Brief Report

Polypharmacy and the Ageing Brain: Anticholinergic Burden in the Ageing Population and the Impact of Gynaecological Medications

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Polypharmacy and the Ageing Brain: Anticholinergic Burden in the Ageing Population and the Impact of Gynaecological Medications

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Abstract

Background: Population ageing is accelerating worldwide, accompanied by a rising prevalence of multimorbidity and polypharmacy. Medicines with anticholinergic properties are commonly prescribed to older adults for a wide range of conditions, including depression, urinary incontinence, Parkinson's disease, allergies, and respiratory disorders. While short-term anticholinergic effects such as dry mouth and constipation are well recognised, increasing evidence suggests that cumulative anticholinergic exposure may contribute to adverse cognitive outcomes in older populations. Objective: This review aims to discuss the concept of anticholinergic burden, outline commonly used tools to quantify exposure, and examine the evidence linking cumulative anticholinergic exposure with cognitive decline and other adverse health outcomes. It also explores strategies to identify and mitigate anticholinergic burden in clinical practice. Methods: Relevant literature on anticholinergic medications, burden scales, and associated clinical outcomes was reviewed. Attention was given to validated measurement tools such as the Anticholinergic Cognitive Burden (ACB) scale, Anticholinergic Risk Scale (ARS), and Anticholinergic Drug Scale (ADS), as well as studies examining associations between anticholinergic exposure and cognitive and functional outcomes. Results: Evidence from observational studies indicates that higher cumulative anticholinergic burden is associated with increased risks of cognitive impairment, delirium, falls, functional decline, and possibly dementia. Measurement tools allow clinicians and researchers to estimate cumulative exposure, with several studies identifying clinically meaningful risk at moderate to high burden scores. Conclusion: Anticholinergic burden represents a potentially modifiable contributor to adverse outcomes in ageing populations. Routine assessment of anticholinergic exposure, careful medication review, and deprescribing strategies where appropriate may help reduce avoidable cognitive and functional harm in older adults. Integrating burden assessment into prescribing systems and clinical decision support tools may further support safer pharmacotherapy in an ageing society.

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Introduction

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The world is experiencing a profound demographic transition with the proportion of individuals aged 65 years and older increasing faster than any other age group. [1]In 2020, older adults accounted for approximately 17% of the population,[2]and this figure is projected to rise to around 22% by 2040.[2] This demographic shift signals a substantial increase in demand for healthcare and social support systems tailored to the needs of older people, particularly those living with multiple long-term conditions.[2]

Ageing is accompanied by complex structural, neurological, and neurochemical changes that reduce physiological reserve and increase vulnerability to cognitive impairment.[3] The burden of dementia is expected to rise sharply, global estimates suggest that 57.4 million people were living with dementia in 2019,[4] with projections reaching more than 150 million by 2050 as populations expand and age.[4] This increase is driven not only by longevity but also by the accumulation of modifiable risk factors across the life course, including smoking, obesity, dyslipidaemia, physical inactivity, and potentially anti cholinergic medication exposures.[4]

Medicines with anticholinergic properties are frequently prescribed to older adults for a wide range of conditions, including depression, Parkinson's disease, and chronic obstructive pulmonary disease.[5,6] Several medications used in gynaecology for urinary incontinence, overactive bladder and menopausal symptoms have significant anticholinergic properties.[5] While short-term cognitive side effects of these drugs are well recognised[7], accumulating observational evidence suggests that cumulative anticholinergic exposure may also be associated with longer-term cognitive decline, increased dementia [8] and fall risks.[9]

Multimorbidity is becoming the dominant clinical challenge of later life, with the number of older adults living with four or more chronic diseases predicted to double within the next two decades.[10] Yet healthcare systems, including the UK National Health Service, remain largely structured around single-disease models of care.[10] This mismatch contributes to polypharmacy, where medications prescribed for coexisting conditions may interact in ways that adversely affect brain health.

Given the scale of prescribing and the potentially modifiable nature of this exposure, anticholinergic burden has emerged as an important, yet under-recognised, factor in healthy cognitive ageing.[11]

The annual cost of dementia care in the UK is projected to rise from an estimated £42 billion in 2024 to £90 billion by 2040[12]-exceeding the combined costs associated with many other chronic diseases such as hypertension and diabetes.[13],[14]Addressing preventable contributors to cognitive decline, including medication-related harms, is therefore an urgent clinical and public health priority.

