**Table 1.** Characteristics of AEDs.

| Drug | Generation | Drug Approval Date | Chemical Classification/Structure, Molecular Mass [g/mol] | Mechanism of Action | Pharmacokinetics/Metabolism | Therapeutic Range [mg/L] | Drug-Drug Interactions | Ref. |
|---|---|---|---|---|---|---|---|---|
| Brivaracetam (BRV) | III | 2016 (USA) | ((2S)-2-((4R)-2-oxo-4-propylpyrrolidinyl)butanamide $C_{11}H_{20}N_2O_2$ 212.288 | acting on SV2A, through the synaptic GABA release, sodium channels inhibitor | bioavailability ~100%, $T_{max}$ 1 h, $T_{0.5}$ 7–8 h, <20% bound to plasma proteins, metabolized by hydrolysis and oxidation, >95% excreted in urine with <10% of compound unchanged | 0.2–2.0 | baclofen with BRV increase adverse effect, CBZ may increase the thyroid function activities of BRV and VPA decreases. | [94,95,97] |
| Carbamazepine (CBZ) | I | 1965 (UK) 1968 (USA) | Benzo(b)(1)benzazepine-11-carboxamide $C_{15}H_{12}N_2O$ 236.269 | inhibition of the voltage-gated sodium channel (VGSC) | bioavailability 75–85%, $T_{max}$ 19 ± 7 h, $T_{0.5}$ 35 h protein binding 65–85%, hepatic metabolism via CYP3A4/5 and in a lesser extent CYP 2C8, main active epoxide metabolite—(CBZE), excreted in the urine as N-glucuronide (15%) | 4–12 | PHT, PB, PRM increase CBZ clearance and reduce its half-life. VPA inhibits epoxide hydrolase, and CYP 3A4 inhibitors increase CBZ and CBZE blood levels | [10,29,43,69,189,190] |
| Cenobamate (CNB) | new | 2019 (USA) | ((1*R*)-1-(2-chlorophenyl)-2-(tetrazol-2-yl)ethyl) carbamate $C_{10}H_{10}ClN_5O_2$ 267.670 | positively modulates γ-$GABA_A$ and inhibits voltage gated sodium channels | bioavailability 88%, $T_{max}$ 1–4 h, $T_{0.5}$ 50–60 h, 60% protein bound in plasma, extensively metabolised in the liver via glucuronidation and oxidation | NA | CNB inhibits CYP2C19: decreases PHT and PHB; induces CYP3A4: decreases LTG; PH causes decreases CNB | [1,2,185–187] |
| Clobazam (CLB) | I | 1975 (anxiolytic) 1984 (anticonvulsant) 2011 (USA) | 7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione $C_{16}H_{13}$ Cl $N_2O_2$ 300.740 | inhibitory effect of GABA on neuronal excitability by increasing neuronal membrane permeability to chloride ions | bioavailability ~100%, $T_{max}$ 1–4 h, $T_{0.5}$ 10–30 h plasma protein-binding 80–90%, main metabolite -N-desmethylclobazam (N-CLB), hepatic elimination (98%), excreted renally | 0.03–0.3 | CBZ, PHT, PB induced CLB metabolism and increased N-CLB levels, cimetidine (an inhibitor of several CYPs (CYP 2C19) increased N-CLB concentration | [29,82,191] |
| Eslicarbazepine Acetate (ESL) | III | 2010 (Europe) 2013 (USA) | 5-oxo-6*H*-benzo(b)(1)benzazepine-11-carboxamide $C_{15}H_{12}N_2O_2$ 296.326 | competitive inhibitor of VGSC | bioavailability > 90%, <40% protein binding, $T_{max}$ 1–4 h, $T_{0.5}$ 13–2 0h, main metabolite: S-licarbazepine, renal elimination (>90%), mainly as ESL (52%) and ESL-glucuronide (41%) | 3–26 | interaction with other AEDs: PHT, PB, CBZ, oral contraceptive (ethinylestradiol and levonorgestrel) and simvastatin | [4,29,45,79,80,193] |

**Table 1.** *Cont.*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ethosuximide (ESM) | I | 1960 (USA) | 3-ethyl-3-methylpyrrolidine-2,5-dione $C_7H_{11}NO_2$ 141.168 | voltage-gated T-type calcium channels | bioavailability 90–100%, $T_{max}$ 1–7 h, $T_{0.5}$ 25–60 h, protein binding unknown, hepatic extensive metabolism by CYP3A4 and CYP2E1, clearance may be saturable (nonlinear) at higher doses, renal elimination 20% | 40–100 | CBZ, PHB, PHT, PRM, and rifampicine increase elimination, in consequence, decrease the plasma level of ESM. STP, isoniazid inhibits metabolism of ESM and increase ESM plasma levels | [27,29,38] |
| Felbamate (FBM) | II | 1993 (USA) | 2-phenyl-1,3-propanediol dicarbamate $C_{11}H_{14}N_2O_4$ 238.239 | weak inhibitor on GABA- and benzodiazepine receptor, antagonist at the strychnine-insensitive glycine recognition site of NMDA receptor-ionophore complex | bioavailability > 90%, $T_{max}$ 1–4 h, $T_{0.5}$ 20–23h , protein binding 20–36%, hepatic metabolism (50% to inactive products) | 30–60 | CBZ, PHT, PB increase whereas VPA decreases its metabolism | [119,120] |
| Gabapentin (GBP) | II | 1993 (USA) | 1-(aminomethyl)cyclohexaneacetic acid $C_9H_{17}NO_2$ 171.237 | inhibits $\alpha$2-$\delta$ subunit of voltage-gated calcium channels | non-linear pharmacokinetics, bioavailability < 60%, $T_{max}$ 2–3 h, $T_{0.5}$ 5–9 h, not metabolized, not protein bound, renal elimination | 2–20 | hydrocodone, cimetidine, morphine, and naproxen increase, whereas antacids decrease its concentration | [138,193] |
| Lacosamide (LCM) | III | 2008 (Europe) 2009 (USA) | (R)-2-acetamido-N-benzyl-3-methoxypropionamidel $C_{13}H_{18}N_2O_3$ 250.294 | inhibits sodium channel, selective inhibitor of depolarized neurons, binds to collapsin response mediator protein-2 (CRMP-2) | bioavailability~100%, $T_{max}$ 1–4 h, $T_{0.5}$~13h, <15% bound to plasma proteins, as a CYP2C19 substrate, excreted unchanged (40%) with its inactive O-desmethyl metabolite (30%) | 3–10 | strong interaction with selective serotonin 5-HT3 receptor antagonist (dolasetron) or antiretroviral protease inhibitor (saquinavir). Interact with beta-blockers like metoprolol and diltiazem or verapamil | [161,162,194] |
| Lamotrigine (LTG) | II | 1994 (USA) | 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine $C_9H_7Cl_2N_5$ 256.091 | inhibits a voltage-sensitive sodium channels, modulates the release of aspartate and glutamate | bioavailability > 95%, $T_{max}$ 1–3 h, $T_{0.5}$ 15–35 h, protein binding 66%, extensively metabolized via glucuronidation | 2.5–15 | LTG increases VPA | [29,195] |
| Levetiracetam (LEV) | II | 1999 (USA) | (-)-(S)-$\alpha$-ethyl-2-oxo-1-pyrrolidine acetamide $C_8H_{14}N_2O_2$ 170.212 | acting on SV2A, indirectly GABAergic neurotransmiter and ionic currents modulater, in vitro inhibitor of N-type calcium channels | bioavailability ~100%, $T_{max}$ 1.3 h, $T_{0.5}$~6–8 h, enzymatic hydrolysis to inactive carboxylic acid metabolite (L057), 66% excreted in the urine as unchanged drug | 5–41 | LEV interact with alcohol, antihistamines, antipsychotics or benzodiazepines, SSRI and other seizure drugs like CBZ, VPA or ZNS | [96,98] |

**Table 1.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Oxcarbazepine (OXC) | II | 2000 (USA) | 10,11-dihydro-10-oxo-5H-dibenz (b,f) azepine-5-carboxamide $C_{15}H_{12}N_2O_2$ –252.269 | inhibition of the voltage-gated sodium channel (VGSC) | bioavailability >9 5%, $T_{max}$ 1–3 h, $T_{0.5}$ 1–5 h, 60% protein binding, main active metabolite - 10,11-dihydro-10-hydroxy-carbazepine, clearance route: hepatic (50%) and renal (50%) | 10–35 | dose dependent effect of the metabolism of dihydropyridine antagonists, oral contraceptives and some antiepileptic drugs (CBZ) | [29,43,68,191] |
| Perampanel (PER) | III | 2012 (USA) | 2-(2-oxo-1-phenyl-5-pyridin-2-ylpyridin-3-yl)benzonitrile $C_{23}H_{15}N_3O$ 349.393 | selective, noncompetitive AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) type glutamate receptor antagonist | bioavailability: ~100%, $T_{max}$ 0.5–2 h, $T_{0.5}$~105 h 95% plasma protein binding, extensive hepatic metabolism (>90%), excreted as oxidative and conjugated metabolites with urine and feces | 0.1–1.0 | PER interacts with other AEDs (OXC, TPM, VPA, CBZ, PHT), alcohol, benzodiazepines, narcotics, barbiturates, antihistamines | [4,29,44,45,168,169,191] |
