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Benzodiazepines for pediatric epilepsies and their risks in a cohort within the French health care data

Short title: Risks of benzodiazepines for pediatric epilepsy

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

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Abstract:

Objectives: The management of antiseizure treatment in patients with epilepsy relies on the benefit-risk ratio. Data on antiseizure medication (ASM) use in children are limited. We described antiseizure medication use in children with epilepsy (CwE) in France, with a focus on the chronic use of benzodiazepines and related implications.

Methods: We conducted a 5-year cohort study from January 2012, using data from the French national healthcare data system (SNDS). We included CwE, identified through ICD-10 codes and medications from January 2012 to December 2015 and followed them until December 2016. We described antiseizure medications and assessed whether the risk of initiating a polytherapy after a bitherapy depends on whether or not benzodiazepine was included in the bitherapy.

Results: We identified 62,885 CwE. Valproate was the most reimbursed ASM (40%) followed by lamotrigine (17.6%), levetiracetam (9.3%), clobazam (6.1%), and carbamazepine (5.8%). Prescriptions were initiated at the hospital in 74,5% of CwE. We observed a decrease in the number of CwE with at least one benzodiazepine reimbursement from 15.3% in 2013 to 10.1% in 2016 ($p < 0.0001$). The prevalence of CwE with levetiracetam reimbursements increased while that of CwE with valproate decreased. A switch from a bitherapy to a polytherapy was more likely when the bitherapy included a benzodiazepine (sHR = 1.20 [1.03 - 1.39]).

Significance: The prevalence of CwE with at least one benzodiazepine reimbursement decreased during the study period. Benzodiazepines were associated with an increased use of subsequent ASM polytherapy.

Keywords: antiseizure medications, benzodiazepine, epilepsy

Key points:

- Using the French national healthcare data system, we identified the prescription of antiseizure medication in children with epilepsy
- Looking at the antiseizure medication, valproate was the most reimbursed followed by lamotrigine, levetiracetam, clobazam, and carbamazepine.
- We observed a decrease in the daily use of benzodiazepines over the study period (2012-2015)
- There was a higher cumulative incidence of polytherapy in children who received a bitherapy with a benzodiazepine as compared to those not using any benzodiazepine

Introduction

Epilepsies affect about 1% of the general population, with a higher incidence in children and adolescents. Globally, 20%–30% of all patients with epilepsy have drug-resistant epilepsy (DRE)^{1 2}. The disease management is in part based on the use of antiseizure medications (ASM). The aim is seizure freedom when possible and, in DRE, maintaining the patient's quality of life should be the ultimate goal³. The choice of ASM is based on a benefit-risk balance. Epilepsy impacts cognition and this effect can be worsened by the prescribed ASM,^{4 5} which is a matter of concern, particularly in children and adolescents.

The ASM management begins with a monotherapy, followed by another monotherapy if needed. Then, a first bitherapy is introduced, followed by other bitherapies when seizure freedom is not achieved or when the benefit-risk balance seems inadequate. The choice of the two combined ASM is frequently based on the concept of “rational bitherapy”, which refers to the use of two ASM with different mechanisms of action. This concept is deemed more relevant, to avoid side effects, than improving the antiseizure effect^{5 6}. Lowering the number of concomitant ASM also decreases the risk of treatment-related cognitive effects^{5 7}. Benzodiazepines are used as rescue drugs for prolonged or acute repetitive seizures or as daily ASM for chronic treatment. In France, two benzodiazepines are approved for generalized- or focal-onset seizures in combination with other ASM: clobazam (CLB) in children of 6 years and older, and clonazepam (CNZ) without age restriction; the latter can also be used in monotherapy.

Several concerns can be raised regarding the chronic use of benzodiazepines for pediatric epilepsies. First, while chronic benzodiazepine use has been associated with an increased risk of dementia in adults^{8 9}, there are very few studies assessing the cognitive and behavioural impact of benzodiazepines on children with epilepsy (CwE), including potential long-term risks. Second, the pharmacological properties of benzodiazepines raise questions regarding the risk of withdrawal effect with seizure recurrence or worsening leading to a need to increase the ASM regimen in benzodiazepine users¹⁰. Here, using the French healthcare data system (Système National des Données de Santé, SNDS) from 2012 to 2016, we aimed to describe the ASM use in children and adolescents with epilepsy in France, with a focus on the use of benzodiazepines, specifically assessing the risk of polytherapy prescriptions after a bitherapy depends on whether or not benzodiazepine was in the bitherapy.

