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Review article

Teratogenic potential of third-generation antiepileptic drugs: Current status and research needs

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ABSTRACT

The aim of this review was to scrutinize the current literature available on teratogenic safety of third-generation antiepileptic drugs (TGAEDs) considering their clinical implications and to highlight for further research need in the interest of the diseased population in general and women with epilepsy in particular. For evaluation of the teratogenic potential of TGAEDs, this review summarized the existing information on controlled clinical trials conducted by the pharmaceutical companies, case reports, scholarly articles (prospective and retrospective studies), and experimental tests carried out so far. Firstly, clinical reports have reviewed on each drug followed by non-clinical studies reported hitherto. The Pub-Med and Google search engine was used to explore the relevant articles with pertinent keywords like pregnancy, epilepsy, seizures, women with epilepsy, antiepileptic or anticonvulsant drugs, first-second/new and third/ newest generation antiepileptic drugs, teratogenicity, teratological potential, birth defects, congenital anomalies, epilepsy and pregnancy registries, malformation surveillance program. The search was also carried out by the individual name of 20 third-generation AEDs. This review declared that although much research has been carried out on clinical and non-clinical implications for the assessment of the teratogenic potential of FGAEDs and SGAEDs, reports on the teratogenic safety of TGAEDs are still limited. It is concluded that there is an urgent need to exaggerate a large number of clinical intervention trials/reports and experimental studies to draw a definite conclusion for the teratogenic safety of TGAEDs. This is a pioneer attempt by our laboratory to review the teratogenic potential of third-generation antiepileptic drugs.

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Introduction

The women of childbearing age account for 25% of all people with epilepsy and most of these women will require long-term treatment with antiepileptic drugs (AEDs) [1]. In pregnant population, the predominance of epilepsy in pregnant women has been estimated to be 0.3–0.7% [2–5], whereas pervasiveness of antiepileptic drug use in pregnant women is 0.2%–0.5% [6,7]. Since the inception of the first anticonvulsant, the journey for development of potential and safe antiepileptic agents to control seizures in the general population is still on the way of progress to find out an efficacious drug which may have characteristics of without or minimal side effects including congenital malformations (Table 1).

For clinical management of diverse forms of epilepsy or seizures in pregnant women, first-generation and second-generation anticonvulsant agents are available in the pharmaceutical market globally. The vast variety of clinical literature clearly revealed that *in utero* exposure to first-generation antiepileptic drugs (FGAEDs) are associated with increased rate (2–6 fold) and diversity of major and/or minor congenital malformations in children in comparison to non-treated (2.8%) or general population (2.2%), irrespective of drug doses, gestation period, strain variability and mono or polytherapy [8–27]. The most common malformations in exposed offspring are similar to those seen in the general population like heart defects, hypospadias, clubfoot, limbs defects, cleft lip or palate, skeletal anomalies, spina bifida, *etc.* [20,25,28]. The FGAEDs are still front-line drugs of choice by some physicians due to their broad spectrum efficacy and tolerability, but these drugs associated with increased side effects in general and metabolic complications in particular as compared to newer AEDs. These FGAEDs are still prescribed (8.3%, fallen from 73.3%) to pregnant women with epilepsy despite knowing the fact that these drugs may induce mild to severe birth defects in children [29]. Thus, FGAEDs may be useful for the epileptic population including adult women, but may not be safe for pregnant women with epilepsy (PWWE) considering their teratogenic safety in offspring [30–32].

After considering the therapeutic index and possible teratogenic potential of FGAEDs, several second-generation antiepileptic drugs (SGAEDs) were licensed for clinical use as adjunctive treatment with the concern that these AEDs are novel in action, having improved pharmacokinetic profile with poor drug interaction to AEDs and other drug classes, better pharmacodynamic activity (specific receptor binding capacity) and fewer congenital birth defects. According to a study, prescription of SGAEDs during pregnancy has been increased from 26.7% in 2004 to 91.7% in 2015 [29]. Both prospective and retrospective studies elucidated that these SGAEDs were almost free from side effects including metabolic dysregulation, hence became the better

Table 1
List of AEDs available and their development in the time scale.

First-generation antiepileptic drugs (FGAEDs) (from 1857 to 1980)	Second-generation antiepileptic drugs (SGAEDs) (from 1980 to 2000)	Third-generation antiepileptic drugs (TGAEDs) (from 2000 to till date)
Potassium bromide (1857)	Vigabatrin (1989)	Fosphenytoin (2007)
Phenobarbital (1912)	Oxcarbazepine (1990)	Rufinamide (2008)
Phenytoin (1939)	Lamotrigine (1991)	Lacosamide (2008)
Ethosuximide (1960)	Felbamate (1994)	Stiripentol (2008)
Primidone (1960)	Gabapentin (1994)	Piracetam (2010)
Sulthiame (1960)	Topiramate (1995)	Retigabine or Ezogabine (2011)
Diazepam (1963)	Tiagabine (1996)	Clobazam (2011)
Clonazepam (1964)	Levetiracetam (2000)	Pregabalin (2012)
Carbamazepine (1965)	Zonisamide (2007)	Perampanel (2012)
Valproic acid (1970)		Eslicarbazepine (2013)
Clorazepate (1976)		Brivaracetam (2016)
		Safinamide (2017)
		Ganaxolone (2017)
		Cannabidiol (2018)

