PrescQIPP Community Interest Company

Anticholinergic drugs

This project reviews appropriate treatment with anticholinergic drugs. An increasing number of systematic reviews and meta-analyses report that drugs with anticholinergic effects are associated with an increased risk of cognitive impairment and all cause mortality in older people. This project identifies the risk and examines tools and actions that health care professionals can take to minimise the use of drugs that may adversely affect cognitive function.

A briefing, MUR community pharmacy sheet and power point presentation are available at www.prescqipp.info

Recommendations

- Prescribe anticholinergic drugs with caution in older or frail people or people with complex multi-morbidities.[1] Older/frail patients are more likely to experience adverse effects with anticholinergics such as constipation, urinary retention, dry mouth/eyes, sedation, confusion, delirium, photophobia, falls and reduced cognition.
- Research suggests a link to increased mortality with the number and potency of anticholinergic agents prescribed.[1-3] Use toolkits to review anticholinergic burden (ACB) (see attachment 1 and attachment 2 for examples).
- Minimise the use of anticholinergic drugs where possible.[1,2]
- Review at regular intervals. Discontinue medication if there is no absolute need or switch to medication with a lower ACB score or from a different class.[2]
- Review medication in older people that have had a fall or are at increased risk of falling as part of a multifactorial risk assessment.[4]
- In patients with dementia, perform a medication review to identify and minimize use of drugs that may adversely affect cognitive function. Avoid prescribing anticholinergics with acetylcholinesterase inhibitors.[5]

Background

Anticholinergic drugs are prescribed for a wide range of conditions, including Parkinson's disease, overactive bladder, chronic obstructive pulmonary disease, nausea and vomiting, depression and psychosis. Some drugs, e.g. oxybutynin or hyoscine are used for their anticholinergic effects. Others have anticholinergic activity not related to their primary mode of action, e.g. ranitidine or carbamazepine. There has been a lot of interest in the potential harm caused by drugs that have anticholinergic effects. Combining treatments with anticholinergic activity might have cumulative harmful effects when given to a person with more than one clinical condition. This potential for harm increases with frailty and age. Furthermore, anticholinergic drug use is closely related to serious negative outcomes on older adults' health status, with increased risk of falls[6] and higher mortality rates.[7]

Pharmacology

Drugs with anticholinergic effects block the neurotransmitter acetylcholine and inhibit smooth muscle function in the lungs, gastrointestinal tract and urinary tract. Five distinct muscarinic receptor subtypes (M1–M5) are known to exist resulting in the potential for side effects.

These include constipation, dry mouth, dry eyes, urinary retention and falls. Dizziness, sedation, confusion, agitation, delirium and even cognitive impairment have been reported as central adverse effects.[1,7] Clinically, older patients with existing cognitive impairment and those with early stage dementia, age associated memory impairment, or mild cognitive impairment, can be especially vulnerable to these cognitive side effects.

The central nervous system (CNS) side effects caused by anticholinergic drugs may vary depending on the ability of the drugs to penetrate the blood-brain barrier (BBB) and the pharmacologic activity on CNS receptors. Penetration of the BBB depends on passive and active transport. All muscarinic receptor subtypes (M1–M5) are present in the brain:

- M1 receptor, predominantly located in the neocortex, is the most abundant subtype in the CNS, hippocampus, and neostriatum.
- M2 receptors are also located throughout the brain.
- The M3 receptor is present throughout the CNS but in relatively lower density.
- M4 receptors are abundant in the neostriatum.
- M5 receptors have been localized in the hippocampus and projection neurons of substantia nigra, pars compacta, and ventral tegmental nuclei.

The absolute presence of receptors and the binding to receptors does not determine potency or pharmacologic effect. Clinical studies suggest that cognitive impairment, in particular memory loss, may result from antagonism of M1 and, to some extent, M2 or M4 receptors in the CNS. The factors determining the penetration of any pharmacologically active parent compound or metabolite include:

- Serum concentration (passive diffusion)
- Active transport ("in" or "out")
- Lipophilicity (predisposition to dissolve in fat vs. water)
- The electrical charge (polarity)
- Molecular size and configuration (bulk, not purely molecular weight).[8]

Evidence for cognitive impairment

An initial study in 2011, involving more than 13,000 men and women aged 65 years and over, from the UK, found that anticholinergic activity appears to increase the risks of both cognitive brain impairment and death in older people. The researchers examined the medication records of participants using a tool they developed which grades levels of blockade of acetylcholine. Each drug taken by the participants was given a ranking based on the strength of its anticholinergic activity, or ACB score; 0 for no effect, 1 for mild effect, 2 for moderate effect and 3 for severe effect. The key findings were:

