PHARMACOLOGICAL TREATMENT OF FOCAL EPILEPSY IN ADULTS: AN EVIDENCE BASED APPROACH

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ABSTRACT

Introduction: Focal seizures represent the most common seizure type and focal epilepsies the most common epilepsy type. Anti-seizure medications (ASMs) still represent the main form of treatment for epilepsy.

Areas covered: The aim of this review article is to provide an overview of available evidence about current and upcoming pharmacological options and strategies for adults with focal epilepsy focusing on the last 5 years.

Expert opinion: Seventeen drugs are currently approved for the treatment of focal seizures including cenobamate as the very latest option. Ten of these drugs are also licensed for monotherapy. Level A evidence for initial monotherapy is available for seven drugs with no robust data supporting that one drug is superior to the other. Safety, tolerability as well as pharmacoeconomic reasons would then drive treatment decisions. Data on adjunctive treatment are available for 13 ASMs showing again no obvious difference in terms of efficacy. Evidence on specific drug combinations is almost non-existent and the final decision of combining specific drugs is based on the experience of the individual clinician rather than on robust evidence. Current outcome measures do not consider number of previously failed drugs and the observation period is often too short.

Key words: epilepsy, focal, treatment, outcome, antiepileptic drugs, antiseizure medications, cenobamate

1. INTRODUCTION

Epilepsy is a serious neurological disorder affecting over 70 million people worldwide with incidence rates around 50 (40-70) per 100,000 per year in high income countries and above 80-100 per 100,000 per year in low income countries [1]. Epilepsy poses a substantial economic burden for health systems, individuals and their families [2]. Focal seizures represent the most common seizure type and focal epilepsies the most common epilepsy type [3].

Antiseizure medications (ASMs) still represent the main form of treatment for epilepsy including focal epilepsies. The number of ASMs currently available is now becoming large and some debate has started on their classification in terms of generation. In this paper, the distinction into two generations of compounds has been adopted following Perucca et al. 2020 [4]. This distinction is mainly based on the chronological order these drugs have been marketed and those introduced after 1989 are generally referred to as second-generation drugs [4]. The development of these second generation ASM was aimed at addressing the shortcomings of older, first-generation drugs (barbiturates, benzodiazepines, carbamazepine, ethosuximide, phenytoin, and valproic acid), such as their unfavourable pharmacokinetics and drug interaction profiles, ineffectiveness in controlling the seizures, and propensity to induce many adverse effects [4]. Despite some of these drugs have shown some advantages in terms of pharmacokinetics, potential for interactions and tolerability [5], the proportion of drug-resistant patients remains dramatically unchanged and patients on polytherapy still present with often unacceptable medication-related side effects [6].

Treatment outcome studies in epilepsy have shown that one third of patients are controlled on a single ASM, another third requires a combination of two or more drugs to be seizure free, while, in the remaining third, chances of becoming seizure free are considerably low and these patients have uncontrolled seizures lifelong [7]. The definition of drug-resistance proposed by the International League Against Epilepsy (ILAE) has introduced the concept of sustained seizure freedom which represents the only efficacy outcome measure consistently associated with improved quality of life [8]. Using this measure, a systematic review and meta-analysis of placebo-controlled studies of ASMs has pointed out that the overall pooled-risk difference in favour of new ASMs compared with placebo is only 6% (95% CI 4%-8%) with a number needed to treat (NNT) of 16 [9]. A prospective trial of adults with drug-resistant focal epilepsy pointed out that less than 1 in 10 patients with drug resistant focal epilepsy achieve seizure freedom on a newly introduced ASM and provided validated estimates of seizure freedom according to number of previously failed trials ranging from 12% after two failed drugs to <3% after at least six failures [10].

The aim of this review article is to provide an overview of available evidence about current and upcoming pharmacological options and strategies for adults with focal epilepsy focusing on the last 5 years. References were identified by searches of Medline/PubMed and the Cochrane library for human studies published in English between June 30th, 2015, and June 30th, 2020, with the search terms: (seizure* OR epilepsy) AND (focal) AND (treatment*) AND (mono* OR adjunc* OR add*) AND outcome. This search generated 211 abstracts. Articles were selected based on originality and relevance to the present topic. Additional references were identified from the author's own files and from chosen bibliographies. A total of 63 papers have been included in this article.

