anticholinergic activity of a drug is based on the amount of [3H]QNB displaced by the drug under investigation. Where available, Ki values from competitive radioligand binding studies using [3H]QNB in human brain (or cloned human brain) were used.
(2) Inputted into Martindale (Pharmaceutical Press, 2014), American Hospital Formulary Service (American Hospital Formulary Service, 2015) and the Summary of Product Characteristics (DataPharm, 2015) to determine whether or not the drug was described as having had any anticholinergic properties, and/or penetrated the BBB and/or had been reported to cause cognitive impairment.
(3) Searched via Pubmed, Embase and Google scholar to identify muscarinic binding affinity, penetration across BBB and any medical literature on anticholinergic cognitive adverse effects (where information was not identified from previous steps).

Two authors (DB and DH) reviewed the information retrieved. For each drug, they independently assigned a score of 0, 1, 2 or 3 (or 'unable to score') based on the antimuscarinic potency, selectivity of drug to muscarinic receptors, penetration through BBB and reports of cognitive adverse effects. Because other mechanisms may be involved in the causation of cognitive impairment besides antimuscarinic effects, reports of cognitive impairment were used as confirmation and to validate our scoring system, rather than to aid assignment of scores. If a drug was known to cross the BBB and had reports of cognitive impairment, the assigned score would depend on the Ki values for muscarinic receptors. If a

Table 1 Assignment of scores for individual drugs

Description of criteria	Ki > 10 000 nM or published *in vitro* data showing no antimuscarinic activity or comment in Martindale or SPC, stating no antimuscarinic effects	Ki 1001–10 000 nM or published *in vitro* data showing minimal or equivocal antimuscarinic action or comment in Martindale or SPC, stating minimal, weak or mild antimuscarinic effects	Ki 100–1000 nM or published *in vitro* data showing moderate antimuscarinic effects or comment in Martindale or SPC, stating some or moderate antimuscarinic effects	Ki < 100 nM or published in vitro data showing strong antimuscarinic effects or comment in Martindale or SPC, stating strong antimuscarinic effects	None of these data available
Anti-muscarinic score	0	1	2	3	Not known

This table must be used in conjunction with the methods described.

drug had high antimuscarinic potency but penetrated the brain poorly, then its AEC score was reduced accordingly (refer to Table 1). Where no initial agreed decision could be reached between the two authors, this was resolved by asking the third and fourth authors (JS and DT) to independently score the drug, and then the mode of the scores was used.

There were two steps in assigning the antimuscarinic score. First, the antimuscarinic activity was assessed using the Table 1 above, and then the score was refined according to the degree of penetration into the BBB by the drug. Refer to Table 2 for level of evidence available for antimuscarinic activity.

If there were no Ki data available and no published reports of clinical or in vitro antimuscarinic activity, a score could not be assigned.

Refining the score according to degree of penetration across the blood–brain barrier

If there was evidence that the drug or its active metabolites readily penetrated the BBB from either published data on cerebrospinal fluid drug levels or published evidence of clinical effects indicating well-described central actions (e.g. frequent sedation or neuropsychiatric symptoms), the score assigned remained unchanged.

Table 2 Level of evidence available

Level of evidence	Information available
Level 1	Ki value for M_1 receptor binding available in human (or cloned human) brain
Level 2	Ki value for muscarinic receptor binding (non-specific) or Ki value for muscarinic binding in rodent brain
Level 3	Comment in Martindale or SPC or other publication, stating whether drug has anticholinergic properties or not

If there was published evidence that for a drug or its metabolites, penetration across the BBB is known to be limited in some way, or there was published evidence of weak or limited central effects (e.g. infrequent reports of only mild neuropsychiatric symptoms), the score was downgraded by one point.

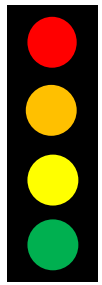
If there was published evidence that a drug or its metabolites had little or no penetration across the BBB, or there was published research demonstrating the absence of central effects, no reports of neuropsychiatric symptoms in clinical studies of the drug and no research suggesting of any central anticholinergic effects, a score of 0 was assigned.

Results

Our searches identified several publications quantifying the antimuscarinic effects of drugs which were not included in the PDSP Ki database. These included some antihistamines (Kubo *et al.*, 1987; Liu and Farley, 2005), antipsychotics (Hals *et al.*, 1988; Chew *et al.*, 2006), antidepressants (El-Fakahany and Richelson, 1983; Nomura *et al.*, 1987; Rudd *et al.*, 2005), bladder anticholinergics (Ohtake *et al.*, 2007), certain opioids (Hustveit, 1994) and some other medicines commonly used by older adults (Chew *et al.*, 2008). These drugs were included in our evaluations, giving a total of 165 drugs assessed. For many of the drugs on the list, information regarding penetration into the brain was determined from Martindale (Pharmaceutical Press, 2014), the Summary of Product Characteristics (DataPharm, 2015) or American Hospital Formulary Service (American Hospital Formulary Service, 2015). For the others, we used information retrieved from primary or secondary references uncovered by electronic searches (Basak *et al.*, 1996; Crivori *et al.*, 2000; Di *et al.*, 2003).

