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False-Negative Studies May Systematically Contaminate the Literature on the Effects of Inducers in Neuropsychopharmacology. Part I: Focus on Epilepsy

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Guest Editorial

False negative studies may systematically contaminate the literature on the effects of inducers in neuropsychopharmacology. Part I: Focus on epilepsy

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Conflict of interest: No commercial organizations had any role in the writing of this paper for publication. Dr. de Leon personally develops his presentations for lecturing, has never lectured using any pharmaceutical or pharmacogenetic company presentation, and has never been a consultant for pharmacogenetic or pharmaceutical companies. In the past, Dr. de Leon has received researcher-initiated grants from Eli Lilly (one ended in 2003 and the other, as co-investigator, ended in 2007), from Roche Molecular Systems, Inc. (ended in 2007), and in a collaboration with Genomas, Inc., from the NIH Small Business Innovation Research program (ended in 2010). He was on the advisory boards of Bristol-Myers Squibb (2003/04) and AstraZeneca (2003). Roche Molecular Systems supported one of his educational presentations, which was published in a peer-reviewed journal (2005). His lectures have been supported once by Sandoz (1997), twice by Lundbeck (twice in 1999), twice by Pfizer (twice in 2001), three times by Eli Lilly (2003, twice in 2006), twice by Janssen (2000 and 2006), once by Bristol-Myers Squibb (2006), and seven times by Roche Molecular Systems, Inc. (once in 2005 and six times in 2006).

Running title: False negative inducer studies part I

Key words: anticonvulsants; clobazam; drug interactions; drug labeling; oxcarbazepine; tiagabine; topiramate; vigabatrin.
Ioannidis has pointed out that many published research findings in medicine\(^1\) (including highly cited clinical research, epidemiology, genome-wide association studies, new technologies called “omics,” and brain volume measures using imaging techniques) are false. Two major biases can contribute to these false positives: (1) financial and other conflicts of interest, and (2) biases associated with the quest for statistical significance.

The statistical and methodological literature has given less attention to the possibility that systematic false negatives contaminate the literature. This editorial is divided in two, part I which focuses on epilepsy, and part II which will focus on bipolar disorder, and proposes that the neuropsychopharmacology literature on drug-drug interactions (DDIs) studying drug metabolic inducers is seriously contaminated not by false positives, but by false negative findings. The author is suggesting that inducer effects are systematically denied or at least undervalued, and the available published literature systematically deemphasizes their clinical relevance. Moreover, this happens both in epilepsy and bipolar disorder literature where inducers increase the metabolism of many drugs metabolized by the Cytochrome P450 (CYP) and/or Uridine Diphosphate Glucuronosyltransferase (UGT) enzymes.

Why is this happening? DDIs are an annoyance for clinicians and therefore a complication for pharmaceutical company marketing. Pharmaceutical companies introducing a new drug want to sell as much of this new drug as possible and have a natural tendency to ignore or suppress interferences with reaching this goal. Promotion of a new drug that may be competing with other established drugs may be facilitated by undervaluing or understating its inductive properties and its concentration variations when co-prescribed with inducers.

How is this happening? Since the 1990s, the Food and Drug Administration (FDA) has progressively developed a set of regulations\(^2\) requiring the systematic investigation of the pharmacokinetic properties of any new drug. In this author’s view, information on drugs approved before the late 1990s is problematic, and FDA regulations are insufficient in producing clear, easy-to-use guidelines for prescribers.\(^3\) The current set of pharmacokinetic studies\(^2\) utilized to market a new drug
usually includes determinations of its metabolic pathways through an in vitro study in hepatocytes, and an in vivo radiolabel drug study in a small number of individuals to study drug elimination. Then, DDI studies\(^2\) using relevant inhibitors and inducers in human individuals (healthy controls or patients) are conducted. It is relatively easy to design DDI studies that undervalue inducer effects by using single doses of the inducer or drug, or by using doses or treatment duration of the inducer that do not provide maximum inductive effects.

Next, this editorial proposes to demonstrate to the skeptical reader that a consistent pattern of denial and undervaluation of inducer effects exists in the neuropsychopharmacology literature. This pattern may be defined as systematic since it contaminates different pharmacological categories: (1) CYP3A4 drugs, (2) non-metabolized drugs, and (3) mild inducer drugs. Moreover, it contaminates the “narrative” of both epilepsy (part I) and bipolar disorder (part II) pharmacological treatments which are characterized by polypharmacy, including the use of potent inducers such as carbamazepine, or the more recently introduced mild inducers.

