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Jose de Leon

University of Kentucky, jdeleon@uky.edu

Vincenza Santoro

University of Messina, Italy

Concetta D'Arrigo

University of Messina, Italy

Edoardo Spina

University of Messina, Italy

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INTERACTIONS BETWEEN ANTIEPILEPTICS AND SECOND-GENERATION ANTIPSYCHOTICS

Jose de Leon,¹ Vincenza Santoro,² Concetta D'Arrigo,² Edoardo Spina²

¹University of Kentucky Mental Health Research Center at Eastern State Hospital, Lexington, KY, and Psychiatry and Neurosciences Research Group (CTS-549), Institute of Neurosciences, University of Granada, Granada, Spain.

²Section of Pharmacology, Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Messina, Italy

Corresponding author: Jose de Leon, M.D., UK Mental Health Research Center at Eastern State Hospital, 627 West Fourth St., Lexington, KY 40508. Phone (859) 246-7487. Fax (859) 246-7019.
e-mail: jdeleon@uky.edu

ABSTRACT:

Introduction: Pharmacokinetic and pharmacodynamic drug interactions (DIs) can occur between antiepileptics (AEDs) and second-generation antipsychotics (SGAPs). Some AED and SGAP pharmacodynamic mechanisms are poorly understood. AED-SGAP combinations are used for treating comorbid illnesses or increasing efficacy, particularly in bipolar disorder.

Areas covered: This article provides a comprehensive review of the interactions between antiepileptics and second-generation antipsychotics. The authors cover pharmacokinetic AED-SGAP DI studies, the newest drug pharmacokinetics in addition to the the limited pharmacodynamic DI studies.

Expert opinion: Dosing correction factors and measuring SGAP levels can help to compensate for the inductive properties of carbamazepine, phenytoin, phenobarbital and primidone. More pharmacokinetic studies are needed to establish the clinical relevance of combining: i) AED strong inducers with amisulpride, asenapine, iloperidone, lurasidone and paliperidone; ii) valproate with aripiprazole, asenapine, clozapine and olanzapine; and iii) high doses of oxcarbazepine (≥ 1500 mg/day) or topiramate (≥ 400 mg/day) with aripiprazole, lurasidone, quetiapine, risperidone, asenapine and olanzapine. Two pharmacodynamic DIs are beneficial: i) valproate-SGAP combinations may have additive effects in bipolar disorder, and ii) combining topiramate or zonisamide with SGAPs may decrease weight gain. Three pharmacodynamic DIs contributing to decreased safety are common: sedation, weight gain and swallowing disturbances. A few AED-SGAP combinations may increase risk for osteoporosis or nausea. Three potentially lethal but rare pharmacodynamic DIs include pancreatitis, agranulocytosis/leucopenia and heat stroke. Collaboration from all interested parties including: i) drug agencies and pharmaceutical companies; ii) clinicians using these combinations; iii) researchers with expertise in meta-analyses, pharmacoepidemiology, and DI pharmacology; and iv) grant agencies) is needed to progress in this area.

Keywords: Amisulpride; anticonvulsants; antipsychotics; aripiprazole; asenapine; bipolar disorder; carbamazepine; clozapine; eslicarbazepine; drug interactions; ethosuximide; felbamate; gabapentin; iloperidone; lacosamide; lamotrigine; levetiracetam; lurasidone; olanzapine; oxcarbazepine; paliperidone; pharmacokinetics; phenobarbital; phenytoin; pregabalin; primidone; quetiapine; retigabine; risperidone; rufinamide; stiripentol; tiagabine; topiramate; valproate; vigabatrin; ziprasidone; zonisamide.

Highlights box

- Drug-drug interactions (DIs) between antiepileptics (AEDs) and second-generation antipsychotics (SGAPs) are frequently clinically relevant.
- More pharmacokinetic DI studies are needed for: i) AED strong inducers with amisulpride, asenapine, iloperidone, lurasidone and paliperidone; ii) valproate with aripiprazole, asenapine, clozapine and olanzapine; and iii) high doses of oxcarbazepine (≥ 1500 mg/day) or topiramate (≥ 400 mg/day) with SGAPs dependent on CYP3A4 (aripiprazole, lurasidone, quetiapine and risperidone) or UGTs (asenapine and olanzapine) for their metabolism.
- The pharmacodynamic science of AED-SGAP DIs is in its infancy.
- Possible beneficial pharmacodynamic DIs are: i) valproate-SGAP combinations for bipolar disorder, and ii) combining topiramate or zonisamide with SGAPs to decrease weight gain.
- Pharmacodynamic AED-SGAP DIs may increase risk for sedation, weight gain, swallowing disturbances, osteoporosis, nausea, pancreatitis, agranulocytosis/leucopenia and heat stroke.

1. Introduction

Antiepileptics (AED) can be divided into first-generation AEDs (FGAEDs) and second-generation AEDs (SGAEDs). Their clinically relevant drug interactions (DIs) with antipsychotics (APs) are the focus of this review. APs can similarly be divided into first-generation APs (FGAPs) and second-generation antipsychotics APs (SGAPs). Prior DI reviews [1, 2] included a particularly comprehensive review [2], but since its publication [2], no studies of clinically relevant DIs between FGAPs and AEDs have appeared. This article provides an updated review of clinically relevant DIs between AEDs and SGAPs. The introduction provides a brief description of AEDs, SGAPs, their pharmacokinetics, their pharmacodynamics and co-prescription.

1.1. AEDs

AED drugs are widely used not only for the treatment of epilepsy, but also for the management of a variety of non-epileptic neurological conditions and psychiatric disorders [3]. The FGAEDs include carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone and valproate (Table 1). The SGAEDs include eslicarbazepine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, retigabine, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide (Table 1). Some SGAEDs (eslicarbazepine, retigabine, stiripentol, and vigabatrin) are not marketed in the US. When compared with FGAEDs, most SGAEDs except for felbamate are characterized by better safety profiles with fewer adverse drug reactions (ADRs) and less DI risk than FGAEDs. The only FGAED that continues to be a first-line choice AED may be valproate, but its teratogenicity risk is contributing to its decreased use in females of fertile age. There are no definitive studies comparing the efficacy of all FGAEDs and the most important SGAEDs in the same study, but in the developed countries SGAEDs, particularly lamotrigine, levetiracetam, and oxcarbazepine, have partially substituted for FGAEDs due to their better safety profiles [4,5].

1.2. SGAPs

In recent years, SGAPs (amisulpride, aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) (Table 2) have progressively replaced FGAPs in the developed countries due to better safety profiles for reversible extrapyramidal symptoms and tardive dyskinesia, and better marketing. SGAPs are widely used not only for schizophrenia and bipolar disorder, but for adjuvant treatment of major depressive disorder, psychosis and behavioral disorders in dementia, psychosis associated with Parkinson's disease, resistant obsessive-compulsive disorder, aggressive behavior and irritability in autism spectrum disorders [6].

1.3. Pharmacokinetics

There are two basic types of DIs, pharmacokinetic and pharmacodynamic DIs. Pharmacokinetic DIs can be established and quantified by the study of changes in plasma drug concentrations, usually called therapeutic drug monitoring (TDM), and can occur at absorption, distribution, metabolism or excretion of a drug and/or its metabolite(s). The most important pharmacokinetic DIs are the metabolic DIs. This subsection in pharmacokinetics focuses on the metabolism of AEDs and SGAPs and the clinical consequences of pharmacokinetic DIs. Figure 1 discusses the possibility of non-metabolic pharmacokinetic DIs based on the P-glycoprotein (P-gp) or protein binding [7].

1.3.1. Metabolism

The cytochrome P450 (CYP) isoenzymes are the most important oxidative enzymes; the uridine diphosphate glucuronosyltransferases (UGTs) are the most important conjugation enzymes. CYP substrates, inhibitors and inducers are well established while those for UGTs are less known.

1.3.1.1. AED metabolism. FGAEDs are extensively metabolized in the liver by CYPs and UGTs (Table 1). By contrast [8], many SGAPs have less propensity for pharmacokinetic DIs because they are not metabolized at all (gabapentin, pregabalin and vigabatrin) and are renally cleared, or undergo minimal hepatic biotransformation (levetiracetam and rufinamide) (Table 1). Four FGAEDs, namely carbamazepine, phenytoin, phenobarbital and primidone, induce the activity of multiple enzymes including CYPs, UGTs and epoxide hydrolase (Table 3) [9]. Once steady state is present, inducers need a

few weeks, usually 2-4 weeks, to reach maximum effects and to disappear. Thus, sometimes it takes up to one month to see the whole effect of adding or discontinuing an inducer. Among FGAEDs, valproate is a broad-spectrum inhibitor of various drug-metabolizing enzymes including CYP2C9 and UGTs. Some of the newer AEDs may at times act as enzyme inhibitors. Eslicarbazepine, felbamate, oxcarbazepine and topiramate are weak inhibitors of CYP2C19, while stiripentol is a potent inhibitor of CYP1A2, CYP2C19, CYP2D6 and CYP3A4. Eslicarbazepine, felbamate, oxcarbazepine (particularly at dosages ≥ 1500 mg/day) [10], rufinamide and topiramate (particularly at dosages ≥ 400 mg day) [11] can induce the activity of CYP3A4 and possibly some UGTs.

1.3.1.2. SGAP metabolism. With the exception of amisulpride and paliperidone, SGAPs are targets of metabolic DIs because they undergo extensive hepatic biotransformation via CYPs and UGTs, which are highly inducible and readily inhibited. SGAPs appear not to be clinically relevant inhibitors or inducers [12] (see competitive inhibition in footnote 2, Table 2).

1.3.2. Clinical consequence of pharmacokinetic DIs

Metabolic DIs change the concentration-dose (C/D) ratio that reflects how the drug is cleared from the body at steady state. For SGAPs, the C/D ratio can be represented by a line (linear kinetics). Complicating predictions, some AEDs do not follow linear kinetics (Table 1), thus their C/D ratios may change with different concentrations. Inhibitors increase the C/D ratio (lower substrate doses provide the same concentration) while inducers decrease the C/D ratio (higher substrate doses are required to reach the same concentration). Pharmacokinetic DI studies can be used to estimate correction factors, which are >1 in inducers and <1 in inhibitors. A correction factor of 2 indicates that you need to double the dose for the same effect. A correction factor of 0.5 indicates that you need to halve the dose for the same effect. The further the correction factor is from 1, the more relevant the DI may be. The therapeutic window or index also determines the clinical relevance of correction factors. Failing to correct for the therapeutic window after adding or discontinuing inducers or inhibitors may have much greater clinical consequences in drugs with narrow therapeutic windows.

1.4. Pharmacodynamics

Most articles reviewing DIs ignore pharmacodynamic mechanisms of AED and SGAP, which are poorly understood. This subsection provides a very brief reference to the pharmacodynamics of AEDs and SGAPs; they are described more comprehensively in Figures 2 to 5 and their detailed footnotes. At the end of this section, a subsection comments on the types of pharmacodynamic DIs.

