

Use of antiepileptic drugs in women of fertile age

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ABSTRACT

INTRODUCTION: We studied the use of antiepileptic drugs (AEDs) in women of fertile age and pregnant women in a 16-year-period in Denmark.

METHODS: We included all women of fertile age (age 18-44 years) and pregnant women from 2001 to 2016 identified from Danish registers.

RESULTS: The median proportion of women of fertile age who took AEDs increased from 10.7% (95% confidence interval (CI): 10.5-10.9%) in 2001 to 27.1% (95% CI: 26.8-27.4%) in 2016. Lamotrigine, levetiracetam, gabapentin and pregabalin have been increasingly used over time and have been the main AEDs used in recent years. The use of valproate in women of fertile age decreased slightly from 2.1% (95% CI: 2.0-2.2%) to 1.9% (95% CI: 1.8-2.0%), which was explained by a decrease in the use after 2014 among women aged 18-24 years. The increased use of AEDs was likely owed to use for other indications than epilepsy. The overall use of AEDs in pregnant women increased from 3.8% (95% CI: 3.3-4.3%) in 2001 to 6.9% (95% CI: 6.2-7.6%) in 2016, and the use of valproate decreased from 0.6% (95% CI: 0.4-0.8%) in 2001 and to 0.2% (95% CI: 0.1-0.4%).

CONCLUSIONS: The overall use of AEDs in women of fertile age and pregnant women has increased in the past 16 years, especially due to an increased use of lamotrigine. However, valproate use in pregnant women and in younger women of fertile age has become less frequent.

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A growing number of studies have addressed treatment with antiepileptic drugs (AEDs) during pregnancy and adverse outcomes in children, including congenital malformations and impaired neurodevelopment. Maternal use of valproate in particular during pregnancy has been associated with an increased risk of congenital malformations [1], autism spectrum disorder, poor cognitive skills, attention-deficit/hyperactivity disorder and impaired academic performance [2].

Because of this growing concern regarding the use of valproate in pregnancy, the European Medicine

Agency (EMA) issued a warning concerning its use; if possible, the use of valproate should be avoided in girls and women of fertile age [2] and should be considered only in girls and women with refractory epilepsy who do not respond to other AEDs [3].

The concern increases the need to investigate the use of AEDs in Danish women of fertile age and pregnant women. AEDs are used to manage epilepsy; however, especially the newer AEDs are also increasingly used in the treatment of psychiatric disorders (e.g. bipolar diseases), migraine, trigeminal neuralgia and neuropathic pain [4]. The many new indications for which this drug are given mean that a considerably larger cohort of fertile/pregnant women are now taking AEDs, which adds to the need for continuous surveillance of AED use among women of fertile age and pregnant women.

We analysed the use of AEDs in Danish women of fertile age and in Danish pregnant women from 2001 to 2016. We describe the use of individual AEDs in general and the use of valproate in particular. The findings of the study allowed us to evaluate whether the use of AEDs has been adjusted in Denmark according to recommendations issued by the EMA and especially whether AED use is affected by the warning concerning the use of valproate in women of fertile age and in pregnant women. The findings are relevant for establishing if Denmark has adjusted its prescription practice in the light of the EMA's warning or if further intervention is needed.

METHODS

This was a retrospective cross-sectional study including women of fertile age, defined as women aged 18-44 years, and all women (of any age) who gave birth in the period from 1 January 2001 to 31 December 2016 in Denmark.

We included registered pregnancies leading to live-births at any gestational length and stillbirths from 22 weeks of gestation. We excluded women with unknown length of pregnancy and women who did not live in Denmark one year prior to their pregnancy. Information about drugs used and about the women was linked via the Danish personal identification system using the Danish CPR number [5].

ORIGINAL ARTICLE

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with pregnant woman.



The study relies on the data sources described in the following.

Women of fertile age

Data on prescriptions filled by women of fertile age were obtained from the Danish National Prescription Registry [6]. Their age was determined annually when they filled their first prescription. The size of the underlying population was based on data collected from Statistics Denmark on 1 January each year [7]. In Denmark, AEDs are issued on prescription only, and all sales of AEDs outside hospitals are registered in the Danish National Prescription Registry and have been so since 1994 [6].

