POLYPHARMACY IN BIPOLAR DISORDER - A FOCUS ON DRUG - DRUG INTERACTIONS

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Abstract:
Background: *Drug-drug interactions (DDI) are actually quite commonplace and are responsible for considerable patient morbidity and mortality. The two major varieties of DDI are pharmacodynamic and pharmacokinetic interactions (cytochrome P450 system). Conditions such as bipolar disorder (with many psychiatric and somatic comorbidities) are complex symptom clusters and bipolar patients may need different medications for different phases of their illness.*
Objective: *The objective of the study is evaluation of drug- drug interactions in treatment of bipolar disorder with/ without psychiatric and somatic comorbidities.*
Method: *Retrospective review study of the psychiatric charts of randomly taken 100 inpatients with bipolar disorder (according to DSM IV TR), with/ without psychiatric and somatic comorbidities, admitted to Obregia Hospital over the last two years. First we collected data about patients age, gender, principal diagnosis, psychiatric and somatic comorbidities, psychiatric and somatic medications, smoking, coffee and alcohol use. Then, we reevaluated patient's treatment received in hospital and collected data about oral contraceptives, antibiotics and symptomatic drugs use. We analyzed statistically these data and assessed the DDI.*
Results: *The results had shown that the vast majority of subjects had psychiatric and somatic comorbidities. And by that, this increased the risk of polypharmacy and drug- grug interactions via cytochrome P450. Drug interactions of vignettes are common situations. All interactions cannot provide but if possible, should be avoided for complicated therapeutic schemes.*
Conclusions: *Not seeing is not equivalent of not occurring. The more psychiatric drugs a patient is taking, the risk for injurious DDIs and cumulative toxicity is greater.*
Key words: *cytochrome P450, comorbidities, adverse effects, pharmacokinetics.*

Rezumat:
Introducere: *Interacţiunile medicamentoase sunt des întâlnite şi sunt responsabile pentru mortalitate şi morbiditate considerabile în rândul pacienţilor. Cele două mari clase de interacţiuni medicamentoase sunt cele farmacodinamice şi farmacocinetice (prin intermediul citocromului P450). Pacienţii cu tulburare bipolară (cu numeroase comorbidităţi psihiatrice şi somatice) prezintă un complex de simptome şi necesită diferite medicamente pentru diferitele faze ale bolii.*
Obiectiv: *Obiectivul acestui studiu este reprezentat de evaluarea interacţiunilor medicamentoase întâlnite în tratamentul pacienţilor bipolari cu/fără comorbidităţi psihiatrice şi somatice.*
Metoda: *Studiu retrospectiv, randomizat al foilor de observaţie a 100 de pacienţi cu tulburare bipolară (conform DSM IV TR) cu/fără comorbidităţi psihiatrice şi somatice internaţi în Spitalul Obregia în ultimii doi ani. Pentru început am colectat date despre vârsta şi sexul pacienţilor, diagnosticul principal, comorbidităţile psihiatrice şi somatic, medicaţia psihiatrică şi somatic, fumatul, consumul de cafea şi*

alcool. Apoi am extins studiul, reevaluând tratamentul primit de pacienţi pe perioada internării în spital şi am adunat date despre consumul de antibiotice, medicamente simptomatice şi contraceptive orale. Am analizat statistic aceste date şi am evaluat interacţiunile medicamentoase.
Rezultate: *Rezultatele au arătat că marea majoritate a subiecţilor avea comorbidităţi psihiatrice şi somatice. Acest fapt a dus la creşterea riscului apariţiei polifarmaciei şi a interacţiunilor medicamentoase prin intremediul citocromului P450. Interacţiunile din vignette sunt situaţii comune. Toate interacţiunile medicamentoase nu se pot prevedea dar, pe cât posibil, ar trebui evitate schemele terapeutice complicate.*
Concluzii: *Dacă nu se vede nu înseamnă că nu se întamplă! Şi cu cât un pacient primeşte mai multe medicamente psihiatrice şi somatice, cu atât riscul pentru efecte adverse datorate interacţiunilor medicamentoase şi toxicităţii cumulative este mai crescut.*
Cuvinte cheie: *citocrom P450, comorbidităţi, efecte adverse, farmacocinetica.*

