

2023 - Pros and Cons in General Internal Medicine and Geriatrics

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The demographic shift and the physical activity

By 2024, it is estimated that the population of individuals aged over 65 years will outnumber those under the age of 15 in the WHO European Region. This trend means new social, economic and health challenges, which demand a focus on ageing better. The new WHO report underscores the key role of physical activity and diet quality as pivotal factors influencing the health of individuals (1). Physical activity and healthy diets throughout the lifespan can help prevent non-communicable diseases (NCDs), such as cardiovascular diseases, cancer, diabetes, dementia, and mental health issues, the core of general medicine, internal medicine, and geriatrics. The WHO report identifies 3 key takeaways for older adults for health maintenance: a) diets high in fruits and vegetables and low in ultra-processed foods high in sugar, salt and saturated fats. The Mediterranean diet is a good example; b) a minimum of 150 minutes per week of moderate physical activity to reduce the risk of all-cause mortality by 28%. Additional activities that maintain balance and mobility and reduce loss of muscle mass and bone density are recommended, and engaging in even higher levels of physical activity can reduce the risk of all-cause mortality by 35%. Policy-makers are responsible for providing health surveillance systems in all countries to enhance the development of better policies.

There is a lack of good data to suggest a limit to the amount or intensity of exercise that may harm health. However, it should also be noted that certain sports activities may increase the risk of injury, especially during the activity. Finally, as overuse muscle

strain is the most common complaint amongst previously sedentary older adults following exercise intervention, new subjects ready to start exercise should be educated about what to expect and what types of pain are normal (2,3).

Artificial intelligence (AI)

AI is increasingly used in medicine to improve the diagnosis and treatment of diseases and to avoid unnecessary patient screening. But AI medical devices could also harm patients and worsen health inequities if not designed, tested, and used with care. Clinicians must be actively engaged in iterative communication with AI developers to ensure models align with medical ethics and context. Ensuring the fairness of AI requires collaboration between experts across disciplines. While AI has demonstrated potential for healthcare insights, concerns around bias remain. A fair model is expected to perform equally well across subgroups like age, gender and race. Patient preferences and prognosis are crucial considerations, as equal treatment does not always mean fair treatment. An example is age, which frequently factors into treatment decisions and outcomes. Despite extensive developments in AI methodologies, it remains challenging to translate them into actual clinical practice due to the nature of healthcare, which involves biological, ethical and social considerations. Clinicians, policymakers, sociologists and industry experts must work together and take active steps towards addressing fairness in AI. The future of medical education will differ from the traditional approach in many ways, and widespread integra-

tion of AI technology will be substantial. While these technologies will continue to evolve and improve, it is already clear that medical education can benefit from their potential to enhance learning outcomes, improve patient care, and transform medical practice (4).

Machine learning boosts drug discovery

Researchers collaborated with industry and supercomputers to carry out one of the world's largest virtual drug screens. By doing so, they boosted virtual screening with machine learning, enabling a 10-fold time reduction in the processing of 1.56 billion drug-like molecules. In their efforts to find novel drug molecules, researchers often rely on fast computer-aided screening of large compound libraries to identify agents that can block a drug target. The size of these collections of small organic molecules has seen a massive surge over the past years.

With libraries growing faster than the speed of the computers needed to process them, the screening of a modern billion-scale compound library against only a single drug target can take several months or years – even when using state-of-the-art supercomputers. Therefore, quite evidently, faster approaches are desperately needed. Studies on a comparable scale remain elusive in most settings.

Thus, the authors released large datasets generated as part of the study into the public domain: Their ready-to-use screening library for docking that enables others to speed up their respective screening efforts and their entire 1.56 billion compound-docking results for two targets as benchmarking data. This data will encourage the future development of tools to save time and resources and will ultimately advance the field of computational drug discovery (5).

Shifting the pain management paradigm

Pain is a complex and multifaceted biomechanism that is experienced differently by each person, a crucial sensation for survival, and it can also lead to depression and long-term suffering if not managed correctly. Alarming, chronic pain affects more than 30 per cent of people worldwide. A person's perception of pain is unique and influenced by various factors, including

genetics, past experiences, and emotional state. Pain can destroy a person's quality of life for prolonged periods. Psychosocial elements (such as mood, stress levels, and support systems) also shape how a person perceives and copes with pain. This complexity of factors has plagued healthcare professionals for a long time, making chronic pain treatment incredibly challenging. Traditional therapies offer temporary relief, but long-term use can lead to dependence and addiction. Clinicians are, therefore, looking for alternative treatments while also seeing the benefits of taking a more holistic approach to the pain management paradigm.