| Phenobarbital (PHB) | I | 1912 (Germany) | 5-ethyl-5-phenyl barbituric acid $C_{12}H_{12}N_2O_3$ 232.235 | interaction with $GABA_A$ and increase in chloride ions in neuron and finally reduce neuronal excitability | bioavailability > 95%, $T_{max}$ 2–3 h, $T_{0.5}$ 30–173 h in adults; 50 h in children, 20–45% plasma protein binding, extensively (>70%) metabolized by isoenzymes of cytochromes CYP2C9, CYP2C19, and CYP2E1 | 10–40 | interactions are results of inducing effect of phenobarbital on CYP1A2, CYP3A6, CYP2B, CYP2C, CYP3A4 and UTGs and is observed decreased level of AEDs and beta-blockers, calcium channel blockers, digoxin, hormonal contraceptives statins: lovastatin, simvastatin, cerivastatin, and atorvastatin, vitamin | [14–18] |
| Phenytoin (PHT) and Fosphenytoin (FOS) | I | 1908 (Germany) 1953 (USA 1996 (USA) | 5,5′-diphenylhydantoin $C_{15}H_{12}N_2O_2$ 252.268 (3-phosphoryloxymethyl)phenytoin $C_{16}H_{15}N_2O_6P$ 362.274 | modulation of voltage-gated sodium channels-enhances rapid inactivation of sodium channels | hepatic metabolism in 98%, by the isoenzyme CYP2C9 and CYP2C9. Biological half—life elimination is generally in the range 7–42 h and can be extended because of saturable pharmacokinetics, $T_{0.5}$ 15 min to convert FOS to PHT. Phenytoin is an inducer of CYP3A4, CYP2C9, CYP2C19, CYP1A2 and UGT | 10–20 (total) 1–2 (free) | decreased level of CBZ and CBZE, clonazepam, FBM, LTG, OXC, PER, PRM, RFM, TPM, VPA, ZNS, TGB, decreased level of digoxin, hormonal contraceptive, ibrutinib, nilotinib, proton pump inhibitors, quinidine, sirolimus, tacrolimus, statins, telaprevir, vitamin D and folic acid | [25–29] |

**Table 1.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Piracetam (PIR) | I | 1970 (Europe) | (2-oxo-pyrrolidin-1-yl)-acetamide $C_6H_{10}N_2O_2$ 142.158 | nootropic modulator of cerebral function, positive allosteric regulator of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor | bioavailability ~100%, $T_{max}$ 1–1.5 h, $T_{0.5}$~5 h, not protein-bound, renal elimination as unchanged drug (not known major metabolism) | NA | PIR increases level of CBZ, cisplatine, digoxine, estradiol acetate, lithium, carbonate, procainamid, tiapride, vancomycin | [86] |
| Pregabalin (PGB) | II | 2004 (USA) | (S)-3-(aminomethyl)-5-methylhexanoic acid $C_8H_{17}NO_2$ 159.226 | inhibits α2-δ subunit of voltage-gated calcium channels | bioavailability > 90%, $T_{max}$ 1–2 h, $T_{0.5}$ 5–7 h, not metabolized, not protein bound, renal elimination | 2–5 | GBP and PHT decrease its concentration | [29,138] |
| Primidone (PRM) | I | 1954 (USA) | 5-Ethyl-5-phenyl-1,3-diazinane-4,6-dione $C_{12}H_{14}N_2O_2$ 218.252 | binds synaptic and extrasynaptic $GABA_A$ receptors | bioavailability 60–100%, $t_{0.5}$ 10–12 h (PEMA), 29–3 6h (PHB), renal excretion 40–60% unchanged, hepatic metabolism CYP2C9, CYP2C19, active metabolites—phenylethylmalonamide (PEMA) and PHB | 5–12 (PRM), 15–40 as (PHB) | interactions similar to PHB, are results of inducing effect of phenobarbital on CYP1A2, CYP3A6, CYP2B, CYP2C, CYP3A4 and UTGs | [26,29,35] |
| Rufinamide (RFM) | III | 2007 (Europe) 2008 (U[29,126,196]SA) | 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4- carboxamide $C_{10}H_8F_2N_4O$ 238.194 | sodium channel inhibitor | bioavailability 70–85%, $T_{max}$ 4–6 h, $T_{0.5}$ 6–10 h, ~40% bound to plasma proteins, no active metabolites, excreted renally (66% as CGP 47292 metabolite and 2% as unchanged drug) | 5–30 | RFM as a mild interactor, increase the clearance of oral contraceptives (ethinyl estradiol, norethindrone) | [197,198] |
| Stiripentol (STP) | III | 2018 (USA) | 4,4-dimethyl-1-(3,4-(methylendioxy)-phenyl)-1penten-3-ol $C_{14}H_{18}O_3$ 234.295 | increases the activity of $GABA_A$ receptors | non-linear pharmacokinetics, bioavailability not available, $T_{max}$ 0.5–2 h, $T_{0.5}$ 4.5–13 h, protein binding 96%, extensive metabolism by the CYP1A2, CYP2C19, and CYP3A4 hydroxylation and renal excretion 30–60%, $C_{max}$ 0.02 and 1.88 mg/L after 50 and 200 mg dose. | 4–22 | inhibits CYP 1A2, 3A4, 2C19, 2D6: increases CBZ, CLB, PHT, PB and VPA | [199–201] |
| Sulthiame (STM) | I | 1950 (Germany) | 4(1,1dioxothiazinan-2-yl) benzenesulfon amide $C_{10}H_{14}N_2O_4S_2$ 290.359 | membranę—a permeant inhibitor of the enzyme carbonic anhydrase | Dose-dependent, plasma $T_{0.5}$ 40–90h, whole blood $T_{0.5}$ 253–313 h bioavailability ≤9 0%, $T_{max}$ 0.5–2 h, $T_{0.5}$ 5–9 h, protein binding 98% extensively metabolized by CYP3A4 | 5–35 | CBZ and PRM, PHT increase the elimination of STM; antacids decrease GI absorption. | [4,38,42] |
| Tiagabine (TGB) | II | 1996 (Denmark) 1997 (USA) | N-(4,4-di(3-methylthien-2-yl)but-3-enyl)nipecotic acid $C_{20}H_{25}NO_2S_2$ 375.548 | inhibits GABA reuptake into neurons and glia | | 0.02–0.3 | CBZ, PHT, PB increase its clearance, VPA increases free fraction | [29,202] |

**Table 1.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Topiramate (TPM) | II | 1996 (USA) | 2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate $C_{12}H_{21}NO_8S$ 361.362 | Inhibits voltage-dependent sodium and calcium channels, it also inhibits carbonic anhydrase activity. Enhances the inhibitory effect of GABA. | bioavailability >80%, $T_{0.5}$ 20–30 h, metabolism mainly by hydroxylation, hydrolysis glucuronidation, and sulfonation 20–30% metabolized in monotherapy, increase to 50–70% in polytherapy with CBZ and PHT | 5–20<br>2–10 | TPM clearance is increased by CBZ, OXC, and PHT, but decreased by lithium, propranolol, amitriptyline | [26,45,113] |
| Valproic acid (VPA) | II | 1967 (France)<br>1978 (USA) | 2-propylpentanoic acid $C_8H_{16}O_2$ 144.211 | increases the inhibitory activity of GABA, blocks voltage-gated ion channels, inhibits histone deacetylase | non-linear pharmacokinetic, bioavailability 90–100%, $T_{max}$ 1–7 h, $T_{0.5}$ 9–16 h, protein binding 85–95%, extensive metabolism via β-oxidation glucorunidation and CYP-mediated oxidation | 50–100 | inhibits CYP2C9, CYP3A4, and epoxide hydrolase: increases CBZ, ESM, LTG, PHB and RFM | [29,126,196] |
| Vigabatrin (VGB) | III | 2003 (Mexico)<br>2009 (USA) | **4-amino-5-hexenoic acid** $C_6H_{11}NO_2$ 129.157 | inhibits GABA-transaminase | bioavailability 60–80%, $T_{max}$ 1–2 h, $T_{0.5}$ 5–8 h, protein binding 17%, not metabolized, renal elimination | 0.8–36 | FBM increases its elimination | [29,126,203] |
| Zonisamide (ZNS) | II | 1989 (Japan)<br>2000 (USA) 2005 (Europe) | 1,2-benzisoxazole-3-methanesulfonamide 1,2-benzoxazol-3-ylmethanesulfonamide $C_8H_8N_2O_3S$ 212.226 | double mechanism of action due to weak enzyme inhibition and modulation of GABA-ergic and glutamate neurotransmission by changing voltage sensitive sodium and calcium channels | bioavailability ≥ 90%, $T_{max}$ 2–5 h, $T_{0.5}$ ~60 h protein binding (40–50%), hepatic metabolism through CYP3A4 (acetylation and reduction, forming N-acetyl zonisamide and 2–sulfamoylacetyl phenol), excreted primarily in urine as parent drug and as the glucuronide of a metabolite | 10–40 | significantly increases CBZ elimination via induction of CYP3A4, PHT and PB induce ZNS metabolism | [10,29,45,157, 191,192] |