INTRODUCTION

Treatment over the last several decades has moved from a focus on time - limited therapy of an acute illness to preventive or maintenance therapy for chronic illnesses. For this reason, patients are much more likely to be on more than one medication at the same time and potential for drug interactions increases over the life span of the individual. (1)

Drug interactions are a particular concern in patients with bipolar disorders. Conditions such as bipolar disorder (with many psychiatric and somatic comorbidities) represent complex symptom clusters that wax and wane over the course of the illness. Patients with these illnesses may need different medications for different phases of their illness. While mood stabilizers are usually the foundation for the treatment of a patient with bipolar disorder, the patient may at different phases of the illness need to have antipsychotics, antidepressants or anxiolytics added and may even need treatment with > 1 mood stabilizer.

The prescriber is not planning a drug interaction, though one may occur because drugs interact on the basis of the mechanisms underlying their pharmacodynamics and pharmacokinetics rather than on the basis of their therapeutic indications. (1) The pharmacokinetics of a drug defines its potential for drug interactions. The Cytochrome P450 (CYP) system of enzymes is of primary importance to the pharmacokinetics of psychotropic drugs. (2) The P450 system is a family of mostly hepatic enzymes that perform oxidative (phase I) metabolism. The major enzymes of CYP450 are: 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, 3A457. P450 substrates are agents that are metabolized by particular P450 enzymes. P450 inhibitors impair the ability of specific P450 enzymes to metabolize their target substrates, thus producing increased blood levels of those substrates. Conversely, inducers cause an increase in the production of particular P450 enzymes, leading to increased metabolism of substrate of those P450 enzymes. Enzymatic inhibition is the most frequent, whereas induction usually requires several days to 2 or more weeks to exert a meaningful effect on drugs metabolism. (3)

OBJECTIVE AND METHOD

The objective of this study is evaluation of drug interactions in treatment of bipolar disorder with/without psychiatric and somatic comorbidities. This is a retrospective review study of psychiatric chart of randomly taken 100 inpatients with bipolar disorder (according to DSMIVTR), with/without psychiatric and somatic comorbidities, admitted to Obregia Hospital over the last two years. First we collected data about patients age, gender, principal diagnosis, psychiatric and somatic comorbidities, psychiatric and somatic medications, smoking, coffee and

alcohol use. Then, we reevaluated patient's treatment received in hospital and collected data about oral contraceptives, antibiotics, symptomatic drugs (e.g. non- steroidal anti-inflammatory drugs, proton pump inhibitors, H2 blockers, analgesics and antipyretics, etc) use. We analyzed statistically these data and assessed the DDI (drug interactions).

