BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

The impact of anticholinergic burden on clinical outcomes in older hospitalised surgical patients

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Abstract

Polypharmacotherapy is an ever-increasing issue with an ageing patient population. Anticholinergic medications make up a large proportion of patient medication but cause significant side effects, contributing to well-documented issues within the older population and in hospital medicine.

This review explores the documented impact of anticholinergic burden in older surgical patients on postoperative delirium, infection, length of stay and readmission, urinary retention, ileus and mortality. It also highlights the need for further high-quality research into anticholinergic burden management among older surgical patients to further impact practice and policy in the area.

Key words: Anticholinergic burden; Care of older people; General surgery; Perioperative medicine; Polypharmacy

Submitted: 25 January 2023; accepted following double-blind peer review: 9 October 2023

Introduction

The high prevalence of polypharmacotherapy is a consequence of the increasing rate of multimorbidity in the ageing population worldwide (Magin et al, 2021). The summative effect of taking multiple drugs with anticholinergic properties – the so-called 'anticholinergic burden' – has adverse impacts on physical function and cognition (Al-Rihani et al, 2021; Egberts et al, 2021; Lisibach et al, 2021). Anticholinergic burden is also a potential risk factor for adverse events that disproportionately affect older adults (Hilmer and Gnjidic, 2022). Many medications used to treat common chronic conditions have weak anticholinergic properties and their cumulative effect may have important implications for older adults (Lavrador et al, 2021), although the overall effect of anticholinergic burden in older surgical patients is unclear and its effect on surgical outcomes is not well studied (Rossi et al, 2014; Ablett et al, 2019). This article focuses on the evidence linking anticholinergic burden with adverse clinical outcomes in older individuals undergoing surgery and looks at whether anticholinergic burden is an important modifiable perioperative risk factor in this population.

Anticholinergic drug burden

The effect of anticholinergic burden on older adults is well described. Polypharmacotherapy predisposes to higher anticholinergic burden, which is emerging as a risk factor for adverse events that disproportionately affect older patients (Mueller et al, 2020; Hilmer and Gnjidic, 2022). Around 100 individual drugs have anticholinergic properties (Tillemans et al, 2021), and many of these are routinely used to treat chronic conditions such as cardiovascular disease, hypertension, depression, urinary incontinence, pain and allergies (Ghossein and Kang, 2023). Table 1 gives an overview of commonly used anticholinergic drugs.

Mechanism of action and pathways for adverse effects

The mechanism of action of anticholinergic drugs gives insight into their therapeutic use and potential adverse effects. Cholinergic receptors are found in the parasympathetic and sympathetic nervous systems, typically on the postsynaptic ganglia, and respond to acetylcholine (Tiwari et al, 2013). The autonomic nervous system plays an important role in multiple body systems, including the cardiac, respiratory and digestive systems (Tiwari et al, 2013).

How to cite this article:
Evans T, Binns H, Mandal AKJ, De'Ath HD, Missouris CG. The impact of anticholinergic burden on clinical outcomes in older hospitalised surgical patients. Br J Hosp Med. 2024. https://doi.org/10.12968/hmed.2023.0034

Anticholinergic medications work primarily by binding to muscarinic receptors and inhibiting the action of acetylcholine at receptor sites in the peripheral nervous system and CNS (Ghossein and Kang, 2023). Significant effects include blockade of parasympathetic neurotransmission, resulting in reduced skeletal and smooth muscle contraction, which can cause reduced bowel and bladder action. These can be desired effects in some cases but can contribute to urinary retention and ileus and reduced gut motility in others (Verhamme

Table 1. Commonly prescribed medications with recognised anticholinergic burden

Drug class or target body system	Examples	Drug class or target body system	Examples
Antidepressants	Amitriptyline	Corticosteroids	Corticosterone
	Citalopram		Dexamethasone
	Doxepin		Hydrocortisone
	Escitalopram		Prednisolone
	Fluoxetine	Gastrointestinal	Atropine
	Imipramine		Cimetidine
	Mirtazapine		Dicycloverine
	Nortriptyline		L-hyoscyamine
	Paroxetine		Loperamide
	Phenelzine		Propantheline
Antihistamines	Cetirizine		Ranitidine
	Chlorphenamine	Immunosuppression	Azathioprine
	Clemastine		Ciclosporin
	Cyproheptadine	Infection	Ampicillin
	Diphenhydramine		Cefalothin
	Fexofenadine		Cefamandole
	Hydroxyzine		Cefoxitin
	Loratadine		Clindamycin
	Promethazine		Cycloserine
Antiepileptics	Carbamazepine		Gentamycin
	Phenobarbital		Piperacillin
Antipsychotics	Chlorpromazine		Tobramycin
	Clozapine		Vancomycin
	Doxepin	Nausea and vertigo	Prochlorperazine
	Fluphenazine	Pain	Opiates
	Haloperidol	Parkinson's disease	Amantadine
	Levomepromazine		Bromocriptine
	Lithium		Orphenadrine
	Olanzapine		Procyclidine
	Quetiapine		Trihexyphenidyl (benzhexol)
	Risperidone		
	Thioridazine		