From a historical perspective, denial and undervaluation of inducer effects usually occur first in the literature on antiepileptic drugs (AEDs) (part I), and then in the literature on bipolar disorder (part II). Tiagabine is the best example of denial and undervaluation of inducer effects in a CYP3A4 drug among the AEDs. Topiramate and vigabatrin are briefly discussed as AED drugs allegedly not influenced by inducers since they are purportedly not metabolized. More attention is paid to the issues of mild inducer drugs since they have been almost completely neglected by prior literature. Among AEDs, topiramate, oxcarbazepine, clobazam and vigabatrin exemplify the denial and undervaluation of inductive effects of mild inducing drugs. The section on mild inducers is the most extensive since it clearly establishes the pattern of false negative findings. Only after companies were “forced” by the FDA to thoroughly study these drugs did it become clear that some of them are mild inducers.

**DRUGS METABOLIZED BY CYP3A4 IN EPILEPSY**

**Tiagabine**
Tiagabine was marketed as an AED for adjunct treatment of partial epilepsy. Several companies have been involved in its advertising process in various countries. The recommended dosages of tiagabine were approved for adjunctive therapy for partial-onset seizures in randomized clinical trials (RCTs) which included patients taking other AEDs that induce tiagabine metabolism, including carbamazepine, phenytoin, phenobarbital and primidone. The inattention to the fact that recommended doses were established using patients who were “expectedly” taking inducers had catastrophic consequences.

Tiagabine was approved by the FDA in 1997. These were times of high but naïve expectations about off-label indications for AEDs. Probably all pharmaceutical companies wanted to follow the example of Pfizer which was extremely successful in encouraging the off-label prescription of gabapentin. A effort to promote tiagabine for off-label uses in psychiatry was supported by some “experts”. In the rush to encourage off-label prescription of tiagabine, it was forgotten that tiagabine RCTs were conducted in induced patients and the FDA-approved doses were for induced patients. Psychiatrists encouraged to prescribe off-label did not know much about pharmacokinetics and induction, and they prescribed tiagabine in doses recommended by the package insert, 32-56 mg/day (http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=cf97a72e-951e-a7db-a574-adac12a6b189).

Unfortunately, tiagabine does not share gabapentin’s innocuous ADR profile. Tiagabine is an AED but can exacerbate seizures in patients with partial-onset epilepsy and cause de novo seizures in non-epileptic patients, particularly when taken in overdoses. This tiagabine ADR has never been systematically well-studied but is probably a dose-dependent ADR. Some psychiatrists started prescribing tiagabine in standard doses for off-label uses, particularly in patients with anxiety. Then reports of 31 cases of new-onset seizures in psychiatric patients reached the FDA. In 2005, the FDA sent a letter to prescribers and asked the company to add a boldface warning in the prescribing information describing this risk. Later on, it became clear that tiagabine, like gabapentin, does not appear to work for off-label indications such as bipolar, generalized anxiety or post-traumatic stress disorders.
Could the seizures in non-induced psychiatric patients have been prevented? Yes; had psychiatrists had known more pharmacokinetics they would have prescribed much lower tiagabine dosages to their patients. Tiagabine is mainly metabolized by CYP3A4. It has been common knowledge since the 1990s that there are no CYP3A4 poor metabolizers, but inducers and inhibitors are major problems for CYP3A4 drugs. Moreover, in 1996 the FDA became aware that a CYP3A4 drug, terfenadine, was associated with relevant DDIs when the potential lethality of adding CYP3A4 inhibitors to terfenadine was demonstrated. Since 1996 the FDA has progressively increased the requirements for conducting DDI studies for newly marketed drugs. A tiagabine study in volunteers on the effects of erythromycin, a potent CYP3A4 inhibitor, was conducted by the company before marketing. As in the case of inducers, one can design inhibitor studies to fail. In this case, the company studied 13 healthy volunteers. They were given tiagabine doses 10 times lower than those used in the RCTs (4 mg/day), along with low inhibitor doses of erythromycin (1000 mg/day). The discussion section of the erythromycin DDI article did not explain the perplexing finding that a CYP3A4 substrate, tiagabine, was not inhibited by a powerful CYP3A4 inhibitor, erythromycin. Hachad et al. commented that “this lack of effect of erythromycin is unexpected and remains unexplained.”

