Mederev Clinical & Research Update – November 2021

Potentially inappropriate medications (PIMs): frequency and extent of GP-related variation in PIMs: a register-based cohort study

Potentially inappropriate medications (PIMs) pose an increasing challenge in the ageing population. This nationwide study in Denmark aimed to assess the extent of PIMs and the prescriber-related variation in PIM prevalence.

The complexity of managing multiple concurrent chronic conditions challenges modern healthcare. Multimorbidity may require polypharmaceutical treatment (>5 medications),[3] and this holds a risk of both undertreatment and overtreatment.[4] Potentially inappropriate medications (PIMs)[5] can be defined as medications in which the risks of use are likely to outweigh the benefits, or safer alternatives exist, and PIMs can thus serve as a proxy for overtreatment.[5–7] PIMs are common in older individuals. The prevalence ranges from 21% to 79% in different healthcare contexts, such as hospitals and general practice,[8–10] and PIMs may have serious consequences for the individual in terms of lower quality of life, higher risk of emergency visits and higher number of hospital admissions.[8 11] Moreover, PIMs may generate substantial financial costs for both the individual and society.[4]

The most prevalent PIM criteria were: 1. Beta blocker with bradycardia or heart block, 2. Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, 3. Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors, 4. Long-term use of benzodiazepines defined as use of more than 90 DDDs within 6 months, 5. Anticholinergics in patients with delirium or dementia, 6. Long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) defined as use of more than 90 DDDs within 6 months and concomitant use of two or more drugs with anticholinergic properties.

Implications for Practice

- PIMs can be identified through the formal STOPP criteria for potentially inappropriate drugs, drug–drug combinations and drug–disease combinations that are included in the second version of the validated STOPP/START list, which was developed by O'Mahony and colleagues.[26]
- Barriers for deprescribing PIMs can be caused by patient-related factors, provider-related factors and the organisational, structural and sociocultural context..
- Long-term use of NSAIDs and benzodiazepines were Identified as the most prevalent PIMs with the most pronounced GP-related variations.
- RMMRs can be utilised to identify polypharmacy, PIMs and develop deprescribing plans.

BMJ Open. 2021; 11(7): e046756. Original research: Potentially inappropriate medications (PIMs): frequency and extent of GP-related variation in PIMs: a register-based cohort study (nih.gov)

Use of bladder antimuscarinics is associated with an increased risk of dementia: a retrospective population-based case–control study

This study used data from the Taiwan National Health Insurance Research Database to determine the association between the exposure dose and duration of bladder antimuscarinics and the subsequent dementia risk in participants aged 55 years or more and defined a dementia cohort.

Dementia risk was evaluated with respect to the exposure dose and duration of treatment with seven bladder antimuscarinics (oxybutynin, propiverine, tolterodine, solifenacin, trospium, darifenacin, and fesoterodine) used for at least 1 year before the index date, after adjusting for age, sex, comorbidities, and medications.
There are five subtypes (M_1–M_5) of muscarinic ACh receptors, and the M2 and M3 muscarinic Ach receptors are the major receptors that mediate smooth muscle contraction, proliferation, and remodelling of the bladder[17,18]. In contrast, evidence from recent post-mortem human brain studies have implicated the involvement of the M_1 muscarinic Ach receptors in various psychiatric disorders[19,20]. Some studies have further demonstrated the dominant functional distribution of the M_1 muscarinic receptors for ACh uptake in the human brain[21,22]

The study results implied that bladder antimuscarinics might possibly produce subtle effects on M_1 activity, in addition to their known antagonistic effects on the M_2 and M_3 receptors. Because of the potential effect of bladder

antimuscarinics on the M1 muscarinic receptor, bladder antimuscarinics has been supposed to cause dementia development.

Implications for Practice

- Long term use of bladder antimuscarinic drugs has been supposed to cause dementia development.
- The positive association that observed in the study between bladder antimuscarinics and dementia risk should be considered a part of numerous factors involved in dementia patho-mechanism.
- A medication review may enable the assessment of efficacy for antimuscarinic medications with potential for deprescribing when eficacy is low.

Sci Rep. 2021; 11: 4827. Use of bladder antimuscarinics is associated with an increased risk of dementia: a retrospective population-based case–control study (nih.gov)

Treatment of Parkinson's Disease with Cognitive Impairment: Current Approaches and Future Directions

Cognitive impairment risk in Parkinson's disease increases with disease progression and poses a significant burden to the patients, their families and society. There are no disease-modifying therapies or preventative measures for Parkinson's disease mild cognitive impairment (PD-MCI), or Parkinson's disease dementia (PDD). This article reviews current and previously investigated treatments and those under investigation, including pharmacologic, non-pharmacologic and surgical procedures.

There are currently no effective pharmacologic or non-pharmacologic treatments for PD-MCI. The only recommended treatment for PDD currently is rivastigmine, a cholinesterase inhibitor. Donepezil and galantamine—other cholinesterase inhibitors—are possibly useful. Memantine, a N-methyl-D-aspartate (NMDA) receptor antagonist, is considered investigational in PDD. Drug repurposing (atomoxetine, levodopa, insulin, atomoxetine for PD-MCI; ambroxol and ceftriaxone for PDD) and novel medications (SYN120, GRF6021, NYX-458 for PD-MCI; ANAVEX2-73, LY3154207, ENT-01, DAAOI-P for PDD) currently have insufficient evidence.

PD-MCI is present in 25–30% of persons with PD without dementia [1] and it increases the relative risk of dementia compared to those with PD without MCI (relative risk of 39.2 at 3 years) [2]. At 5 years, the risk of dementia is 6.5 times higher in individuals with PD-MCI, independent of sex, age, years of education and motor function [3]. Dementia is present in 24–31% of persons with PD [2,4]. The risk of dementia in persons with PD is 4 to 6 times higher than healthy individuals matched for age, sex, and education [5]. At least 75% of persons with PD who survive more than 10 years develop dementia [5].
Neurotransmitters implicated in cognitive changes and psychosis in PD include dopamine, serotonin, norepinephrine, acetylcholine, and N-methyl-D-aspartate (NMDA).

Treating cognitive changes in PD starts with an assessment for potentially reversible contributors to cognitive changes. Major pharmacologic culprits are anticholinergic medications (e.g., antihistamines, antispasmodics), benzodiazepines, and opioids. Medications used to treat motor symptoms in PD can also contribute to cognitive symptoms. In the context of cognitive complaints, the general order in which PD medications are discontinued is as follows: anticholinergics, MAO-B inhibitors, amantadine, dopamine agonists, and COMT inhibitors, followed by reduced levodopa [19].

Implications for Practice

- Utilise medication reviews to identify medications contributing to cognitive impairment.
- Consider deprescribing anticholinergic medications, benzodiazepines and opioids.
- Consider review of PD medications when cognitive changes are apparent.
- Rivastigmine is recommended for PDD. Donepezil and galantamine are possibly useful.
- Case-conferencing between GP, Facility Clinical Managers and Mederev Clinical Pharmacist can assist with medication management and deprescribing plans.
- Clinicians should recommend exercise, especially the aerobic type, for individuals with PD and cognitive impairment.

Behav Sci (Basel). 2021 Apr; 11(4): 54. Treatment of Parkinson's Disease with Cognitive Impairment: Current Approaches and Future Directions (nih.gov)