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Review

# Clinically significant pharmacokinetic drug interactions of antiepileptic drugs with new antidepressants and new antipsychotics

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ABSTRACT

Antiepileptic drugs (AEDs) are frequently co-prescribed with new antidepressants (ADs) or new antipsychotics (APs). A PubMed search with no time limit was used to update the review of the clinically significant pharmacokinetic (PK) drug interactions DIs (DIs) between AEDs with new ADs and APs. Our best interpretation of what to expect regarding dosing changes in the average patient after combining AEDs with new ADs or new APs is summarized on updated tables that integrate the information on *in vitro* metabolism studies, therapeutic drug monitoring (TDM) studies, case report/series and prospective studies. There will be a need to periodically update these dose correction factors as new knowledge becomes available. These tables will provide some orientation to clinicians with no TDM access and may also encourage clinicians to further study TDM. The clinical relevance of the inductive properties of carbamazepine, phenytoin, phenobarbital and primidone on new ADs and new APs and the inhibitory properties of valproic acid and some new ADs, are relatively well understood. On the other hand, PK DI studies combining new AEDs with weak inductive properties (particularly oxcarbazepine doses ≥ 1200 mg/day), topiramate doses ≥ 400 mg/day, clobazam, eslicarbazepine, and rufinamide), with new ADs and new APs are needed. Valproic acid may be 1) an inhibitor and/or inducer of clozapine and olanzapine with potential for clinically relevant DIs, 2) an inhibitor of paliperidone, and 3) a weak inducer of aripiprazole. Fluoxetine and fluvoxamine are relevant inhibitors of phenytoin and valproic acid and possibly of clobazam, lacosamide, phenobarbital, or primidone.



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## 1. Introduction

When polypharmacotherapy is used, there is a potential risk of drug interactions (DIs) [1]. A clinically relevant DI occurs when the efficacy or safety of a drug is altered by the concomitant administration of another medication. In a few cases DIs may prove beneficial, resulting in an increased efficacy or reduced risk of adverse drug reactions, and therefore certain drug combinations may be used advantageously in clinical practice. However, more often, DIs are harmful, leading to diminished efficacy or increased toxicity of one or more of the administered medications.

DIs represent a frequent complication associated with the use of antiepileptic drugs (AEDs) [2]. AEDs are generally administered for prolonged periods, often for a lifetime, increasing the probability of co-medication with other AEDs or drugs used for the management of associated disorders. In this respect, AEDs are increasingly prescribed in combination with psychotropic agents for a variety of reasons [3]. Firstly, there is a relatively high incidence of psychiatric disorders in patients with epilepsy. Secondly, a number of AEDs, notably carbamazepine, valproic acid and lamotrigine, are increasingly used in the management of psychiatric disorders, generally as mood stabilizers, and may be co-administered with psychoactive medications. Thirdly, AEDs are extensively prescribed for the management of various non-epileptic conditions (i.e., neuropathic pain, migraine), further enhancing the possibility of combination therapy.

In recent years, new psychotropic drugs, in particular antidepressants (ADs) and antipsychotics (APs), have been introduced into clinical practice. In addition to older or traditional ADs, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), newer ADs including selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and other ADs with varying mechanisms of action are currently available [4]. Some of these agents, notably SSRIs, have progressively replaced older compounds for the treatment of depressive disorders, mainly because of their improved tolerability and safety profile. New ADs are also widely used for the treatment of other psychiatric conditions including anxiety disorders, obsessive-compulsive disorder, eating disorders, and various forms of chronic pain such as diabetic neuropathic pain and fibromyalgia [4]. Concerning APs, over the past two decades, second-generation APs (amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine,risperidone, and ziprasidone) have become the drugs of choice for the management of psychotic disorders due to better safety profiles for reversible extrapyramidal symptoms and tardive dyskinesia as compared to first-generation APs [5]. Moreover, new APs are increasingly prescribed 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 [5].

Considering the frequent co-prescription of AEDs with new psychotropic agents, it is essential for clinicians to be aware of the potential DIs between these compounds. In recent years, a number of comprehensive reviews of clinically relevant pharmacokinetic DIs involving AEDs [2,6–11], new ADs [12,13], new APs [14,15], or combinations [3,16–20] have been published. The purpose of this article is to provide an updated review of clinically significant pharmacokinetic DIs between AEDs and new ADs and APs.

Articles for this review were obtained from a PubMed search with no time limit. Searches were conducted for each of the AEDs, new ADs or new APs. Only articles published in peer-reviewed journals were included, while meeting abstracts were excluded. Information was also obtained from the individual product inserts of each AED, new AD or new AP. Additional DI information was also obtained from citations of the articles that were retrieved during our search, and these were also included in our review. This search was beyond the articles previously found and listed in the authors' published literature reviews and DI studies.

## 2. Basic mechanisms of DIs between AEDs and new psychotropic agents

Based on their mechanisms, DIs can be classified as either pharmacokinetic (PK) or pharmacodynamic (PD).

### 2.1. PK DIs

PK DIs consist of changes in the absorption, distribution, metabolism or excretion of a drug and/or its metabolite(s) after the addition of another drug. These DIs are associated with a modification in plasma concentration of either the drug or its metabolite(s) and usually are easily verified by therapeutic drug monitoring (TDM). PK parameters of AEDs, newer ADs and newer APs are summarized in Tables 1– , respectively.

The majority of clinically important PK DIs between AEDs and new psychotropic agents occur at a metabolic level and usually involve the hepatic cytochrome P450 (CYP) system and, to a lesser extent, the uridine diphosphate glucuronosyltransferase (UGT) system [21]. In recent years, the *in vitro* characterization of the major drug-metabolizing enzymes with identification of substrates, inhibitors and inducers of different CYP isoforms has greatly improved the prediction of metabolic DIs, providing an invaluable resource in helping to anticipate and avoid potential DIs [21]. In principle, concomitant treatment with drugs metabolized by the same enzyme or co-administration of a drug with another medica-