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REVISIÓN BIBLIOGRÁFICA NOVIEMBRE 2021: Selección de artículos

REVISTAS FARMACÉUTICAS

Drug Safety

Safety of Eslicarbazepine Acetate in Elderly Versus Non-Elderly Patients with Focal Seizures: From Pooled Data of Clinical Studies to 8 Years of Post-Marketing Experience

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Introduction
The prevalence of epilepsy increases in elderly patients aged > 65 years, and treatment is challenging because clinical data are limited.

Objective
Our objective was to evaluate the safety of eslicarbazepine acetate (ESL) in patients aged ≥ 65 years versus non-elderly patients with focal seizures.

Methods
The safety data of seven phase II and III, double-blind, open-label, randomized clinical studies of ESL in adults were pooled. At least possibly related treatmentemergent adverse events (TEAEs) and ESL post-marketing adverse drug reactions (ADRs) were analyzed separately by age categories.

Results
The most frequently reported at least possibly related TEAEs in elderly (N = 120) versus non-elderly patients (N = 1863) were dizziness (10.8 vs. 20.3%), somnolence (9.2 vs. 12.6%), and hyponatremia (6.7 vs. 1.5%). Elderly patients presented a higher incidence of serious TEAEs (22.5 vs. 7.6%) and at least possibly related serious TEAEs (6.7 vs. 2.5%), probably because treatment was complicated by comorbidities and comedications. After an estimated cumulative exposure of over 2 million patient-months worldwide and 8 years of post-marketing surveillance, hyponatremia was the most frequently reported ADR (n = 232), accounting for 14.6% and 6.8% of the ADRs reported in elderly (n = 473) and non-elderly patients (n = 2406), respectively. This was followed by ADR/safety information such as drug–dose titration not performed (7.0 vs. 5.4%), product use in

unapproved indication (4.9 vs. 1.9%), off-label use (3.4 vs. 2.2%), dizziness (3.4 vs. 3.5%), and seizure (2.1 vs. 5.8%).

Conclusion
No specific safety issue was identified from the pooled studies for elderly compared with non-elderly patients. After 8 years of post-marketing surveillance, the qualitative safety of ESL remains similar to that observed in the clinical studies.

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Pharmacoepidemiology and Drug Safety

Trends in benzodiazepine and alternative hypnotic use in relation with multimorbidity among older adults in Quebec, Canada

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Abstract
Background

Benzodiazepines and other hypnotic alternatives are associated with increased risks of adverse events. Heightened awareness of risks may have changed prescribing habits over the years. However, these trends are not fully described, especially in vulnerable people such as multimorbid older adults.

Objective
We aimed to describe the annual prevalence of benzodiazepine and other hypnotic use in relation to multimorbidity among older adults in the province of Quebec, Canada, from 2000 to 2016.

Method
We conducted a population-based study using the Quebec Integrated Chronic Disease Surveillance System. We included all individuals aged ≥ 66 years covered by the public drug plan. For each year, we evaluated the sex- and age-standardized proportion of benzodiazepine and other hypnotic users, defined as individuals with at least one drug claim in the year. We stratified our results according to multimorbidity and used log-binomial regression to study trends.

Results
The proportion of individuals using benzodiazepines decreased from 34.8% in 2000 to 24.8% in 2016 (p for trend < 0.001). Multimorbid people (≥ two chronic diseases) remained the highest users over the years, with 43.3% and 30.6% of them being users in 2000 and 2016, respectively. Conversely, the proportion of users increased for other

hypnotics, particularly for trazodone and quetiapine, rising from 5.4% to 8.4% (p<0.001), and especially among multimorbid individuals (from 7.4% to 11.6%).

Conclusion
Older adults used benzodiazepines less frequently but quetiapine and trazodone more frequently in recent years. The use of these medications, particularly in multimorbid people at risk of adverse events, must be addressed.

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Patient characteristics and safety outcomes in new users of ticagrelor and clopidogrel - An observational cohort study in Sweden

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Abstract
Purpose

We aimed to describe characteristics of new users of ticagrelor or clopidogrel following a recent coronary event, and to compare incidences of selected safety outcomes.

Methods
This observational cohort study used data from national Swedish registers. Patients first dispensed ticagrelor or clopidogrel (June 2011–December 2013) were identified from the Prescribed Drug Register and followed until censoring or 31 December 2014. Cohorts were restricted to patients with a recent coronary event-related hospital contact identified in the Patient Register.