Neuroplastic changes can heighten the sensitivity of the body's pain-processing nerves; even minor threats to the body can trigger pain, amplifying these nerve signals and resulting in disproportionate levels of pain relative to the actual harm. Researchers translated some ground-breaking concepts from neuroscience into tangible solutions to train the body's natural ability to regulate pain by enhancing the neural circuits that naturally turn down the volume of pain-related nerve signals sent to the brain. This transdiagnostic pain management, looking at mechanisms that are common across different types of chronic pain, could help to meet the dire need for novel therapies for neuropathic pain (including fibromyalgia, complex regional pain syndrome, and phantom limb pain) where current treatments are largely ineffective or insufficient.

Various conditions display an overlap with neuroplasticity in the nervous system, and engaging in numerous repetitions of therapeutic tasks can help address the maladaptive neuroplastic changes and promote healthier alterations in the nervous system. To this end, a solution harnesses sensory perception tasks, delivered through video games, to provide the necessary engagement and ensure that patients participate for sufficient time to benefit from the intersection of pharma and digital health. This could lead to novel treatment options for patients with chronic pain, potentially reducing the reliance on opioids.

Chronic musculoskeletal pain (CMP)

CPM is prevalent and undertreated in older adults and is associated with serious functional consequences: cognitive problems, mobility decline, fear of

falling, falls, and reduced participation in life roles. A few pharmacologic approaches are safe and effective for older adults with CMP, and evidence for the effectiveness of non-pharmacologic treatments for this common condition is very limited. Compared to light physical exercise, mind-body exercise may prove to be more beneficial for older adults living with CMP.

Tai Chi, as a movement-based mind-body exercise, can relieve pain symptoms, improve cognition and physical function, and lower the risk for falls in older adults. Future large-scale randomized-controlled trials are needed to investigate the effectiveness of Tai Chi in alleviating pain and lowering risk in older adults. Although there is no silver bullet, neuroplasticity training is now an additional tool in the clinician's armamentarium, allowing them to not only reach for their pharmacopeia but also turn to technology to help improve the lives of their patients in pain. Pain management requires a thorough assessment of the pain per the patient report, which entails the explication of an accurate pain history and the performance of a physical examination of the patient experiencing pain. The pain management plan should be tailored to the patient's needs. Interventions recommended to manage pain necessitate evidence-based practice.

Pulsed-field ablation (PFA)

PFA is as effective and safe as conventional thermal ablation for treating paroxysmal atrial fibrillation (AF), according to research presented at ESC Congress 2023. Guidelines recommend catheter ablation after failure of drug therapy in patients with paroxysmal AF.

Conventional ablation technology uses thermal energy (either heat/radiofrequency energy or cold/cryothermal energy) to ablate the tissue. Unlike thermal ablation, PFA uses high-energy electrical pulses to destroy tissue through electroporation.

Preclinical and clinical studies have demonstrated that PFA seems to preferentially ablate the heart tissue, with minimal or no damage to surrounding structures such as the oesophagus and phrenic nerve, as well as no pulmonary vein stenosis, all complications that can occur with conventional thermal ablation (8).

Chronic Obstructive Pulmonary Disease (COPD)

Exacerbations and Pneumonia Hospitalizations Among New Users of Combination Maintenance Inhalers. Clinical guidelines on COPD recommend inhalers containing long-acting muscarinic antagonists (LAMAs) and long-acting β -agonists (LABAs) over inhalers containing inhaled corticosteroids (ICSs) and LABAs. However, data from randomized clinical trials comparing these combination inhalers (LAMA-LABAs vs IC-LABAs) have been conflicting and raised concerns of generalizability.

A cohort study evaluated combination LAMA-LABA inhalers (aclidinium-formoterol, glycopyrronium-formoterol, glycopyrronium-indacaterol, tiotropium-olodaterol, orumeclidinium-vilanterol) and combination ICS-LABA inhalers (budesonide-formoterol, fluticasone-salmeterol, fluticasone-vilanterol, or mometasone-formoterol). The primary effectiveness outcome was first moderate or severe COPD exacerbation, and the primary safety outcome was first pneumonia hospitalization. Among 137 833 patients (mean age: 70.2 ± 9.9 years; 69 530 females - 50.4%). Compared with ICS-LABA use, LAMA-LABA use was associated with an 8% reduction in the rate of first moderate or severe COPD exacerbation and a 20% reduction in the rate of first pneumonia hospitalization.

