Tidsskriftet Tidsskrift for Den norske legeforening

Use of anticholinergic drugs in older patients

CLINICAL REVIEW

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Many medicines prescribed for older patients have an unintended anticholinergic effect in addition to the primary intended effect. This may lead to adverse reactions such as dizziness and memory loss, particularly in older people. Before prescribing new medicines, it is therefore important to assess the total anticholinergic burden by means of specific screening tools, such as AGS Beers Criteria® and the STOPP/START criteria. If the anticholinergic burden is high, drugs should be replaced or discontinued.

Medicines with anticholinergic properties are regularly prescribed for older and often frail patients. Epidemiological studies show that approximately 50 % of the older population use at least one of these medicines (1). Anticholinergic properties are associated with significant adverse effects such as unsteadiness, delirium and impaired cognitive function.

The purpose of this article is to provide information about medicines with an anticholinergic effect, provide an overview of age-related pharmacological changes and describe tools that can be used in everyday clinical situations to reduce prescribing of these drugs.

Acetylcholine and anticholinergics

Acetylcholine is an important neurotransmitter in the parasympathetic nervous system. Acetylcholine can be found in all autonomic ganglia and acts by binding to either muscarinic or nicotinic receptors. Anticholinergics act by depressing the effect of acetylcholine on muscarinic receptors in the central nervous system and on nicotinic receptors in the peripheral nervous system. Anticholinergics are used in the treatment of Parkinson's disease, incontinence, nausea, asthma and some eye diseases (2).

Anticholinergic activity

More than 600 drugs have unintended anticholinergic activity (2). The main medication classes with anticholinergic activity are antihistamines, antipsychotics, tricyclic antidepressants and drugs for Parkinson's disease. In older patients, anticholinergic activity is associated with impaired cognitive function, psychosis and delirium. These anticholinergic effects on the central nervous system are largely due to antagonism of muscarinic receptors in the brain. Older persons are more susceptible than younger people to developing acute changes in mental function as a consequence of drugs, and drugs are the cause of about one-third of the cases of delirium in older patients (2, 3).

Anticholinergic burden

The term *anticholinergic burden* refers to the cumulative effect on an individual who uses one or more medicines with anticholinergic activity. Medicines are often prescribed to older people on the basis of an anticipated therapeutic effect without considering the possibility of an anticholinergic burden (1). A high anticholinergic burden is associated with increased risk of mortality and morbidity, longer hospital stays and functional and cognitive decline in older people (2).

Numerous factors contribute to the anticholinergic burden in older people. These include age-related changes in the metabolism and efficacy of drugs, pathophysiological changes, comorbidity and polypharmacy (1, 2, 4, 5).

Age-related changes

Age-related changes affect the way drugs are metabolised (pharmacokinetics), as well as the effect of the drugs (pharmacodynamics). Owing to interindividual variability, however, significance and occurrence cannot be predicted (3).

Age-related changes affect the absorption, distribution, metabolism and elimination of drugs. Gastric acid secretion, gastrointestinal blood flow, pancreatic trypsin and gastrointestinal motility are reduced. The number of absorbing cells is also reduced, which consequently decreases the absorption rate and alters the distribution rate, leading to delayed onset of drug effect. The plasma concentration of albumin decreases in old age, leading to an increased free fraction of active drug. It is the free fraction that reflects the pharmacological activity of a drug (5). The permeability of the blood-brain barrier increases, permitting diffusion of large, fat-soluble molecules. These last two age-related changes can cause a higher concentration of active ingredient for a given drug dose in the body of older patients compared to younger ones (2, 3).

Fat-soluble drugs have a larger distribution volume in older people of normal weight. This is due to the proportional increase in fat (because of decreasing muscle mass) and less intracellular water. The consequence may be delayed clearance and hence a prolonged drug half-life (3).

A declining glomerular filtration rate and/or underlying disease may affect kidney function. Drugs with a narrow therapeutic index that are excreted via the kidneys should therefore be used with particular caution. Impaired kidney function results in a prolonged drug half-life and risk of adverse effects (3, 4).

Pharmacodynamic effects include therapeutic effects, adverse effects and toxic effects. These depend mainly on the drug concentration at the receptor site, the receptor response, response triggered in the cell and homeostatic mechanisms. The number, sensitivity and density of receptors change with increasing age. As a result, less active ingredient is needed to block a receptor and thereby achieve

blockade and clinical efficacy (3). Receptor density is dynamic, however. It is reduced through prolonged use of agonists. Although receptor density generally declines in older people, it may be substantially increased by prolonged use of antagonists. Clinically, the latter effect may lead to rebound effects: in other words, problems may recur in exacerbated form when the drug is discontinued (3–5).