**Table 2.** Recent methods for analysis of AEDs in biological matrices.

| Analyzed Drugs | Biological Matrix | Sample Preparation | Method | Column and Mobile Phase | LOQ; Calibration Range | Application | Co-Detected Compounds | Ref |
|---|---|---|---|---|---|---|---|---|
| Brivaracetam | plasma | Protein precipitation with acetonitrile | UHPLC-MS/MS m/z: 213.07 → 168.15 (BRV), 210.10 → 175.19 (IS) | Synergi Fusion column (75 m × 2.0 mm, 5 µm) 0.1% formic acid in water/acetonitrile, gradient mode | 0.1 mg/L; 0.1–10 mg/L | Therapeutic drug monitoring in epilepsy patients | Brivaracetam-d7 (IS) | **[99]** |
| Brivaracetam | liver and kidney tissue homogenates, blood (rats) | SPE (off-line) | LC-MS/MS m/z: 214.0 → 168.0 (BRV-AC), 230.0 → 184.0 (BRV-OHAC), 233.0 → 188.0 (IS) | Waters Atlantis T3 C18 (50 mm × 2.1 mm, 5 µm) Water and acetonitrile (99:1, v/v), gradient mode | 0.001 mg/L; 0.001–0.2 mg/L | In vitro metabolism assay | BRV metabolites (carboxylic-BRV-AC and hydroxylated-BRV -OHAC); Seletracetam (IS) | **[107]** |
| Brivaracetam | plasma | LLE with tert-Butyl methyl ether | UHPLC-MS/MS m/z: 213.12 → 237.06 (BRV), 237.06 → 193.25 (IS) | Aquity BEH C18 column (100 mm × 2.1mm, 1.7 µm) acetonitrile:0.1% formic acid in water | 0.002 mg/L; 0.002–2 mg/L | Pharmacokinetics study in rats and therapeutic drug monitoring, pharmacokinetic study, forensic analysis | CBZ (IS) | **[102]** |
| Carbamazepine | urine | Dispersive LLME (a mixture of acetonitrile and urine sample—homogenous solution) with solid sodium chloride) | GC-FID | HP–5 capillary column (30 m × 0.32 mm,0.25 µm) Carrier gas: nitrogen | 0.033 mg/L; 0.04–100 mg/L | To determine and detect carbamazepine and phenobarbital in urine | PHB | [58] |
| Carbamazepine | plasma and urine | Ultrasound—assisted emulsification microextraction (SAEME) with 1-octanol in water | GC-FID | DB5 (25 m × 0.32 mm; 0.25 µm) Carrier gas: helium | 1.2 mg/L (plasma); 5.0–500 mg/L (plasma) 0.6 mg/L (urine); 2.5–500 mg/L (urine) | Analysis of carbamazepine in biological samples | None | [46] |
| Carbamazepine | dried blood spot (DBS) | LLE with acetonitrile and sodium hydroxide (24:1, v/v) followed by derivatization with N-methyl-N-trimethylsilyl-trifluoroacetamide and trimethylchlorosilane | GC-MS m/z: 193 (CBZ), 201 (VPA), 281 (PHT), 267 (IS) | DB5 (30 m × 0.25 mm, 0.25 µm) | 0.07 mg/L; 0.5–120 mg/L | TDM 169 patients with epilepsy (PWE) on mono- or polytherapy of CBZ, PHT or/and VPA were included in the analysis | VPA, PHT, 5-(p-methylphenyl)-5-phenylhydantoin (IS) | [63] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Carbamazepine | plasma | Protein precipitation with acetonitrile | HPLC-UV ***λ***=220 nm | Nova-Pak® C18 Mixture of dihydrogen phosphate buffer (pH 6.0)–acetonitrile-2–propanol (63:22:15, v/v/v) | 0.07 mg/L; 0.3–15 mg/L | Determination of AED for a large number of a patient sample | CBZE, PHB, PHT | [47] |
| Carbamazepine | plasma | Protein precipitation with chloroform | HPLC-DAD ***λ***=220 nm | Intersil DS-4 C18 (150 mm × 4.6 mm, 5 µm) acetonitrile-water (50:50, v/v) | 0.5 mg/L; 0.05–16 mg/L | Clinical study for monotherapy or polytherapy of carbamazepine | Propyloparaben (IS) | [51] |
| Carbamazepine | serum | LLE with ethyl acetate | HPLC-DAD ***λ*** = 210–400 nm | Bonus-RP (150 mm × 0.46 mm, 5 µm) acetonitrile/$K_2HPO_4$ buffer solution (45:55) | **0.1** mg/L; 0.1–9.1 mg/L | TDM of CBZ | None | [55] |
| Carbamazepine | dried saliva spots (DSS) | LLE with methanol and formic acid (pH 5.5) using Whatman TM903 protein saver card | HPLC-DAD ***λ***=210 nm | Zorbax SB-C18 (250 mm × 4.6 mm, 1.8 µm) 35% acetonitrile/65% water-methanol-trimethylamine (75.5:24.2) | 0.1 mg/L; 0.1–10 mg/L | Alternative for AEDs blood monitoring | PHT, PHB | [60] |
| Carbamazepine | plasma | Microextraction by packed sorbent (MEPS) | HPLC-DAD ***λ***=215 nm (CBZ, CBZE, PB, LTG, PHT and LIC) ***λ***=237 nm (OXC) ***λ***=280 nm (IS) | LiChroCART® Purospher Star column C18 (55 mm × 4 mm, 3 µm) acetonitrile (6%), mixture (94%) water-methanol-triethyloamine (73.2:26.5:0.3; v/v/v) | NA; 0.1–15 mg/L | Routine TDM of CBZ, LTG, OXC, PB and PHT | LTG, OXC, PB, PHT, CBZE, LIC, ketoprofen (IS) | [65] |
| Carbamazepine | plasma or serum | One step extraction by simultaneous protein and phospholipids precipitation | UHPLC-MS/MS m/z: 237.2 → 194.15 (CBZ), 253.2 → 208.14 (OXC), 255.2 → 194.15 (MHD), 297.3→ 194.09 (ESL) | Intersil RP-HPLC (250 mm × 4.6 mm; 5 µm) acetonitrile-methanol-ammonium acetate in water (32:3:65, v/v/v) | 0.5 mg/L; 0.5–40 mg/L | TDM | OXC, ESL, MHD, gatifloxacin (IS) | [52] |
| Carbamazepine | plasma and saliva | Protein precipitation with methanol | LC-MS/MS m/z: 237 → 194 (CBZ), 253 → 180 (CBZE), 251 → 108 (LCM) | Zorbax SB-C18 (100 mm × 3 mm, 3.5 µm) 0.1% formic acid in water and methanol (35:65, v/v) | 1.1 mg/L; 1.1–17.6 mg/L | Preclinical pharmacokinetic studies and TDM | CBZE, LCM (IS) | [53] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Carbamazepine | plasma | LLE with ethyl acetate | SFC-ESI-MS/MS (supercritical fluid chromatography/mass spectrometry m/z: 237.2 → 194.1 (CBZ), 253.1 → 180.1 (OXC), 255.1 → 193.0 (MHD) 338.2 → 78.0 (TPM) 285.2 → 193.1 (IS) | UPC2TM BEH, 2EP (100 mm × 3 mm; 1.7 µm) carbon dioxide and methanol | 0.01 mg/L; 0.01–15 mg/L | TDM | TPM, OXC, MHD, diazepam (IS) | [54] |
| Carbamazepine | DBS | LLE with methanol and ammonium formate with 0.15% formic acid in water using Whatman TM903 protein saver card | LC-MS/MS m/z: 237.2 → 178.9 (CBZ–I), 237.3 → 194.1 (CBZ–III), 245.2 → 200.1 (CBZ-d8) 247.4 → 204.1 (CBZ-d10), LTG-13C$_3$ (IS), LEV-d6 (IS), VPA-d6 (IS) | Acquity UPLC BEH, C18 (50 mm × 2.1 mm, 1.7 µm) 10 mM ammonium formate with 0.15% formic acid and 100% methanol | 2.5 µM/L (0.6 mg/L); 5–30 µM/L (1.2-7.1 mg/L) | Routine laboratory DBS analysis as an alternative matrix | LTG, LEV and VPA CBZ-d8 (IS), CBZ-d10 (IS), LTG-13C$_3$ (IS), LEV-d6 (IS), VPA-d6 (IS) | [64] |
| Carbamazepine | exhaled breath condensate (EBC) | Samples directly analyzed without pretreatment | HPLC-FLD $\lambda_{ex}/\lambda_{em}$ = 290/480 nm | Copper nanoclasters (CuNCs) coated with cetyl trimethylammonium bromide with 0.1 M/L phosphate buffer (pH = 5) | 0.08 mg/L; 0.2-20 mg/L | Routine quantification of CBZ in clinical practices using a non-invasive sampling method | None | [61] |
| Cenobamate | plasma (rats) | Protein precipitation with acetonitrile | LC-MS/MS m/z: 268.06 → 198 (CNB), 216.09 → 198.01 (IS) | Spursil C-18 10 mM ammonium formate and acetonitrile (60:40, v/v) | NA; 0.01-5 mg/L | Pharmacokinetic studies in healthy subjects | carisbamate (IS) | [186] |
| Cenobamate | plasma | Protein precipitation | LC-MS/MS | NA | 0.02 mg/L; 0.02-10 mg/L | Pharmacokinetic studies in healthy subjects | GBP, LEV, PGB | [2] |
| Cenobamate | whole blood, plasma, urine and faeces | Protein precipitation | LC-MS/MS coupled with radio flow-through detector | NA | NA; 0.08-40 mg/L | Pharmacokinetics and mass balance assessment in healthy male subjects | CNB's eight metabolites | [187] |