Pregnant women

Data on filled prescriptions was obtained in the same manner as for the group of women of fertile age. Information about births was obtained through the Danish Medical Birth Register. As the number of pregnant women using AEDs was low, we did not age-stratify by exposure.

We included the most frequently used AEDs from the Anatomical Therapeutic Chemical Classification System: N03: phenobarbital, clonazepam, carbamazepine, oxcarbazepine, valproate, lamotrigine, topiramate, gabapentin, levetiracetam, zonisamide, pregabalin. N03 drugs are classified as antiepileptic drugs [8].

From 1978 to 1993, six AEDs were released; and after 1993, eight new drugs were released within a decade [9-11]. The drugs investigated in this paper include three drugs released before 1993 – valproate, carbamazepine and phenobarbital – and the eight drugs released from 1993 onwards, including lamotrigine and levetiracetam.

We calculated proportions with exact 95% confi-

dence intervals (CI) using STATA, version 15.2 (StataCorp, College Station, Texas)

Trial registration: none.

RESULTS

Participants

The number of women of fertile age using AEDs was 13,842 in 2001 and 25,270 in 2016. We included data on women who were pregnant from 2001 ($n = 60,618$) to 2016 ($n = 56,818$) according to the Danish Medical Birth Register. A total of 229 pregnant women used AEDs in 2001; by 2016 the number of pregnant women who used AEDs had risen to 389.

Main analyses

In both women of fertile age and pregnant women, we observed an increase in the use of new drugs such as lamotrigine and levetiracetam from 2001 to 2016 (**Figure 1**, **Figure 2** and **Figure 3**). The use of old drugs, including carbamazepine, phenobarbital and valproate, decreased from 2001 to 2016 (Figure 1 and Figure 3) [9].

In the group of women of fertile age, we observed a median increase in the overall use of AEDs from 10.7‰ (95% CI: 10.5-10.9‰) in 2001 to 27.1‰ (95% CI: 26.8-27.4‰) in 2016. There was a slight decrease in the use of valproate; from 2.1‰ (95% CI: 2.0-2.2‰) to 1.9‰ (95% CI: 1.8-2.0‰) in 2016 (**Figure 1**). When we divided the group of women of fertile age (18-44 years) into two groups; 18-24 and 25-44 years, respectively, we found no change in the use of valproate in the 25-44-year-old group (2.1‰ (95% CI: 2.0-2.2‰) in 2001 and 2.1‰ (95% CI: 2.0-2.2‰) in 2016), and a decrease was observed in the 18-24-year-old group (2.1‰ (95% CI: 1.9-2.3‰) in 2001 and 1.4‰ (95% CI: 1.3-1.6‰) in 2016) (Figure 2). In 2016, lamotrigine and levetiracetam were the leading and fourth-most frequently used AED in Danish women of fertile age, and a steady increase in the use of lamotrigine was observed in the group of women of fertile age; from 2.6 ‰ (95% CI: 2.5-2.7‰) in 2001 to 10.9‰ (95% CI: 10.7-11.1‰) in 2016 (Figure 1).

Overall, use of all AEDs during pregnancy among Danish pregnant women rose from 3.8‰ (95% CI: 3.3-4.3‰) in 2001 to 6.9‰ (95% CI: 6.2-7.6‰) in 2016 (Figure 3). In particular, the use of lamotrigine increased from 1.4‰ (95% CI: 1.1-1.7‰) in 2001 to 4.6‰ (95% CI: 4.0-5.2‰) in 2016 (Figure 3). Lamotrigine and levetiracetam were the two most used AEDs among these women. In pregnant women, the use of valproate declined from 0.6‰ (95% CI: 0.4-0.8‰) in 2001 to 0.2‰ (95% CI: 0.1-0.4‰) in 2016 (Figure 3).

The proportion of pregnant women who used valproate during their pregnancy in 2016 was equal to the

proportion of pregnant women using carbamazepine. We identified no use of phenobarbital in pregnant women in 2016.

DISCUSSION

In both women of fertile age and pregnant women, the overall use of AEDs increased, whereas the use of valproate decreased slightly in both groups from 2001 to 2016. However, in the group of fertile women, only a slight decrease in the use of valproate from a median of 2.1‰ (95% CI: 2.0-2.2‰) to 1.9‰ (95% CI: 1.8-2.0‰) was observed, and this decrease was driven by the younger age group (18-24 years). In pregnant women, valproate use decreased from 0.6‰ (95% CI: 0.4-0.8‰) of all pregnancies in 2001 to 0.2‰ (95% CI: 0.1-0.4‰) in 2016.