Table 1. Commonly prescribed medications with recognised anticholinergic burden (continued)

Drug class or target body system	Examples	Drug class or target body system	Examples
Anxiolytic	Alprazolam	Respiratory system	Ipratropium
	Chlordiazepoxide		Theophylline
	Diazepam	Spasticity	Baclofen
	Flurazepam		Diazepam
	Oxazepam		Methocarbamol
	Temazepam		Pancuronium
Cardiovascular	Captopril		Tizanidine
	Chlorthalidone	Immunosuppression	Azathioprine
	Digoxin		Ciclosporin
	Diltiazem	Urinary antispasmodics	Darifenacin
	Dipyridamole		Dosulepin
	Furosemide		Fesoterodine
	Hydralazine		Flavoxate
	Hydrochlorathiazide		Oxybutynin
	Isosorbide mononitrate		Propiverine
			Solifenacin
	Methyldopa		Tolterodine
	Nifedipine		
	Triamterene		
	Warfarin		

adapted from Tune et al (1992); Chew et al (2008); Scottish Government Polypharmacy Model of Care Group (2018)

et al, 2008; Nejadeh et al, 2022). Other effects, including dry mouth (disturbance of exocrine function of glandular tissue), are attributable to blockade of cholinergic receptors (Ghossein and Kang, 2023).

Heinrich et al (2021a) highlighted the importance of understanding relevant pathophysiological mechanisms to successfully manage anticholinergic burden in older surgical patients. Undesirable effects of anticholinergic medications arise from their effect on G-protein coupled muscarinic receptors, which are abundant in both the peripheral nervous system and CNS (Al-Rihani et al, 2021).

Peripheral antimuscarinic effects are usually associated with short-term use of anticholinergics. However, many of these medications cross the blood–brain barrier and affect the CNS directly – this is more pronounced in older adults where age-related changes in the blood–brain barrier disrupt its function. This may exacerbate the severity and rate of postoperative delirium in patients with significant anticholinergic burden (Lisibach et al, 2021). Furthermore, the cholinergic system is intrinsic to learning and memory (Taylor-Rowan et al, 2021) which may explain links with delirium and longer-term cognitive impairment. A reduction in cholinergic neuronal receptors is seen in older patients, and this, combined with decreased renal and hepatic function, may result in drug toxicity even at therapeutic doses (Tillemans et al, 2021).

Undesirable effects of anticholinergic drugs are plentiful. Dry mouth, urinary incontinence, constipation and heat intolerance are among the milder effects (Herrero-Zazo et al, 2021), and there is an association with delirium (Egberts et al, 2021; Heinrich et al, 2021b; Tillemans et al, 2021) and increased mortality (Graves-Morris et al, 2020). There is also some association between anticholinergic burden and increased risk of

falls, cognitive impairment and progression of neurodegenerative disease (Rosso et al, 2020; Xu and Tan, 2022).

Complex confounding factors such as frailty and comorbidity play a role in the effects of pharmacotherapy in older adults and Stewart et al (2021) and Taylor-Rowan et al (2021) agreed that attributing anticholinergic burden as a single factor in patient outcomes is impossible. The exact definition and root cause of adverse outcomes associated with anticholinergic burden is difficult to clarify (Al-Rihani et al, 2021).

Anticholinergic burden classification scales

Although there is no consensus or gold standard international scale for anticholinergic burden, several scales are generally accepted by the medical community. The anticholinergic burden (ACB) scale was recognised as most reliable by Lisibach et al (2021) in their comparison of different scales, scoring 75% in their overall assessment. They used an adapted AGREE II (Appraisal of Guidelines for Research and Evaluation) tool to assess and compare the systematic quality of the classification scales. Many articles cite the ACB scale as the most popular and widely used clinical tool for assessing anticholinergic burden, and Graves-Morris et al (2020) and Taylor-Rowan et al (2021) recognise the ACB scale as the most used scale globally.

