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UTILIZATION AND POLYPHARMACY ASPECTS OF ANTI-EPILEPTIC DRUGS IN ELDERLY VERSUS YOUNGER PATIENTS WITH EPILEPSY

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Abstract:
AEDs (antiepileptic drugs) used by several patients with epilepsy in combination. Regarding poly-pharmacy, the group of elderly is susceptible. This research objective was to analyze the utilization of AEDs changes, and the poly-pharmacy extent with other central nervous system agent drugs in old age versus younger patients (as studied through PubMed Database of Norway).
This pharmacoepidemiological research comprised all antiepileptic prescriptions, antipsychotic and antidepressant drugs from Norwegian Pharmacies (as gathered through PubMed Database, through NorPD "Norwegian Prescription Database). In this study, variables are the utilization of daily doses, patients, the age of patients, gender and particular reimbursement AEDs codes. The AEDs usage has amplified almost in all groups of ages in this specific Norwegian population-based study (data gathered through PubMed Database). Similarly, the usage of AEDs in neuropathic pain in elderly (mainly pregabalin and gabapentin) have augmented with a ratio of more than 10-fold (as per data gathered from 2004 to 2015, 0.7 to 9.6 DDDs/1000 elderly per day), while the user's prevalence is four times more as compared with younger patients. In 35% of elderly polypharmacy between antidepressant, antiepileptic and antipsychotic drugs happened in the elderly while 38% in epileptic younger patients. The utilization of enzyme-inducers was ordinary and happened frequently in elderly patients. There were 42 different interactions which found among these drugs.
AEDs usage in elderly associated to younger is cumulative, specifically under neuropathic pain. Poly-pharmacy with an antidepressant, antiepileptic and antipsychotic drugs was recognized through one-third patient. Increased drug usage awareness gained with probable interactions of a drug and increased the safety of patients.
Keywords: *Antidepressant, antiepileptic, antipsychotic drugs, polytherapy, pharmacoepidemiology, utilization, elderly*

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1.0 INTRODUCTION:

According to the PubMed Database elderly people in Norway are consisted 22% of the overall population in Norway. The life expectancy average of the prescribed population is due to better health services, living conditions, and quality medicines. Aging always marks different physiological changes which may assume the pharmacokinetics of the drug. In older age, the third most general neurologic disorder is epilepsy and there is a higher rate of risk for them regarding new epilepsy onset. Different signs of comorbidities and psychiatric are general in epileptic patients. AEDs are also appropriate for use in some other epileptic indications like psychiatric disorder and neuropathic pain (Baftiu et al., 2018).

All those patients who are using AEDs while treating neuropathic pain exceeded in recent years, according to PubMed Database. Antipsychotic and antidepressant drugs are extensively utilized in geriatric patients and other blends comprising AEDs are common. Most of the AEDs have a high risk of pharmacokinetic and pharmacodynamics dealings by concurrent usage with some other drugs. As mentioned above the basic object of this study was to analyze AEDs utilization changes and aspects of polypharmacy in old age patients versus younger epileptic patients from 2004-2015 through PubMed Database Records (Gayatri and Livingston, 2016).

2.0 MATERIALS AND METHODS:

The base of this descriptive study is pharmaco-epidemiological based population; the main data has been gathered through PubMed (with the support of NorPD "The Norwegian Prescription Database"). It is also based on 2004 to the 2015 year's data of antipsychotic and antidepressant drugs which dispensed from Norwegian pharmacies. Psychiatric disorders are the main indication and in this research, the main variables were an age group, gender, DDDs (daily defined doses), ID (encrypted person identifiers rather than simple identity), the category of prescription and indication or reimbursement specific codes such as "ICD-10/CPC-2) (Baftiu et al., 2018).

All diagnosis was antipsychotic, antidepressant and antiepileptic drugs prescribed for utilization, with their specific codes of reimbursement. In this research paper elderly patients were described as ≥60 years of age and young patients <60 accordingly, as gathered data further categorized into ten years spanning age groups. Norwegian population data from 2004 -2015 was published in PubMed but supplied by Static Norway (Baftiu et al., 2018).

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

(Source: Baftiu et al., 2018)

2.1Data analyses

SQL (Structured Query Language) was used to analyze the data in the "MySQL" system of database administration. Similarly, reimbursement codes were used to DDDs patients' calculation in epilepsy and some other symptoms. The AEDs usage is obtained as patient's numbers for every DDDs/1000 indication of subgroup inhabitants per day, hereunder DDDs/1000 inhabitants of old age per day and younger inhabitants DDDs/1000 per day. We did not

perform any differential statistical analysis between groups since the data are descriptive and all population was covered (Cross, 2015).

