Seizure: European Journal of Epilepsy 85 (2021) 26–38

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

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

Review

Alternatives to valproate in girls and women of childbearing potential with Idiopathic Generalized Epilepsies: state of the art and guidance for the clinician proposed by the Epilepsy and Gender Commission of the Italian League Against Epilepsy (LICE)

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ARTICLE INFO

Keywords:
Idiopathic Generalized Epilepsies
antiseizure medications
women
efficacy
teratogenicity
prescription rules

ABSTRACT

Following recent European Medication Agency restrictions on valproate (VPA) use in girls and women of childbearing potential (WOCP), the Commission on Epilepsy and Gender of the Italian League against Epilepsy integrated current literature and legislative data in order to provide clinicians with guidance on antiseizure medication (ASM) prescription for Idiopathic Generalized Epilepsies (IGEs) in this population, avoiding VPA. We reviewed the updated literature on ASMs and examined the teratogenicity of those showing efficacy in IGEs. For all relevant ASMs, we considered the indications for use and the pregnancy and contraception-related recommendations given in the Italian Summary of Product Characteristics (SmPC) and on the websites of the European Medicines Agency (EMA) and other European Union (EU) countries' regulatory agencies. With the exception of absence seizures, the literature lacks high quality studies on ASMs in IGEs. In girls and WOCP, levetiracetam and lamotrigine should be considered the first-choice drugs in Generalized Tonic-Clonic Seizures Alone and in Juvenile Myoclonic Epilepsy, lamotrigine in Juvenile Absence Epilepsy, and ethosuximide in Childhood Absence Epilepsy. Although supported by the literature, several ASMs are off label, contraindicated or burdened by special warnings in pregnancy. Some discrepancies emerged between the various SmPC warnings for different brands of the same active principle. We provided a therapeutic algorithm for each IGE syndrome and highlighted the need for revised prescription rules, consistent with the latest literature data, uniformity of SmPC warnings for the same active principle, and more data on the efficacy of new ASMs in IGEs and their safety in pregnancy.

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https://doi.org/10.1016/j.seizure.2020.12.005
Received 7 October 2020; Received in revised form 12 December 2020; Accepted 16 December 2020
Available online 21 December 2020

1. Introduction

Valproic acid (VPA) is a recognized first-line agent for both focal and generalized seizures. Regrettably, as shown by comparisons with unexposed controls and children exposed to other antiseizure medications (ASMs), intrauterine exposure to VPA carries a 2- to 7-fold increased risk of major congenital malformations (MCMs) [1–3], with an average dose-dependent prevalence of approximately 10% [2,4]. It has also been associated with poorer cognitive development [5–8] and with significantly increased rates of autistic traits and autism [7,8]. These findings have led the European Medicines Agency (EMA) to impose tight restrictions on VPA use in girls and women of childbearing potential (WOCP). Currently, VPA is formally contraindicated in girls and WOCP in whom other treatments are unsuitable. This also applies in pregnancy. Eligible girls and WOCP must also be following a specific pregnancy prevention program [9].

In contrast with focal epilepsies, for which several alternative ASMs are available, suitable options for the treatment of idiopathic generalized epilepsy (IGE) are limited. Consequently, the need to avoid VPA makes the management of these patients even more problematic [10–12].

The aims of this study, led by the Epilepsy and Gender Commission of the Italian League Against Epilepsy (Lega Italiana Contro l'Epilessia - LICE), are to review the current evidence on the efficacy and teratogenicity of the alternative ASMs, together with current Italian legislation on their prescription, and to offer guidance on treatment with ASMs, avoiding VPA, for girls and WOCP with IGE.

2. Material and methods

2.1. Literature searches

The PubMed, Embase and Cochrane electronic databases up to February 2020 were searched for literature published in English. Relevant references were retrieved. Efficacy data were sought and considered separately for the four well-established IGE syndromes [13] and for all generalized seizure types. With regard to tonic-clonic seizures (TCSs), we considered only studies that focused on generalized tonic-clonic seizures (GTCSs) or ones with mixed populations in which data on GTCSs were clearly distinct from those on focal to bilateral TCSs. Whenever the latest update of the International League Against Epilepsy (ILAE) evidence review, published in 2013 [10], was found to have attributed an A or B level of evidence to one or more ASMs in any IGE syndrome or seizure type, further studies on those ASMs were considered only if they had been published after this review. Otherwise, we reviewed all relevant studies. To analyze teratogenicity, all and only the relevant ASMs, listed in alphabetical order in the results, were considered. In this case, we sought to identify and include all systematic reviews, as well as all studies of any kind published after the most recent systematic reviews [3,8]. Relevant references were retrieved. Conference proceedings were not included. The terms of the literature searches are reported in Table 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed (Supplement 1) [14].

Table 1
Terms of the literature searches

Topic	Search terms
Efficacy	Each specific drug name or "treatment" or "therapy" AND any of these terms: "idiopathic generalized epilepsy", "genetic generalized epilepsy", "childhood absence epilepsy", "juvenile absence epilepsy", "juvenile myoclonic epilepsy", "primary generalized tonic-clonic seizures epilepsy", "absence seizures", "myoclonic seizures", "primary generalized tonic-clonic seizures", generalized tonic-clonic seizures".
Adverse foetal effects	Each specific drug name AND any of these terms: malformation*; abnormalit*; defect*; anomal*, terato*; embryo*; fetus; foetus; fetal; foetal; feto*; foeto*; offspring; pregnancy; utero; intrauterine; infant; prenatal; cognitive development; neurodevelopment; development; IQ

2.2. Survey on prescription rules

For each relevant ASM, we reviewed the Summary of Product Characteristics (SmPC) issued by the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA), considering the formal therapeutic indications and contraindications, the specific recommendations concerning use of the drug in pregnancy, and any contraception issues, including both clinically significant interactions with hormonal contraceptives and specific recommendations on the need for pregnancy prevention [15]. In the event of discrepancies between different brands of the same active principle, we referred to the SmPC of the originator drug.

In analyzing the rules on ASM prescription, we also considered those regulating the off-label prescription and reimbursement, under the terms of Italian law 648/1996, of drugs already authorized for other indications, provided such prescription is supported by national and international medical-scientific research and a prior favorable opinion has been issued by the AIFA technical-scientific board. Notifications of drugs that may be prescribed under this regimen are periodically published in the Official Italian Government Journal (*Gazzetta Ufficiale della Repubblica Italiana*), and these drugs are subject to a special pharmacovigilance program [16].

We also looked for possible differences between the Italian SmPCs and those available on the websites of other European Union (EU) countries' regulatory agencies: EMA [17]– the EMA National Registers [18] and, for United Kingdom (UK), the Home-Electronic Medicines Compendium [19] of the British Medicines and Healthcare Products Regulatory Agency (MHRA) [20].

2.3. Design of prescription algorithms

After acquiring the above-mentioned information, BM, FR, LG, AL and CG designed ad hoc prescription algorithms for each IGE syndrome. This was done using a hierarchical approach: they included only ASMs with efficacy data for the given syndrome (or seizure types characterizing the syndrome); these drugs were then given an order of preference according to their degree of safety in pregnancy. In particular, we suggested an initial treatment, which should be considered as the first choice. A second line, in the event of failure of the first line, was also proposed. Under the caption "Other treatment options" we listed, in alphabetical order, all the drugs that have proved effective in that syndrome, and should be carefully considered only after failure or unsuitability of the second line. When necessary, agreement was reached after discussion. The algorithms were designed in the course of five virtual meetings, held between April 22 and June 1 2020, and they were then further discussed and approved by all the authors.

