Antipsychotic and Antiepileptic Drugs in Bipolar Disorder: The Importance of Therapeutic Drug Monitoring

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Abstract: Bipolar disorder (BD) is a long-term illness with mood swings which are characterized by recurrent episodes of mania/hypomania and depression, with variable interpolations of relatively asymptomatic periods, called euthymic, in which, however, some psychopathological symptoms may persist.

Although mood stabilizers, such as lithium, are the first-line treatment for the prevention of new BD episodes, combination therapy has become the standard of care for BD patients. Besides lithium, the use of a mood stabilizer along with an atypical antipsychotic is recommended in many patients. Recently, atypical antipsychotics (quetiapine, olanzapine, risperidone and aripiprazole) and antiepileptic agents (valproate, lamotrigine and oxcarbazepine) are increasingly used as mood stabilizers. To reduce side effects and optimize treatment it is important to perform accurate monitoring of drug blood levels in these patients, who are often treated with multiple drugs. Therapeutic drug monitoring (TDM) is in fact a powerful tool that, starting from clinical-chemical correlation data, allows to tailor-cut treatment to the specific needs of individual patients; hence the need to have reliable analytical methods available for the determination of plasma levels of drugs and their metabolites. Analyses of biological samples are mainly carried out using high-performance liquid chromatography (HPLC) coupled with different detectors, capillary electrophoresis and gas-chromatography. Various procedures are employed to remove biological interferences before analyzing the samples. This review focuses on currently available analytical TDM methods for atypical antipsychotics and antiepileptic agents used in the treatment of patients with bipolar disorder. Advantages and limitations of the various analytical methods will be reviewed and discussed, together with an evaluation of the role of TDM.

Keywords: Bipolar disorder, atypical antipsychotics, antiepileptic agents, pharmacokinetics, pharmacodynamics, therapeutic drug monitoring.

INTRODUCTION

Bipolar Disorder: Etiology, Symptoms and Treatment

Manic-Depressive Illness, or Bipolar Disorder (BD) as it is called today, is a major psychiatric disorder. BD shows supra-threshold variations of mood and vital energy. Episodes of depression, characterized by low mood, low energy, anhedonia, and apathy, alternate with episodes of intense nervous excitation, hyperactivity, elation of mood or irritability, and grandiose ideas. These states of exaltation are called mania when they are very intense, sometimes needing hospitalization, and impair work or other social activities and relationships of the patients, hypomania when they are limited to elation and hyperactivity and are not accompanied by social and work impairment. Alternation of mania and depression, or recurrences of mania only, constitute the Bipolar I type. Alternation of depression and hypomania, is the Bipolar II type.

These variations of mood and energy also affect thinking and judgment, and in extreme case, patients may present delusions and hallucinations.

Bipolar Disorder affects about equally women and men. Life-time prevalence of Bipolar Disorder type I in the general population is around 1.0% [1], while that of Bipolar Disorder type II is about 2.0% [2]. If we include milder forms, like cyclothymia (alternations of mild depressions and mild hypomania), the prevalence rises to 8.3% [3].

The majority of patients have their first affective episode between 15 and 24 years, although there is often a 5-10 year interval before treatment is obtained [4]. Bipolar disorder is one of the major psychiatric disorders associated with suicide. About 15% of people with bipolar disorder die by suicide [5].

The cause of this disorder is unknown, and many hypotheses have been advanced. Some of them involve the neurotransmitters (serotonergic, dopaminergic and noradrenergic systems). Given the strict relation with seasonal, circadian, and light and heat variations, it is probable that disorders of biological rhythms play a major role in the etiology and pathogenesis of bipolar disorder. Family studies point at a genetic basis for this condition. It should be underlined that the genetic predisposition is often a potential factor and several environmental factors, mostly drug and alcohol abuse, are needed for triggering BD [6].

BD is highly recurrent, with many lifetime episodes. Ten to 15% of patients have more than ten episodes during their lifetime [4]. Prophylactic treatments are necessary. Lithium is the most effective in stabilizing mood, as well as in reducing risk for suicide. Antipsychotics and antiepileptics are also used as mood stabilizers. Atypical antipsychotics are currently replacing typical antipsychotics, not only because

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they are less likely to cause severe adverse effects, such as tardive dyskinesia, neuroleptic malignant syndrome or extrapyramidal symptoms, but also because they appear to have a more specific ameliorative effect on mood, including depressive symptoms. In fact, the American Psychiatric Association recommends atypical antipsychotic drugs in their practice guidelines.

Classic antiepileptic agents, such as carbamazepine and valproic acid, are still widely used in the treatment of acute mania as well as in the maintenance treatment of BD. However, some new antiepileptic agents showed some phase-related efficacy in long-term treatment. Current data are strongest for lamotrigine, which has obtained FDA approval for prevention of bipolar depression.

It is noteworthy that all these agents have a clear antimanic action, and it has been suggested that the prevention of mania or hypomania is necessary for preventing also the depressive phase [7].

Therapeutic Drug Monitoring

The study of the pharmacokinetics of drug interactions and the genetic variability of drug-metabolizing enzymes has become an important topic in the scientific literature of the last few decades [8].

It is well known that the hepatic system of cytochrome P450 (CYP) plays an important role in the biotransformation of several CNS drugs. The CYP enzymes are represented by different isoforms, which may exhibit a particular affinity toward one or more drugs in the hepatic metabolism. For example, the isoform CYP2D6, and also other isoenzymes of CYP such as CYP1A2 and CYP3A3/4, are involved in the metabolism of many atypical antipsychotics (i.e. clozapine, olanzapine and quetiapine) [9] and their activity may be influenced by genetic variations. Concurrent medication with classical and atypical antipsychotics, depending on whether they inhibit or induce CYP isoenzymes, may lead to drug interactions and toxicity.

Other pathways such as glucuronidation are involved in the metabolism of drugs (i.e., mood stabilizers) with the formation of several hydrophilic metabolites. These biotransformation pathways can be inhibited by co-administering drugs used in everyday psychiatric practice. For example, olanzapine glucuronidation reaction is inhibited *in vitro* by lamotrigine and this interaction may represent a clinical problem in individuals receiving simultaneously both drugs [10].

TDM has demonstrated to be particularly useful in avoiding toxicity caused by high doses of the drugs or their interaction during polypharmacy [11] and, together with pharmacogenomics, it can improve pharmacotherapy, allowing to better explain individual variability in drug response [12]. This is particularly useful considering the poor compliance of psychiatric patients.

The study of chemical-clinical correlations and TDM for all atypical antipsychotic and mood stabilizers is important to reduce adverse effects and optimize treatment dosages. This is particularly significant for psychiatric patients, who hardly accept long-term drug treatment and its adverse effects [13, 14]. Moreover, TDM is a useful tool for clinicians in order to understand whether a lack of response to therapy is caused by inefficacy of the drug or by sub-therapeutic drug dosage. Albeit generally safer than the classical neuroleptics, atypical antipsychotics may cause side or toxic effects (e.g., convulsions) which can be related to high plasma concentrations of the active substance or some of its metabolites. Therefore, TDM is still a useful procedure to avoid toxicity. As regards bipolar disorder and the use of mood stabilizers, TDM is useful in various settings and particularly for new drugs; in fact, dosage regimes should be assessed regularly, so that bipolar patients can obtain optimal therapeutic benefits. It is therefore clear that the clinical monitoring of patients can significantly enhance the compliance of the patients [15]. Even in cases of drugs, like risperidone, that do not show any relationship between plasma levels of parent drug and its active metabolite on one hand, and clinical effect on the other, TDM is useful to frame pharmacogenetic data [16]. TDM is also able to distinguish cases of true drug-resistance from those of pseudoresistance; for example, if for some reason, a minimum therapeutic concentration of 23.2 ng/mL of plasma olanzapine is not reached, a patient with schizophrenia will be erroneously classified as drug-resistant if blood levels are not controlled for [17]. Dose adjustment in such cases may allow overcoming resistance and avoiding expenses related to a new drug trial that may work or may not. Another aspect that adds to the cost effectiveness of TDM, is that it may control for side effects in vulnerable patients [18]. Although data are still lacking for a cost/benefit analysis for TDM of BD, the advantages have been clearly remarked in a recent review for antipsychotic drugs from C. Hiemke [19], reporting that the savings by avoiding hospitalization of a patient for a period of 5 weeks corresponds to the costs of 400–500 drug estimations, which roughly matches the cost of monthly TDM of about 40 patients for 1 year.

The present paper deals with the main atypical antipsychotics available world-wide (quetiapine, olanzapine, risperidone and aripiprazole) and antiepileptic agents (lamotrigine, valproic acid and oxcarbazepine) used for the treatment of bipolar disorder, focusing on their pharmacodynamic and pharmacokinetic properties as well as their side and toxic effects. In order to carry-out an efficient clinical monitoring, suitable analytical methods are obviously required, allowing the determination of the analytes with good accuracy and precision at low concentrations as well as in the presence of potential interfering drugs.

Particular attention will also be addressed to their metabolism, pharmacological interactions and analytical methods useful for the therapeutic drug monitoring of the antipsychotic and antiepileptic drugs. A summary of the chemical-clinical properties of these atypical antipsychotics, such as usual dose ranges in both schizophrenic and bipolar disorders, and typical plasma levels is reported in Table **1**. On the other hand, Table **2** shows the characteristics of the antiepileptic agents used as mood stabilizers in patients with BD.

It should be borne in mind that TDM is not just a technique sub-serving research purposes, but also a basic part of drug treatment, a tool that allows to control compliance, as well as a token in the patient-doctor interaction; it requires

Table 1. Usual Doses and Plasma Levels of Atypical Antipsychotics used in BD

Drug	Chemical class	Daily dose range (mg/day)	References	Therapeutic plasma level range [a]
Quetiapine	Dibenzodiazepine	400-800	[25]	n.r.
		(300-500)	[44]	(50 - 400 ng/mL) *(0.130 - 1.043 µmol/L)*
Olanzapine	Thienobenzodiazepine	5-20	[75]	n.r.
		(5-20)	[85]	(8 - 40 ng/mL) *(0.026 - 0.128 µmol/L)*
Risperidone	Benzisoxazole	1-6	[114]	n.r.
		(4-16)	[44]	(10-60 ng/mL) [b] *(0.024 - 0.143 µmol/L)* [c]
Aripiprazole	Dihydroquinolinone	5-30	[148]	n.r.
		(5-30)	[44]	(80-450 ng/mL) *(0.178 - 1.004 µmol/L)*

The values in the brackets are referred to daily dose range in the treatment of schizophrenia.
[a]n.r. = not reported.
[b]Concentration of the active moiety (i.e. the sum of risperidone and 9-hydroxyrisperidone).
[c]The concentration expressed in molar units of the active moiety has been calculated from the concentration expressed in ng/mL, assuming an equimolar concentration of risperidone and 9-OH risperidone.

Table 2. Usual Doses and Plasma Levels of Antiepileptic Agents used in BD

Drug	Chemical class	Daily dose range (mg/day)	References	Therapeutic plasma level range [b]
Lamotrigine	Phenyltriazine	25-400 [a]	[172]	n.r.
		(25-700) [c]	[177]	(1-15 µg/mL) *(0.004 - 0.059 mmol/L)*
Valproic acid	Carboxylic acid	500-3000	[210]	50-125 µg/mL *0.347 - 0.867 mmol/L*
		(600-2500)	[223]	(50-100 µg/mL) *(0.347 - 0.694 mmol/L)*
Oxcarbazepine	Iminostilbene	600-2400	[252]	n.r.
		(300-2700)	[251]	(15-35 µg/mL)[d] *(0.059 - 0.139 mmol/L)*[d]

The values in the brackets are referred to daily dose range in the treatment of seizures.
[a]Max 200 with valproate.
[b]n.r. = not reported.
[c]Max 200 with valproate.
[d]Plasma levels are referred to the main oxcarbazepine metabolite, 10-hydroxycarbamazepine.

close collaboration between various medical specialists and the patient, resulting in improved overall patient care [19].

QUETIAPINE

Quetiapine (2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol, QTP, Fig. (**1a**)) was approved by the Food and Drug Administration (FDA) for the treatment of psychotic disorders, including schizophrenia, in 1997.

More recently, in 8-week trials QTP showed to be efficacious as monotherapy in adults with bipolar I or II disorder, leading to improvements in health-related quality of life [20, 21]. In the year 2004 the producer (AstraZeneca) announced that QTP was approved as monotherapy and adjunct therapy for the treatment of mania associated with bipolar disorder [22]. It should be noted that QTP is the only atypical antipsychotic approved in the US for use as monotherapy in both bipolar mania and depression [23].

QTP is administered as tablets (Seroquel®) containing quetiapine fumarate and the dose regimen differs according to the prescribing indications. For the treatment of schizophrenia, a target dose of 300-400 mg/day (divided in two or three administrations) is recommended, which should be reached gradually increasing the initial 25 mg daily dose. Higher doses (above 800 mg/day) may be required in some patients with persistent symptoms and doses up to 1600 mg/day can be well tolerated [24].

When used for the treatment of depressive episodes associated with bipolar disorder, the target dose is 300 mg administered once daily, while in case of mania as monotherapy or adjunctive therapy, the efficacious dose is normally between 400 and 800 mg/day (divided in two daily doses, and to be reached gradually). In 2007, Seroquel XR®, a con-

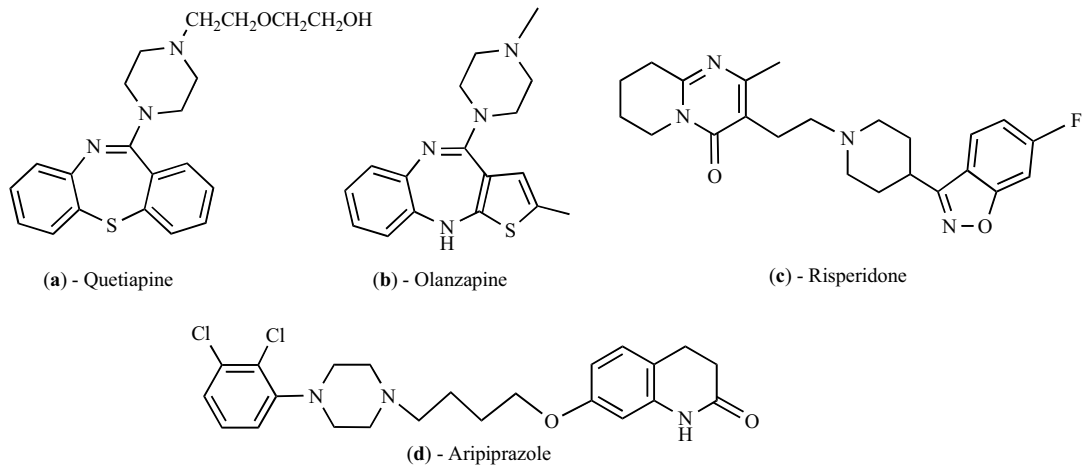


Fig. (1). Chemical structures of the atypical antipsychotics quetiapine (**a**), olanzapine (**b**), risperidone (**c**) and aripiprazole (**d**).

trolled-release tablet formulation containing QTP, has been approved by FDA for the treatment of schizophrenia with a once-daily administration within a 400-800 mg dose range [25], but approval for bipolar disorder has still to be obtained for this formulation.

