

Anticholinergic Burden: A Bibliometric Analysis of Research Trends

ABSTRACT

Background: Anticholinergic burden is linked to adverse outcomes, including mortality, cardiovascular events, falls, cognitive decline, and dementia, particularly in middle- to older-aged populations. This study aims to provide a comprehensive quantitative analysis of the research landscape surrounding anticholinergic burden using bibliometric methods.

Methods: We searched the last 40 years of databases on the Web of Science platform using various keywords related to anticholinergic burden. Bibliometric analysis and mapping were carried out using VOSviewer software, and the most prominent research, countries, institutions, authors, journals, co-citations, and keywords were revealed.

Results: A total of 1239 documents published between 1984 and 2024 were identified, with 2020 having the highest number of publications. Seventy-five countries contributed to studies on anticholinergic burden, with the United States leading with 382 publications and 12 023 citations. "Polypharmacy" was the most frequently used keyword in these articles. Over the last 40 years, the most productive author in this field was Sarah H. Hilmer, with 77 publications and 3255 citations.

Conclusion: This study offers researchers a comprehensive summary and analysis of the research on anticholinergic burden. Anticholinergic burden, a multidisciplinary research focus, continues to attract worldwide interest. The cumulative impact of polypharmacy on anticholinergic burden remains a key area of clinical research. Although numerous scales have been developed to assess anticholinergic burden, there remains a significant need for more accurate methods that account for drug dosages, potencies, and individual predispositions, as there is a lack of strong agreement among existing scales.

Keywords: Anticholinergic burden, bibliometric analysis, geriatrics, polypharmacy

INTRODUCTION

The classification of drugs according to their anticholinergic effects is based on their ability to block cholinergic system signaling in the body. The cumulative anticholinergic effect caused by all the anticholinergic drugs a person takes is called the "anticholinergic burden".¹ This burden is associated with adverse outcomes, including mortality, cardiovascular events, falls, cognitive decline, and dementia, particularly in the middle- to older-aged population.^{2,3} The occurrence of anticholinergic adverse drug reactions is influenced by the anticholinergic burden and the patient's susceptibility to these reactions.⁴

More than 50% of the elderly were reported to be taking at least 1 anticholinergic medication for various complaints, such as mood disorders, pain, incontinence, allergies, anxiety, and insomnia.⁵ Measuring anticholinergic burden is increasingly recommended for older adults. It is crucial for assessing the risk of future adverse events and aiding clinicians in managing treatment decisions. The National Institute for Health and Care Excellence dementia guideline also suggests considering anticholinergic burden as a factor contributing to cognitive impairment.⁶ Patients' anticholinergic burden can be measured using various approaches. In addition to the serum anticholinergic activity (SAA) test, many different anticholinergic burden scales have been developed that are more practical for clinical use. However, there is no consensus on which measure

What is already known on this topic?

- Anticholinergic burden is associated with adverse outcomes such as mortality, cardiovascular events, falls, cognitive decline and dementia, especially in the middle-aged and elderly population.
- Knowledge of anticholinergic burden is important to assess the risk of future adverse events and to assist clinicians in managing treatment decisions.
- Despite extensive research on anticholinergic burden in the literature, there is a lack of quantitative bibliometric analysis to assess the significant progress made in this field.

What this study adds on this topic?

- The findings underscore that anticholinergic burden remains a significant and globally recognized topic, with research cutting across various disciplines.
- While several scales have been developed to quantify this burden, the lack of consistency among these tools highlights the absence of a universally accepted gold standard, reflecting a critical gap in the current methodologies.

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of anticholinergic burden serves as the gold standard, providing the most accurate and clinically useful prognostic information.¹⁷ There are notable differences in how drugs are defined and scored across various scales assessing anticholinergic burden. These differences extend to the selection of outcomes and the validation methodologies used.⁴

Anticholinergic burden studies conducted in different patient groups in the literature drew attention to the relationship of anticholinergic drugs with dementia, cognitive impairment, and delirium;^{18,9} the effect on frailty and quality of life in geriatric patients.¹⁰ Despite extensive research on anticholinergic burden in the literature, there is a lack of quantitative bibliometric analysis to assess the significant progress made in this field. By effectively organizing and mapping large amounts of unstructured data, bibliometric analysis helps academics provide a comprehensive overview, identify knowledge gaps, generate new research ideas, and position their contributions within the field.¹¹ This study aims to investigate trends by conducting a quantitative analysis of authors, journals, and countries over the last 40 years of research on anticholinergic burden through bibliometric analysis.