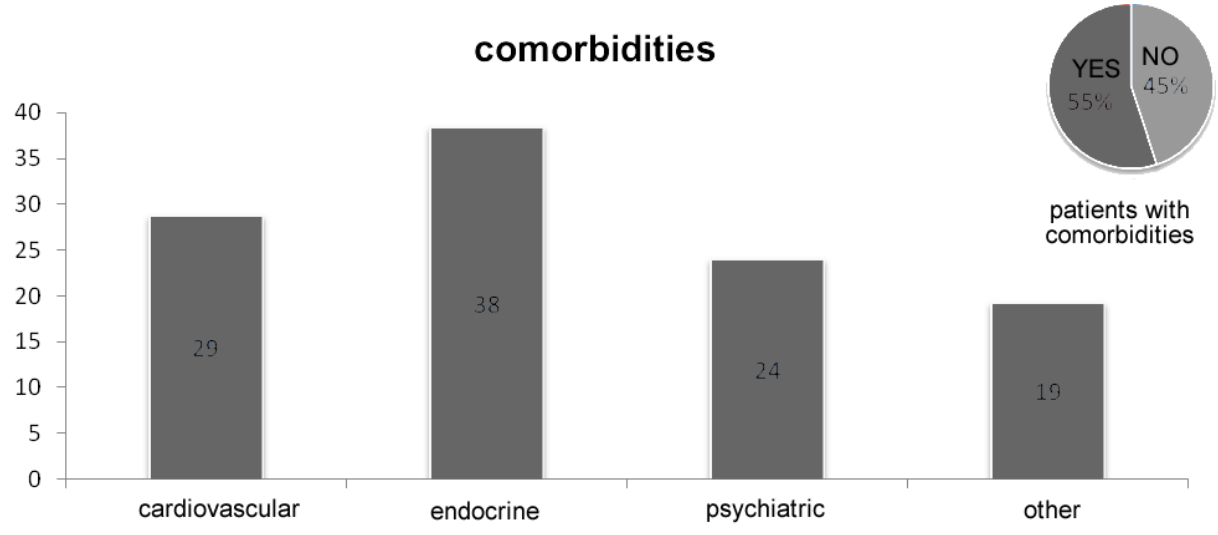
RESULTS AND DISCUSSIONS

Among the 100 bipolar patients we evaluated, 96 patients with treatment were included in the study (see Table no. 1).

Characteristics of patients sample	
age < 40	14
age 40-60	53
age >60	29
Female	62
Male	34

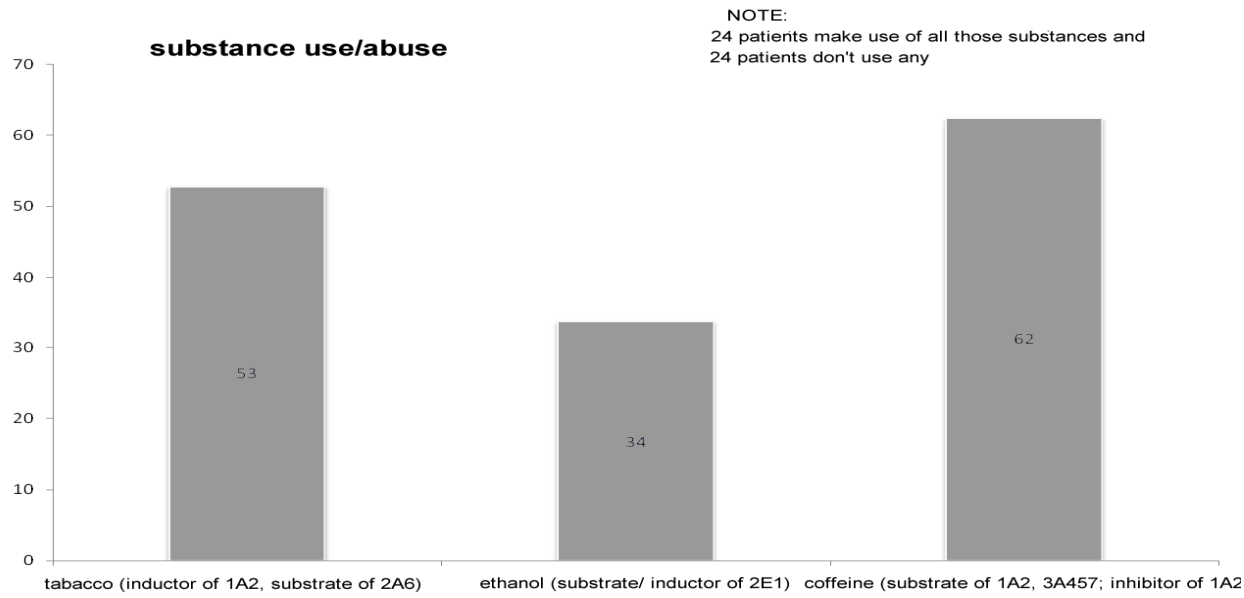
Table 1: Characteristics of patients sample

Not all drug interactions via CYP enzyme system are of clinical significance. In addition, a clinician must take into account factors pertaining to the patient. Younger people tend to metabolize drug faster than older people, men faster than woman. Comorbid medical conditions and gene polymorphism may also affect drug metabolism. Bipolar disorder is associated with an increased rate of certain medical comorbidities compared to the general population. (4) The vast majority (55%) of bipolar patients we evaluated had psychiatric and somatic comorbidities (most frequent- cardiovascular and endocrine comorbidities) (see Graph no. 1).



