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To cite this article: Rafaela Costa, Nuno G. Oliveira & Ricardo Jorge Dinis-Oliveira (2019): Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspects, Drug Metabolism Reviews, DOI: [10.1080/03602532.2019.1620763](https://doi.org/10.1080/03602532.2019.1620763)

To link to this article: <https://doi.org/10.1080/03602532.2019.1620763>



Accepted author version posted online: 24 May 2019.  
Published online: 14 Jun 2019.



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REVIEW ARTICLE



## Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspects

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### ABSTRACT

Bupropion is an atypical antidepressant of the aminoketone group, structurally related to cathinone, associated with a wide interindividual variability. An extensive pharmacokinetic and pharmacodynamic review of bupropion was performed, also focusing on chemical, pharmacological, toxicological, clinical and forensic aspects of this drug without a limiting period. Bupropion is a chiral, basic, highly lipophilic drug, clinically used as racemate that undergoes extensive stereoselective metabolism. Its major active metabolites, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion reach higher plasma concentrations than bupropion. Bupropion exerts its effects mainly by inhibiting dopamine and norepinephrine reuptake and by blocking several nicotinic receptors. Recent reports highlight recreational use of bupropion via intranasal insufflation and intravenous use. Seizures, insomnia, agitation, headache, dry mouth, and nausea are some of the reported adverse effects. Neurologic effects are major signs of intoxication that should be carefully managed. Finally, the characterization of the polymorphic enzymes involved in the metabolism of bupropion is essential to understand factors that may influence the interindividual and intraindividual variability in bupropion metabolite exposure, including the evaluation of potential drug–drug interactions and pharmacogenetic implications.

### ARTICLE HISTORY

Received 15 February 2019  
Accepted 15 May 2019

### KEYWORDS

Bupropion; pharmacokinetics; metabolism; pharmacodynamics; polymorphisms; forensic and clinical aspects

## Introduction

According to the World Health Organization, depressive disorders are the single largest contributors to global disability, as shown by 7.5% of all Years Lived with Disability (World Health Organization 2017). Depression is also the major contributor to suicide. Antidepressants and/or psychotherapy are clinical approaches for the treatment of major depressive disorders. There are several classes of antidepressants: monoamine oxidase inhibitors (MAOIs; e.g. phenelzine), tricyclic antidepressants (e.g. desipramine), selective serotonin reuptake inhibitors (SSRIs; e.g. fluoxetine), serotonin and norepinephrine reuptake inhibitors (SNRIs; e.g. venlafaxine), and the atypical antidepressants (i.e. drugs that act by a mechanism of action other than the previously mentioned; e.g. bupropion). Even though the adverse effects, safety and tolerability profile of antidepressants vary widely between classes, the efficacy of different classes of antidepressants is similar.

Bupropion (synonym: amfebutamone; ( $\pm$  or *rac*)-2-(*tert*-butylamino)-3'-chloropropiophenone; 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-propan-1-one; 2-(*tert*-butylamino)-1-(3-chlorophenyl)propan-1-one) was first described in 1969 (Mehta 1969) and then approved in 1985 by US Food and Drug Administration (FDA) as a major depressive disorder treatment, with a maximum dose of 900 mg/d. Due to high incidence of seizures in bulimic patients, bupropion was subsequently withdrawn from the market (Horne et al. 1988). Further studies evidenced that the seizure risk was dose-dependent and bupropion was reintroduced in the market with a maximum dose of 450 mg/d and contraindicated for patients with increased risk of seizures (Davidson 1989). Besides this immediate release (IR) formulation, delayed-release dosages by the administration of sustained release (SR) and extended release (XL) formulations are also available in order to maintain stable plasmatic concentrations for a specific period of

time with minimum side effects (Jefferson et al. 2005). Bupropion sustained release formulation was approved alone or in combination with transdermal nicotine for the treatment of smoking cessation (Zyban®), whether or not a smoker was depressed (Hurt et al. 1997), and when combined with naltrexone for the treatment of obesity (Yanovski and Yanovski 2015; Saunders et al. 2016). Bupropion extended release formulations were approved for the treatment of seasonal affective disorder (Niemegeers et al. 2013). Other off-label uses illustrate the multifaceted therapeutic potential of bupropion for the treatment of the attention-deficit/hyperactivity disorder (Wilens et al. 2005) and the psychoactive substance dependence, namely methamphetamine dependence (Charntikov et al. 2018). At the pharmacodynamic level, bupropion is a noradrenaline and dopamine reuptake inhibitor (NDRI) but also acts as a non-competitive inhibitor of nicotine  $\alpha_4\beta_2$  receptor and by allosteric blockade of the 5-hydroxytryptamine (5-HT)<sub>3A</sub> receptors (Pandhare et al. 2017).

In view of the relevance of bupropion in the clinical and forensic context, an extensive knowledge on bupropion's chemistry, pharmacokinetics, and pharmacodynamics is crucial to maximize its clinical efficacy and predict its tolerability and safety profile when dealing with intoxications. This approach has also been particularly useful to explain clinical and forensic outcomes of different xenobiotics (Barbosa et al. 2016; Dinis-Oliveira 2016a, 2016b, 2017a, 2017b, 2017c). Further information on the genotoxicity and carcinogenicity data available for bupropion is also included herewith. Overall, this work aims to provide a comprehensive review of the current data regarding the chemical, pharmacological, toxicological and forensic aspects of bupropion.

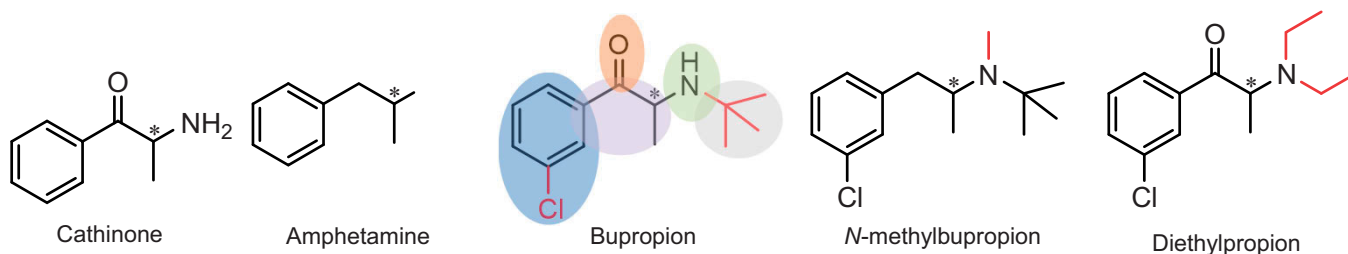
## Methodology

An exhaustive search was made in PubMed concerning the chemical, pharmacokinetic, pharmacodynamic and forensic aspects of bupropion, without time limit.

Additional reports were obtained from the references of the articles identified in the original search.

## Chemical structure and formulation

The cathinone has a phenylalkylamine structure and is the main psychoactive naturally occurring alkaloid found in the leaves of the *Catha edulis* plant, commonly known as khat (Marinetti and Antonides 2013; Watterson and Olive 2014). Structural modifications of the cathinone core originate several compounds, known as synthetic cathinones. In view of their chemical resemblance with amphetamines and due to the presence of the beta-ketone group at the  $\beta$ -position of the side chain, synthetic cathinones are often termed "bk-amphetamines" or " $\beta$ -keto amphetamines" (Kelly 2011; Prosser and Nelson 2012; Miller et al. 2017; Valente and Lebin 2017). Synthetic cathinones are less lipophilic than amphetamines due to the increased polarity added by the  $\beta$ -keto moiety. Functional group substitutions to the core structure of the parent cathinone compound (Figure 1) have yielded a large number of synthetic cathinones, which can be separated into four different chemical families based on the substitutions made (Valente et al. 2014; Miller et al. 2017; Nobrega and Dinis-Oliveira 2018). Many synthetic cathinones (e.g. methcathinone and diethylpropion) were initially synthesized for medical purposes (e.g. anti-depressant and appetite suppressant, respectively). However, they were withdrawn from the market due to its psychostimulant effects and abuse liability (Kelly 2011). Bupropion (Figure 1), a member of the *N*-alkylated cathinone group, is the only synthetic derivative currently used in the clinical setting. Bupropion is a monocyclic phenylaminoketone compound that besides the core structure of the parent drug has a *tert*-butyl moiety attached to the amine group and a chlorine group attached to the position 3' of the aromatic ring. Both the phenyl ring substitution and the size and branching of the *N*-alkyl group reduce the psychostimulant activity (Foley and Cozzi 2003). Similar to cathinone, bupropion has a single chiral center at C2 and



**Figure 1.** Chemical structures of cathinone, amphetamine, bupropion, *N*-methylbupropion and diethylpropion. Note the similarity between, cathinone, amphetamine, and bupropion. The circles aim to demonstrate the 2-(*tert*-butylamino)-1-(3-chlorophenyl)propan-1-one. Asterisk (\*) denotes the stereogenic center.

therefore two enantiomers, *R*(–)-bupropion and *S*(+)-bupropion are possible (Dwoskin et al. 2006; Carroll et al. 2014; Batra and Bhushan 2016; Khan et al. 2016).