Results
The study included 45 987 unique, naïve users of ticagrelor (73% men; mean age 66 years) or clopidogrel (69% men; mean age 69 years). Corresponding to indication, diagnoses before initiation were acute coronary syndrome (93%), myocardial infarction (76%), and percutaneous coronary intervention (69%). The most common medications used in the year before initiation of study therapy were antithrombotic agents (clopidogrel 62%, ticagrelor 43%), mainly low-dose acetylsalicylic acid. Ticagrelor users had a higher incidence (per 1000 person-years) of respiratory bleeding (24.6 [95% confidence interval (CI): 22.1–27.3]; vs clopidogrel users: 14.4 [13.1–15.8]) and dyspnea (25.9 [23.3−28.7]; vs clopidogrel users: 16.8 [15.4–18.4]). Epistaxis accounted for 83–93% of respiratory bleeds. Adjusted analyses found increased risks of gout and acute renal failure with ticagrelor.

Conclusions
Clopidogrel users were older with a higher prevalence of concomitant medications than ticagrelor users. Our study showed increased incidences of dyspnea and respiratory bleeding (mainly epistaxis) among current ticagrelor users compared with clopidogrel users, and increased risks of gout and acute renal failure after adjustment.

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Clinical Pharmacology & Therapeutics

An Interprofessional Student-Run Medication Review Program: The Clinical STOPP/START-Based Outcomes of a Controlled Clinical Trial in a Geriatric Outpatient Clinic

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Abstract

As the population ages, more people will have comorbid disorders and polypharmacy. Medication should be reviewed regularly in order to avoid adverse drug reactions and medication-related hospital visits, but this is often not done. As part of our student-run clinic project, we investigated whether an interprofessional student-run medication review program (ISP) added to standard care at a geriatric outpatient clinic leads to better prescribing. In this controlled clinical trial, patients visiting a memory outpatient clinic were allocated to standard care (control group) or standard care plus the ISP team (intervention group). The medications of all patients were reviewed by a review panel ("gold standard"), resident, and in the intervention arm also by an ISP team consisting of a group of students from the medicine and pharmacy faculties and students from the higher education school of nursing for advanced nursing practice. For both groups, the number of STOPP/START-based medication changes mentioned in general practitioner (GP) correspondence and the implementation of these changes about 6 weeks after the outpatient visit were investigated. The data of 216 patients were analyzed (control group = 100, intervention group = 116). More recommendations for STOPP/START-based medication changes were made in the GP correspondence in the intervention group than in the control group (43% vs. 24%, P = < 0.001). After 6 weeks, a significantly higher proportion of these changes were implemented in the intervention group (19% vs. 9%, P = 0.001). The ISP team, in addition to standard care, is an effective intervention for optimizing pharmacotherapy and medication safety in a geriatric outpatient clinic.

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REVISTAS GERIÁTRICAS

Age and Ageing

Performance of a trigger tool for detecting drug-related hospital admissions in older people: analysis from the OPERAM trial

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Abstract

Background

identifying drug-related hospital admissions (DRAs) in older people is difficult. A standardised chart review procedure has recently been developed. It includes an adjudication team (physician and pharmacist) screening using 26 triggers and then performing causality assessment to determine whether an adverse drug event (ADE) occurred (secondary to an adverse drug reaction, overuse, misuse or underuse) and whether the ADE contributed to hospital admission (DRA).

Objective

to assess the performance of those triggers in detecting DRA.

Design

retrospective study using data from the OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people) trial.

Settings

four European medical centres.

Subjects

multimorbid (≥ 3 chronic medical conditions) older (≥ 70 years) inpatients with polypharmacy (≥ 5 chronic medications) were enrolled in the OPERAM trial ($N = 2{,}008$) and followed for 12 months. We included patients with ≥1 adjudicated hospitalisation during the follow-up.

Methods

the positive predictive value (PPV; number of DRAs identified by trigger/number of triggers) was calculated for each trigger and for the tool as a whole.

Results

of 1,235 hospitalisations adjudicated for 832 patients, 716 (58%) had at least one trigger; an ADE was identified in 673 (54%) and 518 (42%) were adjudicated as DRAs. The overall PPV of the trigger tool for detecting DRAs was 0.66 [0.62–0.69].

Conclusions

this tool performs well for identifying DRAs in older people. Based on our results, a revised version of the tool was proposed but will require external validation before it can be incorporated into research and clinical practice

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BMC Geriatrics

A complex intervention to promote prevention of delirium in older adults by targeting caregiver's participation during and after hospital discharge – study protocol of the TRAnsport and DElirium in older people (TRADE) project

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Abstract

Background

Among potentially modifiable risk factors for delirium, transfers between wards, hospitals and other facilities have been mentioned with low evidence. TRADE (TRAnsport and DElirium in older people) was set up to investigate i) the impact of transfer and/or discharge on the onset of delirium in older adults and ii) feasibility and acceptance of a

developed complex intervention targeting caregiver's participation during and after hospital discharge or transfer on cognition and the onset of delirium in older adults.