option for monotherapy or add-on/adjunctive therapy with other SGAEDs. Despite the improved efficacy of SGAEDs, these agents were not devoid of congenital malformations and associated with sporadic incidences of congenital malformations (major or minor) in clinical and experimental regimes. In the majority of clinical studies, the rate of fetal malformations was slightly higher in SGAEDs exposed children than non-exposed subjects with SGAEDs or general pregnant population [21,25,33–36]; whereas some studies have demonstrated that rate of congenital malformations caused by SGAEDs was lower than FGAEDs [20]. It concluded that there was no strong association with an increased risk of major birth defects with SGAEDs than traditional drugs used as monotherapy. In animal studies, *in utero* exposure to SGAEDS were also associated with various forms of external and internal malformations in fetuses/pups similar to clinical studies, but the frequency of malformations was found to be lower than FGAEDs [25,37–39].

The teratogenic safety of third-generation antiepileptic drugs (TGAEDs) or "newest" AEDs [40] have not been established so far due to the scarcity of clinical and experimental studies. Although, some sporadic incidences of minor congenital malformations have also reported as case reports, post-marketing surveillance [41] and preclinical data related to certain TGAEDs.

Therefore, this review aims to scrutinize the current literature available on teratogenic potential of TGAEDs, to consider clinical implications, and to highlight further research need in the interest of the diseased population and future generations.

Search strategy and inclusion criteria

For evaluation of teratogenic potential of TGAEDs, this review summarized the available information after thorough search of literature on controlled clinical trials conducted by the pharmaceutical companies (product monographs of the drugs), worldwide registries on teratology information service (TIS), global safety database and observational studies, case reports, scholarly or peer reviewed articles (prospective and retrospective studies) published in international journals in English; experimental trials performed and published in various journals related to pharmacology/pharmaceutics, neurology, neuroscience, medicine etc. including WHO data facts sheets published. The Pub Med search and Google search engine was used to explore the relevant articles with pertinent keywords like pregnancy, epilepsy, seizures, women with epilepsy, antiepileptic or anticonvulsant drugs, first, second and third generation antiepileptic drugs, teratogenicity, teratological potential, birth defects, congenital anomalies, epilepsy, and pregnancy registries, malformation surveillance program. The search was also carried out by the individual name of 20 third-generation AEDs. In this article, there was no need for the approval of the ethics committee since this review based on a thorough literature search.

Characteristics of the third generation AEDs

The characteristics associations of AEDs with several parameters like drug structure, molecular weight, pharmacokinetics, pharmacodynamics, and mechanism of action. In this review, we have limited to describe the pharmacokinetic profile of TGAEDs in brief and displayed in Table 2. The literature on the pharmacokinetics of FGAEDs indicates that most of the drugs undergo by hepatic metabolism via common isoenzyme (cytochrome P-450 and uridine glucuronyltransferases). On the contrary to this, several new generation AEDs do not follow this principle and route (hepatic metabolism) but are eliminated unchanged passing through the kidney; hence they are not causing major congenital malformations or severe birth defects [40,42].

Current status and teratogenic safety of third-generation AEDs

The teratogenic safety of TGAEDs or “newest” AEDs [40,42–46] has not been documented well so far due to the lack of clinical and experimental studies. Among the TGAEDs, some drugs are still in the process to obtain the license/approval either from US-FDA or European Union (EU) of drug controlling agencies; hence only product monographs of the concerned drugs are available, although some sporadic case reports and preclinical data are available for a few TGAEDs. Therefore, present review is an attempt to scrutinize the current literature available on teratogenic safety of TGAEDs, and to present some suggestions for pregnant women for instant registration in the pregnancy registry so that further data on this issue may be collected and analyzed for strengthening the current knowledge on teratogenic potential of TGAEDs in the interest of the diseased population (PWWE) and their children.

In the recent past, about 20 TGAEDs or novel agents, including brivaracetam (BRI), carabersat (CRB), carisbamate (CBM), DP-valproic acid (DP-VPA), eslicarbazepine acetate (ESL), fluorofelbamate (FFBM), fosphenytoin (FPHT), ganaxolone (GNX), lacosamide (LCM), losigamone (LSG), pregabalin (PGB), remacemide hydrochloride (RMC), retigabine (RTG), rufinamide (RUF), safinamide (SAF), seletracetam (SEL), soretolide (SRT), stiripentol (STP), talampanel (TLP) and valrocemide (VLR) were developed for treatment of a variety of epileptic disorders in diseased population, including adult and children. Among these agents, some of them are still in the process of approval by FDA/EU for clinical use. These TGAEDs have better efficacy and tolerability than FGAEDs and SGAEDs with no or minimal side effects, improved pharmacokinetic and pharmacodynamic properties. Thus, these newer or novel TGAEDs may be the hope for 30% of the diseased population who are still untreated by the currently available antiepileptic agents [47]; and could be an alternate and safe choice for the pregnant women who have epilepsy. The mechanism of action of these TGAEDs is distinctive than FGAEDs or SGAEDs.