These findings were robust across a range of pre-specified subgroups and sensitivity analyses. In conclusion, LAMA-LABA therapy was associated with improved clinical outcomes compared with ICS-LABA therapy, suggesting that LAMA-LABA therapy should be preferred for patients with COPD (9).

Corticosteroids in the septic shock

Trials and study-level meta-analyses have failed to resolve the role of corticosteroids in the management of patients with septic shock. compared with a placebo was not associated with reduced mortality for patients with septic shock (10).

Vibrating capsule for treating patients with chronic idiopathic constipation

Vibrating capsule contains a computer chip pro-

grammed to make the capsule vibrate in cycles, starting about 15 hours after being swallowed, when the capsule presumably has reached the colon. The premise is that the capsule's mechanical stimulation of the colonic wall augments natural colonic contractility.

The industry-sponsored clinical trial that led to FDA approval involved 312 patients who had chronic idiopathic constipation (1–2.5 spontaneous bowel movements weekly) and inadequate response to standard treatments. Participants were randomized to swallow single use vibrating capsules or placebo capsules 5 nights weekly for 8 weeks. The proportion of patients with an increase of 1 or more complete spontaneous bowel movements weekly was significantly higher with the vibrating capsule than with placebo (39% vs. 22%). For an increase of 2 or more spontaneous bowel movements weekly, the proportions in the two groups were 23% and 11%, respectively. Measures of straining and stool consistency also favoured active therapy.

No major adverse effects were reported.

For the numerical endpoints described above, roughly 6 to 8 patients would need to be treated to benefit 1 patient; and we don't know this treatment's efficacy beyond 8 weeks.

The cost is high, and notably, a recent multisociety guideline on chronic idiopathic constipation doesn't mention the vibrating capsule, so its precise role and appropriateness, particularly in older subjects in whom constipation is a frequent problem, remains to be determined and validated (11).

Benign Prostatic Obstruction (BPO)

BPO is the most common non-malignant urological condition among men, and its incidence rises with age.

Among prostate treatments, GreenLight laser seems to reduce bleeding and would be safer in the ageing population. Functional outcomes and safety profile of <75 years old (Group A) and ≥75 years old (Group B) patients were compared.

In a multicenter setting, retrospectively analyzing all the patients treated with Greenlight Laser vaporization of the prostate (PVP). Focusing on complications, GreenLight laser PVP demonstrated an excellent safe-

ty profile in terms of hospital stay, re-intervention and complications, with an overall 29.6% complication rate in older patients and only two cases of Clarien III. Functional outcomes were similar at 12 months and became in favour of Group A over time.

These data are satisfactory, and the Authors conclude that Greenlight laser photoselective vaporization of the prostate is a safe and efficient procedure for all patients, despite their age, with comparable outcomes and an equal safety profile (12).

Prostate cancer screening

Prostate cancer screening has led to significant decreases in the diagnosis of advanced disease and prostate cancer-specific mortality. However, the cost of the disease has included overdiagnosis of clinically insignificant cancers. Health organizations and oncology societies have developed clinical practice guidelines to facilitate standardized and optimal patient care. Compliance with guidelines has been considered a surrogate for quality cancer care and helps to identify gaps and areas for quality improvement.

Guidelines provide recommendations based on the best evidence available and on expert consensus, are updated annually and revised whenever necessary to reflect new data that may alter clinical practice standards and provide recommendations for early detection and evaluation that seek to avoid overdiagnosis and overtreatment with associated unnecessary adverse effects and long-term quality-of-life effects. All clinicians have to treat patients according to best evidence (13).

Patient frailty

Patient frailty is a known risk factor for adverse outcomes following surgery, but data are limited regarding whether systemwide interventions related to frailty are associated with improved outcomes in patients undergoing surgery.

A retrospective cohort study identified geriatric patients (age ≥65 years) undergoing an emergency general surgery procedure within 48 hours of admission stratified by the procedural risk. Increasing levels of frailty in geriatric emergency general surgery pa-

tients are associated with higher levels of postoperative complications, failure to rescue, and readmission. In elective surgery, implementing a Frailty Screening Initiative using the Risk Analysis Index linked to an electronic health record alert was associated with significantly reduced systemwide, 1-year postoperative mortality from 3.9% to 3.3%. In frail patients, 1-year mortality decreased significantly from 20.2% to 16.0%.

These findings indicate the validity of routine frailty screening as a method for improving outcomes in all surgical patients. In conclusion, increasing levels of frailty in geriatric emergency general and elective surgery patients are associated with higher levels of postoperative complications, failure to rescue, and readmission. Clinicians should consider frailty in assessing the risk of even low-risk surgeries in this population (14,15).

