STUDY PROTOCOL

The impact of long-term exposure to anticholinergics among people with intellectual disabilities: a scoping review protocol

[version 1; peer review: awaiting peer review]

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Abstract

Background: Older adults with intellectual disability often take multiple medicines with anticholinergic activity and sedative properties to manage multi-morbidity; the use of medication with anticholinergic activity has been found to be associated with various cognitive and physical impairments. However, there are limited studies that have examined the long-term impact of anticholinergic use among older adults. Therefore, this protocol is designed to conduct a scoping review to examine the available data on the long-term impact of anticholinergic use in older adults with intellectual disability.

Aim and objectives: The aim of this scoping review is to a) map and b) examine the existing research literature to answer the research question: What is the impact on cognitive and physical outcomes of long-term exposure to medications with anticholinergic activity among older adults with intellectual disabilities?

Methods and analysis: This scoping review will follow the methodology framework of Arksey and O’Malley and its developed version by Levac. The framework consists of a six-stage process to be conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) reporting guidelines. The search strategy will include the following electronic data bases: Pubmed, Cochrane library, EMBASE, Medline, Science Direct, CINAHL Complete and PsycINFO. The search will include terms related to ‘Anticholinergic burden’, ‘Intellectual disability’, ‘Adverse drug reaction’ and ‘long-term impact’ with Boolean operator ‘and’. The scoping review will include studies with at least 3 months exposure to anticholinergics. The collected data will be mapped as a tabular presentation of the various physical and
cognitive adverse effects associated with long-term use of anticholinergics in this group of population.

**Keywords**
Anticholinergic Burden, Intellectual Disability, long-term adverse outcomes, older adults

This article is included in the TILDA gateway.

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### Introduction

People with intellectual disabilities have a higher burden of mortality and comorbidity (co-occurrence of two or more chronic conditions) compared to the general population. In the general population, comorbidity is common among people aged 50 years and older, whereas it is common among all age groups in people with intellectual disabilities. Comorbidity is one of the factors that lead to earlier aging and frailty in this vulnerable group.

Geriatric frailty occurs earlier in people with intellectual disabilities compared to the general population; for instance, frailty index scores in people with intellectual disabilities aged 50 – 59 are similar to people aged 70 – 79 years old in general populations. Intellectual disability-related physical health conditions, sedentary lifestyle and metabolic effects of antipsychotic medicines are considered as factors that lead to earlier comorbidity and poorer quality of life and health outcomes in this group.

Disease patterns differ in adults with intellectual disabilities compared to the general population; for example, people with intellectual disabilities have higher rates of mental health conditions (such as schizophrenia, bipolar disorders and depression), gastrointestinal diseases (such as peptic ulcer and gastro-oesophageal reflux disorders), neurological medical conditions (including epilepsy and dementia) and a lower risk of cardiovascular disorders.

As a result of co-morbidity among people with intellectual disabilities, there is a high prevalence of polypharmacy with a range of 11 – 60% reported depending on definition, region and the studied population. Therefore, there is a higher risk of medication-related harm and Adverse Drug Reactions (ADR). Furthermore, a study conducted in Ireland observed 10 times higher rates of excessive polypharmacy (on 10 medicines or more) in people with intellectual disabilities compared to the community dwelling general older population.

Many medicines possessing anticholinergic and / or sedative activity are used to treat health conditions in older adults. Anticholinergic medicines have peripheral and central adverse effects including dry mouth, constipation, sedation, confusion and blurred vision. A systematic review conducted by Ruxton and colleagues concluded that for older adults, being exposed to a single medicine with anticholinergic activity or a high overall anticholinergic burden were associated with an increased risk of falls, cognitive impairment and all-cause mortality. Another systematic review, published recently by Stewart and colleagues, also found for older adults that higher anticholinergic burden was significantly associated with impaired physical function and poorer quality of life.

The Longitudinal Aging Study Amsterdam has examined the impact of cumulative anticholinergic exposure over 20 years and the researchers have found that among the older adult participants higher cumulative exposure to anticholinergic and sedatives use was associated with poorer physical and cognitive function. Another cohort study conducted over 13 years among older adults concluded that physical impairment was associated with short-term and long-term use of anticholinergic, while cognitive impairment was associated with short-term use only. Furthermore, long-term use of anticholinergic was associated with poorer physical function and higher mortality risk.