Due to the aforementioned pharmacokinetic changes, older people are more likely to have higher concentrations of active ingredient – particularly of fat-soluble drugs – at the receptor sites than younger adults (2, 3, 5).

Anticholinergic adverse effects

The frequency of anticholinergic adverse effects is reported to be up to seven times higher in older than in younger people (2). A distinction is made between central and peripheral anticholinergic adverse effects (2, 6) (Box 1).

Box 1 Central and peripheral adverse effects

Central anticholinergic adverse effects

- dizziness
- unsteadiness
- memory loss
- impaired cognitive function
- delirium

Peripheral anticholinergic adverse effects

- gastrointestinal: nausea, vomiting, obstipation
- skin/mucosa: dry mouth, reduced sweating
- urinary tract: urine retention
- heart: palpitations, arrhythmia
- vascular: orthostatic hypotension
- eyes: blurred vision, dilated pupils

Central anticholinergic effects occur when drugs with anticholinergic activity diffuse through the blood-brain barrier and compete for the same binding sites as acetylcholine on muscarinic receptors in the central nervous system. Several studies have also demonstrated a reduction in the level of the enzyme choline acetyltransferase in the hippocampus and temporal lobe, and degeneration of cholinergic neurons in the basal ganglia (1, 2). Cumulatively these changes lead to undesired central anticholinergic adverse effects. Some patients will be more susceptible to anticholinergic effects as a result of disease that increases the permeability of the blood-brain barrier or reduces cholinergic transmission, such as in Alzheimer's disease and central vascular diseases (1, 2, 4, 5).

Peripheral anticholinergic effects occur when acetylcholine-mediated contractions of smooth muscle and glandular secretion are inhibited. Dry mouth is the most common peripheral adverse effect of anticholinergic drugs,

causing food intake problems, increased risk of cachexia, tooth decay and infections (2, 4, 6).

It is the cumulative anticholinergic burden of drugs, coupled with endogenic substances, that gives rise to anticholinergic effects. It is also important to mention that herbal drugs and dietary supplements may have an anticholinergic effect. However, only limited documentation exists of the efficacy, adverse reaction profile and interaction potential of herbal drugs and dietary supplements. In a recently published article that provides advice on the use of plant-based products, individual risk evaluation is recommended for older people. If the patient is multimorbid and uses several drugs, the use of these products is not advisable (7).

Screening tool for identifying anticholinergic activity

Before new drugs are prescribed, the drugs the patient is already using should be investigated for anticholinergic activity. Various lists and screening tools can be used to determine whether drugs have anticholinergic activity, and to assess their cumulative burden.

Specific screening tools have been developed with criteria designed to limit the prescription of high-risk drugs, such as anticholinergics, for older patients. The two most widely used are AGS Beers Criteria® and the STOPP/START criteria. The AGS Beers Criteria® was developed by a panel of experts in 1991 and last updated in 2019 (8). One disadvantage of the list is that it is geared to clinical treatment in the USA (4). The STOPP and START criteria are a European screening tool which on the one hand is intended to evaluate ongoing treatment (STOPP) and on the other also to ensure that older people > 65 years get drugs of potential benefit (START) (9). Version 2 of the STOPP and START lists has been translated into Norwegian and adapted to the drugs on the Norwegian market (10).

Quantifying anticholinergic burden

There are various tools for estimating a patient's total anticholinergic burden. Serum anticholinergic activity quantifies the burden by means of *in vitro* measurement of atropine equivalent in the patient's serum. Other tools use expert-based scales to rank and sum the anticholinergic burden of drugs. The methods for calculating anticholinergic burden and what is included (cognitive and/or peripheral adverse effects) vary (2, 4, 11). For example, the ranking in the Anticholinergic Risk Scale (ARS) is based on an assessment of the effects of the individual drug on muscarinic receptors *in vitro* and the drug's association with anticholinergic adverse effects as indicated by literature search. The patient's anticholinergic burden is calculated by summing the ARS score of each drug (0 or 1 (no/low burden) to 3 (high burden)). When the

Anticholinergic burden scale or *Anticholinergic Drug Scale* is used, the scores for the individual drugs are also summed to calculate the patient's total burden (2, 4, 6, 11).