Graph 1: Prevalence of comorbidity in patients with bipolar disorder

Some ubiquitous non- psychotropic agents/ influences, such as tobacco, coffee, alcohol, oral contraceptives (especially containing ethinylestradiol) create drug interactions with numerous psychotropic agents. Smoking, alcohol and coffee use were prevalent in this study (see Graph no.2).



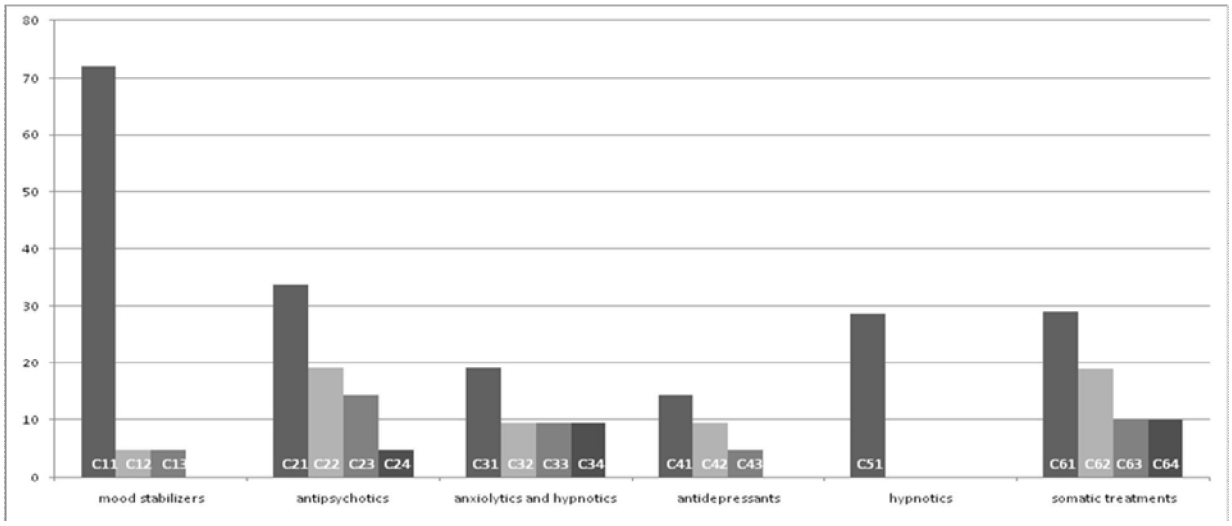
Graph 2: Prevalence of substance use/abuse in bipolar patients

Only a few smoking drug interactions are significant. The major enzyme metabolizing nicotine is probably CYP2A6, with 2B6 and 2D6 playing lesser, but still substantial roles. Cigarette smoke contains polycyclic aromatic hydrocarbons, which are potent inducers of CYP1A2. Plasma levels of haloperidol are around 23% lower in smoking than in non- smoking patients. In our study we have 5 patients with haloperidol and all of them are smoking.

Olanzapine clearance may be higher and half- life 21% shorter in smokers compared to non-smokers, probably via CYP1A2 induction. Smoking cessation can lead to olanzapine intoxication through removal of CYP1A2 induction. (5) (From 14 patients with olanzapine, 9 were smoking). Early studies suggested an increased clearance of benzodiazepines in smokers. One review noted increased clearance by smoking of alprazolam, lorazepam, diazepam but not chlordiazepoxide. (5) Effect of nicotine on heart rate and blood pressure may negate the effect of beta-blockers. Steady-state propranolol levels may be reduced in smokers, via 1A2 induction. (From 19 patients with beta-blockers, 10 were smoking). Smoking induces CYP1A2 and caffeine is metabolized by CYP1A2. Theoretically, ceasing smoking could raise xanthine levels, which could increase lithium excretion (as with theophylline), lowering levels. (5) (From 5 patients with lithium, all of them were smoking).