People with intellectual disabilities receive a high number of medicines that have anticholinergic activity to manage their multi-morbidity. In Ireland, a cross-sectional study found that 51.3% of people with intellectual disabilities were exposed to medicines with anticholinergics and 54.2% had a high drug burden index (DBI) of anticholinergic and/or sedative medicines. Organic brain dysfunction in people with intellectual disability may result in an increased sensitivity to medication with anticholinergic activity. Further, studies have examined the impact of anticholinergic use among people with intellectual disabilities and have concluded that higher DBI is associated with a higher dependency level, daytime dozing, constipation, frailty and dementia. To date, to the best of our knowledge there have been no long-term studies of anticholinergic use in older adults with intellectual disabilities.

The aim of this scoping review is to map and examine the existing research literature on the physical and cognitive impact of long-term exposure to medications with anticholinergic activity among older adults with intellectual disabilities. In addition, the long-term goal of the review is to enhance the prescribing of medications for this vulnerable group of the population.

### Methods

The methodology of this scoping review will be based upon the framework proposed by Arksey and O’Malley, using the developed version proposed by Levac and the reviewers’ manual published by the Joanna Briggs Institute. The review process is organized using six stages and these stages are:

1. Identifying the research question
2. Identifying relevant studies
3. Selecting studies
4. Charting the data
5. Collating, summarising and reporting the results
6. Consultation

In addition, this review study will be conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) reporting guidelines.

#### Stage 1: Identifying the research question

According to the preliminary conducted search, approximately five cross-sectional studies have examined the anticholinergic burden among people with intellectual disabilities. These studies have found that older adults with intellectual disabilities have a higher exposure rate to medication with
anticholinergic activity. It has been concluded that the use of such medication is associated with a higher dependence level, decline in grip strength and timed up-and-go measures and greater likelihood of day-time dozing in people with intellectual disabilities.

There are 13 additional studies that examined the impact of long-term anticholinergic medication (from 1 year up to 20 follow-up years) among different populations. The long-term use of medication with anticholinergic activity was found to be associated with a decline in physical function, higher risk of dementia, poorer cognitive function, recurrent falls, higher risk of Alzheimer’s Disease and a lower health-related quality of life.

Given there have been, to the best of our knowledge, no studies that have investigated the adverse effects associated with the long-term use of anticholinergic in older adults with intellectual disabilities, this scoping review aims to map and examine the existing research literature and address the research question:

What is the impact on cognitive and physical outcomes of long-term exposure to medications with anticholinergic activity among older adults with intellectual disabilities?

The long-term goal of this scoping review is to enhance prescribing pattern among people with intellectual disability.

Stage 2: Identifying relevant studies
The search strategy will include the following electronic databases: PubMed, Cochrane library, EMBASE, Medline, Science Direct, CINAHL Complete and PsycINFO. Moreover, grey literature, preliminary studies and conference papers will be searched to identify ongoing and unidentified relevant data. Ongoing and unidentified data will be explored in the following sources: Google Scholar; The Turning Research into Practice (TRIP) Database; ClinicalTrials.gov; EU Clinical Trial Register; Chinese Clinical Trial Registry (ChiCTR); International Standard Randomised Controlled Trial Number (ISRCTN) registry; Pan African Clinical Trials Registry (PACTR); Australian New Zealand Clinical Trials Registry (ANZCTR); Clinical Trials Registry—India (CTR); the WHO International Clinical Trials Registry Platform search portal (ICTRP); and PROSPERO.

The research terms will describe the following main keywords:

- Anticholinergic: ‘anticholinergic burden’ OR ‘anticholinergic exposure’ OR ‘anticholinergic’ OR ‘cholinergic antagonist’ OR ‘antimuscarinic drugs’ OR ‘muscarinic antagonist’ OR ‘anticholinergic’ OR ‘anticholinergic agent’ OR ‘antimuscarinic’ OR ‘antimuscarinic agent’ OR ‘cholinergic blocking agent’ OR ‘acetylcholine antagonist’ OR ‘cholinergic receptor antagonist’ OR ‘cholinergic antagonists’ OR ‘cholinolytics’

- Long-term exposure: ‘chronic use’ OR ‘long-term use’ OR ‘≥ 3 months’

- Intellectual disability: ‘cognitive impairment’ OR ‘intellectual disabilities’ OR ‘learning disabilities’ OR ‘developmental disabilities’ OR ‘mentally disabled persons’ OR ‘handicap’ OR ‘Down Syndrome’ OR ‘mental retardation’ OR ‘intellectual development disorders’ OR ‘psychosocial mental retardation’ OR ‘mental deficiency’ OR ‘mentally disabled’ OR ‘mentally handicapped’ OR ‘persons with intellectual disability’ OR ‘mentally retarded’

