Management: Drug Interactions

Anticipating and managing antiepilepsy drug (AED) interactions, both between AEDs and with other drugs, is critical for minimizing medication risks. Common drug interactions involve pharmacokinetic (PK) changes due to alterations in drug metabolism, influences on drug protein binding and mechanistically-linked pharmacodynamic interactions (Iyanagi, 2007). Several keys to minimize complications of drug interactions are: 1) counsel patients to monitor for common adverse drug effects, such as dizziness and sedation, when starting or increasing treatments and to report persisting symptoms; 2) minimize drug interactions by switching between AEDs when possible, particularly those associated with drug interactions; and 3) recognize there is considerable individual variability in patients' drug metabolism and tolerability to AEDs, checking AED blood levels can help evaluate suspected PK interactions.

PK interactions due to changes in metabolism and elimination:

Interactions between AEDs:

Several first generation AEDs—phenytoin, carbamazepine, phenobarbital and primidone—induce cytochrome P450 (CYP) oxidative enzymes and increase elimination of other metabolized AEDs (Zacarra, 2014). These enzyme-inducing AEDs (EIAEDs) also increase glucuronidation and renal excretion of several AEDs, e.g. phenytoin and carbamazepine reduce lamotrigine blood concentrations. Conversely, valproic acid (divalproex) inhibits oxidation and glucuronidation of many AEDs, especially phenobarbital, primidone and lamotrigine. Valproic acid also increases concentrations of carbamazepine epoxide, the main metabolite of carbamazepine, and can cause "hidden" toxicity.

Our xenobiotic system uses cytochrome oxidases in our barrier organs (liver, mucosa, skin) to remove foreign molecules; reactions to drug epitopes and clonal synthesis of CYP is genetically determined and varies across individuals (Zanger, 2012). Consequently, metabolism of EIAEDs and their interactions must be clinically monitored, sometimes with blood levels. Many of the newer generation AEDs, such as levetiracetam and pregabalin, have extensive renal excretion (preceded by glucuronide conjugation, demethylation or hydrolysis for some) and are associated with fewer drug interactions than the older AEDs (Johannessen, 2010). These often have predictable elimination and blood concentrations and require less monitoring of drug levels to detect PK interactions compared to older drugs. Several principles to avoid metabolic AED interactions causing clinical symptoms are:

- Anticipate induction effects on AEDs (both CYP oxidation and glucuronidation) and plan for "de-induction" when stopping EIAEDs. For example, the half-life of zonisamide decreases from approximately 60 hours to 30 hours with CYP induction with EIAEDs; patients stopping phenytoin while taking zonisamide experience an approximate doubling of their zonisamide blood concentration. Some AEDs have complex interactions--felbamate has induction and inhibition interactions with other AEDs.
- Beware of "hidden" drug interactions, such as an increase in the carbamazepine epoxide metabolite when valproic acid is added or increases in free levels of protein bound AEDs when other AEDs are added.
- Patients tolerate combined AEDs better when a new drug is added slowly; however, it is frequently preferred to add AEDs with few AED interactions or to convert between AEDs.
- Blood levels are usually not necessary for the newer generation AEDs. Drug concentrations usually correspond to body mass and dose for drugs that are renally excreted; and there is less individual variation in the elimination compared to EIAEDs. Blood levels may still help screen for poor treatment adherence or to evaluate toxicity, particularly when a patient is treated with multiple AEDs.

Interactions influencing free levels of AEDs:

Many AEDs are partially bound to albumin and other plasma proteins; only the "free fraction" of these AEDs penetrates the CNS and provides active anti-seizure activity. Patsolos et al (2017) reviews common conditions that alter protein binding of AEDs:

- AEDs with high protein binding (>90%) are: valproic acid, phenytoin, perampanel, tiagabine, clonazepam, clobazam and its metabolite.
- There is considerable individual variation in AED protein-binding, so clinical monitoring for AED tolerability and seizure response is important. Individual valproic acid free levels, for example, frequently range from 10 to 25% with free fractions increasing at higher valproic acid doses.
- Many patients with long ICU hospitalizations are malnourished with decreased albumin and increased free AED fractions. Pregnancy often decreases albumin binding with AEDs, causing increased free AED concentrations. Total carbamazepine plasma concentrations, for example, typically decrease during pregnancy, especially in the third trimester. Due to decreased protein binding during pregnancy, however, free carbamazepine levels often remain stable and dose adjustments are often not necessary.
- Patients treated with AEDs with high protein binding may need to have free levels checked—this is often needed when chronically ill ICU patients are treated with valproic acid or phenytoin and during pregnancy with carbamazepine treatment.