MATERIAL AND METHODS

All the data in the study were sourced from the Web of Science (WOS) platform, saved in ANSI format, and then imported into VOSviewer¹² (version 1.6.16) after making the required adjustments. Bibliometric analysis and mapping processes were conducted using the VOSviewer software. Data collection was conducted on a single day (July 11, 2024) to minimize the impact of database updates. The search keywords in all fields were “Anticholinergic drug burden” or “Anticholinergic burden” or “Anticholinergic medication burden” or “Anticholinergic drug scale (ADS)” or “SAA” or “Anticholinergic cognitive burden (ACB) scale” or “Anticholinergic risk scale (ARS)” or “Anticholinergic load” or “Anticholinergic load scale” or “drug burden index (DBI).” There was no time limitation for the included studies.

A bibliometric analysis was conducted using VOSviewer to examine research trends, collaborations, and keyword distributions utilizing data from WOS covering the period. The analysis included citation analysis, co-occurrence analysis, and co-authorship analysis, with a minimum keyword occurrence threshold set to 10, filtering out terms appearing less frequently. Country-based analysis was performed by considering countries with at least 5 publications, while institutional and source-based analyses included organizations and journals with a minimum of 5 documents. The full counting method was used to ensure a comprehensive evaluation of research networks, and clusters were identified based on keyword frequency and co-authorship patterns.

VOSviewer is a visualization software tool for creating and mapping bibliometric networks between keywords,

authors, citations, or organizations in a literature search. In these visual maps, different nodes represent elements such as authors, institutions, or countries. The size of the nodes indicates the number of publications or citations, and lines between nodes represent relationships or collaborations. The software is instrumental in understanding collaboration patterns between researchers, analyzing citations, identifying important topics and trends in a specific research area, and examining the influence and relationships between different scientific journals and authors.

In bibliometric studies, ethical committee approval and informed consent are not required because the analysis is based on publicly available data, such as published articles and citation records, which do not involve human participants or personal data.

RESULTS

Trends and Annual Publications

A total of 1239 documents published between 1984 and 2024 were identified. The WOS indexes of these publications were 1105 SCI-E, 580 SSCI, and 102 ESCI. The number of annual and cumulative publications on anticholinergic burden showed an increasing trend from 1984 to 2024. While there were a total of 128 publications between 1984 and 2010, the number of publications increased after 2010. Between 2011 and 2019, a total of 552 publications were identified, with an average of around 60 publications per year. Among these years, 2020 had the highest number of publications, with 139 documents. There has been a significant increase in the number of publications from 2020 onward, with an average of 125 publications per year.

When looking at the types of publications, the literature consisted of 832 (69%) original articles, 191 (15.8%) meeting abstracts, and 163 (13.5%) review articles. This indicates that approximately 85% of the publications in the field are original research findings. There has been a gradual increase in interest in the research topic of anticholinergic burden over the last 40 years.

The research areas of these publications are primarily geriatrics/gerontology and pharmacology/pharmacy. Additionally, the topic of anticholinergic burden is also an intriguing research area for disciplines such as psychiatry, internal medicine, neurology/neuroscience, and public health. The research areas with a high number of publications on anticholinergic burden are presented in Table 1.

Analysis of Countries

When analyzing the co-authorship of countries in the field of anticholinergic burden, it was found that 75 countries contributed to these studies. By setting a threshold of at least 5 publications on this topic, 35 countries met this criterion. Among these, the United States made the largest contribution with 382 publications and 12023 citations, followed by Australia with 222 publications and the United Kingdom with 144 publications. These countries

Table 1. Research Areas of Documents About Anticholinergic Burden

Research Areas	Number of Publication	%
Geriatrics gerontology	398	32.123
Pharmacology pharmacy	396	31.961
Gerontology	200	16.142
Psychiatry	185	14.931
Medicine general internal	111	8.959
Clinical neurology	95	7.667
Neurosciences	69	5.569
Public environmental occupational health	66	5.327
Health care sciences services	54	4.358
Urology/nephrology	41	3.309

also demonstrated the strongest collaborative relationships with other nations. The top 10 countries contributing the most to the literature on anticholinergic burden are shown in the Table 2

When the collaboration networks of 35 countries with at least 5 publications and 5 citations were analyzed, the countries were grouped into 4 clusters, forming 475 links (Figure 1). The strongest collaboration was observed between the United States and Australia. In the network visualization, each node represents a different country, with the size of the nodes corresponding to the number of publications. Countries within the same cluster are represented by the same color. Additionally, the thickness of the links indicates the strength of cooperation between countries.