Fang et al. (2000) successfully developed a method for enantiomeric separation of bupropion. However, analytical enantiomeric resolution shows little interest because of the rapid racemization observed *in vivo* and in solution (42%, 62%, and >94% in 2, 4, and 24 h, respectively, in phosphate buffer, pH 7.4, 25 °C) and, therefore, bupropion is clinically administered as a racemate, with equimolar ratios of both enantiomers (Bryant et al. 1983; Fang et al. 2000).

Similar to *S*-cathinone, *S*-bupropion is thought to be more active than its *R*-enantiomer. Bupropion is a weak base ( $pK_a$ : 7.9 at 25 °C) that is mainly commercialized as a hydrochloride (HCl) salt, available in three different bioequivalent formulations (i.e. the triple daily immediate, the twice daily sustained, and the once daily extended release), but also as hydrobromide (HBr) salt, only available as an extended release formulation that is bioequivalent to the extended release bupropion HCl (Khan et al. 2016). Both salts are described as white to almost white crystalline powders, soluble in water, with bitter taste, producing a sensation of local anesthesia on the oral mucosa (Jefferson et al. 2005; Khan et al. 2016). The immediate release formulation, given TID, was designed to dissolve in the stomach, promoting a rapid release of the drug. Sustained release and extended release formulations were designed to prolong the absorption. The sustained release formulation, incorporates bupropion in a methylcellulose matrix, while the extended release formulation, incorporated bupropion by controlled-release and moisture-barrier coatings (Jefferson et al. 2005). The modified release tablets should not be cut, chewed, or crushed (Jefferson et al. 2005). Bromide preparations were used in the past to treat seizures. Indeed, studies using rats and mice showed a smaller incidence of seizures with bupropion HBr, when compared with bupropion HCl (Henshall et al. 2009). However, when high amounts of bromide are ingested, a toxic syndrome (i.e. bromism), characterized by neurologic, psychiatric, and dermatologic adverse effects, has been described (Bowers and Onoroski 1990; Shader 2009).

## Pharmacokinetics

### Absorption

Bupropion is administered *per os*; the absorption is rapid ( $T_{max}$  1.3–1.9 h) for immediate release formulation and not influenced by the presence of food (Findlay et al. 1981b; Jefferson et al. 2005). As mentioned, there

are also cases described in the literature of misuse of bupropion by nasal insufflation (Hilliard et al. 2013) and intravenous administration (Oppek et al. 2014) in abusive contexts. In humans, absolute oral bioavailability is unknown since an intravenous formulation is currently not available. Nevertheless, similar relative bioavailability results were found for immediate release and sustained release formulations, as evidence by the AUC, and in comparison, a bioavailability of 68% was observed for extended release formulations, probably due to less absorption or increased metabolism (Connarn et al. 2017). Moreover, although the intestinal absorption of bupropion has been reported to be nearly 100% (Jefferson et al. 2005), its bioavailability is reduced due to the extensive first pass metabolism. In fact, studies in rats and dogs suggest that the absolute bioavailability may range between 5% and 20% (Jefferson et al. 2005; Foley et al. 2006a). As expected, absorption is prolonged for the sustained and extended formulations (Jefferson et al. 2005). Hydroxybupropion and threohydrobupropion reach higher concentrations than the parent compound, while erythrohydrobupropion reaches similar concentrations to bupropion. Bupropion and its major active metabolites (i.e. hydroxybupropion, threohydrobupropion and erythrohydrobupropion) need 5 and 8 days, respectively, to reach steady-state plasma concentrations (Johnston et al. 2002; Dwoskin et al. 2006). Peak plasma concentrations ( $C_{max}$ ) are higher in the immediate release formulation, followed by the sustained release formulation and finally in the extended release formulation. On the other hand, the time to reach maximum serum concentrations ( $T_{max}$ ) of bupropion, hydroxybupropion, and threohydrobupropion undergoes opposite relationship (Findlay et al. 1981a; Jefferson et al. 2005; Connarn et al. 2017).

### Distribution

Bupropion is a small and lipophilic molecule with a high volume of distribution (approximately 19 L/kg, at steady state) and a biphasic distribution characterized by a rapid distribution phase followed by a slower elimination phase (Findlay et al. 1981a). An extensive protein binding was reported for bupropion (84%) and hydroxybupropion (77%); for the metabolite threohydrobupropion 42% (Johnston et al. 2002). Jefferson et al. (2005) demonstrated that this level of protein binding is not high enough to have clinical relevance. Bupropion also crosses the blood brain barrier and human placenta (Wang et al. 2012), being classified as a Pregnancy Category C substance by the FDA as it can be associated with congenital cardiac malformations

when administered in the first trimester of pregnancy (Louik et al. 2014).

### Elimination

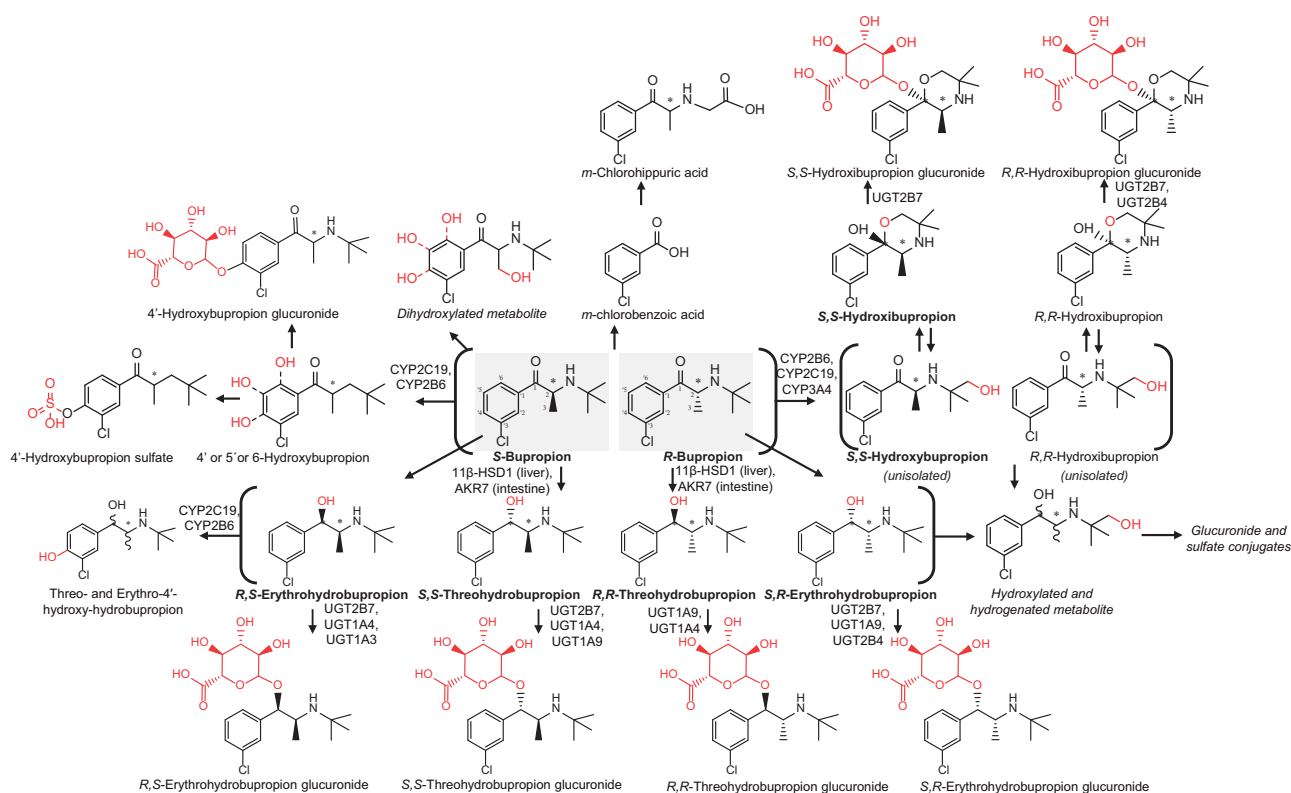
The elimination half-life of bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion has been reported to be of approximately 21, 20, 37, and 33 h, respectively (Jefferson et al. 2005). Human studies using radiolabeled bupropion showed that bupropion and its metabolites are excreted in urine (88%) and in the feces (10%); less than 1% of bupropion is excreted unchanged in the urine and occurs mainly as threohydrobupropion (Findlay et al. 1981a; Hsyu et al. 1997). Following a single oral radiolabeled dose, only 23% of the dose was recovered in urine as bupropion, hydroxybupropion, erythrohydrobupropion, threohydrobupropion and their *N*- and *O*-glucuronides and sulfates conjugates (Petsalo et al. 2007; Gufford et al. 2016). Bupropion is also excreted in human breast milk (Briggs et al. 1993). *R*-Bupropion, *R,R*-hydroxybupropion, *R,R*-threohydrobupropion and *S,R*-erythrohydrobupropion have longer half-lives and plasma area under the curve, being the main enantiomers present in human plasma (Benowitz et al. 2013). Clearance of bupropion, hydroxybupropion and threohydrobupropion are reduced in renal failure patients (Worrall et al. 2004; Turpeinen et al. 2007).