Mechanistically-based pharmacodynamic interactions between AEDs:

Patients treated in adjunctive treatment trials often tolerate lower doses of AEDs than those treated in AED monotherapy trials. This is usually due to adverse "pharmacodynamic" (PD) interactions between AEDs. The mechanisms for adverse PD interactions are poorly understood, however, they are similar to intoxication effects and are most common between AEDs with similar mechanisms, e.g. benzodiazepines may cause increased sedation when

combined. Many patients have adverse PD interactions when treated with combinations of sodium channel modulators. High dose combinations of phenytoin, carbamazepine, oxcarbazepine, lacosamide and lamotrigine often cause sedation, dizziness and blurred vision. These symptoms appear to be due to AED gating of rapidly firing brainstem and cerebellar neurons, resulting in nystagmus, dizziness, imbalance and sedation. Symptoms due to adverse PD interactions often can be reduced by starting AEDs slowly, permitting adaptation to the drugs. Converting between AEDs with PD interactions and minimizing combined therapy, however, is optimal.

Examples of common PD interactions associated with adverse drug effects are:

- Lacosamide is well tolerated at a 600 mg/day dose when not combined with other sodium channel modulators, however, PD interactions causing dizziness and sedation are common when lacosamide is combined with full doses of other sodium channel gating agents, especially oxcarbazepine (Sake, 2010).
- Both PD and PK interactions can complicate AED therapy, particularly with combinations of first generation AEDs.
- PD interactions may influence the efficacy of AEDs in treating seizures, however, this is less well documented. There is evidence that valproic acid and lamotrigine treatment may be synergistic in reducing seizures in some patients with highly drug-resistant epilepsy. Combining AEDs with different anti-seizure mechanisms may be beneficial for some patients in improving tolerability and reducing seizures.
- Isobolograms of animal seizure models demonstrate syngergistic effects for AEDs, suggesting there may be favourable PD interactions that increase AED efficacy. These patterns, however, have been difficult to confirm in trials of patients with drug-resistant epilepsy, partially due to dose-limiting adverse drug effects.

Interactions between AEDs and other drugs:

Many medications have PK and PD interactions with AEDs, however, three treatment areas are especially important: interactions with oral contraceptives, antiretroviral therapies and chemotherapeutic drugs.

Oral contraceptives: Enzyme inducing AEDs reduce oral contraceptive hormonal blood levels and can cause contraceptive failure (Herzog, 2017). Commonly used AEDs that induce ethinyl estradiol metabolism are carbamazepine, eslicarbazepine, felbamate, oxcarbazepine, phenobarbital, phenytoin, rufinamide and topiramate (at high doses). These AEDs, except for topiramate, also reduce progestins. Lamotrigine and perampanel reduce progestins slightly, but not ethinyl estradiol. AEDs that do not interact with either hormone are brivaracetam, gabapentin, lacosamide, levetiracetam, pregabalin, valproic acid, vigabatrin and zonisamide. Patients taking AEDs that significantly induce the metabolism of estrogen and progestins (>20%) can be treated with slightly increased estrogen doses to compensate for this interaction, e.g. estradiol 50 mcg/day instead of 30 mcg/day. It is important to counsel women of childbearing age about this interaction so they can receive appropriate counselling on contraception from their gynaecologist or general physician.

Oral contraceptives can also increase metabolism of lamotrigine and to a lesser degree other AEDs. Most patients with easily controlled seizures do not require dose adjustments due to this interaction. Nearly 30% of women with epilepsy with uncontrolled seizures report increased seizures associated with their menstrual cycle (catamenial seizures), most frequently an increase in seizures in the pre-menstrual luteal phase due to decreases in endogenous progesterone.

Anti-retroviral therapy: Metabolism of antiretroviral drugs can be increased by AEDs that induce CYP or glucuronidation and induce treatment failure. These interactions are complex: phenytoin reduces efavirenz and elavirenz blood levels much greater than carbamazepine (Okulicz, 2018). Non-enzyme inducing AEDs are preferred to minimize risks for drug interactions.