- 20% of participants taking drugs with a total ACB of four or more had died by the end of the two-year study, compared with only 7% of those taking no anticholinergic drugs. This was the first time a link between anticholinergics and mortality had been shown.
- For every additional ACB point scored, the odds of dying increased by 26%.
- Participants taking drugs with a combined ACB of five or more scored more than 4% lower in a cognitive function test than those taking no anticholinergic medications – confirming evidence from previous smaller studies of a link between anticholinergics and cognitive impairment.
- The increased risks from anticholinergic drugs were shown to be cumulative, based on the number of anticholinergic drugs taken and the strength of each drug's anticholinergic effect.
- Those who were older, of lower social class, and with a greater number of health conditions tended to take the most anticholinergic drugs.[7]

In 2011, the LASER –AD study examined the effect of medications with anticholinergic effects on cognitive impairment and deterioration in 224 patients with Alzheimer's disease. The mean number of medications taken was 3.6 (Standard Deviation [SD] 2.4) and the mean anticholinergic load was 1.1 (SD 1.4, range 0–7). The medications with anticholinergic effects were not found to affect cognition over the subsequent 18 months.[9]

Another recent prospective population-based cohort study of 3,434 participants aged 65 years or older with no dementia at study entry, was undertaken to examine whether cumulative anticholinergic use is associated with a higher risk for incident dementia. The most common anticholinergic classes used were tricyclic antidepressants, first-generation antihistamines, and bladder antimuscarinics. During a mean follow-up of 7.3 years, 797 participants (23.2%) developed dementia and 637 (79.9%) of these developed Alzheimer's disease. A 10-year cumulative dose-response relationship was observed for dementia (test for trend, $P < 0.001$); a similar pattern of results was noted for Alzheimer's disease. Results were robust in secondary, sensitivity, and post hoc analyses. This review demonstrated that cumulative anticholinergic use is associated with a higher risk for incident dementia.[10]

A systematic review and meta-analysis by Ruxton and colleagues examined the evidence of cognitive impairment, falls and mortality from drugs with anticholinergic effects.[11] The authors included 18 studies (n=124,286) in the systematic review, with the results of 11 studies included in the meta-analysis. The majority of the studies were of people aged 65 years and over and were conducted in Europe (n=12), the USA (n=4), Canada (n=1) and Australia (n=1). Follow-up ranged from one month to six years. The systematic review found that the individual studies had conflicting results on the effects of drugs with anticholinergic effects as a class. Meta-analysis of three studies showed that exposure to drugs with anticholinergic effects as a class was associated with a significant increase in cognitive impairment (odds ratio [OR]=1.45, 95% confidence interval [95% CI] 1.16 to 1.73). Details of risks associated with specific drugs were not reported. Four studies that assessed risk of falls were included in the meta-analysis, which examined the effects of five drugs; amitriptyline, olanzapine, paroxetine, risperidone and trazodone. The risk of falling was significantly increased with olanzapine (OR=2.16, 95% CI 1.05 to 4.44) and trazodone (relative risk [RR]=1.79, 95% CI 1.60 to 1.97), with some heterogeneity (I2) present in the trazodone analysis (I2=28.2%). Exposure to amitriptyline, paroxetine and risperidone was not associated with an increased risk of falls.[11]

Ruxton et al did report on all-cause mortality relative to the ACB score. This analysis showed a significant association between ACB scale and all-cause mortality, with an increase of 1 point on the scale approximately doubling risk (OR=2.06, 95% CI 1.82 to 2.33).

This study has a number of limitations. The majority of studies included were observational, with only two randomised controlled trials included, one of which was available only as an abstract. Significant heterogeneity was observed in the meta-analysis of some drugs or scoring systems. Limited data were available on the relative risks associated with specific drugs, with results available for only five named drugs.[11]

An expert GP commentary from NICE states that the evidence is not very strong, but there does appear to be an association between some individual drugs and these harms. There also seems to be a correlation between overall anticholinergic burden and mortality. However it also states that that there is little evidence to show that using measures of anticholinergic burden to reduce exposure reduces the harm from these drugs.[1]

Anticholinergic burden scales

Various anticholinergic burden or risk scales have been devised to aid medication reviews so that certain drugs can either be stopped, or the medication regimen altered to reduce this burden.