Mechanism of Action

Chemically, QTP is a dibenzothiazepine derivative, presenting a broad receptor binding profile [26], which includes interactions with the serotonin, dopamine, histamine and adrenergic receptors [27]. The drug exhibits higher affinity for serotonin 5-HT_2 receptors (in particular the 5-HT_{2A} receptor) than for dopamine D_2 receptors [28], sharing this feature with the majority of atypical antipsychotics. QTP acts as an antagonist at the dopamine D_2 and serotonin 5-HT_2 receptors, and is a partial agonist at the $5HT_{1A}$ receptor; this particular binding profile of mesolimbic and mesocortical receptors has been related to its antipsychotic action, while affecting little the activity of the nigrostriatal dopamine system, hence having a low potential for extrapyramidal side effects [29]. It has been proposed that the 5-HT_2/D_2 antagonism can be related to the mood stabilizing properties of QTP in bipolar depression and mania [40], while the higher degree of serotonin 5-HT_2 receptor blockade has been correlated to the antidepressant activity [30]. The antidepressant and mood-stabilizing properties of QTP in patients with schizophrenia or bipolar depression have been correlated with the effects of the parent drug and its principal circulating metabolite, norquetiapine, on 5-HT_2 and D_2 receptors (long-term treatment was shown to induce 5-HT_2 receptor down-regulation and increase of synaptic dopamine and serotonin) and with the inhibition of the norepinephrine transporter by norquetiapine [31]. The importance of norquetiapine has also been underlined in a recent paper, where it was shown that norquetiapine is a potent inhibitor at the human norepinephrine transporter and is active on 5-HT_{1A} and 5-HT_7 receptors, thus mediating, at least in part, the antidepressant properties of QTP [32].

Side Effects

In patients with bipolar disorder under treatment with QTP, as a mono- and combination therapy, the most common side effects are dry mouth, sedation, dizziness and somnolence [33, 34], but also postural hypotension and weight gain [35]. Cases of tachycardia have also been reported; however, prolongation of the QT interval is rarely significant [36]. QTP, as well as other atypical antipsychotics such as olanzapine and risperidone, has been associated with the development or exacerbation of diabetes mellitus [37]. Cases of increased triglyceride and cholesterol concentrations have been reported during QTP treatment [36]. The interaction with α-adrenergic and histamine receptors can explain some of the side effects, such as somnolence and orthostatic hypotension [38]. Since cataract formation has been observed in dogs receiving QTP and asymptomatic changes in the lens of the eye have occurred in patients treated for a long period [39], in the US a periodical ocular examination is suggested when therapy with QTP is started [36, 40]. However, to date, only one case of cataract most probably due to QTP has been reported [41].

Pharmacokinetics and Interactions

After oral administration, QTP is well absorbed, showing almost 100% bioavailability and 83% plasma protein binding [42]. QTP exhibits linear pharmacokinetics and the mean elimination half-life is quite short, being 5.8 hours in men and 6.6 hours in women [42, 43].

QTP undergoes extensive hepatic metabolism, mainly through the CYP3A4 isoenzyme [40], leading to the formation of at least 11 metabolites [44]. Recent studies have found that the main metabolite in humans is norquetiapine (Fig. (**2**)), corresponding to the *N*-desalkylated metabolite; this metabolite has a peculiar receptor affinity and pharmacological profile [31]. Other important metabolic pathways are represented by the formation of the pharmacologically inactive metabolites quetiapine sulfoxide and the parent acid metabolite [34]. *O*-desalkyl-quetiapine and 7-hydroxy-quetiapine were also found after QTP incubation with human liver microsomes. The CYP3A4 isoenzyme is clearly responsible for the formation of the sulfoxide and the dealkylated metabolites, while the formation of 7-hydroxy quetiapine may be due at least in part to the CYP2D6 isoenzyme [45].

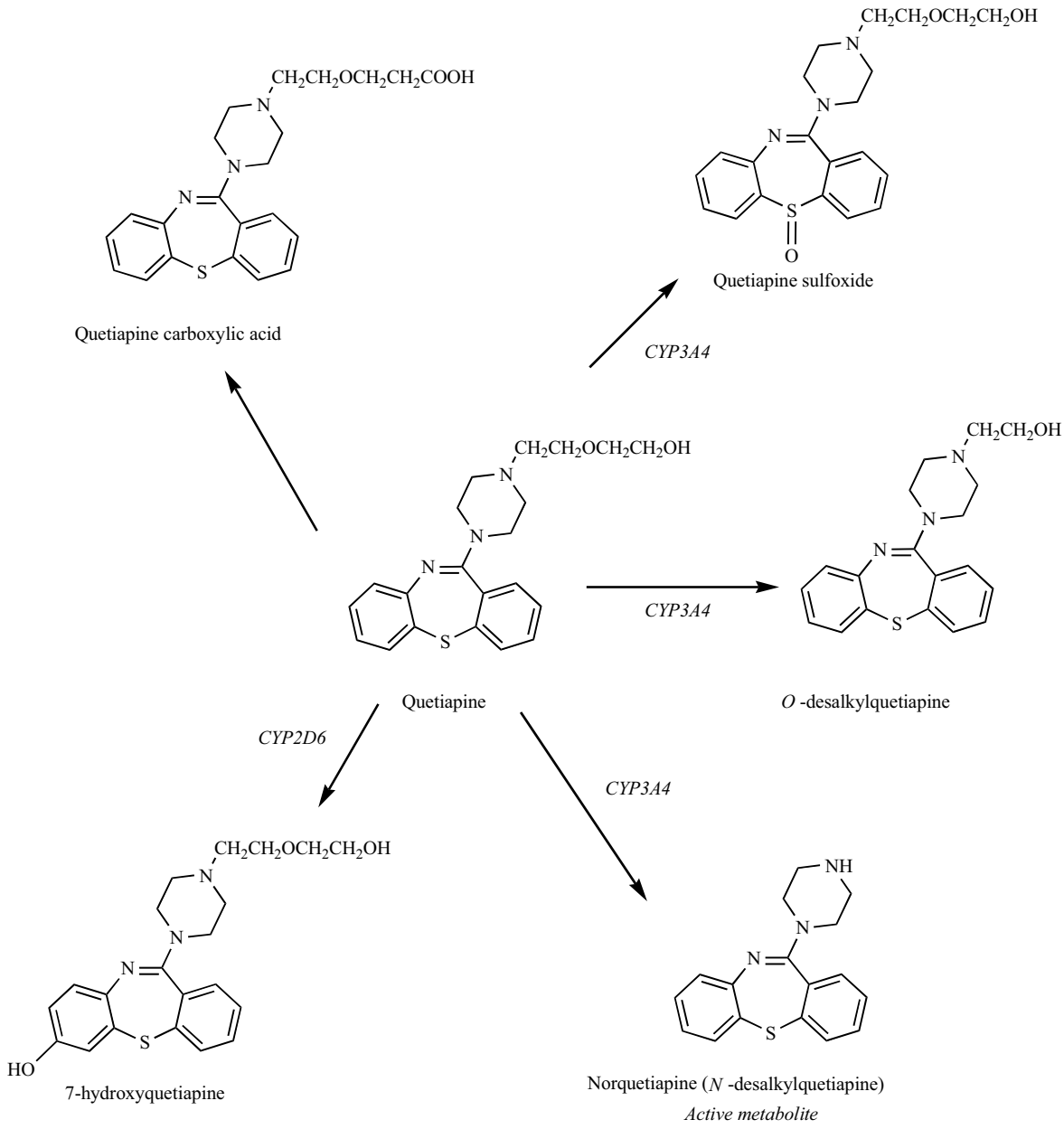


Fig. (2). Main metabolic pathways of quetiapine.

The pharmacokinetics of QTP are scarcely influenced by gender or smoking [42]. QTP must be used with caution in patients treated simultaneously with antihypertensive and other drugs which prolong QT interval [36].

CYP3A4 inhibitors, like fluvoxamine and clozapine [46], and the antiepileptic agent phenytoin [47] may increase serum concentration of QTP, while inducers, like carbamazepine, enhance QTP metabolism [45], but it is also true that QTP itself can play the part of an isoenzyme inhibitor, inasmuch it may increase plasma levels of 10,11-dihydro-10,11-epoxycarbamazepine (the main active metabolite of carbamazepine) [48]. The inhibition of CYP3A4 due to fluconazole, ketoconazole and erythromycin should also be considered when using QTP [44]. Valproate is often used as co-medication with QTP in bipolar patients; being a CYP3A4 and CYP2D6 modulator, it can increase QTP plasma concentrations [49], though another study reported that this combination therapy resulted in small and statistically non-significant pharmacokinetic changes [50]. In such cases, TDM is useful in assessing the drug-drug interaction.

Therapeutic plasma levels of QTP in the treatment of schizophrenia correspond to 50-400 ng/mL [44]. Optimal therapeutic plasma levels for the treatment of bipolar disorders are not reported, albeit a pharmacokinetic study was conducted on both pediatric and adult patients suffering from psychotic disorders (including bipolar disorder) and treated with QTP, 200 or 400 mg/day. At steady state, in adults, the mean C_{min} (minimum plasma concentrations) were 47.8 ng/mL for the 200 mg/daily dose and 86.8 ng/mL for the 400 mg/daily dose, while the mean C_{max} (maximum plasma concentrations) were 660.3 ng/mL and 1124.6 ng/mL for the 200 and the 400 mg/daily doses, respectively [51].

In postmortem samples, blood QTP concentrations indicative of toxicity were evaluated as higher than 1 μg/mL [52].

Methods of Analysis

The analysis of QTP in biological samples, sometimes along with its metabolites, is usually carried-out by means of HPLC using ultraviolet (UV) [53-59] or mass spectrometry detection [60-65]. Only one paper reported the use of HPLC with electrochemical detection to analyze two hydroxylated QTP metabolites in human plasma, while using HPLC-UV to determine QTP levels [66]. As regards the biological matrix, the analysis is mainly carried-out on plasma samples, while one study analyzed human milk [54] to assess lactating infant exposure to QTP when breast feeding mothers were on QTP. Sample pre-treatment procedures usually consist in liquid-liquid extraction with organic solvents [53, 54, 61, 63, 66] or solid-phase extraction [55, 56, 58-60, 62, 64]; one study [65] reported a protein precipitation procedure, while another method [57] employed HPLC with column-switching for the direct analysis of QTP in biological samples.

A recently developed method [55] is able to simultaneously determine QTP together with classical neuroleptics and other atypical antipsychotics using HPLC with UV detection. Sample pre-treatment consists in a solid-phase extraction procedure, using cyanopropyl cartridges; a representative chromatogram corresponding to the analysis of a plasma sample obtained from a patient treated with QTP (1200 mg/day) is reported in Fig. (**3**). QTP is detected without interference from the matrix; plasma level was 170 ng/mL.

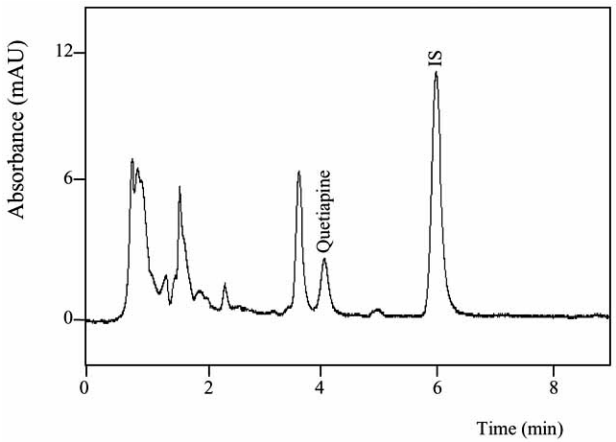


Fig. (3). Chromatogram of a plasma sample from a patient who received 1200 mg/day of quetiapine. Chromatographic conditions: stationary phase, C18 reversed-phase column (150 x 4.6 mm i.d., 5 μm); mobile phase, acetonitrile / 30 mM, pH 3.0 phosphate buffer (30:70, v/v), containing 0.5% (v/v) triethylamine; flow rate, 1.0 mL/min; injection loop, 20 μL; detection, 238 nm.

A few studies reported analytical methods based on gas-chromatography for QTP determination [67-70]; most of them focused on post-mortem specimens using mass spectrometry [67, 68] or both mass spectrometry and nitrogen-phosphorus [69] detection. One method [70] determined QTP and the 7-hydroxy metabolite by both HPLC and GC-MS, but it was not applied to real plasma samples.

Only one method based on capillary electrophoresis has been developed for quality control of pharmaceutical formulations containing QTP [71], but no electrophoretic method has been developed for QTP determination in biological fluids.

OLANZAPINE

Olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3b][1,5]-benzodiazepine, OLA, Fig. (**1b**)) is one of the atypical antipsychotic drugs, also termed second-generation antipsychotics (SGAs) [72]. It has been marketed by Lilly & Co. in 1996 for the treatment of schizophrenia; more recently, the FDA approved OLA for the treatment of bipolar disorder [73], precisely in March 2000 for the short-term treatment of acute manic episodes associated with bipolar disorder, in July 2003 for the use in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder and in January 2004 for maintenance treatment of bipolar disorder [74].

OLA is usually administered *per os* as Zyprexa® coated tablets. In the last few years new formulations became available on the market: Zyprexa Zydis® (disintegrating oral tablets suitable for patients who have trouble swallowing and when non-compliance is suspected) and Zyprexa IntraMuscular® (non-depot intramuscular preparation) for acute control of agitation [11].

OLA is usually administered at doses between 5-20 mg/day. For the rapid control of agitation and abnormal behavior in patients with schizophrenia or mania, OLA may be given intramuscularly by means of not more than three injections in any 24-hour period and the maximum daily dose should not exceed 20 mg [73]. However, a double-blind, randomized trial evaluated the pharmacokinetics and tolerability of 30 or 40 mg/day of oral OLA relative to the highest approved dose of 20 mg/day of oral OLA in stable bipolar subjects, with positive results [75].

Mechanism of Action

OLA is a selective monoaminergic antagonist with high affinity binding for the following receptors: serotonin 5-$HT_{2A/2C}$, 5-HT_6, dopamine D_1–like and D_2–like (D_2, D_3 and D_4), histamine H_1 and adrenergic α_1 receptors; it is also a moderate antagonist of serotonin 5-HT_3 and muscarinic $M_{1\text{-}5}$ receptors [76, 77]. It has been proposed that the drug efficacy for the treatment of schizophrenia and mania in BD is mediated through a combination of dopamine and serotonin type 2 (5-HT_2) receptor antagonism: a higher affinity at D_4 receptors compared to D_2 receptors has been proposed to rationalize the efficacy against positive symptoms and low potential for extrapyramidal side effects; similarly, a higher affinity for the 5-HT_{2A} receptors compared to the D_2 receptors may explain the improvements in negative symptoms and the reduced EPS liability [78]. The mechanism of action of OLA in the treatment of depression associated with Bipolar I Disorder is unknown. Currently it is unclear which receptors underline the antidepressant effect of OLA in bipolar

treatment without destabilizing mood; probably, it appears that OLA through its antagonism of both 5-HT_{2A} and D_2 receptors is an effective mood-stabilizing agent [30].

Side Effects

In comparison with classical neuroleptics, such as phenothiazines and butyrophenones, OLA has the advantage of producing minimal extrapyramidal symptoms, hyperprolactinemia, or tardive dyskinesia, when administered at the medium-dose range [44] and is much less associated with seizures and agranulocytosis than clozapine [79]. Its main adverse effects are weight gain, elevated plasma glucose and triglycerides (>500 mg/dL); moreover it can cause dry mouth, edema and orthostatic hypotension [73]. Finally, according to recent findings, patients treated with OLA show a higher risk for developing diabetes mellitus or worsening its course [80].

Pharmacokinetics and Interactions

After oral administration, OLA is well absorbed from the gastrointestinal tract. Peak plasma levels are reached in 5-8 hours. OLA is predominantly bound to albumin (90%) and α1-acid glycoprotein (77%) [81]. Mean half-life is about 30 hours. The drug is extensively metabolized by the liver to the 4- and 10-*N*-glucuronide metabolites; the CYP1A2 isoenzyme is responsible for the formation of 4-*N*-desmethylolanzapine, whilst the 2D6 isoform is related to the formation of 2-hydroxymethylolanzapine; the flavin-containing monooxygenase system is involved in oxidation of OLA [81]. The 10-*N*-glucuronide is the most abundant metabolite, but the formation of 4-*N*-desmethylolanzapine is correlated with the clearance of OLA. All OLA metabolites are significantly less active than the parent compound [82]. A schematic drawing of metabolic pathways involved in the processing of OLA is reported in Fig. (**4**).