3. Results

3.1. Efficacy data

3.1.1. Childhood Absence Epilepsy (CAE) and Juvenile Absence Epilepsy (JAE)

According to the 2013 ILAE evidence review, ethosuximide (ESM) and VPA show established efficacy (level of evidence A) and lamotrigine (LTG) possible efficacy (level of evidence C) in absence seizures (ASs) [10]. These findings are based on a Class I study in which 446 out of 453 initially enrolled children were randomized to treatment with ESM (n = 156), VPA (n = 148) or LTG (n = 149). Freedom from failure rates at 16-20 weeks were similar for ESM and VPA (53% and 58%), and in both cases higher than for LTG (29%). Attention disturbances were significantly more common with VPA than with ESM [21]. These results

were confirmed at 12-month follow-up with freedom from failure rates of 45%, 44% and 21% for ESM, VPA and LTG, respectively [22].

A Cochrane review [23] based its conclusions mainly on the findings of the study just cited [22], as the other available ones presented limitations (poor methodological quality or small sample sizes). The authors concluded that ESM is the optimal drug for initial empirical monotherapy in children and adolescents with ASs. However, when GTCSs are present, VPA should be preferred, as ESM is probably ineffective on seizures of this type [23].

A few open-label studies on levetiracetam (LEV) showed modest to good efficacy in CAE and JAE [24,25]. In a retrospective study of 72 patients with new-onset absence epilepsies, the responder rate was 25% [26]. Of note, one observational study reported aggravation of ASs by LEV [27].

In an observational study of 13 patients with drug-resistant JAE treated with zonisamide (ZNS) (average follow-up 34 months), seizures were reduced by >75% in three (23%) and by 50%-75% in five (38.5%) cases. Seizure freedom was achieved in five patients (38.5%) (two of these also had GTCSs) [28].

A multicenter phase III double-blind study of perampanel (PER) in IGE failed to demonstrate any efficacy of the drug in CAE or JAE, probably due to the small sample size [29]. The GENERAL study evaluated, in a real-world setting, the efficacy of PER as add-on therapy in different IGEs. Among 37 of the patients (10 CAE, 21 JAE, 6 adult-onset absences), 48.4% were free from ASs and 51.4% were free from all types of seizure after 12 months [30].

In a retrospective study on the use of brivaracetam (BRV) in IGE, 7 out of 19 patients with ASs were responders (with 5 achieving total freedom from seizures). However, none of the three patients with CAE responded to the treatment [31].

Albeit studied in few observational clinical trials [32,33], both prior to the ILAE review, expert panel opinions suggest that topiramate (TPM) should be considered in drug-resistant absence epilepsy [11,34].

Although no trials are available for clobazam (CLB) and clonazepam (CZP) in CAE and JAE, these drugs should be considered as possible add-on treatments in treatment-resistant absences, according to several expert opinions [11,34,35].

3.1.2. Juvenile Myoclonic Epilepsy (JME)

Due to the lack of double-blind randomized controlled trial (RCT) studies, no ASM was assigned an A or B level of evidence for the treatment of JME in the ILAE review. However, VPA was identified as the drug of choice for this condition, except in women of childbearing age [22]. Individuals with JME accounted for a quarter of those with IGE in the SANAD study, which demonstrated superior effectiveness of VPA compared with LTG and TPM in IGE overall [36]. The effectiveness of VPA in JME was confirmed in the more recent EpiPGX Consortium report based on a retrospective analysis of 305 JME patients undergoing 688 ASM trials with VPA, LTG, LEV, carbamazepine (CBZ) and TPM. VPA had the best response rate (42.7%), however the difference versus LEV (response rate 37.1%) was not significant [37]. Although the most appropriate VPA dose has not been definitively established, two studies support low doses of VPA (500-1000 mg/day) for initial treatment of JME [38,39].

Prior to the availability of VPA, phenobarbital (PB) and primidone (PRM) were commonly used in JME, showing efficacy in up to 86% of patients in real-life experiences [40,41], however no RCT studies are available on these drugs.

Three observational studies in newly-diagnosed JME supported the use of LEV as the initial therapy in this setting [42–44]. Two large placebo-controlled studies [45,46] evaluated LEV as an adjunctive treatment in patients with drug-resistant IGEs. In the first, LEV produced a greater mean reduction in GTCS frequency than placebo (56.5% vs 28.2%). In the second, the number of days per week with myoclonic jerks was significantly reduced in 58.3% of patients under treatment with LEV versus 23% of those receiving placebo. A subanalysis of both studies confirmed a significantly better response rate for LEV than for placebo in JME [47].

LTG, as a monotherapy, was associated with seizure reduction and improvement in global clinical status in two open-label studies, in which it was administered, respectively, after VPA failure and in newly diagnosed JME [48,49]. In a comparative prospective open-label study, time to withdrawal and long-term seizure freedom did not differ significantly between the LTG and VPA groups [50]. In another cohort of patients in whom LTG was introduced after VPA failure, responders numbered 35 out of 62 (56%); responses tended to be better in patients without GTCSs and when VPA was withdrawn due to adverse events rather than inefficacy [51]. LTG was also reported to exacerbate myoclonic seizures or to cause them de novo in 5.4% of JME patients [52]. The combination of LTG and VPA might have a supra-additive effect and hence allow the use of a lower dose of VPA [41]. However, it can provoke or aggravate tremor [41,53].

An RCT compared TPM (N = 19) and VPA (N = 9) titrated to optimal effect in adolescents/adults with JME. Among patients completing 26 weeks of treatment, 67% of the TPM group and 57% of the VPA group were seizure free (SF) during the 12-week maintenance period. Complete control of GTCSs was obtained in 10/12 patients on TPM versus 3/4 on VPA [54]. Hence, TPM was considered potentially effective as an initial monotherapy in JME (level of evidence D) in the ILAE review [22]. Subsequently, in a prospective double-blind randomized open-label study comparing TPM and VPA in 34 JME patients, no significant efficacy differences were found in relation to either myoclonic seizures or GTCSs, but the severity of adverse events was significantly higher in the VPA group [55]. However, other authors found TPM to be less tolerated than VPA in patients with JME, particularly in terms of neuropsychological adverse events [56]. A Cochrane review updated in 2019 concluded that there was not sufficient evidence to support TPM for the treatment of JME, as TPM seemed better tolerated but not more effective than VPA [57].

In a retrospective analysis of 15 JME patients treated with ZNS either as their first drug, administered in a monotherapy regimen (13/15), or as an add-on treatment to VPA (2/15), 80% were considered good responders; 69%, 62% and 38% of patients were free from GTCSs, myoclonic seizures and ASs respectively. ZNS showed good tolerability [58]. In another retrospective study, of 13 IGE patients (6 with JME) treated with ZNS, 8/11 patients who were still taking ZNS at 12 months were responders at that timepoint, and 6 (including 3 with JME) were SF [59].

CZP and CLB should be considered for adjunctive treatment of myoclonic seizures both in children and in adults, according to small observational trials [60] and expert opinions [35,61].

In a small case series, lacosamide (LCM) was effective in two out of three patients with JME [62]. In another study, adjunctive LCM in 49 IGE patients was not effective on myoclonic seizures [63]. Of note, new-onset myoclonic seizures, absence status and worsening of absences have been reported in IGE patients treated with LCM [64].

In the GENERAL study on PER, 60 patients had JME. At 12-month follow-up, 61.7% of them were free from all types of seizure. In a subanalysis of efficacy in relation to seizure type, 61.9% became free from GTCSs, 68.2% from myoclonic seizures, and 56.3% from absences. [30].

Finally, a multicenter, retrospective cohort study recruited 61 patients with IGE resistant to other treatments and starting BRV. Among the 15 patients with JME, the responder rate was 60%, with 40% being SF at three months [65].

3.1.3. Generalized Tonic-Clonic Seizures (GTCSs) Alone

In the 2013 ILAE review, no drug for TCSs, including both GTCSs and focal to bilateral TCSs, was assigned an A or B level of evidence.