Anticholinergic Burden in Gynaecological Practice

Overactive bladder (OAB) is a chronic condition that affects the quality of life in women.[15]

The International Continence Society defines OAB as urinary urgency, with or without urge incontinence, usually accompanied by abnormally frequent daytime urination and nocturia, in the absence of proven infection or obvious pathology.[15] The prevalence increases with age, with over 20% of those affected being older than 65 years.[16] If conservative measures are unsuccessful, the current recommendations suggest starting pharmacological therapy as first-line management, particularly with anticholinergic medications.[17] Several classes of medications, including antidepressants, antipsychotics, and treatments for menopause, have significant anticholinergic properties.[5]This can lead to a cumulative effect on the patient, raising the anticholinergic burden (ACB) and causing significant adverse effects.

Ageing and the Brain: Increasing Vulnerability to Pharmacological Insults

The prefrontal cortex, hippocampus, and cerebellum, regions critical for executive function, memory, and coordination, are particularly affected in normal ageing.[3] Ageing is also associated

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with cortical thinning[3], most prominently in the frontal and temporal lobes, enlargement of the ventricular system, and reduced synaptic density.[18,19]

Cognitive Changes

Individuals experience varying rates of cognitive decline.[20] Declarative and working memory commonly decline, as does processing speed[3]. Older adults may experience reduced attentional capacity, particularly in tasks requiring divided attention or multitasking.[3] In healthy ageing, these effects are often subtle and compatible with preserved independence; however, they lower the threshold at which additional insults, such as illness, polypharmacy, or neurodegenerative disease, can precipitate clinically significant impairment.[3]

Neurochemical Changes

Cholinergic pathways are essential for cognitive processes and behaviours, including wakefulness, mood, learning, motor function, motivation, and short-term memory. [21]As we age, the effectiveness of nicotinic receptors declines, leading to a significant reduction or elimination of cholinergic neurons and certain subtypes of nicotinic acetylcholine receptors (nAChRs). [22]This decline contributes to the cognitive challenges faced in later life.[22] Dopaminergic and noradrenergic activity also decreases,[21] affecting executive function, motivation, and arousal. [21]In parallel, changes occur in blood–brain barrier integrity [23]and in sex hormone signalling, including reduced oestrogen and androgen receptor activity, all of which influence neuronal survival and synaptic function.[23]

Neurosteroids in Cognition and Menopause

Neurosteroids associated with sex hormones may offer neuroprotective benefits against the effects of brain ageing. Notably, estrogen functions as a neuroprotective antioxidant.[24] The brain has high oxygen consumption, increasing its susceptibility to lipid peroxidation. Estrogen not only regulates metabolism but also supports mitochondrial function in neurons, including biogenesis, apoptosis, and structural integrity, while protecting mitochondrial DNA from oxidative damage.[24]

With increasing life expectancy, postmenopausal women experience prolonged estrogen deficiency, which negatively affects ageing and increases the risk of dementia-potentially worsened by polypharmacy, particularly anticholinergic use.

Impact of Anticholinergic Medicines on the Ageing Brain

Anticholinergic effects are classically divided into peripheral and central manifestations. Peripheral effects include dry mouth, tachycardia, constipation, and urinary retention-symptoms that are usually recognised and monitored.[7] Central nervous system effects, however, are often less apparent and include cognitive impairment, reduced attention, behavioural disturbance, and, in severe cases, delirium or hallucinations. [7]These central effects are particularly relevant in older adults because age-related reductions in cholinergic reserve magnify pharmacological blockade.

Anticholinergic burden and adverse clinical outcome: An evidence review

A meta-analysis of 25 studies on whether anticholinergic burden is a prognostic factor for future cognitive decline in older adults suggested a consistent link between the use of anticholinergic medications and an increased risk of dementia.[25]

Observational studies increasingly suggest that cumulative anticholinergic exposure is associated with clinically meaningful outcomes.[26] Large primary care cohort analyses have reported associations between anticholinergic use and incident dementia. However, the risk appears to be driven predominantly by certain drug classes rather than all medications with anticholinergic activity.[26]

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Longitudinal analyses indicate that use in adults aged 40 years and older is associated with an increased risk of recurrent falls over extended follow-up, regardless of whether therapy was newly initiated or discontinued during the observation period.[27] Hospital-based studies further suggest that a high anticholinergic burden at discharge may be associated with a modest increase in one-year mortality.[28]

