Anticholinergic side-effects and prescribing guidance

- **Anticholinergic (antimuscarinic) medications**: associated with increased risks of impaired cognition and falls in patients over the age of 65 years. Recent research also points to a link to mortality increasing with the number and potency of anticholinergic agents prescribed.
- **Anticholinergic Syndrome**: is a state of confusion with characteristic features related to dysfunction of the autonomic parasympathetic (cholinergic) nervous system. Symptoms classified into systemic and CNS manifestations:
    - ***Systemic (peripheral) symptoms***: Blurred vision, photophobia, non-reactive mydriasis, loss of accommodation response, flushed and dry skin, dry mouth, tachycardia, hypertension and fever. Gastrointestinal and urinary motility are frequently reduced
    - ***CNS symptoms:*** Delirium, agitation, disorientation, and visual hallucinations. Ataxia, choreoathetosis, myoclonus and seizures may also occur without peripheral symptoms.

Medication Issues: several commonly prescribed medications that may not be thought of as anticholinergic have significant anticholinergic effects, which when taken with known anticholinergic medication can increase the risk of adverse effects. Many medication groups e.g. antihistamines, tricyclic antidepressants, drugs for asthma and COPD, cold preparations, hyoscine have varying degrees of anticholinergic activity and have the potential to cause **Anticholinergic Syndrome**.

Clinicians should be aware of the risk for chronic anticholinergic toxicity and the fact that not all the symptoms may manifest in patients and if they do suffer some symptoms they could be wrongly attributed to another diagnosis

Evidence

- A study of patients over 65 found that 20% of participants who scored four or more had died by the end of the two year study period compared with 7% of patients with a score of zero.
- For every additional ACB point scored the risk of dying is increased by 26%.
- 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.
- Compared to those not taking anticholinergics, people taking drugs with definite anticholinergic effects had a 68% increased odds of dying by two years (odds ratio [OR] 1.68, 95% CI 1.30 to 2.16) & people taking drugs with possible anticholinergic effects had a 56% increased risk of dying (OR 1.56, 95% CI 1.36 to 1.79).

Current Recommendations on Reviewing Anticholinergics

- **NICE guidance on the management of urinary incontinence in women** (NICE NG123) states that when offering anticholinergic medicines to treat overactive bladder the current use of medicines that affect the total anticholinergic load should be taken into account, along with the risk of adverse effects including cognitive impairment. In addition it recommends that immediate release oxybutynin should not be offered to older women who are at higher risk of a sudden deterioration in their physical or mental health.
- **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.
- **NICE guidance on dementia** (NG97) recommends that people with suspected dementia are referred to a specialist dementia diagnostic service once reversible causes of cognitive decline have been investigated. These causes include: delirium, depression, sensory impairment [such as sight or hearing loss], or cognitive impairment from medicines associated with increased anticholinergic burden. As part of this process consider minimising the use of medicines associated with increased anticholinergic burden, and if possible look for alternatives.

Key Messages

- Try all suitable alternative non-pharmacological interventions before initiating anticholinergics.
- Ensure you are aware of the anticholinergic burden of drugs and cumulative anticholinergic effects of multiple drugs.
- Monitor patients for signs of anticholinergic syndrome.
- Identify older or frail people or people with complex multimorbidities on anticholinergic drugs. Minimise the use of anticholinergic drugs where possible.
- Review patient's treatment 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: identify and minimize use of drugs that may adversely affect cognitive function. Avoid prescribing anticholinergics with acetylcholinesterase inhibitors, and 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.

Considerations to optimise medicines use

- **H2 antagonists/PPIs**: check if there has been no proven peptic ulcer, GI bleeding or dyspepsia for 1 year. Continued use may contribute to C difficile infection.
- **Laxatives**: check if previous use of opioid analgesics has been reduced or stopped; if regular bowel movements are occurring without difficulty; if the patient is eating and drinking and has an adequate fluid intake. If more than one laxative is used, reduce and stop one at a time – reducing the stimulant laxative first and increasing the dose of the osmotic laxative if necessary.
- **Antihypertensives**: check if the BP is too low; if the risks outweigh the benefits stop one antihypertensive at a time – restart if BP increases above NICE target (140/90 for under 80 years, 150/90 for over 80 years).
- **ACEIs** in elevated vascular risk **NNT 280** and in impaired LV function **NNT 30** to prevent one death (all-cause mortality). ACEI plus indapamide **NNT 55** to prevent one stroke.
- **Nitrates**: check if the patient has had no chest pain for six months or has reduced mobility.
- **Lipid lowering drugs**: re-evaluate the patient risk profile; stop in metastatic disease. (It is impossible to give evidence based guidance on whether to continue or stop statins in the over 80s due to the paucity of trial data however in primary prevention they *may increase* all-cause mortality).
- **Aspirin**: if used in primary prevention re-evaluate need (massive NNT); query doses above 150mg for cardiovascular indication and its use in dizziness which is not clearly attributable to cerebrovascular disease. Post stroke/TIA **NNT 100** to prevent one stroke, MI or vascular death. Stopping aspirin prescribed for secondary prevention has **NNH 250**.
- **Dipyridamole**: Clopidogrel is now preferred over dipyridamole in ischaemic stroke and peripheral artery disease. However post stroke/TIA the combination of dipyridamole plus aspirin has similar NNT to clopidogrel **NNT 100** to prevent one vascular event.
- **Anticoagulants**: if started following hip or knee surgery are they still required? Consider if long term warfarin use is still required e.g. if VTE provoked by surgery, other trigger factors or below knee. Warfarin may be indicated e.g. in AF with another risk factor **NNT** with warfarin instead of aspirin **40** to prevent one stroke (no difference in mortality).
- **Benzodiazepines**: check if physical and psychological health and personal circumstances are stable and consider withdrawal which should be gradual.
- **Antipsychotics**: in dementia patients with BPSD review and discontinue unless there is extreme risk or distress for the patient. Standardised symptom evaluations and drug cessation attempts should be undertaken at regular intervals. Withdrawal after long term therapy should be gradual and closely monitored.
- **Antidepressants**: for a single episode of depression treat for six to nine months; for multiple episodes treat for at least two years; do not use dosulepin; consider ACB score and potential to worsen dementia, glaucoma, constipation and urinary retention; SSRIs can induce hyponatraemia; withdrawal should be gradual.
- **Drugs for dementia**: review according to NICE guidance – they can be continued if having a worthwhile effect.
- **Opioid analgesics**: check if pain is still severe enough to warrant a regular opioid as the risk of falls/constipation can outweigh the benefits; consider non-drug options e.g. regular paracetamol; review laxatives.