VPA has traditionally been considered the first-choice drug for GTCSs in clinical practice, even though no Class I or II studies are available. In fact, most data come from expert opinions and from a small number of Class III and IV comparative studies demonstrating the

overall efficacy of VPA versus TPM and/or LTG in IGE [36,66]. The most recent report, on a small prospective randomized comparative study of VPA versus LTG, which focused on newly diagnosed GTCSs in adults, confirmed the superiority of VPA as the first-line drug: at 12 months, 76.7% of the patients in the VPA group versus 56.67% those in the LTG one were SF [67]. No studies on VPA for refractory GTCSs are available.

In a small double-blind placebo-controlled crossover study in patients with treatment-resistant GTCSs, 50% of those treated with LTG as opposed to placebo recorded an at least 50% reduction in seizures [68]. In a regulatory double-blinded study, 117 patients experiencing medication-refractory GTCSs were randomized to receive LTG or placebo. During the combined escalation and maintenance phases, the median percent reduction in GTCSs was 66.5% with LTG versus 34.2% with placebo [69]. The original trial data were later confirmed in a pediatric population [70] and by a double-blind placebo-controlled trial on LTG extended release as adjunctive therapy for patients with GTCSs [71].

An open label active-controlled trial compared the efficacy and tolerability of monotherapy with LEV versus VPA over a six-month period. Thirty-one out of 45 patients in the LEV group and 47 out of 58 in the VPA group had GTCSs Alone. Seizure recurrence and seizure freedom were similar in the two treatment groups. Time to treatment withdrawal was longer in patients treated with LEV than in those receiving VPA, while the time to first seizure favored VPA, although the differences were not statistically significant [44]. In a multicenter double-blind placebo-controlled parallel-group study, 164 adults and children with IGE experiencing ≥3 GTCSs during the 8-week baseline period were randomized to LEV or placebo as an adjunctive treatment and evaluated for 20 weeks. LEV produced a greater mean reduction in GTCS weekly frequency than placebo (56.5% vs 28.2%). The responder rate was 72.2% for LEV and 45.2% for placebo [45].

A phase III open label long-term follow-up study evaluated LEV, in individualized doses, as an add-on therapy in patients with uncontrolled IGE. Among 217 patients, 152 had GTCSs; 62.5% of these experienced a seizure freedom period lasting ≥6 months [72].

In a multicenter double-blind randomized placebo-controlled phase III trial, 252 patients aged over 16 years with drug-resistant TCSs were randomized to receive LEV or placebo. The median percent reduction in seizure frequency in those with GTCSs was 73.9% for LEV versus 27% for placebo [73].

An RCT evaluated add-on TPM versus placebo in 80 patients experiencing ≥3 refractory GTCSs during the 8-week baseline period. At the end of the 12-week maintenance period following titration to target doses, the median percent reduction in GTCSs compared with baseline was 56.7% in the TPM group versus 9% in the placebo one [74].

Several uncontrolled and retrospective studies reported the effectiveness of ZNS in patients with GTCSs. In a small series, out of 10 patients with GTCSs (including two with GTCSs Alone), 6 were GTCS free and one recorded a ≥50% reduction in GTCSs after 6 and 12 months of treatment with ZNS [59].

In a multicenter Class I phase III placebo-controlled study, 164 patients with refractory GTCSs in IGE were assigned to treatment with PER or placebo during a 4-week titration period followed by a 13-week maintenance period. 162 patients completed the analysis (81 PER, 81 placebo). Compared with placebo, PER conferred a greater median percent change in GTCS frequency per 28 days and produced a >50% GTCS responder rate. During the maintenance period, 12.3% of placebo-treated patients and 30.9% of PER-treated patients achieved GTCS freedom [29]. In the real-life GENERAL study of PER, 115 out of 149 patients with IGE had GTCSs in the preceding year (51 had GTCSs Alone). After 12 months, the GTCS freedom rate was 69% and the GTCS responder rate was 75.7%. Six of the 115 (5.2%) experienced a >10% increased frequency of GTCSs. Thirty-two of the 51 patients (62.7%) with GTCSs Alone became SF [30].

The 311 study was a global multicenter open-label single-arm study of once-daily adjunctive PER oral suspension in pediatric IGE patients with focal seizures with/without focal to bilateral TCSs and GTCSs. In 31 patients with GTCSs, the median percent reduction in seizure frequency from baseline was 69%; the 50% responder and SF rates were 64% and 55% respectively. Safety and tolerability were confirmed [75].

An open-label study evaluated safety and tolerability of adjunctive LCM in 49 patients affected by IGE with uncontrolled GTCSs. During the pilot safety study, 29 patients remained free from GTCSs, while 64% and 36% of patients were SF for at least 6 and 12 months respectively. This GTCS improvement needs to be interpreted cautiously as the study was not designed to evaluate the efficacy of LCM [63].

In a multicenter phase III randomized double-blind non-inferiority trial of LCM versus CBZ-CR involving 888 patients with newly diagnosed epilepsy, 11% and 9% respectively in the LCM and CBZ-CR arms had TCSs without clinical or EEG indication of focal onset. The authors found comparable efficacy and SF rates between LCM and CBZ [76]. These results should be interpreted with caution: first, because the age at seizure onset was unusually old for IGE patients, and second, because the trial was not designed specifically for IGE [77]. In a case series, 7 out of 9 patients with IGE treated with LCM showed a ≥50% reduction in GTCS frequency. All 7 remained SF for >1 year, and 2 of them for >5 years. However, in 2 out of 5 patients, both with JME, ASs worsened. One of these was a patient with no previous history of myoclonic seizures who developed a myoclonic absence status [78].

In the previously cited multicenter retrospective cohort study on adjunctive BRV in IGE, 41 out of 61 patients had GTCSs; 16 (39%) were responders and among them 11 (26.8%) became GTCS free [65]. In a real-life experience of the off-label use of BRV in a sample of 37 adult patients with a confirmed IGE diagnosis, 9 patients had GTCSs Alone and 22 had GTCSs as a component of their IGE. After a mean treatment period of 10.4 ± 7.1 months, 6 out of 9 patients affected by GTCSs Alone and 15/22 patients with GTCSs in the context other IGEs were SF [31].

Despite extensive use of CZP, CLB, PB and PRM for GTCSs in clinical practice, efficacy data in these seizures are lacking. High-dose PB has been associated with aggravation or new onset of absences [79,80].

While no evidence is available from randomized studies of CBZ and oxcarbazepine (OXC) in IGE, case series and extrapolated data from reviews or studies focusing on TCSs in newly diagnosed epilepsy support their efficacy in reducing the frequency of GTCSs [81–88]. It should be emphasized that CBZ, particularly in monotherapy, may exacerbate seizures, particularly absence and myoclonic seizures, in some individuals with IGE [89].

Previous investigations of the use of phenytoin (PHT) in TCSs failed to distinguish clearly between patients with GTCSs versus focal to bilateral TCSs. A 2016 meta-analysis reviewed RCTs in which PHT or VPA was used as the initial monotherapy for TCSs: no differences in outcomes were found between the two treatments, either in focal or in generalized epilepsy. The authors concluded that misclassification of seizure/epilepsy type probably influenced the results of the review [90].

3.1.4. Idiopathic Generalized Epilepsies analyzed with no further syndrome specification

One of the arms of the "SANAD" RCT, conducted in patients with newly diagnosed epilepsy, included 716 children and adults in whom VPA rather than CBZ was considered, by a clinician, to be the most appropriate standard monotherapy option. More than half of these patients were classified as having IGE (66 CAE, 45 JAE, 119 JME, 42 generalized epilepsy with GTCSs on awakening, and 168 unspecified IGE). The patients, divided into evenly sized groups, received VPA, LTG or TPM in target doses consistent with everyday practice. VPA gave significantly better results than LTG and TPM in terms of time to treatment failure, while it performed better than LTG but did not significantly differ from TPM in time to 12-month remission. The superiority of VPA over the comparators was greater in IGE patients. No subanalysis focusing on types of IGE was performed [36].