### Metabolism

Figure 2 presents the metabolic pathway of bupropion. Several studies suggest that both bupropion enantiomers undergo extensive, stereoselective and interindividual differences of the phase I and II hepatic metabolism by (i) hydroxylation of the *tert*-butyl moiety to an unisolated hydroxybupropion, followed by ring closure, to the phenylmorpholinol metabolite (also sometimes referred to as hydroxybupropion); (ii) aromatic hydroxylation at 4'position to produce 4'-hydroxy-bupropion; (iii) reduction of the ketone group by 11 $\beta$ -hydroxysteroid dehydrogenase-1 (11 $\beta$ -HSD-1) and aldoketoreductase(s) to the diastereoisomers *erythro* and *threo* amino alcohols, threohydrobupropion and erythrohydrobupropion, followed by further aromatic hydroxylation at 4'position to produce threo/erythro-4'-hydroxy-hydrobupropion or aliphatic hydroxylation; (iv) side-chain cleavage to *m*-chlorobenzoic acid, followed by glycine conjugation to *m*-chlorohippuric acid; (v) hydration of bupropion; (vi) aliphatic and aromatic hydroxylation of threo/erythrohydrobupropion; and (vii) glucuronide or sulfate conjugation of phase I metabolites.

The pharmacological and toxicological effects of bupropion are attributed not only to bupropion but also to its three active metabolites hydroxybupropion (50% as potent), threohydrobupropion and erythrohydrobupropion (both 20% as potent), which circulate at higher plasmatic concentrations comparatively to bupropion (Benowitz et al. 2013; Sager et al. 2016a). Indeed, metabolites of bupropion have significant impact on its efficacy since they have 25–50% potency compared with bupropion on the basis of antidepressant screening tests in an animal model (Bondarev et al. 2003; Damaj et al. 2010). In addition, hydroxybupropion has a longer elimination half-life than the parent drug, and the cerebrospinal fluid and plasma levels of hydroxybupropion are 5- to 10-fold higher than the parent drug after oral administration of bupropion HCl (Bondarev et al. 2003; Damaj et al. 2004; Jefferson et al. 2005; Damaj et al. 2010). In this context, hydroxybupropion is likely to play a very important role in the effects of oral bupropion, which could accurately be thought of as functioning largely as a prodrug to hydroxybupropion. Though bupropion is clinically administered as a racemic mixture (i.e. *R,S*-bupropion), *in vitro* and *in vivo* studies have demonstrated that *R*-bupropion and its metabolites are major determinants of the pharmacological and toxicological effects in comparison to the enantiomer *S*-bupropion and its metabolites (Kharasch et al. 2008; Gufford et al. 2016). Moreover, plasma concentrations of *R,R*-hydroxybupropion are more than 20-fold higher than *S,S*-hydroxybupropion and bupropion enantiomers (Suckow et al. 1997; Coles and Kharasch 2007; Xu et al. 2007; Kharasch et al. 2008). The lower concentration and higher *in vivo* clearance of *S*-bupropion are predominantly explained by higher clearance of the major metabolite threohydrobupropion from *S*-bupropion (Sager et al. 2016b). Nevertheless, contradictory results also exist, since while *R*- and *S*-bupropion have similar antidepressant activity, only *S,S*-hydroxybupropion (but not *R,R*-hydroxybupropion) proved to be pharmacologically active (Musso et al. 1993). Indeed, *in vitro* and rodent behavioral studies indicate that *S,S*-hydroxybupropion plays an important role in the efficacy of the marketed product, both as an antidepressant and smoking cessation aid (Bondarev et al. 2003; Damaj et al. 2004; Damaj et al. 2010; Grabus et al. 2012). Moreover, the affinity of *S,S*-hydroxybupropion at the dopamine transporter is comparable to that of bupropion (Bondarev et al. 2003; Damaj et al. 2004). Based on the metabolic profile, stereospecific liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods to simultaneously quantify bupropion, hydroxybupropion, threohydrobupropion, and





**Figure 2.** Stereoselective metabolic pathway involved in the oxidation, reduction, and glucuronidation and/or sulfation of bupropion enantiomers and its metabolites. AKR: Aldo-keto reductase; UGT: UDP-glucuronosyl transferase; 11 $\beta$ -HSD1: 11 $\beta$ -hydroxysteroid dehydrogenase type 1. Asterisk (\*) denotes the stereogenic center; bold denotes known active metabolites.

erythrohydrobupropion, have been developed (Masters et al. 2016a).

Loboz (Loboz et al. 2005) demonstrated that the carbonyl group can be reduced by carbonyl reductase(s) leading to the formation of *S,S*-threohydrobupropion, *R,R*-threohydrobupropion, *S,R*-erythrohydrobupropion, and *R,S*-erythrohydrobupropion. These are metabolites with two stereogenic centers and therefore can exist as four possible stereoisomers (i.e. *dl*-erythro and *dl*-threo – terms used for diastereomers with two adjacent chiral carbons with two similar groups on the same or opposite sides of the carbon chain, respectively). Connarn et al. (2015) studied the metabolism of bupropion using several human liver and intestine samples and concluded that threohydrobupropion formation was mainly catalyzed by carbonyl reductase enzymes (Matsunaga et al. 2006): (i) the microsomal 11 $\beta$ -hydroxysteroid dehydrogenase-1 (11 $\beta$ -HSD-1) in the liver; and (ii) the cytosolic aldo-keto reductase 7 (AKR7) in the intestine. These authors also verified that threohydrobupropion was the only metabolite formed in the intestine, accounting for 25% of the total amount of threohydrobupropion and that the metabolism of bupropion by CYP2B6 to hydroxybupropion and its metabolism by carbonyl reductases in the liver was equally important

(Connarn et al. 2015). Bhattacharya et al. (2019) demonstrated using hepatic microsomal incubations that erythrohydrobupropion formation is catalyzed by 11 $\beta$ -HSD-1, with a minor contribution from the AKR family.