| Clobazam | serum | LLE with ethyl acetate and reconstitution with acetonitrile:water (80:20, v/v) | LC-MS/MS m/z: 301 → 259 (CLB), 287 → 245 (N-CLB) | Symmetry C18 (75 mm × 4.6 mm, 3.5 µm) methanol:water:acetonitrile (50:30:20, v/v/v) with 0.05% formic acid | 0.025 mg/L; 0.025–0.525 mg/L | TDM, applied in the clinical laboratory routine | Clonazepam, N-CLB, tenazepam (IS), clonazepam-d4 (IS), clonazepam-8-chloroisomer-13C$_6$ (IS) | [84] |

**Table 2.** *Cont.*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Clobazam | plasma | Protein precipitation with methanol | LC-MS/MS m/z: 301 → 259 (CLB), 287 → 245 (N-CLB) | Phenomenex Kinetex Biphenyl (50 mm × 2.1 mm, 1.7 µm) 5 mM ammonium formate with 0.01% ammonium hydroxide and methanol | 0.002 mg/L; 0.002–0.75 mg/L | Bioequivalence/pharmacokinetic studies | N-CLB | [85] |
| Eslicarbazepine acetate | plasma | SALLE | HPTLC-UV $\lambda$=217 nm (ESL and OXC) $\lambda$= 265 nm (CBZ and OXC) | Pre-coated silica gel plate G 60-$F_{254}$ (20 cm x20 cm, 6–8 µm) n-hexane- methylene chloride—ethanol-glacial acetic acid (50:40:10:0.1 v/v/v/v) | 72.82 ng/spot (14.56 mg/L); 150–1000 ng/spot (30–200 mg/L) | Clinical study in epileptic patients and pharmaceutical sample | OXC, CBZ | [49] |
| Eslicarbazepine acetate | plasma or serum | One step extraction by simultaneous protein and phospholipids precipitation | UHPLC-MS/MS m/z: 237.2 → 194.15 (CBZ), 253.2 → 208.14 (OXC), 255.2 → 194.15 (MHD), 297.3→ 194.09 (ESL) | Intersil RP-HPLC (250 mm × 4.6 mm; 5 µm) acetonitrile-methanol-ammonium acetate in water (32:3:65, v/v/v) | 0.5 mg/L; 0.5–40 mg/L | TDM | CBZ, OXC, MHD, gatifloxacin (IS) | [52] |
| Eslicarbazepine acetate | postmortem blood, serum and plasma | Protein precipitation with methanol | LC-MS/MS m/z: 237.3 → 194.2 (CBZ), 253.1 → 236.1 (CBZE), 297.2 → 194.1 (ESL), 172.2 → 154.2 (GBP), 251.1 → 108.1 (LCM), 171.1 → 154.0 (LEV), 256.1 → 166.0 (LTG), 253.2 → 180.1 (OXC), 231.1 → 188.2 (PB), 160.2 → 142.2 (PGB), 217.2 → 159.2 (STP), 376.1 → 247.1 (TGB), 143.1 → 143.1 (VPA), 130.1 → 71.2 (VGB), 211.2 → 119.1 (ZNS) | Phenomenex Gemini C18 (150 mm × 2.1 mm, 5 µm) 2 mM ammonium acetate in water/2 mM ammonium acetate in methanol), gradient mode | 0.5 mg/L; 0.5–50 mg/L | Routine forensic toxicology and therapeutic drug monitoring | CBZ, CBZE, ESL, OXC, S-licarbazepine, GBP, LCM, LTG, LEV, PGB, PB, PHT and its metabolite, retigabine and metabolite, STP, TPM, TGB, VPA, VGB, ZNS, tolbutamide (IS), 10,11-dihydrocarbamazepine, GBP-d10 | [81] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Ethosuximide | plasma | Microextraction with toluene combined with derivatization | LC-MALDI-TOF MS for analysis of ESM in plasma (MRM 190.05 and 379.09) and nano UPLC-LTQ Orbitrap for protein modification analysis | Concentrated column Symmetry C18 (180 mm × 20 mm, 5 µm) Nano-flow column BEH (Ethylene Bridged Hybrid) C18 column (150 mm × 75 mm, 1.7 µm) 0.1% formic acid and acetonitrile with 0.1% formic acid | 5 mg/L; 5–500 mg/L | Healthy volunteer after intake 500 mg ESM | ESM-d3 (IS) | [40] |
| Ethosuximide | plasma dried plasma spots (DPS) | Methanol protein precipitation | LC-UV $\lambda$=210 nm | Column XBrigde C18 (250 mm × 4.6 mm, 3.5 µm) acetonitrile and 50 mM phosphate buffer at pH = 4.5 | 9.6 mg/L; 9.6–192 mg/L | TDM—epilepsy patients undergoing mono- or polytherapy | Linezolid (IS), LEV, LTG, FBM, RFM, ZNS and monohydroxycarbamazepine | [41] |
| Felbamate | plasma | Protein precipitation with acetonitrile | HPLC-UV $\lambda$=210 nm | Synergi Hydro-RP column (150 mm × 4.0 mm, 4 µm) potassium dihydrogen phosphate buffer 50 mM pH = 4,5/acetonitrile/methanol (65:35, v/v) | 5 mg/L; 30–80 mg/L | Therapeutic drug monitoring in plasma of 655 patients with epilepsy | LTG, 10,11-dihydro-10-hydroxy-5H-dibenzo[b,f]azepine-5-carboxamide, OXC metabolite), 4-methylprimidone (IS) | [123] |
| Felbamate | plasma and DPS | Protein precipitation with methanol | HPLC-UV $\lambda$=210 nm | XBridge C18 (250 mm × 4.6 mm, 3.5 µm) 50 mM phosphate buffer at Ph = 4.5/acetonitrile, gradient mode | 9.6 mg/L (plasma and DPS); 2.4–96 mg/L (plasma and DPS) | TDM | LEV, LTG, ESM, RFM, ZNS, CBZ, linezolid (IS) | [41] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Felbamate | plasma | Protein precipitation with methanol | UHPLC-MS/MS m/z: 239.2 → 178.2 (FBM), 237.1 → 194.2 (CBZ), 253.2 → 180.2 (CBZE), 301.2 → 259.2 (CLB), 142.0 → 72.0 (ESM), 172.2 → 137.2 (GBP), 256.1 → 211.1 (LTG), 171.1 → 126.1 (LEV), 231,2 → 188.1 (PB), 253.2 → 182.2 (PHT), 219.2 → 162.2 (PRM), 376.2 → 149.1 (TGB), 340.2 → 264.2 (TPM), 143.1 → 143.1 (VPA), 130.1 → 71.2 (VGB), 213.1 → 132.1 (ZNS) | Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 µm) 10 mM ammonium acetate with 0,1% formic acid/methanol, gradient mode | 4.2 mg/L; 4.2–105 mg/L | TDM | CBZ, CBZE, CLB, clonazepam, diazepam, ESM, GBP, LTG, LEV, nitrazepam, PB, PHT, PRM, TGB, TPM, VPA, VBG, ZNS | [67] |
| Gabapentin | serum | Protein precipitation with acetonitrile | UHPLC-MS/MS m/z: 172 → 154 (GBP), 182 → 147 (GBP-d10), 256 → 43 (LTG), 261 → 48 (LTG-13C,15N$_4$), 171 → 69 (LEV), 177 → 69 (LEV-d6), 213 → 132 (ZNS), 219 → 138 (ZNS-13C6) | ACQUITY UPLC BEH C18 column (30 mm × 2.1 mm, 1.7 µm) 2 mM ammonium acetate in water and 2 mM ammonium acetate in methanol, both containing 0.1% formic acid, gradient elution | 0.1 mg/L; 0.1–100 mg/L | 10 epileptic patients | LTG, LEV, ZNS and monohydroxy derivative of OXC | [75] |
| Gabapentin | blood | Protein precipitation with methanol | LC-MS/MS m/z: 172.1 → 154.1 (GBP), 160.1 → 142.1 (PGB), 182.2 → 164.2 (GBP-d10), 166.2 → 148.1 (PGB-d6) LC-TOF-MS | Poroshell 120 EC C-18 (100 mm × 2.1 mm, 2.7 µm) water and acetonitrile containing 0.1% formic acid | 0.5 mg/L; 0.5–50 mg/L | 1091 blood samples for toxicological analysis | GBP-d10 (IS), PGB, PGB-d6 (IS) | [139] |
| Gabapentin | blood | Protein precipitation with acetonitrile | LC-MS/MS m/z: 172.1 → 154.0 (GBP), 160.1 → 55.2 (PGB), 182.1 → 164.0 (GBP-d10), 166.2 → 148.1 (PGB-d6) | Poroshell 120 EC C-18 (100 mm × 2.1 mm, 2.7 µm) water and acetonitrile containing 0.1% formic acid | 0.5 mg/L; 0.5–50 mg/L | Blood samples for toxicological analysis | Baclofen, GBP-d10 (IS), PGB, PGB-d6 (IS) | [140] |
| Gabapentin | serum | LLE with hexanol followed by derivatization with hexyl chloroformate | GC-MS m/z: 240 (GBP), 228 (PGB), 212 (VGB), 184 (IS) | HP5-MS (30 m × 0.25 mm, 0.25 µm) Carrier gas: helium | 0.5 mg/L; 0.5–50 mg/L | Therapeutic drug or compliance monitoring | PGB, VGB, 3-(4-chlorophenyl)-propionic acid (IS) | [141] |
| Gabapentin | DBS | microwave-assisted derivatization with heptafluorobutanol | GC-MS m/z: 195 (GBP), 205 (GBP-d10) | HP5-MS (30 m × 0.25 mm, 0.25 µm) Carrier gas: helium | 1 mg/L; 1–30 mg/L | 15 healthy volunteers | GBP-d10 (IS) | [142] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Lacosamide | postmortem whole blood, clinical serum and plasma | LLE with alkaline condition (0.01 M NaOH pH 12) and ethyl acetate | GC-MS m/z: 91 (LCM), 100 (IS) | HP-5 MS UI (30 m × 0.25 mm, 0.25 μm) Carrier gas: helium | 0.5 mg/L; 2–100 mg/L | Routine forensic toxicology and therapeutic drug monitoring | Moclobemide (IS) | [165] |