Analysis of Co-Occurrence Keywords

While there were a total of 1509 keywords used in the anticholinergic burden research, 129 keywords met the threshold of being used at least 5 times. "Polypharmacy" was the most used keyword with 147 occurrences, followed by "anticholinergic burden" with 139 occurrences and "dementia" with 94 occurrences. The top 20 most used keywords are presented in Table 3. These keywords form 5 clusters when mapped according to the total strength

Table 2. The Countries Contributing the Most to the Anticholinergic Burden Research

Rank	Country	Documents	Citations
1	USA	382	12023
2	Australia	222	5937
3	England	144	3151
4	Canada	100	2954
5	Scotland	63	1371
6	Italy	56	1537
7	New Zealand	39	1378
8	Netherlands	50	1035
9	France	64	1168
10	Germany	55	863

of their co-occurrence links. The largest cluster, with 48 items, is Cluster 1 (red), which includes keywords such as "anticholinergic burden," "anticholinergic agents," "Beers criteria," "cognitive impairment," "elderly," "falls," "inappropriate prescription," "sedative," "stroke," and "urinary incontinence." Used together 27 times, "polypharmacy" and "anticholinergic burden" were the keywords with the strongest association. Overlay visualization between 2010 and 2022 is used to show the evolution of the keywords over time (Figure 2). Accordingly, the keywords that were used more frequently in 2020 and later were "ageing," "medication review," "deprescribing," "anticholinergic burden," "frailty," "sedatives," and "polypharmacy."

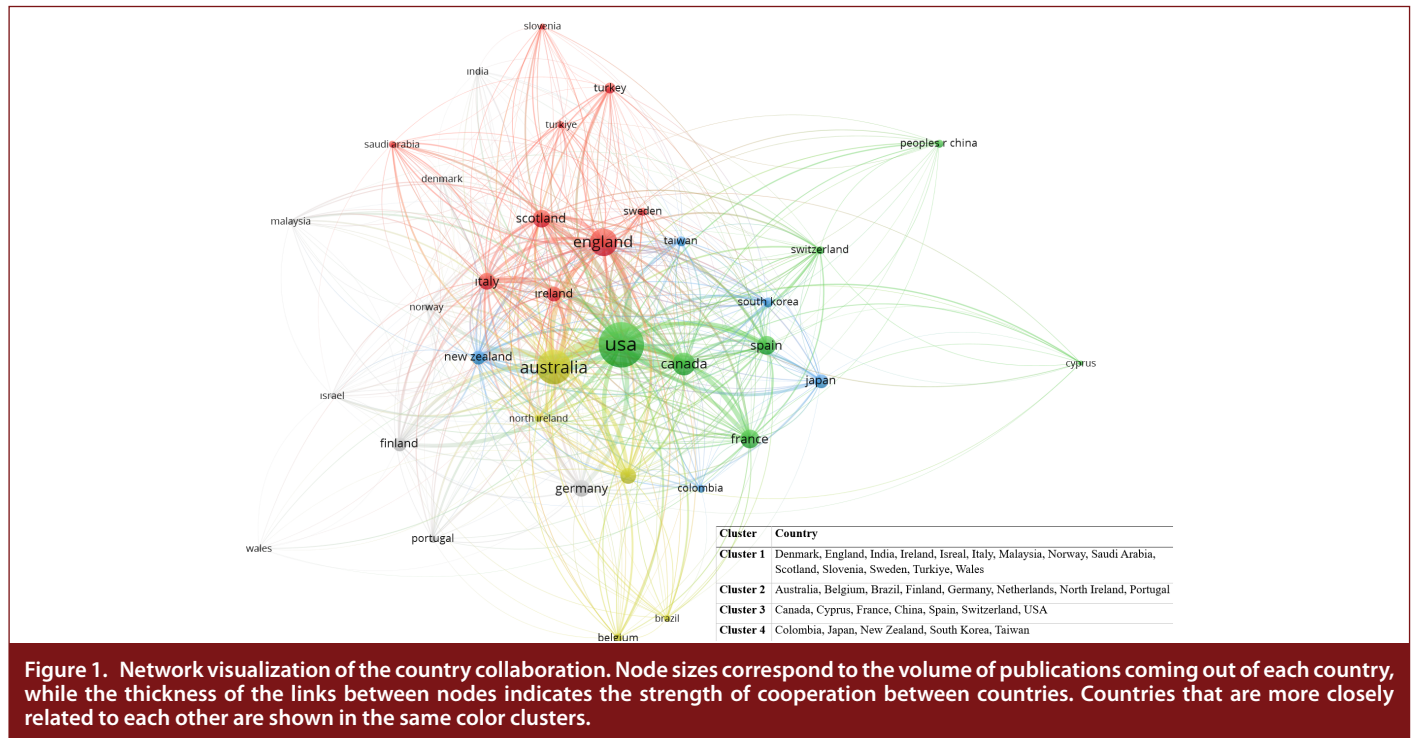
Analysis of Authors, Journals, Organizations, and Publications