Strengths

We included all women of fertile age and pregnant women in Denmark for a 16-year period. We had information on all filled prescriptions for AEDs in the study population. The linkage of data based on the CPR number ensures accurate identification of individuals and their prescription of AEDs [5].

Limitations

The study has several limitations. The register data include no information on drug compliance, and such information would naturally add to their relevance. Studies have shown that women filling a prescription for AED were also more likely to take the drug [12].

We had no information on other drugs that the pregnant women and women of fertile age might have consumed, or if they consumed more than one drug at a time. We defined women of fertile age as women aged 18-44 years, which includes the majority of women of fertile age. Naturally, women may become fertile at a younger age than 18 years and some may remain fertile beyond the age of 44 or stop being fertile before the age of 44. Nevertheless, our definition includes the vast majority of women of child-bearing potential. When we stratified the group of women of fertile age into two groups (18-24 and 24-44 years), the decrease in the use of valproate was observed only in the young group. The reason for this may be that doctors consider the probability of pregnancy more relevant in younger women and therefore are more cautious with prescribing valproate to this group – in line with the EMA’s warning regarding the use of valproate in women of fertile age in general [2]. Among the reductions observed in the young age group, the steepest decline was observed from 2012 to 2016. Despite EMA’s warning against the use of valproate in women of fertile age, valproate was still used by 1.9‰ (95% CI: 1.8-2.0‰) women of fertile age in 2016.

FIGURE 1

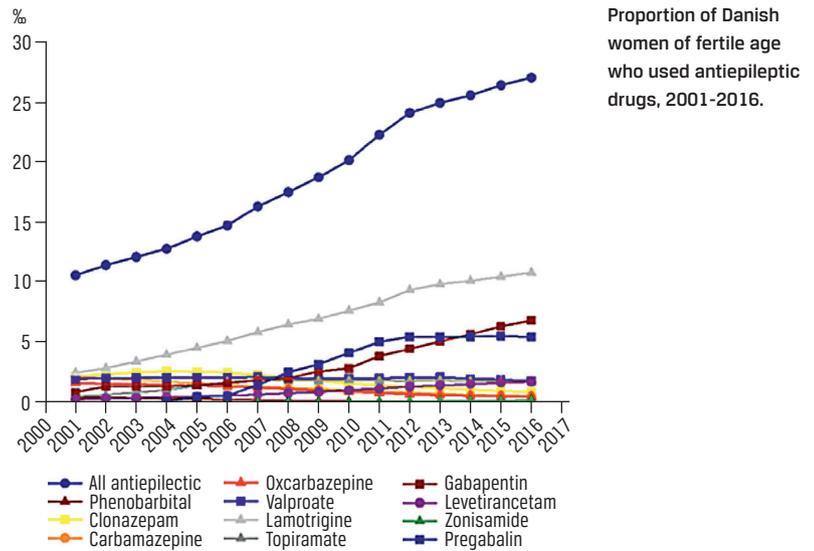
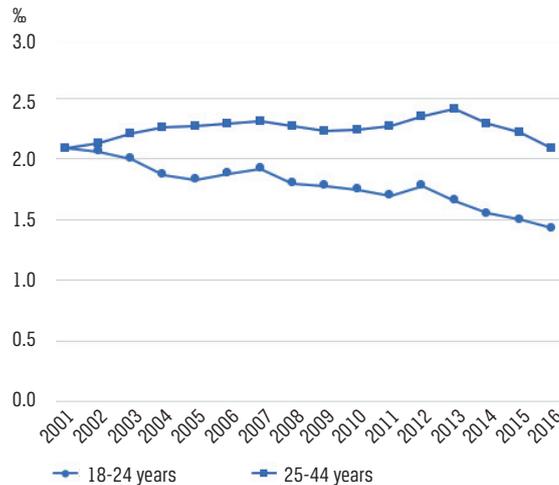


FIGURE 2

Proportion of Danish women of fertile age who used valproate during their pregnancy 2001-2016, by age group.