The risks of using OLA in combination with other drugs should be carefully evaluated. In particular, caution should be used when OLA is administered in combination with other centrally acting drugs or alcohol; moreover, OLA may enhance the effects of certain antihypertensive agents and antagonize the effects of levodopa and dopamine agonists [76]. Therapeutic doses of OLA should affect little or not at all the activity of CYP; however, in a study of 17 psychiatric patients, significant and substantial inhibition of the CYP1A2 activity was shown, that may contribute to drug interactions [83]. Conversely, some known inhibitors or inducers of CYP enzymes can interact with the metabolism of OLA. In fact, the CYP1A2 inhibitor carbamazepine (an antiepileptic agent often administered as a mood stabilizer) positively increases OLA levels when the two drugs are co-administered; a similar effect on the metabolism of OLA is obtained with the antidepressant fluvoxamine [44]. In the last few years, this interaction has been exploited in clinical trials suggesting that the co-administration of a sub-therapeutic dose of fluvoxamine (25 mg/day) reduces by 26% daily OLA dose requirement [84], thus reducing overall treatment costs.

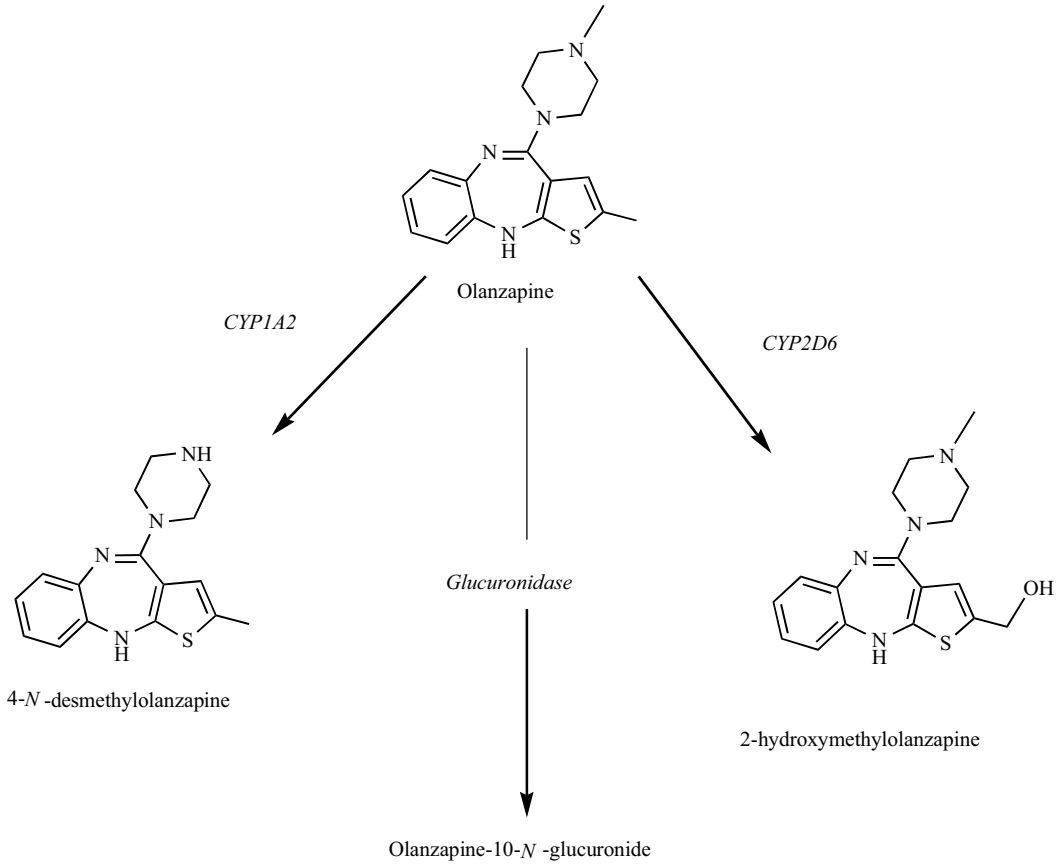


Fig. (4). Main metabolic pathways of olanzapine.

Therapeutic plasma levels of OLA correspond to a 8-40 ng/ml window [85]. In clinical studies, steady state plasma concentrations of OLA are seldom reported to be higher than 150 ng/mL, although potential toxicity has been suggested to occur at values close to 100 ng/mL [86].

Methods of Analysis

Several papers reported the determination of OLA in biological fluids or tissues, based on the use of HPLC with UV (or diode-array) [87-92], mass spectrometry [65, 93-100] or electrochemical [101-107] detection and by means of gas chromatography with nitrogen phosphorus detection (GC-NPD) [108]. Some of these analytical methods simultaneously determine OLA together with its metabolites [103-107] or other CNS drugs [65, 95, 97, 107]. Usually, the stationary phases used in the HPLC methods are represented by reversed-phase columns (C6, C8,C18 or cyano-column) and the mobile phases can be acidic [65, 88, 95, 97, 99, 103, 104], neutral [93, 101], or basic [91]. The sample pre-treatment employed to clean-up the biological matrix has been carried out mainly by means of liquid-liquid extraction (LLE) with organic solvents [87, 88, 90, 93-95, 98, 102], solid-phase extraction (SPE) procedures with different kinds of cartridges [89, 99-101, 103, 104, 106, 107], or using a simple protein precipitation step [65, 97, 105].

A recently developed method [107] is able to simultaneously determine OLA and lamotrigine in the same plasma sample drawn from patients with bipolar disorder undergoing combination treatment with these two drugs, using HPLC with a coulometric detector connected in series with a diode array detector. The sample pre-treatment consists in a solid-phase extraction procedure, using phenyl cartridges; a representative chromatogram corresponding to the analysis of a plasma sample obtained from a bipolar patient treated with OLA (20 mg/day) and lamotrigine (250 mg/day) is reported in Fig. (**5**). Plasma levels are 26.8 ng/mL for OLA, 2.6 ng/mL for N-desmethylolanzapine and 2.5 μg/mL for lamotrigine. This method has been successfully applied to the analysis of plasma from thirteen bipolar patients.

RISPERIDONE

Risperidone (3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl}-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido [1,2-α]pyrimidine-4-one, RISP, Fig. (**1c**)), is an atypical antipsychotic with a benzisoxazolic structure, not chemically related to other atypical antipsychotics such as olanzapine. RISP (Risperdal® by Janssen-Cilag) has been approved in 1993 for the treatment of schizophrenia, but it also proved to benefit schizoaffective and bipolar disorders [109, 110], especially when used in combination with antidepressant drugs [111]. In 2003, the FDA approved RISP for the short-term treatment of mixed and manic states associated with bipolar disorder; in 2006, the FDA approved it for the treatment of irritability in children and adolescents with autism [112].

Risperidone is currently available as oral tablets (Risperdal®, 0.25-4 mg strength range), orally disintegrating tablets (Risperdal®M-TAB™, 0.5-2.0 mg strength range), and oral solution (Risperdal ®, 1 mg/mL). Equivalence studies of these formulations showed that they can be considered bioequivalent [113]. RISP is usually administered at doses between 4-16 mg/day for the treatment of schizophrenia and at 1-6 mg/day for the treatment of mania [44, 114].

Recently, a depot intramuscular injectable formulation (Risperdal Consta® and Risperdal Long-Acting®) has become available for patients who have difficulty taking oral medication for any reason. This formulation could be administered at 2-week intervals and appears to be bioequivalent to tablet administration (although a lower maximum plasma concentration was observed), with comparable efficacy and emergence of adverse effects [44].

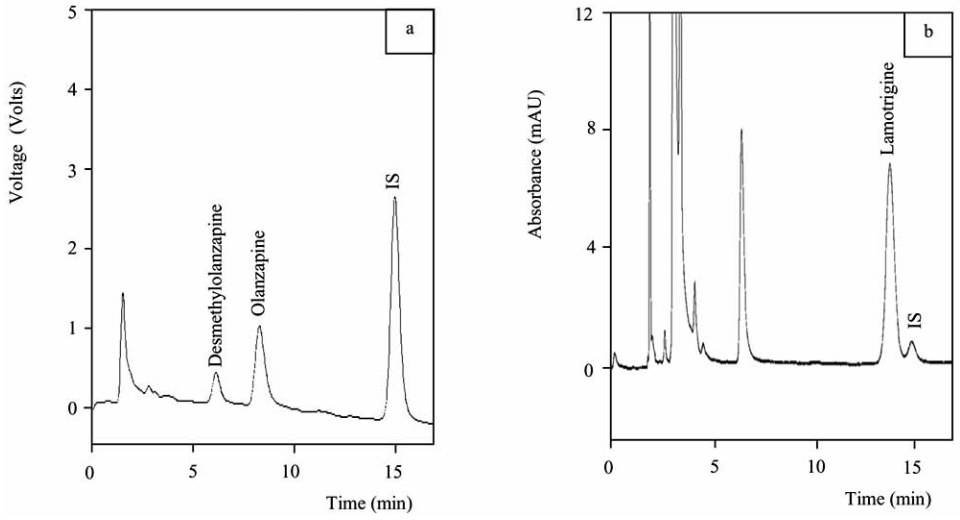


Fig. (5). Chromatograms of a plasma sample from a patient treated with olanzapine (20 mg/day) and lamotrigine (250 mg/day). Chromatographic conditions: stationary phase, C8 reversed-phase column (150 x 4.6 mm i.d., 5 μm); mobile phase, methanol / 50 mM, pH 3.5 phosphate buffer (27:73, v/v), containing 0.63% (v/v) triethylamine; flow rate, 1.2 mL/min; injection loop, 20 μL; coulometric detection, +500mV; diode array detection 220 nm.

Paliperidone (Invega®) is an extended release formulation (Oral Release Osmotic System) containing the primary active metabolite of RISP, 9-hydroxyrisperidone. It has been approved by the FDA for the treatment of schizophrenia in 2006 and later for the treatment of mania [112].

Mechanism of Action

RISP shows strong affinity for 5-HT_{2A} and 5-HT_7 receptors, for dopamine D_2 receptors, and high affinity for α_1 and α_2 adrenoceptors, and histamine H_1 receptors [44, 115], while it has weaker affinity for D_1, D_3 and D_4 receptors. A high 5-HT_{2A}/D_2 affinity ratio has been proposed to characterize the receptor binding profile of atypical antipsychotics [116]. The dose-dependence of 5-HT_2 receptor blockade by RISP, which is observed at lower doses, and its D_2 blocking effects, which are manifested progressively with increasing dosage, may be the basis of the efficacy of RISP in non-psychotic conditions at doses lower than the ones used to treat major psychoses [117].

Side Effects

RISP can cause extrapyramidal symptoms at high doses [118]; in fact, this side effect may decrease with the reduction of the administered dose. Other frequent side effects consist in weight gain, tachycardia, and hyperprolactinemia [119], as well as headache, dizziness and abdominal pain [120]. RISP can rarely prolong the QT interval in elderly patients [121].

RISP toxicity manifests primarily as lethargy, spasm/dystonia, hypotension, tachycardia and dysrhythmia, for patients who may accidentally or purposely (with a suicidal intention) take RISP doses as high as 180 mg [122]. Other symptoms reported with overdose comprise drowsiness, slurred speech, altered levels of consciousness, hypertension, electrocardiographic abnormalities, atypical motor behavior, and tremor [123].

Pharmacokinetics and Interactions

RISP is well absorbed after oral administration. The oral bioavailability of both RISP and its 9-hydroxy metabolite is approximately 100% and the maximum plasma concentrations are reached after 1.4 hours (RISP) and 1.8 hours (active moiety) [124]. Early experiments found that RISP is extensively bound (90%) to plasma proteins, while protein binding for the active 9-hydroxy metabolite is lower (77%) [125].

RISP is mainly hydroxylated in the liver by cytochrome P450 isoenzymes (CYP2D6 and CYP3A4 isoforms); 9-hydroxyrisperidone (RISP-9OH) is the main active metabolite, which can be present in plasma at much higher levels than those of the parent drug [11]. Moreover, it seems that this metabolic pathway is stereoselective; CYP2D6 would be responsible for the formation of the most abundant enantiomer (+)-9-hydroxyrisperidone while CYP3A4 would produce the less abundant (-)-9-hydroxyrisperidone [11]. On the other hand, 7-hydroxylation and oxidative *N*-dealkylation at the piperidine nitrogen pathways are less important. RISP-9OH possesses similar pharmacological activity to that of the parent drug. For this reason, the "active moiety" during RISP treatment, is considered to be the sum of RISP and RISP-9OH concentrations [11]. Plasma steady-state levels of the "active moiety" are usually in the 10-60 ng/ml range. The elimination half-life of the "active moiety" is about 22 hours [44].

Age, impaired renal and hepatic function, body weight and concomitant administration of other drugs can influence the levels of the "active moiety" in human plasma [11]. Moreover, potent inhibitors of the CYP2D6 isoform such as the Selective Serotonin Reuptake Inhibitors, or *SSRI* antidepressants (i.e. fluvoxamine, paroxetine, fluoxetine), can increase RISP plasma levels in both poor and extensive metabolizers [11]. These interactions are of crucial importance if it is considered that the combined RISP-SSRI therapy for bipolar disorder has increased in the last few years [11]. A complex interaction has been found between RISP and carbamazepine; in fact, during co-administration of the two drugs, carbamazepine seems to reduce RISP and active moiety levels because of its CYP2D6 induction, while RISP increases carbamazepine plasma levels [44].

Methods of Analysis

Since the "active moiety" during RISP therapy is the sum of RISP and its 9-hydroxy metabolite, almost all analytical methods developed for the therapeutic drug monitoring of this drug simultaneously determine the two active species. Several papers have been published on the determination of the active moiety' levels in the plasma of patients treated with RISP.

Most of them proposed HPLC methods with UV or Diode Array detection [55, 126-133]; other methods used electrochemical detection [134-138] or mass spectrometry [139-145]. For the sample pretreatment, most of methods used liquid-liquid extraction with organic solvents [127, 128, 130-132, 134-138, 142, 144, 145]; a few of them used SPE procedure [55, 129] or deproteinization techniques [126, 143].

ARIPIPRAZOLE

Aripiprazole (7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dihydro- 2(1H)-quinolinone, ARP, Fig. (**1d**)) is an atypical antipsychotic drug approved by FDA at the end of 2002 [11] for the treatment of patients with schizophrenia or schizoaffective disorder. In 2004, it was approved as monotherapy for the treatment of manic and mixed episodes associated with Bipolar Disorder type I, with or without psychotic features, in adults. In May of 2008 ARP obtained FDA approval also as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar Disorder type I with or without psychotic features in adults [146], and also in adolescents and pediatric patients [147].

The drug is commercially available in tablets, orodispersible tablets (both containing 5, 10 or 15 mg of ARP) and as oral solution, containing 1 mg/mL of the drug. The daily dose ranges between 5 and 30 mg. The starting and target dose is 15 mg/day when the drug is used as monotherapy for the treatment of Bipolar Disorder type I in adults, and 30 mg is the maximum daily dose [148].

Mechanism of Action

The mechanism of action of ARP is quite peculiar. It behaves as a partial agonist to both dopamine D_2 and serotonin 5-HT_{1A} receptors. The anxiolytic properties of ARP could be explained by its partial agonistic activity on the 5-HT_{1A} receptor [149]. More recently however, it has been suggested that ARP may act as a selective dopamine D_2 partial agonist while its effect on serotonin receptors is questionable [150]. The partial agonist activity at the D_2 receptor may explain its efficacy in the treatment of both, positive and negative symptoms of schizophrenia, and the very low incidence of extrapyramidal side effects [151, 152]. The stabilization of the dopamine receptors instead of their blockade has also been suggested as a mechanism of action [153].