The introduction of an hydroxyl group in the bupropion enantiomers metabolism also occurs by oxidative hydroxylation resulting in the creation of a second chiral center (Figure 2) and hence there is the potential for four stereoisomers hydroxylated metabolites to be formed (Suckow et al. 1997). *In vitro* studies suggest that CYP2B6 is the principal isoenzyme implicated in the formation of hydroxybupropion, while CYP2C19, CYP3A4, CYP1A2, and CYP2E1 have a minor role (Faucette et al. 2000; Hesse et al. 2000; Faucette et al. 2001; Sager et al. 2016a). Indeed, bupropion has been demonstrated to be a sensitive *in vitro* and *in vivo* phenotypic probe for CYP2B6 activity and CYP2B6 drug interactions (Coles and Kharasch 2008a). Since it is clinically important in the treatment of major depression and smoking cessation, Coles and Kharasch (2008b) studied the stereospecific hydroxylation/bioactivation of bupropion to hydroxybupropion using recombinant CYP2B6 and human liver microsomes. In recombinant CYP2B6, *S,S*-hydroxybupropion formation rate was three-fold higher than the formation rate of *R,R*-

hydroxybupropion. Regarding human liver microsomes, the authors observed a high variability in bupropion hydroxylation between the different human liver microsomes although *S,S*-hydroxybupropion formation rate was consistently 1.5-fold higher than *R,R*-hydroxybupropion in all human liver microsomes. While hydroxybupropion has two chiral centers, only *R,R*-hydroxybupropion and *S,S*-hydroxybupropion enantiomers were yet detected, possibly due to steric hindrance that precludes the formation of *R,S* and *S,R*-hydroxybupropion (Fang et al. 2000). Hydroxybupropion racemizes at a slower pace (only 2% in 24 h at 25 °C and pH 7.4 phosphate buffer) compared with bupropion (Fang et al. 2000). Since CYP2B6 is highly polymorphic and has high inter-individual variability of approximately 100-fold, different pharmacological and toxicological effects could be anticipated (Zanger and Klein 2013; Kharasch and Crafford 2019). CYP2B6\*6 allele is the most frequent and clinically relevant reduced variant allele, expressed in 15–60% of individuals, depending on ethnicity (Zanger and Klein 2013). On the other hand, CYP2B6\*4 allele has been associated with increased catalytic activity, thus increasing hydroxylation of bupropion. CYP2B6\*1/\*6 and CYP2B6\*6\*4, CYP2B6\*1/\*1, and CYP2B6\*1/\*4 are intermediate, extensive, and ultra-rapid metabolizers, respectively (Ma et al. 2018). Benowitz et al. (2013) reported CYP2B6\*18 allele was also associated with reduced hydroxybupropion formation. Additional studies (Hoiseth et al. 2015; Kharasch and Crafford 2019) found statistically significant lower hydroxybupropion  $C_{max}$  with CYP2B6\*6\*6 but not with CYP2B6\*6\*1. Moreover, CYP2B6 genetic polymorphisms have been reported to affect the anti-smoking efficacy of bupropion (Lee et al. 2007). Nevertheless, since bupropion clearance was not affected by CYP2B6 reduced function, it is suggested that the additional clearance pathways of bupropion are able to compensate the reduced hydroxylation rates. Besides the inter-individual variability in terms of expression and activity (Zanger et al. 2007), it should be noted that CYP2B6 is also susceptible to induction and inhibition (Turpeinen et al. 2006; Walsky et al. 2006) and is involved in the metabolism of detoxification or bioactivation of several xenobiotics such as methadone, propofol, efavirenz, tamoxifen, ketamine, cyclophosphamide, nicotine, ecstasy, and phencyclidine (Ekins and Wrighton 1999; Dinis-Oliveira 2016b, 2017b, 2018). Stereoselective metabolism of hydroxybupropion enantiomers is unlikely, since no hydroxybupropion metabolism was evidenced *in vitro* (Coles and Kharasch 2008b), and no further oxidative or reductive metabolite of hydroxybupropion was identified *in vivo* (Petsalo et al. 2007).

Regarding the aromatic hydroxylation, Sager et al. (2016a) proposed the 4' position as the hydroxylation site, and identified 4'-hydroxybupropion, erythro-4'-hydroxy-hydrobupropion and threo-4'-hydroxy-hydrobupropion in human liver microsome incubations and human urine. Also, they estimated that 4'-hydroxybupropion accounts for 20% of threohydrobupropion clearance and for 70% of erythrohydrobupropion clearance. Sager et al. (2016b) also identified CYP2C19 as the major enzyme responsible for the 4' hydroxylation and, therefore, genetic variability in CYP2C19 activity may have a large impact on bupropion activity and toxicity. It was also demonstrated in liver S9 fractions that *S,S*-hydroxybupropion, *S,S*-threohydrobupropion and *R,S*-erythrohydrobupropion were mainly formed from *S*-bupropion, while *R,R*-hydroxybupropion, *R,R*-threohydrobupropion and *S,R*-erythrohydrobupropion were mainly formed from *R*-bupropion (Sager et al. 2016a).

Masters et al. (2016a) analyzed the plasma and urine of 15 healthy volunteers using the method previously described and verified that *R*-bupropion, *R,R*-hydroxybupropion and *S,R*-erythrohydrobupropion were the main enantiomers present in the plasma, displaying concentrations similar to racemic bupropion, hydroxybupropion and erythrohydrobupropion, respectively. The authors estimated that *R,R*-hydroxybupropion had a 35-fold higher  $C_{max}$  and a 65-fold higher AUC than *S,S*-hydroxybupropion. Moreover, *S,S*-hydroxybupropion had a shorter  $t_{1/2}$  (14.6 h) compared with *R,R*-hydroxybupropion (19.3 h). As for threohydrobupropion, *S,S*-threohydrobupropion had a two-fold higher  $C_{max}$  than its enantiomer. *S,S*-threohydrobupropion had also a shorter  $t_{1/2}$  (8.2 h) compared with *R,R*-threohydrobupropion (45.5 h). *R,R*-/*S,S*-threohydrobupropion AUC ratio was 4 (Masters 2016a). Authors also stated *R*-/*S*-bupropion ratio was higher early after ingestion, decreasing with time. A similar tendency was shown with *S,S*-/*R,R*-threohydrobupropion ratio. Bhattacharya et al. (2019) found comparable results in human liver microsomes. They reported that *S*-bupropion was the enantiomer with higher hepatic clearance, mainly due to the five-fold higher formation of *S,S*-threohydrobupropion. *S,S*-threohydrobupropion was the metabolite with higher  $CL_{int}$ , contributing 37% to the total racemic bupropion clearance. *S,S*-hydroxybupropion and *R,S*-erythrohydrobupropion also had higher hepatic clearance than the respective enantiomers. Taken together, these data suggest that *S*-bupropion has a lower systemic bioavailability, mainly by metabolization to *S,S*-threohydrobupropion.

Gufford et al. (2016) studied the stereoselective glucuronidation of bupropion metabolites in human liver microsomes and their excretion in human urine. UGT2B7 catalyzed the stereoselective formation of glucuronides of hydroxybupropion, *S,S*-hydrobupropion, *S,R*-, and *R,S*-hydrobupropion; UGT1A9 catalyzed the formation of *R,R*-hydrobupropion glucuronide. Approximately 10% of the administered bupropion dose was recovered in the urine after metabolization, with the glucuronide metabolites accounting for approximately 40%, 15%, and 7% of the total excreted hydroxybupropion, erythro-hydrobupropion, and threo-hydrobupropion, respectively.

Petsalo et al. (2007) analyzed human urine after a single dose of bupropion by liquid chromatography/time-of-flight mass spectrometry (LC-TOFMS) followed by confirmation of the metabolite identifications by LC-MS/MS. These authors found a total of six phase I metabolites and 14 phase II metabolites, namely hydroxybupropion, threo-hydrobupropion, erythrohydrobupropion, and their respective glucuronide conjugates, *m*-chlorohippuric acid, a glucuronide conjugate of a dihydroxy metabolite, a hydroxylated and hydrogenated metabolite and its glucuronide and sulfate conjugates and a sulfate conjugate of an aromatic hydroxylated metabolite.