1.4.1. AED pharmacodynamics

Figure 2 summarizes the AED's mechanism of action in epilepsy, bipolar disorder, anxiety, pain, migraine prophylaxis and weight loss [3, 13-19]. Figure 3 summarizes the AED's mechanism of action associated with major safety issues [20-36].

1.4.2. SGAP pharmacodynamics

Figure 4 summarizes the SGAPs' mechanism of action, explaining their efficacy in schizophrenia, other psychoses and other psychiatric disorders [6, 37-42]. Many AP ADRs are explained by their blockade of neurotransmitter receptors (Figure 5) [43-59].

1.4.3. Pharmacological knowledge and pharmacodynamic DIs

Pharmacodynamic DIs take place directly at the site of action of a drug or indirectly by interfering with another physiological mechanism. They result in a modification of the pharmacological action of a drug without any change in the plasma concentration and are more difficult to identify and measure than pharmacokinetic DIs. These DIs can be additive (i.e., equal to the sum of the effects of the individual drugs), synergistic (i.e., combined effects are greater than expected from the sum of individual effects) or antagonistic (i.e., combined effects are less than additive) [9]. They can be associated with positive effects (increased efficacy and/or safety) or negative effects (decreased efficacy and/or safety).

1.5. Co-prescription of AEDs and SGAPs

AEDs and SGAPs are often prescribed together because co-morbidities may occur: i) AEDs are usually administered for prolonged periods in people with epilepsy and SGAPs may be needed to treat the highly prevalent psychiatric disorders seen in people with epilepsy; ii) autism spectrum disorders are

associated with very high risk of epilepsy, frequently with poor prognosis, and some SGAPs have been approved in the US market for the treatment of irritability in children with these disorders (Figure 4); or iii) AEDs may be used to treat non-epileptic conditions (e.g., neuropathic pain and migraine) in patients taking SGAPs.

In other cases clinicians co-prescribed them to decrease ADRs (AED medications may be used to treat seizures associated with some SGAPs, clozapine is particularly associated with dosage-related seizures) or increase efficacy: several AEDs (carbamazepine, lamotrigine, and valproate) and SGAPs are approved for bipolar disorder. Therefore, combinations of AEDs and SGAPs are increasingly used in the management of bipolar disorder. Other AEDs are being studied as potential mood stabilizers (oxcarbazepine and zonisamide). Other adjunctive therapies are less established as effective in the literature including: i) valproate or carbamazepine added to SGAPs in people with schizophrenia or schizoaffective disorder to better treat the psychosis or for the management of aggressive behaviors, and ii) lamotrigine added to clozapine for the management of treatment-resistant schizophrenia.

In summary, 1) AEDs and SGAPs are frequently co-prescribed, 2) they have clinically relevant DIs, and 3) there is no recent comprehensive review of this subject.

2. DI studies and their clinical relevance

This section provides a comprehensive review of DI studies including three sections that order compounds alphabetically: 1) the metabolic DI studies, starting with a review of the effects of each AED on each SGAP and then the effects of the SGAPs on the AEDs; 2) predictions of the metabolic DIs for new AEDs and SGAPs; and 3) a review of the limited studies on pharmacodynamic DIs. Articles for this review were obtained from a PubMed search with no time limit and through hand-searching of a number of recent journals and recent reviews. Searches were performed for each of the AEDs and SGAPs. This search was beyond the articles previously found and listed in the authors' published literature reviews [9, 12] and DI studies.

2.1. Pharmacokinetic DI studies

2.1.1. Carbamazepine

Carbamazepine is a powerful inducer of several drug-metabolizing enzymes including CYPs, namely CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4, as well as UGTs, such as UGT1A1, UGT2B7, UGT2B15.

2.1.1.1. Carbamazepine on aripiprazole. Carbamazepine decreased the mean area under the curve (AUC) of aripiprazole and dehydro-aripiprazole serum concentrations by 71% and 69%, respectively, in a study of 30 mg/day of aripiprazole for 14 days and then 4-6 weeks of carbamazepine titrated to concentrations of 8-12 µg/mL [60]. Similarly, a study of 18 schizophrenia patients treated with aripiprazole found 400 mg/day of carbamazepine, administered for 1 week, caused a significant decrease in aripiprazole and dehydro-aripiprazole concentrations by 64% and 68%, respectively [61]. A routine TDM study indicated that carbamazepine lowered dose-adjusted concentrations of aripiprazole by 88% [62].

2.1.1.2. Carbamazepine on clozapine. In a TDM clozapine study, patients on carbamazepine had a mean 50% lower C/D ratio of clozapine than the monotherapy group [63]. In a comparison of the effects of carbamazepine and oxcarbazepine on clozapine serum concentrations in 12 patients, Tiihonen et al. found that the clozapine concentration was 47% lower with carbamazepine than with oxcarbazepine [64]. Carbamazepine's inducing effect on CYP1A2- and CYP3A4-mediated clozapine metabolism probably explains these results.

2.1.1.3. Carbamazepine on olanzapine. A DI study of 11 healthy volunteers assessed a single 10 mg olanzapine dose before and after administration of carbamazepine 400 mg/day for 18 days [65]. Carbamazepine resulted in a 46% increase in olanzapine clearance and in a 34% decrease in its AUC. In carbamazepine patients the median dose-normalized olanzapine concentrations were 36-71% lower than in those in monotherapy according to TDM studies [66-69]. Specifically, Linnet and Olesen evaluated the influence of carbamazepine on olanzapine glucuronidation in a TDM study [67]. Two median differences were significant between 16 carbamazepine patients and 31 in monotherapy: i) free olanzapine C/D ratio was 38% lower (3.6 nmol/l/mg versus 5.8 nmol/l/mg), and ii) glucuronidated fraction (79% versus 43%)

[67]. Carbamazepine lowered free olanzapine concentration by increasing glucuronidation metabolism. All of these studies clearly indicated that carbamazepine increases olanzapine metabolism by CYP1A2- and UGT-induction.

2.1.1.4. Carbamazepine on paliperidone. CYP inhibitors or inducers were not expected to have a significant influence on paliperidone metabolism but the US package insert describes 400 mg/day of carbamazepine as decreasing the mean steady-state serum peak concentration (C_{max}) and the AUC of paliperidone by approximately 37%, due to a 35% increase in the renal clearance of paliperidone. This is attributed to carbamazepine induction of the renal P-gp.

2.1.1.5. Carbamazepine on quetiapine. Carbamazepine (600 mg/day) decreased quetiapine C_{max} by 80% and AUC by 87% and increased oral clearance by a 7.5-fold increase in a pharmacokinetic study of 18 psychiatric patients [70]. TDM studies [71-74] provided similar results. In particular, in a large routine TDM database, the mean quetiapine C/D ratio was 9 times lower (0.02 versus 0.18) and significantly lower (95% confidence intervals 0.02-0.03 versus 0.17-0.19, $p < 0.001$) for the 39 carbamazepine-treated patients versus the 1123 patients on quetiapine monotherapy [72]. The DI clinical implications were demonstrated in three patients taking carbamazepine 400-800 mg/day in which serum quetiapine concentrations could not be detected (<25 ng/mL) despite taking 700 mg/day [75]. These massive pharmacokinetic changes are explained by the potent inducing effect of carbamazepine on CYP3A4-mediated quetiapine metabolism.

2.1.1.6. Carbamazepine on risperidone. A case report first reported that serum risperidone active moiety (risperidone and its pharmacologically active metabolite 9-hydroxy-risperidone) doubled after carbamazepine discontinuation, leading to an ADR [76]. A subsequent study indicated that risperidone moiety was approximately 1.4 times lower in 11 carbamazepine patients versus 23 patients on risperidone alone [77]. In 5 patients assessed on and off carbamazepine co-medication, risperidone moiety was 1.5 times lower on carbamazepine [77]; in 11 other patients it was 1.8 times lower [78]. The clinical

relevance of the increase in risperidone metabolism attributed to the carbamazepine CYP3A4-inducing effects was demonstrated by an acute psychotic exacerbation in a case report [79].

2.1.1.7. Carbamazepine on ziprasidone. Carbamazepine (400 mg/day) lowered ziprasidone mean C_{max} by 27% and mean AUC_{0-12h} by 36% in 19 healthy volunteers taking 40 mg/day of ziprasidone [80]. Carbamazepine probably induced CYP3A4-mediated ziprasidone metabolism.

2.1.1.8. SGAPs on carbamazepine. Two weeks after the addition of risperidone (1 mg/day) the mean steady-state carbamazepine concentrations mildly increased by 19% in 8 epileptic patients [81], probably due to competitive inhibition of CYP3A4. Adding quetiapine led to a pharmacokinetic DI and ADRs in 2 patients [82], probably due to the competitive inhibition of CYP3A4.

2.1.2. Lamotrigine

Lamotrigine does not appear to be a CYP inhibitor or inducer but is a weak UGT inducer [9].

2.1.2.1. Lamotrigine on clozapine. A case report associated a clozapine ADR with a 3-fold increase in serum clozapine concentrations when lamotrigine was added [83]. However two studies (a randomized clinical trial [RCT] in 34 hospitalized treatment-resistant patients [84] and a pharmacokinetic study in 11 patients stabilized on clozapine [85]) found no serum clozapine concentration changes during lamotrigine treatment up to 200 mg/day.

2.1.2.2. Lamotrigine on olanzapine. Although UGT1A4 metabolizes both lamotrigine and olanzapine, two studies of healthy volunteers using low lamotrigine doses (50 and 200 mg/day) found no effects on olanzapine pharmacokinetics [86, 87]. A mild (15%) but significant increase in steady-state olanzapine serum concentration was found in 14 patients taking olanzapine (10-20 mg/day) after adding 100 mg/day of lamotrigine [85]. By using a mixed model, Botts et al. confirmed that lamotrigine behaved as an olanzapine inhibitor in smokers, increasing the C/D ratio by 35%, whereas the lamotrigine produced a mild non-significant decrease in olanzapine C/D ratio in nonsmokers [69].

2.1.2.3. Lamotrigine on quetiapine. A large TDM study reported a slight (17%) and significant 17% decrease in quetiapine C/D ratio in 147 lamotrigine patients when 1123 were on quetiapine monotherapy [62].

2.1.2.4. Lamotrigine and risperidone. An ADR case report described a 5-6-fold elevation in risperidone levels after adding lamotrigine [88]. However, a study of 10 psychotic patients stabilized on risperidone (3-6 mg/day), demonstrated that up to 200 mg/day of lamotrigine had no influence on serum risperidone moiety [85].

2.1.2.5. SGAPs on lamotrigine. There was no influence on lamotrigine levels in: i) a TDM study (N=829) with clozapine, risperidone or olanzapine co-prescription [89], and ii) an aripiprazole study with 30 mg/day in 18 bipolar patients [90].

2.1.3. Phenobarbital/phenytoin

Phenobarbital and phenytoin are considered powerful and promiscuous inducers of CYPs, (including CYP1A2, CYP2C, and CYP3A4) as well as UGTs.