Side Effects

Overall ARP presents a positive safety and tolerability profile. It has a low potential for weight gain and metabolic disruption [154]. QTc prolongation and hyperprolactinemia are not frequent as well as extrapyramidal side effects [155, 156]. The main side effects are represented by nausea, vomiting, light-headedness, somnolence, constipation and postural dizziness [44]. In particular, the risk for somnolence was evaluated higher when the drug is administered for the treatment of mania, rather than for schizophrenia [157].

Pharmacokinetics and Interactions

Oral bioavailability of tablets is about 87% and the pharmacokinetics is linear. Steady-state is reached after 14 days, albumin binding is high and maximum plasma levels occur after 3 hours, while the mean elimination half-life is about 75 hours [149]. Therapeutic steady-state plasma levels correspond to 80-450 ng/mL [11].

ARP is extensively metabolized by the liver by the CYP3A4 and CYP2D6 enzymes [158].

The main metabolic pathways are represented by dehydrogenation, hydroxylation and *N*-dealkylation, that take place in the liver due to the cytochrome P450 system (CYP3A4 and CYP2D6 enzymes), being dehydroaripiprazole the main active metabolite [152]. In particular, dehydroaripiprazole reaches plasma levels corresponding to about 40% of the parent drug and has been shown to have affinities for D_2 receptors similar to the parent drug [148].

The role played by CYP3A4 in the metabolism of aripiprazole is responsible for possible drug interactions. ARP dose should be increased when carbamazepine (a CYP3A4 inducer) is simultaneously administered. On the contrary, ARP dosage should be reduced if carbamazepine is suspended [159].

Methods of Analysis

The analysis of ARP in biological fluids has been carried out mainly using HPLC coupled to different detectors. Mass spectrometry detection is often employed [160-163], while less frequent is the use of UV detection [164]. Gas-chromatography coupled with mass spectrometry detection has also been employed for the determination of ARP together with its main metabolite in plasma samples obtained from psychiatric patients [165].

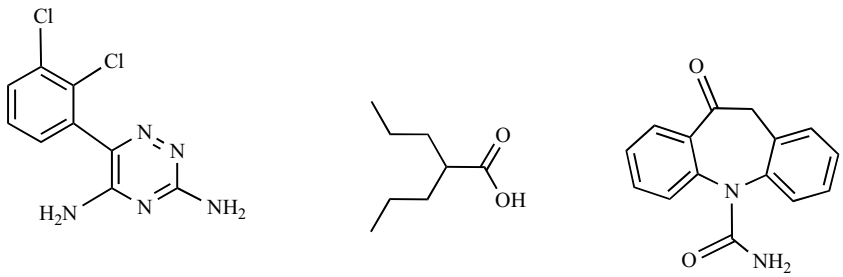
The biological fluids most commonly analyzed are plasma or serum; few papers report the analysis of ARP together with the active metabolite dehydroaripiprazole [160, 161, 165].

The sample pre-treatment consists in liquid-liquid extraction [161, 162] or protein precipitation [160, 163], while a solid-phase extraction procedure was employed before gas-chromatographic analysis [165]. An interesting method is the use of a column switching procedure for the direct pre-treatment and analysis of serum samples [164].

Recently, two different methods, with a common pre-treatment sample procedure based on solid-phase extraction with cyanopropyl cartridge, have been developed and applied to analysis of ARP in human plasma. One method is based on HPLC with diode-array detection, while the second one is based on capillary zone electrophoresis. Results obtained with both methods are satisfactory for the analysis of ARP plasma levels [166].

LAMOTRIGINE

Lamotrigine (6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, LMT, Fig. (**6a**)) is an antiepileptic agent. It has been introduced in US since 1994 as adjunctive therapy for partial seizures, generalized seizures of the Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in adult and pediatric patients (≥2 years of age) [167, 168]. If there is a need to switch from a single enzyme-inducing antiepileptic drug or from valproate [168] to LMT, the latter may provide a suitable monotherapy for the treatment of partial seizures in adult patients. In psychiatry, LMT is useful for its activating properties [169]. In June 2003, it was approved for



(**a**) - Lamotrigine (**b**) - Valproic acid (**c**) - Oxcarbazepine

Fig. (6). Chemical structures of the antiepileptic agents lamotrigine (**a**), valproic acid (**b**) and oxcarbazepine (**c**).

the maintenance treatment of adults with Bipolar Disorder type I to prevent recurrence of mood episodes. Moreover, current American Psychiatric Association practice guidelines for the treatment of bipolar disorder have included LMT as a first-line treatment option for bipolar depression, as well as an alternative to lithium or valproate in the acute treatment of rapid cycling bipolar disorder or in the maintenance treatment of bipolar disorder [170, 171].

LMT is usually administered *per os* as Lamictal® tablets or chewable/dispersible tablets at daily doses ranging from 25 to 700 mg (maximum dose is 200 mg if administered together with valproate) for the treatment of seizures. In the management of BD, a dose range of LMT between 25 and 400 mg /day (maximum dose is 200 mg with valproate) is suggested [172].

Mechanism of Action

LMT is chemically unrelated to existing antiepileptic drugs. The main mechanism of anticonvulsant effect involves the blockade of voltage-dependent sodium channels, thereby stabilizing neuronal membranes and, consequently, modulating the release of excitatory neurotransmitters such as glutamate and aspartate [173]. The mechanisms by which LMT exerts its therapeutic action in BD have not been established, but the reduction of the antiglutamatergic effect, due to neuronal voltage-dependent sodium and calcium channel blockade, seems to be related to its antidepressant effect [174].

Side Effects

The most commonly observed adverse effects during LMT monotherapy are represented by dizziness, ataxia, somnolence, headache, double vision, blurred vision, nausea, vomiting and rash [172]. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant treatment with valproate [175].

Pharmacokinetics and Interactions

LMT is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The LMT chewable/dispersible tablets were found to be equivalent to LMT compressed tablets [168]. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours and elimination half-life is about 30 hours [176]. Drug plasma levels at the steady state range from 1.02 to 15.37 μg/mL [177] with pronounced inter-individual variability [178]. LMT undergoes extensive metabolism, primarily by glucuronidation, and its main inactive metabolite is lamotrigine 2-*N*-glucuronide [176]. The minor 2-*N*-methylated lamotrigine metabolite, whose formation is probably catalyzed by a methyltransferase, seems to cause dose-dependent cardiovascular effects. These effects are not anticipated in humans because only trace amounts of this metabolite (< 0.6% of LMT dose) have been found in human urine [179].

However, it is conceivable that plasma concentrations of this metabolite could be increased in patients with a reduced capacity to metabolize LMT (i.e., in patients with liver disease). A scheme of the main metabolic pathways for lamotrigine is reported in Fig. (**7**).

Carbamazepine, phenytoin, phenobarbital and primidone have been shown to increase the apparent clearance of LMT, which on the contrary decreases with valproate. Valproate has been shown to double LMT's elimination half-life [180].

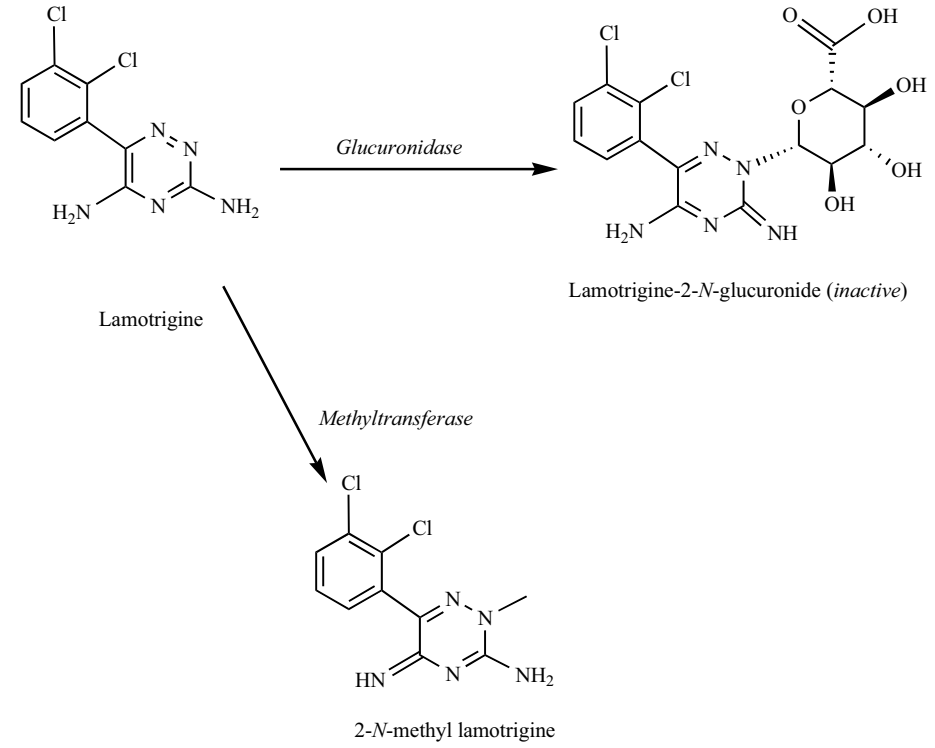


Fig. (7). Main metabolic pathways of lamotrigine.

Recent papers suggest that LMT plasma levels can be decreased by oral contraceptives [181, 182] as well as pregnancy [183, 184], with a consequent increased risk of seizures.

For these reasons, determination of plasma concentrations of the drug and its metabolites seems to be necessary in patients at risk, such as the elderly or patients with renal insufficiency or hepatic disease and in presence of some other co-medications.

Methods of Analysis

Few studies can be found in the literature regarding the determination of LMT as a single analyte or together with other drugs or its metabolites in biological fluids by means of HPLC with UV (or diode array) [107, 185-195], or mass spectrometry [196-198] detection and by means of gas-chromatography (GC) [199-201] or capillary electrophoresis (CE) methods [202-205]. Only a few papers describe the determination of LMT and its metabolites in biological fluids by means of HPLC with DAD detection [195], electrokinetic chromatography (MEKC) [205], Automated Sequential Trace Enrichment of Dialysates HPLC [206] and HPLC mass spectrometry [196]. The pre-treatment of biological samples is usually carried out by means of deproteinization by solvents [186, 187, 196], liquid-liquid extraction [185], solid phase extraction (SPE) [188, 205] and solid phase micro-extraction (SPME) [200] procedures. Only one method [107] based on HPLC with coulometric and diode array detectors allows for the simultaneous analysis of LMT and OLA in the same plasma sample of bipolar patients (see Fig. (**5**)).

VALPROATE

VPA (2-propyl-pentanoic acid, VPA, Fig. (**6b**)) is an organic solvent, whose anticonvulsant properties were serendipitously discovered in 1962 while testing a series of drugs as potential anticonvulsants. The drug was later approved for the treatment of epilepsy in France in 1967 and, in 1983, in the USA; FDA approval of VPA for mania occurred in 1995. Finally, in 1996 VPA received FDA approval also for migraine [207].

Regarding the treatment of BD, VPA is considered a front line therapy (alternative to lithium) for the treatment of acute mania, cyclothymia, mixed states and rapid cycling bipolar disorder [208].

VPA (Depakin® and Depakin Chrono®) is administered in the form of sodium salt or valproic acid and hemisodium mixture; several different formulations are available on the market, including oral (long-release tablets, modified-release granulate, oral solution) and injectable formulations.

The treatment of seizures usually starts at 600 mg/day dosage , then gradually increased to a daily dose corresponding to 1-2 g, up to a maximum of 2.5 g daily [209]; for bipolar disorder, VPA is used in doses ranging between 500 and 3000 mg/day [210].

Mechanism of Action

VPA presents anticonvulsant activity and this seems to be related to its efficacy in the treatment of bipolar disorder [211], the full mechanism involved in VPA action is however still unknown.

VPA can decrease membrane excitability by interacting with ion channels. It is able to block voltage-dependent sodium channels [212]. However, these effects could not be observed in hippocampus slice models, hence, the effects of VPA are probably not due to effects on sodium channels in this tissue [213]. T-type Ca^{2+} channels may also be involved, as VPA can block these channels, thus reducing the T-type Ca^{2+} currents [214]. Another proposed mechanism involves the GABA system; VPA elevates whole brain GABA levels and potentiates GABA responses, probably by enhancing glutamic acid decarboxylase (which converts glutamic acid into GABA) and inhibiting GABA degradation [215]. Other possible mechanisms of action are reduced GABA release and attenuation of neuronal excitation induced by glutamate NMDA receptors [216]. It has been suggested that the regulation of signaling pathways may play a role in the mechanism of action of VPA as a mood-stabilizer in BD; in fact, it has been demonstrated that chronic administration of VPA determines a reduction of protein kinase C, but also a modulation of several genes [217].

Most likely, the efficacy of VPA in epilepsy, migraine, and BD is due to a combination of the biochemical mechanisms and its effects at a genomic level [218].

Side Effects

The most common side effects of VPA are gastrointestinal symptoms (nausea, vomiting, and heartburn) [209], while less frequent are dermatological effects (rash, alopecia) and neurological effects (drowsiness, irritability and ataxia) [219].

Moreover, being a potent teratogen, VPA is associated with significantly increased risk of fetal abnormalities (in particular spina bifida aperta); this risk is reduced with lower doses and serum levels, as well as with monotherapy and supplementary folic acid [211].

The most severe events occurring with VPA treatment, albeit extremely rare and idiosyncratic, are frequently fatal idiopathic hepatitis [220] and hemorrhagic pancreatitis [221, 222].

Pharmacokinetics and Interactions

VPA presents good bioavailability after oral administration (between 96 and 100%) [211] and peak serum concentration occurs approximately 1–3 h after administration [219]. Therapeutic plasma levels are usually reported in the 50-100 μg/mL range [223].

Protein binding is considerable; the free fraction of VPA in human plasma has been reported to be between 7% and 37% [224].

Hepatic metabolism is relevant, mainly by glucuronidation, but also by a variety of complex pathways, in particular by β-oxidation [225]. It has been shown in animal models that several of the metabolites formed by β-oxidation present anticonvulsant activity, even though most probably their pharmacological activity is limited due to their low brain concentrations [226]. Valproate inhibits the metabolism of

lamotrigine which may result in serious toxic reactions. Interactions with co-administered drugs are variable and unpredictable, thus plasma monitoring becomes advisable, especially in case of polypharmacy. In any case, caution is recommended when administering VPA with other drugs such as warfarin or aspirin, which can interfere with blood clotting [209].

Methods of Analysis

From an analytical point of view, the determination of VPA presents some difficulties, due to the fact that the molecule neither significantly absorbs the UV light nor is fluorescent. For this reason, analysis is mainly carried out after a derivatization step, or using an indirect detection method.

HPLC has been widely employed for VPA analysis in biological fluids, using MS [227, 228], fluorescence [229-232] and UV [224, 233-235] detection or both diode-array and fluorescence detection [236]. As mentioned above, derivatization prior to analysis is often employed in order to overcome detection problems [224, 227, 229-232, 235, 236]. The sample pre-treatment procedures often consist in liquid-liquid extraction with organic solvents [227, 229, 230, 233], while one paper reports the use of a protein precipitation procedure with acetonitrile [235]; recently, a solid-phase extraction procedure using hydrophilic-lipophilic balance cartridges has been developed [228]. One recent paper determines the VPA metabolite 2-propyl-4-pentenoic acid together with the parent compound in plasma samples obtained from patients [227]. Some papers also report the determination of the free fraction of the drug [224, 232, 236].