Still, pharmaceutical companies claim that these drugs may recommend to pregnant population due to the absence of teratogenic effects in experimental or clinical trials (stage II and III). It is surprising to note that despite being the unique mechanism of action (specific receptors binding capacity) how these drugs could be free from the congenital birth defects and even to be free from the functional anomalies in offspring. Therefore, critical evaluation of these drugs required on their teratogenic potential before recommendation to clinics. Since there is a lack of clinical and experimental literature, hence each drug of TGAEDs has been evaluated for its teratogenic safety in clinical and non-clinical settings. In this review, clinical reports available on each drug were assessed first, followed by non-clinical studies reported hitherto. To the best of authors' knowledge, this is a pioneer attempt to review on teratogenic potential of third-generation antiepileptic drugs.

Eslicarbazepine acetate (ESL)

It was licensed in Europe in 2009 by the European Medicines Agency (EMA) (Zebinix™), [48] and in 2013 by the US Food and Drug Administration (FDA) (Aptiom™) as adjunctive therapy for the partial onset of seizures, with or without secondary generalization [49]. It is a third-generation member of the dibenzazepine family of AEDs with a distinctive mechanism of action. It blocks voltage-gated sodium channels. ESL does not bind to receptors for benzodiazepine, GABA or glutamate [50]. It is a derivative of CBZ and OXC. ESL has not been used off-license for non-epilepsy disorders.

Table 2
Characteristics of third-generation antiepileptic drugs.

SN	AEDs and their Approval	Use of the Drug for	Protein binding	Pharmacokinetic profile	Mechanism of Action	Teratogenic Status
1.	Fosphenytoin (FPHT) / FDA 2007	Status epilepticus of the tonic-clonic seizures	95-99%	**Half-life:** 8-15 min. **Absorption:** Rapidly and completely absorbed **Elimination:** The conversion half-life of fosphenytoin to phenytoin is approximately 15 minutes **Bioavailability:** 100% appears in plasma if taken intravenously or intramuscularly **Peak plasma concentration:** Intravenous: maximum plasma fosphenytoin concentration at the end of the infusion Intramuscular: approximately 30 minutes post-dose **Metabolites:** Phenytoin	FPHT works on modulation of voltage-dependent sodium channels.	**Clinical studies:** Limited data are available in pregnant women **Animal studies:** Increased frequencies of fetal malformations (brain, cardiovascular, digit, and skeletal anomalies) [74].
2.	Lacosamide (LCM) / FDA 2008	Adjunctive therapy for treatment of partial seizures	<15%	**Half-life:** 12-13 Hrs **Absorption:** Completely absorbed from the gut after oral administration **Elimination:** About 95% is excreted in the urine as unchanged by renal excretion if ingested orally **Bioavailability:** 100%, if taken orally **Peak plasma concentration:** Within 0.5-4 hrs after administration **Metabolites:** O-desmethyl	LCM selectively enhances sodium channel. It blocks NMDA receptors with a specific action on receptors.	**Clinical studies:** No adequate and well-controlled studies. **Animal studies:** Increased embryo-fetal and perinatal mortality, growth deficit in rats [67]. Growth retardation and increased major congenital malformations in chick [68] and zebrafish embryos [69].
3.	Rufinamide (RUF) / FDA 2008	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS)	23-34%	**Half-life:** 8-12 Hrs **Absorption:** Rapidly and extensively metabolized in the liver **Elimination:** By hepatic metabolism or microsomal cytochrome P450 isoenzyme **Bioavailability:** About 85% appears in plasma if taken orally **Peak plasma concentration:** Within 5-6 Hrs **Metabolites:** No known active metabolites	RUF prolongs the inactive state of voltage-dependent sodium channels and limits sustained repetitive firing of sodium-dependent action potentials in neurons.	**Clinical studies:** No adequate and well-controlled studies in pregnant women **Animal studies:** Increased incidences of fetal visceral and skeletal abnormalities in rats and rabbits [64].
4.	Stiripentol (STP) / European Medicine Agency (EMEA) in 2008	Dravet's syndrome	99%	**Half-life:** Variable **Absorption:** Rapid and nearly completely absorbed from the gut **Metabolism:** Five different metabolic pathways of STP recorded **Elimination:** Nearly 18% recovers in feces and 73% in the urine over 12 h. **Bioavailability:** low **Peak plasma concentration:** Within 1.5 hr after a single oral dose. **Metabolites:** 13 metabolites detect in humans.	STP inhibits the synaptosomal uptake of GABA, increases both the release of GABA and the duration of the activation of GABAA receptors.	**Clinical studies:** No adequate and well-controlled studies in pregnant women **Animal studies:** Not found teratogenic when tested in the rat and rabbit [70]. But embryotoxic and fetotoxic effects took place at high doses. [52]
5.	Clobazam (CLB) / FDA 2011	adjunctive treatment of seizures associated with Lennox-Gastaut syndrome	80-90%	**Half-life:** 36-42 Hrs **Absorption**: Rapidly and extensively absorbed following oral administration **Metabolism:** Extensively metabolized in the liver **Elimination:** Approximately 11% of the dose excreted in the feces, and approximately 82% excreted in the urine **Bioavailability:** 100% **Peak plasma concentration:** 0.5-4 hrs after single- or multiple-dose administrations **Metabolites:** N-desmethylclobazam	The exact mechanism of action for clobazam, a 1,5-benzodiazepine, is not fully understood but is thought to involve potentiation of GABAergic neurotransmission.	**Clinical studies:** No adequate and well-controlled studies in pregnant women **Animal studies:** Embryofetal mortality and incidences of fetal skeletal variations were increased [71].
6.	Retigabine (RTG) / FDA 2011	Adjunctive treatment of	80%	**Half-life:** 8-11 Hrs **Absorption:** Rapidly and extensively absorbed from the gut	RTG activates potassium currents, hence reduces the excitability of	**Clinical studies:** No adequate and well-controlled studies in pregnant women