However, there is no single standard anticholinergic burden scale to aid in conducting medication reviews in older or frail patients who take multiple medications. Most scales are constructed using expert opinion panels.[12] Further problems are that anticholinergic adverse effects increase with increasing

dose, and multiple low-level anticholinergic drugs can add up to the same anticholinergic burden (or more) as a single high-level anticholinergic.[13] The Drug Burden Index (DBI) attempts to resolve some of these problems, particularly by including dosage information and sedative drugs.[14] Different scales have been compared; however limitations include differences in exposure to medicines, dosing, route of administration and false positives.[15-18]

NHS Scotland polypharmacy guidance lists the Anticholinergic Risk Scale (ARS), which was developed using 500 most prescribed medications.[3,19] They also note that anticholinergic effects are dose dependent.[20] They ranked medication with anticholinergic potential on a scale of 0–3 (0: limited or none; 1: moderate; 2: strong; 3: very strong potential) based on information available on the dissociation constant for the muscarinic receptor and rates of anticholinergic adverse effects, i.e. based on in vitro data which may not always reflect in vivo effects.[19] The ARS has since been modified (subsequently referred to as mARS) and includes newer medications with anticholinergic properties that are available in the United Kingdom (see Appendix 1). Medications with moderate to severe anticholinergic effects according to other scales were added to the list.[16] Medications identified as having significant anticholinergic properties in the British National Formulary (BNF) were also included and medications not available in the UK were excluded. The table also lists therapeutic alternatives with no or minimal anticholinergic effects.[3]

Current recommendations on reviewing polypharmacy

NICE guidance on falls in older people (CG161) recommends that people who have had a fall or are at increased risk of falling should have their medication reviewed as part of a multifactorial risk assessment; psychotropic medications (including neuroleptics, sedatives, hypnotics and antidepressants) should be reviewed and if possible discontinued to reduce their risk of falling.[4]

The NICE guidance on dementia (CG42 currently being updated) recommends that a diagnosis of dementia should be made only after a comprehensive assessment, including a medication review to identify and minimise use of drugs that may adversely affect cognitive functioning.[5]

A NHS England dementia diagnosis and management resource for GPs recommends that drugs with strong anticholinergic activity such as tricyclic antidepressants (e.g. amitriptyline), older drugs for bladder problems (e.g. oxybutynin) and first generation antihistamines (promethazine, chlorpheniramine) should be stopped if possible or substituted for a drug with less anticholinergic activity.[21]

The Department of Health dementia toolkit also recommends to consider stopping or reducing anticholinergic drugs.[22]

The 2015 American Geriatric Society Beers Criteria for Potentially Inappropriate medication use in older patients strongly recommends to avoid anticholinergic drugs (based on moderate quality evidence).[23]

Table 1, on the following page, recommends anticholinergics and other drugs to be used with caution or avoided in dementia.[4,22,23] Further resources to aid the polypharmacy decision making process can be found at the end of the document.

Table 1: Anticholinergic drugs to be used with caution with potential actions[4,22,23]

Therapeutic area	Action
Antimuscarinics for bladder instability	Avoid if possible. Oxybutynin may cause acute confusional states in the elderly especially those with pre-existing cognitive impairment (may reduce MMSE in people with dementia). Do not offer oxybutynin (immediate release) to frail older women.[3] If an antimuscarinic is needed review continued need/effectiveness after 3 - 6 months.[3] See PrescQIPP bulletin 58 on urinary incontinence for further information on auditing and reviewing patients, https://www.prescqipp.info/urinary-incontinence/category/99-urinary-incontinence Mirabegron (β3-adrenoreceptor agonist) may be an option for treating symptoms of over active bladder (OAB) where antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects. Use in line with NICE TA290[24] and local policies.
Antiemetics	Domperidone and ondansetron preferred to cyclizine, metoclopramide, prochlorperazine (and other phenothiazines).[22]
First generation antihistamines	Brompheniramine, chlorphenamine, diphenhydramine, hydroxyzine, promethazine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine, promethazine, triprolidine are highly anticholinergic. Clearance reduced with advanced age and tolerance develops when used as a hypnotic; risk of confusion, dry mouth, constipation and other anticholinergic effects or toxicity. Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate. Avoid if possible. If not, loratadine and fexofenadine preferred to chlorpheniramine, promethazine, hydroxyzine.[23] If the patient has a dermatological problem, non-pharmacological measures, e.g. attention to washing powder, natural fabrics, reducing use of perfumed products etc. as well as proper use of emollients regularly and in sufficient quantity can make a difference.[3]
Antidepressants	Avoid tricyclic antidepressants especially with high antimuscarinic activity e.g. amitriptyline. SSRIs are associated with a reduced incidence of side effects in the elderly. Trial of gradual withdrawal should be attempted for all anti-depressants after 6 –12 months of initial treatment.[3]
Analgesics	Avoid tramadol and pethidine in particular.[22]
Sedatives	All sedatives to be used with caution – long acting benzodiazepines and anti-psychotics especially. Whilst complete withdrawal may not be an achievable goal there is still benefit to be gained in reducing use to the minimum effective dose. Avoid long acting benzodiazepines, e.g. nitrazepam. Newer hypnotics, e.g. zopiclone are associated with reduced hangover effects but all licensed for short-term use only.[3]