What should one conclude about the tiagabine story? (1) Off-label prescription of a drug using the best available data at the time may look problematic retrospectively, once it is clear that the drug is subject to clinically relevant induction. (2) Inducers significantly increase tiagabine metabolism, as one would expect for any drug mainly metabolized by CYP3A4. The instructions for prescribing tiagabine off-label should have recommended decreasing doses to 1/3 to ½ of epilepsy doses in patients not taking AED inducers. This is based on prescribing information that indicates doses of 32 and 56 mg/day in an induced population corresponds respectively to doses of 12 and 22 mg/day in a non-induced population. The mean doses of these two ranges are 44 mg/day for induced patients and 17 mg/day in non-induced. Thus, non-induced patients should take approximately 0.39 of the approved dose (17/44=0.39), that is, between 1/3 and ½ of the dose approved for induced epilepsy patients.
Topiramate

Inducers may markedly increase the metabolized fraction of a drug, which may in turn require major dose adjustment. Topiramate is mainly eliminated unchanged in the urine, but is partly metabolized (approximately 20%) by CYP. Topiramate clearance increases two-fold when taking carbamazepine or phenytoin, which requires doubling the dose.\textsuperscript{10}

Vigabatrin

Vigabatrin is another allegedly non-metabolized AED. Several companies have been involved in the marketing process for vigabatrin in various countries. According to the prescribing information (http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a5d389d2-d0e1-4395-a2a2-b552808e7f98) vigabatrin is not significantly metabolized and is eliminated primarily through renal excretion. A critical literature review suggests a more complex picture. In a company isotope study using a single vigabatrin dose to explore drug clearance in 6 healthy male subjects, Durham et al.\textsuperscript{11} found that about 95% of total radioactivity was recovered in the urine, with the parent drug representing most of it (82%); a metabolite accounted for 3-5% of radioactivity and another for 1-2%. There are no studies on whether or not repeated dosing increases vigabatrin’s metabolized fraction or not. Even assuming that <10% of vigabatrin is metabolized, there is no doubt that the fraction of vigabatrin that is metabolized increases remarkably in patients taking inducers, although the increase has not been sufficiently well quantified in the literature. Vigabatrin has very rarely been prescribed as monotherapy and most patients studied in the literature were taking several other antiepileptic drugs; most frequently they were taking powerful inducers such as carbamazepine or phenytoin.

According to the prescribing information, population pharmacokinetic studies indicate that several AEDs, including carbamazepine and primidone, appear to have no effect on plasma concentrations of vigabatrin. Other DDI studies present a more complex picture. Vigabatrin peak concentrations, after a single dose of 2 g/day in 6 healthy male volunteers,\textsuperscript{11} were higher than after repeated dosing of 3 g/day for
4 weeks in 8 patients of both genders taking inducers.\textsuperscript{12} In a small open study of 19 patients, the median vigabatrin clearance increased by a factor of 1.56 (or 156\%) on carbamazepine, when compared with monotherapy.\textsuperscript{13}

**MILD INDUCERS IN EPILEPSY**

The epilepsy literature provides no review focused on the effects of mild inducers. This section reviews in detail the studies on four mild inducers: oxcarbazepine, topiramate, vigabatrin and clobazam, to stress that their effects may be more important than previously thought.

**Oxcarbazepine**

Oxcarbazepine is thought not to induce its own metabolism as carbamazepine does;\textsuperscript{14} the literature generally agrees that its inductive effects are less pronounced than those of carbamazepine.\textsuperscript{15} There is more disagreement on whether oxcarbazepine’s inductive effects are mild and can be ignored, or are clinically relevant. Unfortunately, the literature has not paid attention to Patsalos et al.,\textsuperscript{16} who described four patients taking oxcarbazepine doses ≥1,500 mg/day who showed inductive effects. They proposed that only high oxcarbazepine doses may have inductive effects. This author believes that the idea that only high oxcarbazepine doses have inductive effects is correct; this may explain the conflicting literature findings. Oxcarbazepine frequently shows no inductive effects in the low to moderate doses used in controlled studies; however, it appears to be a mild but clinically relevant inducer in naturalistic studies.