Methods

Study design - Data source

We conducted a 5-years historical cohort study using the French national healthcare database. The SNDS includes the inter-scheme consumption data” (Données de Consommation Inter-Régimes, DCIR) and the French hospital discharge database (Programme de Medicalisation des Systemes d’Information, PMSI), linked via unique patient identifiers^{11 12}. The DCIR contains individualized, reimbursement claims of individuals insured with the main insurance schemes in France including prescribed drugs. The PMSI provides hospital discharge summary with diagnoses coded with the international classification of diseases ICD-10. Long term disease status as well as some sociodemographic characteristics are also available. These data are prospectively and exhaustively recorded and cover 99% of the entire French population (~67 million). The general scheme for salaried workers and their dependents covers 76% of the population, and provides the best data quality.

Study population

The study population was composed of CwE aged 0 to 17 years at study entry. Epilepsy was confirmed based on the presence of at least one of the following criteria: (1) at least three reimbursements for ASM within a 6-month period, (2) at least two reimbursements for ASM within a 6-month period and a Long Term Disease (LTD) registration for epilepsy (ICD-10 G40 or G41), or (3) at least two reimbursements of ASM within a 6-month period beginning at most 3 months before hospitalization with a diagnosis code of epilepsy.

Reimbursements for gabapentin or CNZ as monotherapy were not considered for the definition of epilepsy. While they have alternative medical uses, in particular for neuropathic pain, these drugs are not currently used in the medical practice as ASM monotherapy. Likewise, the unique reimbursement of rectal diazepam or buccal midazolam were not considered eligibility criteria either.

In addition, to be included, children had to be covered by the general health insurance scheme for at least 1 year at the first fulfilment of the definition of epilepsy (or since birth for those included before the age of 1 year).

Study periods

The observation period started on January 1, 2012 and ended on December 31, 2016, with a look-back period (from January 1, 2011 to December 31, 2011) to capture baseline characteristics; the inclusion period started on January 1, 2012 and ended on December 31, 2015, which allowed us to follow all patients up for at least 1 year. The index date is the date of the first fulfilment of the definition of epilepsy. Children were then followed until their 18th birthday, death, withdrawal from the general health insurance scheme or 31 December 2016, whatever came first.

Definitions

Comorbidities were identified with ICD-10 codes from LTD status and hospital discharge summary, focusing on neurodevelopmental disorders, structural abnormalities on neuroimaging, psychiatric comorbidities, genetic disorders and neurodegenerative disorders.

ASM were identified through the Anatomical Therapeutic Chemical [ATC] Classification codes (international standardized classification of drugs).

A stable bitherapy was defined as a bitherapy (i.e. two concomitant ASM) maintained for at least 6 months and a “rational bitherapy” as a bitherapy including two ASM with different mechanisms of action. Off-label use was defined relatively to age only, as the database does not allow identifying other off-label situations (namely seizure type and epilepsy syndrome) with adequate accuracy. When patients switched from mono- to biotherapy (i.e. two concomitant ASM), or bi- to polytherapy (i.e. at least three concomitant ASM), only bi- and polytherapies maintained for at least 3 months were considered, to avoid considering as association of drugs patterns of drug deliveries related to successive treatments. More details are provided in supplementary material 1.

Statistical analysis

The prevalence and incidence of use of benzodiazepines with their 95% confidence interval (CI) as well as the ASM delivered were described and those totalizing 90% of all dispensed prescriptions were reported (drug utilization 90%, DU90%). DU90% is a simple indicator reflecting prescribing or drug use. It has been proposed as a means of focusing on the most commonly used drugs to make reporting easier. ASM were ranked in order of number of drug boxes delivered each year in the population. Drugs included in the DU90% are those accounting for 90% of the ASM boxes delivered.