2.1.3.1. Phenobarbital/phenytoin on clozapine. Two patients had a psychotic exacerbation after adding phenytoin, which decreased clozapine levels by 65-85% [91]. Lane et al. described a patient with a remarkable elevation of clozapine levels 2 weeks after phenobarbital discontinuation [92]. Facciola et al. found that serum clozapine concentrations were significantly lower in 7 phenobarbital-treated patients than in 15 monotherapy patients (232 ± 104 ng/ml versus 356 ± 13 ng/ml) and attributed this decrease to CYP1A2- and CYP3A4-induction [93].

2.1.3.1. Phenytoin on quetiapine. Quetiapine clearance increased more than 5-fold from 80.3 ± 35.9 l/hr to 440 ± 214 l/hr when comparing 10 patients on 750 mg/day after receiving phenytoin (300 mg/day) [94].

2.1.4. Oxcarbazepine

Oxcarbazepine is a keto-analog of carbamazepine. Unlike carbamazepine, this AED seems to be a modest CYP3A4 inducer [9]. As previously mentioned, carbamazepine was associated with lower clozapine levels in 12 patients when compared with oxcarbazepine [64]. Minimal and not significant

serum concentration modifications occurred after a 5-week treatment of oxcarbazepine (900-1200 mg/day) in psychotic patients stabilized on risperidone (2-6 mg/day; n=12) or olanzapine (5-20 mg/day; n=13) [95].

2.1.5. Topiramate

Topiramate is a weak inhibitor of CYP2C19 and a weak inducer of CYP3A4 [9]. Adding up to 200 mg/day of topiramate brought no serum concentration modifications for clozapine (250-500 mg/day, n=10), olanzapine (10-20 mg/day, n=12), risperidone (3-6 mg/day, n=9) or quetiapine (200-600 mg/day, n=7) [96]. It cannot be ruled out that higher topiramate doses may have an inductive effect in these SGAPs.

2.1.6. Valproate

Valproate has traditionally been considered a broad-spectrum metabolic enzyme inhibitor. It inhibits CYP2C9 competitively, CYP2C19 and CYP3A4 weakly and has no effects on CYP1A2, CYP2D6, and CYP2E1. It inhibits UGT enzymes (UGT1A4 and UGT2B7) [9]. A recent human hepatocyte study surprisingly demonstrated that valproate may induce some enzymes (CYP3A4 and P-gp gene expression) [97].

2.1.6.1. Valproate on aripiprazole. A decrease of 26% in the aripiprazole C_{max} and of 24% in the aripiprazole AUC with minimal effects on the active metabolite of aripiprazole after valproate addition was found in an open study of 10 schizophrenia patients [98]. Similarly, in a TDM study aripiprazole C/D was 24% lower in 7 patients co-medicated with valproate than in 23 on aripiprazole monotherapy [62]. Aripiprazole is a CYP3A4 and P-gp substrate; thus valproate may mildly induce CYP3A4 and/or P-gp. Both can decrease intestine drug absorption.

2.1.6.2. Valproate on clozapine. Early studies provided conflicting findings of increases and decreases of clozapine metabolism by valproate, which were unlikely to be clinically significant [reviewed by 99].

The three best studies [100-102] suggested that valproate might inhibit clozapine conversion to norclozapine via CYP1A2 or CYP3A4. In contrast, Finley and Warner found in four male patients that

clozapine concentrations decreased by 41% when valproate was administered [103]. By using a statistical mixed model that estimated the effect sizes of co-medications on clozapine levels after correcting for confounding variables, Diaz et al. found that valproate appeared to act as a clozapine inhibitor in non-smokers and as an inducer in smokers [99]. These findings may account for the inconsistent valproate results on clozapine metabolism.

2.1.6.3. Valproate on olanzapine. As valproate and olanzapine share common metabolic pathways, a metabolic DI can occur. TDM studies found no valproate influence on olanzapine metabolism [69, 104]. However, in four patients stabilized on olanzapine, valproate (1000-2700 mg/day) decreased olanzapine levels by 50% with a psychiatric deterioration in three of them [105]. Valproate co-administration (600-2000 mg/day) was associated with a significant decrease in mean serum olanzapine concentrations from 32.9 ± 9.7 ng/mL at baseline to 27.4 ± 9.8 ng/mL at week 2, and to 26.9 ± 9.2 ng/mL at week 4 in 18 psychotic patients who had no relapses [106]. Serum olanzapine concentration drop varied from 2 to 4 weeks and with valproate concentration and is likely to be explained by valproate induction on olanzapine metabolism by CYPs or UGT. These changes, although statistically significant, were small and presumably not clinically significant. However, as the valproate and olanzapine combination is increasingly used, further studies are necessary to elucidate the mechanisms (induction, competitive inhibition and/or protein binding displacement), severity and duration of this DI and to understand whether there are any circumstances (e.g., high or low olanzapine or valproate doses) in which this DI may acquire clinical relevance [107].

2.1.6.4. Valproate on quetiapine. Valproate studies on quetiapine metabolism provided inconsistent results. A 77% increase in quetiapine C/D, when compared to quetiapine monotherapy in 9 patients taking valproate, led Aichorn et al. to propose a CYP3A4-inhibition of quetiapine metabolism by valproate [108]. However no relevant changes in quetiapine metabolism were found in two TDM routine studies [72, 73] and in a formal pharmacokinetic study in 34 psychotic patients taking 300 mg/day of quetiapine and 1000 mg/day of divalproex [109].

2.1.6.5. Valproate on risperidone. No major changes in risperidone moiety were found in: i) a pharmacokinetic study comparing 23 patients on monotherapy versus 10 on valproate (1200-1500 mg/day) [77], ii) its extension to 3 patients on/off valproate [77], and iii) another pharmacokinetic study of 22 bipolar patients taking valproate (1000 mg/day) in which half were randomized to placebo or risperidone up to 4 mg/day [110]. This is consistent with the absence of an inhibitory effect of valproate on CYP2D6 or CYP3A4, the major risperidone metabolic pathways.

2.2. Predicting metabolic DIs for new compounds

2.2.1. Other AEDs

The DI information for other SGAEDs is limited. Eslicarbazepine and rufinamide (as well as the older felbamate) are mild CYP3A4-inducers. Rufinamide is also a possible UGT-inducer. Eslicarbazepine, felbamate and rufinamide have limited potential to induce SGAP metabolism. As CYP2C19 is not important in SGAP metabolism, the weak CYP2C19 inhibition by eslicarbazepine and felbamate is not likely to be relevant. Stiripentol is a potent inhibitor of CYP2C19, CYP1A2, CYP2D6, and CYP3A4 but is only used in Europe for the treatment of severe myoclonic epilepsy in infancy and is not likely to be co-prescribed with SGAPs.

2.2.2. New SGAPs

2.2.2.1. Asenapine. UGT1A4 and CYP1A2 metabolize asenapine. Valproate (1000 mg/day for 9 days) substantially reduced the formation of the N-glucuronide (AUC reduced 7.4-fold) and moderately reduced that of N-desmethyl-asenapine (AUC reduced 30%) but did not affect asenapine AUC in an open-label, randomized, 2-way crossover study in 24 healthy male volunteers receiving 5 mg of asenapine alone or a low valproate dose. The study's authors, who were from the asenapine-marketing company, concluded that low-dose valproate, although almost completely inhibiting asenapine glucuronidation, did not affect asenapine clearance [111]. Asenapine's package insert indicates that: 1) 800 mg/day of carbamazepine for 15 days had small effects on asenapine AUC (16% decrease), and 2) no dosage adjustments are required.

Independent studies using multiple dosing are required to verify that the valproate and carbamazepine DIs with asenapine have no clinical relevance.

2.2.2.2. Iloperidone. Iloperidone is metabolized by CYP2D6 and CYP3A4 [112]. CYP3A4 inhibitors have clinically relevant effects on iloperidone levels. There are no published studies of potent CYP3A4 inducers which are expected to relevantly increase iloperidone metabolism.

2.2.2.3. Lurasidone. Lurasidone is metabolized by CYP3A4 [113]. According to the US package insert, rifampin, a potent CYP3A4-inducer, decreased lurasidone AUC 5-fold. There are no published studies of potent CYP3A4 inducers which are expected to dramatically increase lurasidone metabolism. It is possible that in high doses oxcarbazepine or topiramate may influence lurasidone levels.

2.3. Limited studies on pharmacodynamic DIs

This subsection classifies pharmacodynamic DIs as those increasing efficacy, increasing safety, decreasing efficacy, and decreasing safety. The most important are included in Table 5.

2.3.1 Pharmacodynamic DIs increasing efficacy

Several SGAPs have been approved in the US for mania as adjuvant therapy to valproate (and lithium), including aripiprazole, asenapine, quetiapine, risperidone and olanzapine. In the RCTs, tested SGAPs were significantly more efficacious than adding placebo to valproate (or lithium). Thus, an additive (or synergistic) effect (see subsection 1.4.3.) between valproate and SGAPs is expected in mania (Table 5). In a review, Ketter described the response rate to valproate (and lithium) as increasing from 21% to 42% when adding SGAPs [114], which suggests additive rather than synergistic effects.

2.3.2. Pharmacodynamic DIs increasing safety

Topiramate and zonisamide can decrease weight (Figure 2 and Table 5). Topiramate has been associated with reversing SGAP-induced weight gain in an open study [115].

2.3.2. Pharmacodynamic DIs decreasing efficacy

Figures 2-5 indicate that AEDs and SGAPs sometimes have opposite actions. All SGAPs, but particularly clozapine and to a lesser extent olanzapine and quetiapine (Figure 5), have potential to

decrease the seizure threshold and therefore contribute to seizures [53]. If a patient with epilepsy needs an SGAP, the potential for increased seizures needs to be considered. This is easily managed by monitoring AED treatment closely and considering increased AED doses, but in patients with not-well-controlled seizures, adding an SGAP that lowers the seizure threshold may produce a clinically relevant pharmacodynamic DI.

In epileptic patients, some AEDs (ethosuximide, levetiracetam, tiagabine, topiramate, vigabatrin and zonisamide) have rarely been associated with psychosis (usually a transient paranoid psychosis; Figure 3). As the pharmacodynamic mechanism is unknown, clinicians may want to remember this risk when considering co-prescribing them with SGAPs in patients whose psychosis is not well-controlled. In epileptic patients, some AEDs (particularly barbiturates, topiramate and vigabatrin, and less frequently felbamate, levetiracetam, tiagabine, and zonisamide) have been associated with depression (Figure 3). Clinicians may want to remember this risk when considering co-prescribing these AEDs with SGAPs in patients with bipolar disorder or treatment-resistant depression since they have the potential to antagonize the antidepressant SGAP properties. A Food and Drug Administration (FDA) meta-analysis of the placebo RCTs suggests that patients taking AEDs have an increased risk of suicidal thoughts and behaviors observed 1 week after taking the medication; the risk continues for at least 24 weeks which has led to a warning in the package inserts of all anticonvulsants [116]. Recently, reviews questioned the FDA warning in the prescription packages for all AEDs [117] and large pharmacoepidemiological studies suggested contradictory findings for AEDs in general [118,119]. In our opinion, 1) the FDA decision to include a warning about increased suicide risk in all antiepileptic prescribing information has increased awareness, but oversimplified a complex matter; 2) the risk of completed suicide in persons with suicidal ideation is probably low, while completed suicide risk increases 40-fold after a prior attempt [120]; and 3) other factors such as medical and psychiatric illnesses can partially explain the increased suicide risk in patients taking AEDs.