Chemotherapy: EIAEDs, both via CYP oxidation and glucuronidation, reduce exposures to many chemotherapy agents and may cause treatment failure (Christa, 2016). EIAEDs induce metabolism of several alkylating agents (e.g. busulfan, cyclophosphamide, procarbazine), vinca alkaloids (vinblastine,

vincristine and vindesine), taxanes (docetaxel and Paclitaxel), anti-metabolites (MTS, HD-MTX), camtothetic derivitives (Irinotecan, topotecan), and podophyllotoxin derivitives (Etoposide, Teniposide). Temozolomide, an important chemotherapy agent for treating gliomas, is not induced by EIAEDs; valproic acid may inhibit temozolomide metabolism. Everolimus concentrations are reduced by EIAEDs.

Non-enzyme inducing AEDs are usually preferred for treating seizures in patients treated with chemotherapy agents (e.g. levetiracetam, lacosamide, gabapentin, brivaracetam, valproic acid). Valproic acidtreatment, though, may inhibit metabolism of nitrosoureas, cisplatin and etoposide and increase their toxicity. Levetiracetam competes with methotrexate for renal tubular excretion and may increase drug toxicity if doses are not adjusted.

Several chemotherapy agents can reduce phenytoin, carbamazepine and valproic acid blood concentrations by interfering with absorption or their protein binding. These include cisplatin, vinblastine and high doses of methotrexate. Procarbazine at high doses inhibits phenytoin metabolism; this increases risks for phenytoin hypersensitivity reactions.

Clinically important interactions between AEDs and **other drugs** are listed:

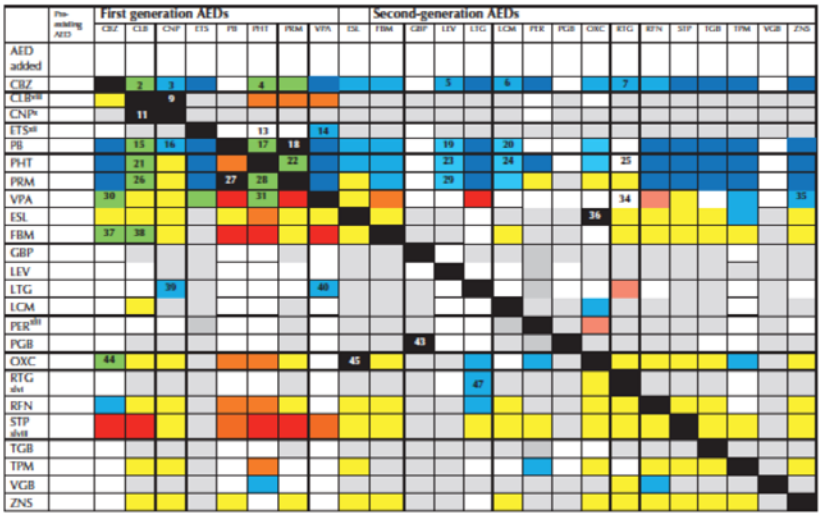
1) Macrolide antibiotics such as erythromycin inhibit carbamazepine metabolism and frequently trigger intoxication symptoms from high carbamazepine blood levels;

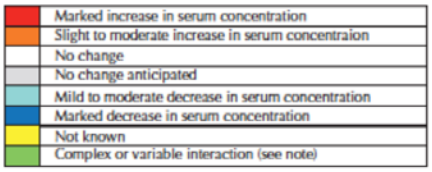
2) Warfarin is induced by EIAEDs and must be adjusted (or use non-inducers) when combined. Several newer anticoagulants can be substituted, although rivaroxaban metabolism by CYP3A4 is induced by EIAEDs and inhibited by valproic acid.

3) Antimicrobial drugs: EIAEDs increase metabolism of doxycycline, indinavir, itraconazole, metronidazole and praziquantal. Valproic acid may inhibit metabolism and increase concentrations of carbapenem antibiotics (imipenem, meropenem and panipenem).

Several psychotropic drugs induce EIAEDs: haloperidol, risperdone, chlorpromazine, clomipramine and sertraline. These interactions are often modest and dose dependent and AED concentrations can be checked if an interaction is suspected.

Table 2. Pharmacokinetic interactions between AEDs[1]. The vertical column refers to the AED which is added. The boxes on each line illustrate the expected changes in serum concentrations of the pre-existing drug. The magnitude of each interactions and its clinical relevance reflects the authors' judgment and need to be interpreted flexibly because intersubject variability in magnitude and consequences can be considerable.





Epileptic Disorders

Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. Epileptic Disord. 2014 Dec;16(4):409-31.