Anticholinergic Burden Scale: lists the anticholinergic activity of commonly prescribed drugs

A total score of 3 OR MORE in the ACB is considered clinically relevant: 70% chance of TWO or MORE adverse effects

The list below is NOT an exhaustive list and should be used as a guide

ACB Score 1		ACB Score 2	ACB Score 3	
Alimemazine Tartrate	Hydrocortisone	Amantadine	Amitriptyline	Olanzapine
Alprazolam	Isosorbide Dinitrate	Belladonna	Amoxapine	Orphenadrine
Alverine Citrate	Isosorbide Mononitrate	Carbamazepine	Atropine	Oxybutynin
Aripiprazole	Levocetirizine	Cyclobenzaprine	Brompheniramine	Paroxetine
Asenapine	Loperamide	Cyproheptadine	Carbinoxamine	Perphenazine
Atenolol	Loratadine	Loxapine Succinate	Chlorphenamine	Promethazine
Bupropion	Metoprolol	Nefopam Hydrochloride	Chlorpromazine	Propantheline
Captopril	Morphine	Oxcarbazepine	Clemastine	Propiverine
Cetirizine	Morphine/Cyclizine	Pimozide	Clomipramine	Quetiapine
Chlortalidone	Nifedipine		Clozapine	Solifenacin
Cimetidine	Paliperidone		Darifenacin	Thioridazine
Clorazepate dipotassium	Prednisolone		Desipramine	Tolterodine
Codeine Phosphate	Quinidine Bisulfate		Dicycloverine	Trifluoperazine
Colchicine	Quinidine Sulfate		Dimenhydrinate	Trihexyphenidyl
Desloratadine	Ranitidine		Diphenhydramine	Trimipramine
Diazepam	Risperidone		Doxepin	Trospium Chloride
Digoxin	Theophylline		Doxylamine/ pyridoxine	
Dipyridamole	Trazodone		Fesoterodine	
Disopyramide	Triamterene		Flavoxate	
Fentanyl	Venlafaxine		Hydroxyzine	
Fluvoxamine	Warfarin Sodium		Hyoscyamine Sulfate	
Furosemide			Imipramine	
Haloperidol			Methocarbamol	
Hydralazine			Nortriptyline	

References

- University of East Anglia, University of Cambridge and other institution in the US and UK: http://www.academia.edu/1881491/Anticholinergic_medication_use_and_cognitive_impairment_in_the_older_population_The_Medical_Research_Council_Cognitive_Function_and_Ageing_Study[1]
- NHS Scotland Polypharmacy Guidance – Medicines Review: http://www.polypharmacy.scot.nhs.uk/polypharmacy-guidance-medicines-review/for-healthcare-professionals/hot-topics/anticholinergics/
- Polypharmacy Guidance Realistic Prescribing 3rd Edition 2018 https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/04/Polypharmacy-Guidance-2018.pdf
- Anticholinergic Cognitive Burden Scale, Medicines Optimisation Polypharmacy Prescribing Comparators July 2017 https://www.nhsbsa.nhs.uk/sites/default/files/201802/PolyPharmacy%20Specification%20v1%200%20July%202017_0.pdf
- NICE NG123 April 2019 'Urinary incontinence and Pelvic organ prolapse in women' https://www.nice.org.uk/guidance/ng123 section 1.4.26-1.4.29
- NICE CG161 June 13 'Falls in older people assessing risk and prevention ' https://www.nice.org.uk/guidance/cg161
- NICE NG97 June 18 'Dementia: assessment, management and support for people living with dementia & their carers https://www.nice.org.uk/guidance/ng97 section 1.2.1-1.2.8 and section 1.6

Document History	Consultation Process	Amendments
Produced by West Essex Medicines Management Team	MOPB October 2018	
Version 2.0 Medicines Management Team at West Essex CCG	MOPB January 2020	NICE guidance updates incorporated Jan 2020 ePACT2 ACB scale incorporated Jan 2020