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Utilisation and polypharmacy aspects of antiepileptic drugs in elderly versus younger patients with epilepsy: A pharmacoepidemiological study of CNS-active drugs in Norway, 2004-2015

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ABSTRACT

Background and purpose: Many patients with epilepsy use antiepileptic drugs (AEDs) in combination. The elderly is a vulnerable group regarding polypharmacy. The purpose of this study was to investigate changes in utilisation of AEDs, and the extent of polypharmacy with other CNS-active drugs in elderly versus younger patients in Norway.

Methods: This pharmacoepidemiological study included all prescriptions of antiepileptic, antidepressant and antipsychotic drugs from Norwegian pharmacies in the Norwegian Prescription Database (NorPD) (2004-2015). Variables included number of patients, utilisation in defined daily doses, age, gender, and diagnosis specific reimbursement codes for AEDs.

Results: The use of AEDs has increased in all age groups in this population-based study in Norway. In the elderly, AEDs used in neuropathic pain (mainly gabapentin and pregabalin) have increased more than 10-fold (from 0.7 to 9.6 DDDs/1000 elderly/day, 2004-2015), while the prevalence of users is four times more than in younger patients. Polypharmacy between antiepileptic, antidepressant and antipsychotic drugs occurred in 35% of elderly and 38% of younger patients with epilepsy. The use of enzyme-inducers was common, and occurred more often in elderly patients. A total of 42 different interactions that may have clinical implications were identified among these drugs.

Conclusion: The use of AEDs in elderly compared to younger patients is increasing, especially in neuropathic pain. Polypharmacy with antiepileptic, antidepressant and/or antipsychotic drugs was documented in more than one third of the patients. Awareness of increased drug utilisation, polypharmacy with potential drug interactions, and focus on elderly patients are important for increased patient safety.

1. Introduction

The number of people older than 60 years constituted 22% of the total population in recent years in Norway, and is expected to increase further in the years to come (SSB, 2017; WHO, 2016). The average life expectancy of the population has increased due to better living conditions, health services and medicines. Ageing results in many physiological changes that may affect the pharmacokinetics of drugs. In the elderly, epilepsy is the third most common neurologic disorder, and they are at higher risk of new onset epilepsy (Christensen et al., 2007; Stefan 2011). Psychiatric and other comorbidities are common among patients with epilepsy (Brodie and Kwan, 2005; Tellez-Zenteno et al., 2007; Henning and Nakken, 2010; Karouni et al., 2010; Landmark et al., 2012; Italiano and Perucca, 2013).

Some antiepileptic drugs (AEDs) are also approved for use in other indications than epilepsy, such as neuropathic pain and some

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psychiatric disorders. The number of patients taking AEDs to treat neuropathic pain has in recent years exceeded the number of patients with epilepsy (Landmark et al., 2009; Baftiu et al., 2016). Antidepressant and antipsychotic drugs are widely used in geriatric patients, and combinations including AEDs are common (Halvorsen et al., 2016; Bathena et al., 2017). Many AEDs have a risk of pharmacodynamic and pharmacokinetic interactions by concomitant use with other drugs (Spina et al., 2012; Beiske et al., 2015; Halvorsen et al., 2016; Mevaag et al., 2017). The extent of polypharmacy in large settings and possible clinical implications are, however, scarcely described and discussed in the literature.

Drug utilisation may be followed closely at the patient and population level as part of pharmacovigilance which is defined as "the science and activities that involve the discovery, evaluation, understanding and prevention of adverse effects and other drug related problems" (WHO, 2017). Prescription databases are useful in studying specific patient populations such as the elderly. The Norwegian Prescription Database (NorPD) has been used in previous studies with focus on utilisation of AEDs in epilepsy and other indications in Norway (Landmark et al., 2009; Karouni et al., 2010; Landmark et al., 2011; Baftiu et al., 2016).

The purpose of this study was to investigate changes in utilisation of AEDs and polypharmacy aspects in the elderly versus younger patients with epilepsy in Norway from 2004-2015. Furthermore, we wanted to evaluate the clinical implications of safety aspects for improved treatment and pharmacovigilance with special emphasis on the elderly.

2. Material and methods

This study is a descriptive population-based pharmacoepidemiological study using data from The Norwegian Prescription Database (NorPD) which is a validated population-based source of pharmacoepidemiological data (Furu, 2008; Wettermark et al., 2013). All antiepileptic, antidepressant and antipsychotic drugs dispensed from all pharmacies in Norway during the period 2004-2015 were included. The detailed data on AEDs and diagnosis-related reimbursement codes were provided by NorPD on request. The data on antidepressant and antipsychotic drugs were accessed through the open version of NorPD and included all prescriptions with reimbursement and non-reimbursement. Their main indication is psychiatric disorders. Variables included gender, age groups spanning 10 years, encrypted person identifiers instead of identity (ID), defined daily doses (DDDs), prescription category (public refund or not refund) and specific codes for reimbursement or indication (ICD-10/ICPC-2 from 2008). All diagnosis where antiepileptic, antidepressant and antipsychotic drugs are indicated for use, have their own diagnose-specific reimbursement codes in Norway. Elderly patients were defined as ≥60 years and younger patients < 60 years old due to the data being provided in age groups spanning ten years. Population data of Norway from 2004 to 2015 was supplied by Statistics Norway (SSB, 2017).