Citations were analyzed according to contributing authors, journals, and organizations, with the top 10 presented in Table 4. A total of 1831 organizations contributed to documents in this field, with 178 meeting the threshold of having at least 5 documents. The University of Sydney led with the most publications, citations, and links, boasting 121 publications and 3940 citations. In terms of authorship, 5290 authors contributed, with 158 having at least 5 publications and 5 citations each. The most productive authors in this field over the last 40 years are ranked by number of publications and the top 10 are presented in Table 4. Sarah H. Hilmer leads the field with 77 publications and 3255 citations, followed by Danijela Gnjidic with 44 publications and S. Nishtala with 24 publications. We have ranked the most popular journals in this field over the last 40 years according to the number of publications they have published. A total of 441 different journals have contributed to the literature in this field. The *Journal of the American Geriatrics Society* with 70 publications and *Drugs&Aging* with 66 publications were the most popular journals in this field.

The most cited articles were ranked to identify the most influential publications in the field (Table 5). O'Mahony et al had the highest citation count in 2015, with their work published in the *Journal Age and Aging*. Notably, when evaluating the top 10 articles, those that developed scales or criteria to measure anticholinergic burden and related issues generally had the highest citation counts.

DISCUSSION

This study provides a comprehensive quantitative analysis of the research landscape surrounding anticholinergic burden over the last four decades, utilizing bibliometric methods. The findings underscore that anticholinergic burden remains a significant and globally recognized topic, with research cutting across various disciplines. A key focus within this area is polypharmacy, which is frequently examined due to its association with numerous adverse outcomes, including increased mortality, a higher incidence of falls, adverse drug reactions, extended hospital stays, and higher rates of early readmissions. Even though individual



drugs may exhibit low levels of anticholinergic activity, the cumulative effect from polypharmacy can result in a considerable anticholinergic burden. While several scales have been developed to quantify this burden, the lack of consistency among these tools highlights the absence of a universally accepted gold standard, reflecting a critical gap in the current methodologies.

Anticholinergic burden is a popular, multidisciplinary, and global research topic. Considering the increase in publications since 2010, peaking in 2020, the interest in anticholinergic burden, a research area for the past 40 years, has surged in recent years. Notably, the research in this field spans multiple disciplines, including geriatrics, pharmacology, pharmacy, neurology, neurosciences, and psychiatry. Important studies on anticholinergic burden have seen contributions from 75 different countries, with the United States leading significantly with 382 publications

and approximately 12000 citations. Australia and the United Kingdom follow as influential contributors. The prominence of these countries in this field may be attributed to the development of frequently used research scales by their researchers. Key articles introducing the ACB scale,¹³ ADS,¹⁴ ARS,¹⁵ and DBI¹⁶ scales, which are highly cited, feature affiliations with researchers from the United States.

Among the authors who have published on anticholinergic burden, Sarah N. Hilmer has the most publications and citations. Hilmer and her colleagues developed the DBI, which has become one of the most frequently used and cited scales. As of 2024, Hilmer, with an *h*-index of 58, has made significant contributions to the fields of polypharmacy, deprescribing, and geriatric pharmacology.¹⁷⁻²⁰ Second in terms of contributions to the field is Danijela Gnjidic, who has co-authored many papers with Hilmer.