2. CURRENT PHARMACOLOGICAL OPTIONS AND STRATEGIES: AN EVIDENCE BASED APPROACH

2.1 Monotherapy

Around 60% to 70% of people with epilepsy will achieve a long term remission from seizures [11] and many of them on a single ASM (monotherapy). Of the 17 drugs currently licensed for focal seizures, 10 have a monotherapy indication by either the Food and Drug Administration (FDA) or the European Medicine Agency (EMA) (**Table 1**). The ILAE Subcommission on ASM Guidelines published a systematic review in 2013, including 64 comparative randomized controlled trials (RCTs) and 11 meta-analyses, undertaken between 1940 and 2012 [12]. This document showed that Level A of evidence [13] for initial monotherapy for adults with focal epilepsy is available for levetiracetam (LEV), zonisamide (ZNS), controlled-release carbamazepine (CBZ-CR) and phenytoin (PHT) as all these drugs have Class 1 studies; lamotrigine (LTG) and gabapentin (GBP) have class I studies in elderly (≥60 years) adults with focal epilepsy [12].

Since then, Level A of evidence supported by Class 1 studies became available for lacosamide (LCM) and eslicarbazepine acetate (ESL) [14,15], subsequently confirmed by a network meta-analysis [16]; while, regarding elderly patients, class 1 RCT on LEV [17] added this compound to the list of drugs with a Level A of evidence. A subsequent meta-analysis suggested that LTG, LEV, and GBP have even higher efficacy than CBZ-CR in elderly people [18]. A network meta-analysis showed that despite the lack of significant differences in efficacy across treatments, LCM, LTG, and LEV have the highest probability of ranking best for achieving seizure freedom in elderly people. CBZ and CBZ-CR showed a poor tolerability profile, leading to higher withdrawal rates when compared to LEV and VPA [19].

A meta-analysis of RCTs of PHT and valproate (VPA) monotherapy involving 669 patients showed no difference in 12 months seizure freedom between the two drugs but this meta-analysis included a heterogeneous group of subjects with focal and generalised seizures [20]. Limited and very low-certainty evidence support the use of clonazepam (CLN) in monotherapy for the treatment of epilepsy [21]. No difference in efficacy and tolerability was found in a small trial comparing CLN to CBZ for the treatment of mesial temporal lobe epilepsy but over all data do not support the use of CLN in monotherapy for newly diagnosed patients.

Current pharmacotherapy of epilepsy consists of orderly, sequential drug trials, in which ASMs are chosen under the concept of individual patient-oriented (or -tailored) pharmacotherapy. It is, therefore, evident, that if data on efficacy show that LEV, LTG, ZNS, LCM, PHT and CBZ-CR are equally effective [4], data on tolerability may then guide therapeutic strategies. However, a network analysis of monotherapy studies showed that all these options seem to be equally tolerated and just CBZ (immediate release) seems to be burdened by lower tolerability as compared to other compounds especially LTG [22]. In this context, individualised treatment strategies considering comorbidities, patient's preference and pharmacoeconomic reasons are often adopted.

Safety of ASMs is another important parameter that may guide treatment decisions. Among drugs licensed for the treatment of focal seizures in adults, vigabatrin and retigabine are known to have serious safety concerns. Vigabatrin was approved for focal seizures in 1989 and after around 10 years, the drug was associated with irreversible visual field defects [23]. Since then, vigabatrin has been used mostly as an orphan drug used in infantile spasms. Retigabine was approved in 2011 for focal seizures but two years later the FDA issued a warning for blue discoloration of the skin, eyes, and retina pigmentation which led to the drug being withdrawn from the market in 2017 [24].

Malformation risk is another important aspect regarding safety of ASMs. It is established that exposure to VPA in utero is associated with a lower intelligence quotient [25] as well as an

increased risk of developing autism spectrum disorder [26] as compared to unexposed children. However, data from the EURAP register have also showed that CBZ-CR > 700 mg is associated with an increased risk of malformations as compared to LTG≤325 mg and LEV [27]. As a consequence prescription patterns in women with epilepsy have changed substantially during the past two decades [28], with a substantial increase in the use of LTG and LEV who are widely considered first choice in women of childbearing age.