Other scales are held in equal esteem and used globally, with Lisibach et al (2021) highlighting the ACB, anticholinergic drug scale (ADS) and anticholinergic risk scale (ARS) as the most used, followed by the Drug Burden Index (DBI) (Al-Rihani et al, 2021). However, the DBI assesses any drug with potential sedative effects as well as anticholinergic medications, preventing direct comparison with other scales (Hilmer et al, 2007). The German anticholinergic burden scale is a robust tool for reviewing anticholinergic burden, although its use is limited outside Germany, in part because of a lack of validation at the time of publication (Lisibach et al, 2021). Most published data are derived from the ACB, ADS and ARS. Table 2 gives an overview of the main anticholinergic burden classification scales and their key features.

Table 2. Overview of commonly used anticholinergic burden scales

Name of scale	Country	Reference	Study design	Methodology	No. of drugs scored	Scoring level	Overall systematic quality*
Anticholinergic cognitive burden (ACB) scale	USA	Boustani et al (2008), Campbell et al (2012)	Systematic review	Systematic review of drugs with anticholinergic activity and expert opinions	88	0–3	75%
Anticholinergic drug scale (ADS)	USA	Carnahan et al (2006)	Cross-sectional study	Based on a scale previously published and expert opinions	117	0–3	61%
Anticholinergic risk scale (ARS)	USA	Rudolph et al (2008)	Cohort study	Review of drugs with potential anticholinergic effects and expert opinion	49	0–3	67%
German anticholinergic burden scale (GABS)	Germany	Kiesel et al (2018)	Systematic review	Systematic review of drugs with anticholinergic activity and expert opinions	504	0–3	75%
Drug burden index (DBI)	USA	Hilmer et al (2007)	Cross-sectional study	A group of experts developed a formula with a simple additive model	128	Formula (not score)	NA

*Adapted from Lisibach et al (2021) and Villalba-Moreno et al (2016). *As assessed by Lisibach et al (2021) using an adapted AGREE II tool*

Surgical outcomes and anticholinergic burden

Postoperative delirium and neurocognitive decline

Postoperative delirium is a widely recognised adverse effect, associated with long-term cognitive and functional decline and increased mortality (Heinrich et al, 2021a). There are mixed associations between anticholinergic burden and the development of postoperative delirium. Heinrich et al (2021a) performed a prospective observational study of older patients undergoing elective surgery and used data from ACB, ARS and ADS. Of 837 patients, 19% fulfilled criteria for postoperative delirium, highlighting the significance of delirium as a postoperative complication of surgery. However, the data were unable to confirm a direct correlation between anticholinergic burden and development of postoperative delirium. The authors acknowledged that there are limitations because of the different scales used, and the actual load and significance of the anticholinergic agents used cannot be accurately quantified. They suggested that factors other than preoperative anticholinergic burden have a greater influence on the development of postoperative delirium and concluded that future analyses should also examine the influence of intraoperative and postoperative administration of anticholinergic drugs.

Other studies are more supportive of a causative link between use of anticholinergic drugs and postoperative delirium. Mueller et al (2020) conducted a randomised controlled intervention trial of 651 patients admitted for surgery for gastrointestinal, urogenital or gynaecological cancer. Approximately 10% developed postoperative delirium and patients with significant anticholinergic burden on the ADS (score ≥1) were 2.2 times more likely to develop postoperative delirium than those without. The significance of the management of anticholinergics is highlighted, as 16% of patients had a significant longstanding anticholinergic burden. Mueller et al (2020) also explored the potential role of intraoperative administration of benzodiazepines as a further area for research on postoperative anticholinergic burden and postoperative delirium.

Tillemans et al (2021) conducted a randomised controlled trial into the use of haloperidol as delirium prophylaxis in older patients after hip surgery. While there was a numerical association between anticholinergic burden and postoperative delirium, no significant statistical link was identified between anticholinergic burden and the duration or severity of delirium. However, Heinrich et al (2021b) identified a positive correlation between severity of neurocognitive decline and use of anticholinesterase inhibitors (which have substantial anticholinergic effect) in presurgical patients aged 65 years or above admitted for elective general surgery. They found a statistical correlation between scores on the ADS and ARS and the severity of postoperative neurocognitive decline, with higher scores predictive of major neurocognitive decline.

Postoperative infection

Golubovsky et al (2021) found associations between anticholinergic drug use and postoperative urinary tract infection following lumbar spine surgery in a retrospective cohort study. To date, there is no evidence supporting postoperative infection (wound infection, peritonitis, peritoneal collections) as a direct consequence of increased anticholinergic burden.