Methods

The study is designed according to the guidelines of the UK Medical Research Council (MRC) for development and evaluation of complex interventions and comprises two steps: development and feasibility/piloting. The development phase includes i) a multicenter observational prospective cohort study to assess delirium incidence and cognitive decline associated with transfer and discharge, ii) a systematic review of the literature, iii) stakeholder focus group interviews and iv) an expert workshop followed by a Delphi survey. Based on this information, a complex intervention to better and systematically involve family caregivers in discharge and transport was developed. The intervention will be tested in a pilot study using a stepped wedge design with a detailed process and health economic evaluation. The study is conducted at four acute care hospitals in southwest Germany. Primary endpoints are the delirium incidence and cognitive function. Secondary endpoints include prevalence of caregiver companionship, functional decline, cost and cost effectiveness, quality of discharge management and quality of admission management in admitting hospitals or nursing homes. Data will be collected prior to discharge as well as after 3, 7 and 90 days.

Discussion

TRADE will help to evaluate transfer and discharge as a possible risk factor for delirium. In addition, TRADE evaluates the impact and modifiability of caregiver's participation during patient's transfer or discharge on delirium incidence and cognitive decline providing the foundation for a confirmatory implementation study.

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Prevalence of potentially harmful multidrug interactions on medication lists of elderly ambulatory patients

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Abstract

Background

It has been hypothesized that polypharmacy may increase the frequency of multidrug interactions (MDIs) where one drug interacts with two or more other drugs, amplifying the risk of associated adverse drug events (ADEs). The main objective of this study was to

determine the prevalence of MDIs in medication lists of elderly ambulatory patients and to identify the medications most commonly involved in MDIs that amplify the risk of ADEs.

Methods

Medication lists stored in the electronic health record (EHR) of 6,545 outpatients ≥60 years old were extracted from the enterprise data warehouse. Network analysis identified patients with three or more interacting medications from their medication lists. Potentially harmful interactions were identified from the enterprise drug-drug interaction alerting system. MDIs were considered to amplify the risk if interactions could increase the probability of ADEs.

Results

MDIs were identified in 1.3 % of the medication lists, the majority of which involved three interacting drugs (75.6 %) while the remainder involved four (15.6 %) or five or more (8.9 %) interacting drugs. The average number of medications on the lists was 3.1 ± 2.3 in patients with no drug interactions and 8.6 ± 3.4 in patients with MDIs. The prevalence of MDIs on medication lists was greater than 10 % in patients prescribed bupropion, tramadol, trazodone, cyclobenzaprine, fluoxetine, ondansetron, or quetiapine and greater than 20 % in patients prescribed amiodarone or methotrexate. All MDIs were potentially risk-amplifying due to pharmacodynamic interactions, where three or more medications were associated with the same ADE, or pharmacokinetic, where two or more drugs reduced the metabolism of a third drug. The most common drugs involved in MDIs were psychotropic, comprising 35.1 % of all drugs involved. The most common serious potential ADEs associated with the interactions were serotonin syndrome, seizures, prolonged QT interval and bleeding.

Conclusions

An identifiable number of medications, the majority of which are psychotropic, may be involved in MDIs in elderly ambulatory patients which may amplify the risk of serious ADEs. To mitigate the risk, providers will need to pay special attention to the overlapping drug-drug interactions which result in MDIs.

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Drugs and Aging

Quantifying Anticholinergic Burden and Sedative Load in Older Adults with Polypharmacy: A Systematic Review of Risk Scales and Models

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Abstract

Background

Patients taking medication with high anticholinergic and sedative properties are at increased risk of experiencing poor cognitive and physical outcomes. Therefore, precise quantification of the cumulative burden of their drug regimen is advisable. There is no agreement regarding which scale to use to simultaneously quantify the burden associated with medications.

Objectives

The objective of this review was to assess the strengths and limitations of available tools to quantify medication-related anticholinergic burden and sedative load in older adults. We discuss specific limitations and agreements between currently available scales and models and propose a comprehensive table combining drugs categorized as high, moderate, low, or no anticholinergic or sedative activity as excerpted from the selected studies.

Methods

A targeted search was carried out using the National Library of Medicine through PubMed using medical subject heading terms and text words around the following search terms: (anticholinergic OR sedative) AND (load OR burden OR scale) for studies published between 1 January 1945 and 5 June 2021. In addition, the following databases were searched using the same terms: MEDLINE-EBSCO, APA PsycInfo, CINAHL Plus, Cochrane Library, Scopus, OAIster, OVID-MEDLINE, Web of Science, and Google Scholar. Screening by titles was followed by an abstract and full-text review. After blind evaluation, agreement between reviewers was reached to establish drug characteristics and categories.