Capillary electrophoresis has also been employed for the analysis of VPA for therapeutic drug monitoring purposes. The lower sensitivity of capillary electrophoresis, compared to HPLC methodologies, does not represent a problem for the analysis of VPA, given that therapeutic plasma levels are in the μg/mL range. Direct UV detection is not possible, therefore one paper reports a method based on contactless conductivity detection [237], while two other methods make use of indirect fluorescence [238] (even if the authors report that the application to serum samples was still problematic due to matrix interference) and UV [239] detection. In particular, this method [239] makes use of a benzoate buffer as the background electrolyte, containing cetyltrimethylammonium bromide in order to obtain an anionic electro-osmotic flow and a faster (an electrophoretic run lasts 3 minutes) and efficient analysis, while the sensitivity obtained (limit of quantitation corresponding to 450 ng/mL) is appropriate for therapeutic drug monitoring. A representative electropherogram is reported in Fig. (**8**). It corresponds to the analysis of a sample obtained from a patient treated with VPA (1g/day); VPA concentration reported corresponds to 48 μg/mL.

All the methods reported in literature make use of a sample pre-treatment procedure consisting in protein precipitation with acetonitrile [237, 238] or methanol [239].

Gas-chromatography has also been employed for VPA analysis. Different biological matrices have been examined, including plasma [240-243], serum [244], urine [245] and tears [246]. Derivatization is required in order to make VPA accessible to GC-analysis. An interesting recent paper reports a sample pre-treatment consisting in a water-phase derivatization step following a headspace solid-phase microextraction (HS-SPME) procedure; analysis is then carried out by GC-MS [243].

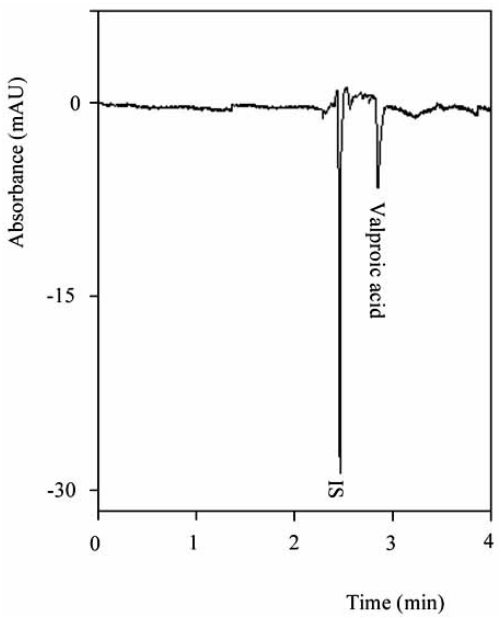


Fig. (8). Electropherogram of a plasma sample from a patient treated with valproic acid (1 g/day). Electrophoretic conditions: uncoated fused silica capillaries (effective length: 8.5 cm); BGE composition: 15 mM benzoate buffer (pH 6.0), containing and CTAB (0.5 mM) and methanol (25%, v/v); capillary temperature: 25°C; separation voltage: –30 kV; indirect UV detection: 210 ± 20 nm.

OXCARBAZEPINE

Oxcarbazepine (10,11-dihydro-10-oxo-5H-dibenzo[b,f] azepine-5-carboxamide, OXCBZ, Fig. (**6c**)) is a relatively new drug which is used as an antiepileptic agent for the treatment of partial seizures and generalized tonic-clonic seizures [247, 248] as well as for bipolar affective disorders [249]. It is structurally related to well-established antiepileptic drug carbamazepine (5H-dibenzo[b,f]azepine-5-carboxamide) of which it is a keto-derivative [250] and shows a similar action.

Oxcarbazepine is administered orally as coated tablets (Trileptal®, Tolep® in Italy) containing 300-600 mg of the drug. The usual daily doses range from 300 to 2700 mg for the treatment of seizures [251] and 600-2400 for BD [252].

Mechanism of Action

The exact mechanism of action of the active species of OXCBZ is currently unknown, especially for BD. However electrophysiological studies evidenced that it blocks voltage-dependent sodium channels and consequently stabilizes excitable membranes. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels could contribute to the antiepileptic action [253, 254].

Pharmacokinetics and Interactions

OXCBZ is well absorbed from the gastrointestinal tract. It is reduced rapidly after oral absorption to its therapeutically active metabolite 10,11-dihydro-10-hydroxy-5H-dibenzo [b,f]azepine-5-carboxamide (CBZ-10OH, Fig. (**7**)) that exhibits efficacy comparable to the parent drug [255, 256].

Oxcarbazepine plasma levels result in the hundreds of nanograms per milliliter range while its metabolite CBZ-10OH plasma levels are in the tens of micrograms per milliliter range [257]. Consequently, CBZ-10OH represents the main active compound during chronic OXCBZ therapy.

This metabolic pathway probably depends on a non-inducible aldo-keto-reductase [258]. Approximately 40% of CBZ-10OH is bound to serum proteins, predominantly to albumin. OXCBZ and CBZ-10OH do not bind to α1-acid glycoprotein. CBZ-10OH is mainly eliminated into the urine after glucuronidation [259, 260]. Both OXCBZ and CBZ-10OH showed anticonvulsant efficacy similar to carbamazepine in standard animal seizure models [261]. A small percentage of CBZ-10OH is metabolized to trans-10,11-dihydro-10,11-dihydroxy-5H-dibenzo[b,f]azepine-5-carboxamide (CBZ-DiOH) which does not show pharmacological activity [262]. 3-hydroxycarbamazepine (CBZ-3OH) has also been reported to be a minor metabolite of oxcarbazepine [260]. A scheme of the main metabolic pathways for oxcarbazepine is reported in Fig. (**9**).

Side Effects and Interactions

Although OXCBZ is usually well tolerated, adverse effects are still possible during treatment [263, 264]; its pharmaco-toxicological profile is not fully understood.

OXCBZ is often used for patients who are intolerant to carbamazepine treatment, because it seems to be safer and less prone to cause severe side effects. In fact, although OXCBZ tends to cause clinical side effects similar to those of carbamazepine (such as diplopia, ataxia, somnolence, equilibrium impairment), their incidence and severity are reduced [265, 266]. Idiosyncratic reactions seem to be less common with OXCBZ than with carbamazepine [263]. Other most common side effects are dizziness, headache and abdominal complaints, whereas a more serious side effect is hyponatremia [267]. OXCBZ is relatively free of clinically relevant drug interactions [268], thus facilitating its use during polypharmacy. Strong inducers of cytochrome P450 enzymes (i.e., carbamazepine, phenytoin and phenobarbital) have been shown to decrease the plasma levels of CBZ-10OH (29%-40%) [269].

Methods of Analysis

Several papers deal with the determination of OXCBZ and its metabolites or other CNS drugs in human plasma [270-283], saliva [284-286] and urine [287, 288] from epileptic patients. Currently, HPLC with UV detector is much more widespread [271-276, 278, 280, 281, 283-288]; other papers used HPLC coupled with mass spectrometry [270] or diode array detection (DAD) [279, 282]. One paper demonstrates the separation of OXCBZ and its metabolites from biological sample by means of capillary electrokinetic chromatography (MEKC) [289]. The pre-treatment of biological

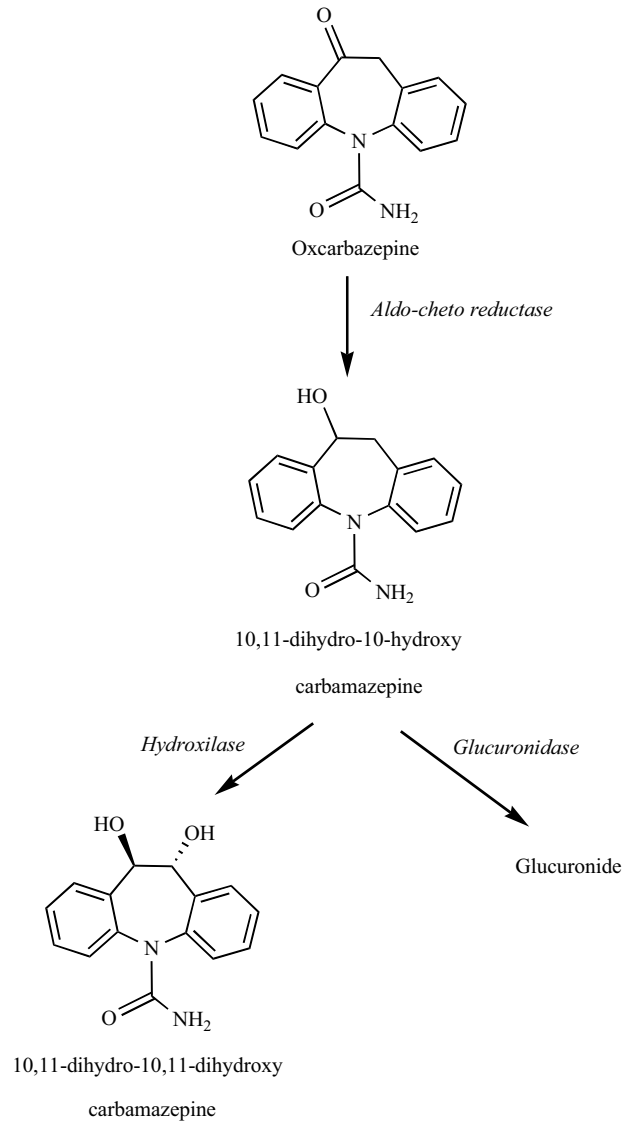


Fig. (9). Main metabolic pathways of oxcarbazepine.

samples is usually carried out by means of solid phase extraction (SPE) [274, 276, 278-280, 289], liquid-liquid extraction (LLE) [270, 271, 273] and deproteinization [272, 275, 276, 284, 285] procedures.

Recently, a fast and reliable method [290] has been developed for the simultaneous determination of OXCBZ together with its metabolites in plasma and saliva samples drawn from bipolar patients undergoing treatment with OXCBZ, using HPLC with a diode array detector. The sample pre-treatment consists in a novel micro-extraction by packed sorbent (MEPS) procedure. A representative chromatogram corresponding to the analysis of a plasma sample obtained from a bipolar patient treated with OXCBZ (900 mg/day) together with lithium, duloxetine and lorazepam is reported in Fig. (**10a**), while a chromatogram corresponding to the analysis of a saliva sample obtained from the same bipolar patient is reported in Fig. (**10b**). Plasma and saliva levels found correspond to 14.0 μg/mL and 12.0 μg/mL for CBZ-10OH, 2.05 μg/mL and 2.15 μg/mL for CBZ-DiOH, 0.158 μg/mL and 0.109 μg/mL for OXCBZ, respectively.

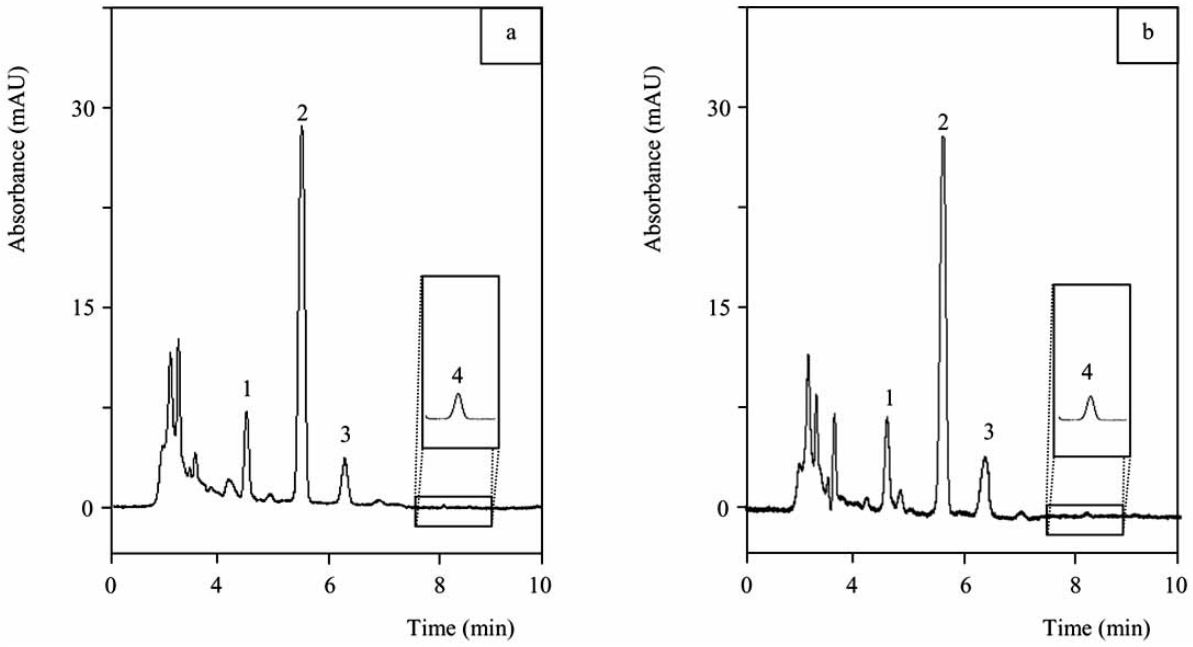


Fig. (10). Chromatogram of a plasma sample from a bipolar patient who received 900 mg/day of oxcarbazepine (**a**) and of a saliva sample from the same bipolar patient (**b**). Chromatographic conditions: stationary phase, C18 reversed-phase column (150 x 4.6 mm i.d., 5 µm); mobile phase, acetonitrile / 10.2 mM, pH 3.0 phosphate buffer (28:72, v/v), containing 0.35% (v/v) triethylamine; flow rate, 1.2 mL/min; injection loop, 20 µL; detection, 240 nm. Peak legend: 1: 10,11-dihydro-10,11-dihydroxy carbamazepine; 2: 10,11-dihydro-10-hydroxy carbamazepine; 3: melatonine (IS); 4: 3-hydroxycarbamazepine; 5: Oxcarbazepine.

CONCLUDING REMARKS

Bipolar patients usually require multiple classes of medications over the course of their lifetime and during any specific episode of the illness, because of the complex nature of BD symptoms. Atypical antipsychotics and antiepileptic agents, used as mood stabilizers, have substantially improved the treatment of bipolar disorders. In light of the increasing use of polypharmacy in the treatment of BD it is crucial to minimize the potential risk for drug interactions. Thus, it is important to carry out a reliable TDM of bipolar patients, in order to enhance their compliance to treatment and decrease the incidence of side effects and hospitalization. The present review focused on some atypical antipsychotic drugs and antiepileptic agents, which have been recently introduced in the treatment of bipolar disorder; usually, these drugs are administered in polypharmacy (together with Lithium and other drugs). Plasma concentration measurements of atypical antipsychotic drugs and antiepileptic agents could be carried out, especially when used at high dosage and in patients subjected to polypharmacy. Daily dose, analytical methods and therapeutic level ranges have been reported for selected drugs for BD.

Particular attention was given to the atypical antipsychotics olanzapine and quetiapine, while, among the antiepileptic agents, we have presented lamotrigine and valproic acid, which have been successfully used as mood-stabilizers.

Ongoing studies suggest the use of the atypical antipsychotic risperidone and aripiprazole in short and long-treatment of Bipolar Disorder. While risperidone is particularly effective in acute mania, aripiprazole seems to be promising in long-term treatment, usually combined with lithium or anticonvulsants.

Also the antiepileptic agent oxcarbazepine seems to be promising for the treatment of patients affected by bipolar disorder, especially in those patients with symptoms of anxiety and irritability.