Measuring Anticholinergic Burden

Although clinicians are generally familiar with the individual adverse effects of anticholinergic medicines, cumulative exposure is rarely recognised in routine practice. [29]This is especially important for urogynaecology and menopause specialists, as anticholinergics are widely used in older adults. In the context of multimorbidity and polypharmacy, the combined effect of several such medicines can lead to a clinically significant anticholinergic burden.[29]

Evolution of tools for measuring Anticholinergic

Burden

The first widely accepted effort to measure anticholinergic exposure was the anticholinergic cognitive burden (ACB) scale, introduced in 2008 as a practical clinical tool for identifying medications with anticholinergic activity and estimating their cumulative effects on cognition[7]. The ACB scale assigns scores to both prescribed and over-the-counter medicines and provides a simple additive measure of total exposure, allowing clinicians and researchers to quantify the overall cognitive burden associated with a patient's medication regimen[7].

Subsequently, several alternative tools were developed, such as the anticholinergic drug scale (ADS),[30] anticholinergic risk scale (ARS),[31]drug burden index (DBI) [32], and other regionally adapted tools, such as the German anticholinergic burden score,[33] to reflect prescribing patterns and formularies in specific healthcare systems. Despite methodological differences, comparative evaluations suggest that the ACB and German Anticholinergic Burden scales demonstrate strong validity and reliability in predicting clinically relevant outcomes, particularly cognitive impairment.[34]

Table 1. Commonly prescribed medicines with anticholinergic activity and their anticholinergic cognitive burden (ACB) Scores. [35].

Drug Class	Medication (Example)	Typical Indication	ACB Score*
Tricyclic antidepressant	Amitriptyline	Depression, neuropathic pain	3
Antimuscarinic (bladder)	Oxybutynin/ Tolterodine/solifenacin	Urinary incontinence	3
Antihistamine (1st generation)	Diphenhydramine	Allergy, sleep aid	3
Antidepressant	Paroxetine	Depression, anxiety	3
Antidepressant (SSRI)	Sertraline	Depression	1
Loop diuretic	Furosemide	Heart failure, oedema	1
Opioid analgesic	Codeine	Pain	1
Antidepressant	Duloxetine	Depression/ anxiety	0
Bladder incontinence	Mirabegron	Urge incontinence	0
ACB Score 0 – No anticholinergic activity ACB Score 1 – Possible anticholinergic effect			

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ACB Score 2 – Definite anticholinergic effect ACB Score 3 – Strong anticholinergic effect

Table 2. Calculation of Total Anticholinergic Cognitive Burden (ACB) Score[7].

Step 1: List all current medications. Step 2: Assign each medication an ACB score (0–3). Step 3: Add the scores to obtain total ACB. Total ACB Score= $\sum_{i-1}^{n}$ (ACB score of each medication)
Interpretation 0–2 → Low risk ≥3 → Clinically significant risk ≥5 → High risk – medication review strongly recommended

Measures to Reduce Anticholinergic Burden in Clinical Practice

Deprescribing should focus first on medicines with strong anticholinergic activity (score 2–3), especially when prescribed for conditions with safer alternatives.[36]

Another strategy would be replacing anti-cholinergic bladder medications with non-anticholinergic options like beta agonists.[37]

These tools can help general practitioners and pharmacists to identify patients who may be at risk from potentially inappropriate anticholinergic exposure. In several major clinical information systems used in England, it is already possible to calculate ACB scores or to query databases to identify patients with high cumulative scores.[38] Wider and more consistent integration of such calculators across healthcare platforms could support routine risk stratification and enable targeted medication review.[38,39]

Conclusion

Population ageing is accompanied by a rising prevalence of multimorbidity, polypharmacy, and cognitive impairment. Among potentially modifiable contributors, anticholinergic burden represents an under-recognised iatrogenic exposure that acts on a biologically vulnerable ageing brain characterised by declining cholinergic function and reduced neurophysiological reserve. Quantification tools such as the Anticholinergic Cognitive Burden scale enable clinicians to identify high-risk prescribing patterns and provide a practical framework for risk assessment. Incorporating an assessment of anticholinergic burden into standard medication reviews, along with support from multidisciplinary care and digital prescribing systems, presents an opportunity to mitigate avoidable harm.

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