| Lacosamide | plasma | SPE through HF Bond Elut C18 and derivatization using N-methyl-N-tert-butyldimethylsilyltrifluoroacetamide with 1% tert-butyldimethylsilylchloride in acetonitrile | GC-MS m/z: 91 (LCM), 132 (IS) | DB-5 MS (30 m × 0.25 mm, 0.25 μm) Carrier gas: helium | 0.2 mg/L; 0.2–20 mg/L | Therapeutic drug monitoring | LEV-d6 (IS) | [167] |
| Lacosamide | serum | Protein precipitation with methanol and SPE-mass spectrometry online | LC-MS/MS m/z: 251.1 → 108.1 (LCM), 255.1 → 91.0 (IS) | Phenyl SPE cartridge with water containing 10 mM ammonium acetate, 0.1% formic acid and 0.01% trifluoroacetic acid | 0.05 mg/L; 5–50 mg/L | Therapeutic drug monitoring | Lacosamide-13C, d3 (IS) | [166] |
| Lacosamide | plasma | Protein precipitation with methanol and LLE with ethyl acetate | HPLC-DAD $\lambda$=220 nm (LCM, LEV) $\lambda$=239 nm (ZNS, IS) | LiCHroCART Purospher Star C18 (55 mm × 4 mm, 3 μm) water/acetonitrile, gradient mode | 0.5 mg/L; 5–300 mg/L | Pharmacokinetic studies in human and for therapeutic drug monitoring | LEV, ZNS, antipyrine (IS) | [105] |
| Lacosamide | urine and bulk | Protein precipitation with methanol | UHPLC-DAD $\lambda$=205 nm | Hypersil BDS C18 (150 mm × 4.6 mm, 5 μm) 0.05 M/L phosphate buffer pH = 6,50/methanol/acetonitrile (80:10:10, v/v/v) | 0.093 mg/L; 0.1–70 mg/L | Application to pharmaceutical dosage form (tablets) and human urine LCM determination | LEV, catechol (IS) | [103] |
| Lamotrigine | plasma | Deproteinization with 10% acetic acid followed by LLE with diethyl ether:dichloromethane (64:36) | HPLC-UV $\lambda$=210 nm | RP-18 column (250 mm) acetonitrile and 0.1M potassium dihydrogen phosphate (25:75, v/v) | 2 mg/L; 2–50 mg/L | 22 epileptic patients | Barbital sodium (IS) | [151] |
| Lamotrigine | plasma | Protein precipitation using methanol with 1% acetic acid | HPLC-UV $\lambda$=210 nm | Acclaim C-18 (150 mm × 4.6 mm, 5 μm) potassium dihydrogen phosphate buffer (50 mM) and methanol (61:39, v/v) | NA; 2.4–120 mg/L | 186 clinical samples | OXC, 10,11-dihydro-10-hydroxycarbazepine, Fluconazole (IS) | [71] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Lamotrigine | plasma | Protein precipitation with methanol | HPLC-UV $\lambda$=210 nm | XBridge C18 (250 mm × 4.6 mm, 3.5 µm acetonitrile and 50 mM/L phosphate buffer at pH = 4.5, gradient elution | 0.6 mg/L; 0.6–24 mg/L | 61 epileptic patients | Linezolid (IS) | [152] |
| Lamotrigine | plasma | Protein precipitation with methanol | HPLC-UV $\lambda$=260 nm | Diamonsil $C_{18}$(150 mm × 4.6mm, 5 µm) 0.1% trifluoroacetate and methanol (59:41, v/v) | 1 mg/L; 1–50 mg/L | 67 patients with epilepsy | Diazepam (IS) | [153] |
| Lamotrigine | serum | LLE with diethyl ether | HPLC-UV $\lambda$=220 nm | Capcell Pak C18 (250 mm × 4.6 mm, 5 µm) acetonitrile and 0.05 M $NaH_2PO_4$ (26.5:73.5, v/v, pH = 4.5) | NA | 214 epileptic patients | Chloroxazone (IS) | [154] |
| Lamotrigine | plasma | Protein precipitation with acetonitrile | LC-MS/MS m/z: 256.1 → 58.0 (LTG), 237.1 → 194.1 (CBZ), 247.2 → 204.1 (CBZ-d10) | XSelect CSH C18 XP (100 mm × 2.1 mm, 2.5 µm) 5 mM ammonium acetate (with 0.1% of formic acid) and acetonitrile, gradient elution | 0.005 mg/L; 0.005–10.5 mg/L | TDM in schizophrenic patients | CBZ, CBZ-d10 (IS), antipsychotics, antidepressants, anxiolytics | [156] |
| Levetiracetam | plasma | Protein precipitation with acetonitrile | LC-MS/MS m/z: 171.1 → 154.1 (LEV), 172.5 → 126.1 (UCB L057), 256.3 → 167.3 (IS) | Agilent Zorbax SB-C18, (100 mm × 2.1 mm, 3.5 µm) 0.1% formic acid in water with acetonitrile (40:60, v/v), isocratic elution | 0.5 mg/L; 0.5–100 mg/L | Pharmacokinetic study of LEV in patients with epilepsy | LEV metabolite (UCB L057), Diphenhydramine (IS) | [100] |
| Levetiracetam | plasma | Protein precipitation and LLE with methanol and ethyl acetate | HPLC-DAD $\lambda$=220 nm (LCM, LEV) $\lambda$=239 nm (ZNS, IS) | LiChroCART®Purospher®StarC18 (55 mm × 4 mm, 3 µm) water/acetonitrile (90:10, v/v), gradient elution | 2.5 mg/L; 2.5–40 mg/L | Therapeutic drug monitoring in 11 distinct epileptic patients | Antipyrine (IS), LCM, ZNS | [105] |

**Table 2.** *Cont.*

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| Levetiracetam | plasma/serum | Protein precipitation with methanol | HPLC-UV<br>$\lambda$=205 nm | Venusil XBP C18, (250 mm × 4.6 mm, 5 µm)<br>50 mM pH = 5.5 potassium dihydrogen phosphate-acetonitrile (90:10, v/v), isocratic elution | 1 mg/L;<br>1–60 mg/L | Therapeutic drug monitoring in epilepsy patients | Gabapentin (IS) | [108] |
| Levetiracetam | plasma | Protein precipitation with zinc sulphate | HPLC-UV<br>$\lambda$ (NA) | LichroCART 250–4.6 RP-18 (250 mm × 4.6 mm, 5 µm)<br>50 mM pH = 4.5 potassium dihydrogen phosphate buffer and acetonitrile/methanol (3/1) (65:35, v/v), isocratic elution | 5 mg/L;<br>5–80 mg/L | Therapeutic drug monitoring in epilepsy patients in daily clinical practice | NA | [109] |
| Levetiracetam | plasma and CRRT effluent sample | Protein precipitation with acetonitrile | HPLC-UV<br>$\lambda$=210 nm | Synergi Hydro-RP (150 mm × 4.6 mm, 4 µm)<br>50 mM phosphate buffer and acetonitrile, gradient elution | 2 mg/L;<br>2–80 mg/L | Therapeutic drug monitoring in patients undergoing continuous renal replacement therapy (CRRT) | Caffeine (IS) | [110] |
| Oxcarbazepine | plasma | SALLE | HPTLC-UV<br>$\lambda$=217 nm (ESL and OXC)<br>$\lambda$= 265 nm (CBZ and OXC) | Pre-coated silica gel plate G 60-$F_{254}$ (20 cm × 20 cm, 6–8 µm)<br>n-hexane-methylene chloride-ethanol-glacial acetic acid (50:40:10:0.1, v/v/v/v) | 34.58 ng/spot (6.92 mg/L);<br>85–1000 ng/spot (17–200 mg/L) | Clinical study in epileptic patients and pharmaceutical sample | ESL or CBZ mixture | [49] |
| Oxcarbazepine | plasma | Protein precipitation by methanol with 1% acetic acid | HPLC-UV<br>$\lambda$=210 nm | Acclain C18 (Thermo, 150 mm × 4.6mm, 5 µm)<br>potassium dihydrogen phosphate buffer (50 mM) and methanol (61:39) | 2.4 mg/L;<br>2.4–120 mg/L | Clinical practice | LTG, MHD, fluconazole (IS) | [71] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Oxcarbazepine | plasma | MEPS | HPLC-DAD<br>$\lambda$=215, 237, 280 nm | LiChroCART Purosher Star RP acetonitrile (6%)/water-methanol-triethyloamine (94%) (73.2:26.5:0.3; v/v/v) | 0.1 mg/L;<br>0.1–5 mg/L; | Routine TDM of CBZ with, LTG, OXC, PB and PHT | CBZ, LTG, PB, PHT, CBZE, licarbazepine, ketoprofen (IS) | [65] |
| Oxcarbazepine | plasma | Protein precipitation with acetonitrile | LC-MS/MS<br>m/z: 253.1 → 180.2 (OXC), 255.1 → 194.2 (HOXC) | Synergi Hydro-RP (50 mm × 2.0 mm, 4 μm) water-formic acid (100/0.1, v/v) and acetonitrile – methanol-formic acid (50/50/0.1, v/v/v) | 0.02 mg/L;<br>0.02–10 mg/L | Clinical study, pharmacokinetic sample assay in order to support a clinical trial | HOXC | [66] |