The classification of drugs was according to the Anatomical Therapeutic Chemical (ATC) classification codes where AEDs are defined as NO3A, antidepressant drugs are N06A and antipsychotic drugs are N05A. Mood-stabiliser lithium is classified as N05A in the ATC system. In addition, a research file with data on concomitantly dispensed prescriptions of AEDs (N03A), antidepressant (N06A) and antipsychotic drugs (N05A, including lithium), 2004-2012 was used. A 3-month period (September to November 2012, $n_{elderly}$ = 9553, $n_{younger}$ = 21306)) was chosen to generate data regarding the extent of polypharmacy. This was used as a measure of concomitant pharmacological treatment and psychiatric comorbidity as previously described (Karouni et al., 2010). In this study, the term polypharmacy specifically refers to the use of an AED in combination with other antiepileptic, antipsychotic and/or antidepressant drugs. To document the extent of drug combinations that may cause pharmacokinetic interactions, we chose the most pronounced enzyme inducers and inhibitors as well as the most susceptible drugs to be affected by such interactions based on existing literature and interaction databases (Mula, 2008; Landmark and Patsalos, 2010; Patsalos, 2013a, 2013b; Halvorsen et al., 2016). The study was approved by the Norwegian Institute of Public Health. The data were pseudonymous with no patient identification, as each patient was given a running number in the data file. Statistics Norway provided security for protection of patient information.

Table 1
Demographic data and detailed information of the use of antiepileptic (in epilepsy and non-epilepsy indications), antidepressant and antipsychotic drugs in elderly and younger patients 2004-2015 (years 2004, 2010 and 2015 are presented in the table).

	2004	2010	2015
Number of inhabitants in Norway*	4577457	4858199	5165802
< 60 years (younger)	3694134	3844344	4044006
≥60 years (elderly)	883323	1013855	1121796
AEDs in epilepsy [a]			
Number of patients < 60	48358	43974	41668
Number of patients ≥60	16003	15080	17896
DDDs/1000 < 60 inhabitants/day	7.0	6.5	6.2
DDDs/1000 ≥60 inhabitants/day	8.5	8.0	9.5
AEDs in neuropathic pain [b]			
Number of patients < 60	4166	28814	33636
Number of patients ≥60	3460	22658	32018
DDDs/1000 < 60 inhabitants/day	0.2	2.9	3.5
DDDs/1000 ≥60 inhabitants/day	0.7	6.5	9.9
AEDs in psychiatry [c]			
Number of patients < 60	5974	26015	22831
Number of patients ≥60	1331	5296	6425
DDDs/1000 < 60 inhabitants/day	0.6	2.8	3.2
DDDs/1000 ≥60 inhabitants/day	0.5	1.9	3.1
AEDs in migraine [d]			
Number of patients < 60	13	312	601
Number of patients ≥60	2	15	64
DDDs/1000 < 60 inhabitants/day	0.0007	0.02	0.03
DDDs/1000 ≥60 inhabitants/day	0.0005	0.003	0.01
Antidepressant drugs (N06A)			
Number of patients < 60	180577	182421	197565
Number of patients ≥60	99237	114698	125043
DDDs/1000 < 60 inhabitants/day	40.1	42.0	42.3
DDDs/1000 ≥60 inhabitants/day	83.9	95.4	94.8
Antipsychotic drugs (N05A)			
Number of patients < 60	61822	64915	74318
Number of patients ≥60	42763	39159	38932
DDDs/1000 < 60 inhabitants/day	7.5	8.8	8.8
DDDs/1000 ≥60 inhabitants/day	9.9	10.7	11.3

Based on Baftiu et al. (2016).

* Number of inhabitants was supplied by Statistics Norway (SSB, 2017).

[a] Code 7. ICD-2/ICPC-10 codes: G40, N88.

[b] Codes 22, 46, 99. ICD-2/ICPC-10 codes: −71, −90. Other G50, N92, 0 (non-reimbursement for gabapentin and pregabalin).

[c] Code 18. ICD-2/ICPC-10 codes: −73, −F3. Other −72, −74, F2, F3, F4, −F4, F30, F31, F32, F33, F41, F41.0, P73, P74, P76.

[d] Code 36. ICD-2/ICPC-10 codes: G43, N89.

2.1. Data analyses

The data were analysed using Structured Query Language (SQL) in a database administration system (mySQL). For further analysis of the use in epilepsy and other indications, reimbursement codes were used to calculate the number of patients and DDDs in each case. Specific searches were performed as shown in Table 1 and all included indications as previously described (Baftiu et al., 2016). The utilisation of AEDs is presented as number of patients for each indication and as DDDs/1000 subgroup inhabitants/day, hereunder DDDs/1000 elderly inhabitants/day and DDDs/1000 younger inhabitants/day. No statistical analysis of differences between the groups was performed since the whole population was covered and the data are descriptive.