2.2 Adjunctive treatment

When monotherapy fails, adjunctive treatment represents a potential option. Given the number of ASMs the number of combinations is substantial, and each combination has both advantages and disadvantages, which are different and variable related to individual case scenarios. Mechanism of action is often considered when combining drugs although robust evidence supporting specific combined treatment is almost non-existent. The combination VPA and LTG is often mentioned as an example of a favourable pharmacodynamic interaction. However, in focal epilepsies, evidence is based on an unblind randomised, 60-week superiority trial in 207 patients with focal and generalised seizures that showed that VPA-LTG is as effective as CBZ-CR [29].

Meta-analyses on efficacy and safety of individual ASMs as adjunctive treatment are available for 13 compounds (**Table 2**). All these drugs have shown very similar response rates, meaning at least 50% seizure reduction, while data on withdrawal risk seems to favour LTG, LEV, GBP and BRV.

LTG and LEV showed to be effective and well tolerated representing the best choice again in adjunctive treatment [30,31]. Psychiatric side effects in predisposed patients should be considered especially for LEV [32]. The use of OXC is based on low quality findings and safety data suggest a high risk of treatment withdrawal due to side effects [33]. LCM seems to be effective and well tolerated but not at high doses (>400 mg per day) [34]. Perampanel (PRP) seems to be effective from 4 mg but data on seizure response suggest minimum benefits from high doses (>10 mg) [35]. Data on GBP suggest a minimum effective dose 900 mg per day with a target dose of 1800 mg [36] while for tiagabine (TGB) the optimal dose seems to be around 30 mg per day [37]. Despite meta-analyses do not seem to disfavour TGB, the association with cases of status epilepticus [38] made this drug less and less popular. There are three trials comparing pregabalin (PGB) to LTG, LEV and GBP, showing that PGB has higher response rates than LTG (RR 1.47; 95%CI 1.03-2.12) but not higher than LEV or GBP [39].

Less usual options include stiripentol (STP), vigabatrin (VGB), felbamate (FLB) and clobazam (CLB) as they are usually used in difficult to treat generalised syndromes. STP and FLB are not even approved for focal seizures. Data on STP are mainly available in children but there is no conclusive evidence that it is effective in focal epilepsies [40]. VGB seems to be effective as adjunctive treatment in focal epilepsies but, as already mentioned, the use is burdened by the visual field problems [41]. Data on FLB in focal epilepsies are not conclusive but do not seem to support its use in this context [42]. Evidence on CLB is still limited but a small trial on 197 patients seems promising [43].

There is no clear evidence that one ASM is superior to another one as adjunctive treatment. A systematic review of 62 placebo controlled RCTs and 8 head-to-head RCTs including 14,272 patients showed that differences among ASMs are of relatively small magnitude to allow a definitive conclusion about which drug has superior effectiveness. TPM and LEV seem to be more efficacious, whereas GBP and TGB may be less efficacious. Withdrawal rates were higher with OXC and TPM and lower with GBP and LEV [44].

3. DRUGS FOR ORPHAN INDICATIONS

In 2017, everolimus was approved for the treatment of focal seizures in patients with Tuberous Sclerosis Complex (TSC). Everolimus belongs to a specific class of compounds called mTOR inhibitors [45]. Dysregulation of mTOR pathways has been implicated in tuberous sclerosis complex (TSC), focal cortical dysplasia (FCD), ganglioglioma and hemimegaloencephaly [46]. The efficacy of everolimus in TSC is based on a Phase III RCT showing that high-exposure everolimus (9-15 ng/mL) is associated with a median percentage reduction in seizure frequency of 39.6% as compared to 29.3% with low-exposure everolimus (3-7 ng/mL) and 14.9% with placebo [47]. The open label extension phase provided further data on the efficacy and safety of everolimus [48]. A study investigating the antiepileptic efficacy of everolimus in patients with Focal Cortical Dysplasia Type II and drug-resistant seizures is planned (NCT03198949) [45].

Cannabidiol (CBD) is currently licensed for the treatment of epilepsy in people with Lennox-Gastaut and Dravet syndrome aged 2 or more. These syndromes cannot be considered focal epilepsies despite these patients can have focal seizures as part of the syndrome. Data on efficacy of CBD on focal seizures are more than scant and most of the data come from children [49].