Metabolism of bupropion also varies between species (Butz et al. 1981; Welch et al. 1987). Rat metabolizes bupropion primarily by side-chain cleavage to *m*-chlorobenzoic acid and *m*-chlorohippuric acid (Welch et al. 1987), while mice and dogs metabolize bupropion primarily to hydroxybupropion. Mice and rat liver microsomes are 80-fold and 10-fold less active generating threo-hydrobupropion, respectively (Meyer et al. 2013) than human liver microsomes. Guinea pigs metabolize bupropion mostly to threo-hydrobupropion (Suckow et al. 1986), with minor concentrations of hydroxybupropion. Bhattacharya et al. (2019) studied stereospecific metabolism in human, marmoset monkey, rat, and mouse liver microsomes and reported that marmoset monkeys were the most similar to humans regarding bupropion metabolism. Moreover, comparing to rats, mice were more similar to humans in terms of bupropion metabolism and therefore mouse behavioral models measuring various aspects of nicotine dependence have been used (Damaj et al. 2010). Because bupropion is extensively metabolized in the liver, hepatic impairment will affect maximum concentrations and the elimination half-life of bupropion.

### Metabolic interactions

Bupropion is a strong *in vivo* CYP2D6 inhibitor, increasing the concentration of CYP2D6-metabolized drugs,

such as desipramine (Reese et al. 2008), atomoxetine (Todor et al. 2016), and nebivolol (Gheldiu et al. 2016). However, *in vitro* studies suggested that bupropion and hydroxybupropion were weak CYP2D6 inhibitors (Hesse et al. 2000), while threo-hydrobupropion and erythro-hydrobupropion were relatively stronger CYP2D6 inhibitors (Reese et al. 2008). Sager et al. (2017) further studied bupropion's inhibition of CYP2D6 using human liver microsomes, HepG2 cells and human hepatocytes and evidenced that hydroxybupropion was responsible for 65% of total CYP2D6 inhibition, while threo-hydrobupropion and erythrohydrobupropion accounted for 21% and 9%, respectively. The 4'-hydroxy-metabolites did not account for any relevant inhibition. CYP2D6 inhibition by bupropion and hydroxybupropion also proved to be stereoselective (Sager et al. 2017). Indeed, *S*-bupropion and *R,R*-hydroxybupropion have 14-fold and 3-fold higher inhibition potency than the respective enantiomers; the stereoselective activity of threo-hydrobupropion and erythrohydrobupropion was not evaluated. Bupropion and its metabolites also significantly suppressed CYP2D6 transcription in HepG2 cells and in human hepatocytes but the mechanism was not fully characterized (Sager et al. 2017). Based on these results, pharmacological interactions are expected with drugs that also inhibit CYP2D6 activity, such as selective serotonin reuptake inhibitors (SSRIs) (Foley et al. 2006). Moreover, due to the possibility of inducing a hypertensive crisis, bupropion should not be used concomitantly with monoamine oxidase inhibitors (MAOIs) (Fiedorowicz and Swartz 2004; Spina et al. 2012; Nirogi et al. 2015).

### Pharmacodynamics

The exact mechanism of action of bupropion is not fully understood and although it differs from other antidepressants, its efficacy is similar between different classes of antidepressants (Patel et al. 2016). Early studies evidenced bupropion inhibits the firing of *locus coeruleus* noradrenaline neurons in rat brain (Cooper et al. 1994) and also inhibits striatal dopamine reuptake in mice brain (Stathis et al. 1995). More recently, Shalabi et al. (2017) studied the ability of bupropion, *S*-(-)-cathinone and several deconstructed analogs of bupropion for the interaction of dopamine, serotonin, and noradrenaline transporters (i.e. DAT, SERT, and NAT) in rat brain synaptosomes. Results demonstrated that bupropion is a weak inhibitor of DAT reuptake and a 10-fold weaker inhibitor of NAT reuptake and that this compound does not act as a dopamine and noradrenaline releasing agent. The same was observed by Bredeloux



et al. (2007); these authors concluded that, although chemically related to *d*-amphetamine, a well-established releaser of dopamine, bupropion and its metabolites behaved *in vivo* only as dopamine uptake inhibitors and were devoid of dopamine-releasing effects. Conversely, other studies suggest that bupropion may induce the release of dopamine and noradrenaline (Arias et al. 2009). Shalabi et al. (2017) also observed that *S*-(-)-cathinone exerted its effects by promoting the release of dopamine and noradrenaline and was a weak inhibitor of DAT and NAT. Both cathinone and bupropion did not exert effects in the reuptake or release of serotonin. The loss of the keto-group or chloro-group resulted in less potency in dopamine reuptake with no other significative changes compared to bupropion. As for the amine substituents, smaller substituents had higher potency at promoting the release of dopamine, noradrenaline and serotonin and were associated with the least selective effect over DAT, NAT and SERT. *S,S*-hydroxybupropion had a higher potency than the corresponding enantiomer and comparable potency with the parent drug at DAT and NAT uptake inhibition in rat brain synaptosomes. Bupropion also increased striatal vesicular dopamine reuptake, due to increase VMAT2 activity in rats (Rau et al. 2005).

It has been suggested that the non-nicotine medication with the best evidence for efficacy in the treatment of nicotine dependence is indeed bupropion (Kalkhoran et al. 2018). The efficacy of bupropion sustained release formulation for the treatment of nicotine dependence is presumed to be due to the blockade of dopamine reuptake in the mesolimbic dopamine system, an area of the brain believed to mediate the reward for nicotine use (Watkins et al. 2000). Another mechanism possibly contributing to bupropion's efficacy as an antidepressant and smoking cessation treatment is its effect on several nicotinic acetylcholine receptors (nAChR). Damaj et al. (2004) evidenced bupropion was a non-competitive inhibitor of nicotine  $\alpha_3\beta_4$  receptor, while *S,S*-hydroxybupropion was a non-competitive inhibitor of nicotine  $\alpha_4\beta_2$  receptor in rat brain. Vazquez-Gomez et al. (2014) showed that bupropion is also a weak inhibitor of  $\alpha_7$  nicotinic receptors in dorsal raphe nucleus and hippocampal rat neurons. Like bupropion, hydroxybupropion is also a non-competitive antagonist of nACh receptors, such as  $\alpha_4\beta_2$  and  $\alpha_3\beta_4$ , but it is even more potent in comparison. Recent data (Pandhare et al. 2017) evidenced that bupropion and hydroxybupropion are non-competitive inhibitors of 5-HT<sub>3A</sub> receptors, with IC<sub>50</sub> values of 87  $\mu$ M and 112  $\mu$ M, respectively (Pandhare et al. 2017). Lukas et al. (2010) synthesized several analogs of *S,S*-hydroxybupropion

with different selectivity profiles to DAT, NAT,  $\alpha_3\beta_4$ -nAChR, and  $\alpha_4\beta_2$ -nAChR inhibition.

Bupropion reversed tetrabenazine-induced sedation and reduced immobility in forced swim test in mice (Musso et al. 1993). The authors also found no statistically significant differences between *S*-bupropion and *R*-bupropion in reversing tetrabenazine-induced sedation in mice. However, this experiment was made under conditions that promoted the racemization of bupropion. In contrast, bupropion failed to reverse tetrabenazine-induced sedation in rat (Welch et al. 1987). Compared with bupropion, *S,S*-hydroxybupropion had similar potency in the forced swim test in mice, while *R,R*-hydroxybupropion had no significant effect (Damaj et al. 2004). Bupropion also increased immobility in rats in a dose-dependent manner (Foley and Cozzi 2003). However, bupropion did not produce the stereotypy usually seen upon amphetamine administration (Martin et al. 1990). According to Martin et al. (1990), both hydroxybupropion and threohydroxybupropion produce a biphasic effect on locomotor activity, decreasing immobility at lower doses and increasing immobility at higher doses. Both antidepressant activity and smoking cessation efficacy of bupropion was proven to be dose-dependent (Hsyu et al. 1997; Johnston et al. 2001, 2002). Moreover, hydroxybupropion levels were found to correlate with clinical efficacy in depression (Laib et al. 2014) and smoking cessation (Zhu et al. 2012).