2.3.3. Pharmacodynamic DIs decreasing safety.

There are multiple pharmacodynamic DIs that have potential to increase ADRs by additive or synergistic effects. These DIs are likely to be clinically relevant but have not been systematically studied. They can be divided into common, probably less common and rare, but potentially lethal, categories.

Three common pharmacodynamic DIs are sedation, weight gain and swallowing disturbances (Table 5). A recent well-controlled 12-month study indicated that the valproate-olanzapine combination was worse for metabolic syndrome than the valproate-risperidone combination [121]. Dysphagia is particularly frequent in patients with intellectual disabilities or dementia. Although it has not been studied additive or synergistic pharmacodynamic DI actions on swallowing disturbances are likely between AEDs and SGAPs. Table 5 emphasizes two probably uncommon pharmacodynamic DIs, nausea/vomiting and osteoporosis, which have never been studied, and includes three rare, but potentially lethal pharmacodynamic DIs: pancreatitis, agranulocytosis and heat stroke. Carbamazepine and clozapine should not be combined due to their risk for agranulocytosis. Valproate and other SGAPs besides clozapine have occasionally been associated with neutropenias due to not well-understood mechanisms. Rahman et al. have described neutropenia and leucopenia cases with the combination of valproate and quetiapine [122].

3. Conclusion

This section and Table 5 provide a summary of the most important practical DI information for clinicians.

3.1. Pharmacokinetic DIs and clinical implications

Carbamazepine, phenobarbital, phenytoin and primidone are potent inducers that are likely to have clinically relevant effects on several SGAP levels (Table 5). Adding any of these inducers (in the absence of other inducers) may be associated with a decrease in SGAP serum concentration that may be associated with lack of efficacy. The discontinuation of these inducers (when other inducers are not prescribed) may be associated with an increase in SGAP serum concentration that may be associated with ADRs. The best

way to control for these DIs is by checking SGAP TDM. As SGAP TDM may not be available, Table 5 provides a best estimation of a correction factor (Figure 1) based on the limited available literature.

The pharmacokinetic DIs associated with valproate or the mild AED inducers eslicarbazepine, felbamate, oxcarbazepine, rufinamide and topiramate (Table 5) are not likely to be clinically relevant in most patients taking SGAPs, but it cannot be ruled out that in some unusual patients they may have clinical relevance. In that sense, clinicians may need to be watchful when using high doses of oxcarbazepine (≥ 1500 mg/day) [10] or topiramate (≥ 400 mg/day) [11], particularly with highly inducible SGAPs such as quetiapine or lurasidone.

3.2. Pharmacodynamic DIs and clinical implications

As described in Section 2.3, the literature is very limited in the description of pharmacodynamic DIs but in our experience these types of DIs are very relevant in clinical practice (Table 5). Two pharmacodynamic DIs can be considered positive: i) the additive effects for mania and bipolar maintenance when combining valproate and SGAPs and ii) the decrease in weight that may be associated with combining topiramate or zonisamide with SGAPs.

In our experience with neurologists managing AED prescriptions and psychiatrists prescribing SGAPs, these specialists rarely pay enough attention to the other's prescriptions, which may lead to high potential for pharmacodynamic DIs. Three additive DIs are common: increased sedation, weight gain and swallowing disturbances. However, different AEDs and SGAPs have different risks for sedation or weight gain (Table 5). As swallowing impairment is usually a neglected ADR in published studies, there is no information on whether different AEDs or SGAPs have different risks for swallowing impairment. From the probably uncommon pharmacodynamic DIs, Table 5 highlights the potential for increased risk for osteoporosis and nausea for a few combinations of AEDs and SGAPs. Finally, Table 5 describes three potentially lethal pharmacodynamic DIs: pancreatitis, agranulocytosis/leucopenia and heat stroke. These ADRs are very rare and we are not sure that combinations of AEDs and SGAPs increase their risk but

pharmacological mechanisms suggest that it is a possibility and clinicians need to remember that in order to prevent or quickly diagnose these ADRs.

4. Expert opinion

We have excellent understanding of the clinical relevance of DIs associated with the inductive properties of carbamazepine, phenytoin, phenobarbital and primidone and with the inhibitory properties of valproate. Unfortunately, the DI studies with SGAPs are rather limited but adding or discontinuing phenytoin, phenobarbital and primidone are likely to have clinically relevant effects on SGAP treatments. Table 5 provides correction factors based on the limited available literature. These correction factors were calculated using the available pharmacokinetic studies which summarize the data, assuming that the average patient represents the population well; however, there is extensive pharmacokinetic variability between patients, and TDM measurements should be advised for optimal titration of the dosage in each individual. In spite of their limitations, these correction factors are useful because: 1) many clinicians have no access to antipsychotic TDM and, as a matter of fact, there is limited clinical data on some SGAP TDM (amisulpride, aripiprazole, paliperidone, quetiapine, and ziprasidone) and very limited data on three compounds (asenapine, iloperidone and lurasidone); and 2) in our experience, having the correction factor helps clinicians to make decisions. With a correction factor of 5, quetiapine and lurasidone are poor SGAP choices for patients taking powerful AED inducers. The correction factors may not fully account for all of the possible risks of treatment because of the limited studies available; thus, there will be a need to periodically update these correction factors as new knowledge becomes available.

Eslicarbazepine, felbamate, and rufinamide are thought to be mild inducers but there are no studies on SGAPs to verify their limited clinical relevance. A serious limitation of the SGAP DI literature is the lack of studies in clinical samples with high doses of oxcarbazepine (≥ 1500 mg/day) or topiramate (≥ 400 mg/day) that would establish whether or not they induce in a clinically relevant way SGAPs dependent on CYP3A4 (aripiprazole, lurasidone, quetiapine and risperidone) or UGTs (asenapine and olanzapine) for their metabolism. As Table 5 indicates, it is very likely that AED inducers have major effects in

lurasidone metabolism since rifampin, another potent and widespread inducer, increased lurasidone metabolism by a factor of 5. Clinicians may need to be very careful with iloperidone and particularly asenapine. Asenapine metabolism by UGT1A4 and CYP1A2 suggests asenapine has major potential for being induced by carbamazepine, phenytoin, phenobarbital and primidone. There is no way of providing a correction factor since we are unaware of any other drug with similar metabolism to asenapine. On the other hand, one would like to see asenapine DI studies with repeated dosing in clinical samples, to be reassured that valproate effects on asenapine metabolism can be ignored by clinicians. We suspect that the valproate effects are small in most patients taking SGAPs but we keep surprising ourselves by finding unexpected valproate DIs, particularly as a possible inducer of: i) clozapine in smokers [99], or ii) olanzapine [106], which may be relevant in extreme conditions (valproate levels ≥ 80 $\mu\text{g/ml}$ and olanzapine doses ≤ 10 mg/d) [107]. Paliperidone studies with strong inducers published by independent investigators are needed.

It is not easy to conduct DI studies using clinically relevant doses. Pharmaceutical companies tend to invest in simple pharmacokinetic DI studies in volunteers frequently using single dosing to get approval for the marketing of their drugs, but this type of pharmacokinetic study rarely reflects clinical practice. DI information on package inserts is usually not designed to provide easy information to help clinicians to correct pharmacokinetic DIs with dose changes. The pharmacokinetic science on AED-SGAP combinations may be in its adolescence and needing maturation, while pharmacodynamic DI science appears to be in its infancy. None of the studies combining AEDs with mood stabilizers and SGAPs explore whether the combinations are additive or synergistic. Recent meta-analyses determined the effects of different monotherapies in mania, bipolar depression or maintenance but there is no published meta-analysis of the combinations, although most patients are treated with combinations. There are almost no well-controlled studies of AEDs or SGAPs in patients with aggressive behaviors or in adults with epilepsy and intellectual disabilities, although clinicians use AED-SGAP combinations frequently in them.

It would be naïve to simply conclude that more studies of AED-SGAP DIs are needed. They are obviously needed, but the lack of funding for clinical research is a major limitation. To progress in this area, collaboration from all interested parties is needed, including: i) drug agencies and pharmaceutical companies; ii) clinicians using AED-SGAP combinations; iii) researchers with expertise in a) meta-analyses, b) pharmacoepidemiology, and c) DI pharmacology; and iv) grant agencies.

Drug agencies should be more insistent upon rapid approval of new SGAPs in bipolar disorder and require: i) thorough studies of the pharmacodynamic and pharmacokinetic DIs with carbamazepine, lamotrigine, lithium and valproate; and ii) clear package insert guidelines of how to better avoid or correct for pharmacodynamic and pharmacokinetic DIs. Carbamazepine is an anti-manic agent and probably a mood stabilizer, but it took too many years to get FDA approval for a bipolar disorder indication due to lack of interest from the pharmaceutical companies. Carbamazepine use is limited by its potential for toxicity, teratogenicity and DIs. If oxcarbazepine is judged to be as effective as carbamazepine in bipolar disorder, carbamazepine should replace oxcarbazepine. The FDA may need to think “out of the box” and look for new ways to encourage pharmaceutical companies possibly interested in marketing oxcarbazepine in bipolar disorder by providing special “deals”, assuming the companies seriously want to study DI issues, including the possible impact of high oxcarbazepine doses. Similarly, as several AEDs with chemical formulations similar to already marketed AEDs are being studied for approval for epilepsy (e.g., DP-valproic acid or phosphatidylcholine esteric conjugate of valproic acid) the FDA and other agencies need to think “out of the box” about encouraging and simplifying the process of approval of these new AEDs for bipolar disorder.

Clinicians frequently co-prescribe AEDs and SGAPs. Neurologists may prescribe SGAPs in their patients with epilepsy or other non-epileptic conditions (pain or migraine) that need treatment for psychosis, bipolar disorder or other SGAP off-label conditions. Psychiatrists may prescribe AEDs as mood stabilizers or for off-label indications in patients taking SAGPs. Thousands of US patients take these combinations. There is great need of naturalistic studies describing possible additive or synergistic

efficacy and, more importantly, the long-term safety of these combinations. Are early sedation or early nausea and vomiting more frequent in some of these combinations than in the various monotherapies? Is swallowing impairment or osteoporosis a long-term issue in vulnerable patients taking some of these combinations for years?