4. NEW DRUG OPTIONS: CENOBAMATE

Cenobamate (CNB) has been recently approved by U.S. Food and Drug Administration (FDA) for the treatment of focal seizures in the adults and it is awaiting approval from the European Medicine Agency (EMA). CNB inhibits the voltage-gated persistent component of the sodium currents and is an allosteric GABA(A) channel modulator in a non-benzodiazepine fashion [50]. It has demonstrated broad-spectrum efficacy in alternative preclinical models of epilepsy.

CNB is available only as oral formulation and showed linear pharmacokinetics with long half-life (30-76 hours) and steady-state attained after approximately two weeks supporting the once-daily dosing [51]. There is no data on pharmacokinetics in subjects with liver impairment, while renal impairment may be associated with reduced clearance and 200 mg is the maximum recommended dose in this population [52]. CNB has some potential interactions with other ASMs because it decreases plasma concentrations of CYP2B6 and CYP3A substrates and increases plasma concentrations of CYP2C19 substrates. As a consequence, CNB can increase blood levels of PHT and desmethyl-CLB (the active metabolite of CLB) and can reduce blood levels of LTG and CBZ [52]. VPA, LEV and LCM seem to have no interactions with CMB. A Phase III, open-label, safety study of CNB in 1,339 patients showed that PHT and PB require a dose reduction ranging between 25% and 33% to maintain the same blood levels [53].

Efficacy of CNB is based on Phase II and III studies. A Phase II RCT of 222 patients (age 18-65) with focal epilepsy compared CNB 200 mg against placebo [54]. CNB was started at 50 mg and increased by 50 mg increments every two weeks to a target dose of 200 mg, reached by 67% subjects. Responder rate (at least 50% seizure reduction) was 50.4% and seizure free rate 28.3% [54]. A Phase III RCT on 437 patients (age 18-70) with focal epilepsy compared placebo with CNB 100 mg, 200 mg and 400 mg showing responder rates of 25%, 40%, 56%, 64% and seizure free rates of 1%, 4%, 11% and 21% for placebo, CNB 100 mg, 200 mg and 400 mg respectively [55]. Data on seizure freedom have been considered particularly promising given that a systematic review of RCTs of ASMs reported seizure freedom rates up to 6.5% for previous ASMs [44]. A proof-of-concept study in a small sample of six patients showed also

promising therapeutic effect in photosensitive epilepsy for doses higher than 200 mg [56]. However, this would be relevant for generalised rather focal syndromes.

Even though the results are statistically significant and very encouraging, it has to be acknowledged that some of the estimates have a very wide confidence interval, which does introduce uncertainty regarding the magnitude of the treatment effect over placebo, as suggested by a recent systematic review with meta-analysis [57].

Treatment-emergent adverse events (TEAEs) reported in >10% included somnolence 22.1%, dizziness 22.1%, headache 12.4%, nausea 11.5% and fatigue 10.6% [54]. The Phase III study reported TEAEs leading to discontinuation in 5% of patients in the placebo group, 10% for CNB 100 mg, 14% for CNB 200 mg and 20% for CNB 400 mg [55]. One serious case of drug reaction with eosinophilia and systemic symptoms (DRESS) occurred in the 200 mg CNB group but no deaths were reported [55]. This was not the only case of DRESS and two other cases were observed during previous development phases for a total of 3 cases, including one fatality, out of the first 953 subjects exposed to CNB, leading to a frequency of 3 cases per 1,000. Prevalence of DRESS with other ASMs seems to range between 1 per 5,000 and 1 per 10,000 [58]. Concerns regarding an increased risk of DRESS with CNB led to a Phase III open label safety study which involved 1,339 patients [53]. CNB was started at 12.5 mg and increased with increments every 2 weeks to 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg. The most common TEAEs included somnolence in 28.1%, dizziness in 23.6%, and fatigue in 16.6% but no cases of DRESS were reported suggesting that a slow titration regime may limit such a risk [53].

5. CONCLUSIONS

Out of 17 drugs approved for focal seizures, 10 are also licensed for monotherapy, one has the orphan indication of focal seizures in TSC and two are rarely used given safety and tolerability issues. Level A evidence for initial monotherapy is available for LEV, PHT, LTG, CBZ-CR, ZNS, LCM, ESL with no robust data supporting that one drug is superior to the other is terms of efficacy. Safety and tolerability profile favour LEV and LTG for initial monotherapy especially in women of childbearing age and elderly.