Table 3. Keywords Most Commonly Used in the Field of Anticholinergic Burden

Rank	Keyword	Occurrences	Rank	Keyword	Occurrences
1	Polypharmacy	147	11	Cognition	51
2	Anticholinergic burden	139	12	Cholinergic antagonist	48
3	Dementia	94	13	Anticholinergic drug	42
4	Eldery	75	14	Drug burden index	41
5	Anticholinergic	68	15	Older people	40
6	Delirium	67	16	Mortality	37
7	Older adults	58	17	Cognitive impairment	34
8	Deprescribing	54	18	Pharmacoepidemiology	32
9	Aged	52	19	Frailty	32
10	Anticholinergics	52	20	Overactive bladder	31

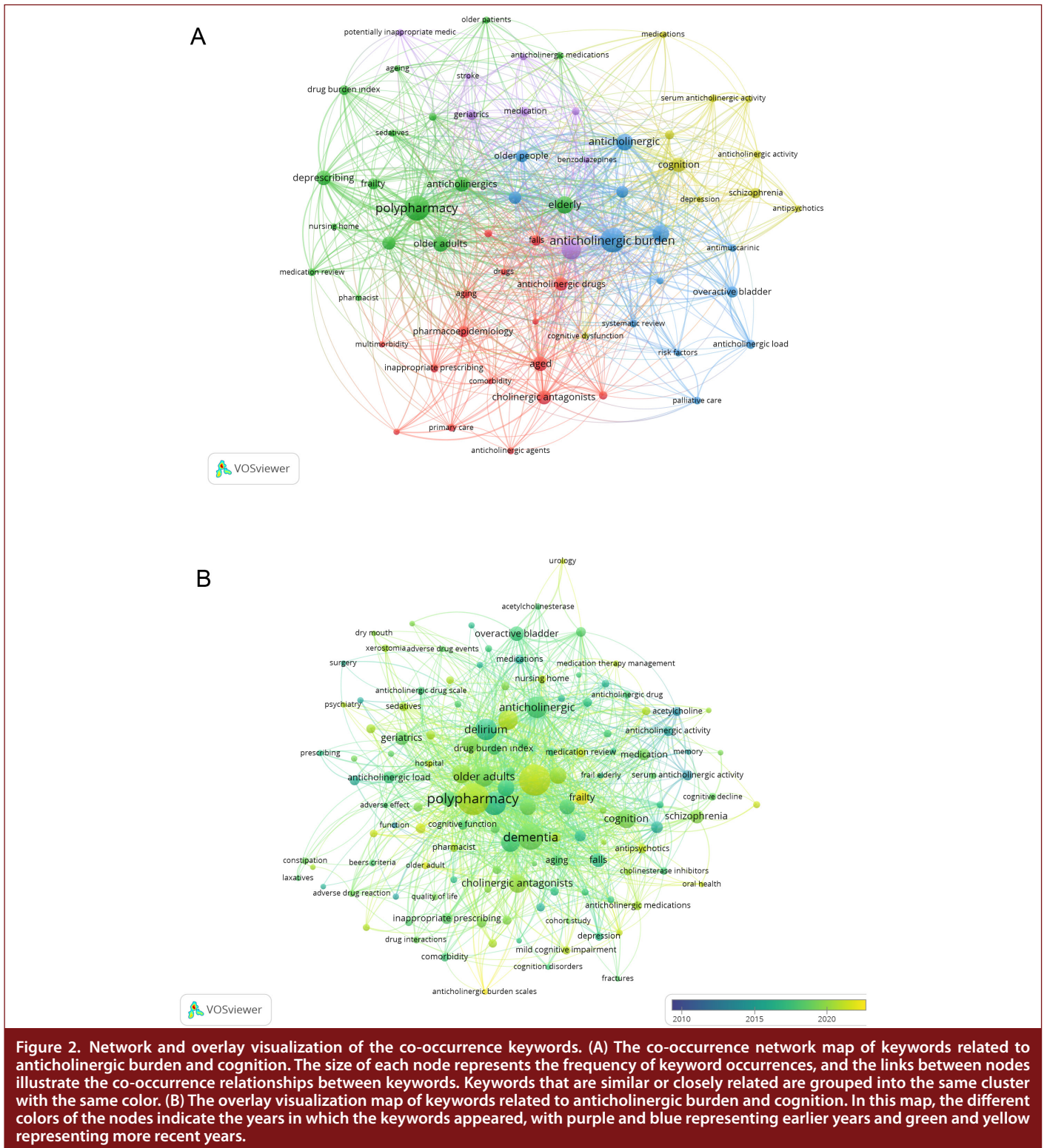


Figure 2. Network and overlay visualization of the co-occurrence keywords. (A) The co-occurrence network map of keywords related to anticholinergic burden and cognition. The size of each node represents the frequency of keyword occurrences, and the links between nodes illustrate the co-occurrence relationships between keywords. Keywords that are similar or closely related are grouped into the same cluster with the same color. (B) The overlay visualization map of keywords related to anticholinergic burden and cognition. In this map, the different colors of the nodes indicate the years in which the keywords appeared, with purple and blue representing earlier years and green and yellow representing more recent years.