In the best published pharmacokinetic study, Andreasen et al.\textsuperscript{17} compared 17 days of 1200 mg/day of oxcarbazepine and 800 mg/day of carbamazepine in healthy volunteers; clearance of a CYP3A-dependent quinidine metabolite respectively increased around 90\% and 180\%. If one assumes that this study accurately reflects what happens to CYP3A4 drugs, doses of these drugs would need to be almost doubled when oxcarbazepine is added versus almost tripling them when carbamazepine is added.

Oral contraceptives are metabolized by CYP3A4; therefore, oxcarbazepine can decrease their plasma levels and can cause loss of contraceptive efficacy unless other measures are taken. What is important is that an RCT was thoughtfully designed to demonstrate that oxcarbazepine may be induced by
using relatively high doses. Oxcarbazepine 1200 mg/day was studied in 22 healthy female volunteers who were taking an oral contraceptive containing 50 mg of ethinyl estradiol and 250 mg of levonorgestrel using a randomized design controlled with placebo. Both components had a reduced AUC of 47% with oxcarbazepine use.\textsuperscript{18} This RCT was planned after an open trial of 900 mg/day of oxcarbazepine reduced the AUC of ethinyl estradiol and levonorgestrel by 48% and 32%, respectively.\textsuperscript{19}

The only controlled oxcarbazepine study with second-generation antipsychotics showed no effect, but only used 900-1200 mg/day of oxcarbazepine for 5 weeks.\textsuperscript{20} As CYP3A4 is relevant in metabolizing some second-generation antipsychotics, it is possible that higher oxcarbazepine doses may induce several antipsychotics in a clinically relevant way.\textsuperscript{21}

A controlled study in healthy subjects performed by a pharmaceutical company suggested that oxcarbazepine doses of 1200 mg/day do not influence lamotrigine metabolism in patients taking 200 mg/day.\textsuperscript{22} Therapeutic drug monitoring (TDM) studies\textsuperscript{23,24} using long-term treatment suggested that serum lamotrigine levels may be mildly reduced when oxcarbazepine is co-administered, and lamotrigine doses may need to be increased by approximately 20-30%. The clinical relevance of this DDI is demonstrated by two cases of lamotrigine-induced oral ulcers (initial signs of Stevens-Johnson syndrome) two months after oxcarbazepine discontinuation.\textsuperscript{25}

In summary, high doses of oxcarbazepine can induce CYP3A4 and UGT1A4. Following this brief review of the literature, it appears that doses $\geq$1,200 mg/day of oxcarbazepine may have relevant inductive properties. Controlled studies using $\geq$1,200 mg/day of oxcarbazepine are needed to establish the magnitude of its inductive effects in the average patient and the correction factor needed to compensate. Naturalistic studies and case reports need to consider the possibility that some individuals may be particularly sensitive to oxcarbazepine inductive effects and demonstrate induction in lower doses. Oxcarbazepine de-induction may take up 2 months to completely manifest.

\textbf{Topiramate}
Topiramate also appears to be a weak inducer of several metabolic enzymes, but induction may be influenced by topiramate dosing levels. After an in vitro study, Nallani et al. proposed that, in doses ≥400 mg/day, topiramate inductive properties may have clinical significance for CYP3A substrates. In a cohort of 12 women with epilepsy receiving stable dosages of valproate along with a combination norethindrone, 1 mg/ethinyl estradiol, 35-μg tablet, topiramate doses of 200 mg/day, 400 mg/day, or 800 mg/day caused a statistically significant dose-related decrease in the mean ethinyl estradiol AUC by 18–30% at the 200- to 800- mg/day dose level. The pharmacokinetics of norethindrone remained unchanged. In contrast, another study found that topiramate doses of 50–200 mg/day did not significantly affect the clearance of either ethinyl estradiol or norethindrone.

The topiramate company completed an open-label controlled risperidone DDI study in which 12 healthy subjects received a single oral dose of risperidone 2 mg; serial blood samples were taken for 72 hours after administration. Topiramate was progressively increased up to 200 mg/day on days 10-14. The AUC of the total risperidone moiety was 10% lower on topiramate than at baseline. Migliardi et al. found that in dosages up to 200 mg/day, topiramate had no significant effects on clozapine, olanzapine, risperidone and quetiapine concentrations. There are no studies on antipsychotic TDM at higher topiramate doses.