- Adverse drug reaction: ‘adverse effect’ OR ‘drug toxicity’ OR ‘adverse outcomes’ OR ‘side effects’ OR ‘drug related side effects’ and ‘adverse reactions’ OR ‘side effects of drugs’ OR ‘drug side effects’ OR ‘adverse drug reactions’ OR ‘adverse drug event’ OR ‘anticholinergic toxicity’ OR ‘anticholinergic effect’ OR ‘anticholinergic syndrome’ OR ‘peripheral anticholinergic syndrome’ OR ‘central anticholinergic syndrome’ OR ‘anticholinergic toxicity’ OR ‘anticholinergic effect’ OR ‘cognitive function’ OR ‘cognitive disorder’ OR ‘cognitive impairment’ OR ‘dementia’ OR ‘delirium’ OR ‘physical function’ OR ‘physical activity’ OR ‘frailty’ OR ‘falls’ OR ‘accidental falls’ OR ‘hip fracture’ OR ‘mortality’ OR ‘death’ OR ‘constipation’ OR ‘urinary incontinence’

Searches will include terms related to ‘anticholinergic’, ‘intellectual disability’, ‘long-term impact’ and ‘adverse drug reaction’ with Boolean operator “and”. An academic librarian will be consulted regarding the appropriate Medical Subject Heading (MeSH) terms used for each electronic database.

The search strategy will be restricted to articles published in English language and age group (40 years and over). There will be no restriction on publication date, place of issue, publisher and type of studies. In addition, a reference list of the included studies will be screened to ensure that relevant articles are included in the scoping review. Moreover, the International Association for the Scientific Study of Intellectual and Developmental Disabilities (IASSIDD), Health Special Interest Research Group, the Intellectual Disability UK Research organisation, US and Australians Organisation for people with Intellectual Disability will be contacted by email to request any research information that might be relevant.

The search strategy will be discussed and developed within the research team that consists of five members. The initial search date began in February 2021.

Stage 3: Selecting studies
This stage is aimed at identifying the studies that meet the inclusion criteria and will be included in the scoping review. The inclusion and exclusion criteria will be discussed and developed within the research team. The inclusion criteria for this scoping review are outlined in Table 1.

Firstly, duplicate studies that have been retrieved from different databases will be excluded. Then, the studies will be screened
using the title and abstract to ensure their eligibility to the inclusion criteria. After that, the full article will be retrieved for the included articles. The search records will be saved in a Word document and it will include details on the electronic database, keywords, MESH-terms, search limitations (language, age, publication date, etc), results and number of included studies. The word document will be updated with information on each stage of search and review.

Criteria for assessing study eligibility

**Study design.** There will be no restriction on study design and all types of studies will be included.

**Study population.** Intellectual disability is defined as: “a disability characterized by significant limitations in both intellectual functioning and adaptive behaviour, which covers many everyday social and practical skills.” It usually occurs before the age of 18 years\(^2\).

According to the published research, there is no specific age range used to describe older adults with intellectual disability. However, people aged ≥40 years with intellectual disability often have similar comorbidities to people aged ≥70 years in the general population\(^4\). For instance, the age of 55 years was found to be the mean age for developing dementia in people with Downs syndrome\(^25\). On the other hand, the World Health Organization (WHO) has reported that dementia is associated with older adults, aged 65 years or older, in the general population compared to a range of 51 – 56 years old in people with Downs syndrome. Moreover, 55.9 years was found to be the mean age for developing epilepsy in the same population.

According to the preliminary search, most of the published studies consider that older adults with intellectual disabilities are aged 40 years and over\(^4,12,13,26\). Therefore, studies with a population aged ≥ 40 years with intellectual disability could be included to identify the largest number of studies. All stages and severity of intellectual disability including early onset of dementia, will be included.

Adults and children with intellectual disability who are aged <40 years will be excluded from the study.

**Intervention.** All types of tools used to identify anticholinergic burden could be included in the study.

‘Chronic use’ or ‘long term use’ of medicine has been defined as the use of medicine for 3 months or longer\(^27\). However, there is no accepted definition of anticholinergic long-term exposure and the team have decided to include studies with a similar cumulative exposure of at least 3 months. Based on guidelines for other drugs with safety concerns such as benzodiazepines, long-term use is considered as daily or near-daily use for at least 3 months\(^28\).

According to our initial exploratory research, most studies in general older adults have examined the long-term impact of anticholinergic over a period of 1 – 2 years\(^11,18,20,30\) years follow-up.

**Context.** There is reported data that people with intellectual disability who are living in a residential care setting, such as community housing and a nursing home facility, have a higher rate of using medications with anticholinergic activity\(^26\).