What Strength Flu Vaccine for Older Adults?

High-dose influenza vaccine is recommended for adults older than 65, but the supporting data are relatively weak, consisting largely of findings from small observational studies and meta-analyses.

A sufficiently powered randomized trial would require tens of thousands of participants; and be very expensive. Danish researchers decided to see if their national health registry might supply enough clinical information to make such a trial feasible. In an industry-supported pilot project conducted during the 2021–2022 flu season, they randomized more than 12,000 Danish adults (65–79 old) to receive either standard-dose or high-dose quadrivalent vaccine. All clinical data were retrieved successfully from the national health registry. Receipt of the high-dose vaccine was associated with a significantly lower likelihood of hospitalization for influenza or pneumonia (0.2% vs. 0.4%) and significantly lower all-cause mortality (0.3% vs. 0.7%).

Incidence of other postvaccine clinical events was similar between groups, as were vaccine-associated adverse events.

Studies of high-dose vaccines invariably end with a call for bigger, better studies. Meanwhile, yet more imperfect data favours the high-dose product (16).

Benefit from cardiac resynchronization therapy (CRT)

CRT varies by QRS characteristics. The patient-level data from pivotal CRT trials have documented that CRT is associated with reduced heart failure hospitalization (HFH) or death in patients with QRS ≥ 150 ms and LBBB or IVCD, but not for those with RBBB. When selecting patients for cardiac resynchronization therapy (CRT), aggregating right bundle branch block (RBBB) and intraventricular conduction delay (IVCD) into a single “non- left bundle branch block (LBBB)”, category should be reconsidered (17).

Bradycardia prevalence and prognostic significance

Bradycardia in persons screened for atrial fibrillation (AF) using an implantable loop recorder (ILR) were compared with unscreened persons. There is increasing interest in heart rhythm monitoring and technologies to detect subclinical AF, which may lead to an incidental diagnosis of bradycardias.

In Diederichsen et al study (18) ILR screening led to a 6-fold increase in bradycardia diagnoses and a significant increase in pacemaker implantations compared with usual care but no change in the risk of syncope or sudden death. Authors conclude: please, don't place a pacemaker for asymptomatic bradycardia!

SARS-CoV-2 infection

SARS-CoV-2 infection is believed to increase risk for several medical conditions long after acute illness. Such post-COVID-19 conditions (PCCs) involve multiple organ systems, including pulmonary, cardiovascular, cerebrovascular, thromboembolic, neurocognitive, mental health, metabolic, renal, and gastrointestinal disorders.

The COVID-19 pandemic sparked an urgent search for treatments to prevent disease progression. Several effective monoclonal antibodies were quickly developed for outpatients, but limited information is available on the effectiveness of oral antivirals used to treat acute COVID-19 in preventing the development of PCCs.

The protease inhibitor nirmatrelvir–ritonavir (N-R) became the first oral COVID-19 treatment. A large phase 3 randomized clinical trial and observational studies demonstrated N-R's clinical and virologic benefits with minimal adverse events. However, with broader use, many reports have suggested that N-R leads to the rebound of infection even more often than was initially reported. The rebound was most common among older and immunosuppressed patients and, paradoxically, among those who had received more vaccine doses (vaccination per se did not reliably prevent rebound). An intriguing finding is that rebound was more frequent with earlier than delayed treatment.

In summary, results demonstrate that the COVID-19 rebound is observed at an increased but unpredictable rate in patients receiving N-R. Further consideration of the dosage, timing, and duration of treatment with N-R is essential to inform optimal use of this drug.

A retrospective target trial emulation study comparing matched cohorts receiving N-R versus no treatment was carried out in non-hospitalized Veterans Health Administration care, patients who were at risk for severe COVID-19 and tested positive for SARS-CoV-2. Eighty-six per cent of the participants were male, with a median age of 66 years, and 17.5% were unvaccinated. Baseline characteristics were well balanced between participants treated with N-R and matched untreated comparators. No differences were observed between participants treated with N-R and their matched untreated comparators in the incidence of most PCCs examined individually or grouped by organ system, except for lower combined risk for venous thromboembolism and pulmonary embolism. Out of 31 potential PCCs, only combined thromboembolic events seemed to be reduced by N-R.

The Authors concluded that ascertainment of PCCs using International Classification of Diseases codes may be inaccurate, and valuation of many outcomes could have resulted in spurious associations with combined thromboembolic events by chance. These concerns suggest that the decision to use N-R is not straightforward and demands exploration of improved COVID-19 treatment management strategies and/or alternative oral therapies (19- 21).

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