To evaluate the variation over time in the prevalence of use of benzodiazepines, we used a Poisson regression model including the calendar year as a covariate and the duration of follow-up as offset.

The cumulative incidence of initiation of a polytherapy in patients receiving a stable bitherapy including a benzodiazepine was compared to those on a bitherapy without a benzodiazepine with a Fine and Gray model, taking into account the competitive risks of discontinuation of the initial bitherapy (i.e. switch to monotherapy, switch to another bitherapy or ASM discontinuation) with inverse probability of treatment weighting (IPTW). The propensity score includes sex, hospital admission for epilepsy in the month before the initiation of the stable bitherapy, number of different ASM delivered in the last 6 months (<3 or ≥ 3), time from first ASM to first bitherapy (< or ≥ 1 year) and the ASM taken before the start of the bitherapy (see supplementary material 2). The process of IPTW allows to balance the covariates between groups (those exposed and those non-exposed to the treatment) and thus controlling for confounding variables by structuring the weighted population in a way that the treatment is no longer dependent on the confounder. In a sensitivity analysis, we excluded CwE exposed to benzodiazepines in the period preceding the initiation of bitherapy.

All hypotheses were tested with a level of two-tailed statistical significance of $p < 0.05$. Analyses were conducted using SAS guide software.

Quality insurance

This study was conducted according to the European Centre for Pharmacovigilance and Pharmacoepidemiology (ENCePP) methodological standards and code of conduct. This study is reported as per the STROBE¹³ and RECORD-PE guidelines¹⁴ (supplementary material 3)

Regulatory and ethical aspects

This study was approved by the French « Commission Nationale Informatique et Libertés » (French data protection agency, regulatory authorization DE-2017-159).

Results

Studied population

We identified 62,885 CwE in the inclusion period, resulting in a 217,586.2 person-year follow-up with a median of 3.6 years (interquartile range, 2.2–4.9) (figure 1). A total of 19,387 (30.8%) CwE had been hospitalized for epilepsy at least once, and 4860 (7.7%) had been hospitalized for status epilepticus. The main characteristics of the whole study population can be found in table 1.

ASM and rescue drug use

Valproate (VPA) was the mostly used ASM in children over the study period, followed by lamotrigine (LTG), levetiracetam (LVT), CLB and carbamazepine (CBZ) (figure 2). While the prescription of ASM was mostly initiated at the hospital (table 1), 28.2% of CwE had been admitted at least once in the month before the ASM initiation. The renewal of ASM prescriptions was also mainly done at the hospital. Of all CwE, 21,936 (34.9%) received at least one off-label ASM, based on their age.

Among the 62,885 CwE, 14,109 (22.4%) received a bitherapy and 7.4% a polytherapy over the study period. The five most common bitherapies in incident users are shown in figure 2. A bitherapy was initiated after a single monotherapy in 36.7% of the CwE while 63.3% were administered a bitherapy after at least two successive monotherapies. Among the CwE receiving a bitherapy, 208 (1.5%) received at least one “non-rational bitherapy”.

We also identified that 4,641 (7.4%) of all CwE received a polytherapy over the study period. The five most common polytherapies were VPA+LTG+CLB (8.8%), VPA+LVT+CLB (3.6%), VPA+topiramate (TPM)+CLB (3.1%), VPA+LTG+LVT (2.7%) and VPA+stiripentol (STP)+CLB (2.6%). The five most common polytherapies in incident users were VPA+LTG+CLB (12.4%), VPA+LVT+CLB (5.7%), VPA+LTG+ethosuximide (ETH) (3.5%), LTG+LVT+CLB (3.4%) and VPA+STP+CLB (3.2%).

Over the study period, the number of new users of benzodiazepines decreased over time (figure 3). More precisely, new users of LVT increased over time while new users of VPA seemed to decrease in more recent years, with a similar pattern when considering prevalent users (Figure 2). Figure 3 shows the decrease in prevalent users of benzodiazepines over the study period, from 15.3% in 2013 to 10.1% in 2016 (RR = 0.65 IC95% [0.62;0.68],

p<0.0001). Overall, 44.5% of all CwE were reimbursed rescue medication at least once over the study period, and 24% were reimbursed rescue medication at least twice per year.