The LaLiMo Trial was a multicenter open-label prospective randomized controlled parallel trial comparing the efficacy and safety of

Table 2
Anti-seizure medications (ASMs) other than valproate for Idiopathic Generalized Epilepsy (IGE).

ASM	Treatment regimen age limits *648/96* off label*	Use in pregnancy Contraindicated xxx Severe warning xx Special warning x	Contraception Recommended + Mandatory ++ Not specified -	PK interactions with EPCs
BRV	No	x	+	No
CBZ	**GTCSs** mono, add-on no age limits	xxx	++	YES (E+P)
CLB	No ***648/96**** *drug resistant severe epilepsies* *> 3 years – pediatric*	x	-	No
CZP	**GTCSs** Mono, add-on No age limits	xxx	-	No
ESM	**AS** ("Petit Mal") mono, add-on no age limits	xxx	-	No
LCM	No	x	-	No
LEV	**GTCSs, My** ≥ 12 years add-on treatment ***648/96**** ***JME*** *mono* *> 12 years - pediatric* ***AS*** *add-on* *pediatric*	-	-	No
LTG	**GTCSs, AS, My** mono, add-on ≥ 13 years only add-on 2- 12 years **AS** mono 2 -12 years ***648/96**** ***JME*** *mono* *≥ 12 years*	x	-	YES dose-dependent (P) reciprocal (↓ LTG for E)
OXC	No	xx	++	YES (E+P)
PB	**GTCSs** no age limits	x	-	YES (E+P)
PER	**GTCSs** add-on ≥ 12 years	x	+	YES dose-dependent (P)
PHT	**GTCSs, My** mono, add-on no age limits	x	-	YES (E+P)
PRM	**GTCSs, My** mono, add-on no age limits	x	-	YES (E+P)
TPM	**GTCSs** > 6 years (mono) ≥ 2 years (add-on) ***648/96 **** ***AS*** *(drug resistant)* *add-on* *pediatric*	xx	+	YES dose-dependent (E)
ZNS	No ***648/96 **** ***AS*** *(drug resistant)* *add-on* *pediatric*	xx	+	No

Seizure indications, contraindications and warnings in girls and women of childbearing potential (WOCP), need for use of contraception, and pharmacokinetic interactions with combined hormonal contraceptive steroids, as reported in the Italian Summary of Product Characteristics (SmPC, available on Agenzia Italiana del Farmaco-AIFA, 2020, April).
Strength of warning regarding risks in pregnancy is based on the authors' judgement on SmPC statements. Since some differences have been found between the SmPCs of originator drugs and those of some equivalent ("generic") drugs, the table refers to the SmPCs of the originator drugs.
See text on the SmPCs released in other European countries.
Legend: AS = Absence seizure, add-on = adjunctive treatment, ASM = anti-seizure medication, BRV = brivaracetam, CBZ = carbamazepine, CLB = clobazam, CZP = clonazepam, E = Estrogen quote of E/P contraceptives, EPCs = combined estro-progestin contraceptives, ESM = ethosuximide, GTCS = generalized tonic-clonic seizures, IGE = Idiopathic Generalized Epilepsy, JME = Juvenile Myoclonic Epilepsy, LCM = lacosamide, LTG = lamotrigine, LEV = levetiracetam, mono = monotherapy, My = generalized epileptic myoclonia, OXC = oxcarbazepine, P = progestin quote of E/P contraceptives, PB = phenobarbital, PER = perampanel, PHT = phenytoin, PK = pharmacokinetic, PRM = primidone, TPM = topiramate, ZNS = zonisamide
648/1996*: Italian law which allows off-label use (monitored by a special pharmacovigilance program) and drug reimbursement by the Italian National Health System.

LTG versus LEV as initial monotherapy in patients with newly diagnosed epilepsy. Four hundred nine patients were enrolled (144 with IGE). The proportion of SF patients at the end of the observation period was similar between LEV and LTG (45.2% vs 47.8%) and no differences in efficacy were found in IGE patients [91].

The KOMET study was a multicenter randomized open-label parallel study conducted in 1,688 new-onset epilepsy outpatients. Patients were randomized (1:1) to LEV or a standard ASM treatment, the latter chosen by the clinician between extended-release VPA (VPA-ER) or controlled-release CBZ (CBZ-CR). Primary generalized seizures were diagnosed in 34.8% of the patients (65.8% in the VPA/LEV arm). Efficacy did not differ significantly between LEV and the comparators, although there emerged trends favoring VPA-ER in the VPA/LEV arm [88].

Finally, a meta-analysis comparing LTG with VPA in IGE included five RCTs and four observational cohort studies, for a total of 1,732 patients. The results suggested better seizure control with VPA [92].

3.2. Prescription rules

Table 2 summarizes the pregnancy- and contraception-related contraindications and warnings concerning the use of the different ASMs, as reported by the relevant Italian SmPCs [15,16]. In Italy, VPA is the only drug whose indications cover all generalized seizure syndromes and types. There are no age restrictions on its use as either a monotherapy or add-on therapy.

CZP, too, is licensed for the treatment of all seizure syndromes and types in adults, whereas in children it may be used only as a monotherapy or add-on therapy of absences and GTCSs.

In ASs, ESM is licensed for monotherapy and add-on therapy without any age limit, while LTG can be prescribed to patients over two years of age. LEV, TPM and ZNS do not have a formal AIFA license, however, under the terms of Italian law 648/1996, they can be prescribed and reimbursed in pediatric drug-resistant typical ASs.

In GTCSs, CBZ, PB, PHT and PRM can all be prescribed as monotherapy or add-on treatments, without restrictions. LTG is licensed for monotherapy or add-on therapy of GTCSs in patients aged ≥13 years, and only for adjunctive therapy in patients aged 2-12 years. TPM is licensed for the treatment of GTCSs in patients aged >6 years as either a monotherapy or add-on therapy, and only as an add-on treatment in children aged 2-6 years. LEV can be prescribed for GTCSs only as add-on therapy in patients aged ≥12 years. PER, too, can be used as an add-on treatment for GTCSs in patients ≥12 years, but it must be prescribed by neurologists, child neuropsychiatrists or pediatricians in the context of an AIFA therapeutic plan.

In myoclonic seizures, PRM is licensed for monotherapy or add-on treatment. LEV is licensed specifically for JME and only as an add-on treatment for patients aged ≥12 years; however, under the terms of law 648/1996, its prescription as a monotherapy in individuals aged >12 years is reimbursable. LTG is licensed for mono or add-on therapy of myoclonic seizures in patients aged ≥13 years, whereas under the 648/1996 legal provisions, it is authorized for use only in JME, as a monotherapy in patients >12 years old.

LCM and BRV are not licensed for the treatment of any type of seizure on the IGE spectrum.

Under Italian law 648/1996, CLB is permitted for pediatric use in severe drug-resistant epilepsies (with no further specification) in patients over three years of age.

A possible dose dependency of teratogenic effects was reported only in the SmPCs of CBZ, LTG and PB.

With regard to the SmPCs released by other European regulatory agencies, the SmPCs authorized through a centralized procedure by the EMA (those referring to BRV, LCM, LEV, PER, ZNS), or subject to an EMA harmonization procedure (LTG, TPM), are currently (until 31.12.2020) the same across the EU, European Economic Area (EEA) and the UK. The SmPCs of ASMs already on the market at the time of the establishment of the EMA (CBZ, CLB, CNZ, ESM, PB, PHT, PRM, OXC), having been authorized at national level, may show differences in content between EU countries [17].

In pregnancy, CZP is contraindicated in Italy but not in France or Spain, for example; similarly, CLB is contraindicated in pregnancy and during breastfeeding in the UK, and only during breastfeeding in France and in other countries, such as Italy; while ESM is contraindicated during pregnancy in Italy but not in some other European countries.

