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Adverse Effects of Psychotropic Drugs in Old Age

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Forumsalen, Campus, Skellefteå,
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Abstract
BACKGROUND: With increasing age, many of us accumulate an increasing burden of disease warranting the use of medications. Hence, the use of most classes of drugs increases with age, especially so in elderly women. At the same time, the oldest people in society often are excluded from pharmacological studies. In the absence of strong evidence, much of the knowledge about the effects of several drugs in the elderly is derived from observational studies, prone to bias and confounding. The use of psychotropic drugs in elderly people is particularly controversial, especially in people suffering from major neurocognitive disorders, as they have been associated with several adverse effects as well as limited clinical effect.
AIMS: This thesis aims to explore the associations between several types of psychotropics and two of the most severe adversities attributed to their use, increased mortality and the risk of hip fracture.
METHODS: This thesis uses quantitative, comparative and epidemiological methods, prospective and retrospective. Two of the four papers are based on data collections conducted by the Department of Community Medicine and Rehabilitation, Umeå University, whereas the other two are based on Swedish nationwide registers. In all four papers multivariable regression models were used to investigate the associations between the exposures and outcomes, adjusted for possible confounding variables.
RESULTS: In a population-based sample of very old people, and in old people with major neurocognitive disorder, ongoing use of psychotropic drugs was not independently associated with increased mortality. Analyses did show, however, a significant impact of sex on the mortality risk, with tendencies for antidepressant drug use to be protective in men, but not in women, and for benzodiazepines to increase the mortality risk in men, but not in women.
In two cohorts of old people, based on several nationwide registers, investigating the associations between psychotropic drug use and hip fracture revealed that users of antidepressants, as well as users of antipsychotics, had significantly increased risks of hip fracture, independent of a wide range of covariates. However, when studying how the risk changed over time, the strongest associations were found before the initiation of treatment with the respective drug, and no dose-response relationships were found.
DISCUSSION: The finding that psychotropic drug use was not independently associated with an elevated mortality risk was not in line with previous research, most of which have been based on data from large registers, and shown an increased risk of mortality. One reason for this difference is that the cohorts studied in this thesis were thoroughly investigated and characterised, making it possible to perform extensive adjusting for confounding variables. Hence, we expect a lesser amount of residual confounding, than in most other studies. Another explanation is that we studied ongoing drug use at baseline, rather than associations following initiation of treatment. This might have introduced a selection bias in our studies, where the individuals most sensitive to adverse effects would have discontinued treatment or passed away. The finding of a significant impact of sex on the risk of mortality adds to the unexplored field of sex differences in drug responses in old age. In our register studies of psychotropic drug use and the risk of hip fracture, novel methods were applied. We have tried to overcome the hurdles of several types of confounding through the investigation of associations before and after the initiation of the respective drug. Our finding that the association between psychotropic drug use and hip fracture was not only present, but indeed strongest, before the initiation of treatment indicates a strong presence of residual confounding and confounding by indication, and points toward the absence of a causal relationship.
CONCLUSION: The evidence supporting causal relationships between psychotropic drug use and serious adverse events in old age is insufficient. Our results point towards bias and confounding having strong influences on the observed associations between psychotropic drug use and mortality, and hip fracture, respectively.

Keywords
Geriatric medicine, psychotropic drugs, adverse effects, mortality, hip fracture, cohort study, old age.

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