2.2Calculations

For the specific calculation of the DDDs/1000 for inhabitants per day utilization of different antidepressant, antiepileptic and antipsychotic drugs in older age and younger inhabitant, according to the reason, the following calculations were managed:

"DDDs/(1000 old age/younger populaces)/day = Sum DDDs sub-group (old age/younger) * 1000/(365*populaces number ≥ / < 60 years).

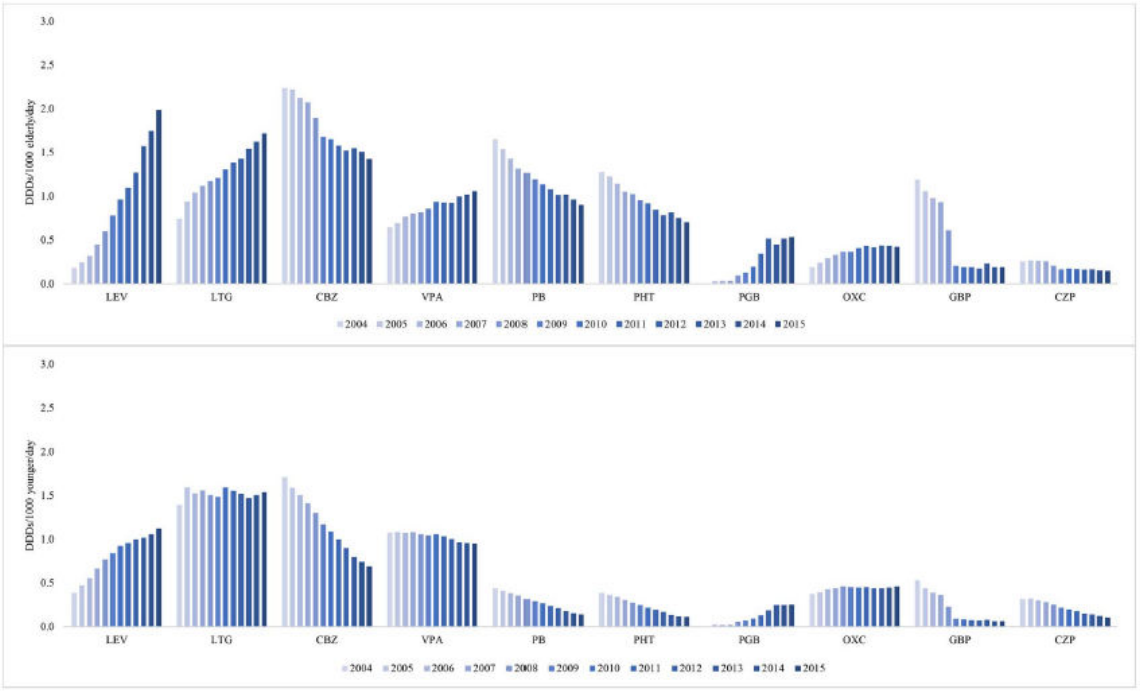
The users' pervasiveness was considered by patients' number dividing ≥ / < 60 years of every sign with inhabitants' number in the ≥ / < 60 age groups (Baftiu et al., 2018).

3.0Results

This specific research covered data about the prescription of AEDs for all signs, and focus associated usage of AEDs with some other drugs regarding antidepressant, antiepileptic and antipsychotic in old age as compared with young age patients.

3.1AED utilization changes in epilepsy and some other disorders both in old age versus younger patients

According to calculation the AEDs using a number of old age patients, specifically for the major signs, has elevated by 200% as compared with younger patients; clearly shown in Table 1 from 20796 patients marked in 2001 till 61756 patients marked in 2015. The AED's user prevalence also elevated from the ratio 2.4% to the ratio of 5.0% in old age and 1.6% to 2.4% in prescribed younger patients from 2004 till 2015. There were two major signs of neuropathic pain and epilepsy according to this data. According to the PubMed Database in 2015, 17896 old age patients (which were 1.6%) and 41668 young age patients (which were 1.0%) are routinely used AEDs to cure their epilepsy disease. The given number has been persistent over many years. The DDDs use measure was averagely 8.7 DDDs/1000 (which SD = 0.) in old age populace/day in the disease of epilepsy versus 6.6 (which SD = 0.3) in young age patients, mentioned in Table 1). According to given "Figure 1" there was a tendency regarding a chosen newer AEDs as levetiracetam, lamotrigine, and oxcarbazepine in the patients of epilepsy, ensconcing 50% of total AEDs in old age and young age patients respectively (Baftiu et al., 2018).