Table 2 (*Continued*)

SN	AEDs and their Approval	Use of the Drug for	Protein binding	Pharmacokinetic profile	Mechanism of Action	Teratogenic Status
		partial onset of seizures		**Elimination:** By renal route **Bioavailability:** About 50–60% appears in plasma, if taken orally but not affected by food. **Peak plasma concentration:** Within 1.5 h after administration **Metabolites:** N-glucuronides and an N-acetyl derivative (inactive forms)	neurons. The drug is specific for the M-type potassium current.	**Animal studies:** Increased incidences of fetal skeletal variations, increased pre- and postnatal mortality, decreased body weight gain and delayed reflex development in the offspring [75,76].
7.	Perampanel (PER) / FDA 2012	Adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures	95-96%	**Half-life:** 105 Hrs **Absorption:** Rapidly and completely absorbed after oral administration **Elimination:** 22% of administered radioactivity recovered in the urine and 48% in the feces **Bioavailability:** 74-80% of total radioactivity in systemic circulation **Peak plasma concentration:** 0.5 to 2.5 hours under the fasted condition **Metabolites:** Oxidative and conjugated metabolites	PER acts as a non-competitive AMPA glutamate receptor antagonist.	**Clinical studies:** No adequate and well-controlled studies **Animal studies:** Increase in visceral abnormalities (diverticulum of the intestine), embryo lethality and reduced fetal body weight [96,97]
8.	Pregabalin (PGB) / FDA 2012	Adjunct for partial seizures	No binding with protein	**Half-life:** 5.8-6.3 Hrs **Absorption:** Rapidly and extensively absorbed from the gut **Elimination:** Roughly 98% eliminated as unchanged by renal excretion **Bioavailability:** About 90% **Peak plasma concentration:** Within 1.0 h after administration **Metabolites:** N-methylated derivative	PGB acts on voltage-gated calcium channels and attenuates depolarization-induced calcium influx at nerve terminals.	**Clinical studies:** Increased incidence of major birth defects [59] skeletal, cardiac, skin and peripheral vascular systems malformations **Animal studies:** Fetal malformations (limb, vertebral column, and craniofacial abnormalities) were increased significantly [60].
9.	Eslicarbazepine acetate (ESL) / FDA 2013	Adjunctive treatment of partial onset of seizures	30%	**Half-life:** 8-17 Hrs **Absorption:** Rapidly and extensively metabolized in the liver **Elimination:** By hepatic metabolism **Bioavailability:** About 95% appears in plasma if taken orally **Peak plasma concentration:** 1-4 Hrs **Metabolites:** S-licarbazepine (major) and R-licarbazepine and oxcarbazepine (minor)	ESL inhibits sodium channel-dependent release of neurotransmitters and stabilizes the inactive form of the sodium channel and sustains repetitive neuronal firing.	**Clinical studies:** No adequate and well-controlled studies. Costa et al., 2018 reported five cases of congenital anomalies among 79 pregnant cases exposed to ESL [41]. **Animal studies:** Skeletal variations and fetal growth retardation, a persistent reduction in offspring body weight [48,49]
10.	Brivaracetam(BRI)/ FDA2016	As adjunctive therapy in partial onset of seizures	<20%	**Half-life:** 7-8 hrs **Absorption:** Rapid and completely within 2 hrs **Elimination:** By hepatic metabolism, poor renal clearance. **Bioavailability:** >95% in the urine within 72 h, if taken orally **Metabolites:** Primary: carboxylic acid Secondary: Hydroxy acid	BRI has inhibitory effects on voltage-dependent sodium currents.	**Clinical studies:** No adequate and well-controlled studies **Animal studies:** Embryotoxicity observed in rabbits, except that no teratogenic risks detected [72,73].
11.	Safinamide (SAF) / FDA 2017	Adjunctive treatment to levodopa/ carbidopa in patients with Parkinson's disease (PD)	89%	**Half-life:** 20-26 Hrs **Absorption:** 95% after oral administration **Metabolism:** Nearly 70% metabolized to a major inactive metabolite. SAF is predominantly metabolized by non-microsomal enzymes (cytosolic amidases/ MAOA); CYP3A4 and other CYP iso-enzymes play only a minor role in its overall biotransformation. **Elimination:** Primary route of excretion is through the kidney (76% of safinamide dose recovered in the urine, primarily in the form of inactive metabolites) **Bioavailability:** Absolute bioavailability of safinamide is 95% after oral administration **Peak plasma concentration:**	SAF suppresses sustained repetitive firing by blocking sodium channel. It also blocks calcium channels and inhibits release of glutamate and aspartate.	**Clinical studies:** Data not available **Animal studies:** Slightly enlarged ureter(s), globular heart, edema of hind limbs and displaced testes, malrotated limbs [77]

Table 2 (*Continued*)