Data on adjunctive treatment are available for 13 drugs showing again no obvious difference in terms of efficacy while data on tolerability favour LEV, LTG, LCM and BRV. CNB is the latest drug approved for focal seizures with promising efficacy results, but patients need to be informed about the increased risk of DRESS syndrome.

6. EXPERT OPINION

Meta-analyses and systematic reviews published in the last few years have facilitated the recognition of knowledge gaps and information needed to provide evidence-based treatment decisions in people with epilepsy. Class 1 studies are now routinely available for new anti-seizure medicines (ASMs) but randomised controlled trials have limitations in terms of duration of the follow up and outcome measures. For all drugs, outcome measures such as response rates or seizure free rates are based on a 12-week period at best. Data on sustained seizure freedom are needed and to have comparable results the ILAE definition of drug-resistance can be considered the theoretical framework to develop meaningful outcome measures based on number of previously failed drug trials and duration of the observation.

Regarding monotherapy of focal epilepsies, of the 10 drugs currently approved for focal seizures, there is a Level A of evidence based on Class 1 studies in more than half. There is,

however, no evidence that one drug is more effective than another one and safety, tolerability as well as pharmacoeconomic reasons would then become preponderant when choosing the most appropriate drug. Current data suggests that levetiracetam and lamotrigine are the best options when all these factors are considered especially in women of childbearing age or elderly.

For the adjunctive treatment of focal epilepsies, the scenario is similar with no evidence that one drug is superior to the other and data on tolerability seem to favour levetiracetam, lamotrigine, lacosamide and brivaracetam. Of the currently 17 approved drugs, 13 are routinely used while vigabatrin and tiagabine, despite approved for the use in focal seizures, are very rarely prescribed due to safety concerns; everolimus, is approved only in patients with tuberous sclerosis complex while cenobamate has been just recently marketed. Cenobamate is the latest option approved for the treatment of focal seizures and seizure free rates seem to be remarkably promising as compared to other ASMs, but this is not based on head-to-head comparison. The lack of multiple formulations (e.g. liquid or intravenous), the long titration regime and the increased risk of drug reaction with eosinophilia and systemic symptoms (DRESS) represent potential limitations and further data will be needed.

Data on the synergistic effect of specific combinations of ASMs are almost entirely non-existent and the decision to combine two specific compounds is based entirely on the experience of the individual clinician. In focal epilepsy, there is only a single study suggesting that the combination lamotrigine and valproate is as effective as carbamazepine. Studies clarifying this point are urgently needed.

Research into the pharmacological treatment of focal epilepsies in the next 5 years will need to move towards precision medicine and novel mechanisms of action given that available options have provided very similar results in terms of efficacy. Studies exploring potentially synergistic combinations are needed and they would have a strong impact on clinical practice. Head-to-head comparison studies are needed to clarify differences among ASMs in terms of efficacy and tolerability, but outcome measures will need to consider the number of previously failed drugs and longer observation periods.

7. ARTICLE HIGHLIGHTS

- 17 drugs are currently licensed for the treatment of focal seizures
- Level A of evidence for the initial monotherapy of focal seizures is available for 7 drugs with no difference in terms of efficacy
- Data on adjunctive treatment is available for 13 drugs with no difference in terms of efficacy
- Lamotrigine and levetiracetam represent the best options when efficacy safety and tolerability are considered
- Evidence of specific drug combinations is non-existent and clinical practice is based on the experience of the individual clinician
- Head-to-head comparison studies using appropriate outcome measures are needed

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Table 1. Drug options for adults with focal epilepsy.