Topiramate may have complex effects on valproate since it may serve as an inducer by increasing β-oxidation but can also inhibit valproate glucuronidation. At low valproate doses, β-oxidation is the most important valproate metabolic pathway and topiramate may behave as an inducer of valproate metabolism. At high valproate doses, glucuronidation is the most important valproate metabolic pathway and topiramate may behave as an inhibitor of valproate metabolism.

A small controlled study completed by the company in which 13 epilepsy patients were prescribed topiramate for 18 weeks with progressive increases in dosages of up to 400 mg/day for 2 weeks showed no relevant DDI between lamotrigine and topiramate. In a controlled study by independent investigators, topiramate was added to lamotrigine treatment monthly from 100 mg/day to up to 800
mg/day if tolerated; the study demonstrated that in 4 of 7 patients there was a decrease in C/D ratio by 40-50%.  Reimers et al., in a large valproate TDM study controlling for confounding factors, suggested that topiramate may decrease lamotrigine levels, but the topiramate doses were not described.

In summary, high doses of topiramate can induce CYP3A4 and some other enzymes including those involved in metabolism of valproate and lamotrigine. Controlled topiramate studies using ≥400 mg/day are needed to establish the magnitude of its inductive effects on the average patient and the correction factor needed to compensate for them. New naturalistic studies and case reports are needed to explore the possibility that some individuals may be particularly sensitive to topiramate’s inductive effects and demonstrate them in lower doses. A complicating factor is that, in some situations, topiramate may also have drug metabolism inhibitory properties.

**Vigabatrin**

Several companies have been involved in marketing vigabatrin. As indicated in a prior section, the literature describes vigabatrin as a non-metabolized AED; thus, if vigabatrin is not interacting with CYPs, it should not be an inducer (or an inhibitor). However, a 20% average reduction in total phenytoin plasma levels was reported in 3 vigabatrin European RCTs. When the company completed a controlled DDI study in 8 patients with 2 g/day of vigabatrin increased to 3 g/day over 6 weeks, an average drop of 23% in total phenytoin concentration was not evident until the 5th or 6th week. The study did rule out the possibility that this decrease in total phenytoin concentration was due to protein binding effects, but tried to rule out induction with the method that was considered standard at the time. They used the antipyrine clearance test that today is regarded as less informative compared to methodology subsequently developed for use to investigate induction. The company authors stated, “Vigabatrin is excreted largely unchanged in the urine, with relatively little being metabolized in the liver. It would be an unusual finding for a drug which itself is little metabolized by the liver to have a significant effect on hepatic enzymes.” As induction did not appear to explain the decrease in total phenytoin concentrations, they proposed that
this decrease was due “an increase in tissue binding sites for phenytoin resulting in an increased volume of distribution”.

As the decrease in serum phenytoin concentration may compromise seizure control, an Italian investigation group studied 21 patients who were switched from oral phenytoin to intravenous phenytoin 5 days before and after the vigabatrin doses of 2.4±0.5 g/day were added. There was no significant change in serum phenytoin levels when switching between oral and intravenous (IV) phenytoin. The addition of vigabatrin caused a decrease in serum phenytoin levels which was not reversed when phenytoin was switched from the oral to the IV route. For the whole group, mean serum phenytoin decreased significantly from 87±25 μMol/L to 76±31 μMol/L after vigabatrin was added, though in a subgroup of 7 patients, serum phenytoin fell by more than 25%. As the urinary recoveries of phenytoin and its metabolites remained constant throughout the study, the authors concluded that “the oral availability of phenytoin is unaffected by vigabatrin”. They commented that the possibility of a vigabatrin-induced stimulation of phenytoin metabolism “is considered unlikely because vigabatrin is not metabolized significantly and there is no evidence that it may act as an enzyme inducer. Moreover, enzyme induction is rarely selective and vigabatrin is known not to affect the serum concentrations of other oxidized anticonvulsants with the exception of phenobarbital, whose concentrations may be marginally decreased.”

Twenty years later, as vigabatrin is being introduced in the US market, the company in charge of its marketing conducted an in vitro study and reported in the prescribing information that “vigabatrin induces CYP2C9, but does not induce other hepatic CYPs”. The company recommendation is that dose adjustments of phenytoin should be considered if clinically indicated, although they are not routinely required.