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REFERENCES

[1] Kessler, R.C.; Berglund, P.; Demler, O.; Jin, R.; Merikangas, K.R.; Walters, E.E. *Arch. Gen. Psychiatry,* **2005**, *62,* 593.
[2] Szádóczky, E.; Papp, Z.; Vitrai, J.; Ríhmer, Z.; Füredi, J. *J. Affect Disord.,* **1998**, *50,* 153.
[3] Moreno, D.H.; Andrade, L.H. *J. Affect Disord.,* **2005**, *87,* 231.
[4] American Psychiatric Association. *Am. J. Psychiat.*, **2002**, *159,* 1.
[5] Sharma, R.; Markar, H.R. *J. Affect Disord.*, **1994**, *31*, 91.
[6] Goodwin, F.; Jamison, K. *Manic Depressive Illness*, Oxford University Press: New York, **2007**.
[7] Koukopoulos, A. In *Bipolar Psychopharmacotherapy: Caring for the Patient*; Akiskal, H. and Tohen, M. Eds.; John Wiley and Sons: New York, **2006**.
[8] Brøsen, K. *Ther. Drug Monit.,* **1996**, *18,* 393.
[9] Caccia, S. *Curr. Opin. Investig. Drugs*, **2002**, *3*, 1073.
[10] Linnet, C. *Hum. Psychopharm.*, **2002**, *17*, 233.
[11] Raggi, M.A.; Mandrioli, R.; Pucci, V.; Sabbioni, C. *Med. Chem. Rev.*, **2004**, 1, 299.
[12] Albers, L.J.; Ozdemir, V. *Curr. Med. Chem.*, **2004**, *11*, 297.
[13] Mitchell, P.B. *Br. J. Clin. Pharmacol.,* **2001**, *52,* 45.

[14] Fraser, A.D. In *Analytical Toxicology for Clinical, Forensic and Pharmaceutical Chemists,* Brandenberger, H.; Maes, R.A.A., Eds.; Walter de Gruyter: Berlin / New York, **1997**; pp. 17-25.
[15] Cramer, J.A.; Rosenheck, R. *Psychiatr. Serv.*, **1998**, *49*, 196.
[16] Xing, Q.; Qian, X.; Li, H.; Wong, S.; Wu, S.; Feng, G.; Duan, S.; Xu, M.; Gao, R.; Qin, W.; Gao, J.; Meng, J.; He, L. *Int. J. Neuropsychopharmacol.*, **2007**, *10,* 631.
[17] Perry, P.J.; Lund, B.C.; Sanger, T.; Beasley, C. *J. Clin. Psychopharmacol.*, **2001**, *21,* 14.
[18] Eilers, R. *Clin. Pharmacokinet.*, **1995**, *29,* 442.
[19] Hiemke, C. *Eur. Arch. Psy. Clin. N.*, **2008**, *258*-S1, 21.
[20] Calabrese, J.R.; Keck, P.E. Jr; Macfadden, W.; Minkwitz, M.; Ketter, T.A.; Weisler, R.H.; Cutler, A.J.; McCoy, R.; Wilson, E; Mullen, J. *Am. J. Psychiat.,* **2005**, *162*, 1351.
[21] Thase, M.E.; Macfadden, W.; Weisler, R.H.; Chang, W.; Paulsson, B.; Khan, A.; Calabrese, J.R.; BOLDER II Study Group. *J. Clin. Psychopharmacol.*, **2006**, *26*, 600.
[22] Astrazeneca press release. Available from URL: http://www.astrazeneca.com/pressrelease/1160.aspx [Accessed on Apr 21, 2008]
[23] Keating, G.M.; Robinson, D.M. *CNS Drugs*, **2007**, *21*, 695.
[24] Peuskens, J. *Eur. Neuropsychopharm.*, **2004**, *14*, S453.
[25] Astrazeneca press release. Available from URL: http://www.astrazeneca.com/pressrelease/5330.aspx [Accessed on Apr 21, 2008]
[26] Riedel, M.; Mueller, N.; Strassnig, M.; Spellman, I.; Severus, E.; Moeller, H.J. *Neurop. Dis. Treat.,* **2007**, *3*, 219.
[27] Nemeroff, C.B.; Kinkead, B.; Goldstein, J. *J. Clin. Psychiat.*, **2002**, *63*, 5.
[28] Richelson, E.; Souder, T. *Life Sci.*, **2000**, *68*, 29.
[29] Goldstein, J.M. *Drugs Today*, **1999**, *35*, 193.
[30] Yatham, L.N.; Goldstein, J.M.; Vieta, E.; Bowden, C.L.; Grunze, H.; Post, R.M.; Suppes, T.; Calabrese. J.R.; *J. Clin. Psychiat.*, **2005**, *66*, 40.
[31] Goldstein, J.M.; Christoph, G.; Grimm, S.; Liu, J.W.; Widzowski, D.; Brecher, M. Unique mechanism of action for the antidepressant properties of the atypical antipsychotic quetiapine. *20th European College of Neuropsychopharmacology Congress, Vienna, October 13–17,* **2007**.
[32] Jensen, N.H.; Rodriguiz, R.M.; Caron, M.G.; Wetsel, W.C.; Rothman, R.B.; Roth. B.L. *Neuropsychopharmacol.*, **2008**, *33*, 2303.
[33] Dunner, D.L. *Bipolar Disord.* **2005**, *7*, 307.
[34] Keating, G.M.; Robinson, D.M. *Drugs*, **2007**, *67*, 1077.
[35] Adler, C.; Fleck, D.; Brecher, M.; Strakowski, S. *J. Affect. Disord.*, **2007**, 100, S15.
[36] *Martindale – The Complete Drug Reference*, 34th Edition, Sweetman, S.C., Ed., Pharmaceutical Press: London, **2004**; p. 718.
[37] Guo, J.J.; Keck, P.E. Jr.; Corey-Lisle, P.K.; Li, H.; Jiang, D.; Jang, R.; L'Italien, G.J. *Pharmacotherapy*, **2007**, *27*, 27.
[38] Pollak, P.; Zbuk, K. *Clin. Pharmacol. Ther.*, **2000**, *68*, 92.
[39] Shahzad, S.; Suleman, M.I.; Shahab, H.; Mazour, I.; Kaur, A.; Rudzinskiy, P.; Lippmann, S.; *Psychosomatics*, **2002**, *43*, 354.
[40] AstraZeneca. Seroquel® (quetiapine fumarate) tablets: prescribing information. Available from URL: http://www.seroquel.com [Accessed Apr 21, 2008]
[41] Valibhai, F. ; Phan, N.B.; Still, D.J.; True, J. *Am. J. Psychiatry*, **2001**, *158,* 966.
[42] DeVane, C.L.; Nemeroff, C.B. *Clin. Pharmacokinet.*, **2001**, *40*, 509.
[43] Caccia, S. *Clin. Pharmacokinet.*, **2000**, *38*, 393.
[44] Raggi, M.A.; Mandrioli, R.; Sabbioni, C.; Pucci, V. *Curr. Med. Chem.,* **2004**, *11*, 279.
[45] Grimm, S.W.; Richtand, N.M.; Winter, H.R.; Stams, K.R.; Reele, S.B. *Brit. J. Clin. Pharmaco.*, **2005**, *61*, 58.
[46] Castberg, I.; Skogvoll, E.; Spigset, O. *J. Clin. Psychiat.*, **2007**, *68*, 1540.
[47] Wong, Y.W.J.; Yeh, C.; Thyrum, P.T. *J. Clin. Psychopharmacol.*, **2001**, *21*, 89.
[48] Fitzgerald, B.J.; Okos, A.J. *Pharmacotherapy*, **2002**, *22*, 1500.
[49] Aichhorna, W.; Marksteinera, J.; Walcha, T.; Zernigb, G.; Sariab, A.; Kemmlera, G. *Int. Clin. Psychopharm.*, **2006**, *21*, 81.
[50] Winter, H.R.; DeVane, C.L.; Figueroa, C.; Ennis, D.J.; Hamer-Maansson, J.E.; Davis, P.C.; Smith, M.A. *Hum. Psychopharmacol.*, **2007**, *22*, 469.
[51] Winter, H.R.; Earley, W.R.; Hamer-Maansson, J.E.; Davis, P.C.; Smith, M.A.; *J. Child Adol. Psychop.*, **2008**, *18*, 81.
[52] Parker, D.R.; McIntyre, I.M. *J. Anal. Toxicol.*, **2005**, *29*, 407.
[53] Belal, F.; Elbrashy, A.; Eid, M.; Nasr, J.J. *J. Liq. Chromatogr. R. T.*, **2008**, *31*, 1283.
[54] Rampono, J.; Kristensen, J.H.; Ilett, K.; Hackett, L.P.; Kohan, R. *Ann. Pharmacother.*, **2007**, *41*, 711.
[55] Mercolini, L.; Grillo, M.; Bartoletti, C.; Boncompagni, G.; Raggi, M.A. *Anal. Bioanal. Chem.*, **2007**, *388*, 235.
[56] Saracino, M.A.; Mercolini, L.; Flotta, G.; Albers, L.J.; Merli, R.; Raggi, M.A. *J. Chromatogr. B*, **2006**, *843*, 227.
[57] Sachse, J.; Koeller, J.; Haertter, S.; Hiemke, C. *J. Chromatogr. B*, **2006**, *830*, 342.
[58] Frahnert, C.; Rao, M.L.; Grasmader, K. *J. Chromatogr. B*, **2003**, *794*, 35.
[59] Mandrioli, R.; Fanali, S.; Ferranti, A.; Raggi, M.A. J. Pharmaceut. Biomed., **2002**, *30*, 969.
[60] Barrett, B.; Holcapek, M.; Huclova, J.; Borek-Dohalsky, V.; Fejt, P.; Nemec, B.; Jelinek, I. *J. Pharmaceut. Biomed.*, **2007**, *44*, 498.
[61] Lin, S.N.; Chang, Y.; Moody, D.E.; Foltz, R.L. *J. Anal. Toxicol.*, **2004**, *28*, 443.
[62] Li, K.Y.; Li, X.; Cheng, Z.N.; Peng, W.X.; Zhang, B.K.; Li, H.D. *Acta Pharmacol. Sin.*, **2004**, *25*, 390.
[63] Zhou, Z.; Li, X.; Li, K.; Xie, Z.; Cheng, Z.; Peng, W.; Wang, F.; Zhu, R.; Li, H. *J. Chromatogr. B*, **2004**, *802*, 257.
[64] Li, K.Y.; Cheng, Z.N.; Li, X.; Bai, X.L.; Zhang, B.K.; Wang, F.; Li, H.D. *Acta Pharmacol. Sin.*, **2004**, *25*, 110.
[65] Kirchherr, H.; Kuehn-Velten, W. N. *J. Chromatogr. B*, **2006**, *843*, 100.
[66] Davis, P.C.; Wong, J.; Gefvert, O. *J. Pharmaceut. Biomed.*, **1999**, *20*, 271.
[67] Anderson, D.T.; Fritz, L.K. *J. Anal. Toxicol.*, **2000**, *24*, 300.
[68] Flammia, D.D.; Valouch, T.; Venuti, S. *J. Anal. Toxicol.*, **2006**, *30*, 287.
[69] Wise, S.; Jenkins, A.J. *J. Forensic Sci.*, **2005**, 50, 209.
[70] Pullen, R.H.; Palermo, K.M.; Curtis, M.A. *J. Chromatogr.*, **1992**, *573*, 49.
[71] Pucci, V.; Mandrioli, R.; Ferranti, A.; Furlanetto, S.; Raggi, M.A. *J. Pharmaceut. Biomed.*, **2003**, *32*, 1037.
[72] Conley, R.R. Kelly, D.L. *Med. Chem. Rev.*, **2005**, *2*, 177.
[73] *Martindale – The Complete Drug Reference*, 34th Edition, Sweetman, S.C., Ed., Pharmaceutical Press: London, **2004**; p. 710.
[74] Lilly®: Facts About Zyprexa® (olanzapine) Available from URL: http://www.lilly.com/news/pdf/zyprexa_factsheet_final_110707.pdf [Accessed on May 13, 2008]
[75] Mitchell, M.; Riesenberg, R.; Bari, M.A.; Marquez, E.; Kurtz, D.; Falk, D.; Hardy, T.; Taylor, C.C.; Mitchell, C.P.; Cavazzoni, P. *Clin. Ther.*, **2006**, *28*, 881.
[76] Lilly. ZYPREXA® (Olanzapine Tablets), ZYPREXA® ZYDIS® (Olanzapine Orally Disintegrating Tablets), ZYPREXA® (Intra-Muscular Olanzapine for Injection). Available from URL: http://pi.lilly.com/us/zyprexa-pi.pdf [Accessed on Jun 25, 2008]
[77] Bymaster, F.P.; Calligaro, D.O.; Falcone, J.F. *Neuropsychopharmacol.*, **1996**, *14*, 87.
[78] Capuano, B.; Crosby, I.T.; Lloyd, E.J.; Taylor, D.A. *Aust. J. Chem.*, **2002**, *55*, 565.
[79] Raggi, M.A. *Curr. Med. Chem.*, **2002**, *9*, 1397.
[80] Bonanno, D.G.; Davydov, L.; Botts, S.R. *Ann. Pharmacother.*, **2001**, *35*, 563.
[81] Callaghan, J.T.; Bergstrom, R.F.; Ptak, L.R.; Beasley, C.M. *Clin. Pharmacokinet.*, **1999**, *37*, 177.
[82] Calligaro, D.O.; Fairhurst, J.; Hotten, T.M.; Moore, N.A.; Tupper, D.E. *Bioorg. Med. Chem. Lett.*, **1997**, *7,* 25.
[83] Carrillo, J.A.; Herraiz, A.G.; Ramos, S.I.; Gervasini, G.; Vizcaino, S.; Benitez, J. *J. Clin. Psychopharmacol.*, **2003**, *23,* 119.
[84] Albers, L.J.; Ozdemir, V.; Marder, S.R.; Raggi, M.A.; Aravagiri, M.; Endrenyi, L.; Reist, C. *J. Clin. Psychopharmacol.*, **2005**, *25*, 170.
[85] Olesen, O.V.; Linnet, K. *Ther. Drug Monit.*, **1999**, *21*, 87.
[86] Robertson, M.D.; Mc Mullin, M.M. *J. Forensic Sci.*, **2000**, *45*, 418.
[87] Dusci, L.J.; Hackett, L.P.; Fellows, L.M.; Ilett, K.F. *J. Chromatogr. B.*, **2002**, *773*, 191.
[88] D'Arrigo, C.; Migliardi, G.; Santoro, V.; Spina, E. *Ther. Drug Monit.*, **2006**, *28*, 388.