Table 3 displays the anti-muscarinic score calculated by the method described in the preceding texts

Table 3 Anticholinergic effect on cognition scores



Limited data so unable to score		Drugs with AEC score of 0		Drugs with AEC score of 1	Drugs with AEC score of 2	Drugs with AEC score of 3
Alendronic Acid	Ramipril	Alprazolam	Lovastatin	Amiodarone	Amantadine	Alimemazine (trimeprazine)
Allopurinol	Rivaroxaban	Amlodipine	Lurasidone	Aripiprazole	Chlorphenamine	Amitriptyline
Anastrozole	Rosuvastatin	Amoxycillin	Meloxicam	Bromocriptine	Desipramine	Atropine
Apixaban	Spironolactone	Aspirin	Metoclopramide	Carbamazepine	Dicycloverine (dicyclomine)	Benztropine
Baclofen	Tamoxifen	Atenolol	Metoprolol	Citalopram	Dimenhydrinate	Chlorpromazine
Bisoprolol	Topiramate	Atorvastatin	Moclobemide	Diazepam	Diphenhydramine	Clemastine
Bumetanide	Tizanidine	Buproprion	Morphine	Domperidone	Disopyramide	Clomipramine
Captopril	Verapamil	Cepahlexin	Naproxen	Fentanyl	Levomepromazine (methotrimeprazine)	Clozapine
Carbimazole	Zopiclone	Cetirizine	Omeprazole	Fluoxetine	Olanzapine	Cyproheptadine
Carvedilol	Zotepine*	Chlordiazepoxide	Paracetamol	Fluphenazine	Paroxetine	Dothiepin
Chlortalidone		Cimetidine	Pantoprazole	Hydroxyzine	Pethidine	Doxepin
Clarithromycin		Ciprofloxacin	Pravastatin	Iloperidone	Pimozide	Hyoscine hydrobromide
Clonazepam		Clopidogrel	Propranolol	Lithium	Prochlorperazine	Imipramine
Codeine		Darifenacin	Rabeprazole	Mirtazapine	Promazine	Lofepramine
Colchicine		Diclofenac	Ranitidine	Perphenazine	Propantheline	Nortriptyline
Dabigatran		Diltiazem	Risperidone	Prednisolone	Quetiapine	Orphenadrine
Dexamethasone		Enalapril	Rosiglitazone	Quinidine	Tolterodine	Oxybutynin
Dextropropoxyphene		Entacapone	Simvastatin	Sertindole	Trifluoperazine	Procyclidine
Digoxin		Fexofenadine	Theophylline	Sertraline		Promethazine
Erythromycin		Fluvoxamine	Thyroxine	Solifenacin		Trihexyphenidryl (benzhexol)
Flavoxate*		Furosemide	Tramadol	Temazepam		Trimipramine
Hydrocodone		Gabapentin	Trazodone			
Irbesartan		Gliclazide	Trimethoprim			
Lansoprazole		Haloperidol	Trospium			
Levetiracetam		Ibuprofen	Venlafaxine			
Metformin		Ketorolac	Valproate			
Methocarbamol		Lamotrigine	Warfarin			
Methotrexate		Levadopa	Ziprasidone			
Nitrofurantoin		Lisinopril	Zolpidem			
Oxcarbazepine		Loperamide				
Oxycodone		Loratadine				
Phenytoin		Lorazepam				
Pregabalin		Losartan				

*These drugs have confirmed anticholinergic activity but the extent and clinical significance of this is unknown.

for the list of drugs chosen for evaluation. Of the 165 drugs reviewed, there was a disagreement between the first two authors on nine drugs (5%), for which the opinions of the third and fourth authors were then sought independently. In all, 21 drugs received a score of 3, 18 a score of 2, 21 a score of 1, and 62 drugs were given a score of zero. There were insufficient data to score a further 43 drugs.

There was no clear information available on whether or not benzodiazepines were anticholinergic. It appears that although benzodiazepines do not bind to muscarinic receptors, chronic treatment changes both the number and affinity for the muscarinic receptors in the brain. Benzodiazepines might therefore directly or indirectly influence muscarinic receptors (Nordberg and Wahlstrom, 1992). In general, benzodiazepines are best avoided in patients with dementia. Lorazepam is short acting and because it is less lipid soluble than other benzodiazepines, it penetrates the brain more slowly (Tedeschi *et al.*, 1983), causing fewer cognitive adverse effects.

