Epilepsy & Behavior 82 (2018) 133–139

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Off-label use and manipulations of antiepileptic drugs in children: Analysis of the outpatient prescriptions in a tertiary center

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ARTICLE INFO

Article history:
Received 12 December 2017
Revised 7 March 2018
Accepted 8 March 2018
Available online xxxx

Keywords:
Antiepileptic drugs
Off-label
Manipulation
Outclinic
Outpatient
Epilepsy

ABSTRACT

Objectives: Little is known about off-label use and manipulations to achieve the prescribed dose of antiepileptic drugs (AEDs) in outpatient prescriptions. This study aimed to evaluate this practice in a tertiary center for child epilepsy.
Methods: We reviewed off-label use and manipulations of AEDs delivered to the outpatient's epilepsy clinic. Multivariate logistic regressions were used to determine the factors associated with off-label and manipulated uses.
Results: Five hundred eleven consultations generated 897 AED deliveries (1.75/consultation). Off-label use involved 182 (20.3%) of prescribed AEDs. Factors associated with off-label use were polytherapy and new AEDs while increase of age and nondevelopmental and structural–metabolic etiologies have a protective effect. Among the 1725 doses of AEDs prescribed per day, 33.5% generated manipulations ($n = 582$): 40% inadequate ($n = 237$) and 60% adequate (203 syrups, 112 scored tablets, 30 drops medicine). Polytherapy ($p < 10^{-4}$) and the absence of market authorization significantly favored manipulations whereas the increase in age restricted them.
Conclusion: Off-label use and manipulations of AEDs remain an important problem in home care of children with epilepsy. This is mainly a concern for the most vulnerable groups, i.e., young patients, patients undergoing polytherapy, and patients with developmental and epileptic encephalopathy (DEE). International initiatives have been launched to improve the availability of labeled and adapted drugs in this population.

1. Introduction

Epilepsy is the most common child neurological pathology worldwide, with approximately 10.5 million children affected by active epilepsy [1]. Since the first use of bromide as an antiepileptic drug (AED) in 1857, a continuous effort has been provided to develop efficient AEDs. Current therapeutic arsenal count around 24 AEDs, which could be categorized as first generation AEDs (developed before 1990s) and new AEDs (2nd and 3rd generation respectively developed in the 1990s and in the last 5 years). However, 6–28% of children present intractable epilepsy because of a lack of efficacy and/or emergence of side effects [2]. New AEDs have improved tolerability and adherence facilitation with similar efficacy [3], and most of them target drug-resistant focal epilepsy as "add-on therapies" in adult and older pediatric populations. Only few AEDs target younger ages, and a few, such as stiripentol, rufinamide, and recently, cannabidiol and fenfluramine, are registered for rare epilepsy syndromes like Dravet and Lennox–Gastaut syndromes.

Financial incentives have been promoted since 2000 in the United States (US) and since 2006 in the European Union (EU) to encourage pharmaceutical companies to perform specifically pediatric trials and a regulation on medicinal products for pediatric use. However, the registered therapeutic arsenal for pediatric epilepsies remains limited to date probably due to the fact that "most epilepsy syndromes, specifically pediatric, are excluded from drug development" [4]. The low rate of registered AEDs for children and the high rate of pharmacoresistance frequently lead child neurologists to prescribe off-label AEDs. The term "off-label therapies" has been defined as the use of a drug beyond the specifications of its market authorization (MA) in terms of dose or

Abbreviations: AED, antiepileptic drug; MA, market authorization; ADR, adverse drug reactions; DEE, developmental and epileptic encephalopathy; PGenetic, pharmacoresponsive genetic epilepsies; Struct./met., structural–metabolic etiologies confirmed or suspected.

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https://doi.org/10.1016/j.yebeh.2018.03.013
1525-5050/

frequency, indication, age, administration… [5]. Several studies have demonstrated a clear link between off-label use and adverse drug reactions (ADR) [6,7]. In a prospective cohort, off-label and unlicensed drugs increased the risk of ADR by 1.7 compared with licensed drugs [6]. In a recent prospective study about ADR due to antiepileptic drugs in children with an assessment of behavior and cognitive function using standardized tools, the rate of ADR in this population was about one-third, and the most common ADR were behavioral problems and somnolence [8].

Another problem associated with drug prescription in children is the risk of medication error due to the frequent lack of optimal pediatric formulation. Patients and caregivers often need to manipulate the existing formulation(s) of the drug to achieve the dose prescribed. Manipulation may result in inadequate procedures, such as fractioning sachets. But some other conditions, considered adequate from the MA point of view, may also require manipulations, such as preparing syrups or counting drops for drugs that are in solution form.