### Adverse effects

Bupropion is associated with mild to moderate toxicity; adverse drug reactions in Europe increased from 48 in 2010 to 553 in 2015 (Schifano and Chiappini 2018). Insomnia, agitation, headache, dry mouth, nausea, constipation, irritability, and anxiety are the most common reported adverse effects (Johnston et al. 2001, 2002; Dwoskin et al. 2006). Vivid dreams, hallucinations, unusual thoughts or behavior, changes in attention, memory and perception, confusion, tremors, severe blistering, peeling, skin rash or itching, fever, swollen glands, joint pain, increased blood pressure, weight loss, and general ill feeling have also been described (Tucker 1983; Foley and Cozzi 2003; Thase et al. 2008; Saunders et al. 2016). To prevent insomnia, bupropion should not be administered close to bed time and as other antidepressants, bupropion can exacerbate depression and increase suicide thoughts (Dwoskin et al. 2006).

Seizures are the most serious adverse effects of bupropion, which are dose dependent and the risk is approximately 0.4% in immediate release formulation

doses up to 450 mg/d (Davidson 1989), and 0.1% with bupropion sustained release formulation doses up to 400 mg/d (Dunner et al. 1998). To minimize the risk of occurrence, patients must be screened for any underlying condition that might lower their seizure threshold, such as epilepsy, anorexia/bulimia nervosa, head trauma, cancer, abrupt discontinuation of sedatives or ethanol, or any medication that lowers seizure threshold, such as other antidepressants, antipsychotics, tramadol, and theophylline (Jefferson et al. 2005).

Literature data suggests that metabolites may be implicated in the adverse effects of bupropion. Johnston et al. (2002) demonstrated that insomnia was associated with erythrohydrobupropion concentrations, while dry mouth was associated with threohydrobupropion concentrations. Silverstone et al. (2008) evidenced hydroxybupropion administration in mice had higher incidence of seizures followed by threohydrobupropion, erythrohydrobupropion, and bupropion.

In bupropion-related intoxications, major toxicity symptoms are seizures, agitation, confusion, sinus tachycardia, hypertension, nausea and vomiting and hallucinations (Paoloni and Szekely 2002). Metabolic acidosis, delusions, tremors, lethargy, paresthesias, and coma are also reported (Spiller et al. 1994; Paoloni and Szekely 2002; Jepsen et al. 2003; Noda et al. 2017). Many reports highlight sinus tachycardia as the most common cardiac effect, whereas QRS interval widening, QTc prolongation, and cardiac arrest are also mentioned (Druteika and Zed 2002; Paoloni and Szekely 2002; Mercerolle et al. 2008; Bolen et al. 2016). A study using guinea-pig hearts (Caillier et al. 2012) evidenced that high doses of bupropion inhibit the delayed rectifying (IKr) potassium channel and the gap junctional intercellular communication but does not inhibit the sodium channels. Wang et al. (2005) reported a case of a 23-year-old man that presented irritation, aggressive behavior, psychomotor agitation, and paranoid delusions after the intake of 4.2 g bupropion sustained release formulation and 105 mg of midazolam co-ingestion. Noda et al. (2017) reported a case of a 51-year-old woman that ingested 27 g of bupropion. At presentation, the patient was confused and somnolent, but became more agitated and lost consciousness. She had one generalized seizure and was hypotensive. EEG showed encephalopathy with burst suppression. Zhu et al. (2016) reported a case of a 13.5 g ingestion of bupropion by a 21-year-old woman. The patient presented with multiple seizures, sinus tachycardia with prolonged QTc and QRS intervals, metabolic acidosis, dilated pupils, and agitation. After 4 d, the patient developed sinus bradycardia, hypotension, and

transaminitis, which reverted after 12 days of conservative treatment. Heise et al. (2016) reported two cases of refractory cardiogenic shock related with intoxication of bupropion, successfully treated with veno-arterial extracorporeal membrane oxygenation (VA-ECMO). The first case was a 15-year-old girl that experienced tachycardia, multiple seizures, and cardiac arrest. After successful cardiopulmonary resuscitation, her condition deteriorated with hypotension and hypoxia. An echocardiogram showed acute biventricular cardiomyopathy with low fraction of ejection. Concentrations of bupropion and hydroxybupropion were 1883 ng/mL and 2352 ng/mL, respectively. The patient was treated with VA-ECMO and she was discharged 24 days after admission. The second case was of a 16-year-old girl with multiple seizures, tachycardia, QRS widening, hypotension, and metabolic acidosis. The patient had a cardiogenic shock secondary to biventricular cardiomyopathy with a fraction of ejection of 10%, then exhibited bradycardia and did not recover despite the use of intravenous fat emulsion being placed on VA-ECMO. The patient developed compartment syndrome of the right lower leg, below femoral ECMO cannulation with rhabdomyolysis and required a fasciotomy. The patient was discharged to an acute rehabilitation unit 16 days after her admission.

### Abuse potential

Although oral administration of bupropion is thought to have low abuse potential, there is growing evidence of misuse of bupropion (Hilliard et al. 2013; Stall et al. 2014; Schifano and Chiappini 2018). Additionally, 17 cases of drug arrests involving bupropion were reported by the Maine Diversion Alert Program in 2016 (Piper et al. 2018). Abusers claim to want to quit smoking or to be depressed in an attempt to obtain bupropion from physicians and typically occurs in patients with a history of substance abuse and in correctional facilities (Hilliard et al. 2013). Like cathinone, bupropion abuse potential seems dependent on its noradrenergic and dopaminergic activity (Schifano and Chiappini 2018). Abusers usually report euphoria, increased energy and arousal after nasal insufflation of the content of several tablets of bupropion (Hilliard et al. 2013; Reeves and Ladner 2013). One abuser reported a “high” feeling immediately after bupropion insufflation (2100 mg/d), about 20% of cocaine “high” that lasted for 30 min (Yoon and Westermeyer 2013). He also presented nasal bleed after bupropion insufflation, poor appetite and paranoia. A recent case reported intravenous use of bupropion (1200 mg/d) by a 29-year-old woman. Euphoria, stimulant-like effect, irritability,

lability, and low mood during periods of abstinence, were observed (Stassinis and Klein-Schwartz 2016). A 13-year-old female (McCormick 2002) ingested 600 mg of bupropion orally believing the drug was a stimulant. However, psychostimulant effects were not observed. Dagan and Yager (Dagan and Yager 2018) presented a case of a 22-year-old woman with bulimia nervosa and PTSD that abused bupropion extended release formulation for its anorexic effects. The woman reported taking 3000–4500 mg of bupropion daily. During the 2-month period of frequent abuse, the patient experienced headaches, tachycardia, anxiety, insomnia, lost 6 kg, and had several seizures.

### Intoxications and fatal cases

Antidepressants are often encountered in intoxications. In 2016, 124 fatal intoxications reported antidepressants as the primary cause, with bupropion being first ranked in 38 cases (i.e. 27 cases of bupropion immediate release formulations and 11 cases of bupropion modified release formulations) (Gummin et al. 2017). In a retrospective *postmortem* forensic research conducted in Finland between 2009 and 2013, bupropion was detected in 65 cases, 30 being fatal poisonings, namely due to suicide and abuse (Kriikku and Ojanpera 2016). Bupropion is considered moderately dangerous and fatalities usually occur at much higher concentrations than those encountered clinically (Schulz et al. 2012). Doses greater than 5 g may lead to severe neurological and cardiovascular toxicity. The main cause of death is cardiopulmonary arrest as a consequence of hypoxia and metabolic acidosis (Paoloni and Szekely 2002). In humans, the lethal dose low ( $LD_{Lo}$ , oral) has been estimated to be 329 mg/kg. For animals, the following  $LD_{50}$  values have been reported: 482–600 mg/kg (oral, rat), 210 mg/kg (intraperitoneal, rat), 544–575 mg/kg (oral, mouse), and 230 mg/kg (intraperitoneal, mouse) (Tucker Jr 1983; Kleemann et al. 2009). Lethal dose values in mice were smaller for hydroxybupropion, followed by threohydrobupropion, erythrohydrobupropion and finally bupropion (Welch et al. 1987).

Donnelly et al. (2010) studied the toxicokinetics of bupropion in a 23-year-old male who ingested 5.7 g of bupropion sustained release formulation. The patient presented with multiple seizures, hallucinations, bruxism, tremor and ataxic gait. Sinus tachycardia with QT widening and hypoglycemia were also detected. Symptoms subsided over 18 h after ingestion. Donnelly et al. reported bupropion  $C_{max}$  was 1.145 mg/L.  $T_{max}$  (8.25 h) and alpha half-life (10.9 h) were longer than those reported for therapeutic doses. The authors

hypothesized the longer absorption and excretion rates could be due to pharmacobezoar formation.