Researchers with expertise in meta-analysis may need to develop better methods to study: i) safety of AED-SGAP combinations by comparing ADRs in available SGAP RCTs in monotherapy in schizophrenia versus those on adjuvant therapy in bipolar disorder, and ii) how bipolar disorder studies can better compare efficacy of individual drugs versus drug combinations. Researchers with expertise in pharmacoepidemiology need to explore whether rare ADRs such as risk of pancreatitis, agranulocytosis/leucopenia and heat stroke may be more frequently associated with AED-SGAP combinations than with individual drugs. Researchers with expertise in *in vitro* DI studies or *in vivo* clinical studies using isotopes to explore drug clearance need to better study the SGAP metabolic pathways and how they change when inhibitors and inducers are added, particularly in the complicated conditions used in clinical practices such as adding both an inducer and an inhibitor to an SGAP (e.g., adding carbamazepine and fluoxetine to risperidone).

Grant and health agencies need to remember that pragmatic clinical trials are key in treating complex disorders such as epilepsy, schizophrenia and bipolar disorder, where polytherapy is the norm. Pharmaceutical RCTs do not substitute for long-term pragmatic trials that may better inform clinicians of the effectiveness of the various types of mono- and polytherapy frequently used in the real world of clinical practice. Pragmatic trials need to pay better attention to DI.

Progress in the next few years, if this research agenda is followed, should also be accompanied by a better continuous medical education on DIs and improvements in neuropsychopharmacology textbooks, so that clinicians begin to pay more attention to pharmacodynamic and pharmacokinetic DIs associated with the frequent co-prescription of AEDs and SGAPs. Well-educated clinicians will help move the

research agenda by publishing DI case reports of unusual combinations and asking for more DI studies from pharmaceutical companies and researchers.

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OTHER PHARMACOKINETIC ISSUES

P-GLYCOPROTEIN (P-gp)

- 1) P-gp plays a central role in the absorption, distribution and excretion of a wide variety of drugs.
- 2) P-gp is a multidrug efflux transporter, encoded by the MDR1 gene (or ABCB1), highly expressed in the intestine, brain, liver and kidney.
- 3) It acts as a natural defense mechanism against several drugs by limiting their absorption from the gut and penetration into the brain, and promoting their elimination in the bile and urine.
- 4) Like metabolizing enzymes, P-gp activity can be inhibited or induced by other agents, altering the concentration of substrate drug in blood and brain. In particular, some antiepileptic drugs (AED) pharmacokinetic drug-drug interactions (DIs) currently attributed to enzyme induction may, in fact, be due to overexpression of such transporters resulting in the affected drug having limited gastrointestinal absorption or reduced penetration to the brain, or enhanced elimination in the bile and urine.
- 5) Second-generation antipsychotics (SGAPs) have been reported to show various degrees of inhibitory effects on P-gp activity.
- 6) In summary, P-gp activity is probably relevant in explaining AED and SGAP DIs but our current knowledge is too limited to determine P-gp's importance.

PROTEIN BINDING

- 1) Theoretically, protein binding displacement interactions may occur between AED and SGAPs.
- 2) Competition between two drugs for binding sites on plasma proteins may elevate levels of the displaced drug's free fraction in plasma or tissue, thereby potentially increasing its pharmacological effects.
- 3) However, in most circumstances this type of DI is not clinically relevant since the displaced drug is diluted into a large volume of distribution or is rapidly cleared, and the unbound, pharmacologically active concentration remains almost unchanged.
- 4) In quantitative terms, displacement interactions may only be important for drugs that are highly bound to plasma proteins (>90%). A number of SGAPs are extensively bound to plasma proteins (Table 2), while among AEDs only phenytoin, valproate and tiagabine belong to this category (Table 1).
- 5) Clinically relevant DIs due to increased free concentrations have occasionally been described for phenytoin and valproate [7], but the other AEDs or anti-inflammatory drugs usually cause increased valproate or phenytoin free concentrations.
- 6) No clear cases of SGAPs increasing free phenytoin or valproate concentrations have been published in the literature.

Figure 1. Other pharmacokinetic issues.

PHARMACODYNAMICS FOR ANTIEPILEPTIC EFFICACY

<p style="text-align: center;">ANTIEPILEPTIC ACTIVITY</p> <p style="text-align: center;">↓ <i>Activity of voltage-dependent sodium channels</i> carbamazepine, eslicarbazepine, felbamate, lacosamide, lamotrigine, oxcarbazepine, phenytoin, rufinamide, topiramate, zonisamide</p> <p style="text-align: center;">↓ <i>Activity of voltage-dependent calcium channels</i> ethosuximide, gabapentin, levetiracetam, lamotrigine, pregabalin, topiramate, zonisamide</p> <p style="text-align: center;">↑ <i>GABA neurotransmission</i> felbamate, levetiracetam, phenobarbital, primidone, stiripentol, tiagabine, topiramate, vigabatrin, valproate¹</p> <p style="text-align: center;">↓ <i>Glutamatergic neurotransmission</i> felbamate, topiramate, zonisamide</p> <p style="text-align: center;">Other levetiracetam,² retigabine,³</p>
<p style="text-align: center;">MOOD STABILIZER ACTIVITY⁴</p> <p style="text-align: center;"><i>At intracellular signaling system (inositol signaling)</i> carbamazepine, valproate⁵</p> <p style="text-align: center;"><i>Not well understood</i> Lamotrigine</p>
<p style="text-align: center;">ANXIOLYTIC ACTIVITY</p> <p style="text-align: center;">↑ <i>GABA neurotransmission</i> pregabalin⁶</p>
<p style="text-align: center;">FOR PAIN⁷</p> <p style="text-align: center;">↓ <i>Activity of voltage-dependent sodium or calcium channels</i> carbamazepine, gabapentin, oxcarbazepine, pregabalin</p>
<p style="text-align: center;">FOR MIGRAINE PROPHYLAXIS⁸</p> <p style="text-align: center;">↓ <i>Activity of voltage-dependent sodium and calcium channels</i> topiramate</p> <p style="text-align: center;">↑ <i>GABA neurotransmission</i> valproate,¹ topiramate</p> <p style="text-align: center;">↓ <i>Glutamatergic neurotransmission</i> Topiramate</p>
<p style="text-align: center;">WEGHT LOSS (not approved treatment)⁹</p> <p style="text-align: center;"><i>Probably by inhibition of carbonic anhydrase</i> topiramate, zonisamide</p>

Figure 2. Pharmacodynamics for antiepileptic efficacy.

ADRs: adverse drug reactions; AED: antiepileptic drug; RTC: randomized clinical trial.

¹There is general agreement that valproate acts mainly by increasing GABAergic neurotransmission but a more precise description might be that valproate has complex actions, since valproate may act at the voltage-dependent sodium and calcium channels [13].

²Levetiracetam has complex actions including one that appears specific to this compound: binding to synaptic vesicle protein 2A interfering with the recycling of synaptic vesicles and the release of a range of neurotransmitters [14].

³Retigabine appears to open potassium channels [14].

⁴AEDs approved in the US for bipolar disorder include: i) valproate for mania; ii) carbamazepine for the treatment of acute manic and mixed episodes of bipolar disorder; and iii) lamotrigine for prophylaxis, particularly of depressive phases [15]. Treatment guidelines also consider: 1) valproate monotherapy or adjunctive for bipolar depression or prophylaxis, ii) carbamazepine monotherapy or adjunctive for prophylaxis, and iii) lamotrigine monotherapy or adjunctive for bipolar depression [15]. Gabapentin, lamotrigine and topiramate mania RCTs were negative [15]. Oxcarbazepine bipolar disorder RCTs appear promising. There are no published RCTs for eslicarbazepine, levetiracetam or zonisamide.

⁵Valproate is a histone deacetylase inhibitor. It is not known whether this action contributes to its mood stabilizing properties or not [16].

⁶Pregabalin is approved for generalized anxiety disorder in Europe but not in the US. Other AEDs may have antianxiety properties [17].

⁷In the US approved drugs include: i) carbamazepine for trigeminal neuralgia, ii) gabapentin for postherpetic neuralgia, and iii) pregabalin for postherpetic neuralgia and diabetic neuropathic pain. Lacosamide is being studied in RCTs for diabetic neuropathic pain. Oxcarbazepine is usually considered an alternative for trigeminal neuralgia when patients cannot tolerate carbamazepine. Johannessen Landmark considers other AEDs, including levetiracetam, lamotrigine and phenytoin, as acceptable treatments for neuropathic pain [3].

⁸In the US, the only AEDs approved for migraine prophylaxis are topiramate and valproate.

⁹Topiramate and zonisamide treatments are frequently associated with weight loss but are not approved for that indication in the US. These two drugs were associated with too many ADRs in obesity RCTs [18, 19].

PHARMACODYNAMICS FOR ANTIEPILEPTIC SAFETY

<p>SEDATION FGAED and topiramate >² other SGAEDs^{1 >2} felbamate, lacosamide, lamotrigine, tiagabine <i>Possibly the same mechanism that explains antiepileptic efficacy</i></p>
<p>COGNITIVE IMPAIRMENT Definitively in FGAEDs and probably in SGAEDs³ <i>Possibly the same mechanism that explains antiepileptic efficacy</i>⁴</p>
<p>BALANCE DISTURBANCES Most AEDS⁵ <i>Unknown/possibly the same mechanisms that explain antiepileptic efficacy</i></p>
<p>NAUSEA AND VOMITING carbamazepine, eslicarbazepine, felbamate, lacosamide, lamotrigine, oxcarbazepine, phenytoin, rufinamide, topiramate, zonisamide <i>Possibly ↓ activity of voltage-dependent sodium channels</i>⁶ ethosuximide, tiagabine, valproate <i>Unknown</i></p>
<p>DEPRESSION phenobarbital, primidone, topiramate, vigabatrin >² zonisamide >² felbamate, levetiracetam, tiagabine⁷ <i>Possibly ↑ GABA neurotransmission</i></p>
<p>PSYCHOSIS (rare) ethosuximide, levetiracetam, lamotrigine, topiramate, tiagabine, vigabatrin, zonisamide⁸ <i>Unknown mechanisms</i></p>
<p>AGGRESSIVE BEHAVIOR (rare) gabapentin, levetiracetam, lamotrigine, phenobarbital, topiramate, vigabatrin, zonisamide⁹ <i>Unknown mechanisms</i></p>
<p>OSTEOPOROSIS (relatively uncommon) carbamazepine, phenobarbital, phenytoin, primidone¹⁰ <i>Induction of Vitamin D metabolism</i></p>
<p>THYROID DISTURBANCES (relatively uncommon) carbamazepine, phenytoin¹¹ <i>Probably induction of thyroid hormone metabolism</i></p>
<p>IDIOSYNCRATIC (very rare: 1-10/10,000-100,000) Stevens–Johnson syndrome/toxic epidermal necrolysis carbamazepine, ethosuximide, felbamate, lamotrigine, phenobarbital, phenytoin, primidone¹² Agranulocytosis and/or aplastic anemia¹³ carbamazepine, ethosuximide, felbamate, phenobarbital, primidone, valproate Hepatitis/liver failure carbamazepine, felbamate, phenytoin, valproate <i>Immunological and/or toxic mechanisms</i></p>
<p>RISK FOR HEAT STROKE (very rare)¹⁴ topiramate, zonisamide <i>Inhibition of carbonic anhydrase causes sweating inhibition</i></p>
<p>PANCREATITIS (rare)¹⁵ valproate <i>Mechanism is poorly understood</i></p>

Figure 3. Pharmacodynamics for antiepileptic safety.