Enhanced CNS sedation would be expected with olanzapine and alcohol, and raised heart rate and increased postural hypotension have been reported in literature. There is no published

evidence that alcohol reduces antipsychotic efficacy. (In our study there were 5 patients with olanzapine and alcohol use).
Additive sedation was been reported in literature for interactions between mirtazapine and alcohol, or trazodone and alcohol. (5) (From 14 patients taking mirtazapine, 10 patients were consuming alcohol; from 29 patients taking trazodone, 10 patients were consuming alcohol).
Oral contraceptive use wasn't evaluated properly because usually this was not mentioned in patients' charts. However, we found 10 patients consuming oral contraceptives. Notable interactions exist between hormonal contraceptive agents and specific psychotropic drugs that warrant clinical consideration. Carbamazepine can lower the efficacy of birth control pills (and the contraceptive vaginal ring) via inductions of hepatic CYP3A4 isoenzymes that metabolize the exogenously administered estrogen. These interactions are important because they can result in unexpected pregnancies. (6)
Psychiatric drugs were represented by mood stabilizers, antipsychotics, anxiolytics and antidepressants (see Graph no. 3).



Graph 3: Psychiatric and somatic medications (C11-valproate, C12-carbamazepine, C13-lithium, C21-quetiapine, C22-risperidone, C23-olanzapine, C24-haloperidol, C31-clonazepam, C32-lorazepam, C33-alprazolam, C34-nitrazepam, C41-mirtazapine, C42-venlafaxine, C43-escitalopram, C51-trazodone, C61-beta-blockers, C62-HMG CoA reductase inhibitors, C63-angiotensin II blockers, C64-insuline)

The most frequent used mood stabilizers were: valproate (72 patients; it has a complex metabolism, 10% is metabolized by CYP2D6 and 2C19 enzymes), lithium (5 patients; it may interact with other drugs, particularly via changes in renal excretion), carbamazepine (5 patients; it is principally metabolized by CYP3A4 (also 2C8), but is also a potent inducer of CYP3A4 and other oxidative mechanisms in the liver; this autoinduction takes up to four weeks to occur, although it is virtually complete after a week; CBZ is metabolized to carbamazepine epoxide (CBZ-E), which may be more toxic than CBZ itself). Among the antypsichotics, the most

frequent were: quetiapine (34 patients; it is metabolized primarily by CYP3A4), risperidone (19 patients; it is metabolized by CYP2D6 to 9-hydroxy-risperidone) and olanzapine (14 patients; it is metabolized by CYP1A2 and 2D6, with little or no effect 1A2, 2D6, 2C19, 2C9 and 3A4 at normal doses) and rarely: haloperidol (5 patients; haloperidol's metabolism is quite complex, relying principally on CYP3A4, with secondary contributions from 2D6 and 1A2), sertindol (it is extensively metabolized by CYP2D6 and 3A4 and is a weak 2D6 and 3A4 inhibitor; it is contraindicated in patients also receiving drugs known to prolong the QT interval), amisulpride. Anxiolytics and hypnotics were present in the treatment of almost all patients, usually: clonazepam (19 patients), lorazepam (10 patients) , alprazolam (10 patients), nitrazepam (10 patients). Benzodiazepines are mainly metabolized by CYP2C si CYP3A3/4. (5)

In bipolar depressive patients, antidepressants represented a more frequent choice than lamotrigine or quetiapine: mirtazapine (14 patients; it does not inhibit CYP2D6, 1A2 and 3A and so interactions via these enzymes are unlikely; it is mainly metabolized by CYP2D6 and 1A2 and if one of enzyme is inhibited, the other takes over, so mirtazapine appears less susceptible to P450 interactions), venlafaxine (10 patients; it is metabolized by CYP2D6 to O-desmethylvenlafaxine, a major active metabolite and by CYP3A4 to N-desmethylvenlafaxine; other minor metabolic pathways exist; it has a low potential for CYP2D6 and 3A4 inhibition), escitalopram (5 patients; it would be expected to have similar characteristics with citalopram: it is a weak inhibitor of CYP2D6 and is metabolized mainly by 3A4; a review concludes that citalopram is neither a source nor a cause of clinically important drug interactions). Trazodone (29 patients; it is metabolized by CYP2D6 and inhibits 3A4) was used mostly as a hypnotic agent.