Therapeutic area	Action
Antipsychotics	Risk of hypotension is a dose related effect reduced by the 'start low go slow approach.' Atypical antipsychotics are associated with a similar falls risk to traditional ones. Attempted withdrawal MUST always be gradual to avoid precipitation of withdrawal symptoms, e.g. rebound agitation, etc. Prochlorperazine is frequently inappropriately prescribed for dizziness due to postural instability and the most frequently implicated drug causing drug induced Parkinson's disease.[3]
Antiparkinson	Benztropine, trihexyphenidyl: not recommended for prevention of extrapyramidal side effects with antipsychotics; more effective agents available for treatment of Parkinson's disease, e.g. procyclidine, orphenadrine.[23]
Antispasmodics	Hyoscine, dicyclomine, propantheline, atropine: highly anticholinergic; uncertain effectiveness.[23]

Actions

Identify older or frail people or people with complex multimorbidities on anticholinergic drugs.

Minimise the use of anticholinergic drugs where possible. If an older adult is prescribed an anticholinergic medication which has been assigned a score of 2 or 3, or if they are on a range of drugs that add up to an ACB score of 3 or more, then an informed decision should be made to either discontinue medication if there is no absolute need, or to switch to medication with a lower ACB score or from a different class.

Review at regular intervals for efficacy or tolerance.

Review medication in older people that have had a fall or are at increased risk of falling as part of a multifactorial risk assessment.

In patients with dementia:

- Perform a medication review to identify and minimize use of drugs that may adversely affect cognitive function.
- Avoid prescribing anticholinergics with acetylcholinesterase inhibitors.
- If there is a suspicion of anticholinergic induced impaired cognition, carry out a mini mental state examination (or equivalent) and consider switching or stopping if confirmed and clinically appropriate.

Use supportive polypharmacy resources (see below) to aid the decision making process.

Summary

- Systematic reviews and meta-analyses show that there appears to be some association between anticholinergic drugs and cognitive impairment, falls and mortality. Taken alongside the other known adverse effects of these drugs, it seems sensible to be cautious when prescribing any medication with anticholinergic effects. The current evidence supports using various anticholinergic risk scales and tools when reviewing treatments for older or frail people, or people with complex co-morbidities.

Useful resources that support the decision making process.

PrescQIPP IMPACT (Improving Medicines and Polypharmacy Appropriateness Clinical Tool) tool. March 2016
https://www.prescqipp.info/polypharmacy-impact/category/272-polypharmacy-impact

SIGN. Polypharmacy guidance. March 2015.
http://www.sign.ac.uk/pdf/polypharmacy_guidance.pdf

All Wales Medicines Strategy Group. Polypharmacy: Guidance for Prescribing. July 2014.
www.awmsg.org

All Wales Medicines Strategy Group. Polypharmacy: Guidance for Prescribing. Supplementary Guidance – BNF Sections to Target. July 2014.
www.awmsg.org

NHS Highland. Polypharmacy: Guidance for Prescribing In Frail Adults. June 3013.
www.nhshighland.scot.nhs.uk

NHS Cumbria STOPP START Toolkit Supporting Medication Review. February 2013.
www.cumbria.nhs.uk

Related PrescQIPP resources

Polypharmacy and deprescribing webkit
https://www.prescqipp.info/polypharmacy-deprescribing-webkit

IMPACT (Improving Medicines and Polypharmacy Appropriateness Clinical Tool) tool
https://www.prescqipp.info/polypharmacy-impact/category/272-polypharmacy-impact

Care homes webkit https://www.prescqipp.info/carehomes

Bulletin 87 Care homes: Medication and falls
https://www.prescqipp.info/care-homes-medication-and-falls/category/138-care-homes-medication-and-falls

Reducing antipsychotic prescribing in dementia toolkit
https://www.prescqipp.info/resources/category/109-reducing-antipsychotic-prescribing-in-dementia-toolkit

Bulletin 112. Care homes: Good practice guide to prescribing and medication reviews
https://www.prescqipp.info/care-homes-good-practice/category/231-care-homes-good-practice-guide

Urinary incontinence https://www.prescqipp.info/resources/viewcategory/224-urinary-incontinence

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Additional PrescQIPP resources

 Briefing

 Data pack

 Implementation resources

Available here: https://www.prescqipp.info/resources/category/294-anticholinergic-drugs

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