Kantonsspital Baden
Apotheke

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Detection and prevention of delirium triggered by adverse drug events

1. Introduction:

Adverse drug events (ADEs) are frequent complications experienced during hospitalization, especially in the geriatric population. ADEs are still considered to be heavily underreported while half are classified as pADEs (preventable ADEs). Thus, the prediction of ADEs becomes more important every day to identify patient at high risk and alert the physician or a multidisciplinary care team to perform specific interventions.
A common ADE in elderly hospitalized patients is delirium having a huge impact on health outcomes, hospitalization length of stay, and health care costs. One of the many risk factors are drugs, especially anticholinergic (ACH) medications. Owing to multiple indications, prescription of these drugs increases with hospitalization. The most common method for determining the ACH burden in a person is an expert based list of medications with ACH properties, the so-called ACH scales. These scales assign a number from 1 (=low) to 3 (=high) to a specific substance according to its ACH properties. In a small study conducted in the intensive care unit (ICU) of our hospital, we observed that patients with delirium had a higher ACH burden compared to those without. As this drug-drug interaction was often unnoticed by interaction check programs, delirium may remain unrecognized. Hence, the ability to predict patients at high risk would enhance proper screening and be a potential source of prevention.

2. Aim:

a. To predict delirium and identify risk factors in different population groups
b. To prevent delirium by automatically calculating anticholinergic burden of drug therapy, displaying alerts in the electronic patient record (EPR) and automatically directing daily lists of orders with candidate medications to experts for review

3. Objectives:

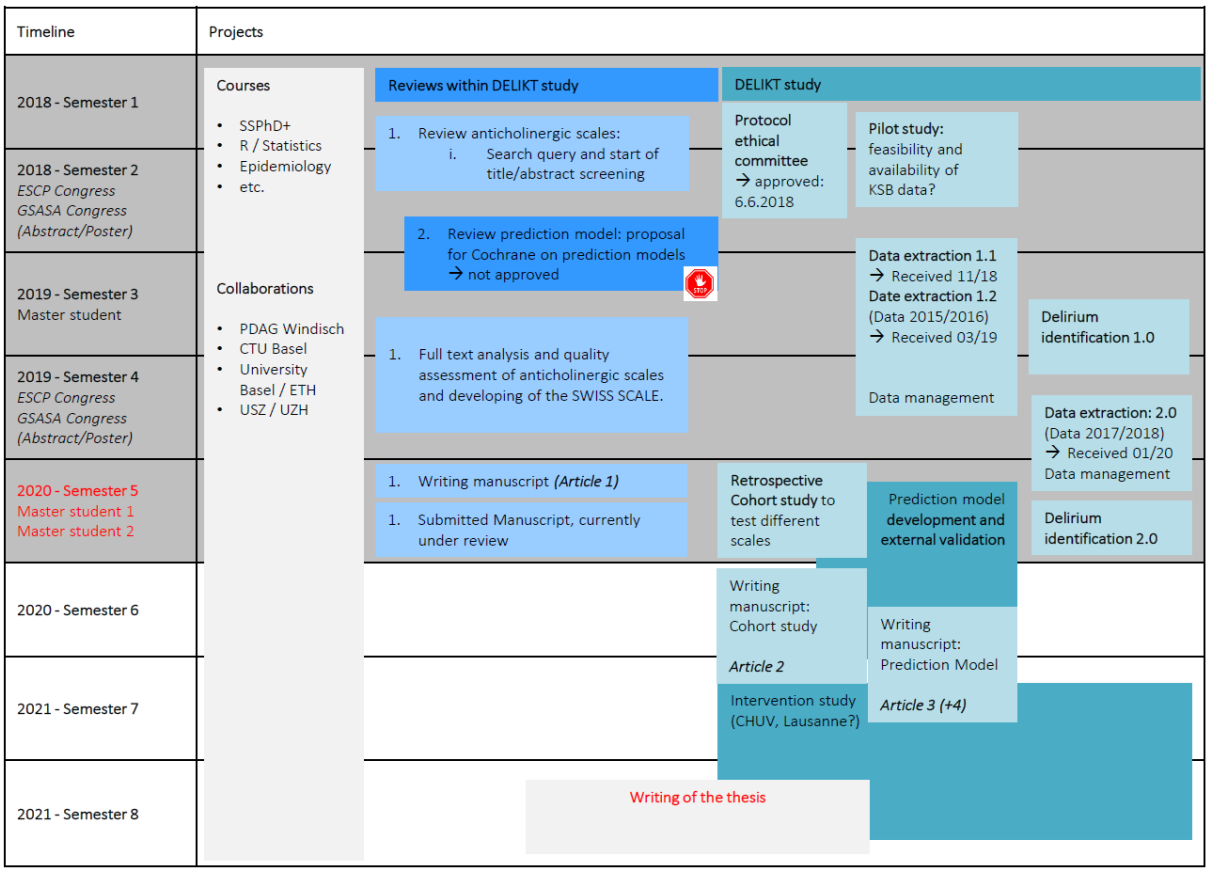
a. To identify the best anticholinergic burden scales to develop the Swiss ACH burden scale (SABS)
b. To establish the association between delirium and the SABS
c. To develop and validate a prediction model to identify patient at high risk for delirium including the SABS
d. To decrease the incidence of delirium by implementing the prediction tool in the hospital's CPOE

4. Changes:

The PhD thesis has been extended by one year until end of 2021.