In this study there will be no restriction on the care setting, so all care settings where people with intellectual disabilities live (such as nursing homes, institutions, community group homes, independently or with family) will be included.

**Outcome.** The scoping review will examine both cognitive and physical adverse effects associated with long-term use of anticholinergic. The adverse effects of anticholinergics are divided into peripheral and central adverse effects (Table 2)\(^31\).

Therefore, all studies which examined any adverse effects associated with anticholinergic long-term use, will be included. There is no restriction on assessment tools used to identify and assess the adverse effects.

The study will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart to demonstrate the process of study selection\(^33\).

### Stage 4: Charting the data

A data extraction framework will be used to assess the full articles for each one of the included studies. A table form will be developed to record the key information in each of the articles, for instance: author, title, aim, type of the study, population characteristics, method, conclusion, and implication (Table 3). This will take the form of an excel spreadsheet.

A member of the research team (LAA) is responsible for charting the data using the data extraction framework. Two reviewers (LAA and MO’D) will independently perform data extraction (charting the data), using the developed table form to reduce bias and ensure reliability. LA and MO’D will pilot

### Table 1. Inclusion criteria for eligible studies.

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Context</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older adults (aged ≥40)</td>
<td>Long-term exposure to Anticholinergic</td>
<td>Any care setting</td>
<td>Reported and measured physical and cognitive adverse effects</td>
</tr>
</tbody>
</table>

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\(^1\) Table 2.

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Table 2. Known outcomes associated with anticholinergic use.

<table>
<thead>
<tr>
<th>Peripheral anticholinergic outcomes</th>
<th>Central anticholinergic outcomes</th>
<th>Other anticholinergic Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthermia and anhidrosis</td>
<td>Headache</td>
<td>Falls</td>
</tr>
<tr>
<td>Tachycardia, arrhythmias and flushing</td>
<td>Reduced cognitive function</td>
<td>Frailty</td>
</tr>
<tr>
<td>Constipation, vomiting and dry mouth</td>
<td>Behavioural disturbance</td>
<td>Higher Dependence level in daily activities</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Blurred vision, narrow-angle glaucoma, mydriasis</td>
<td>Insomnia</td>
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<tr>
<td>Reduced sweat</td>
<td>Agitation</td>
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<td>Confusion</td>
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<td>Seizures</td>
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<td></td>
<td>Higher Dependence level in daily activities</td>
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</tbody>
</table>

Stage 5: Collating, summarising and reporting the results

The data extraction framework will provide an overview of the available information regarding the impact of long-term use of anticholinergics among people with intellectual disability. The tabulated summary from the data extraction framework will serve as the preliminary synthesis of findings and will include the key information from each study and will describe any outcomes and patterns from identified studies. The extracted data will then be reviewed in order to establish any factors that may explain differences in outcome findings across the studies. The findings of the preliminary synthesis process will then be critically reviewed by the review team. This will include evaluating any potential sources of bias from the studies identified, including bias identified relating to the outcomes assessed in each study. Two reviewers (MO’D, LA) will have screened full texts of potential studies for inclusion to reduce bias. This process will also serve to identify gaps in the existing literature and evidence base and inform areas to be studied in future.

The collected data will be mapped as a tabular presentation of the various physical and cognitive adverse effects associated with long-term use of anticholinergics in older adults with intellectual disability. In addition, other population characteristics such as age, sex, level of intellectual disability, place of residence (independent, residential setting or community group home), comorbidity (co-occurrence of 2 or more chronic conditions) and polypharmacy (on 5 medications or more) will be presented in a chart or table form as appropriate.

Stage 6: Consultation

Stakeholders and experts will be consulted to comment on the research question and to clarify potential missing or ongoing relevant studies that were not considered. These groups will include the Royal College of Psychiatrists of Ireland (Intellectual disability subgroup), Daughters of Charity Service, Down Syndrome Ireland, National Intellectual Disability Memory Service, Tallaght Hospital and IASSIDD will be consulted verbally or by email.

charting the data on one study that meets the inclusion criteria to check consistency of assessment and the usability and reliability of the data extraction form. Any disagreements with data extraction will be resolved by consensus With a third reviewer if necessary (MH).
**Ethics and dissemination**

The scoping review does not require ethical approval since it is designed to synthesize information from published data. This review is conducted under the auspices of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA) in Ireland. The findings will be submitted for publication in scientific journals and presented in conferences.

**Study status**

Electronic searching started in February–March–April 2021 and is ongoing. The results from five databases (Cochrane, EMBASE, Medline, PsycINFO, CINHAL) have been screened according to the established inclusion criteria.

**Data availability**

No data are associated with this article.

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**References**


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