| Oxcarbazepine | plasma | Protein precipitation with methanol | UHPLC-MS/MS<br>m/z: 253.1 → 179.9 (OXC), 255.9 → 210.8 (LTG); 254.8 → 193.7 (MHD); 357 → 263.7 (TPM); 170.9 → 125.8 (LVT); 173.9 → 128.8 (LVT-d3); 369 → 269.9 (TPM-d12) 217.9 → 185.7 (IS) | Waters BEH C18 (50 mm × 2.1 mm; 1.7 μm) water with 0.1% formic acid/methanol | 0.20 mg/L;<br>0.20–20 mg/L | Clinical application in 259 samples from patients treated for epilepsy TDM | LTG, LVT, TPM, MHD, LVT-d3 (IS), TPM-d12 (IS), 3,5-diamino-6-[2methoxyphenyl]-1,2,4-triazine (IS) | [74] |
| Oxcarbazepine | plasma | LLE with ethyl acetate | SFC-ESI-MS/MS (supercritical fluid chromatography/mass spectrometry<br>m/z: 253.1 → 180.1 (OXC) 237.2 → 194.1 (CBZ), 255.1 → 193.0 (MHD), 338.2 → 78.0 (TPM), 285.2 → 193.1 (IS) | UPC2TM BEH, 2EP (100 mm × 3 mm; 1.7 μm) carbon dioxide and methanol | 0.01 mg/L;<br>0.01–8 mg/L | TDM, simultaneous quantification of several AED, pharmacokinetics study | CBZ, TPM, MHD, diazepam (IS) | [54] |
| Piracetam | plasma | Protein precipitation with 20% perchloric acid | HPLC-UV<br>$\lambda$ = 200 nm | RP-18 Merck LiChroSpher 100 (250 mm × 4mm, 5 μm), gradient mode aqueous solution of 0,01% perchloric acid/methanol/acetonitrile | 2 mg/L;<br>1–100 mg/L | Bioequivalence study | None | [88] |
| Piracetam | plasma and cerebrospinal fluid | Direct sample injection | Micellar electrokinetic chromatography (MEKC) Beckman P/ACE MDQ system with UV detection | Fused capillary (40.2 cm × 50 μm) | 1 mg/L;<br>5–500 mg/L | Application to analyze piracetam in patients with aphasia | Imidazole (IS) | [89] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Piracetam | serum and urine (tablets, syrup) | Protein precipitation serum with acetonitrile, urine diluted | HPLC-UV $\lambda$=205 nm | Hibar Bondapak ODS C18 (250 mm × 4.6 mm, 5 µm) trimethylamine in water/acetonitrile (70:30, v/v) with phosphoric acid pH = 6,5 | 0.0093 mg/L; 0.02-10 mg/L | Application to analyze piracetam in human serum and urine (also in bulk drugs) | LEV | [90] |
| Perampanel | plasma | Deproteinization by acetonitrile | HPLC-FLD $\lambda_{ex}/\lambda_{em}$ = 290/430 nm | Phenomenex (100 mm × 4.6 mm, 2.6 µm) sodium acetate buffer–acetonitrile (40:60, v/v) | 0.002 mg/L; 0.002-1 mg/L | Clinical study in 30 patients treated with PER (2–10 mg/d) receiving different AED co-therapy | Mirtazapine (IS) | [172] |
| Perampanel | plasma | LLE with diethyl ether | HPLC–FLD $\lambda_{ex}/\lambda_{em}$ = 290/430 nm | YMC pack pro C18 (150 mm × 4.6 mm, 5 µm) acetonitrile water-acetic acid-sodium acetate (840:560:3:1.8, v/v/v/w) | 0.001 mg/L; 0.001-0.5 mg/L | Clinical studies and TDM at laboratories where LC-MS/MS system are not available | ER-167615 (IS) | [170] |
| Perampanel | DPS | LLE with methanol | HPLC-UV $\lambda$=320 nm | Reverse-phase monolithic column water-acetonitrile (60:40, v/v) with phosphoric acid | 0.025 mg/L; 0.025-1 mg/L | TDM | None | [175] |
| Perampanel | serum | Acetonitrile stacking for on-line sample pre-concentration | CE-FL (Capillary electrophoretic methods with fluorescence detection) $\lambda_{ex}/\lambda_{em}$ = 240-400/495 nm | Fused–silica capillary Electolyte–50 mM chloroacetic acid with 0.5% polyvinylalcohol (pH = 2.15) | 0.009 mg/L; 0.01–1 mg/L | TDM and toxicological analysis | None | [174] |
| Phenobarbital | whole blood | Fully automated dried blood spot extraction system. Volumetric absorption microsampling (VAMS), extraction with acetonitrile/water (80:20, v/v) with 5 mM ammonium acetate | UHPLC-MS/MS m/z: 231.0 → 187.8 (PHB), 143 → 143 (VPA), 251.1 → 102.2 (PHT), 237 → 194.1 (CBZ), 253.1 → 180 (CBZE), 148.9→ 148.9 (VPA-d6), 236 → 193 (PHB-d5), 261 → 218.1 (PHT-d10), 247 → 204.1 (CBZ-d10), 263.1 → 220.2 (CBZE-d10) | Chromolith reversed phase (RP-18) endcaped (100 mm × 4.6 mm) 5 mM ammonium acetate and 5 mM ammonium acetate in acetonitrile/water (95:5, v/v) | 1.0 mg/L; 1.0–160.0 mg/L | Assessment levels of AEDs in patients | PHB-d5 (IS), CBZ, CBZ-d10, CBZE, CBZE-d10 VPA, VPA-d6, PHT, PHT-d10 | [21,22] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Phenobarbital | plasma | SPE reversed-phase cartridges (Waters Oasis HLB) washed out by acetonitrile (10 mM ammonium buffer pH 3.5, 2:98 v/v) | online-SPE-LC-HRMS/MS m/z: 231.08 → 188.08 (PHB), 251.08 → 208.08 (PHT), 237.10 → 194.09 (CBZ), 253.09 → 210.09 (CBZE) | Zorbax SB-C-18 (250 mm × 4.6 mm, 5 μm) acetonitrile, methanol and 10 mM acetate buffer pH = 5.5 (10:20:70, v/v/v) | PHB, PHT 0.008 mg/L; 0.008–2.5 mg/L | TDM for epilepsy patients | PHT, CBZ, CBZE, LTG (IS) | [23] |
| Phenobarbital | plasma | Protein precipitation with acetonitrile | LC-MS/MS m/z: 231.1 → 231.1 (PHB), 253.1 → 182.1 (PHT), 237.2 → 194.1 (CBZ), 253.0 → 210.0 (CBZE), 256.1 → 43 (LTG), 253.1 → 208.0 (OXC), 255.1 → 194.1 (MHD), 171.1 → 126.1 (LEV), 143.1 → 143.1 (VPA), 338.2 → 78 (TPM) | Zorbax SB-C18 (50 mm × 4.6 mm, 2.7 μm) acetonitrile/water | 0.15 mg/L; 0.4–60 mg/L | TDM for epilepsy patients | CBZ and its CBZE, LTG, OXC and 10-hydroxycarbazepine, LEV, PHT, VPA, TPM and diphenhydramine (IS) | [24] |
| Phenytoin | plasma | Protein precipitation with acetonitrile | LC-ESI-MS/MS m/z: 251.1 → 208.1 (PHT), 237.1 → 194.0 (CBZ), 255.1 → 237 (CBZ-OH), 256 → 211(LTG), 253.1 → 180.1(OXC), 171.1 → 126 (LEV), 143.1 → 143.1 (VPA), 338.1 → 78.1 (TPM), 211 → 119 (ZNS) | Phenomenex Kinetic C18 (100 mm × 2.1 mm, 2.6 μm) 5 mM ammonium and acetonitrile with 5 mM ammonium acetate | PHT, ZNS TPM: 0.01–10 mg/L VPA 0.05–50 mg/L LEV, LTG, CBZ, CBZE OXC: 5–5000 μg/L | Therapeutic drug monitoring in patients with epilepsy | ZNS, TPM, VPA, LEV, LTG, CBZ, CBZ-OH, OXC | [30] |
| Phenytoin | whole blood, plasma | DBS extracted of methanol/water (80:20, v/v) and 0.1% formic acid plasma diluted and precipitated methanol/water 0.1% formic acid | LC-MS/MS m/z: 253.2 → 182.2 | Synergii Fusion column (50 mm × 2 mm, 4 μm) water/0.1% formic acid and methanol/0.1% formic acid | 1.0 mg/L; 0.1–100 mg/L | Determination of PHT in paediatric patients | None | [31] |
| Phenytoin and phosphenytoin | plasma | free fraction of phenytoin obtained after ultrafiltration using Milipore protein filter | LC-MS/MS m/z: 252.98 → 182.1 (PHT), m/z: 253.98 → 104.0 (FOS) | Restek Ultra BiPh (50 mm × 2.1 mm, 5 μm) formic acid in water and formic acid in methanol | NA; 0.1–4 mg/L | Measurement of free phenytoin in human plasma | FOS | [32] |
| Pregabalin | plasma | Derivatization with 4-fluoro-7-nitrobenzofurazan | HPLC-FLD $\lambda_{ex}/\lambda_{em}$ = 470/530 nm | TSK-gel ODS-140HTP (50 mm × 2.1 mm, 2.3 μm) acetonitrile, methanol, and 50 mM/L phosphate buffer pH = 2 | 0.05 mg/L; 0.05–10 mg/L | 40 patients with pain | Gabapentin (IS) | [143] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Pregabalin | plasma, DPS, DBS | plasma: oasis mixed-mode cation exchange (MCX) extraction cartridge bed<br>dry blood/plasma spots: LLE with methyl tert-butyl ether and diethyl ether (80/20, v/v) | HPLC-MS/MS<br>m/z: 160.1 → 141.9 (PGB), 164.1 → 145.9 (IS) | Poroshell 120 EC-C18 methanol, acetonitrile, and 5 mM ammonium formate solution (80/10/10, v/v/v) | Plasma:<br>0.02–16 mg/L<br>Blood/plasma spots:<br>0.01–10 mg/L | Bioequivalence study performed in 14 healthy human volunteers after administration of 300 mg PGB | Pregabalin-d4 (IS) | [144] |