5. Steps and planning:

Duration: 4 years (2018-2021)



6. End status by June 2021:

A first publication with the title “Quality of anticholinergic burden scales and their impact on clinical outcomes – a systematic review” was published in October 2020 in the European Journal of Clinical Pharmacology (abstract see appendix 1).

A second publication entitled “High anticholinergic burden at admission associated with in-hospital mortality in older patients: A comparison of 19 different anticholinergic burden scales” is currently in the second review round after first revisions in the Journal Age and Ageing and has additionally been presented at the GSASA congress in 2020 (oral presentation, 1st prize, abstract see appendix 2).

A third publication entitled “Evaluation of the association of anticholinergic drug burden and delirium in older hospitalised patients – a cohort study comparing 19 anticholinergic burden scales” is currently under review in the British Journal of Clinical Pharmacology. Furthermore, it has been presented as a poster and oral communication at the SGAIM (Swiss Society of General Internal Medicine) congress 2021 (abstract see appendix 3).

Meanwhile, we started to work on two prediction models (1) on in-hospital mortality together with a fourth master student (Nora Haltinner), and (2) on incident delirium using the data from the first 24h of admission. For the (1) prediction model we wrote an abstract and submitted it to the online ESCP congress in Lisbon taking place in fall 2021 (see abstract appendix 4). The prediction model for delirium has been constructed as well and we are currently writing the manuscript (no abstract yet).

One of the last steps within this entire project is as well the development of the Swiss Anticholinergic Burden Scale (SABS) and to implement the prediction model for delirium in the CPOE. Currently, we are working on developing the SABS and hope to be able to submit it by fall 2021. For the implementation of the prediction model, IT clarifications have to be done first and we will have to write a new protocol for the ethics in order to prove its potential as a prevention tool.

Baden, den 21.6.21

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Appendix 1 (Abstract Systematic Review)

"Quality of anticholinergic burden scales and their impact on clinical outcomes – a systematic review"

Abstract

Purpose: Older people are at risk of anticholinergic side effects due to changes affecting drug elimination and higher sensitivity to drug's side effects. Anticholinergic burden scales (ABS) were developed to quantify the anticholinergic drug burden (ADB). We aim to identify all published ABS, to systematically compare them and to evaluate their associations with clinical outcomes.

Methods: We conducted a literature search in MEDLINE and EMBASE to identify all published ABS and a Web of Science citation (WoS) analysis to track validation studies implying clinical outcomes. Quality of the ABS was assessed using an adapted AGREE II tool. For the validation studies we used the Newcastle-Ottawa Scale and the Cochrane tool Rob2.0. The validation studies were categorized into six evidence levels on the propositions of the Oxford center for Evidence-based Medicine with respect to their quality. At least two independent researchers performed screening and quality assessments.

Results: Out of 1297 records we identified 19 ABS and 104 validations studies. All ABS were recommended for use despite quality differences. The Anticholinergic Cognitive Burden (ACB) scale and the German Anticholinergic Burden Scale (GABS) achieved the highest percentage in quality. Though most ABS are validated, we lack validation studies for newer scales and only two studies compared eight ABS simultaneously. The four most investigated clinical outcomes delirium, cognition, mortality and falls showed contradicting results.

Conclusion: There is need for good quality validation studies comparing multiple scales to define the best scale and to conduct a meta-analysis for the assessment of their clinical impact.

Appendix 2 (Abstract Cohort study on in-hospital mortality)

"High anticholinergic burden at admission associated with in-hospital mortality in older patients: A comparison of 19 different anticholinergic burden scales"

Abstract

Background: Drugs with anticholinergic properties are often prescribed to older people vulnerable to adverse events. Although no gold standard is established to assess a patient's anticholinergic burden, a recent review identified 19 anticholinergic burden scales (ABS). No study has compared the impact of all 19 ABS. We evaluated whether a high anticholinergic burden is associated with in-hospital mortality and length of stay (LOS) for each ABS.

Method: A retrospective cohort study conducted at Local Hospital in Place, Country, used electronic health record data collected over 2015 to 2018. Included were inpatients age ≥65, hospitalised ≥48 h with no stay >24 h in intensive care. Patients anticholinergic burden score was classified using a binary (<3: low, or ≥3: high burden) and categorical approach (0: no, 0.5–3: low, or ≥3: high burden). In-hospital mortality and LOS were analysed using multivariable logistic and linear regression, respectively.