SN	AEDs and their Approval	Use of the Drug for	Protein binding	Pharmacokinetic profile	Mechanism of Action	Teratogenic Status
				Within 2 hrs after a single oral dose. **Metabolites:** 'safinamide acid' (NW-1153), 'Odebenzylated safinamide' (NW-1199) and 'N-dealkylated acid' (NW-1689)		
12.	Ganaxolone (GNX) / Designated as an orphan drug by FDA in June 2017	Partial-onset of seizures, CDKL5 Disorder in children	99%	**Half-life:** 20 Hrs **Absorption:** Rapidly and extensively absorbed from the gut **Metabolism:** Metabolized by the microsomal cytochrome CYP3A4 isoenzyme **Elimination:** About 80% excreted via the fecal route, and nearby 20% excreted via the renal route if ingested orally **Bioavailability:** Not known **Peak plasma concentration:** Within 1.5-2 hrs after administration. It associates with a high-fat meal (about 3 times higher than a regular meal) **Metabolites:** NA	GNX is a potent positive modulator of GABAA receptors and its sub-units.	**Clinical studies:** NA **Animal studies:** Ganaxolone did not cause any malformations of the fetus in rats or mice and did not significantly affect the development of offspring in reproductive toxic studies. [98]
13.	Cannabidiol (CBD) / FDA 2018	Treatment of seizures associated with Lennox Gastaut syndrome or Dravet syndrome	>94%	**Half-life:** 56-61 Hrs **Metabolism:** In liver and the gut (primarily in the liver) by CYP2C19 and CYP3A4 enzymes, and UGT1A7, UGT1A9, and UGT2B7 isoforms **Elimination:** Excreted in feces, with minor renal clearance **Bioavailability:** Not known **Peak plasma concentration:** 2.5 to 5 hours at steady state **Metabolites:** Primary: 7-OH-CBD Secondary: 7-COOH-CBD	The precise mechanisms by which EPIDIOLEX exerts its anticonvulsant effect are unknown.	**Clinical studies:** No adequate and well-controlled studies **Animal studies:** Embryofetal mortality at the highest dose was observed in rats and decreased fetal body weight and increased fetal structural variations in rabbits with maternal toxicity. [99]
14.	Remacemide hydrochloride (RMC) / Designated as an orphan drug for the treatment by the FDA in 2000	Treatment of acute ischemic stroke, epilepsy, Huntington's disease, and Parkinson's disease	75%	**Half-life:** 3-4 Hrs **Absorption:** Rapidly and extensively absorbed from the gut **Elimination:** NA **Bioavailability:** NA **Peak plasma concentration:** Within 1.0 h after administration **Metabolites:** Desglycinyl formed within 2 hrs and 90% bound to plasma proteins. FPL12495	RMC inhibits sustained repetitive firing in cultured neurons by blocking voltage-activated sodium channels.	**Clinical studies:** NA **Animal studies:** NA
15.	Carisbamate (CBM) / Yet to be approved (under process for FDA approval)	As adjunctive therapy in the partial onset of seizures	44%	**Half-life:** 12hrs **Absorption:** Rapid and extensively metabolized from the gut **Elimination:** By hepatic metabolism (about 94% in urine) **Bioavailability:** About 95%, if taken orally **Peak plasma concentration:** Within 1–3 Hrs **Metabolites:** S-glucuronide, chloromandelic acid, chlorobenzoic acid, and chlorophenylglycine	Molecular actions of CBM that contribute to its antiepileptic activity have not been elucidated and remain under investigation.	**Clinical studies:** NA **Animal studies:** NA
16.	Seletracetam (SEL) / Likely to be approved (under phase II trial under the supervision of FDA)	Treatment of epilepsy with partial onset seizures	10%	**Half-life:** 8 Hrs **Absorption:** Rapid and nearly completely absorbed from the gut **Metabolism:** 25% of ingested seletracetam metabolizes. The primary metabolic mechanism is the hydrolysis of acetamide to a carboxylic acid. **Elimination:** Excreted as unchanged drug (25%) by the renal route **Bioavailability:** 92 %, if taken orally. **Peak plasma concentration:** Within 1 hr after a single oral dose. **Metabolites:** Inactive carboxylic acid	SEL reduces high-voltage-activated calcium currents, but the drug does not modulate the low-voltage-activated T-type calcium currents.	**Clinical studies:** NA **Animal studies:** NA
17.	Talampanel (TLP) / Application Submitted for approval at FDA	Parkinson's Disease	67-88%	**Half-life:** 4 Hrs **Absorption:** Rapid and well absorbed from the gut **Metabolism:** NA	TLP blocks AMPA receptor channel complex. The central mechanism of action of the drug is currently unknown.	**Clinical studies:** NA **Animal studies:** NA

Table 2 (*Continued*)