ADR: adverse drug reaction; AED: antiepileptic drug; FGAED: first-generation antiepileptic drug; SGAED: second-generation antiepileptic drug.

¹All FGAEDs are definitively associated with sedation [20]. A meta-analysis found that most SGAEDs (gabapentin, levetiracetam, pregabalin, topiramate and zonisamide) were associated with somnolence when compared with placebo [20]. Other SGAEDs including oxcarbazepine, vigabatrin [20],

eslicarbazepine, retigabine, and rufinamide [21] also are probably associated with sedation. Felbamate, lacosamide, lamotrigine, and tiagabine appear to be associated with low sedation risk [20, 22].

²Drugs preceding ">" will produce this ADR more frequently than drugs following ">".

³FGEADs are associated with cognitive impairment in studies using neuropsychological testing. There are few neuropsychological studies on SGEADs. Different authors agree that phenobarbital has the worst cognitive profile among FGEADs, and topiramate among SGEADs, but disagree on the relative impairment associated with specific compounds and how topiramate compares with FGEADs [23, 24]. Vigabatrin can be associated with visual defect fields.

⁴[24]

⁵FGEADs (except for ethosuximide) are definitively associated with ataxia and other balance disturbances [20]. A meta-analysis indicated most SGEADs (lamotrigine, oxcarbazepine, pregabalin, tiagabine, topiramate and zonisamide) are associated with balance disturbances while gabapentin and levetiracetam may not be [25]. Other AEDs including felbamate, vigabatrin [20], eslicarbazepine, lacosamide, retigabine, and rufinamide [25] are probably associated with balance disturbances.

⁶Beydoun et al. proposed that nausea and vomiting may be explained by decreased activity of voltage-dependent sodium channels [26]. Review articles focused on AED pharmacodynamics do not comment on possible mechanisms that may explain AED-induced nausea and vomiting.

⁷Different reviews provide different frequencies of each AED-induced depression. A comprehensive review described frequencies >10% for phenobarbital, primidone, topiramate and vigabatrin; 7% for zonisamide in high doses; ≤4% for felbamate, levetiracetam and tiagabine; and <1% for the rest of the studied AEDs. On the other hand, carbamazepine, lamotrigine, oxcarbazepine and valproate may have antidepressant properties in patients with epilepsy [27].

⁸It is difficult to assess when psychosis is really an AED ADR rather than a manifestation of the underlying or associated illnesses. AEDs associated with psychosis include levetiracetam, lamotrigine, topiramate, tiagabine, vigabatrin [28], ethosuximide [29] and zonisamide [30]. Studies using lamotrigine and topiramate in bipolar disorder do not describe increased psychotic symptoms.

⁹It is difficult to assess when aggressive behavior is really an AED ADR rather than an underlying or associated illness. AEDs associated with irritability or aggression are gabapentin, levetiracetam, lamotrigine, phenobarbital, topiramate, vigabatrin [31] and zonisamide [30].

¹⁰Oxcarbazepine may also be associated with osteoporosis risk. Valproate also appears to be associated with osteoporosis but the mechanism is not well understood.

¹¹Oxcarbazepine may be associated with mild thyroid disturbances.

¹²Other AEDs less clearly associated with Stevens–Johnson syndrome/toxic epidermal necrolysis are oxcarbazepine, valproate and zonisamide.

¹³Valproate is frequently associated with thrombocytopenia and more rarely, with neutropenia. Valproate-induced thrombocytopenia appears to be dose-related and explained by direct toxic mechanism rather than by immunological mechanism.

¹⁴The literature describes most cases of heat stroke associated with topiramate [32] or zonisamide [33] as occurring in children but adult cases during a heat wave have been described [34].

¹⁵The literature describes valproate-induced pancreatitis as very rare. A comprehensive review in Germany indicated that milder cases are much more common than the literature suggests [35]. In a review of all 5 years of data from a facility for 322 adults with intellectual disabilities, the frequency of pancreatitis in patients taking valproate was not rare; it was 7% (5/72 patients) [36]. The first author has similar experience that pancreatitis is not rare in these facilities.

PHARMACODYNAMICS FOR SGAP EFFICACY

<p><i>BLOCKADE OF D₂ RECEPTORS AT BASAL GANGLIA AND CORTEX¹</i></p> <p>Explains antipsychotic efficacy in schizophrenia All SGAPs are approved²</p> <p>Explains antipsychotic efficacy in other psychoses None are approved in the US³</p> <p>Possibly explains anti-manic properties⁴ aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone are approved in the US as monotherapy⁵</p> <p>Possibly explains postulated mood-stabilizing properties (maintenance in bipolar disorder) aripiprazole and olanzapine are approved in the US as monotherapy⁶</p> <p>Possibly explains anti-irritability action in autism aripiprazole and risperidone are approved in the US</p> <p>Possibly explains postulated anti-OCD properties when added to serotonergic antidepressants⁷ None are approved in the US but reasonable data exist on risperidone^{7,8}</p>
<p>DEPRESSION</p> <p>Treatment of bipolar depression quetiapine is approved in the US</p> <p>Adjunctive therapy of treatment-resistant depression aripiprazole, quetiapine, olanzapine are approved in the US⁹</p> <p><i>Mechanism of action is unknown¹⁰</i></p>

Figure 4. Pharmacodynamics of efficacy for second-generation antipsychotics

5-HT: serotonin receptor; AP: antipsychotic; D: dopamine receptor; RCT: randomized clinical trial; SGAP: second-generation antipsychotic.

¹All APs are D₂ antagonists except for aripiprazole which is a partial agonist (some authors have proposed that occasionally aripiprazole can be associated with worsening of psychosis). Brain imaging studies indicate that antipsychotic efficacy may be associated with D₂ blockade at the basal ganglia and cortex.

²Amisulpride is approved in Europe but has not been studied for approval in the US.

³No SGAP is approved for psychosis (or behaviors) in dementing illness. Paliperidone is approved for schizoaffective disorder in the US.

⁴[37]

⁵Aripiprazole, asenapine, quetiapine, risperidone, and olanzapine have been approved for adjunctive therapy with lithium or valproate. Other SGAPs have not been studied in RCTs.

⁶Quetiapine has been approved for adjunctive therapy with lithium or valproate.

⁷[6]

⁸[6]

⁹Olanzapine is approved in combination with fluoxetine. Risperidone had some positive results in RCTs [38].

¹⁰The mechanisms proposed in bipolar depression include: i) a high ratio between 5-HT_{2A}/D₂ receptors [37], and ii) a possible role for 5-HT_{2A} or α₂ blockade [39]. Common mechanisms proposed for adjunctive treatment in major depressive disorder include 5-HT_{2A} blockade that may be shared by approved SGAPs [38]. Specific mechanism include: i) 5-HT_{1A} partial agonism only for aripiprazole [38]; and 5-HT_{2C} antagonist and inhibition of noradrenaline transporter by norquetiapine, the main active metabolite of quetiapine [40]. Ziprasidone at clinical dose blocks reuptake of serotonin, noradrenaline and dopamine [41], which may suggest potential for antidepressant properties but the only published ziprasidone trial in bipolar depression indicated this compound had no more efficacy than placebo [42].

PHARMACODYNAMICS FOR SGAP SAFETY

BRAIN
EXTRAPYRAMIDAL SYMPTOMS amisulpride, paliperidone, risperidone > ¹ asenapine, iloperidone, lurasidone, olanzapine, ziprasidone > ¹ quetiapine > ¹ clozapine ² Blockade of D₂ receptors at nigrostriatal system²
HYPERPROLACTINEMIA amisulpride, paliperidone, risperidone > ¹ asenapine, iloperidone, lurasidone, olanzapine, ziprasidone > ¹ quetiapine, clozapine > ¹ aripiprazole ³ Blockade of D₂ receptors at tubero-infundibular system⁴
WEIGHT GAIN clozapine, olanzapine > ¹ asenapine, paliperidone, quetiapine, risperidone > ¹ amisulpride, aripiprazole, iloperidone, lurasidone, ziprasidone ² Blockade of H₁ (and others including 5-HT_{2C} and M) receptors⁵
SEDATION clozapine > ¹ asenapine, olanzapine > ¹ quetiapine > ¹ other SGAPs ⁶ Blockade of brain H₁ receptors⁷
MEMORY IMPAIRMENT <i>Associated with high blockade of brain muscarinic receptors in schizophrenia patients⁶</i> Possible with clozapine ⁸
↓ SEIZURE THRESHOLD clozapine > ¹ olanzapine, quetiapine > ¹ other SGAPs ⁹ D₂, H₁ and α₁ receptor blockade, actions at neurosteroids or by pharmacological kindling¹⁰
PERIPHERAL (with/without brain component)
HYPERGLYCEMIA/HYPERLIPIDEMIA <i>Secondary to weight gain (see above)</i> Direct effects on glucose/lipid metabolism clozapine, olanzapine, quetiapine ¹¹
SEXUAL SIDE EFFECTS clozapine, risperidone, olanzapine > ¹ aripiprazole, quetiapine, ziprasidone ¹² Hyperprolactinemia (see above) and blockade of peripheral α, M and H receptors¹³
ORTHOSTATIC HYPOTENSION clozapine, iloperidone, risperidone, quetiapine, ziprasidone ¹⁴ Blockade of peripheral α₁ receptors
ANTICHOLINERGIC SYMPTOMS (Tachycardia, constipation, dry mouth, urinary retention, or blurred vision) ¹⁵ clozapine > ¹ olanzapine > ¹ quetiapine Blockade of peripheral muscarinic receptors
NAUSEA aripiprazole, lurasidone, ziprasidone Unknown¹⁶
PROLONGATION OF QT_C iloperidone, ziprasidone > ¹ amisulpride, asenapine, clozapine, lurasidone, quetiapine, risperidone, olanzapine > ¹ aripiprazole ¹⁷ Blockade of heart potassium repolarizing channels
AGRANULOCYTOSIS clozapine (<1%) Probably immunological
NEUTROPENIA (very rare) Possibly ALL Unknown
RISK FOR HEAT STROKE (very rare) Most published cases also involve FGAPs ¹⁸ Dopaminergic blockade interferes with temperature regulation Muscarinic blockade from antiparkinsonian or from AP (see anticholinergic) inhibits sweating

Figure 5. Pharmacodynamics of safety for second-generation antipsychotics

5-HT: serotonin receptor; ADR: adverse drug reaction; AP: antipsychotic; D: dopamine receptor; FGAP: first-generation antipsychotic; H: histamine receptor; M: muscarinic receptor; SGAP: second-generation antipsychotic.