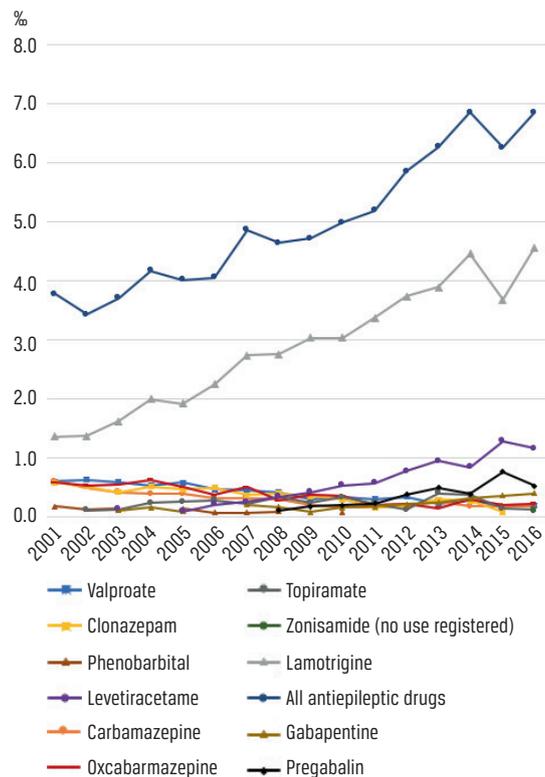


We observed a substantial decrease in the use of valproate in both fertile women and pregnant women. This may reflect both that women with ongoing treatment are being taken off valproate and that the number of new valproate users is decreasing.

Despite the EMA’s recent warning against valproate and the large amount of literature on the harmful effects of valproate [1], its use remained stable in the 25-44-year age group and decreased only in the group of 18-24-year-olds (thereby lowering the total use of valproate in women of fertile age). The steady decline in the number of users of valproate observed from 2012 with little change in the ongoing decline after 2014

 **FIGURE 3**

Proportion of Danish pregnant women who used antiepileptic drugs during their pregnancy, 2001-2016.



may indicate that the EMA warning was not a significant contributing factor to the decline. Instead, the large amounts of information available already before the EMA warning was issued may have contributed to the observed decline. However, continuous use of valproate by women of fertile age after 2014 may also reflect that some women with epilepsy may not achieve seizure freedom with other drugs.

Some of the AEDs in this study are associated with an increased risk of congenital malformations, and such malformations may lead to miscarriage or induced abortion [13]. However, a Danish study found that only a slightly increased risk for spontaneous abortion was associated with AED use in pregnancy [14], and the underestimation may therefore be limited.

The increased use of AEDs among pregnant women may be due to the fact that a growing number of women with chronic diseases, including epilepsy, give birth [15]. For example, the proportion of pregnant women with epilepsy rose from 0.5% in 1989-1993 to 0.78% in 1999-2003 and then to 0.98% in 2009-13 [15]. This may account for some of the increase in the use of AEDs among pregnant women. However, because the proportion of women who use AEDs is much higher than the proportion of women with epilepsy, the increased use of AEDs is likely due to use for other indications than epilepsy [16].

Generalisability

A recent Swedish study also investigating initiation of valproate treatment in women [17], included data from 2011 to 2017 among women aged 0-45 years with epilepsy and/or psychiatric diagnoses. The Swedish study compared these women with men aged 0-45 years with the same diagnoses and found a slight decrease in initiation of valproate treatment in women before the EMA warning in 2014 [2], and after the warning they found a significant decrease in initiation of valproate treatment, i.e. 2,293 women initiated valproate treatment from 2011 to 2014 and only 1,300 from 2014 to 2017.

A comparable Norwegian study included data from 2010 to 2015 and found a 5% decrease in the number of women being prescribed valproate, which again shows a trend that is comparable to the one established in our study [18].

A Dutch study covered seven European countries, including Denmark [10]. The authors observed an annual increase between 6% and 15% in the use of AEDs, which was entirely due to an increase in the use of the newer AEDs marketed since the 1990s. These results are thus in keeping with the result of the present study, where an increase was observed for newer AEDs accompanied by a slow decrease in the use of valproate, especially since 2014. In Denmark, the authors found an annual 6% linear increase in the use of AEDs; they assumed that this increase was due to an increase in the use of newer AEDs. These results are thus in keeping with the result reported in the present study, where the increase found is also due to the use of newer AEDs.