SN	AEDs and their Approval	Use of the Drug for	Protein binding	Pharmacokinetic profile	Mechanism of Action	Teratogenic Status
	(under phase II trial)			**Elimination:** NA **Bioavailability:** NA **Peak plasma concentration:** Within 2.5 hr after a single oral dose. **Metabolites:** Several metabolites, mainly 4'- N-acetyl.		
18.	Fluorofelbamate (FFBM) / Yet to be approved	Status epilepticus	NA	**Half-life:** 16.7 Hrs **Absorption:** Through different metabolic pathways **Elimination:** By the urinary route **Bioavailability:** 82–100% appears in plasma if taken orally **Peak plasma concentration:** Within 2–6 h. **Metabolites:** Nil	Fluorofelbamate decreases responses to NMDA and kainate receptor activation and reduces voltage-dependent sodium currents.	**Clinical studies:** NA **Animal studies:** NA
19.	Soretolide (SRT) / NA	NA	75%	**Half-life:** 3-9 Hrs **Absorption:** Rapid and nearly completely absorbed from the gut **Metabolism:** By microsomal cytochrome CYP1A2 and CYP2C19 isoenzymes **Elimination:** NA **Bioavailability:** NA **Peak plasma concentration:** Within 1-2 hrs after a single oral dose. **Metabolites:** An active metabolite transforms into a carboxylic acid.	The mechanism of action of SRT is unknown.	**Clinical studies:** NA **Animal studies:** NA
20.	Carabersat (CRB) / Yet to be approved	As adjunctive therapy in the partial onset of seizures	NA	**Half-life:** 24 Hrs **Absorption:** NA **Elimination:** By hepatic metabolism **Bioavailability:** Enhanced by food, if taken orally **Metabolites:** Unknown	CRB does not affect sodium channels, GABAergic or glutamate pathways.	**Clinical studies:** NA **Animal studies:** NA
21.	Losigamone (LSG) / Likely to be approved	For clonic seizures	60%	**Half-life:** 4-7 Hrs **Absorption:** Rapidly and extensively absorbed from the gastrointestinal tract **Elimination:** About 15% of drug taken orally excreted as unchanged by renal excretion **Bioavailability:** NA **Peak plasma concentration:** Within 2-3 hrs after administration **Metabolites:** From S (+)-enantiomer (M1 & M2) and from R(−)-enantiomer (M3-M5)	LSG presynaptically affects sodium channels by reducing the frequency of spontaneous and stimulus-induced epileptiform discharges in hippocampal slices.	**Clinical studies:** NA **Animal studies:** NA
22.	Valrocemide(VLR)/ NA	Refractory epilepsy	NA	**Half-life:** 6.4-9.4 Hrs **Absorption:** Rapid and well absorbed from the gut **Metabolism:** NA **Elimination:** About 10–20% excretes unchanged in the urine, and 40% of the dose excretes as valproyl glycine. **Bioavailability:** 88% **Peak plasma concentration:** Within 2.5 hr after a single oral dose. **Metabolites:** NA	The mechanism of action of VLR is not known yet.	**Clinical studies:** NA **Animal studies:** NA

Source: Łuszczki JJ., 2009 (Modified and truncated), NA: Not available.

Clinical studies

There are no adequate and well-controlled studies in pregnant women. In a significant research Costa et al. (2018) reviewed 4849 case reports (829 from the clinical study and 4020 from post-marketing surveillance) in which 79 pregnancy notifications identified and only 5 cases identified with congenital anomalies. This study concludes that exposure to ESL during pregnancy does not associate with congenital anomalies, and these birth defects have limited within the normal range (1–4%) of exposed pregnant population. Hence, no clear relationship has established with ESL and major congenital birth defects [41].

Animal studies

Teratogenic effects of ESL in animal models are limited. The manufacturer company of the drug characterized this drug as pregnancy category "C". The product monograph of the drug as

well as some studies demonstrated that oral administration of ESL to pregnant mice (150, 350, 650 mg/kg/day), rats (65, 125, 250 mg/kg/day) and rabbits (40, 160, 320 mg/kg/day) throughout organogenesis, increased incidences of fetal malformations/ teratogenicity at all doses in mice, whereas increased rates of skeletal variations and fetal growth retardation were detected in rats and rabbits, respectively. Furthermore, there was a persistent reduction in offspring body weight of mice and rats, at all clinically relevant doses [49,51,52]. Therefore, ESL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregabalin (PGB)

It is a gamma-aminobutyric acid analog, sometimes called as gabapentinoid because it has great structural similarity with gabapentin (GBP). In USA and Europe, PGB (Lyrica) is licensed to treat central and peripheral neuropathic pain, adjunct therapy for partial seizures, generalized anxiety disorder and sleep disorder including spinal cord injury and diabetic peripheral neuropathy [53]. Although it has structural similarity to GBP, its mechanism of action is diverse. PGB binds with high affinity to $\alpha_2\delta$ type1and 2 subunits of voltage-gated calcium channels at nerve terminals. This $\alpha_2\delta1$ subunit binding is thought to be responsible for its anticonvulsive characteristic. Once ligation occurs at the $\alpha_2\delta1$ subunit, a reduction in the excessive release of multiple excitatory neurotransmitters like glutamate, norepinephrine, and substance-P take place in the brain [54–56]. PGB does not bind to opiate, serotonin or dopamine receptors [57]. It is more efficient than GBP [23].

Clinical studies

There are no adequate and well-controlled studies in pregnant women. The clinical reports (prospective, retrospective or case report) are minimal on this issue [58,59]. Recently, a multicentre, prospective, observational and cohort clinical study based on data collection from Teratology Information Services (TIS) in seven European countries (France, the United Kingdom, Italy, Finland, Switzerland, the Netherlands, and Turkey) between 2004 and 2013 elucidated that exposure to PGB (150 mg daily) during the first trimester of pregnancy in 164 subjects (96%) induced increased incidence of major birth defects (9.6% than 2.8% in controls) [59]. The rate of central nervous system malformations was substantially higher in PGB exposed subjects than controls — the other malformations associated with skeletal, cardiac, skin and peripheral vascular systems. Previously, in a data-based study, Veiby et al. [58] also documented a major malformation in one exposed infant, and although overall major birth defect (MBD) rates did not increase above those of the unexposed control cohort subjects. This analysis was limited by the small sample size of 30 pregnant women with epilepsy exposed to monotherapy of PGB.