There is an assumed risk in any combination (resulting from adequate information and required by clinical situation) **and an unknown risk** (arising from lack of information, idiosyncrasies, slow metabolism, etc). Drug interactions of the vignettes are common situations. All interactions cannot provide but if possible, should be avoided for complicated schemes (see Table no. 2).

olanzapine-ciprofloxacin	carbamazepine-valproate	benzodiazepines-antacids	gingko biloba-valproate
olanzapine-benzodiazepines	carbamazepine-oral contraceptives	beta-blockers-diazepam	cimetidine-valproate
olanzapine-carbamazepine	carbamazepine-metoclopramide	ranitidine-diazepam	valproate-oral contraceptives
erythromycin-alprazolam	carbamazepine-paracetamol	omeprazole-diazepam	diazepam-oral contraceptives
erythromycin-quetiapne	carbamazepine-beta-blockers	St. John Wort-alprazolam	valproate-diazepam
erythromycin-trazodone	carbamazepine-cimetidine	lorazepam-carbamazepine	valproate-lorazepam
quetiapine-carbamazepine	carbamazepine-erythromycin	carbamazepine-trazodone	venlafaxine-trazodone

tetracycline-lithium	carbamazepine-glipizide	gingko biloba-trazodone	venlafaxine-erythromycin
carbamazepine-lithium	valproate-glipizide	escitalopram-metoprolol	venlafaxine-cimetidine
valproate-lithium	valproate-clonazepam	omeprazole-escitalopram	mirtazapine-diazepam
NSAIDs-lithium	valproate-aspirin	sertindole-cimetidine	sertindole-macrolide

Table 2: Common drug interactions found in treatment of bipolar patients

Ciprofloxacin (inhibits CYP1A2) increases levels of olanzapine. (7) This may be associated with orthostatic hypotension on initial dose titration, especially when used intramuscularly. It may enhance the effects of antihypertensives.(7) Concomitant IM olanzapine and IM benzodiazepines are contraindicated and may be separated by at least one hour. (5) Olanzapine is widely used in the treatment of acute mania and it has been shown effective as a bipolar maintenance treatment too. Olanzapine is associated with significant weight gain and sedation (especially when is co-administered with mood stabilizers). These are the main causes of discontinuation. (8) Carbamazepine increases olanzapine clearance by 44% and reduces half- life by 20%, probably by CYP1A2 induction, but dose adjustment is not needed as olanzapine has a wide therapeutic index. (5) Nicotine (potent induced CYP1A2) can lower olanzapine levels. (7)

Erythromycin (inhibits CYP3A4) can increase levels of CYP3A4 metabolized psychotropic drugs (e.g. alprazolam, quetiapine, trazodone). Quetiapine is metabolized almost exclusively via the CYP enzyme 3A4. Erythromycin and other macrolide antibiotics could rise the plasma level of antipsychotic and produce a risk of sedation or orthostatic hypotension unless the dose of antipsychotic is reduced. (Generally, orthostatic hypotension will not occur once steady-state is reached, except among some elderly patients). Quetiapine may demonstrate reduced effectiveness if administered with CYP3A4 enzyme inducers, such as carbamazepine. In this situation, a clinician should consider increasing the dose of antipsychotic. (2) In literature there was a case of cervical dystonia with the combination of quetiapine and valproate. (5) Carbamazepine 600- 800mg/day decreases quetiapine plasma levels by 80%, presumably by CYP3A4 induction, a potentially clinically significant. Toxic levels of CBZ-E (the toxic CBZ metabolite) raised 3-4 fold have been reported in literature with concurrent quetiapine. (5)