Stronger warnings on PHT were found in the SmPC issued by the MHRA [20]. To evaluate these various drugs' contraindications, it is recommended to consult the national drug registers of the different countries [18].

3.3. Teratogenicity and adverse effects on behavioral and cognitive development

3.3.1. Carbamazepine

Several thousand pregnancies exposed to CBZ have been reported. These pregnancies showed an increased risk of MCMs, with an OR of 1.37 (95% CI, 1.10-1.71) according to one meta-analysis [3] and a RR of 1.50 (95% CI, 1.03-2.19) according to another [2]. They also showed an increased risk of minor malformations (OR, 10.81; 95% CrI, 1.40-373.90) [3] compared with untreated epilepsy. Pooled MCM prevalence was 4.93% in one of the abovementioned meta-analysis studies [2]. In the EURAP pregnancy registry, the prevalence was 4.5% for doses ≤700 mg/day (range, 3.5-5.8), and 7.2% for doses >700 mg/day (range, 5.4-9.4) [4]. In the UK registry, prevalence was 1.9% for doses <500 mg/day, and 5.3% for doses >1000 mg/day [93]. Systematic reviews with meta-analysis failed to find an association between CBZ exposure and specific MCMs, with the sole exception of orofacial clefts/craniofacial malformations, which were significantly more frequent in children of treated women than in controls born to mothers without epilepsy (RR 6.6, CI 1.19 to 31.49); instead, the difference versus children of women with untreated epilepsy was not significant [2].

No significant overall neurodevelopmental delay has been reported in association with intrauterine exposure to CBZ [5–8,94]. Although mean performance IQ was significantly lower in exposed subjects than in the pooled group of controls, this significance was lost when they were compared with only the epilepsy controls in a meta-analysis of cohort studies [5]. However, two single studies reported lower verbal abilities

[95,96], and one of those an increased frequency of IQ < 85 [95].

3.3.2. Clobazam

Exposure to CLB was associated with prenatal growth retardation (OR, 4.47; 95% CrI, 1.60-11.18) and preterm birth (OR, 3.42; 95% CrI, 1.41-7.92) [3]. Data on other outcomes are limited.

3.3.3. Clonazepam

Prenatal exposure to CZP was associated with a significant increase in hypospadias (OR, 6.17; 95% CrI, 1.17-24.80) [3]. Data on other outcomes are very limited.

3.3.4. Ethosuximide

Albeit analyzing a limited number of exposures, a systematic review found ESM to be associated with a significant higher risk of MCMs compared with controls (OR, 3.04; 95% CrI, 1.23-7.07), particularly cleft lip/palate (OR, 22.22; 95% CrI, 4.56-87.64) and clubfoot (OR, 12.99; 95% CrI, 1.66-76.39) [3]. No data were found on cognitive development after intrauterine exposure to ESM.

3.3.5. Lamotrigine

Data on several thousand intrauterine exposures to LTG largely support an overall malformation rate comparable to those found in the offspring of healthy mothers and of unexposed mothers with epilepsy, and lower than the rates reported in VPA or CBZ exposure [2,3]. Some studies [4,97], but not others [93,98], found a dose-dependent teratogenic effect. In particular, according to data from the EURAP registry, an exposure level of ≤325 mg/day was associated with a malformation rate of 2.5% (range, 1.8-3.3), which is no higher than that of the expected background, whilst higher doses were associated with a rate of 4.3% (range, 2.9-6.2) [4].

Despite earlier indications of a more than 10-fold increased risk of orofacial clefts [99], and of an increased risk of clubfoot [100,101], no specific pattern of MCMs has since been reported or confirmed on the basis of pooled data or data from a large case-malformed control study (EUROCAT) (2017) [2,102].

Several studies failed to demonstrate a detrimental effect on later cognitive assessment in exposed children [6,94,103–106]. Intrauterine exposure to LTG was significantly associated with autism/dyspraxia according to a network meta-analysis; however, when results were adjusted for higher quality studies in terms of the adequacy of follow up of cohorts, the association was no longer significant; moreover, the authors pointed out that several known confounders could not be assessed in most of the included studies [8].

3.3.6. Levetiracetam

Children exposed to LEV in the womb showed rates of MCMs comparable to those of control children [2,3,107], to the expected background rate, and to the rates of children exposed to low doses of LTG [4]. No dose-response association was found [2–4]. Reported exposures number more than one thousand [108].

Although preliminary data are reassuring, there is a consistent lack of evidence regarding possible cognitive adverse outcomes after intrauterine exposure to LEV [6,8,94].

3.3.7. Oxcarbazepine

The MCM rates of children exposed to OXC were comparable to those of children exposed to low doses of LTG and to the expected background rate [2–4]. No specific patterns of MCMs or dose dependencies have been reported. However, reported exposures number only several hundred [108]. There is no reported evidence on cognitive outcomes after intrauterine exposure to OXC [6]. Although OXC was associated with an increased risk of autism/dyspraxia in a network meta-analysis, the association was no longer significant when considering only epilepsy as the indication for use [8].

3.3.8. Phenobarbital

In a Cochrane systematic review with meta-analysis, children prenatally exposed to PB (23 studies, 709 children) showed a 7.1% prevalence of MCMs (95% CI, 5.36-9.08) with a RR for malformations of 2.84 versus children born to women without epilepsy (95% CI, 1.57-5.13) and a significantly increased risk compared with children prenatally exposed to LTG, LEV and gabapentin. Conversely, they did not have a higher risk than children born to women with untreated epilepsy or children prenatally exposed to CBZ, TPM, PHT, OXC, PRM or ZNS [2]. In another systematic review, the OR of MCMs was 1.84 (95% CI, 1.35-2.47) [3]. The EURAP registry highlighted a dose dependency, reporting a malformation rate of 2.7% for doses ≤80 mg (95% CI, 0.3-9.5), 6.2% for doses of 80 to 130 mg (95% CI, 3-11.1), and 11.7% for doses >130 mg (CI 95%, 4.8-22.6). The ORs compared with LTG ≤ 325 mg were: 5.81 for doses >130 mg (95% CI, 2.40-14.08) and 2.46 for doses of 80 to 130 mg (95% CI, 1.16-5.23); there was no significant risk for doses below 80 mg/day [4]. The OR for high versus low doses of PB was 5.41 (95% CI, 1.05-27.89). Other investigators found no correlation with doses [98,109], however most published studies included small numbers of exposed cases or did not provide specific information on doses [2]. Data on a possible specificity for heart anomalies are conflicting [2,110,111], while limited data suggest an increased risk of cleft lip/palate [2–4]. In one study, intrauterine exposure to PB was associated with prenatal growth retardation (OR, 1.88; 95% CI 1.07-3.32) [3].

Data on cognitive effects in monotherapy with PB are limited and inconclusive [6,110].

3.3.9. Phenytoin

PHT has been associated with a significant increase in overall MCMs, with a prevalence of about 6%, and no apparent dose effect [2,4]. Cleft palate and clubfoot, in particular, were found to be significantly increased. Data on a possible cognitive effect are scarce and inconsistent [6,110].

3.3.10. Topiramate

Data on the overall teratogenicity of TPM, based on fewer than 1,000 exposed pregnancies, show a slightly higher risk compared with unexposed controls [2,3]. However, this risk was no longer significant when restricting the analysis to studies found, in a meta-analysis, to be of higher quality in terms of the adequacy of follow-up of cohorts [3]. TPM carried a non-significant higher risk compared with low doses of LTG in the EURAP cohort and no dose dependency was found [4]. Nevertheless, two meta-analyses confirmed an approximately 6-fold increased risk of oral clefts [3,112]. A more recent population-based study from the U.S. (2,452 exposures vs 1,322,925 controls) demonstrated a higher risk when TPM was taken for epilepsy and at higher doses. In particular, compared with unexposed controls, the RR was 8.30 (95% CI, 2.65-26.07) among women with epilepsy (median dose 200 mg/day) and 1.45 (95% CI, 0.54-3.86) among women with other indications (median 100 mg/day). The RR for oral clefts was 1.64 (95% CI, 0.53-5.07) at doses ≤100 mg and 5.16 (95% CI, 1.94-13.73) at doses >100 mg. However, the sample size of women taking <100 mg was small and some confounders could not be ruled out. The authors also compared TPM with LTG, finding an RR similar to that found in controls. They calculated the pooled primary RR of their study with those of 6 previous studies and, in line with a previous meta-analysis, found it to be 5.27 (95% CI, 2.88-9.65) [113].