Risk of polytherapy initiation after bitherapy with or without benzodiazepine

Among the 10,606 new users of a stable bitherapy, 1,270 switched to a polytherapy. As shown in figure 4, the risk of a CwE switching to a polytherapy was higher when the bitherapy included a benzodiazepine (sHR = 1.20 [1.03 - 1.39]). Besides, among the 5,981 new users of a stable bitherapy that haven't receive any benzodiazepine in the period preceding its initiation, 618 switched to a polytherapy (sHR = 1.22 [0.96 - 1.56]; p=0.129).

Discussion

In French CwE, we observed a decrease in the daily use of benzodiazepines over the study period but only minor changes in the most common monotherapies, bitherapies or polytherapies except for LVT, which use increased over the study period. In addition, we a higher cumulative incidence of polytherapy in the CwE that received a bitherapy with a benzodiazepine as compared to those not using any benzodiazepine. The off-label use reflects the well-identified limitations in the pediatric drug development in general as well as for ASM^{15 16}.

Despite population-based, our study has some limitations. First, the SNDS does not provide clinical information concerning seizure frequency or control. It also does not provide accurate information on seizure types and epilepsy syndromes, thus precluding the identification of off-label use except that related to age. Prevalence of off-label use is thus probably underestimated. Second, the observation period ended in 2016, due to the very long process to obtain the data. However, trends in drug use are likely to persist (as shown in more recent data from other countries¹⁷). More importantly, the higher risk of initiating a polytherapy from a bitherapy including a benzodiazepine is probably due to the pharmacological properties of benzodiazepines, and it is thus very unlikely that these findings would have changed with the inclusion of more recent data. However, this is an observational study, and despite statistical analysis accounted at best potential confounding factors available in the database, we cannot waive the possibility that this finding reflects the results of residual confounding from other factors not available in the database (such as the seizure type or the epilepsy syndrome, etc.). Third, other risks of benzodiazepine chronic use, such as those of short- and long-term cognitive impacts, could not be studied because the SNDS these features are not available.

We found that 22.4% of all CwE received a bitherapy and 7.4% a polytherapy during the study period. These patients are most likely to fulfil the criteria for DRE¹. This proportion of DRE in our population is consistent with other epidemiological data, that indicates a proportion of DRE in children between 20% and 35%^{2 18 19}. CLB is the most commonly benzodiazepine prescribed in France, and the use of CNZ and CLB decreasing over the study period differs from the recent Norwegian report where CNZ was more commonly prescribed than CLB. In Norway, the evolution of prescriptions from 2009 to 2018 indicates a decrease in CNZ use and an increase in CLB use¹⁷. CLB does not have any special status in France, contrary to the orphan designation it has in some other countries. There is no data regarding

the safety or the efficacy of both of these drugs that might explain this, and it might be related to some regulatory changes in France in 2011 that made the prescription of CNZ more restrictive (only to be done by certain specialists, only secured prescriptions and only for a limited period of time)^{20 19 18}

Preventing overuse of daily benzodiazepine in ASM regimens is sensible, especially looking at the associated risk of higher likelihood of switching to a polytherapy when an earlier bitherapy contained a benzodiazepine, as observed in our study. This phenomenon has never been demonstrated but is in line with our clinical experience. The use of a polytherapy after a bitherapy suggests that the initial bitherapy did not lead to adequate seizure control and that switching to another bitherapy was not possible. This might be due to a rebound effect with a recurrence of the original symptoms (seizure frequency and seizure intensity) each time a discontinuation or a down-titration of the benzodiazepine is tried¹⁰. The SNDS database does not contain data on seizure control, which limits our interpretation of what led to the switch to a polytherapy in such cases. This finding is of particular concern, since polytherapies are associated with higher side effect risks including cognitive and behaviour side effects at a time when cognitive development is at its paroxysm⁵. CwE receiving monotherapies have been shown to experience significantly fewer cognitive side effects than those receiving polytherapies (RR, 0.61; 95%CI 0.47–0.79)²¹.