Mowry et al. (2016) described a fatal intoxication of bupropion of a 15-year-old, found agitated after suspected ingestion of 20–30 extensive release bupropion tablets. The patient suffered a cardiac arrest. After successful cardiorespiratory resuscitation, she arrived at the emergency room. At that point, she was tachycardic, hypotensive and had multiple unresponsive seizures (despite lorazepam, midazolam, and levetiracetam) and was hyperthermic (39.7°C). EEG was compatible with brain death. Subsequently, the patient developed cerebral edema and herniated. *Antemortem* concentration of bupropion and hydroxybupropion were 1.931 mg/L and 2.453 mg/L, respectively.

Spiller et al. (2008) reported five cases of fatal intoxications of bupropion with *postmortem* concentrations. The first case was a 16-year-old boy that experienced multiple seizures, vomits, agitation and hallucinations after ingesting 9 g of bupropion. The cause of death was cardiopulmonary arrest. *Postmortem* analysis evidenced concentrations of bupropion of 5.4 mg/L and salicylate of 33 mg/L in the femoral blood. The second case was an 18-year-old female found in cardiopulmonary arrest. Autopsy evidenced pulmonary edema and 21 intact tablets of bupropion extended release 300 mg in the stomach along with 3–4 non-intact apparently white tablets. *Postmortem* analysis revealed concentration of bupropion >20 mg/L in the femoral vein. Case number 3 was a 29-year-old female also found in cardiopulmonary arrest. Autopsy evidenced pulmonary edema and 20 partially dissolved tablets in the stomach, with two similar tablets in the esophagus, and one in the duodenum. *Postmortem* analysis revealed a concentration of bupropion of 7.0 mg/L and citalopram 4.0 mg/L in the femoral blood. Case 4 was a 36-year-old man that arrived soon to the emergency room. Activated charcoal was administered. Despite the efforts, the patient deceased. Eighteen tablets of bupropion extended release 300 mg were found in the stomach and proximal small bowel during autopsy. *Postmortem* analysis showed a concentration of bupropion of 3.1 mg/L, diphenhydramine of 0.29 mg/L and lamotrigine of 3.6 mg/L on femoral vein blood. Case 5 was a 24-year-old female found in cardiopulmonary arrest. *Postmortem* analysis showed concentrations of bupropion and hydroxybupropion of 7.6 mg/L and 5.65 mg/L, respectively.

Kunz et al. (2018) reported a case of a 39-year-old man with history of drug abuse and schizophrenia that deceased due to restraint-related asphyxia in a context of excited delirium following bupropion and amphetamine

ingestion. The man exhibited violent behavior, agitation, acute exhaustive mania, delirium, imperviousness to pain, and abnormal strength. Femoral blood collected 50 min after death evidenced amphetamine levels of 255 ng/mL and bupropion levels of 1600 ng/mL.

Ramcharitar et al. (1992) were the first to study the *postmortem* distribution of bupropion using a GC/MS method in a 40-year-old female who died due to bupropion and ethanol co-ingestion. Concentrations of bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion in heart blood were 4.2 mg/L, 5.0 mg/L, 4.6 mg/L, and 0.6 mg/L, respectively. Liver and kidney analysis showed higher concentrations of the metabolites compared with bupropion. Bupropion and its metabolites were also encountered in gastric contents. Rohrig and Ray (1992) applied a GS-MS method to a *postmortem* analysis and verified concentrations of bupropion, hydroxybupropion and threohydrobupropion were 20.8 mg/L, 1.7 mg/L, and 17.8 mg/L, respectively, in heart blood and 13.8 mg/L, 17.7 mg/L, and 236.7 mg/L, respectively, in the liver. The authors also reported a total gastric content of 1582 mg of bupropion. Schmit et al. (2017) further studied the *postmortem* redistribution of bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion in a 28-year-old woman, using a LC-MS/MS method. Analysis was performed in intracranial blood, urine, bile, liver, kidney, and vitreous humor samples. The samples were collected approximately 48 h after death and the autopsy evidenced pharmacobezoar formation consisting of at least 40 tablets of bupropion sustained release 300 mg in the stomach. Concentrations of bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion were 1.9 mg/L, 8.1 mg/L, 59.3 mg/L, and 7.3 mg/L, respectively, in intracranial blood. Threohydrobupropion was the metabolite with higher concentrations in all the samples analyzed. The liver had high concentrations of both bupropion and its metabolites. Concentration of bupropion was similar in blood and in vitreous humor. The authors suggested vitreous humor could be a valuable specimen for toxicological analysis.

### Analytical clinical and forensic aspects

Several methods have been described for analysis of bupropion and its metabolites. Coles and Kharasch (2007) developed a stereoselective LC-MS/MS method to analyze bupropion and hydroxybupropion in the human plasma and urine. Denooz et al. (2010) described a ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method to

simultaneously quantify bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion in human whole blood. Yeniceli et al. (2011) reported a liquid chromatography-electrospray mass spectrometry (LC-ESI-MS) method for bupropion and hydroxybupropion analysis in rat brain microdialysates and rat plasma. Wang et al. (2012) quantified bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion in human umbilical cord plasma and placental tissue by LC-MS/MS. Laib et al. (2014) reported a high-performance liquid chromatography assay using an ultraviolet (UV) detection (HPLC-UV) method to identify hydroxybupropion in serum. Teitelbaum et al. (2016a) firstly developed a stereoselective LC-MS/MS method to analyze bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion in human plasma, and bupropion, hydroxybupropion, threohydrobupropion, erythrohydrobupropion, and glucuronide metabolites in human urine (Teitelbaum et al. 2016b). A reversed phase chiral-LC-MS/MS to stereoselectively analyze bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion in human plasma and bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion and glucuronide metabolites in human urine, was developed (Masters et al. 2016a, 2016b). Shah et al. (2017) developed a sensitive LC-MS/MS method to quantify bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion in human plasma and reported peak plasma concentrations ( $C_{max}$ ) of  $112.3 \text{ ng/mL} \pm 11.32$ ,  $245.0 \text{ ng/mL} \pm 26.95$ ,  $285.4 \text{ ng/mL} \pm 31.39$ , and  $45.2 \text{ ng/mL} \pm 3.61$ , respectively, in 12 healthy human following 100 mg of bupropion sustained release oral ingestion.

Simultaneous detection of bupropion and other antidepressants has also been presented by several authors. Petrides et al. (2014) described a turbulent flow liquid chromatography-tandem mass spectrometry (TFC-MS/MS) method to simultaneously quantify citalopram, sertraline, bupropion, and hydroxybupropion in serum. Ramirez Fernandez et al. (2016) reported a UHPLC-MS/MS method for detection of bupropion and other antidepressants in hair.

Laizure et al. (Laizure and DeVane 1985) studied the stability of bupropion and its metabolites and found that bupropion is not stable in the plasma (pH = 7.4) at room temperature (22 °C) and at 37 °C, with 74% and 23% remaining bupropion after 24 h, and 54% and 5% after 48 h, respectively. Similar degradation was observed when bupropion was incubated with phosphate buffer. Bupropion was only stable at pH of 2.5 and therefore authors concluded bupropion degrades in a log-linear



manner, proportionally to temperature and pH, possibly due to the hydrolysis of the carbon-nitrogen bond in the amine group. On the other hand, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion were stable in all the conditions tested (37 °C, pH 2.5–10 during 48 h). More recently, it was evidenced that bupropion and hydroxybupropion were stable when stored at –65 °C and at –22 °C for 297 days and also resisted at least five freeze–thaw cycles (Jain et al. 2012).