Postoperative urinary retention

Walter et al (2014) found an almost threefold increase in failed postoperative void trial following urogynaecological surgery in patients with a high anticholinergic burden on ARS compared to those with a low ARS score. Teng et al (2021) found an informal link between postoperative faecal impaction and urinary retention and anticholinergic use following hip fracture surgery, although this was not the primary focus of their study. Verhamme et al (2008) and Nejadeh et al (2022) proposed that anticholinergic blockade of parasympathetic neurotransmission and consequent reduced smooth muscle contraction may lead to constipation and urinary retention. However, a direct causative link between postoperative urinary retention and anticholinergic burden remains to be established.

Postoperative ileus

There is lower level evidence that anticholinergic burden increases likelihood of postoperative ileus (Nejadeh et al, 2022), with anecdotal evidence of individual cases of ileus thought to have anticholinergic causes.

Length of stay and readmission rate

McIsaac et al (2019) demonstrated stepwise increases in length of stay, with mean length of stay of 7.8 days in patients with ARS score 1–2 vs 6.8 days for those patients with no anticholinergic burden. In addition, cost of care and readmission rates also increased with ARS score. Ablett et al (2019) identified a significant correlation between moderate ACB score (using the ACB scale) and 30-day readmission rate. These studies accept that multiple patient factors make the definitive cause of this correlation difficult to attribute solely to anticholinergic drug use.

Mortality

There is inadequate research into the effect of anticholinergic burden on mortality in older surgical patients. Ablett et al (2019) highlighted this as a limitation of existing research, particularly relating to emergency general surgery. Their prospective cohort study of 452 patients admitted with emergency general surgical conditions did not indicate a relationship between ACB score and mortality at 30 and 90 days.

In a retrospective cohort study of over 76 000 patients, Herrero-Zazo et al (2021) found some links between anticholinergic burden and mortality across hospital specialties. They included surgical specialties, although this was only defined as 'trauma and orthopaedics' and 'other surgery'. ARS score of 1 yielded a significant correlation with increased inpatient and post-discharge mortality across all specialties but this was not consistent in patients with higher ARS scores. This suggests that factors other than simply anticholinergic burden also influence overall outcomes of surgery in older patients. The authors acknowledged the importance of specialist perioperative input from medical teams in the management of older patients and pharmacological optimisation in the surgical environment.

McIsaac et al (2019) conducted a large retrospective cohort study of patients aged over 65 years admitted for elective general surgical procedures. Using the ARS, the authors highlighted an increased mortality rate associated with high anticholinergic burden, demonstrating a 15% increase in mortality in patients with ARS score 1–2 and 14% in those with ARS score ≥3.

Limitations of evidence

While the literature examining the effect of anticholinergic burden in older patients, including in pre- and perioperative settings, is broad and wide ranging, there are limitations to the conclusions drawn from it. Despite showing correlation between anticholinergic burden and negative postoperative outcomes, definitive evidence linking these solely to the anticholinergic burden of these patients is difficult for several reasons, not least the complexity of management of highly comorbid and frail patient groups who may already have considerable other factors predisposing them to adverse postoperative outcomes.

Attempts to categorically demonstrate improved outcomes with prescriptive changes to anticholinergic drug administration would require tightly controlled trial conditions, which may pose ethical and logistical dilemmas. Management of these situations would likely be complex and possibly out of reach for the scope of evidence it may provide.

Conclusions

There is some supportive evidence of associations between anticholinergic burden and increased multisystem adverse effects in older surgical patients, although there is no conclusive proof that anticholinergic burden is an independent contributor to this. Nevertheless, using a standardised anticholinergic burden measurement scale to facilitate pharmacological rationalisation and deprescribing may improve surgical outcomes in older patients prescribed multiple drugs. With universal recognition that an ageing population will mean that more surgical procedures are performed on older adults, there is significant scope for further research into the effect of anticholinergic burden on surgical outcomes, particularly within the context of emergency general surgery.

Key points

- An ageing and increasingly comorbid patient population is being encountered in all medical and surgical specialties.
- Polypharmacotherapy and accompanying anticholinergic drug burden are associated with increased adverse effects in older surgical patients.
- Multiple scales for determining the anticholinergic burden exist but their use and application remain of uncertain clinical value.
- Management of these patient groups is complex and difficult to navigate.
- There is huge scope for further research into anticholinergic burden on older surgical patient populations and the impact of pharmacological optimisation on clinical outcomes.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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