Table 4. The mean total, free, percentage free, and percentage bound AED concentrations measured in the various serum samples

Antiepileptic drug (n)	Laboratory reference range, mg/L	Mean total concentration, mg/L (range)	Mean free concentration, mg/L (range)	Mean % free concentration (±SEM)	Mean % bound concentration
Brivaracetam (9)	Not established	2.1 (0.4–6.1)	1.1 (0.2–3.9)	64.5 ± 1.4	35.5
Carbamazepine (10)	4–12	10.2 (3.7–15.3)	2.6 (0.7–3.8)	25.2 ± 0.7	74.8
Carbamazepine-epoxide (10)	Up to 2.3	2.0 (0.1–3.6)	1.0 (0.06–1.9)	50.2 ± 1.1	49.8
Clobazam (11)	30–300[a]	307.8[a] (50.8–619.7)	33.1[a] (6.3–63.4)	9.8 ± 0.5	90.2
Desmethyl-clobazam (11)	300–3,000[a]	1,542.7[a] (73.8–4,933.0)	184.7[a] (10.7–71.3)	10.8 ± 0.7	89.2
Clonazepam (10)	20–70[a]	58.7[a] (16.8–147.3)	4.8[a] (1.0–12.7)	9.5 ± 2.2	90.5
Gabapentin (10)	2–20	7.0 (1.8–14.9)	7.3 (1.5–14.6)	102.7 ± 1.8	0
Eslicarbazepine (12)	3–35	24.0 (9.5–40.0)	13.3 (7.9–16.3)	56.2 ± 3.2	43.8
Ethosuximide (10)	40–100	56.3 (23.3–79.1)	43.5 (20.0–56.9)	78.2 ± 1.4	21.8
Felbamate (7)	30–60	59.7 (20.3–89.2)	24.4 (10.8–45.4)	52.1 ± 1.5	47.9
Lacosamide (10)	10–20	11.9 (8.8–15.8)	10.2 (7.3–13.6)	86.0 ± 0.8	14.0
Lamotrigine (10)	3–15	10.0 (1.7–18.7)	3.3 (0.5–5.9)	34.3 ± 1.2	65.7
Levetiracetam (10)	12–46	35.8 (15.8–83.4)	34.6 (15.5–43.9)	96.6 ± 1.2	3.4
10-Hydroxycarbazepine (10)	3–35	25.3 (11.1–41.2)	15.2 (6.8–23.1)	60.5 ± 1.2	39.5
Perampanel (9)	200–1,000[a]	(605.3–1,709.3)	(6.3–57.4)	2.4 ± 0.5	97.6
Phenobarbital (10)	10–40	20.3 (10.5–36.1)	10.6 (5.3–17.8)	52.2 ± 1.0	47.8
Phenytoin (10)	10–20	22.7 (9.2–33.8)	1.9 (0.4–3.2)	7.8 ± 0.6	92.2
Pregabalin (10)	2–8	6.5 (0.8–22.5)	6.6 (0.9–23.3)	102.7 ± 2.3	0
Primidone (11)	5–10	11.8 (4.2–29.5)	7.7 (3.2–19.3)	66.5 ± 1.7	33.5
Retigabine (9)	Not established	13.0 (4.2–31.7)	1.5 (0.5–3.0)	12.0 ± 1.34	88.0
Rufinamide (12)	30–40	19.0 (6.6–32.7)	16.3 (4.6–22.9	72.3 ± 6.1	27.7
Stiripentol (10)	4–22	8.7 (4.6–18.2)	0.3 (0.01–1.2)	3.9 ± 1.3	96.1
Tiagabine (8)	20–200[a]	349.1 (156.6–536.1)	15.4 (26.0–17.7	2.2 ± 0.31	97.8
Topiramate (10)	5–20	9.8 (3.7–20.4)	7.8 (2.9–17.3)	80.5 ± 3.1	19.5
Valproic acid (20)	50–100	84.1 (38.2–128.2)	15.8 (4.2–33.0)	7.3–26.1[b]	73.9–92.7[b]
Vigabatrin (9)	2–36	17.1 (4.1–53.3)	14.2 (3.6–45.6)	82.6 ± 1.9	17.1
Zonisamide (10)	10–40	14.3 (2.1–33.5)	8.31.5–19.8	56.3 ± 1.0	43.7

[a]μg/L.
[b]Data are in accordance to saturable protein binding.

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