Animal studies

The teratogenic safety of PGB in preclinical regimen has not well established so far. PGB has been categorized as 'C' by FDA, considering its low probability of teratogenicity. However, drug manufacturing company and its associated scientists revealed that PGB is not teratogenic in rodents, even at higher doses (500, 1250, 2500 mg/kg/day) in mice, rats and rabbits during a sensitive phase of organogenesis [60–62]. The highest dose (2500 mg/kg/day) was about 77 times elevated at the maximum human dose regimen, 600 mg/kg/day with 123 μg•h/ml AUC_{0-24}. On the contrary to this, Etemad et al. [63] reported that rate of fetal malformations namely limb, vertebral column, and craniofacial abnormalities were increased significantly in PGB exposed groups, even at lower doses (20, 40 and 80 mg/kg/day) in mice during the period of organogenesis. Similar observations have also reported from our laboratory after prenatal exposure to clinically relevant doses (41, 82 and 123 mg/m^2/day) of PGB in rats (data under publication). Thus, there are insufficient data in animal models to draw a definite conclusion on the teratogenic safety of PGB. Therefore, teratogenic potential of PGB may not be ruled out in clinical and pre-clinical conditions.

Rufinamide (RUF)

This drug was licensed in 2008 by FDA. Its mechanism of action is based on the prolongation of the inactive state of voltage-gated sodium channels and controls the repetitive firing of excitatory neurons by inhibiting the action potentials of sodium-dependent channels [64,65]. RUF does not bind to receptors for GABA, NMDA or AMPA/kainite [66].

Clinical studies

There are no adequate and well-controlled studies in pregnant women. The potential teratogenic risks for humans are still unknown.

Animal studies

The teratogenic effects of RUF in animal studies have not been well-known so far except the preclinical studies conducted by the manufacturer of the drug company, for obtaining the license. The product monograph demonstrated that RUF induced developmental toxicity and teratogenicity as increased incidences of fetal visceral and skeletal abnormalities in rats and rabbits, when clinically relevant doses (20, 100, and 300 mg/kg/day in rats and 30, 200, and 1000 mg/kg/day in rabbits) were administered orally to pregnant animals during the period of organogenesis [64]. A thorough literature survey indicates that there is a scarcity of scholarly articles related to RUF potential to induce congenital birth defects.

Lacosamide (LCM)

FDA licensed this drug in 2008 [67].

Clinical studies

There are no adequate and well-controlled studies in pregnant women. The potential teratogenic risks for humans are still unknown.

Animal studies

Studies in animals didn't indicate any teratogenic effects in rats or rabbits, but embryotoxicity observed in rats and rabbits at the maternal toxic dose, 400 mg/kg (MHRD) [67], whereas growth retardation and increased congenital malformations were reported in a dose-dependent manner in chick embryos at sub-therapeutic (0.12 mg) and supra-therapeutic (1.6 mg) doses respectively [68]. The similar pattern of growth retardation and increased malformations/teratogenicity index (tail, heart, scoliosis) were also reported in a dose-dependent pattern in zebrafish embryos [69].

Stiripentol (STP)

This drug was conditionally approved by EMA in 2007 and by FDA in 2008 [70].

Clinical studies

There are no adequate and well-controlled studies in pregnant women. The potential teratogenic risks for humans are still unknown.

Animal studies

Stiripentol was not found teratogenic when tested in the rat and rabbit but at high doses embryotoxic and fetotoxic effects took place [52]; in one study in the mouse, a low incidence of cleft palate formation observed at a maternotoxic dose (800 mg/kg/day) [70].

Clobazam (CLB)

FDA licensed this drug in 2011 [71].

Clinical studies

There are no adequate and well-controlled studies in pregnant women. The potential risk for humans is unknown.

Animal studies

The drug product monograph demonstrated no teratogenic effects in mice and rats when pregnant dams were exposed with clobazam at doses up to 400 mg/kg of body weight/day. No external, visceral or skeletal malformations or anomalies attributable to clobazam. Although, four cases of cleft palate observed at 100 mg/kg dose. In rabbits, a single case of unilateral exophthalmus, exencephalus combined with ceolosomy and syndactyly of the forelimb were found at 4 mg/kg dose group, whereas one hydrocephalus with an umbilical hernia was noted in the 20 mg/kg dose group [71].

Brivaracetam (BRI)

FDA licensed this drug in 2016 [72].

Clinical studies

There is a limited amount of data from the use of brivaracetam in pregnant women. The potential risk for humans is unknown.

Animal studies

The product monograph (2016) of the drug demonstrated that BRI has no teratogenic potential in either rat or rabbit. Thus, animal studies didn't detect any teratogenic risks of BRI. Oral administration of BRI (0, 150, 300, or 600 mg/kg/day) to pregnant rats and (0, 30, 60, 120, or 240 mg/kg/day) to pregnant rabbits during the period of organogenesis didn't produce any significant embryo-fetal toxicity and teratogenicity in rats, but embryotoxicity was observed in rabbits at a maternally toxic dose of BRI with an exposure level at 8-fold of the clinical AUC exposure at the maximum recommended dose [72,73].