| Pregabalin | DPS, DBS | Derivatization with n-propyl chloroformate in the presence of n-propanol followed by LLE with ethyl acetate | HPLC-MS/MS<br>m/z: 288.00 → 228.04 (derivatized PGB), 272.03 → 212.00 (derivatized IS) | YMC-Pack Octyl column (50 mm × 4.0 mm, 3 μm) acetonitrile and 0.15% formic acid | DBS: 0.2 mg/L;<br>0.2–20 mg/L<br>DPS:<br>0.4 mg/L;<br>0.4–40 mg/L | 12 epileptic patients | 4-aminocyclohexanecarboxylic acid (IS) | [145] |
| Primidone | plasma | Online extraction with use restricted access carbon nanotubes (RACNTs) | LC-UV<br>$\lambda$=210 nm | C18 (250 × 4.6 mm, 5 μm) column in switching system monopotassium phosphate buffer 0.01 M/L, pH = 6.0: acetonitrile:methanol (55:25:20, v/v/v) and water or methanol:water (90:10, v/v).<br>30 mg of the RACNTs in a column (10 × 4.6 mm) | 0.2 mg/L;<br>0.2–40 mg/L | TDM of PRM and PHB in patients with mental illness | Hydantoin (IS), PHB, CBZ | [36] |
| Primidone | plasma and DPS | On dried sample spot devices (DSSDs) and plasma extracted with acetonitrile | LC-MS/MS<br>m/z: 219.0 → 119.0 (PRM), 256.0 → 210.9 (LTG), 253.2 → 180.0 (OXC), 171.1 → 154.0 (LEV), 140.0 → 140.0 (ESM), 338.0 → 280.0 (TPM), 210.99 → 147.1 (ZNS), 171.1 → 154.0 (LEV), 251.05 → 108.1 (LCM), 239.0 → 107.1 (RFM), 255.0 → 108.1 (10-OH-OXC) | C18 Hypersil Gold column (50 mm × 2.1 mm, 1.9 μm) water/0.1% formic acid and acetonitrile/0.1% formic acid | 0.32 mg/L;<br>0.7–26.3 mg/L | TDM in 129 undergoing mono and polytherapy for epilepsy | LCM-d3 (IS), LCM, LEV, ESM, ZNS, RFM, LTG, 10-OH-OXC, OXC, TPM | [37] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Rufinamide | brain tissue and plasma from rats | Protein precipitation with methanol | HPLC-UV $\lambda$=215 nm | Phenomenex Kinetex C18 (250 mm × 4.6 mm, 5 µm) 10 mM ammonium acetate buffer (pH = 4.7 ± 0.1, adjusted with glacial acetic acid) and acetonitrile (84.7:15.3, v/v), isocratic elution | 0.0138 mg/L (plasma); 105.24 ng/g (brain); 0.1–2 mg/L (plasma) 300–6000 ng/g (brain) | Pharmacokinetic studies | Piribedil (IS) | [181] |
| Rufinamide | mouse plasma and tissues (brain, liver, kidney) | Protein precipitation with acetonitrile and LLE (extracted dichloromethane) | HPLC-UV $\lambda$=210 nm | LiChroCART Purospher Star column C18 (55 mm × 4 mm, 3 µm) water/acetonitrile (82:18, v/v), isocratic elution | 0.1 mg/L; 0.1–30 mg/L | Preliminary pharmacokinetic studies to support non-clinical pharmacokinetic based studies on RFM | Chloramphenicol (IS) | [178] |
| Rufinamide | human, rat and rabbit plasma | Protein precipitation with methanol | LC-MS/MS m/z: 239 → 127 (RFM), 251 → 108 (IS) | Zorbax SB-C18 (100 mm × 3 mm, 3.5 µm) water with 0,5% formic acid/methanol (50:50, v/v) | 0.005 mg/L; 0.04–2 mg/L | Therapeutic drug monitoring | Lacosamide (IS) | [179] |
| Rufinamide | postmortem whole blood, clinical serum and plasma | Protein precipitation with methanol | LC-MS/MS m/z: 237.3 → 194.2 (CBZ), 253.1 → 236.1 (CBZE), 297.2 → 194.1 (ESL), 172.2 → 154.2 (GBP), 251.1 → 108.1 (LCM), 171.1 → 154.0 (LEV), 256.1 → 166.0 (LTG), 253.2 → 180.1 (OXC), 231.1 → 188.2 (PB), 160.2 → 142.2 (PGB), 217.2 → 159.2 (STP), 376.1 → 247.1 (TGB), 143.1 → 143.1 (VPA), 130.1 → 71.2 (VGB), 211.2 → 119.1 (ZNS) | Phenomenex Gemini C18 (150 mm × 2.1 mm, 5 µm) 2 mM ammonium acetate in water/2 mM ammonium acetate in methanol), gradient mode | 0.5 mg/L; 0.5–50 mg/L | Routine forensic toxicology and therapeutic drug monitoring | CBZ, CBZE, ESL, OXC, S-licarbazepine, GBP, LCM, LTG, LEV, PGB, PB, PHT and its metabolite, retigabine and metabolite, STP, TPM, TGB, VPA, VGB, ZNS, tolbutamide (IS), 10,11-dihydrocarbamazepine, GBP-d10 | [81] |
| Rufinamide | plasma and DPS | On dried sample spot devices (DSSDs) and plasma extracted with acetonitrile | LC-MS/MS m/z: 239.0 → 107.1 (RFM), 256.0 → 210.9 (LTG), 253.2 → 180.0 (OXC), 171.1 → 154.0 (LEV), 140.0 → 140.0 (ESM), 338.0 → 280.0 (TPM), 210.99 → 147.1 (ZNS), 171.1 → 154.0 (LEV), 251.05 → 108.1 (LCM), 219.0 → 119.0 (PRM), 255.0 → 108.1 (10-OH-OXC) | C18 Hypersil Gold column (50 mm × 2.1 mm, 1.9 µm) water/0.1% formic acid and acetonitrile/0.1% formic acid | 0.65 mg/L; 1.3–42.4 mg/L | Therapeutic drug monitoring | LCM-d3 (IS), LCM, LEV, ESM, ZNS, PRM, LTG, 10-OH-OXC, OXC, TPM | [37] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Rufinamide | plasma and DPS | Methanol protein precipitation | HPLC-UV $\lambda$=210 nm | Column Xbridge C18 (250 mm × 4.6 mm, 3.5 µm) Acetonitrile and 50 mM phosphate buffer at pH = 4.5 | 9.6 mg/L; 9.6–192 mg/L | TDM–epilepsy patients undergoing mono- or polytherapy | Linezolid (IS), LEV, LTG, FBM, ZNS and CBZ-OH | [41] |
| Stiripentol | plasma | Protein precipitation with acetonitrile | HPLC-FLD $\lambda_{ex}/\lambda_{em}$ = 200/400 nm | Inertsil® ODS-80A (10 mm × 4.6 mm, 5 µm) 25 mM phosphate buffer (pH = 2.6) and acetonitrile (43:57, v/v) | 0.05 mg/L; 0.05–40 mg/L | 37 patients with Dravet syndrome | None | [184] |
| Sulthiame | whole blood, plasma, urine | Protein precipitation with methanol (plasma) hemolyzed whole blood, or hemolyzed red blood cells urine was vortexed, sonificated and after centrifugation diluted | LC-MS/MS m/z: 289.0 → 225.1 | XSelect HSS T3 water/acetonitrile | 0.01 mg/L; 0.1–50 mg/L | Oral doses of 50, 100, and 200 mg of sulthiame tablets were administered healthy adult male volunteers | sulthiame-d4 (IS) | [42] |
| Tiagabine | postmortem blood, serum and plasma | Protein precipitation with methanol | LC-MS/MS m/z: 237.3 → 194.2 (CBZ), 253.1 → 236.1 (CBZE), 297.2 → 194.1 (ESL), 172.2 → 154.2 (GBP), 251.1 → 108.1 (LCM), 171.1 → 154.0 (LEV), 256.1 → 166.0 (LTG), 253.2 → 180.1 (OXC), 231.1 → 188.2 (PB), 160.2 → 142.2 (PGB), 217.2 → 159.2 (STP), 376.1 → 247.1 (TGB), 143.1 → 143.1 (VPA), 130.1 → 71.2 (VGB), 211.2 → 119.1 (ZNS) | Phenomenex Gemini C18 (150 mm × 2.1 mm; 5 µm) 2 mM ammonium acetate in water/2 mM ammonium acetate in methanol | 0.05 mg/L; 0.05–10.0 mg/L | Forensic and toxicological analysis, TDM | CBZ, CBZE, ESL, OXC, S- licarbazepine, GBP, LCM, LTG, LEV, PGB, PHB, PHT and its metabolite 5-(p-hydroxyphenyl)-5-phenylhydantoin, retigabine (ezogabine) and its metabolite N-acetyl retigabine, RFM, STP, TPM, VPA, VGB, ZNS | [81] |
| Topiramate | plasma | LLE using dichloromethane and derivatization with 4-chlor-7-nitrobenzo-furazan | LC- FLD $\lambda_{ex}/\lambda_{em}$ = 475/530 nm | Reversed phase column Eclipse18 (150 mm × 4.6 mm, 5 µm) 0.05 M potassium phosphate buffer, pH = 5.5 and acetonitrile (61.5/38.5, v/v) | 0.01 mg/L; 0.01–24 mg/L | Therapeutic drug monitoring in 27 patients with epilepsy | bendroflumethiazide (IS) | [114] |