However, the drugs are assessed somewhat differently, so that the tools are not directly comparable. Moreover, most of the methods do not take dosage into account, and presuppose a simple linear effect mechanism that can probably not be applied directly to clinical conditions (4, 6). Despite their drawbacks, the tools are well suited to estimating the cumulative burden of anticholinergics (2, 6).

In order to quantify anticholinergic burden in an everyday clinical context, Nishtala et al. developed a Pocket Reference Card for clinical use, i.e. a list of drugs with anticholinergic activity (low, moderate and high anticholinergic activity) (2, 12). The Danish Medicines Agency has also made a list of anticholinergic drugs, using a modified *Anticholinergic Risk Scale* and *Anticholinergic Burden Scale* adapted for the Danish market (6). In Table 1 we have adapted the information from the cited sources to the Norwegian pharmaceuticals market. However, assessment of anticholinergic burden is only part of the evaluation of drugs in older patients. Other drugs, such as benzodiazepines, may have the same adverse effects (dizziness, unsteadiness and cognitive impairment), without it being due to anticholinergic effect.

Table 1

Anticholinergic activity of drugs registered in Norway (2, 4, 6, 12, 13)

	Pronounced effect	Low to moderate effect	Alternative drugs (little/no anticholinergic effect)
Antidepressants			
Selective serotonin reuptake inhibitors / selective serotonin and noradrenaline reuptake inhibitors		Citalopram Fluoxetine Fluvoxamine Paroxetine Reboxetine Escitalopram Sertraline	
Tricyclic antidepressants	Amitriptyline Clomipramine Doxepin Nortriptyline		
Other antidepressants			Duloxetine Venlafaxine Mirtazapine
Antipsychotics			
First generation	Levomepromazine	Haloperidol Perphenazine[1]	

	Pronounced effect	Low to moderate effect	Alternative drugs (little/no anticholinergic effect)
Second generation	Clozapine	Olanzapine[1] Quetiapine[1] Risperidone Amisulpride[2] Lurasidone[2] Sertindole[2] Paliperidone[2] Cariprazine[2]	Aripiprazole Ziprasidone
Antihistamines			
First generation	Alimemazine Dexchlorpheniramine Promethazine Hydroxyzine		
Second generation		Cetirizine Fexofenadine Desloratadine Loratadine Bilastine[2]	Ebastine
Antiemetics	Cyclizine Meclozine Scopolamine	Domperidone Metoclopramide	Ondansetron may be an alternative to metoclopramide
Anti-Parkinson's drugs	Biperiden	Selegiline Pramipexole Entacapone	Carbidopa Levodopa
Urological agents	Oxybutynin Darifenacin Tolterodine[1] Fesoterodine Solifenacin	Tamsulosin[2]	Mirabegron may be an alternative in cases of overactive bladder syndrome. Doxazosin may be an alternative in cases of benign prostate hyperplasia
Other		Carbamazepine Oxcarbazepine Loperamide Baclofen	

[1] *Variable anticholinergic activity reported, in some sources substantial*

[2] *Anticholinergic activity not known*

Discontinuation strategies

If patients experience anticholinergic adverse reactions, it should be considered whether the drug can be discontinued, or the dose reduced, or whether it can be replaced with an alternative with less anticholinergic activity.

Limited efficacy or unacceptable adverse reactions indicate discontinuation. There are no evidence-based guidelines for discontinuation of anticholinergic drugs. In general, it is important reduce the dose as fast as possible in the event of severe adverse reactions. Most drugs can be discontinued directly, but some may cause severe or unpleasant reactions if discontinued abruptly. For this reason, they should be tapered before final discontinuation if possible. This applies in particular to anticonvulsants, antipsychotics and antidepressants. Factors such as duration of treatment may also be important (the longer the treatment duration, the slower the tapering), as may how close one is to the minimum effective dose (2), (4–6).

Summary

Medicines with anticholinergic activity may have pronounced adverse effects on older patients. The STOPP and START criteria, AGS Beers Criteria®, or our list of drugs with anticholinergic activity on the Norwegian market should be checked before prescription. If the patient is already using multiple drugs, their drugs list should be reviewed to quantify the total anticholinergic burden. Attempts can be made to replace drugs with high anticholinergic activity or discontinue drugs that are not necessary. If these steps are not possible, the dose should be reduced to the minimum that produces an adequate effect.

The article has been peer-reviewed.

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Publisert: 7 April 2021. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.20.0775
Received 28.9.2020, first revision submitted 15.12.2020, accepted 16.2.2021.