[89] Jasinska, A.; Starczewska, B.; Polkowska, M.; Puzanowska-Tarasiewicz, H. *Anal. Lett.,* **2005**, *38*, 815.
[90] Boulton, D.W.; Markowitz, J.S.; DeVane, C.L. *J. Chromatogr. B*., **2001**, *759*, 319.
[91] Olesen, O.V.; Linnet, K. *J. Chromatogr. B*, **1998**, *714*, 309.
[92] Llorca, P.M.; Coudore, F.; Corpelet, C.; Buyens, A.; Hoareau, M.; Eschalier, A. *Clin. Chem*., **2001**, *47*, 1719.
[93] Zhang, G.; Terry, A.V. Jr.; Bartlett, M.G. *J. Chromatogr. B*, **2007**, *858*, 276.
[94] Nirogi, R.V.S.; Kandikere, V.N.; Shukla, M.; Mudigonda, K.; Maurya, S.; Boosi, R.; Yerramilli, A. *J. Pharmaceut. Biomed*., **2006**, *41*, 935.
[95] Zhou, Z.; Li, X.; Li, K.; Xie, Z.; Cheng, P.W.; Wang, F.; Zhu, R.; Li, H. *J. Chromatogr. B*, **2004**, *802*, 257.
[96] Gervasini, G.; Vizcaino, S.; Herraiz, A.G.; Benitez, J.; Carrillo, J.A. *Clin. Chem*., **2003**, *49*, 2088.
[97] Kollroser, M.; Schober, C. *Rapid. Commun. Mass Sp.*, **2002**, *6*, 1266.
[98] Berna, M.; Ackermann, B.; Ruterbories, K.; Glass, S. *J. Chromatogr. B*., **2002**, *767*, 163.
[99] Bogusz, M.J.; Kruger, K.D.; Maier, R.D.; Erkwoh, R.; Tuchtenhagen, F. *J. Chromatogr. B*., **1999**, *732*, 257.
[100] Berna, M.; Shugert, R.; Mullen, J, *J. Mass Spectrom*., **1998**, *33*, 1003.
[101] Catlow, J.T.; Barton, R.D.; Clemens, M.; Gillespie, T.A.; Goodwin, M.; Swanson, S.P. *J. Chromatogr. B*, **1995**, *668*, 85.
[102] Aravagiri, M.; Ames, D.; Wirshing, W.C.; Marder, S.R. *Ther. Drug Monit.*, **1997**, *19*, 307.
[103] Raggi, M.A.; Casamenti, G., Mandrioli, R.; Volterra, V. *J. Chromatogr. B,* **2001**, *750*, 137.
[104] Raggi, M.A.; Mandrioli, R., Sabbioni, C., Ghedini, N.; Fanali, S.; Volterra, V. *Chromatographia*, **2001**, *54*, 203.
[105] Theisen, F.M.; Haberhausen, M.; Schulz, E.; Fleischhaker, C.; Clement, H-W.; Heinzel-Gutenbrunner, M.; Remschmidt, H. *Ther. Drug Monit*., **2006**, *28*, 750.
[106] Sabbioni, C.; Saracino, M.A.; Mandrioli, R.; Albers, L.; Boncompagni, G.; Raggi, M.A. *Anal. Chim. Acta*. **2004**, *516*, 111.
[107] Saracino, M.A.; Koukopoulos, A.; Sani, G.; Amore, M.; Raggi, M.A. *Ther. Drug Monit.*, **2007**, *6*, 773.
[108] Ulrich, S. *Ther. Drug Monit.*, **2005**, *27*, 463.
[109] McElroy, S.L.; Keck, P.E. Jr. *Biol. Psychiat.,* **2000,** *48,* 539.
[110] Tohen, M.; Zarate, C.A. Jr. *J. Clin. Psychiat.,* **1998,** *59,* 38.
[111] Raggi, M.A. *Curr. Med. Chem.,* **2002**, *9,* 1397.
[112] U.S. Food and Drug Administration. Available from URL: http://www.fda.gov/CDER/DRUG/infopage/antipsychotics/default.htm [Accessed on July 02, 2008]
[113] Gutierrez, R.; Lee, P.I.D.; Huang, M.-L.; Woestenborghs, R.; *Pharmacotherapy,* **1997,** *17,* 599.
[114] Janssen. RISPERDAL® (Risperidone Tablets/Oral Solution), RISPERDAL® M-TAB™ (Risperidone Orally Disintegrating Tablets). Available from URL: http://www.janssen.com/janssen/shared/pi/risperdal.pdf. [Accessed on July 02, 2008]
[115] Schotte, A.; Janssen, P.F.M.; Gommeren, W.; Luyten, W.H.M.L.; Van Gompel, P.; Lesage, A.S.; De Loore, K.; Leysen, J.E. *Psychopharmacol.,* **1996,** *124,* 57.
[116] Megens, A.A.H.P.; Awouters, F.H.L.; Schotte, A.; Meert, T.F.; Dugovic, C.; Niemegeers, C.J.E.; Leysen, J.E. *Psychopharmacol.,* **1994,** *114*, 9.
[117] Yoon, D.J. *Clin. Psychopharmacol. Neurosci*., **2003**, *1*, 147.
[118] Knable, M.B.; Heinz, A.; Raedler, T.; Weinberger, D.R. *Psychiat. Res.,* **1997,** *75,* 91.
[119] Brunelleschi, S.; Zeppegno, P.; Risso, F.; Cattaneo, C.I.; Torre, E. *Pharmacol. Res.,* **2003,** *48*, 405.
[120] *Martindale – The Complete Drug Reference*, 34th Edition, Sweetman, S.C., Ed., Pharmaceutical Press: London, **2005**; p. 719.
[121] Yerrabolu, M.; Prabhudesai, S.; Tawam, M.; Winter, L.; Kamalesh, M. *Heart Dis.,* **2000,** *2,* 10.
[122] Acri, A.A.; Henretig, F.M. *Am. J. Emerg. Med.,* **1998,** *16,* 498.
[123] Cheslik, T.A.; Erramouspe, J.; *Ann. Pharmacother.,* **1996,** *30,* 360.
[124] Borison, R.L.; Diamond, B.; Pathiraja, A.; Meibach, R.C.*Psychopharmacol. Bull.,* **1994**, *30,* 193.
[125] Mannens, G.; Meuldermans, W.; Snoeck, E.; Heykants, J. *Psychopharmacology,* **1994,** *114,* 566.
[126] Foroutan, S.M.; Zarghi, A.; Shafaati, A.; Khoddam, A. *Iranian J. Pharm. Res.,* **2006**, *5*, 37.
[127] LLerena, A.; Berecz, R.; Dorado, P.; Sanz de la Garza, C.; Norberto, M.J.; Caceres, M.; Gutierrez, J.R. *J. Chromatogr. B*, **2003**, *783*, 213.
[128] Avenoso, A.; Facciolà, G.; Salemi, M.; Spina, E. *J. Chromatogr. B,* **2000**, *746,* 173.
[129] Nagasaki, T.; Ohkubo, T.; Sugawara, K.; Yasui, N.; Furukori, H.; Kaneko, S. *J. Pharmaceut. Biomed.,* **1999**, *19,* 595.
[130] Olesen, O.V.; Linnet, K. *J. Chromatogr. B,* **1998**, *714,* 309.
[131] Olesen, O.V.; Linnet, K. *J. Chromatogr. B,* **1997**, *698,* 209.
[132] Shen, Y. L.; Wu, H. L.; Ko, W. K.; Wu, S. M. *Anal. Chim. Acta*, **2002**, *460*, 201.
[133] Raggi, M.A.; Bugamelli, F.; Sabbioni, C.; Saracino, M.A.; Petio, C. *J. Sep. Sci*., **2005**, *28*, 245.
[134] Balant-Gorgia, A.E.; Gex-Fabry, M.; Genet, C.; Balant, L.P. *Ther. Drug Monit.,* **1999**, *21,* 105.
[135] Aravagiri, M.; Marder, S.R.; Van Putten, T.; Midha, K.K. *J. Pharm. Sci.,* **1993**, *82,* 447.
[136] Aravagiri, M.; Marder, S.R.; Wirshing, D.; Wirshing, W.C. *Pharmacopsychiatry,* **1998**, *31,* 102.
[137] Le Moing, J.P.; Edouard, S.; Levron, J.C. *J. Chromatogr. B,* **1993**, *614,* 333.
[138] Schatz, D.S.; Saria, A. *Pharmacology,* **2000**, *60,* 51.
[139] Aravagiri, M.; Marder, S.R. *J. Mass Spectrom.,* **2000**, *35,* 718.
[140] McClean, S.; O'Kane, E.J.; Smyth, W.F. *J. Chromatogr. B,* **2000**, *740,* 141.
[141] Moody, D.E.; Laycock, J.D.; Huang, W.; Foltz, R.L., *J. Anal. Toxicol*., **2004**, *28*, 494.
[142] Zhang, L.; Jiao, Z.; Yao, Z.; Zhong, Y.; Zhong, M.; Yu, Y. *Chromatographia*, **2005**, *61*, 245.
[143] Bhatt, J.; Subbaiah, G.; Singh, S. *Rapid Commun. Mass Sp*., **2006**, *20*, 2109.
[144] Zhang, G.; Terry, A.V.Jr.; Bartlett, M.G. *Rapid Commun. Mass Sp*., **2007**, *21*, 920.
[145] Cabovska, B.; Cox, S. L.; Vinks, A. A. *J. Chromatogr. B,* **2007**, *852*, 497.
[146] Bristol-Myers Squibb Company press release. Available from URL: http://newsroom.bms.com/article_display.cfm?article_id=5324 [Accessed on Jul 1, 2008]
[147] Company press release. Available from URL: http://newsroom.bms.com/article_display.cfm?article_id=5325 [Accessed on Jul 1, 2008]
[148] Bristol-Myers Squibb Abilify®: prescribing information. Available from URL: http://packageinserts.bms.com/pi/pi_abilify.pdf [Accessed on Jul 1, 2008]
[149] Green, B. *Curr. Med. Res. Opin*., **2004**, *20*, 207.
[150] Wood, M.; Reavill, C. *Expert Opin. Investig. Drugs*, **2007**, *16*, 771.
[151] Davies, M.A.; Sheffler, D.J.; Roth, B.L. *CNS Drug Rev*., **2004**, *10*, 317.
[152] Swainston, H.T.; Perry, C.M. *Drugs*, **2004**, *64*, 1715.
[153] Stahl, S.M. *J. Clin. Psychiat*., **2001**, *62*, 923.
[154] McIntyre, R.S.; Soczynska, J.K.; Woldeyohannes, H.O.; Miranda, A.; Konarski, J.Z. *Expert Opin. Pharmacother*., **2007**, *8*, 1001.
[155] Marder, S.R.; McQuade, R.D.; Stock, E.; Kaplita, S.; Marcus, R.; Safferman, A.Z.; Saha, A.; Ali, M.; Iwamoto, T. *Schizophr. Res*., **2003**, *61*, 123.
[156] Newcomer, J.W. *CNS Drugs*, **2005**, *19*, 1.
[157] Gao, K.; Ganocy, S.J.; Gajwani, P.; Muzina, D.J.; Kemp, D.E.; Calabrese, J.R. *J. Clin. Psychiatry*, **2008**, *69*, 302.
[158] Urichuk, L.; Prior, T.I.; Dursun, S.; Baker, G. *Curr. Drug Metab*., **2008**, *9*, 410.
[159] Citrome, L.; Macher, J.P.; Salazar, D.E.; Mallikaarjun, S.; Boulton, D.W. *J. Clin. Psychopharmacol*., **2007**, *27*, 279.
[160] Molden, E.; Lunde, H.; Lunder, N.; Refsum, H. *Ther. Drug Monit*., **2006**, *28*, 744.
[161] Kubo, M.; Mizooku, Y.; Hirao, Y.; Osumi, T. *J. Chromatogr. B*, **2005**, *822*, 294.
[162] Zuo, X.C.; Wang, F.; Xu, P.; Zhu, R.H.; Li, H.D. *Chromatographia*, **2006**, *64*, 387.
[163] Kirchherr, H.; Kuehn-Velten, W.N. *J. Chromatogr. B*, **2006**, *843*, 100.