**Table 1.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Topiramate | plasma | LLE with ethyl acetate and diethylether (95:5, v/v) | UHPLC-MS/MS m/z: 338.1 → 77.9 (TPM), 298.1 → 77.9 (M1, M2), 354.1 → 77.9 (M3, M4), 350.1 → 77.9 (IS) | Kinetex C-18 (50 mm × 2.1 mm, 2.6 µm) water and methanol | TPM 0.1–20 mg/L TPM metabolites: 2,3-desisopropylidene TPM (M1) 0.01–2 mg/L 4,5-desisopropylidene TPM (M2), 10-OH TPM (M3) and 9-OH TPM (4) M2, M3, and M4 0.001–0.2 mg/L | 10 samples from patients with epilepsy | TPM-d12 (IS) and TPM metabolites: M1, M2, M3 and M4 | [115] |
| Topiramate | plasma, whole blood | LLE of 8mm DBS with ethyl acetate followed by flash methylation with TMAH (trimethylanilinium hydroxide solution) | GC-MS m/z: 171, 229, 352 | DB-5 MS (30 m and 0.25 µm) | 0.5 mg/L; 0.5–30 mg/L | Adult volunteer (Hct=44%) after a single oral dose of 100 mg | 5-(p-methylphenyl)-5-phenyl-hydantoin (IS) | [116] |
| Topiramate | plasma | Protein precipitation with acetonitrile | LC-MS/MS m/z: 338.3 → 77.9 (TPM), 150.0 → 91.0 (phentermine), 452.1 → 344.3 (doxazosin), 355.0 → 41.9 (pioglitazone) | 60–5CN (100 mm × 2.1 mm, 5 µm) acetonitrile/20 mM ammonium formate with 0.3% formic acid (40:60, v/v) | 1 µg/L; NA | 12 healthy male volunteers after single oral dose phentermine and TPM (7,5/46 mg) in extended release capsules | Phentermine, pioglitazone (IS) and doxazosin (IS) | [117] |
| Topiramate | plasma | Plasma samples buffered with a TRIS buffer at a pH 8.2 and LLE with methyl terc-butyl ether | Capillary electrophoresis with capacitively-coupled contactless conductivity detection (CE-C4D), separation voltage 20 kV | Background electrolyte (BGE) composed of 15 mM triethylamine pH = 11.3, hydrodynamic injections by pressure (0.8 psi for 5 s) | 1.0 mg/L; 1–30 mg/L | Plasma samples from hospital patients under treatment with TPM | IS-2-naphtol, PHT, CBZ, LTG, PHB LEV, GBP, OXC, VPA, clonazepam, CLB, diazepam, fluoxetine, omeprazole, venlafaxine, folic acid, captopril and diclofenac | [118] |
| Valproic acid | plasma | Protein precipitation with trifluoroacetic acid (TCA) followed by liquid-liquid microextraction (LLME) with chloroform | GC-FID | HP-5 (30 m × 0.32 mm, 0.25 µm) Carrier gas: nitrogen | 0.2 mg/L; 0.2–100 mg/L | 70 epileptic patients (1–18 years) | 3-heptanone (metabolite) | [127] |
| Valproic acid | plasma | Protein precipitation with acetonitrile followed by dispersive liquid-liquid microextraction (DLLME) with chloroform | GC-FID | HP-5 (30 m × 0.32 mm, 0.25 µm) Carrier gas: nitrogen | 6 mg/L; 6 - 140 mg/L | One epileptic patient treated with 125 mg valproic acid | None | [128] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Valproic acid | plasma | LLE with chloroform | GC-FID | Gs-BP 100% dimethylpolysiloxane (10 m × 0.53 mm, 2.65 µm) | 5 mg/L; 5–320 mg/L | 50 epileptic patients | Octanoic acid (IS) | [129] |
| Valproic acid | plasma | LLE using n-hexane | HPLC-UV $\lambda$=210 nm | Carrier gas: helium C-8 Symmetry (150 mm × 3.9 mm, 5 µm) 40 mM sodium dihydrogen phosphate pH = 3.5 and acetonitrile (56:44, v/v) | 2 mg/L; 2–200 mg/L | Pharmacokinetic study of one healthy subject after administration of 500mg extended release VPA | Nonanoic acid (IS) | [130] |
| Valproic acid | saliva, serum | Protein precipitation with acetonitrile | HPLC-UV $\lambda$=210 nm | Chromolith RP 18e (100 mm × 4,6 mm) acetonitrile and 0.05 M potassium dihydrogen ortho phosphate (pH = 3.0) (45:55, v/v) | NA; 5–100 mg/L | 65 epileptic patients (9–62 years) | None | [131] |
| Valproic acid | plasma | SPE | HPLC-MS/MS m/z: 143.0 → 143.0 (VPA), 140.9 → 140.9 (2-ene-VPA, 4-ene-VPA), 283.9 → 239.9 (IS) | Poroshell SB-C18 column (50 mm × 4.6 mm, 2.7 µm) water-acetonitrile | NA; 20–125 mg/L | 60 epileptic patients (mean age 30 years old) treated with valproic acid 500 mg twice daily | VPA metabolites: 2-ene and 4-ene VPA; Probenecid (IS) | [132] |
| Valproic acid | serum | SPE | UHPLC-MS/MS m/z: 143.0 → 143.0 (VPA), 141.0 → 141.0 (2-ene-VPA, 4-ene-VPA), 138.8 → 138.8 (2,4-diene-VPA), 136.6 → 92.5 (IS) | RHD EC-C18 column (75 mm × 2.1 mm, 1.8 µm) acetonitrile and 10 mM ammonium acetate | NA; 1–200 mg/L | 170 epileptic patients | VPA metabolites: 4-ene-VPA, 2,4-diene-VPA, 2-ene-VPA; Salicylic acid (IS) | [133] |
| Vigabatrin | human plasma, rat plasma, brain and retina | Protein precipitation with acetonitrile followed by derivatization with naphthalene 2,3-dicarboxaldehyde | HPLC-FLD $\lambda_{ex}/\lambda_{em}$ = 400/500 nm | Zorbax Eclipse AAA (150 mm × 4.6 mm, 3.5 µm) methanol and 10 mM potassium phosphate dibasic pH = 6.5, gradient elution | 0.0646 mg/L; 0.0646–6.458 mg/L | Animal study after VGB intraperitoneal administration | GABA, taurine, gabapentin (IS) | [148] |
| (-)-R and (+)-S Vigabatrin | plasma | Protein precipitation with methanol followed by derivatization with o-phthaldialdehyde and N-acetyl-l-cysteine | UHPLC-MS/MS m/z: 391.1 → 149.7 (VGB), 397.1 → 268.0 (IS) | Kinetex EVO C-18 (100 mm × 2.1 mm, 1.7 µm) 5mM ammonium acetate and methanol:acetonitrile (63:37, v/v) | NA; 0.2–50 mg/L | 29 children with West syndrome | Deuterated vigabatrin | [149] |

**Table 2.** *Cont.*

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|---|---|---|---|---|---|---|---|---|
| Zonisamide | plasma | Protein precipitation with acetonitrile and then MEPS | HPLC-UV<br>$\lambda$=240 nm | Acclaim RP 120 C18 (150 mm × 4.6 mm; 5 μm)<br>acetonitrile-water (35:65, v/v) | 0.2 mg/L;<br>0.2–80 mg/L | TDM in clinical practice | None | [158] |
| Zonisamide | plasma | Protein precipitation with methanol and LLE with ethyl acetate | HPLC-DAD<br>$\lambda$=220 nm (LCM, LEV)<br>$\lambda$=239 nm (ZNS, IS) | LiChroCART®Purospher®StarC18 (55 mm × 4 mm, 3 μm)<br>water/acetonitrile (90:10, v/v), gradient elution | 0.5 mg/L;<br>5–300 mg/L | Pharmacokinetic studies in human and for TDM | LEV, LCM, antipyrine (IS) | [105] |
| Zonisamide | serum | Protein precipitation with methanol | UHPLC-MS/MS<br>m/z: 172 → 154 (GBP), 182 → 147 (GBP-d10), 256 → 43 (LTG),<br>261 → 48 (LTG-13C,15N$_4$),<br>171 → 69 (LEV),<br>177 → 69 (LEV-d6),<br>213 → 132 (ZNS),<br>219 → 138 (ZNS-13C6) | ACQUITY UPLC BEH C18 column (30 mm × 2.1 mm, 1.7 μm)<br>2 mM ammonium acetate in water and 2 mM ammonium acetate in methanol, both containing 0.1% formic acid, gradient elution | 0.1 mg/L;<br>0.1–100 mg/L | 10 epileptic patients | LTG, LEV, ZNS and MHD of OXC | [75] |
| Zonisamide | plasma | Reaction with 4-chloro-7-nitrobenzofurazan (NBD-Cl) chemosensor (0.2 M, pH 8 borate buffer with 0.2% methanolic NBD-Cl solution heated at 70°C in a water bath for 20 min, after cooling in ice bath, 0.2 M HCl, extracted by mixture of acetonitrile and methanol (1:1) | HPLC-FLD<br>$\lambda_{ex}/\lambda_{em}$ = 465/550 nm | Zorbax RP-C18 (100 mm × 4.6 mm, 3.5 μm)<br>acetonitrile:methanol:water (pH adjusted to 5 with 0.2 M phosphoric acid) (30:20:50% v/v) | 0.086 mg/L;<br>0.1–3 mg/L | Therapeutic drug monitoring | TPM, sulpiride (IS) | [160] |

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