According to the prescribing information, when co-administered with vigabatrin, phenobarbital concentrations (from phenobarbital or primidone) were reduced by an average of 8% to 16% and sodium valproate plasma concentrations were reduced by an average of 8%. These reductions did not appear to be
clinically relevant. Phenobarbital is mainly metabolized by CYP2C9, and CYP2C9 is a minor pathway in valproate metabolism; thus, it is not surprising that if vigabatrin is a mild CYP2C9 inducer, it may decrease the serum concentrations of these two drugs. A naturalistic study also described small decreases in phenobarbital concentrations after adding vigabatrin.

In summary, it has taken more than 20 years but, due to the in vitro study required to market vigabatrin in the US, it is now clear that vigabatrin induces phenytoin metabolism and that this is probably mediated by CYP2C9 induction. Vigabatrin induction does not start to manifest clinically until the second month of treatment.

Clobazam

Several companies have been involved in marketing clobazam in various countries. Clobazam was first approved in Australia in 1970 and then in France in 1974 for anxiety and epilepsy. Clobazam demonstrated clinical benefit in more than 50 European epilepsy studies which reported data on >3000 pediatric and adult patients, 300 of whom were diagnosed with Lennox-Gastaut syndrome. This led to 2 multicenter RCTs for Lennox-Gastaut syndrome using a double-blind design, and to its subsequent marketing in the US in October of 2011 for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=de03bd69-2dca-459c-93b4-541fd3e9571c).

We currently know that clobazam is mainly metabolized by CYP3A4; then the main metabolite, N-desmethylclobazam (or norclobazam), is mainly metabolized by CYP2C19. The clobazam concentration/dose (C/D) ratio is a measure of CYP3A4 activity and the total (clobazam plus N-desmethylclobazam) C/D ratio is influenced by both CYP3A4 and CYP2C19 activities. According to the prescribing information, in vitro studies indicate that: (1) clobazam did not inhibit CYP or UGT enzymes; (2) N-desmethylclobazam showed weak inhibition of CYP2C9, UGT1A4, UGT1A6 and UGT2B4; (3) clobazam and N-desmethylclobazam did not inhibit P-gp, but were P-gp substrates; and (4) clobazam and N-desmethylclobazam induced CYP3A4 activity in a concentration-dependent manner.
It is surprising that clobazam is a mild CYP3A4 inducer because clobazam is a benzodiazepine, and benzodiazepines are not thought to be inducers. Clobazam is the only 1,5-benzodiazepine available on the market since all other benzodiazepines have a 1,4 structure. Its nitrogen atoms occupy the 1 and 5 position, a keto group is placed in the 4 position, and the remainder of the molecule is analogous to diazepam.\(^{42}\)

As clobazam induces and is metabolized by CYP3A4, one would expect the possibility of auto-induction. The information on clobazam auto-induction is not prominent in the midst of the extensive data published\(^3\) and has received little attention. Greenblatt et al.\(^4\) were the only ones who commented on this issue in the 1980s. They reported that they had not seen signs of self-induction in clobazam metabolism in a pharmacokinetic study using 10 mg/day of clobazam for 22 days on 12 young and 12 elderly adults. To introduce clobazam in the US, its manufacturer was required to complete in vivo DDI-controlled studies which indicated that clobazam is a CYP3A4 inducer since it: (1) decreases midazolam AUC by 27%, and (2) increases the AUC of the metabolite 1-hydroxymidazolam four-fold.\(^4\)

A careful review\(^3\) of an old study completed by a pharmaceutical company suggests its data is compatible with clobazam auto-induction. Bun et al.\(^4\) compared peak and trough weight-corrected concentration from 6 healthy volunteers\(^4\) and 17 patients\(^4\) (6-32 years) with co-medications, measured at days 2, 7 and 21. In patients who were presumably taking inducers, there was a very small increase from day 2 to day 21 compatible with lack of signs of auto-induction. On the other hand, it is interesting that raw data in healthy volunteers presented in the article tables showed that both peak and trough weight-corrected concentrations increased from day 2 to day 7, and then decreased to day 21.\(^4\) According to the clobazam C/D ratio calculations\(^3\) using the article data, 5 of 6 patients had clobazam C/D ratios that were 20-30% higher at day 7 than at day 28. A decrease of clobazam concentrations from day 7 to day 28 is consistent with self-induction.\(^3\)

Currently, it is clear that clobazam can induce CYP3A4, but the prescribing information provides conflicting interpretations of its clinical relevance since it states that “this level of induction does not call for dosage adjustment of drugs that are primarily metabolized by CYP3A4”, but then states that adding
Clobazam may be associated with the loss of oral contraceptive efficacy, and non-hormonal forms of contraception are recommended when using clobazam. Clobazam effects on oral contraceptives must be mediated by CYP3A4 induction.