Caffeine (predominantly metabolized by CYP1A2) can decrease lithium levels. Medication that decreases lithium level may precipitate a relapse in mood symptoms in patients previously stabilized on lithium. (7) Tetracycline antibiotics enhanced toxicity of lithium due to increased lithium absorption and impaired excretion. Lithium is commonly associated with gastrointestinal distress, tremor, headache, weight gain and dermatologic side effects such as acute or exacerbation of psoriasis. Cardiac changes secondary to lithium are often benign. Hypothyroidism occurs in approximately 30% patients on long-term lithium therapy, with female and elderly patients at highest risk. (7) Carbamazepine, valproate enhanced therapeutic effect of lithium and this may increase the risk of neurotoxic side effects and confusion. While this is

mostly in patients with pre- existing brain damage, there is some evidence in literature of minor cognitive impairment with the combination. Non- steroidal anti-inflammatory drugs (except aspirin and sulindac), decreased lithium clearance and raised plasma lithium concentration thereby enhancing toxicity. (9) Studies show a variable effect of ibuprofen, with a 25% increase in lithium levels. As ibuprofen is available over-the-counter, interaction should be considered carefully. Lithium levels should be monitored frequently if the combination lithium plus non-steroidal anti-inflammatory drugs/COX-2 inhibitors is to be used. (5)

Metabolized by CYP3A4, carbamazepine may induce its own metabolism as well as the CYP3A4 isoenzyme. Therefore, inhibitors and inducers of CYP3A4 may affect carbamazepine plasma levels. Carbamazepine can double valproic acid clearance. Valproate may reduce plasma concentration of carbamazepine due to increased metabolism. (9) CBZ reduce contraceptive efficacy due to enhanced hepatic metabolism. (9) The CYP3A4 metabolism of oral contraceptives is accelerated by CBZ to give a reduced contraceptive effect. (5) Carbamazepine's additive dopamine blockade can increase the risk of extrapiramidal symptoms when used with metoclopramide; there is a report in literature of apparent CBZ neurotoxicity occurring after metoclopramide 30mg/day was added, which resolved when metoclopramide was stopped. (5, 10) Co-administration paracetamol with carbamazepine may reduce the bioavailability of paracetamol and hepatotoxicity has been reported in literature. Valproate seems to inhibit several CBZ metabolic pathways, resulting in raised CBZ-E concentrations (which has led to CBZ-E induced psychosis and so watch closely for toxicity) but sometimes with unchanged carbamazepine levels. (5) Carbamazepine increases elimination of some cardiovascular drugs and it may decreases the effect of beta-blocker propranolol. Studies has shown a transient 20% rise in carbamazepine levels with cimetidine, reduced clearance, prolonged half-life and inhibition of non-renal elimination via CYP3A4 inhibition. A rapid 100-200% rise in CBZ levels has been reported in literature with erythromycin use, probably via CYP3A4 inhibition. A review of the interaction concluded that the greatest risk is with high doses of both drugs, and least with clarithromycin, although clarithromycin can rise CBZ levels significantly, leading to toxicity and hyponathremia. (5) Enhanced levels of CBZ and oxcarbazepine can cause central nervous system side effects, specifically sedation, muscle weakness, ataxia and visual disturbances. In addition, carbamazepine is associated with bone marrow suppression and may result in transient leucopenia and rarely aplastic anemia. (7) Carbamazepine and valproate can increase level of glipizide (2C9 was inhibited). This can cause a decrease in the patient's serum glucose with accompanying dizziness, sweating, anxiety and tachycardia.

Using valproic acid with clonazepam may produce absence status in patients with a history of absence-type. (10) Bupropion can increase concentration of valproate level. (9) Adverse effects of valproic acid include sedation, weight gain, hair loss and transient increases in liver enzymes. A slight decrease in valproate absorption with antacids has been noted in literature. (5) Valproate's effect and toxicity may be enhanced by repeated high-dose aspirin, and levels may rise by 12-43%. Valproate levels may rise three-fold when erythromycin is started, resulting in CNS toxicity. There is a case in literature of a fatal seizure with the combination Gingko Biloba