Prenatal growth retardation was found to be significantly more frequent in fetuses exposed to TPM (OR, 2.64; 95% CrI, 1.41-4.63) [3].

No published evidence was found on cognitive outcomes after intrauterine exposure to TPM.

3.3.11. Zonisamide

The prevalence of MCMs (any type) in children exposed to ZNS (N = 90), based on meta-analysis findings [2] relating to a single study [98], was 0.28% (95% CI, 0.25-2.39) [2,98]. We did not find any data on

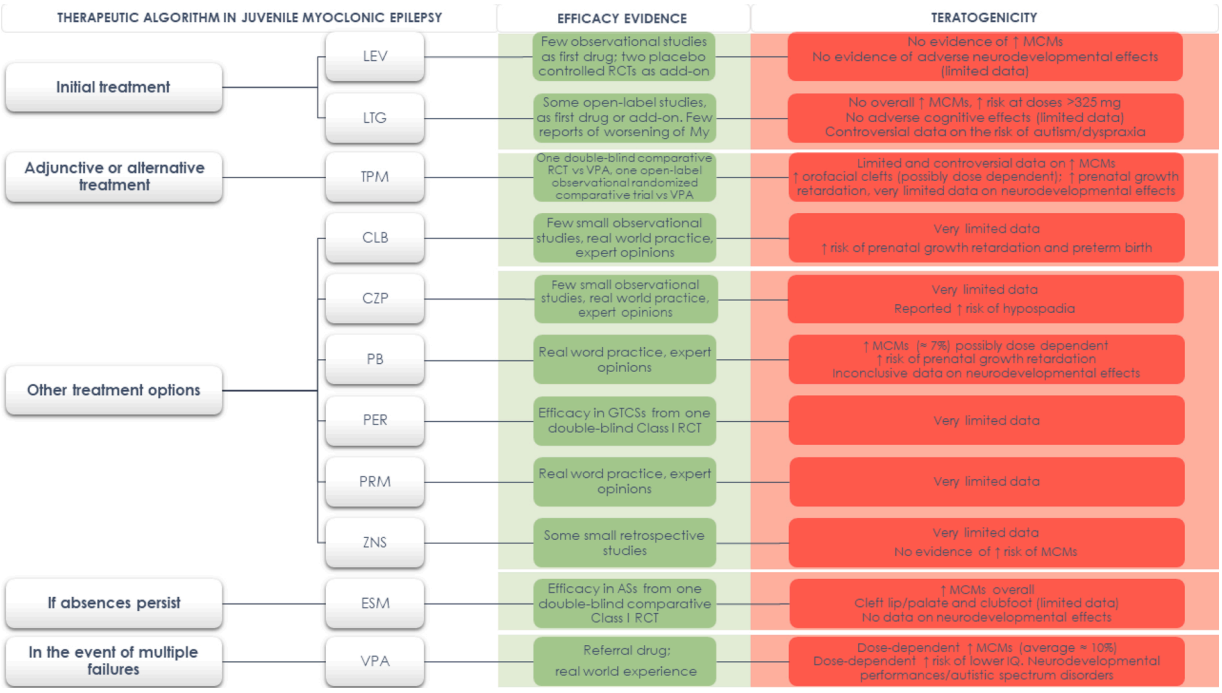

Fig. 1. Therapeutic algorithm in Juvenile Myoclonic Epilepsy.
LEV, levetiracetam; LTG, lamotrigine; CLB, clobazam; TPM, topiramate; CZP, clonazepam; PB, phenobarbital; PER, perampanel; PRM, primidone; ZNS, zonisamide; ESM, ethosuximide; VPA, valproic acid; RCT, randomized controlled trial; My, myoclonic seizures; GTCSs, generalized tonic clonic seizures; ASs, absence seizures; MCM, major congenital malformations.
LTG can worsen myoclonia.
Note that «other treatment options» are listed in alphabetical order.

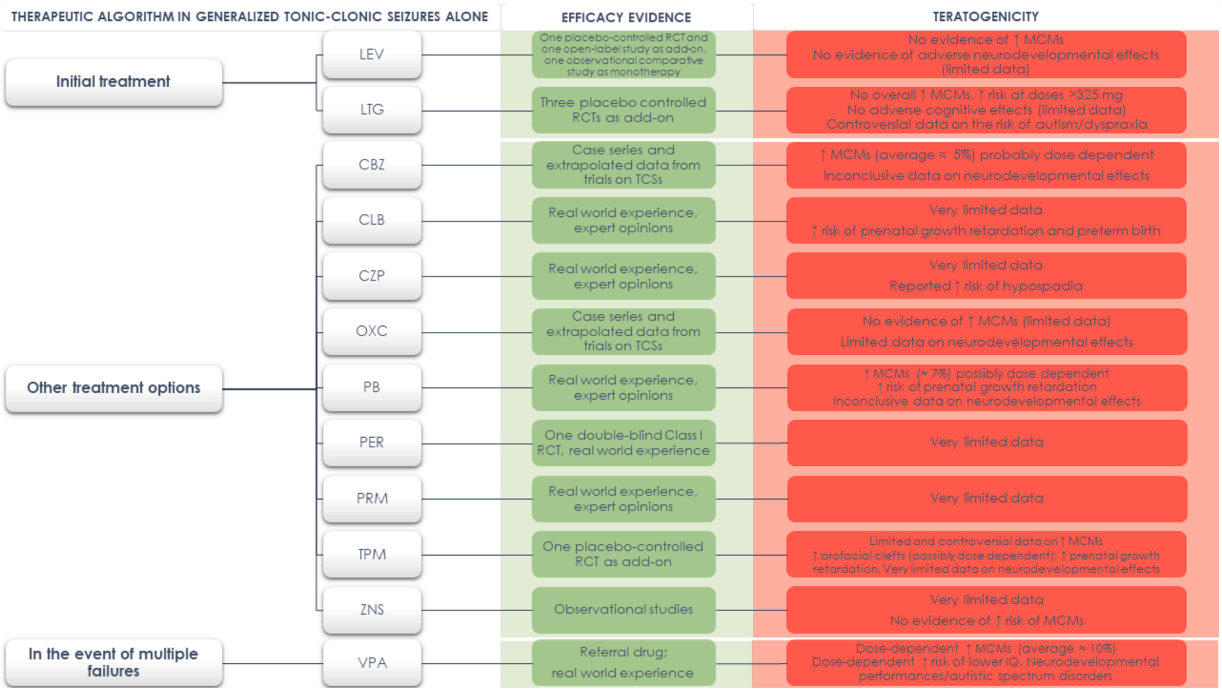

Fig. 2. Therapeutic algorithm in Generalized Tonic-Clonic Seizures Alone.
LEV, levetiracetam; LTG, lamotrigine; CBZ, carbamazepine; CLB, clobazam, CZP, clonazepam; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PRM, primidone; TPM, topiramate; ZNS, zonisamide; VPA, valproic acid; RCT, randomized controlled trial; TCSs, tonic-clonic seizures; MCMs, major congenital malformations.
CBZ and OXC can unmask absences and myoclonia.
Note that «other treatment options» are listed in alphabetical order.