Discussion

We assessed over 165 drugs commonly used in older people and found 60 of them to have a clear capacity to impair cognitive function to varying degrees. Our assessment method is perhaps more transparent than previously described methods, and we have evaluated a larger number of drugs. Before, the only readily available means for discovering the antimuscarinic activity of drugs has been to consult one of the existing lists of drugs with anticholinergic properties (Han *et al.*, 2001; Boustani *et al.*, 2008; American Geriatrics Society 2012 and Beers Criteria Update Expert Panel, 2012). These lists were mostly developed using subjective ratings of anticholinergic activity based on clinical experience of the drugs and observed cognitive impairment. These lists were effectively consensus statements (Rudd *et al.*, 2005) and did not list drugs not considered to have anticholinergic activity, leaving some ambiguity as to whether drugs not mentioned had no anticholinergic activity or were simply not evaluated. Furthermore, whilst many of the lists rated drugs on the basis of their anticholinergic potency, they did not always take into account whether or not the drug was selective for the target tissue or organ or to what extent it penetrated the BBB and was therefore likely to cause CNS effects. Our transparent and systematic approach to developing an explicit systematic AEC scale took these limitations into consideration. It also minimised subjective rating by clinicians (which may vary based on knowledge and experience) by independently rating drugs using strict criteria and evidence-based data.

A limitation of this paper is the incomplete availability of dissociation constant (Ki) values, and therefore, our inability to accurately score many drugs. Similarly, where there were conflicting data on whether or not a drug was actually anticholinergic, we were unable to assign a score. For some classes of drugs, there was sufficient data to rate some drugs, but not others in the same class. Other limitations relate to the fact that the level of evidence for antimuscarinic activity data available to us was somewhat variable (refer to Table 2). Many of our assessments were at least partly based on *in vitro* antimuscarinic activity. *In vitro* use of radio-receptor assay does not account for varying drug dosages (measured in mass units rather than moles), pharmacokinetics or differences as a result of individual patient physiology. Similarly, BBB penetration is variable and can be affected by age, gender and other factors, including dementia (Chancellor *et al.*, 2012; van Assema *et al.*, 2012). In addition, recent work in human-derived neurons and astrocytes suggests that there is not a linear relationship between anticholinergic polypharmacy and *in vivo* effects, suggesting that current scales may underestimate the effect of polypharmacy (Woehrling *et al.*, 2015). Also, because other neurotransmitter systems are also involved in cognitive function, there may be drugs with an AEC score of 0 on this scale, which still affects cognition through other modes of action. Finally, our method, whilst transparent and systematic, remains effectively a consensus view, albeit based on published data.

We aimed to evaluate drugs commonly used in older people so that our results would be of use to clinicians in community or hospital settings. However, it is not a comprehensive list of drugs, and absence of a drug from the list does not imply the drug has no anticholinergic activity. We have not included drugs which are only used in very specialist situations (such as cytotoxic drugs) or where use is generally confined to hospital settings (such as anaesthetic agents).

Because the risk of cognitive impairment, incident dementia and early death have been linked to the cumulative use of anticholinergic drugs (Fox *et al.*, 2011; Gray *et al.*, 2015); it is obviously good practice to use drugs with AEC scores of zero and to avoid those scored 1, 2 or 3. All individual drugs with an AEC score of 2 or 3 in older people presenting with symptoms of cognitive impairment, dementia or delirium should be withdrawn, as these drugs have unequivocal anticholinergic action and central adverse effects. The clinician should discuss with the patient and carer the benefits and potential risks of continued

use of these drugs with the aim of either stopping them or switching to an alternative drug with a lower AEC score (preferably zero). In patients who are not receiving any medication with an AEC score of 2 or 3 but who have a total AEC score of 3 or above 3, a similar patient–clinician review should take place. If withdrawal of a drug is deemed appropriate, this should follow a gradual schedule to avoid rebound anticholinergic effects (Boustani *et al.*, 2008).

Conclusion

We have been able to evaluate and rate 122 drugs for anticholinergic effect on cognition using a systematic method of assessment. Half of the drugs evaluated are likely to induce cognitive impairment to some degree and should normally be avoided in older people. The long-term aim for researchers in this area should be to produce an internationally recognised single unified scale of clinically relevant anticholinergic activity covering all licensed medications which has been validated in clinical settings. We are some way off this, but we hope that this paper, even though it has significant limitations, by covering a larger number of drugs, and by incorporating all available evidence for anticholinergic burden of drugs, is a step in the right direction. We hope researchers will take up the challenge and now assess the utility of the scale in clinical settings.

Conflict of interest

DT has received payments for lectures and advisory boards from Eli Lilly, Lundbeck, BristolMyersSquibb, AstraZeneca, Sunovion and Otsuka. JS, DB and DH declare no potential conflicts of interest.

Key points

- Drugs with anticholinergic action have clear negative effects on cognitive function.
- The number of drugs with important central anticholinergic activity is underestimated.
- We list 60 drugs commonly used in older patients which have central anticholinergic effects.

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