Although she was not part of the initial American team that created the DBI, she contributed to its development and research in various groups after Hilmer's transition to Australia. Gnjidic's most cited work, in which she was the first author, addresses the cutoffs and outcomes of polypharmacy and has received 797 citations.¹⁸ Among

institutions, the University of Sydney has made the most significant contribution to the field, with 121 papers and 3940 citations. This is likely due to the significant publications and influential collaborations by key researchers such as Hilmer and Gnjidic, whose work is highly cited and influential.

Table 4. Top 10 Authors, Journals, and Organizations that Have Most Contributed to the Area of Anticholinergic Burden

Rank	Author	Documents	Citations	Journals	Documents	Citations	Organization	Documents	Citations
1	Sarah N. Hilmer	77	3255	Journal of the American Geriatrics Society	70	2797	Sydney University	121	3940
2	Danijela Gnjidic	44	1274	Drugs&Aging	66	1744	Aberdeen University	46	1184
3	Prasad S. Nishtala	24	1052	International Journal of Clinical Pharmacy	37	164	Pittsburgh University	40	1948
4	Bruce G. Pollock	21	1388	Pharmacoeconomics and Drug safety	31	165	Royal North Shore Hospital	37	2122
5	J. Simon Bell	17	600	Journal of the American Medical Directions Association	29	527	Otago University	34	1348
6	Le Couteur, David G.	16	728	British Journal of Clinical Pharmacology	25	569	Toronto University	33	1591
7	Timothy F. Chen	16	701	Age and Ageing	24	2184	Concord Hospital	28	880
8	Phyo Kyaw Myint	15	487	Journals of Gerontology Series a Biological Sciences and Medical	24	802	Monash University	25	478
9	Maire O'dwyer	15	93	European Journal of Clinical Pharmacology	22	659	Eastern Finland University	22	483
10	Katja Taxis	13	297	American Journal of Geriatric Psychiatry	21	1189	Flinders University	21	833

Polypharmacy is a topic that is most commonly included and investigated in anticholinergic burden research. Although there is no universally accepted definition of polypharmacy, the most commonly used definition is the use of 5 or more medications.²¹ Numerous drugs with anticholinergic properties are widely prescribed, particularly among older adults with chronic conditions.²² Polypharmacy is linked to negative outcomes such as mortality, falls, adverse drug reactions, prolonged hospital stays, and early readmissions.^{23,24} Although individual drugs may have low anticholinergic activity, a significant anticholinergic burden can occur in the presence of polypharmacy. Polypharmacy, potential drug-drug interactions, and anticholinergic use are common among older adults, and the anticholinergic burden is linked to impaired cognitive function.²⁵ Therefore, when prescribing an anticholinergic drug, it is crucial to assess the unavoidable anticholinergic burden, cognitive function, and comorbidities that are sensitive to anticholinergic effects, such as benign prostatic hypertrophy, constipation, and gait problems.²⁶ “Cognition,” “frailty,” “elderly aging,” and “deprescribing” were other key terms that garnered attention in anticholinergic burden studies. These studies were particularly important for the geriatric population. Studies indicate that 47% of the elderly population uses medications with potential anticholinergic effects, while 4% use medications with confirmed anticholinergic effects. Anticholinergic drugs that act on central and/or peripheral cholinergic receptors can cause symptoms, such as cognitive impairments, that may be mistaken for normal signs of aging.²⁷⁻²⁹ An increased risk of Alzheimer's disease and higher rates of cortical gray matter atrophy have been shown even in users of drugs with a low anticholinergic burden, despite having no known clinical effect.³⁰ The inclusion of these drugs in a regimen increases the risk of general cognitive decline, dementia, physical dysfunction, and death, although some studies report conflicting results.^{2,31-34} Clinicians are strongly encouraged to be aware of the anticholinergic burden and its potential effects, and to work towards deprescribing commonly used anticholinergics to reduce the risk of developing long-term cognitive problems in healthy individuals or to improve clinical outcomes in those with cognitive impairment.¹