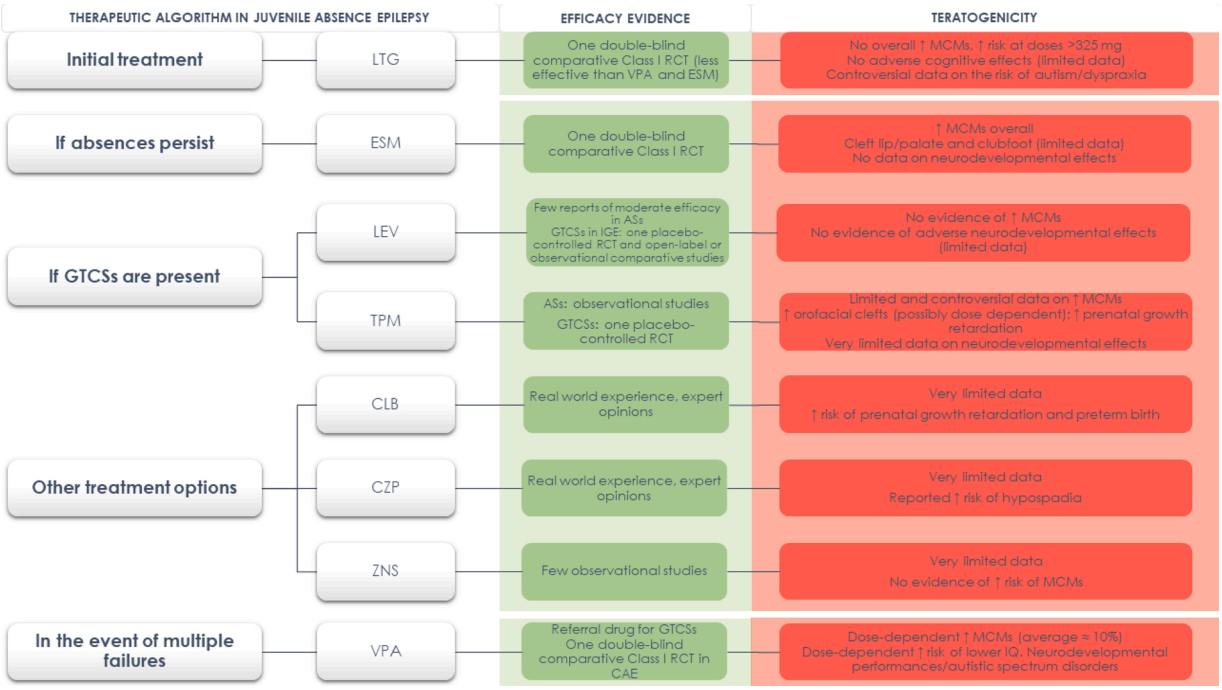

Fig. 3. Therapeutic algorithm in Juvenile Absence Epilepsy.
GTCSs, generalized tonic-clonic seizures; LTG, lamotrigine; ESM, ethosuximide; LEV, levetiracetam; TPM, topiramate; CLB, clobazam, CZP, clonazepam; ZNS, zonisamide; VPA, valproic acid; RCT, randomized controlled trial; ASs, absence seizures; IGE, idiopathic generalized epilepsy, CAE, childhood absence epilepsy; MCMs, major congenital malformations.
Note that «other treatment options» are listed in alphabetical order.

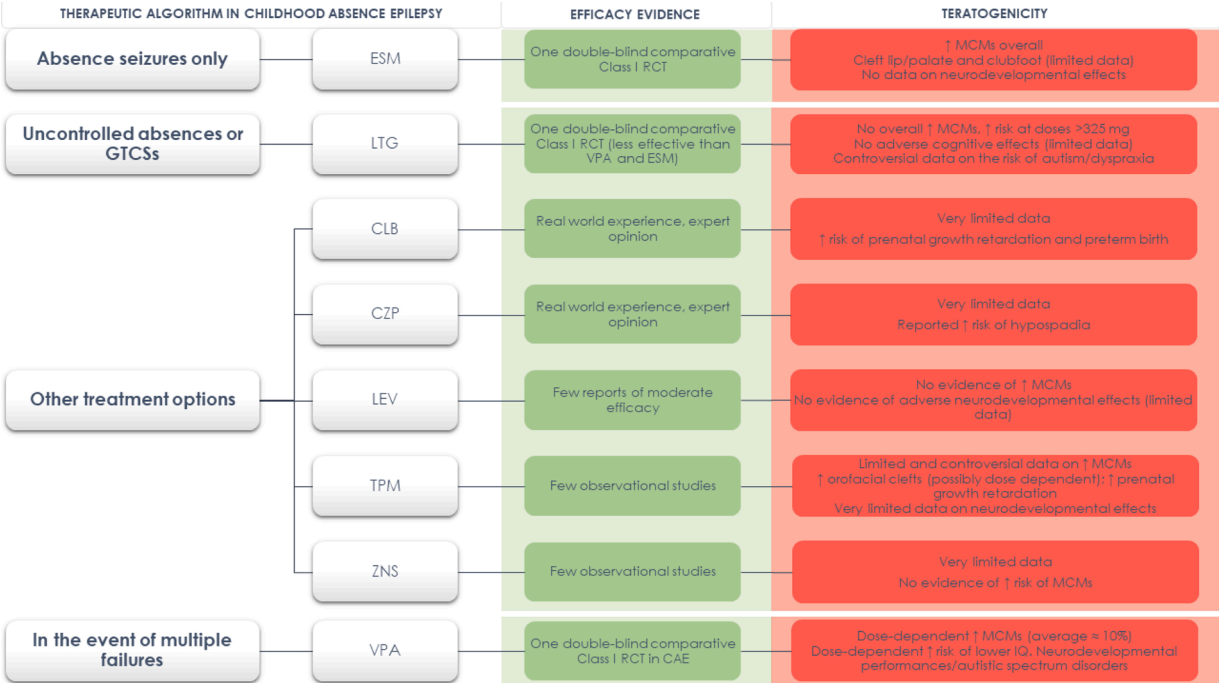

Fig. 4. Therapeutic algorithm in Childhood Absence Epilepsy.
GTCSs, generalized tonic-clonic seizures; ESM, ethosuximide; LTG, lamotrigine; CLB, clobazam, CZP, clonazepam; LEV, levetiracetam; TPM, topiramate; ZNS, zonisamide; VPA, valproic acid; RCT, randomized controlled trial; CAE, childhood absence epilepsy; MCMs, major congenital malformations.
Note that «other treatment options» are listed in alphabetical order.

cognitive outcomes after intrauterine exposure to ZNS.

3.3.12. *Other ASMs*

Only very limited data from small observational studies can be found on PRM, LCM, PER.

3.4. *Prescription algorithms*

Figs. 1–4 show the prescription algorithms for the different IGE syndromes.

4. Discussion

Adverse events associated with intrauterine exposure to VPA are consistently and conspicuously more frequent than those to date reported for any other ASM. On these premises, its use in pregnancy and in girls and WOCP should be limited to cases of absolute necessity [1–9]. However, avoiding VPA in IGE is not without disadvantages, as several authors have pointed out [12,114,115]. In men, VPA is considered the best first choice in different clinical situations, including IGE [11,35]. This raises important ethical issues pertaining to health equity: according to the current restrictions, girls and WOCP, unless other possible treatments have proved unsuitable and they agree to adhere to contraception requirements, should be denied a potentially effective cure, even in the presence of situations that make pregnancy unlikely [12,114,116]. Moreover, fetal adverse events (in particular cognitive effects) associated with other ASMs, especially the newer drugs, have yet to be adequately assessed. Accordingly, in a recent survey, 64% of Italian epileptologists stated that they have difficulties in implementing the EMA and AIFA recommendations [117].

It was mainly to address these difficulties that we set out to summarize and integrate current literature and legislative data, and thus provide guidance on ASM prescription in girls and women of childbearing age, avoiding VPA.