Source "Figure 1" (Baftiu et al., 2018)

According to Table 1, in 2015 32018 numbers of old age patients and 33636 young age patients utilized AEDs for neuropathic pain. The user's prevalence in this pain was 4 times elevated in old age patients as compared with young age patients. The DDDs use elevated more than 10-fold, as measured in 2015 from 2004, 9.6 and 3.5 (old age patients/young age patients) DDDs/1000 subgroup populace/day. They further accounted for 9.1 DDDs per 1000 old age populace per day. Some other anti-epileptic drugs like valproate, lamotrigine, oxcarbazepine, and clonazepam were also utilized less than 0.1% for pain conditions (Ishihara et al., 2016).

3.2Usage of Central Nervous-active drugs in old age patients versus young age patients

These drug classes' usages were analyzed to be equipped with poly-pharmacy study in those patients who were utilizing AEDs since they frequently are utilized in connection due to the usage of AEDs in indications of non-epilepsy and comorbidity epileptic patients. The utilization of antidepressant medicines was in the average of 92 and 41 DDDs per 1000 subgroup populace per day in old age patients and young age populace respectively, according to Table 1, from 2004 to 2015. The old age prevalence which was utilizing antidepressant medicines has been consistent with double values as compared with young age patients (Jones, 2016).

Accordingly, the antipsychotic drug usage accounted for 10 DDDs per 1000 subgroup populace per day in both old age and young populace. While in users' terms with the ratio of 3.5% of old age patients and 1.8% of young age patients utilized the antipsychotic drugs in the time period and olanzapine was highly utilized antipsychotic drug. On the contrary, the mood stabilizer lithium declined during the time in both old age patients and in young age patients too; with the rate of 6% and 20% respectively.

3.3Epileptic patients and poly-pharmacy aspects

It was also observed that poly-pharmacy with the combination of other antidepressant, antiepileptic and antipsychotic drugs in 37% those patients who already taking AEDs for their epileptic issues (with the ratio of 35% of old age populace (n=3347), and in young patients this ratio was 38% (n = 8114), specifically calculated in 2012. There were two most common concomitant usages of drugs with the ratio of 70%, though CNS-active drug combinations were up to nine. Table 2 enumerates the pharmacokinetic interaction extent between antidepressant, antipsychotic and antiepileptic drugs (Pohlen et al., 2017).

Table 2
Quantification of the most common interactions between antiepileptic, antidepressant and/or antipsychotic drugs with implications in elderly and younger patients. The top five most commonly occurring combinations are highlighted.

Antiepileptic drug (AED)	Number of individual patients (n)		Substrate (SUB)	Consequence		Combination frequency	
	< 60 years	≥ 60 years		AED	SUB	< 60	≥ 60
Carbamazepine Induces: CYP 1A2, 2C9, 3A4, UGTs.	2317	1180	**Lamotrigine**	-***	↓↓	**248**	**78**
			Phenytoin	↓↓***	↓↑	46	35
			Valproate	↑↑**	↓↓	**283**	**79**
			Haloperidol	-	↓	17	20
			Olanzapine	-	↓	68	23
			Quetiapine	-	↓↓	23	10
			Risperidone	-	↓↓	63	22
			Amitriptyline	-	↓↓	46	37
			Mianserin	-	↓	40	37
			Lithium*	-	-	12	12
Lamotrigine	4407	1080	Carbamazepine	↓↓	-***	248	78
			Phenobarbital	↓↓	-	58	39
			Phenytoin	↓↓	-	39	18
			Valproate	↑↑	↓	1095	91
			Quetiapine	-	↓	106	19
			Sertraline	↑	-	67	25
Phenobarbital Induces: CYP 1A2, 2C9, 3A4	647	697	**Carbamazepine**	-	↓↓	**141**	**125**
			Lamotrigine	-	↓↓	58	39
			Phenytoin	↑	↓↑	**100**	**212**
			Valproate	↑↑	↓↓	87	46
			Risperidone	-	↓↓	11	5
			Mianserin	-	↓	3	15
Phenytoin Induces: CYP1A2, 2C9, 3A4, UGT. May inhibit: CYP 2C9, 2C19	514	543	Phenobarbital	↑↓	↑	100	212
			Carbamazepine	↓↑	↓↓***	46	35
			Lamotrigine	-	↓↓	39	18
			Valproate	↓	↓↓	45	12
			Risperidone	-	↓	12	5
			Mirtazapine	-	↓	2	15
Valproate Inhibits: CYP 2C9, UGTs	4175	839	Phenobarbital	↓↓	↑↑	87	46
			Phenytoin	↓↓	↓	45	12
			Carbamazepine	↓↓	↑↑**	283	79
			Lamotrigine	↓	↑↑	**1095**	**91**
			Clozapine	-	↓	19	6
			Olanzapine	-	↓	96	42
			Amitriptyline	-	↑	32	13