Results: In total, 27,092 patients were included (mean age 78.1±7.7 years, median LOS 6 days). Of them, 913 died. Depending on the evaluated ABS, from 1,370 to 17,035 patients were exposed to anticholinergics. Patients with high burden measured by all 19 ABS were associated with a 1.32- to 3.03-fold increase in in-hospital mortality compared to those with low or no burden. Similar results were observed for LOS.

Conclusion: The ABS are useful clinical tools to quantify the anticholinergic burden among inpatients. Discontinuing or substituting drugs with high anticholinergic properties (score ≥3) at admission might be a targeted intervention to decrease in-hospital mortality and LOS.

Appendix 3 (Abstract Cohort study on incident delirium)

"Evaluation of the association of anticholinergic drug burden and delirium in older hospitalised patients – a cohort study comparing 19 anticholinergic burden scales"

Abstract

Background: A recent review identified 19 anticholinergic burden scales (ABS) but no study has yet compared the impact of all 19 ABS on delirium incidence. We evaluated whether a high anticholinergic burden as classified by each ABS is associated with incident delirium.

Method: We performed a retrospective cohort study in a regional hospital in Switzerland using data from 2015-2018. Included were patients aged ≥65, hospitalised ≥48h with no stay >24h in intensive care units. Delirium was defined twofold: (i.) ICD-10 or CAM and (ii.) ICD-10 or CAM or DOSS. Patients' cumulative anticholinergic burden score, calculated within 24h after admission, was classified using a

binary (<3:low, ≥3:high burden) and a categorical approach (0:no, 0.5–3:low, ≥3:high burden). Association was analysed using multivariable logistic regression.

Results: Over 25,000 patients (mean age 77.9±7.6 years) were included. Of them, (i) 864 (3.3%) and (ii.) 2,770 (11.0%) patients developed delirium. Depending on the evaluated ABS, 4-63% of the patients were exposed to at least one anticholinergic drug. Out of 19 ABS, (i.)14 and (ii.) 16 showed a significant association with the outcomes. A patient with a high anticholinergic burden score had ORs of 1.21 (CI 95% 1.03-1.42) to 2.63 (CI 95% 2.28-3.03) for incident delirium compared to those with low or no burden.

Conclusion: A high anticholinergic burden within 24h after admission was significantly associated with incident delirium. Although prospective studies need to confirm these results, discontinuing or substituting drugs with a score of ≥3 at admission might be a targeted intervention to reduce incident delirium.

Appendix 4 (Abstract Prediction model in-hospital mortality)

"Developing and validating a prediction model for in-hospital mortality associated with anticholinergic drug burden among older hospitalised patients with dementia"

Abstract

Background: After cardiovascular diseases and cancer, dementia is the third most frequent cause of death in Switzerland among patients aged 65 years and older. A recent cohort study conducted in a regional hospital in Switzerland showed that a high anticholinergic drug burden in older patients is significantly associated with increased in-hospital mortality. We aimed to develop and validate a risk prediction model for in-hospital mortality in older patients with dementia and consider their exposure to anticholinergic drugs as a predefined predictor.

Method: Electronic health record data within the first 24h of admission was collected from 2015-2018. Included were inpatients ≥65 years old, hospitalised ≥48 hours, diagnosed with dementia according to ICD-10 codes. Outpatients and patients with stays >24h in the intensive care unit were excluded. The outcome was in-hospital mortality. The developed model was based on Naïve Bayes using data from 2015-2016 as training set, the years 2017-2018 served as validation set. The candidate variables were obtained with the Minimum Redundancy Maximum Relevance (MRMR) variable selection algorithm and backward selection. Synthetic Minority Oversampling Technique (SMOTE) was applied within the training-set. Performance measures of interest were AUC, sensitivity and specificity.

Results: In total, 2,595 patients were included. The training set contained 1,266 patients (mean age 83.2±6.54 years, 60% female) of which 63 (5.0%) died during hospitalisation. Variables selected for prediction were: self-care index, delirium observation screening score, sodium, CRP, creatinine, GFR, chronic heart failure, hemi-/paraplegia, COPD, cancer, diabetes and the anticholinergic burden scales

Cancelli, ACL, ADS and SCDL. Further, blood pressure, polypharmacy, age, BMI, and temperature were included. A first validation for the final model using the training set showed an AUC of 0.872, a sensitivity of 90.44% and a specificity of 68.50%. Using the validation set, we obtained an AUC of 0.771, a sensitivity of 63.01% and a specificity of 73.65%.

Conclusion: The developed prediction model for in-hospital mortality showed an acceptable performance. It might be a useful tool to identify patients with dementia with a high risk for in-hospital mortality in order to implement interventions and management strategies during hospitalisation to improve patient outcome, however, further validation is required.