Since the decision to avoid VPA is based on clear literature data concerning its teratogenicity, and on strict regulatory constraints, ideal alternative drugs should be not only effective in the specific IGE syndrome, but also incontestably less harmful in the event of pregnancy and formally prescribable as a first monotherapy. Our investigation showed that finding a drug that meets these requirements is not straightforward.

As a first consideration, with the notable exception of absence syndromes, the literature lacks high quality studies, and hence strong recommendations for any ASM in IGE. That said, VPA is the only drug that has proved consistently effective in controlling the three main seizure types characterizing IGEs: ASs, myoclonic seizures and GTCSs. Accordingly, in Italy, it is the only drug licensed, without age restrictions, for all three.

However, several alternative treatments show good efficacy data for single seizure types, and this was our first determinant in designing the algorithms for each syndrome. We then prioritized the drugs with the lowest teratogenic risk profile, supported by a good amount of data, i.e. LEV and LTG. This is in line with the proposal of a group of European experts [118], and we, too, suggest the use of these two drugs in combination before trying other monotherapies [118].

CAE was the only syndrome in which we decided to consider ESM before any other ASM, again in line with the European proposal [118]. This was justified by evidence of its superior efficacy and tolerability in this syndrome. However, as patients with CAE show high rates of remission and medication withdrawal before reaching childbearing age, we believe that, in this population, VPA administration should not be delayed if GTCSs appear.

On the other hand, in some cases, ASMs were included in an algorithm more for their apparently low risk of teratogenicity than for their overall therapeutic profile. This was the case of CBZ and OXC in GTCSs Alone. These drugs would practically never be considered suitable therapeutic options in a man with IGE, as they are known to carry a risk of seizure worsening, and in particular can unmask absences or myoclonic seizures. For this reason, they were included only after careful discussion among the authors. Aggravation or unmasking of myoclonic seizures is also known to be a possibility with LTG; nevertheless, due to the lack of less teratogenic alternatives, it is considered by many clinicians [118], including us, as a first-choice agent in girls and WOCP with JME. Undoubtedly, careful surveillance for this possible complication, both by doctors and by patients, is warranted.

After lengthy discussion, and in accordance with other authors [118], we deemed it unethical to prioritize drugs for which there is still only limited clinical experience, and on which we have hardly any available teratogenic data, even when the efficacy data and prescription rules are favorable. One example is PER, which we think should be considered only after other possible options.

It should, in any case, be emphasized that any drug choice should be made only after verifying the suitability for the single woman, taking into account aspects including her lifestyle, comorbidities, preferences, and the potential impact of mood or cognitive side effects. In our view, this is particularly important with regard to the use of drugs listed as "other options", which, moreover, should be prescribed only by epilepsy specialists.

However, even reaching a balance between efficacy and teratogenic risk may not be enough, as the legal prescription requirements present a number of additional problems. For example, in Italy, prescribing LEV as monotherapy to a patient with JME represents an off-label prescription requiring supplemental pharmacovigilance procedures. Such extra surveillance, compulsory under Italian reimbursement law 648/1996, includes more frequent follow ups and periodic reporting to the authorities. Furthermore, reimbursement is not even contemplated in epilepsy with GTCSs alone. Though prescription rules may show some variation between single countries, they are generally very consistent across Europe as a whole, as borne out by the fact that the SmPCs of several ASMs authorized through a centralized procedure by the EMA, or subject to an EMA harmonization procedure, are currently (until the end of 2020) the same across the EU, EEA and the UK.

A further major problem is the lack of consistency between the SmPCs, which in some cases may include pregnancy as a specific contraindication, and in others contain specific recommendations for use of the agent in pregnancy. Moreover, SmPC content sometimes differs even between different brands of the same active principle.

Furthermore, several ASMs including, notably, both LEV and LTG, have a pharmacokinetic profile that very often leads to them being used at off-label doses in pregnancy.

It is likely and desirable that, in the coming years, further data will corroborate the usefulness of some of the newer ASMs in IGE. During the drafting of this review, new data were published confirming the potential efficacy of LCM in IGEs [119] leading to its recent approval by the EMA and FDA as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults, adolescents and children from 4 years of age with IGE [120]. Finally, an important question, still unanswered, is: when it is right to consider using VPA? This question, for which there is probably no univocal answer, goes beyond the scope of our research, whose purpose was to identify alternatives to VPA. Several issues influence the decision to use VPA, some of which are epilepsy related. These include, most importantly, seizure type and frequency, and the fact that frequent GTCSs are associated with a higher risk of morbidity and even mortality, making their treatment an absolute priority. Pregnancy considerations, the patient's willingness to adhere to contraception requirements, and the individual suitability of effective contraceptive methods are also key issues. It is also important to consider that certain drugs may be unsuitable for a given woman, and we feel it is important to underline that, in our view, not all the available treatment options necessarily have to be exhausted before considering valproate. Finally, shared decision-making with a well-informed woman is the most important element, even if this means that, aware of the risks, she still chooses to undertake a pregnancy while taking VPA. It should be remembered that low doses of VPA are preferable, having been shown to be associated with a lower teratogenic and cognitive risk, and found to be effective in many cases [38–39].

A limitation encountered when attempting to summarize the efficacy data was the heterogeneity of the literature reviewed. Indeed, the data sometimes referred to seizures, and sometimes to syndromes. We chose to present them by syndrome rather than seizure type, and to design algorithms accordingly. This choice was made for several reasons: for clarity, because syndrome diagnoses have prognostic implications and imply differences in treatment, regardless of the presence or absence of a single seizure type (as in the case of CAE and JAE), different chance of

paradoxical effect of certain drugs.

In conclusion, the aim of our survey was to provide clinicians with guidance on the use of ASMs other than VPA in girls and WOCP, while also attempting to highlight inconsistencies and gaps in current knowledge. The difficulties we encountered (i.e., conflicting recommendations and legal impediments to the prescription of various drugs) show that there is now a pressing need to revise the current prescription rules, in order to render them consistent with the most recent literature data, with the restrictions recently imposed on the use of VPA, and with each other. Indeed, from the perspective of possible legal consequences, and in order to improve clarity, making warnings uniform across different brands of the same active principle would be a very important step. Most important of all, there is a need to gather more data on the efficacy of new ASMs in IGEs and on their safety in pregnancy. The latter will be possible if patients and clinicians contribute to large registries on the use of ASMs in pregnancy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclaimer

The medical information provided herein constitutes a general information resource for physicians caring for patients with epilepsy. The suggestions made represent the views of the authors, and they are based on careful consideration of the available evidence.

Declaration of Competing Interest

BM received speaker's or consultancy fees from Eisai, Livanova, Sanofi, Sandoz, UCB and Univadis. FR received speaker's or consultancy fees from Eisai and UCB. LG received speaker's or consultancy fees from Eisai. ALN has received speaker's or consultancy fees from Eisai, Mylan, Sanofi, Bial, GW and UCB Pharma. EZ has received speaker's honoraria from UCB and Eisai. CAG received personal compensation for serving on a scientific advisory board from BIAL-Portela & CaS.A (year 2014), for data safety monitoring board from UCB Pharma (year 2016); honoraria for speaking engagements from UCB Pharma (years 2016-2017), Sanofi (year 2018), Sandoz s.p.a. (year 2018), Eisai (years 2019-2020), Lusofarmaco (year 2020); received research support paid to IRCCS Mondino Foundation from UCB Pharma (as Investigator and Expert – year 2014; as Principal Investigator – year 2020), BIAL-Portela & CaS.A (as Principal Investigator - year 2014), the Italian Ministry of Health (RF 2008). No other author has any conflict of interest to disclose.

Transparency document

The Transparency document associated with this article can be found in the online version.

Acknowledgments

We thank LICE- Lega Italiana Contro l'Epilessia for supporting the study and Catherine Wrenn for editing the English text.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2020.12.005.

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