Serum anticholinergic activity is often considered the gold standard for measuring the overall anticholinergic burden from all the drugs a person takes, including their metabolites. However, it has limitations, such as not providing information about central nervous system burden, and it is also expensive, challenging to use, and difficult to interpret in clinical practice.³⁵ Scales are favored for their practicality and ability to provide easy guidance to clinicians, and the most cited articles on anticholinergic burden are those that involve the development of these scales. The most cited article in our study was “STOPP/START criteria for potentially inappropriate prescribing in older people: version 2.”³⁶ This article does not directly address the issue of anticholinergic burden but offers a screening tool for the evidence-based review of geriatric drug prescriptions. The

Table 5. Most Cited Studies

Rank	Publication Name	First Author	Journal Name	Times Cited*	Year
1	STOPP/START criteria for potentially inappropriate prescribing in older people: version 2	O'Mahony, D.	Age And Ageing	1600	2015
2	The anticholinergic risk scale and anticholinergic adverse effects in older persons	Rudolph, James L.	Archives of Internal Medicine	568	2008
3	Delirium in elderly adults: diagnosis, prevention and treatment	Fong, TG	Nature Reviews Neurology	553	2009
4	A drug burden index to define the functional burden of medications in older people	Hilmer, Sarah N.	Archives of Internal Medicine	498	2007
5	The anticholinergic drug scale as a measure of drug-related anticholinergic burden: Associations with serum anticholinergic activity	Carnahan, Ryan M.	Journal of Clinical Pharmacology	471	2006
6	Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study	Ancelim M.L.	BMJ-British Medical Journal	419	2006
7	Anticholinergic medication use and cognitive impairment in the older population: The medical research council cognitive function and ageing study	Fox C.	Journal of the American Geriatrics Society	417	2011
8	Neuropathogenesis of Delirium: Review of current etiologic theories and common pathways	J.R. Maldonado	American Journal of Geriatric Psychiatry	406	2013
9	Anticholinergic activity of 107 medications commonly used by older adults	M.L. Chew	Journal of the American Geriatrics Society	332	2008
10	Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review.	Salahudeen M.S	BMC Geriatrics	313	2015

*Citations from WoS as of 25.07.2024 have been considered.

ACB scale,¹³ADS,¹⁴ ARS,¹⁵ and DBI²⁰ are the most preferred scales in anticholinergic burden studies. A systematic review of anticholinergic burden scales reported 19 scales and 104 validation studies, most of which were developed in the early 2000s.³⁴ In many studies, these scales are compared with each other. Although these scales employ a similar system for scoring drugs based on their anticholinergic burden, there are differences in the drug lists and the scores assigned. Studies indicate that there are discrepancies between the scales and that no scale of anticholinergic burden can be accepted as the gold standard.^{34,35,37}

In conclusion, anticholinergic burden continues to be a prominent topic in multidisciplinary research. While anticholinergic agents play a crucial role in treating various cardiovascular, respiratory, and CNS-related diseases, they also carry significant side effects, particularly in the elderly. Therefore, it is essential for clinicians to assess the risk-benefit ratio and consider deprescribing anticholinergics when necessary. In this context, studies that provide evidence on anticholinergic burden across different comorbidities, polypharmacy scenarios, and varying drug dosages will offer more effective guidance to clinicians. Although numerous scales have been developed to assess anticholinergic burden, there remains a lack of strong agreement between them. Consequently, there is a pressing need for more accurate methods to quantify anticholinergic burden, taking into account drug dosages, potencies, and individual predispositions. Future

multicenter, collaborative studies should aim to address the inconsistencies among anticholinergic burden scales by reviewing and standardizing the drug lists and scoring systems across all scales. These efforts should focus not only on the pharmacodynamic and pharmacokinetic data assessing the anticholinergic potential of drugs but also on their clinical significance. Additionally, tailored scales that reflect the effects of drugs on specific patient groups, such as older adults, individuals with neurological disorders, or those with chronic conditions, could be developed to improve accuracy and applicability. Furthermore, neuroimaging studies that can more precisely profile the brain damage caused by central anticholinergic burden, along with research examining the correlation between central load and serum levels, may provide valuable guidance for clinicians.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval is not required for bibliometric analysis.

Informed Consent: Informed consent is not required for bibliometric analysis.

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