↓ (decrease)/↑ (increase) = A change in plasma concentration of minor or no clinical relevance, ↓↓ / ↑↑ = A change in plasma concentration with clinical relevance. CYP = Cytochromes P450 family. UGTs = UDP-glucuronosyltransferase.
* Pharmacodynamic interaction.
** Increase of active epoxy metabolite.
*** Possible increase of the active epoxy-metabolite of carbamazepine (contradictory data) (Mula, 2008; Halvorsen et al., 2016; Landmark et al., 2010; Patsalos, 2013a,b).

Source: (Baftiu et al., 2018)

4.0 DISCUSSION:

This specific research offers alterations in the application of the major CNS-active drugs utilization, antidepressant, antipsychotic and antiepileptic drugs in throughout populace with longstanding evaluation where most of the new drugs have entered in the market and multiple regulations in compensation have happened from the tenure 2004 to 2015. Alterations in this drug usage in the old age patients are emphasized and associated to young age patients (Shiozaki and Kajihara, 2018).

4.1Changes in AEDs utilization in old age patient's epilepsy versus younger patients

According to prescribed data, there is an increase in the utilization of AEDs from 2004 till 2015 in local populace due to the AEDs usage in other signs as demonstrated in overall populace. Accordingly, the number of patients utilizing AEDs in epilepsy has been stable over many years. The increased number of old age patients utilizing AEDs in epileptic disease compared with young age patients may be higher prevalence indication of epilepsy in the older age populace. There is a decrease in the use of phenytoin, carbamazepine, and phenobarbital as measured by DDDs/1000 inhabitants/day in both young age patients and older age as well with increasing trend of newer AEDs prescription (Viswanathan, 2016).

4.2Poly-pharmacy clinical implications for the improved safety of patients

It was also observed that poly-pharmacy with anti-epileptic drugs or other drugs of CNS-active in epileptic patients is very common, which further

elevate the pharmacodynamics and pharmacokinetic risk with the interaction of random seizure loss control or highly adverse impacts as consequences. According to this research, there are 42 multiple interactions with probable implications of the clinic were further recognized among the classes of selected drug, expounding the careful monitoring need. The usage of enzyme inducing anti-epileptic drugs (phenytoin, carbamazepine, and phenobarbital) was massive and happened more numerous in combination, specific with antipsychotic drugs. All this upsurges the risk modification of serum deliberations of these given drugs and therefore lack impact but also severe effects (Shiozaki and Kajihara, 2018).

4.3 Methodological Considerations

In this study, the main drugs groups utilized in psychiatry and epilepsy were comprised to give a wider drug utilization overview in a specific populace and also to compare the usage in old age patients versus younger. PubMed Database, which further gathers data from NorPD, giving more strength to the study as NorPD covers the overall country. The overall execution of particular reimbursement codes ("ICD-2/ICPC-10") in the year 2008 provides a thorough indication of the AEDs clinical use of epilepsy along with other disorders (Pohlen et al., 2017).

5.0 CONCLUSION:

The given results explain details about utilization and alteration in AEDs which may further contribute to elevating clinical consideration awareness, particularly, in older age patients. The usage of anti-epileptic drugs in old age patients is elevated, mostly due to pregabalin and gabapentin's extensive usage in neuropathic pain, with specific users' prevalence four times more than in young age patients. This usage is matched more than overall consumption of anti-epileptic drugs in old age patients in the year 2015, with a ratio of 9.6 DDDs/1000 old age inhabitants/day. According to the study, 35% of old age and 38% of younger patient noted polypharmacy while using AED in their epilepsy treatment, with up to 9 drugs of CNS-active use parallel, and inducers of enzyme were frequently utilized in old age patients. The consciousness of elevated AEDs usage, particularly in neuropathic pain in old age patients, also found cautious clinical deliberations when combating poly-pharmacy are of importance for developed patient safety.

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