	Mono	Daily dose range (mg)	Half life (h)	Interactions with other anti-seizure medications (ASMs)
Brivaracetam	No	50-200	6-11	Blood levels reduced by enzyme-inducing ASMs; It increases carbamazepine 10,11 epoxide
Cenobamate	No	200-400	30-76	It increases blood levels of phenytoin, phenobarbital and desmethyl-clobazam; It reduces blood levels of lamotrigine and carbamazepine
Carbamazepine	Yes	400-2000	10-20	Blood levels reduced by enzyme-inducing ASMs and increased by vigabatrin; Carbamazepine 10,11 epoxide levels increased by valproate and brivaracetam
Eslicarbazepine	Yes	800-1600	13-20	Licarbazepine concentrations reduced by enzyme inducing ASM
Everolimus*	No	¥5/m^2	25-35	Blood levels reduced by enzyme-inducing ASMs;
Gabapentin	No	900-2700	5-9	None
Lacosamide	Yes	100-400	12-16	Blood levels reduced by enzyme-inducing ASMs;
Levetiracetam	Yes	1000-3000	6-8	Blood levels reduced by enzyme-inducing ASMs;
Lamotrigine	Yes	100-600	20-40	Blood levels increased by VPA and reduced by enzyme-inducing ASMs;
Oxcarbazepine	Yes	600-2400	7-12	Licarbazepine concentrations reduced by enzyme inducing ASM; It increases blood levels of phenytoin and phenobarbital
Phenytoin	Yes	300	7-42	Blood levels increased by topiramate and oxcarbazepine; Reduced by vigabatrin and valproate (free fraction)
Perampanel	No	6-12	50-130	Blood levels reduced by enzyme-inducing ASMs;
Tiagabine	No	16-56	5-9	Blood levels reduced by enzyme-inducing ASMs;
Topiramate	Yes	100-600	20-30	Blood levels reduced by enzyme-inducing ASMs; TPM can increase PHT blood levels
Vigabatrin[#]	No	1000-6000	4-7	It can decrease phenytoin levels
Valproate	Yes	600-2000	8-17	Blood levels reduced by enzyme-inducing ASMs and topiramate
Zonisamide	Yes	150-450	50-70	Blood levels reduced by enzyme-inducing ASMs;

Mono= monotherapy indication; Enzyme inducing ASMs= phenytoin, phenobarbital, primidone, carbamazepine

[*]in patients Tuberous Sclerosis Complex

[¥]starting dose 5mg/m2 without CYP3A4/PgP inducer; 8 mg/m2 with CYP3A4/PgP inducer. Increase 2 mg/d to blood levels 5-7 ng/mL (max 15 ng/mL)

[#]mainly used for infantile spasms

Table 2. Meta-analytic evidence on efficacy and tolerability of antiseizure medications as adjunctive treatment.

ASMs	Dose mg	N patient	Max duration observation (weeks)	RR ≥50% seizure reduction (95%CI)	RR treatment withdrawal (95%CI)	Ref
Brivaracetam	10-600	2411	16	1.81 (1.53-2.14)	1.27 (0.94-1.74)	[59]
Eslicarbazepine	800-1600	1799	18	1.71 (1.42-2.05)	2.66 (1.42-4.96)	[60]
Gabapentin	600-1800	2607	14	1.89 (1.40-2.55)	1.05 (0.74-1.49)	[36]
Lacosamide	200-600	1311	26	1.70 (1.38-2.10)	1.88 (1.40-2.52)	[34]
Levetiracetam	1000-3000	A=2159 C=296	24	2.37 (2.02-2.78)	1.11 (0.89-1.40)	[31]
Lamotrigine	75-600	A=1569 C=199	24	1.80 (1.45- 2.23)	1.11 (0.91-137)	[30]
Oxcarbazepine	600-2400	1593	26	1.80 (1.27-2.56)	1.75 (1.44-2.13)	[33]
Perampanel	4 8 12	1678	8 13 13	1.51 (1.11-2.13) 1.80 (1.38-2.35) 1.72 (1.11-2.13)	- 0.57 (0.09-3.48) 0.97 (0.20-4.76)	[35]
Pregabalin	150-600	3327	17	2.28 (1.52-3.42)	1.35 (1.11-1.65)	[39]
Tiagabine	16-56	948	22	3.16 (1.97-5.07)	1.81 (1.25-2.62)	[37]
Topiramate	50-600	1650	19	2.71 (2.05-3.59)	2.37 (1.66-3.37)	[61]
Vigabatrin	1000-6000	756	36	2.60 (1.87-3.63)	2.86 (1.25-6.55)	[62]
Zonisamide	100 -500	1636	18	1.86 (1.60-2.17)	1.44 (1.08-1.93)	[63]

A=adult; C=children