[164] Kirschbaum, K.M.; Mueller, M.J.; Zernig, G.; Saria, A.; Mobascher, A.; Malevani, J.; Hiemke, C. *Clin. Chem*., **2005**, *51*, 1718.
[165] Huang, H.H.; Liu, C.H.; Lan, T.H.; Hu, T.M.; Chiu, H.J.; Wu, Y.C.; Tseng, Y.L. *J. Chromatogr. B*, **2007**, *856*, 57.
[166] Musenga, A.; Saracino, M.A.; Spinelli, D.; Rizzato, E.; Boncompagni, G.; Kenndler, E.; Raggi, M.A. *Anal. Chim. Acta*, **2008**, *612*, 204.
[167] Bartoli, A.; Guerrini, R.; Belmonte, A.; Alessandri, M.G.; Gatti, G.; Perucca, E. *Ther. Drug Monit.*, **1997**, *19*, 252.
[168] Lamictal®: Prescribing information. Available from URL: http://us.gsk.com/products/assets/us_lamictal.pdf [Accessed June 13, 2008]
[169] Ketter, T.A.; Post, R.M.; Theodore, W.H. *Neurology.*, **1999**, *53*, 53.
[170] American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiat*, **2002**, *159*, 1.
[171] Calabrese, J.R.; Huffman, R.F.; White, R.L.; Edwards, S.; Thompson, T.R.; Ascher, J.A.; Monaghan, E.T.; Leadbetter, R.A. *Bipolar Disord.*, **2008**, *10*, 323.
[172] *Martindale – The Complete Drug Reference*, 34th Edition, Sweetman, S.C., Ed., Pharmaceutical Press: London, **2005**; p. 363.
[173] Meldrum, B.S. *Epilepsia*, **1996**, *37*, 4.
[174] Ketter, T.A.; Manji, H.K.; Post, R.M. *J. Clin. Psychopharm*., **2003**, *23*, 484.
[175] Faught, E.; Morris, G.; Jacobson, M.; French, J.; Harden, C.; Montouris, G.; Rosenfeld, W. *Epilepsia*, **1999**, *40*, 1135.
[176] Ramsay, R.E.; Pellock, J.M.; Garnett, W.R.; Sanchez, R.M.; Valakas, A.M.; Wargin, W.A.; Lai, A.A.; Hubbell, J.; Chern, W.H.; Allsup, T. *Epilepsy Res*., **1991**, *10*, 191.
[177] Rambeck, B.; Wolf, P. *Clin. Pharmacokinet.*, **1993**, *25*, 433.
[178] Chan, V.; Morris, R.G.; Ilett, K.F.; Tett, S.E. *Ther. Drug Monitor.*, **2001**, *23*, 630.
[179] Hussein, Z.; Posner, J. *Br. J. Clin. Pharmacol.*, **1997**, *43,* 457.
[180] Patsalos, P.N. *Ann. Clin Biochem.*, **1999**, *36*, 10.
[181] Sabers, A.; Oehman, I.; Christensen, J.; Tomson, T. *Neurology*, **2003**, *61*, 570.
[182] Sidhu, J.; Job, S.; Singh, S.; Philipson, R. *Br. J. Clin. Pharmacol.*, **2006**, *61*, 191.
[183] Ohman, I.; Vitols, S.; Tomson, T. *Epilepsia*, **2000**, *41*, 709.
[184] Pennell, P.B.; Newport, D.J.; Stowe, Z.N.; Helmers, S.L.; Montgomery, J.Q.; Henry, T.R. *Neurology*, **2004**, *62*, 292.
[185] Cheng, C.L.; Chou, C.H.; Hu, O.Y.P. *J. Chromatogr. B*, **2005**, *817*, 199.
[186] Contin, M.; Balboni, M.; Callegati, E.; Candela, C.; Albani, F.; Riva, R.; Baruzzi, A. *J. Chromatogr. B*, **2005**, *828*, 113.
[187] Patil, K.; Bodhankar, S.L. *J. Pharmaceut. Biomed.*, **2005**, *39*, 181.
[188] Franceschi, L.; Furlanut, M. *Pharmacol. Res.*, **2005**, *51*, 297.
[189] Bompadre, S.; Tagliabracci, A.; Battino, M.; Giorgetti, R. *J. Chromatogr. B*, **2008**, *863*, 177.
[190] Greiner-Sosanko, E.; Lower, D.R.; Virji, M.A.; Krasowski, M.D. *Biomed. Chromatogr.*, **2007**, *21*, 225.
[191] Dumortier, G.; Pons, D.; Zerrouk, A.; Januel, D.; Saba, G.; Degrassat, K. J. *Liq. Chromatogr. R. T.*, **2001**, *24*, 3171.
[192] Frey, H.O.; Kinkeldei, J.; Quast, M. *Labor. Medizin*, **1994**, *17*, 166.
[193] Vermeij, T.A.C.; Edelbroek, P.M. *J. Chromatogr. B*, **2007**, *857*, 40.
[194] Bugamelli, F.; Sabbioni, C.; Mandrioli, R.; Kenndler, E.; Albani, F.; Raggi, M.A. *Anal. Chim. Acta*, **2002**, *472*, 1.
[195] Saracino, M.A.; Bugamelli, F.; Conti, M.; Amore, M.; Raggi, M.A. *J. Sep. Sci.*, **2007**, *30*, 2249.
[196] Beck, O.; Oehman, I.; Nordgren, H.K. *Ther. Drug Monit*., **2006**, *28*, 603.
[197] Gergov, M.; Weinmann, W.; Meriluoto, J.; Uusitalo, J.; Ojanperae, I. *Rapid Commun. Mass Sp.*, **2004**, *18*, 1039.
[198] Gergov, M.; Ojanpera, I.; Vuori, E. *J. Chromatogr. B*, **2003**, *795*, 41.
[199] Greiner-Sosanko, E.; Giannoutsos, S.; Lower, D.R.; Virji, M.A.; Krasowski, M.D. *J. Chromatogr. Sci.*, **2007**, *45*, 616.
[200] Queiroz, M.E.C.; Silva, S.M.; Carvalho, D.; Lancas, F.M. *J. Chromatogr. Sci.*, **2002**, *40*, 219.
[201] Queiroz, M.E.C.; Carrilho, E.; Carvalho, D.; Lancas, F.M. *Chromatographia*, **2001**, *53*, 485.
[202] Zheng, J.; Jann, M.W.; Hon, Y.Y.; Shamsi, S.A. *Electrophoresis*, **2004**, *25*, 2033.
[203] Theurillat, R.; Kuhn, M.; Thormann, W. *J. Chromatogr. A*, **2002**, *979*, 353.
[204] Thormann, W.; Theurillat, R.; Wind, M.; Kuldvee, R. *J. Chromatogr. A*, **2001**, *924*, 429.
[205] Pucci, V.; Bugamelli, F.; Baccini, C.; Raggi, M.A. *Electrophoresis*, **2005**, *26*, 935.
[206] Cooper, J.D.H.; Shearsby, N.J.; Taylor, J.E.; Fook Sheung, C.T.T. *J. Chromatogr. B.,* **1997**, *702*, 227.
[207] Thomas, R.H. *Psychopharmacol. Bull*., **2003**, *37*, 5.
[208] Lennkh, C.; Simhandl, C. *Int. Clin. Psychopharmacol*., **2000**, *15,* 1.
[209] *Martindale – The Complete Drug Reference*, 34th Edition, Sweetman, S.C., Ed., Pharmaceutical Press: London, **2005**; p. 380.
[210] Steering Committee. *J. Clin. Psychiatry*, **1996**, *57,* 3.
[211] Lagacea, D.C.; O'Brienb, W.T.; Gurvichb, N.; Nachtigala, M.W.; Klein, P.S. *Clin. Neurosci. Res.*, **2004**, *4*, 215.
[212] McLean, M.J.; Macdonald, R.L. *J. Pharmacol. Exp. Ther.*, 1986, *237*, 1001.
[213] Albus, H.; Williamson, R. *Epilepsia*, **1998**, *39*, 124.
[214] Macdonald, R.L.; Kelly, K.M. *Epilepsia*, **1994**, *35*, 41.
[215] Bourina, M.; Prica, C. *Neurosci. Biobehav. R.*, **2007**, *31*, 963.
[216] Löscher, W. *Prog. Neurobiol*., **1999**, *58*, 31.
[217] Manji, H.K.; Moore, G.J.; Chen, G. *Br. J. Psychiatry,* **2001**, *178*, 107.
[218] Rosenberg, G. *Cell. Mol. Life Sci.*, **2007**, *64*, 2090.
[219] Davis, R.; Peters, D.H.; McTavish, D. *Drugs*, **1994**, *47,* 332.
[220] Chang, T.K.; Abbott, F.S. *Drug Metab. Rev.*, **2006**, *38*, 627.
[221] Evans, R.J.; Miranda, R.N.; Jordan, J.; Krolikowski, F.J. *Am. J. Forensic Med. Pathol*., **1995**, *16*, 62.
[222] Gerstner, T.; Büsing, D.; Bell, N.; Longin, E.; Kasper, J.-M.; Klostermann, W.; Hebing, B.; Hanefeld, F.; Eckel, U.; Hoffmann, R.; Bettendorf, U.; Weidner, B.; Wiemer-Kruel, A.; Brockmann, K.; Neumann, F.-W.; Sandrieser, T.; Wolff, M.; König, S. *J. Gastroenterol.*, **2007**, *42*, 39.
[223] Scott, J.; Pope, M. *Am. J. Psychiat*, **2002**, 159, 1927.
[224] Liu, H.; Montoya, J.L.; Forman, L.J.; Eggers, C.M.; Barham, C.F.; Delgado, M. *Ther. Drug Monit*., **1992**, *14*, 513.
[225] Silva, M.F.B.; Aires, C.C.P.; Luis, P.M.B.; Ruiter, J.P.N.; Ijlst, L.; Duran, M.; Wanders, R.J.A.; Tavares de Almeida, I. *J. Inherit. Metab. Dis*., **2008**, *31*, 205.
[226] Loscher, W. *CNS Drugs*, **2002**, *16,* 669.
[227] Cheng, H.; Liu, Z.; Blum, W.; Byrd, J.C.; Klisovic, R.; Grever, M.R.; Marcucci, G.; Chan, K.K. *J. Chromatogr. B*, **2007**, *850*, 206.
[228] Jain, D.S.; Subbaiah, G.; Sanyal, M.; Shrivastav, P. *Talanta*, **2007**, *72*, 80.
[229] Zhong, Y.; Jiao, Z.; Yu, Y. *Biomed. Chromatogr.*, **2006**, *20*, 319.
[230] Lin, M.-C.; Kou, H.-S.; Chen, C.-C.; Wu, S.-M.; Wu, H.-L. *J. Chromatogr. B*, **2004**, *810*, 169.
[231] Rompotis, S.; Parissi-Poulou, M.; Gikas, E.; Kazanis, M.; Vavayannis, A.; Panderi, I. *J. Liq. Chromatogr. R. T.*, **2002**, *25*, 2833.
[232] Hara, S.; Kamura, M.; Inoue, K.; Fukuzawa, M.; Ono, N.; Kuroda, T. *Biol. Pharm. Bull.*, **1999**, *22*, 975.
[233] Amini, H.; Javan, M.; Ahmadiani, A. *J. Chromatography. B*, **2006**, *830*, 368.
[234] Kishore, P.; Kumar, V.; Rajani; S.V.; Krishna, D.R. *Pharmazie,* **2003**, *58*, 378.
[235] Lucarelli, C.; Villa, P.; Lombaradi, E.; Prandini, P.; Brega, A. *Chromatographia*, **1992**, *733*, 37.
[236] Liu, H.; Forman, L.J.; Montoya, J.; Eggers, C.; Barham, C.; Delgado, M. *J. Chromatogr.*, **1992**, *576*, 163.
[237] Belin, G.K.; Kraehenbuehl, S.; Hauser, P.C. *J. Chromatogr. B*, **2007**, *847*, 205.
[238] Jin, L.J.; Wang, T.; Li, S.F.Y. *Electrophoresis*, **1999**, *20*, 1856.
[239] Pucci, V.; Mandrioli, R.; Raggi, M.A. *Electrophoresis*, **2003**, *24*, 2076.
[240] Miljkovic, B.; Pokrajac, M.; Varagic, V.; Levic, Z. *Int. J. Clin. Pharm. Res*., **1991**, *11*, 137.
[241] Romanyshyn, L.A.; Wagner, M.C.; Wichmann, J.K.; Kucharczyk, N.; Sofia, R.D. *Epilepsia*, **1994**, *35*, 406.
[242] Yu, H.-Y.; Shih, M.-C. *Ther. Drug Monit*., **1996**, *18*, 107.
[243] Deng, C.; Li, N.; Ji, J.; Yang, B.; Duan, G.; Zhang, X. *Rapid Commun. Mass Sp*., **2006**, *20*, 1281.
[244] Gaetani, E.; Laureri, C.F.; Vitto, M. *J. Pharmaceut. Biomed.*, **1992**, *10*, 193.

[245] Katayama, H.; Watanabe, M.; Yoshitomi, H.; Yoshida, H.; Kimoto, H.; Kamiya, A.; Hayashi, T.; Akimura, T. *Biol. Pharm. Bull.,* **1998**, *21*, 304.
[246] Nakajima, M.; Yamato, S.; Shimada, K.; Sato, S.; Kitagawa, S.; Honda, A.; Miyamoto, J.; Shoda, J.; Ohya, M.; Miyazaki, H. *Ther. Drug Monit*., **2000**, *22*, 716.
[247] Sachdeo, R.; Beydoun, A.; Schachter, S.; Vazquez, B.; Schaul, N.; Mesenbrink, P.; Kramer, L.; D'Souza, J. *Neurology*, **2001**, *57*, 864.
[248] Beydoun, A.; Kutluay, E. *Expert Opin. Pharmacother*., **2002**, *3*, 59.
[249] Popova, E.; Leighton, C.; Bernabarre, A.; Bernardo, M.; Vieta, E. *Expert Review of Neurotherapeutics*, **2007**, *7*, 617.
[250] Tecoma, E.S. *Epilepsia*, **1999**, *40*, 37.
[251] Lloyd, P.; Flesch, G.; Dieterle, W. *Epilepsia,* **1994**, *35,* SIO.
[252] Pratoomsri, W.; Yatham, L.N.; Bond, D.J.; Lam, R.W.; Sohn, C.H. *Can. J. Psychiatry*., **2006**, *51,* 540.
[253] Kalis, M.M.; Huff, N.A. *Clin. Ther*., **2001**, *23*, 680.
[254] White, H.S. *Epilepsia*, **1999**, *40*, 2.
[255] Faigle, J.W.; Menge, G.P. *Behav. Neurol*., **1990**, *3*, 21.
[256] Viola, M.S.; Bercellini, M.A.; Saidon, P.; Rubio, M.C. *Medicina-Buenos Aire*, **2000**, *60*, 914.
[257] Gonzalez-Esquivel, D.F.; Ortega-Gavilan, M.; Alcantara-Lopez, G.; Jung-Cook, H. *Arch. Med. Res*., **2000**, *31*, 202.
[258] Larkin, J.G.; McKee, P.J.W.; Forrest, G.; Beastall, G.H.; Park, B.K.; Lowrie, J.I.; Lloyd, P.; Brodie, M.J. *Brit. J. Clin. Pharmaco*., **1991**, *31*, 65.
[259] Tartara, A.; Galimberti, C.A.; Manni, R.; Morini, R.; Limido, G.; Gatti, G.; Bartoli, A.; Strada, G.; Perucca, E. *Brit. J. Clin. Pharmaco*., **1993**, *36*, 366.
[260] Pienimäki, P.; Fuchs, S.; Isojärvi, J.; Vähäkangas, K. *J. Chromatogr. B*, **1995**, *673*, 97.
[261] Grant, S.M.; Faulds, D. *Drugs*, **1992**, *43*, 873.
[262] Myllinen, P.; Pienimäki, P.; Raunio, H.; Vahakangas, K. *Hum. Exp. Toxicol*., **1998**, *17*, 668.
[263] Glauser, T.A. *Neurology*, **2000**, *55*, 30.
[264] Glauser, T.A.; Nigro, M.; Sachdeo, R.; Pasteris, L.A.; Weinstein, S.; Abou-Khalil, B.; Frank, L.M.; Grinspan, A.; Guarino, T.; Bettis, D.; Kerrigan, J.; Geoffroy, G.; Mandelbaum, D.; Jacobs, T.; Mesenbrink, P.; Kramer, L. ; D'Souza, J. *Neurology*, **2000**, *54*, 2237.
[265] Glauser, T.A. *Pharmacotherapy*, **2001**, *21*, 904.
[266] Rattya, J.; Turkka, J.; Pakarinen, A.J.; Knip, M.; Kotila, M.A.; Lukkarinen, O.; Myllyla, V.V.; Isojarvi, J.I. *Neurology,* **2001**, *56*, 31.
[267] Borusiak, P.; Korn-Meker, E.; Holert, N.; Boenigk, H.E. *Epilepsy Res*., **1998**, *30*, 241.
[268] Baruzzi, A.; Albani, F.; Riva, R. *Epilepsia*, **1994**, *35*, 14.
[269] Trileptal®: Prescribing information. Available from URL: http://www.pharma.us.novartis.com/product/pi/pdf/trileptal.pdf [Accessed on June 21, 2008]
[270] de Sousa, M.; do Nascimento, F.; Martins, D.; Leite, I.; Cunha, A.; de Lima, G.; Evanir, F.; Frota, F.; de Moraes, O.; de Moraes, A. *J. Pharmaceut. Biomed*., **2007**, *45*, 304.
[271] Mazzucchelli, I.; Franco, V.; Fattore, C.; Marchiselli, R.; Perucca, E.; Gatti, G. *Ther. Drug Monit.*, **2007**, *29*, 319.
[272] Ma, C.; Jiao, Z.; Jie, Y.; Shi, X. *Chromatographia*, **2007**, *65*, 267.
[273] Kimiskidis, V.; Spanakis, M.; Niopas, I.; Kazis, D.; Gabrieli, C.; Kanaze, F.I.; Divanoglou, D. *J. Pharmaceut. Biomed*., **2007**, *43,* 763.
[274] Nirogi, R.; Kandikere, V.; Shukla, M., Mudigonda, K.; Ajjala, D. *Arzneimittel Forschung*, **2006**, *56*, 517.
[275] Contin, M.; Balboni, M.; Callegati, E.; Candela, C.; Albani, F.; Riva, R.; Baruzzi, A. *J. Chromatogr. B*, **2005**, *828*, 113.
[276] Franceschi, L.; Furlanut, M. *Pharmacol. Res*., **2005**, *51*, 297.
[277] Flesch, G.; Tudor, D.; Denouel, J.; Bonner, J.; Camisasca, R. *Int. J. Clin. Pharm. Th*., **2003**, *41*, 299.
[278] Mandrioli, R.; Ghedini, N.; Albani, F.; Kenndler, E.; Raggi, M.A. *J. Chromatogr. B*, **2003**, *783*, 253.
[279] Bugamelli, F.; Sabbioni, C.; Mandrioli, R.; Kenndler, E.; Albani, F.; Raggi, M.A. *Anal. Chim. Acta*, **2002**, *472,* 1.
[280] Souppart, C.; Decherf, M.; Humbert, H.; Maurer, G. *J. Chromatogr. B*, **2001**, *762,* 9.
[281] Matar, K.M.; Nicholls, P.J.; Bawazir, S.A.; Al-Hassan, M.I.; Tekle, A. *Pharmaceutica Acta Helvetiae*, **1999**, *73*, 247.
[282] Vermeij, T.A.C.; Edelbroek, P.M. *J. Chromatogr. B*, **2007**, *857*, 40.
[283] Greiner-Sosanko, E.; Giannoutsos, S.; Lower, D.R.; Virji, M.A.; Krasowski, M.D. *J. Chromatogr. Sci.*, **2007**, *45*, 616.
[284] Jones, M.D.; Ryan, M.; Miles, M.; Tang, P.H.; Fakhoury, T.; De Grauw, T.J.; Baumann, R. *Ther. Drug Monit*., **2005**, *27*, 576.
[285] Miles, M.V.; Tang, P.H.; Ryan, M.A.; Grim, S.A.; Fakhoury, T.A.; Strawsburg, R.H.; DeGrauw, T.J.; Baumann, R.J. *Ther. Drug Monit.,* **2004**, *26*, 300.
[286] Kristensen, O.; Klitgaard, N.A.; Jonsson, B.; Sindrup, S. *Acta Neurologica Scandinavica*, **1983**, *68*, 145.
[287] Volosov, A.; Yagen, B.; Bialer, M. *Epilepsia*, **2000**, *41*, 1107.
[288] Volosov, A.; Xiaodong, S.; Perucca, E., Yagen, B.; Sintov, A., Bialer, M. *Clin. Pharmacol. Ther.*, **1999**, 66, 547.
[289] Pucci, V.; Kenndler, E.; Raggi, M.A. *Biomed. Chromatogr*., **2003**, *17*, 231.
[290] Saracino, M.A.; Girardi, P.; Mercolini, L.; Tallarico, K.; Koukopoulos, A.; Sani, G.; Raggi, M.A. Analysis of oxcarbazepine and metabolites in plasma and saliva of bipolar patients by MEPS-HPLC, *TDM 2008, International Meeting on Therapeutic and Toxic effects of Central Nervous System drugs: the importance of drug monitoring, Bologna, October 2-3,* **2008**. Abstract book p. 113.

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