We identified that prescription of benzodiazepine is associated with a higher risk of ASM polytherapies after a bitherapy with a benzodiazepine. This modifies the benefits-risks ratio of these compounds for a daily use as ASM in CwE, and thus should be accounted for in pediatric epilepsy treatment guidelines. At the French level, we should reconsider the use of 'valproate+clobazam' as a common bitherapy for CwE. Bringing attention to this data could prompt more careful consideration when choosing the initial ASM combination.

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Contributor and guarantor information

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

The contribution of the authors was: -planning and design of the study: Auvin, Tubach; - study conduct: De Rycke, Guillo, Tubach, Tran; -data interpretation and reporting: Auvin, Guillo, Tubach.

Dr Auvin and Dr Tubach accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Competing interests

S. Auvin has served as a consultant or received honoraria for lectures from Angelini Pharma, Biocodex, Biomarin, Eisai, GW Pharma, Neuraxpharm, Nutricia, UCB Pharma, Xenon, Zogenix. He has been an investigator for clinical trials for Eisai, UCB Pharma, Xenon and Zogenix. F. Tubach is head of the Pharmacoepidemiology Centre of the AP-HP and of the Clinical Research Unit of Pitié-Salpêtrière Hospitals; both these structures have received unrestricted research funding, grants and consultancy fees from a large number of pharmaceutical companies that have contributed indiscriminately to the salaries of its employees; F. Tubach did not receive any personal remuneration from these companies. D. Tran, Y. De Rycke and S. Guillo have no competing interest.

Data availability

According to the policy of the SNDS and the data transfer agreement signed between the Cephepi and the French healthcare insurance (CNAM), the data are available only on the CNAM portal for a period of 5 years and only for authorized people, thus, these data cannot be shared. Identification and storage of dataset is under CNAM responsibility, in accordance to SNDS policy.

Transparency

The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

Tables

Table 1: Main characteristics of the children with epilepsy at index date

	Children with epilepsy (n=62,885)
Male	34,083 (54.2%)
Age <i>Median (Q1-Q3)</i>	9 (4-13)
Complementary universal health coverage	18,321 (29.1%)
At least one hospitalization for epilepsy	19,387 (30.8%)
At least one hospitalization for status epilepticus	4,860 (7.7%)
Long-term disease (LTD) status for epilepsy	19,810 (31.5%)
Long-term disease (LTD) status for associated disorders	
neurodevelopmental disorders	17,596 (41.2%)
structural abnormalities on neuroimaging	13,744 (32.2%)
psychiatric disease	2,627 (6.2%)
genetic disorders	1,726 (4%)
neurodegenerative disorder	1,379 (3.2%)
Type of prescribers of first ASM	n=26,531
Hospital	19,772 (74.5%)
GP	2,895 (10.9%)
Neurologist	2,687 (10.1%)
Pediatrician	847 (3.2%)
Type of prescribers of first bitherapy	n=10,552
Hospital	7,885 (74.7%)
GP	1,369 (13%)
Neurologist	738 (7%)
Pediatrician	437 (4.1%)
Type of prescribers of first polytherapy	n=3,444
Hospital	2,742 (79.6%)
GP	419 (12.2%)
Neurologist	130 (3.8%)
Pediatrician	109 (3.2%)
Off-label use (based on the age)	21,936 (34.9%)
Rescue Drug deliveries user*	7,718 (12.3%)

*CwE with at least two reimbursements of a rescue drug over a 3-month period

Legends of the figures

Figure 1: Study flow chart

Figure 2: ASM totalizing 90% of all dispensed prescriptions (DU90%): all antiseizure medications (mono-, bi-, poly-therapy), first antiseizure medication, first bitherapies

Figure 3: Prevalence of benzodiazepine users over the study period

Figure 4: Cumulative incidence of initiation of a polytherapy in patients receiving a stable bitherapy according to whether or not the stable bitherapy included a benzodiazepine (accounting for the competitive risk of switch to monotherapy, switch to another bitherapy of ASM discontinuation) with Inverse probability weighting on propensity score.

Supplementary materials:

Supplementary material 1: Definitions and codes

Supplementary material 2: Propensity score

Supplementary material 3: Strobe and Record

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