Fosphenytoin (FPHT)

This drug has been categorized as "C" and initially approved by FDA, the USA in 1996, after that it was revised many times as in 2006, 2013 and some significant changes took place very recently in 2017 [74].

Clinical studies

There is a limited amount of data from the use of fosphenytoin in pregnant women. The potential risk for humans is unknown.

Animal studies

Preclinical studies related to drug development revealed that there is increased frequencies of malformations (brain, cardiovascular, digit, and skeletal anomalies), in the offspring of rats received FPHT during pregnancy [74].

Retigabine (RTG)

This drug has been categorized as "C". It was licensed in Europe in 2011 by the European Medicines Agency (EMA) (Trobalt) [75], and in 2011 by the US Food and Drug Administration (FDA) (Potiga) as an adjunctive treatment for partial epilepsy [76].

Clinical studies

There is a limited amount of data on the use of RTG in pregnant women. The potential risk for humans is unknown.

Animal studies

Treatment of pregnant rats with retigabine throughout organogenesis increased the incidences of fetal skeletal variations. Treatment of pregnant rabbits with retigabine throughout organogenesis resulted in decreased fetal body weights and increased rates of fetal skeletal variations. Administration of retigabine to rats throughout pregnancy and lactation resulted in increased pre- and postnatal mortality decreased body weight gain, and delayed reflex development in the offspring [76].

Safinamide (SAF)

This drug is under the process of approval from European Medicines Agency (EMA). Recently, it initially approved by FDA, USA in 2017 [77].

Animal studies

The embryo-fetal developmental studies showed malformations in rats and rabbits. In rats, slightly enlarged ureter(s), globular heart, edema of hind limbs and displaced testes observed at the lowest dose level. In rabbits, malrotated limbs observed. Although the incidence of these malformations was low, due to the weak or absent safety margins, safinamide must be considered to be potentially teratogenic [77].

Discussion

The vast variety of clinical and non-clinical literature on *in utero* exposure to antiepileptic drugs and possible birth defects in offspring revealed that administration of FGAEDs not only enhanced the rate of major malformations many folds but also induce variety of birth defects, whereas maternal exposure to SGAEDs restricted the expected birth defects in comparison to FGAEDs, and found almost equal to general population (1-3%). Therefore, the clinical recommendation of SGAEDs during pregnancy was increased considering their teratogenic safety as compared to FGAEDs. Additionally, these agents have better efficacy, tolerability, minimal side effects, drug interactions and improved mechanism of action due to which potential of teratogenicity of these agents reduced greatly. In spite of the possible mechanism of actions of SGAEDs, other confounding mechanisms [78,79] may also be responsible for causing congenital birth defects including bone metabolism (bone mineralization) in developing fetus. Although FGAEDS and SGAEDs are associated with skeletal anomalies in adolescents and adults [80] through

various inducing mechanisms, its central mechanism has not been yet established and is still controversial. However, several workers have projected multifactorial inducing mechanisms like drug doses, exposure period [81–83], variation in GABA neurotransmitter level [82], endocrine dysfunction (thyroid disorders) [84,85], alterations in maternal and fetal status of mineral and trace elements [83], reduced zinc level in maternal plasma [86–88], placental passage of AEDs [89], involvement of Cox-2 gene through enhanced apoptosis [90]; and these mechanisms may be important factor(s) for inducing probable teratogenicity in human and animals.

Recently, Fadel et al. [91] summarized the typical environmental and molecular mechanisms of variable birth defects (including skeletal) based on genetic and environmental factors like nutrition, hormones, genes, environment, and physical activity are responsible for development and growth of fetal bones [92]. Hence, it speculates that prenatal exposure to the antiepileptic agent(s) may induce default programming of bone metabolism in early life which may lead to bone disorders in neonates.

Recommendations and future research needs

While a large number of investigations have reported on clinical and non-clinical implications for the assessment of the teratogenic safety of FGAEDs and SGAEDs, reports on the teratogenic potential of TGAEDs are still limited.

It expects that TGAEDs could be an alternate choice of the physicians especially for a pregnant population suffering from different forms of epilepsy considering their better teratogenic safety profile [41,93–95], but clinical and experimental reports are limited to draw a definite conclusion. Therefore, this study recommends that TGAEDs should also be used with precautions after weighing the teratogenic risks to children and potential benefits to mother, simultaneously.

Therefore, there is an urgent need to carry out a large number of clinical intervention trials, randomized controlled studies, clinical trials, case reports, post-marketing surveillance, and strengthening of worldwide registries on teratology information service (TIS), global safety database for TGAEDs, and experimental studies on various animal models to draw a specific conclusion and treatment regimen on this relevant issue. Since FDA has approved about 20 newer or TGAEDs or some of them are under the process of approval/clinical trials (phase II or III), it expects that these new drugs may be advantageous for the diseased population including pregnant women suffering from different forms of epilepsy as well as for those population who are not responding to first and/or the second generation AEDs, thus causing the “treatment gap”.

Conflict of interest

There is no conflict of interest between authors and funding agency, and the institution.

Author contributions

K.P. Singh: Conceptualization, methodology, validation, writing - review and editing, supervision, project administration. Niharika Verma: Software, formal analysis, resources, data curation, writing - original draft, visualization, funding acquisition.

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