Both conditions of off-label and manipulated drug use remain incompletely documented for AEDs in children, mainly for outpatients' prescriptions. This study aimed to evaluate this use in a tertiary center for pediatric epilepsies and to identify the correlated factors for this practice.

2. Material and methods

2.1. Data collection

This was a prospective cross-sectional study in a tertiary center for child epilepsy (Centre de reference des epilepsies rares, Necker-Enfants Malades Hospital). Data on AEDs (dosage, galenic form, and number of doses/day) were retrieved from a copy of the prescription delivered at the outpatient clinic between January and December 2012. Clinical data were extracted from patients' files and enclosed were date of birth, age, weight, epilepsy syndrome, and type of seizures. All patients and legal guardians gave written consent to participate in this study. The study was approved by our institution's local ethical committee.

Epilepsy syndromes were defined according to the International League Against Epilepsy (ILAE) classification [9] and grouped as follows: structural–metabolic etiologies confirmed or suspected and well-recognized associations, developmental and epileptic encephalopathy (DEE), and pharmacoresponsive genetic epilepsy. Treatment was considered as off-label if the prescription did not respect the MA defined by the French Medical Regulatory Authority regulations in 2012 (Supplementary Table 1) and as manipulated if the prescribed dose required manipulation by the patient and/or his family. We studied 4 types of manipulations. Three types were adequate with MA but were intrinsically manipulated because of their galenic presentation (syrups, drops, and scored tablets that can be divided into 2 equal doses). The last type was defined as inadequate manipulation, such as cutting tablets outside the break bar, fractioning sachets, and taking tablets cut in half with reference to the break bar, all of which are done not to divide the tablet into two equal parts but to facilitate absorption according to MA.

2.2. Statistical analysis

The number of AEDs and patients' age did not have a normal distribution. Hence, Mann–Whitney *U* test and Kruskall–Wallis (presented as follows: H (degrees of freedom) = chi-squared, p-value) tests were used to determine if gender, age, or epilepsy syndrome statistically impacted the number of AEDs. Significant Kruskall–Wallis tests were followed by pairwise comparisons (Steel–Dwass–Critchlow–Fligner test).

Given the binary nature of the presence or absence of an off-label AED in a prescription, we used a logistic regression analysis to identify the factors implicated in off-label prescriptions. First, we performed univariate analysis (χ^2 tests), and then we included the significant factors in a multivariate analysis. The factors studied were age, gender, group of epilepsy syndromes, age class of the most recent AEDs in the prescription, and numbers of AEDs (monotherapy vs polytherapy). A similar approach was applied to study the factors associated with AED manipulations. We added the MA status of the prescription to the factors mentioned above.

A p-value <0.05 was considered as significant. The data were presented as mean ± standard error or median [25th–75th percentiles] and the odds ratio as OR (95% confidence interval, p-value).

3. Results

We collected data from 511 prescriptions from 332 patients who received AEDs after visiting outpatient clinics (1.5 ± 0.7 per patient). Sex ratio was 1.36 male for 1 female. Patients' age ranged from 3 months to 20.8 years (7.1 years [4–11.7], with only 4 patients aged between 18 years and 20.8 years). Epilepsy syndromes were as follows (Table 1): DEE (n = 196, 26.8%), epilepsies attributed to structural–

Table 1
Repartition of patients' consultations according to epileptic syndrome and classification.

Group	Classification	Epileptic syndrome	n
I. Pharmacoresponsive genetic epilepsies (n = 196, 38.4%)	Febrile seizure plus (FS+)		62
	Self-limited focal epilepsy: BECTS		42
	Genetic generalized epilepsies	Childhood absence epilepsy	37
		Generalized tonic–clonic seizures alone	18
		Juvenile absence epilepsy	16
		Epilepsy with myoclonic absences	9
		Juvenile myoclonic epilepsy	8
	Benign infantile epilepsy		2
	Myoclonic epilepsy in infancy		1
	Reflex epilepsy		1
II. Structural–metabolic etiologies (n = 178, 34.8%)	Structural–metabolic etiologies confirmed		127
	Structural–metabolic etiologies suspected		48
	Well-recognized associations	MT with HS	2
		Rasmussen syndrome	1
III. Developmental and epileptic encephalopathies (n = 137, 26.8%)		Dravet syndrome	67
		West syndrome	25
		CSWS	19
		Epilepsy with myoclonic atonic seizures	18
		Lennox–Gastaut syndrome	7
		EMFSI	1

CSWS: epileptic encephalopathy with continuous spike-and-wave during sleep; BECTS: benign epilepsy with centrotemporal spikes; MT with Hs: mesial temporal lobe epilepsy with hippocampal sclerosis; EMFSI: epilepsy with migrating focal seizure in infancy.