Results

After 3163 articles were identified, 13 were included: 11 assigned risk scores to anticholinergic drugs and two to sedative drugs. Considerable variability between anticholinergic scales was observed; scales included between 27 and 548 drugs. We generated a comprehensive table combining the anticholinergic and sedative activities of drugs evaluated and proposed a categorization of these drugs based on available scientific and clinical evidence. Our table combines information about 642 drugs and categorizes 44, 25, 99, and 474 drugs as high, moderate, low, or no anticholinergic and sedative activity, respectively.

Conclusions

Variability and inconsistency exists among scales used to categorize drugs with anticholinergic or sedative burden. In this review, we provide a comprehensive table that proposes a new categorization of these drugs. A longitudinal study will be required to validate the new proposed anticholinergic and sedative burden catalog in an evidence-based manner.

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REVISTAS MEDICINA GENERAL

JAMDA: Journal of the American Medical Directors Association

Antipsychotic Use and Risk of Stroke Among Community-Dwelling People With Alzheimer's Disease

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Abstract

Objectives

Antipsychotic use for neuropsychiatric symptoms in Alzheimer's disease (AD) is common despite the increased risk of cardiovascular events and mortality. There is limited and inconsistent evidence on the possible risk of stroke. We assessed whether antipsychotic initiation increases the risk of stroke in people with a verified diagnosis of AD and whether there is a difference in stroke risk between the 2 most commonly used antipsychotics, risperidone and quetiapine.

Design

Register-based exposure-matched cohort study.

Setting and Participants

The Medication Use and Alzheimer's Disease (MEDALZ) cohort included 70,718 community-dwelling people with AD in Finland during 2005-2011. People with previous strokes were excluded.

Methods

For each incident antipsychotic user (n = 20,467), 1 nonuser was matched according to sex, age, and time since AD diagnosis. Analyses were conducted with inverse probability of treatment-weighted (IPTW) Cox proportional hazards models.

Results

Compared with nonuse, antipsychotic use was associated with an increased risk of stroke within 60 days of antipsychotic initiation [IPTW hazard ratio (HR) 1.73, 95% confidence interval (CI) 1.32-2.28]. However, there was no significant overall association between antipsychotic use and the risk of stroke (IPTW HR 1.09, 95% CI 0.98-1.22). There was no difference in stroke risk between risperidone and quetiapine (IPTW HR 1.12, 95% CI 0.91-1.37).

Conclusions and Implications

Stroke risk is increased shortly after antipsychotic initiation in people with AD, suggesting that even short-term use of antipsychotics should be avoided if possible. If antipsychotics are prescribed, effectiveness and safety should be assessed soon after initiation and treatment limited to the shortest possible duration.

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A Systematic Review of Interventions to Improve Analgesic Use and Appropriateness in Long-Term Care Facilities

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Abstract

Objectives

To systematically review the effectiveness of interventions to improve analgesic use and appropriateness in long-term care facilities (LTCFs).

Design

Systematic review.

Setting and participants

MEDLINE, Embase, PsycINFO, and CINAHL Plus were searched from inception to June 2021. Randomized controlled trials (RCTs), controlled and uncontrolled prospective interventions that included analgesic optimization, and reported postintervention change in analgesic use or appropriateness in LTCFs were included.

Methods

Screening, data extraction, and quality assessment were performed independently by 2 review authors.

Results

Eight cluster RCTs, 2 controlled, and 6 uncontrolled studies comprising 9056 residents across 9 countries were included. The 16 interventions included education (n = 13), decision support (n = 7), system modifications (n = 6), and/or medication review (n = 3). Six interventions changed analgesic use or appropriateness, all of which included prescribers, 5 involved multidisciplinary collaboration, and 5 included a component of education. Education alone changed analgesic use and appropriateness in 1 study. Decision support was effective when combined with education in 3 interventions. Overall, 13 studies reported analgesic optimization as part of pain management interventions and 3 studies focused on medication optimization. Two pain management interventions reduced the percentage of residents reporting pain not receiving analgesics by 50% to 60% ($P = .03$ and $P < .001$, respectively), and 1 improved analgesic appropriateness ($P = .03$). One reduced nonsteroidal anti-inflammatory drugs (NSAIDs) ($P < .001$) and another resulted in 3-fold higher odds of opioid prescription in advanced dementia [95% confidence interval (CI) 1.1-8.7]. One medication optimization intervention reduced NSAID prescription ($P = .036$), and another reduced as-needed opioid (95% CI 8.6-13.8) and NSAID prescription (95% CI 1.6-4.2).

Conclusions and Implications

Interventions involving prescribers and enhanced roles for pharmacists and nurses, with a component of education, are most effective at changing analgesic use or appropriateness. Interventions combining education and decision support are also promising. Medication review interventions can change analgesic prescription, although there is currently minimal evidence in relation to possible corresponding improvements in resident-related outcomes.

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