Comparison of Nine Instruments to Calculate Anticholinergic Load in a Large Cohort of Older Outpatients: Association with Cognitive and Functional Decline, Falls, and Use of Laxatives

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Objective: *A patient's risk for anticholinergic adverse effects is frequently estimated by instruments evaluating the drugs included in his medication profile. It remains unknown, however, which characteristics should be included in such an assessment instrument aiming to reliably predict adverse anticholinergic outcomes.* **Design:** *Cross-sectional study.* **Setting:** *ESTHER cohort (Germany).* **Participants:** *Home-dwelling participants (N = 2,761) aged between 60 and 87 years.* **Measurements:** *The association between anticholinergic load calculated with nine different instruments and four anticholinergic adverse outcomes was investigated in univariate and multivariate analyses. Therefore, linear models complemented with Kendall's tau rank correlation coefficients (τ) were applied for continuous outcomes and generalized linear models were used to derive odds ratios (ORs) with 95% confidence intervals (CIs) for binary endpoints.* **Results:** *Based on the respective identification criteria for anticholinergic drugs, the nine instruments identified between 245 (9%) and 866 (31%) anticholinergic drug users (mean age ± SD: 73 ± 6 years; Mini-Mental State Examination [MMSE] score: 28.3 ± 2.07; Barthel Index: 97.1 ± 7.5; 291 reporting falls; 29 taking laxatives [surrogate for constipation]). In the multivariate analysis, only two instruments indicated a significant association between anticholinergic load and all four outcomes. The instrument considering the prescribed dose showed the strongest association with MMSE scores (τ = −0.10), falls (OR: 2.30; 95% CI: 1.50–3.52), and the use of laxatives (OR: 3.11; 95% CI: 1.04–9.36).* **Conclusions:** *Instruments most reliably predicted anticholinergic*

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adverse events if they were either based on the drugs' serum anticholinergic activity and the suggestions of clinician experts or considered the actual prescribed dose. (Am J Geriatr Psychiatry 2017; ■■:■■–■■)

Key Words: Anticholinergic load, anticholinergic drug scales, drug burden index, aged, cognition/drug effects*, cohort studies, Barthel index, Germany/epidemiology

Today, the anticholinergic load is frequently calculated according to the substances included in a patient's drug regimen. To this end, 13 instruments are available that typically allocate a score between one (mild) and three (severe) to each anticholinergic drug based on its in vitro or clinically confirmed anticholinergic properties.[1] The patient's anticholinergic load is calculated by summing up the individual drugs' scores, with higher scores implying higher risks for adverse anticholinergic outcomes. Because of the variable underlying identification and assessment criteria for anticholinergic properties, the instruments worryingly differ with regard to the selection and rating of listed drugs.[2]

Thus far, over 55 studies have investigated the predictive power of available instruments, that is, the association between anticholinergic load calculated by an instrument and patient-related outcomes with regard to anticholinergic adverse drug reactions (ADRs).[1] Because no gold standard for measuring anticholinergic ADRs has been established, surrogate outcomes are commonly used in such studies. Typical outcomes include cognitive markers such as the Mini-Mental State Examination (MMSE) score, functional markers such as the Barthel Index, and anticholinergic ADRs such as constipation.[1] Potentially because of differences in the evaluated patient samples and the outcome assessment methods applied, the strength of association varied between studies and not all studies found a significant relationship between clinical endpoints and anticholinergic load predicted by the applied instrument (e.g., Kumpula et al.[3]). In total, at least 118 different tests were used to investigate 17 outcomes,[1] thus precluding a direct comparison of the predictive power of the respective instruments.

In only few studies, two or more instruments were applied in a comparative manner,[4–6] and if so, cognitive and functional outcomes were not evaluated concurrently. Hence, it remains unclear which identification and rating criteria of anticholinergic drugs will best reflect overall anticholinergic burden and whether certain instruments are more suitable to identify a particular clinical risk of interest.

In this study, all readily available instruments estimating anticholinergic load were applied to one older cohort and their association to several patient-related outcomes was analyzed.

METHODS

Study Sample

The ongoing ESTHER cohort study has been conducted in Saarland, Germany, since July 2000 with one baseline and four subsequent follow-up assessments. At baseline, general practitioners recruited 9,949 patients between the ages of 50 and 75 years. The study design and sample was previously described in detail.[7] In this cross-sectional analysis, the home visit data from 2,761 participants of the fourth follow-up (2011–2013) was used, comprising sociodemographic and medical data—that is,age, sex, family status, body mass index (BMI), the estimated creatinine clearance (CrCl) based on the Cockcroft-Gault formula, the Cumulative Illness Rating Scale for Geriatrics Severity Index (CIRS-G SI), the Clinical Frailty Scale (CFS), the number of falls, the MMSE score, the Barthel Index, and individual medication profiles.

The ESTHER study was approved by the ethics committees of the Medical Faculty of Heidelberg University (protocol #058/2000) and of the Medical Association of Saarland (protocol #67/2000) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

Calculating the Anticholinergic Load and Defining Anticholinergic Drug Users

Up to now, 13 instruments comprising 12 scales and 1 equation (Drug Burden Index, DBI) are available for calculating the anticholinergic load.[1] Two (of 12) scales