¹Drugs preceding ">" will produce this ADR more frequently than drugs following ">".

²Data from a comprehensive review [43] supplemented with data on asenapine [44], iloperidone [45] and lurasidone [46].

³Data from a comprehensive review [43] supplemented with data on asenapine [44], iloperidone [47] and lurasidone [46].

⁴All APs are D₂ antagonists except for aripiprazole, a partial agonist. The lower propensity of SGAPs other than aripiprazole to cause extrapyramidal symptoms is explained by two theories: i) a high ratio between 5-HT_{2A}/D₂ receptors, and ii) low affinity and fast dissociation from D₂ (only clozapine and quetiapine will be “atypical” since they are displaced by endogenous dopamine) [48].

⁵Studies relating weight gain within different APs and receptor affinity indicate that H₁ affinity is the best predictor of weight gain. Some animal studies indicate that H₁ blockade of other receptors (particularly 5-HT_{2C} and muscarinic) may be needed to produce hyperphagia in animal studies [48].

⁶Data from a comprehensive review [49] supplemented with data on asenapine [44] and iloperidone [45].

⁷H₁ antagonism is probably the major contributing mechanism to sedation but other receptor blockade may also contribute. Aripiprazole and ziprasidone have also been associated with early insomnia and activation [50]. It is unknown whether these compounds’ pharmacodynamic differences or individual susceptibility explain this activation.

⁸Blockade of M₁ and M₂ receptors has been associated with impaired learning and memory in animal studies [51]. It is difficult to detect cognitive impairment in the context of schizophrenia but high antimuscarinic activity was associated with worse memory functioning in an AP meta-analysis. Clozapine had a worse profile than risperidone and olanzapine [52]. Clozapine has definitively high antimuscarinic activity. Olanzapine and high doses of quetiapine may also be associated with clinically relevant antimuscarinic activity [52]. Thus, olanzapine and high doses of quetiapine may occasionally be associated with memory impairment.

⁹A comprehensive review [53] provided no comparative data on amisulpride, asenapine, iloperidone, or lurasidone.

¹⁰[54].

¹¹Other SGAPs may not have direct effects on glucose or lipid metabolism, but this has not been completely established.

¹²A meta-analysis provided no comparative data on amisulpride, asenapine, iloperidone, or lurasidone [55].

¹³[55]. Priapism is rare but is the most severe sexual ADR and is probably explained by α_1 (and possible α_2) receptor blockade [48].

¹⁴Clozapine, iloperidone, risperidone, quetiapine, and ziprasidone need dose titration to avoid orthostatic hypotension. Orthostatic changes are not seen after intramuscular injections of ziprasidone, so ziprasidone probably has low risk of orthostatic hypotension. Other SGAPs with lower risk for orthostatic hypotension are olanzapine (particularly in intramuscular preparation) and asenapine.

¹⁵Clozapine causes hypersalivation. It is believed that clozapine may be a partial agonist at M₁ and M₃ receptors. Norclozapine, clozapine’s main metabolite, is definitively an allosteric agonist of M₁ [51].

¹⁶Antipsychotics, because of their dopaminergic blockade, are considered anti-emetic drugs, so it is not known what mechanism explains the association of these three drugs with nausea in the first one or two weeks of treatment. Other SGAPs may also occasionally be associated with nausea.

¹⁷Data from a comprehensive review [43] supplemented with data on amisulpride [56], asenapine [44], iloperidone [57] and lurasidone [58].

¹⁸Most published cases including SGAPs also had FGAPs co-prescribed [59].

Table 1. Pharmacokinetic parameters of antiepileptics.

	Bioavail-ability (%)	Protein binding (%)	Half-life (h)	Most important way of elimination ¹	Other ways of elimination	Active metabolites	Non-linear kinetics
FIRST GENERATION							
Carbamazepine	75-85	75	5-26	CYP3A4 ²	CYP2C8, CYP1A2, UGT2B7	Carbamazepine epoxide ⁷	Non-linear until induction is stable
Ethosuximide	90-100	<10	25-70	CYP3A4 ²	CYP2E1, renal		
Phenytoin	90	90	7-80	CYP2C9 ²	CYP2C19 (less important: CYP2C18, CYP3A4)		Non-linear ⁶
Phenobarbital	>95	45-60	70-130	CYP2C9 ²	CYP2C19, CYP2E1, N-glucosidation, renal		Non-linear until induction is stable
Primidone	>90	10	5-20	CYP2C9 ²	Renal, CYP2C19, CYP2E1, N-glucosidation,	Phenobarbital	Non-linear until induction is stable
Valproate	>90	70-95	8-16	Several UGTs	β-oxidation, CYP 2C9 (other CYPs are minor)		Non-linear for total concentration ⁶
SECOND GENERATION							
Eslicarbazepine	~100	30	13-20	UGTs ³	Renal	S-licarbazepine	
Felbamate	90	20-25	11-25	CYP3A4 ²	Renal, CYP2E1, UGTs		
Gabapentin	<65	0	5-9	Renal			Non-linear ⁶
Lacosamide	~100	<15	12-16	CYP2C19 ²	Renal		
Lamotrigine	>95	55	25	UGT1A4 ²			
Levetiracetam	100	<10	6-8	Renal	Esterase hydrolysis in blood		
Oxcarbazepine	~100	40	7-12	Renal	UGTs	MHD (monohydroxy derivate) ⁵	
Pregabalin	>90	0	5-7	Renal			
Retigabine	60	80	8-10	Acetylation	UGTs		
Rufinamide	85	30	8-12	Carboxyles-terases			
Stiripentol	≥70	99	4.5-13		CYP1A2, CYP2C19, CYP3A4, UGTs ⁴		
Tiagabine	~100	96	5-9	CYP3A4 ²			
Topiramate	~100	13-17	10-30	Renal	CYP		
Vigabatrin	≥50	0	4-7	Renal			
Zonisamide	~100	50	50-70	CYP3A4 ²	N-acetylation transferase, renal		

CYP: cytochrome P450; UGT: uridine diphosphate glucuronosyl transferase

¹This refers to normal metabolism. Lack of polymorphic enzymes, as well as major inhibition or induction, can change the major way of eliminating the drug from the body. In some CYPs (e.g., CYP2C19) some patients do not have active enzymes; they are called poor metabolizers (PMs). Others may have too much enzyme; they are called ultrarapid metabolizers (UMs). If a drug is metabolized by a CYP associated with PMs or UMs, these subjects metabolize the drug in a different way than average subjects. Adding a potent inhibitor that completely inhibits an enzyme causes a PM “phenocopy” as long the inhibitor effects are present; adding an inducer causes a UM phenocopy as long the inducer effects are present.

²Any substrate competes with others for the corresponding enzyme and inhibits it; the potency of the inhibition is influenced by substrate affinity and dose. In most clinical situations competitive inhibition is probably irrelevant. In unusual polypharmacy situations, adding a competitive inhibitor (such as AEDs, which are not normally considered inhibitors) in a patient taking a drug with a narrow therapeutic window may affect another drug’s drug metabolism due to inhibitor accumulation past the tipping point.

³Eslicarbazepine is a pro-drug that is activated by hepatic esterases to S-licarbazepine. S-licarbazepine is eliminated by UGTs and by the kidney (unchanged).

⁴There are four metabolic pathways. No specific enzyme can be considered as the most important enzyme.

⁵MHD is also called licarbazepine. Oxcarbazepine is a pro-drug and is activated by a cytosolic arylketone reductase that converts it to MHD, the active drug.

⁶Metabolic saturation explains phenytoin non-linear kinetics. Protein binding saturation explains valproate non-linear kinetics for total serum concentrations. Absorption saturation explains gabapentin and rufinamide nonlinear kinetics.

⁷Carbamazepine epoxide is metabolized by an epoxide hydroxylase.

Table 2. Pharmacokinetic parameters of second-generation antipsychotics.

	Bioavailability (%)	Protein binding (%)	Half-life (h)	Most important way of elimination ¹	Other ways of elimination	Active metabolites
Amisulpride	43-48	17	12	Renal	Biliary	
Aripiprazole	87	99	48-68	CYP2D6 ²	CYP3A4	Dehydro-aripiprazole
Asenapine	35 ³	95	1-2	UGT 1A4 ²	CYP1A2, CYP2D6, CYP3A4	
Clozapine	12-81	95	6-33	CYP1A2 ²	CYP2C19, CYP3A4, CYP2D6	Norclozapine ⁵
Iloperidone	96	93	20-24	CYP2D6 ²	CYP3A4, CYP1A2, CYP2E1	P88, ⁶ P95
Lurasidone	9-19 ⁴	99	18	CYP3A4 ²		ID-14823
Olanzapine	60-80	93	20-70	CYP1A2 ²	CYP2D6, UGT1A4, FMO	
Paliperidone	28	30	24	Renal	UGT, CYP2D6, CYP3A4	
Quetiapine	NA	83	5-8	CYP3A4 ²	CYP2D6	Norquetiapine
Risperidone	68	90	3-24	CYP2D6 ²	CYP3A4, renal	9-hydroxy-risperidone
Ziprasidone	60 ⁴	99	4-10	Aldehyde oxidase	CYP3A4	

CYP: cytochrome P450; NA: not available; UGT: uridine diphosphate glucuronosyl transferase

¹This refers to normal metabolism. Lack of polymorphic enzyme, as well as major inhibition or induction, can change the major way of eliminating the drug from the body. In some CYPs (e.g., CYP2D6 and CYP2C19) some patients do not have active enzymes, they are called poor metabolizers (PMs). Others may have too much enzyme; they are called ultrarapid metabolizers (UMs). If a drug is metabolized by a CYP associated with PMs or UMs, these subjects metabolize the drug in a different way than average subjects. Adding a potent inhibitor that completely inhibits an enzyme causes a PM “phenocopy” as long the inhibitor effects are present; adding an inducer causes a UM phenocopy as long the inducer effects are present. When patients are taking major inducers (carbamazepine, phenobarbital, phenytoin or primidone), CYP3A4 may become the most important enzyme eliminating aripiprazole or risperidone.

²Any substrate competes with others for the corresponding enzyme and inhibits it; the potency of the inhibition is influenced by substrate affinity and dose. In most clinical situations competitive inhibition is probably irrelevant. In unusual polypharmacy situations, adding a competitive inhibitor (such as SGAPs which are not normally considered inhibitors) in a patient taking a drug with a narrow therapeutic window may affect another drug’s drug metabolism due to inhibitor accumulation past the tipping point.

³Asenapine is administered sublingually; drinking or eating < 10 minutes after administration may decrease absorption.

⁴Decreased absorption when not administered with food.

⁵Norclozapine does not appear to have antipsychotic efficacy but it may contribute to anticholinergic effects and hypersalivation.

⁶It does not cross the blood-brain barrier. It may contribute to peripheral adverse drug reactions.

Table 3. Effects of antiepileptic drugs on the most common drug-metabolizing enzyme systems.