Lamotrigine does not seem to be associated with an increased risk of adverse outcomes in the offspring [19], but it may be associated with an increased seizure frequency when used during pregnancy in women with epilepsy [20]. However, the use of lamotrigine increased significantly over the study period, and lamotrigine is now clearly the most frequently used AED in women of fertile age and in pregnant women.

CONCLUSIONS

The overall use of AEDs increased for both women of fertile age and for pregnant women from 2001 to 2016. The use of valproate in Danish women of fertile age and pregnant women has decreased in recent years following reports about adverse birth outcomes after valproate exposure in pregnancy. However, the decrease was seen in the pregnant women only and in the younger women of fertile age, not in older women of fertile age (25-44 years of age).

The most frequently used AED in women of fertile age and pregnant women in Denmark is lamotrigine. In 2016, gabapentin, levetiracetam and pregabalin were the three most frequently used AEDs following lamo-

trigine in women of fertile age and pregnant women alike.

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LITERATURE

1. Kaneko S, Battino D, Andermann E et al. Congenital malformations due to antiepileptic drugs. *Epilepsy Res* 1999;33:145-58.
2. European Medicines Agency. Valproate and related substances. EMA, 2019.
3. Perucca P, O'Brien TJ, Eadie M et al. Valproate still has a place in women with epilepsy. *Epilepsia* 2015;56:1175-6.
4. Johannessen Landmark C, Larsson PG et al. Antiepileptic drugs in epilepsy and other disorders – a population-based study of prescriptions. *Epilepsy Res* 2009;87:31-9.
5. Pedersen CB, Gotzsche H, Møller JO et al. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bul* 2006;53(4):441-9.
6. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39(7 Suppl):38-41.
7. Statistics Denmark 2019. www.dst.dk (16 Jun 2019).
8. WHO ATC Methodology. ATC/DDD Index 2019. www.whocc.no/atc_ddd_index/ (16 Jun 2019).
9. Hung OL, Shih RD. Antiepileptic drugs: the old and the new. *Emerg Med Clin North Am* 2011;29:141-50.
10. de Groot MC, Schuerch M, de Vries F et al. Antiepileptic drug use in seven electronic health record databases in Europe: a methodologic comparison. *Epilepsia* 2014;55:666-73.
11. Tolou-Ghamari Z, Zare M, Habibabadi JM et al. A quick review of carbamazepine pharmacokinetics in epilepsy from 1953 to 2012. *J Res Med Sci* 2013;18(Suppl 1):S81-S85.
12. Olesen C, Sondergaard C, Thrane N et al. Do pregnant women report use of dispensed medications? *Epidemiology* 2001;12:497-501.
13. Tomson T, Battino D, Perucca E. Teratogenicity of antiepileptic drugs. *Curr Opin Neurol* 2019;32:246-52.
14. Bech BH, Kjaersgaard MI, Pedersen HS et al. Use of antiepileptic drugs during pregnancy and risk of spontaneous abortion and stillbirth: population based cohort study. *BMJ* 2014;349:g5159.
15. Jølvig LR, Nielsen J, Kesmodel US et al. Prevalence of maternal chronic diseases during pregnancy - a nationwide population based study from 1989 to 2013. *Acta Obstet Gynecol Scand* 2016;95:1295-304.
16. Tsiropoulos I, Gichangi A, Andersen M et al. Trends in utilization of antiepileptic drugs in Denmark. *Acta Neurol Scand* 2006;113:405-11.
17. Karlsson Lind L, Komen J, Wettermark B et al. Valproic acid utilization among girls and women in Stockholm: Impact of regulatory restrictions. *Epilepsia Open* 2018;3:357-63.
18. Landmark CJ, Fossmark H, Larsson PG et al. Prescription patterns of antiepileptic drugs in patients with epilepsy in a nation-wide population. *Epilepsy Res* 2011;95:51-9.
19. Diav-Citrin O, Shechtman S, Zvi N et al. Is it safe to use lamotrigine during pregnancy? A prospective comparative observational study. *Birth Defects Res* 2017;109:1196-203.
20. Tomson T, Perucca E, Battino D. Navigating toward fetal and maternal health: the challenge of treating epilepsy in pregnancy. *Epilepsia* 2004;45:1171-5.