As carbamazepine is mainly metabolized by CYP3A4, it will be interesting to see how clobazam may influence carbamazepine metabolism. Carbamazepine is a potent CYP3A4 inducer, so it is possible that clobazam may not have obvious inductive effects in patients who had maximum induction. Two studies\textsuperscript{48,49} frequently reported in the literature as indicating that clobazam may reduce carbamazepine levels are limited since they did not control for carbamazepine dosing (i.e., using C/D ratios). Sennoune et al.\textsuperscript{50} found no differences in carbamazepine C/D ratio in 34 patients taking carbamazepine versus 17 taking carbamazepine and clobazam. On the other hand, Genton et al.\textsuperscript{51} carefully described a carbamazepine intoxication associated with clobazam treatment in a patient taking topiramate; this is probably explained by N-desmethylclobazam inhibitory effects on carbamazepine metabolism. The contradictory results of clobazam on carbamazepine may represent differences over time (mild CYP3A4 induction may or may not be relevant at a given time) or differences between the inhibition of carbamazepine metabolism by clobazam and/or N-desmethylclobazam.

The clobazam information on the possibility of UGT induction is conflicting. The prescribing information reported that population pharmacokinetic studies during the clobazam RTCs indicated no effects on the metabolism of valproate (82 patients) and of lamotrigine (48 patients). In a TDM study comparing valproate C/D ratio for 20 patients on valproate and 15 patients on valproate and clobazam, Sennoune et al.\textsuperscript{50} agreed with the prescribing information that clobazam may not influence valproate metabolism. However, naturalistic studies provided conflicting results regarding the effects of clobazam on lamotrigine metabolism. Weintraub et al.\textsuperscript{52} retrospectively reviewed the medical records of outpatients at a single epilepsy center and reported that lamotrigine clearance was similar in 409 patients who received lamotrigine monotherapy and 157 patients who received lamotrigine plus clobazam. On the other hand, Reimers et al.\textsuperscript{35} analyzed 744 serum samples from 296 children, and reported that clobazam co-
administration in 7 patients with 13 lamotrigine samples had weak inducing effects similar to those of clonazepam.

In summary, the 1980 literature did not describe clobazam as a mild CYP3A4 inducer, but the studies required to market clobazam in the US have demonstrated that clobazam is a mild CYP3A4 inducer. Careful attention to the table data from the pharmaceutical company in the 1980s has led to the author finding signs of clobazam auto-induction in healthy controls, but not in epilepsy patients taking powerful inducers. Clobazam auto-induction may not start to manifest clinically until the third week of treatment.

CONCLUSION

This editorial with two Parts (this Part I focused on epilepsy) and (next Part II focused on bipolar disorder) was written with the hope of convincing the reader that the neuropsychopharmacology literature is contaminated by a systematic denial and underestimation of inducer effects. (1) It usually occurs first in the AED literature and then is repeated in the literature on bipolar disorder (part II). (2) This part I demonstrated that this denial cuts across pharmacological mechanisms including CYP3A4 and non-metabolized drugs, and is more evident in the case of mild inducer AEDs. Part II will demonstrate that in bipolar disorder also cuts across pharmacological mechanisms including CYP3A4 and non-metabolized drugs, and is more evident in the case of mild inducer AEDs.

References


36. Richens A. Pharmacokinetic and pharmacodynamic drug interactions during treatment with

1989;27:27S-33S.

concentration does not involve a change in phenytoin bioavailability. *Br J Clin Pharmacol.*
1993;36:603-606.


40. Sheean G, Schramm T, Anderson DS, et al. Vigabatrin--plasma enantiomer concentrations and

41. Seif-Eddeine H, Ng YT. Clobazam for patients with Lennox-Gastaut syndrome and epilepsy.


43. de Leon J, Spina E, Diaz FJ. Clobazam therapeutic drug monitoring: a comprehensive review of
the literature with proposals to improve future studies. *Ther Drug Monitor.* 2013;35:30-47.

44. Greenblatt DJ, Divoll M, Puri SK, et al. Reduced single-dose clearance of clobazam in elderly

45. Walzer M, Bekersky I, Blum RA, et al. Pharmacokinetic drug interactions between clobazam and