Antiepileptic	Induction	Enzymes	Inhibition	Enzymes
First-Generation Antiepileptics				
Carbamazepine	Yes	CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4, UGT1A1, UGT2B7, UGT2B15, Epoxide hydrolase	None ¹	N/A
Ethosuximide	None ²	N/A	None ¹	N/A
Phenobarbital, Primidone	Yes	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP3A4, UGT, Epoxide hydrolase	None ¹	N/A
Phenytoin	Yes	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, UGTs, Epoxide hydrolase	None ¹	N/A
Valproic Acid	Unclear		Yes	CYP2C9, UGT1A4, UGT2B7, Epoxide hydrolase, N-glucosidation
Second-Generation Antiepileptics				
Eslicarbazepine	Weak	CYP3A4	Yes	CYP2C19
Felbamate	Weak	CYP3A4	Yes	CYP2C19, β -oxidation
Gabapentin	None ²	N/A	None	N/A
Lacosamide	None ²	N/A	None ¹	N/A
Lamotrigine	Weak	UGT	None ¹	N/A
Levetiracetam	None ²	N/A	None	N/A
Oxcarbazepine	Weak	CYP3A4, UGTs	Weak	CYP2C19
Pregabalin	None ²	N/A	None	N/A
Retigabine	None ²	N/A	None	N/A
Rufinamide	Weak	CYP3A4, UGTs	Weak	CYP2E1
Stiripentol	None ²	N/A	Yes	CYP1A2, CYP2C19, CYP2D6, CYP3A4
Tiagabine	None ²	N/A	None ¹	N/A
Topiramate	Weak	CYP3A4, β -oxidation	Weak	CYP2C19
Vigabatrin	None ²	N/A	None	N/A
Zonisamide	None ²	N/A	None ¹	N/A

CYP: cytochrome P450; N/A: not applicable; UGT: uridine diphosphate glucuronosyl transferase

¹None means that the antiepileptic is not a clinically relevant inhibitor. Antiepileptic drugs, as any substrate (see Table 1), can behave as a competitive inhibitor and in rare circumstances this inhibition may have clinical relevance.

²None means that the antiepileptic is not a clinically relevant inducer.

Table 4. Summary of pharmacokinetic drug interactions between antiepileptics and second-generation antipsychotics.

Antiepileptic	Antipsychotic	Effect	Proposed mechanism
Carbamazepine	Aripiprazole	Mean AUC decrease by 71% and 4-fold increase in clearance	CYP3A4 induction
	Clozapine	Decrease in plasma clozapine concentrations by 50%	CYP1A2 and CYP3A4 induction
	Olanzapine	Decrease in olanzapine dose-normalized concentrations by 36-71%	CYP1A2 and UGT induction
	Paliperidone	Decrease in steady-state C _{max} and AUC of paliperidone by 37%	Renal P-gp induction
	Quetiapine	Decrease of quetiapine peak plasma concentration (C _{max}) by 80%, AUC by 87% and a 7.5-fold increase of its oral clearance	CYP3A4 induction
	Risperidone	Decrease in risperidone total active moiety concentrations by 50%	CYP3A4 induction
	Ziprasidone	Decrease in ziprasidone AUC by 36%	CYP3A4 induction
Lamotrigine	Clozapine	No significant changes in plasma clozapine concentrations	
	Olanzapine	Moderate elevation of plasma olanzapine concentrations by 15%	UGT1A4 competitive inhibition
	Quetiapine	Moderate decrease of plasma quetiapine concentrations by 17%	
	Risperidone	No significant changes in plasma risperidone concentrations	
Oxcarbazepine	Clozapine Olanzapine Risperidone	No significant changes in plasma concentrations of antipsychotics	
Phenobarbital	Clozapine	Decrease in plasma clozapine concentrations by 35%	CYP1A2, CYP3A4 and UGT induction
Phenytoin	Quetiapine	Decrease by 80% of plasma quetiapine concentrations and 5-fold increase of its clearance	CYP3A4 induction
Topiramate	Clozapine Olanzapine Quetiapine Risperidone	No significant changes in plasma concentrations of antipsychotics	
Valproic acid	Aripiprazole	Decrease in plasma aripiprazole concentrations by 24%	CYP3A4 and/or gastrointestinal P-gp induction
	Clozapine	Variable results reported with plasma clozapine concentrations slightly increased, slightly decreased or unchanged	
	Olanzapine	Decrease in plasma olanzapine concentrations by 18-50%	CYPs and/or UGT induction
	Quetiapine	No significant changes in plasma quetiapine concentrations	
	Risperidone	No significant changes in plasma risperidone concentrations	

AUC: area under the curve; CYP: cytochrome P450; P-gp: P-glycoprotein; UGT: uridine diphosphate glucuronosyl transferase.

Table 5. Practical summary of antiepileptic and second-generation antipsychotic drug interactions

ANTIEPILEPTICS	SGAPs	OUTCOME	ACTIONS
PK DI. Powerful inducers: carbamazepine, phenobarbital phenytoin, primidone	quetiapine, lurasidone? ^{>1}	A. ↓ level 2-4 wks after adding inducer ↑ level 2-4 wks after D/C inducer	A. In absence of TDM use correction factor: 5 ²
	olanzapine, clozapine ^{2>1}		2-4
	aripiprazole, iloperidone, risperidone ^{>1}		2
	asenapine? ^{>1}		Unknown
	amisulpride, paliperidone, ziprasidone		Not relevant
PK DI. Mild inducers: ³ eslicarbazepine, felbamate, oxcarbazepine, ⁴ topiramate, ⁴ rufinamide	quetiapine, lurasidone? ^{>1}	↓ mild level 2-4 wks after adding inducer ↑ mild level 2-4 wks after D/C inducer	A. Monitor for ↓ efficacy after adding inducer B. Monitor for ADRs after discontinuing inducer
	olanzapine, clozapine ^{2>1}		
	aripiprazole, iloperidone, risperidone ^{>1}		
	asenapine? ^{>1}		
PK DI. valproate	olanzapine,	↓ mild level	A. Be aware Can't rule out occasional clinical relevance
	clozapine ²	mild ↓ or ↑ level	
PD DI. valproate	SGAP	↑ efficacy in mania/maintenance ⁵	A. Be aware B. Monitor for ADRs
PD DI. FGAEDs, topiramate ^{>1} Other	clozapine, asenapine, olanzapine ^{>}	Additive sedation risk	A. Monitor for sedation
	quetiapine ^{>}		
	Other		
Absence of PD DI. felbamate, lacosamide, lamotrigine, tiagabine	aripiprazole, ziprasidone	These AEDs and SGAPs may not be sedating	Be aware
PD DI. carbamazepine, gabapentin pregabalin, valproate	clozapine, olanzapine ^{>1}	Additive weight gain risk	A. Monitor weight B. Monitor serum glucose and lipids ⁶
	asenapine, paliperidone, quetiapine, risperidone ^{>1}		
	amisulpride, aripiprazole, iloperidone, lurasidone, ziprasidone		
PD DI. topiramate, zonisamide ⁷	SGAPs	Weight loss	Be aware
PD DI. AEDs	SGAPs	Additive impaired swallowing risk ⁸	Monitor closely in patients with intellectual disability or dementia
PD DI. carbamazepine, phenobarbital, phenytoin, primidone ^{>1} oxcarbazepine, valproate	amisulpride, paliperidone, risperidone	Possible additive osteoporosis risk	Monitor closely
PD DI. valproate rarely ⁹	SGAPs more rarely ¹⁰	Possible additive pancreatitis risk	A. Be vigilant (can be lethal)
PD DI. carbamazepine very rarely	clozapine rarely	Both have risk for agranulocytosis	DO NOT COMBINE
PD DI. valproate rarely	SGAPs rarely	Both associated with leucopenia	A. Be vigilant (can be lethal)
PD DI. topiramate, zonisamide rarely	SGAPs rarely ↑ risk with anticholinergic drugs ¹¹	Both associated with heat stroke	In elderly and/or exposed to strenuous exercise/ high temperatures: A. Be vigilant (can be lethal):

		B. Encourage proper hydration.
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ADR: adverse drug reaction; AED: antiepileptic drug; FGAED: first-generation antiepileptic drug; PD DI: pharmacodynamic drug interaction; PK DI: pharmacokinetic drug interaction; SGAP: second-generation antipsychotic; SGAED: second-generation antiepileptic drug; ?: reflects that information on asenapine and lurasidone is limited. It is likely that asenapine may be influenced by potent inducers but it has not been studied.

¹Drugs preceding ">" will produce a more powerful outcome than the drugs listed on the following line.

²Please be aware that a correction factor of 5 was suggested by a phenytoin pharmacokinetic study by Wong et al. [80], but a correction factor of 7.5 was suggested by a carbamazepine pharmacokinetic study [56]. Rifampin, a CYP3A4 inducer, increased lurasidone metabolism by a factor of 5.

³The risk of SGAP-induction reflects what we know from powerful AED inducers.

³High doses of oxcarbazepine (≥ 1500 mg/d) or TMP (≥ 200 mg/d).

⁵The combination of valproate with SGAPs may be more effective than monotherapy. This is particularly well established in mania; this type of combination for bipolar maintenance is standard clinical practice. As far as we know, there is no such data for additive effects for the combination of carbamazepine with SGAPs but this combination is frequently recommended for maintenance by pharmacological guidelines. Any study trying to establish the additive effects of carbamazepine and SGAPs in bipolar disorder will need to correct for pharmacokinetic DIs.

⁶Serum glucose and lipid abnormalities may be associated with weight gain. Drugs can also produce direct effects on glucose and/or lipid metabolism. Clozapine, olanzapine and quetiapine have been definitively associated with hyperglycemia and hyperlipidemia independent of weight gain. Carbamazepine has been associated with increases in total cholesterol and high density lipoprotein (HDL) cholesterol. Some studies have associated phenytoin with hyperglycemia and increases in total cholesterol. Valproate has been associated with lower total cholesterol, which may be positive, but is also associated with lowering HDL and insulin resistance.

⁷Felbamate is associated with weight loss but it cannot be used for that indication due to its high risk for severe ADRs.

⁸Although it has not been studied: i) all SGAPs can interfere with swallowing and cause esophageal dysmotility, ii) AEDs can also interfere with swallowing, and iii) additive or synergistic pharmacodynamic DIs upon swallowing are likely.

⁹Valproate is definitively associated with pancreatitis but the mechanism is not known.

¹⁰Rarely, SGAPs have been associated with pancreatitis, but the connection is not completely established. Some of these cases of pancreatitis were associated with hypertriglyceridemia, which is a known risk factor for pancreatitis. Clozapine, olanzapine and quetiapine have been definitively associated with hyperlipidemias that can occur in the absence of obesity and are probably explained by the direct effects of the drugs on lipid metabolism.

¹¹Clozapine, olanzapine and high doses of quetiapine have anticholinergic (antimuscarinic) activity. Antiparkinsonian drugs can be co-prescribed with SGAPs and have high anticholinergic (antimuscarinic) activity.