plus valproate, probably due to reduced valproate levels via CYP2C19 induction. One study showed that cimetidine reduces the clearance and prolongs the half-life of valproate but ranitidine does not interact. There is a wide interindividual variation and monitoring valproate may be prudent if adding or discontinuing oral contraceptives or steroids. (5)
Benzodiazepine absorption is slightly delayed by antacids, but total absorption remains the same. Beta- blockers (e.g. propranolol, metoprolol) produce a small but significant reduction in diazepam clearance and patients may become more „accident- prone" on the combination. (5) H2- blockers (e.g. cimetidine, ranitidine) may have interactions with benzodiazepines. Cimetidine inhibits the Cyp3A4 metabolism of long- acting benzodiazepines, but not of lorazepam, causing sedation. (9) The other H2- blockers do not interact this way, although ranitidine may slightly reduce the absorbtion of diazepam. Oral contraceptives may increase the effect of longer acting benzodiazepines, probably of minimal significance. Proton- pump inhibitors (omeprazole, but not pantoprazole) can reduce diazepam clearance by up to 50%, probably by 3A4 inhibition). (5) Due to enzyme induction, plasma concentration of the benzodiazepine is reduced by smoking. (9) Valproate can displace diazepam, carbamazepine from plasma protein- binding site, thereby increasing the activity of these drugs. So, doses may need to be reduced. (5) Valproate increases lorazepam levels by up to 40% and coma has been reported with the combination, possibly via reduced lorazepam clearance. Valproate increases clonazepam clearance by 14% and reduces valproate clearance by 18%, probably of minimal significance. St. John's Wort halves alprazolam's half- life, but there was no significant interaction between stat doses of alprazolam 1mg and St. John's Worth. Single dose studies show no effect of olanzapine on the metabolism of diazepam. Mild increases in heart rate, sedation and dry mouth were noted, but no dose adjustment considered necessary. A large study concluded that concomitant clonazepam and carbamazepine results in 22% increase in clonazepam clearance and a 20% decrease in carbamazepine clearance, so slightly higher benzodiazepine doses may be needed. In literature, raised carbamazepine levels have been reported with 100mg/day trazodone. Coma has been reported with concomitant use (Gingko Biloba and trazodone), in an Alzheimer's patient. And a serotonin syndrome has been reported with concomitant use of venlafaxine and trazodone. (5)
Use of venlafaxine with potent CYP3A4 inhibitors (e.g. ketoconazole, erytromycin) or combinations that inhibit both CYP3A4 and 2D6 should be avoided if possible. (5) Cimetidine increase plasma levels of venlafaxine. (9) A 45% reduction in venlafaxine clearance via reduced first-pass metabolism can result in increased venlafaxine levels and patient should be monitored for dose related side-effect, eg. nausea and blood pressure changes. The major metabolite O-desmethylvenlafaxine is unaffected. Escitalopram is a weak 2D6 inhibitor, but can increase levels of metoprolol. Omeprazole increases escitalopram levels but this is unlikely to be clinically significant. The combination of mirtazapine and diazepam, not surprisingly, produces an additive sedative effect and so anyone on the combination should be warned about driving and other activities. Sertindole is contraindicated with cimetidine due to CYP3A4 inhibition. Ranitidine would be a suitable alternative. QT prolongation potential makes combination of macrolide antibiotics plus sertindole a contraindication. (5)

polypharmacy in therapeutic scheme	
<3 psychotropic drugs in therapeutic scheme	10 patients

3-4 psychotropic drugs in therapeutic scheme	72 patients
>4 psychotropic drugs in therapeutic scheme	14 patients

Table 3: Polypharmacy in therapeutic scheme

Polypharmacy increases the risk of adverse events, nonadherence, medication errors and drug interactions. Many patients will require polypharmacy for acute and long- term treatment and, while many clinicians use judicious polypharmacy strategies, most combinations have not been studied. (11) Drug interactions are so numerous that the dictum to „do no harm", is seriously challenged (see Table no. 3). This situation is in part duet o the large number of prescription drugs available to prescribes. The number of drugs available over the counter has also increased. (1) Individuals with psychiatric illnesses are at particular risk for drug interactions. Patients seen by psychiatrists, for example, are six times more likely than patients seen by primary care physicians to be taking multiple medications. Drug combinations often are „uncontrolled experiments" with unknown potential for toxic effects. (10)

CONCLUSIONS

Not seeing is not equivalent of not occurring! The more psychiatric drugs a patient is taking, the risk for injurious drug interactions and cumulative toxicity is greater. And these often lead to drug interactions- induced serious adverse events.

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