Mercerolle et al. (2008) described a liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) method to identify bupropion, hydroxybupropion and threohydrobupropion in human blood and urine. This method was applied to a forensic case of a 35-year-old male who died following a suspected intoxication with bupropion. Toxicological analysis, performed 72 h after drug intake, did not detect bupropion in femoral blood but hydroxybupropion and threohydrobupropion were identified with concentrations of 5.8 mg/L and 30.4 mg/L, respectively. Concentrations of bupropion, hydroxybupropion, and threohydrobupropion in urine were 42.9 mg/L, 100 mg/L, and 617.0 mg/L, respectively. Denooz et al. (2010) developed a ultra-performance liquid chromatography–electrospray ionization-tandem mass spectrometry (UPLC-ESI-MS/MS) method and reported better selectivity and better ability to separate threohydrobupropion and erythrohydrobupropion enantiomers than the LC-ESI-MS/MS previously reported.

From an analytical perspective, it is also important to highlight that bupropion extensively reacts with formaldehyde to form *N*-methylbupropion, being this reaction pH and concentration dependent. Indeed, after 30 d, there was complete conversion of bupropion to *N*-methylbupropion in 20% formaldehyde solution at pH 9.5 (Suma et al. 2006). This reaction has major implications when bupropion intoxication is suspected post-embalming. Several reports (Weintraub and Linder 2000; Paoloni and Szekely 2002; Casey et al. 2011) also evidence the crossreactivity of bupropion with amphetamines' immunoassay method for screening urine. Reidy et al. (2011) reported that threohydrobupropion was the main substance responsible for the false-positive results in the amphetamine Enzyme-Linked Immunosorbent Assay (ELISA) screening kits seen in the presence of bupropion.

### **Treatment of acute intoxications**

Treatment of bupropion-related intoxications is based on supportive care and focused on treatment of symptoms. Diazepam and other benzodiazepines are the first-line treatment for bupropion induced seizures and

hallucinations. Phenytoin can be used in seizures unresponsive to benzodiazepines and antipsychotics should be avoided as they can lower the seizure threshold (Spiller et al. 1994). Additional measures to manage a patient with psychotic symptoms are verbal reassurances and minimization of external stimuli (Paoloni and Szekely 2002; Jepsen et al. 2003). Sodium bicarbonate can be used for metabolic acidosis and QRS widening (Bucklin et al. 2013). Nevertheless, since bupropion QRS widening is not due to sodium channel blockade, bupropion-induced QRS widening is often unresponsive to sodium bicarbonate (Brown and Crouch 2017). Other measures proposed to deal with cardiovascular arrest are intravenous lipid emulsion and extracorporeal membrane oxygenation. Although intravenous lipid emulsion has been suggested as a treatment of refractory bupropion toxicity, it has been associated with serious adverse effects, such as cardiovascular collapse, acute lung injury, and pancreatitis (Bucklin et al. 2013). Therefore, more studies are required to evaluate the benefit of intravenous lipid emulsion in bupropion-related intoxications (Donnelly et al. 2010; Chhabra et al. 2018). VA-ECMO was reported by Heise et al. (2016) to treat refractory cardiogenic shock in two patients.

Literature data highlight the positive impact of gastrointestinal decontamination in reducing the modified release formulations absorption (Livshits et al. 2015). Indeed, reports from autopsies of bupropion-related intoxications reported the presence of unabsorbed pills in the gastrointestinal tract (Spiller et al. 2008). Taking this into consideration, gastric lavage and whole bowel irrigation might be beneficial in selected cases. Another option used to treat acute intoxications is active charcoal administration (Gulec et al. 2016). Indeed, Chao et al. (2012) reported a case treated with charcoal hemoperfusion that resulted in a faster QTc prolongation recovery.

### **Genotoxicity and carcinogenicity**

The genotoxic and carcinogenic potential of bupropion has been addressed in the documentation submitted by pharmaceutical companies to regulatory agencies (e.g. FDA; European Medicines Agency, EMA), in the commercially available compilations of information on prescription drugs (e.g. Physicians' Desk Reference, PDR), in some review articles on the genotoxicity/carcinogenicity of human drugs (Snyder and Green 2001; Brambilla and Martelli 2009; Brambilla et al. 2009; Snyder 2009), and also in a few experimental articles published in periodic scientific journals (Roshdy and



Fyad 2010; Hassan et al. 2011; Bhattacharya et al. 2013).

The preclinical toxicology of bupropion was reported approximately 35 years ago by Tucker (1983). This author based on experimental data considered as unlikely the potential of bupropion to cause teratogenic, mutagenic, or carcinogenic effects in man. Nevertheless, preclinical studies performed to assess the safety of bupropion hydrochloride disclosed some genotoxic potential at gene and chromosome level, although negative genotoxicity data have also been reported. Using the classical reverse mutation Ames test, bupropion increased in two to three times the mutation rate in two of five *Salmonella typhimurium* strains when compared with untreated controls. This information is stated in different literature sources, being the response obtained in the Ames test described as “positive” (Snyder and Green 2001), “weakly positive” (Brambilla and Martelli 2009; Brambilla et al. 2009), or “borderline positive” as mentioned in the prescribing information of Wellbutrin® of 2009. In this document, and in its updated version of 2017, the genotoxic potential of bupropion in an *in vivo* rodent cytogenetic assay has also been referred. In fact, bupropion was found to be clastogenic in one of three *in vivo* rat bone marrow cytogenetic studies. This response occurred at the highest oral dose level (300 mg/kg), whereas at 100 or 200 mg/kg, no genotoxic effects were observed. It is also stated that this *in vivo* response corresponded to a low incidence of chromosomal aberrations induced by bupropion.

### Reviews on genotoxic and carcinogenic potential

Snyder and Green (2001) published a review article based on a survey of information contained in the 1999 PDR (United States) and in existing peer reviewed articles on the genotoxicity of marketed pharmaceuticals. The authors compared the available genetic toxicology information with the rodent carcinogenicity data. Accordingly, the genotoxicity results for bupropion were considered positive, although the carcinogenicity studies were classified as negative (mouse and rat models), leading these authors to categorize the cytogenetic findings as “false positive.” Nevertheless, while considering bupropion as non-carcinogenic, they also noticed that this drug induces preneoplastic proliferative liver lesions. In a subsequent study, Snyder et al. (2004) compared the genotoxicity data with the information arising from computational toxicology approaches (i.e. programs DEREK, TOPKAT, and MCASE). Bupropion was included in the group of “Ames positive drugs” that were poorly predicted by the computational

models. In fact, only the MCASE program was sensitive, detecting an aromatic amine alert, which was, however, disregarded by these authors, being considered an improper structural alert for the positive response observed. The authors concluded that the positivity of bupropion in the Ames test is not attributable to structure/pharmacology, mentioning that the mechanisms involved are unknown. In addition, no structural alerts were noticed with any program for the positive results observed in the *in vivo* cytogenetic assay (chromosomal aberrations). The information concerning the above-mentioned results of bupropion in terms of genotoxicity, carcinogenicity, and *in silico* evaluation is also present in the updated review by Snyder (Snyder 2009). In addition, other authors performed an *in silico* assessment of the mutagenic potential displayed by a large number of chemicals with available results for the Ames test (Hayashi et al. 2005). In this report, bupropion was categorized in a group of “exceptional chemicals,” that although being mutagenic consistently presented negative results using the commercially available *in silico* systems (i.e. DEREK, MCASE, TOPKAT/AWorks).

References to bupropion are also included in other comprehensive reviews on the genotoxicity and *in vivo* carcinogenicity of drugs (Brambilla and Martelli 2009; Brambilla et al. 2009). The data concerning bupropion carcinogenicity in mice was also reported as negative whereas inconclusive results were considered in the rat model. More recently, Amerio et al. (2015) published a systematic review of psychotropic drugs in the US, using the FDA-required preclinical long term studies, and classified bupropion in the group of drugs associated with carcinogenesis, mentioning the negative results in mice (150 mg/kg/d lifetime exposure), but positive results in rats (300 mg/kg/d, lifetime exposure), with an increased incidence of nodular proliferative hepatic lesions.

### Genotoxic evaluation in mammalian endpoints

Only a few experimental studies addressing the genotoxic effects of bupropion are available. Nevertheless, the assessment of the *in vitro* genotoxic effects of bupropion hydrochloride (Wellbutrin®) in human peripheral blood lymphocytes (whole blood) was reported, resorting to the cytokinesis blocked micronucleus assay (CBMN), sister chromatid exchanges assay (SCE), and comet assay (Bhattacharya et al. 2013). In this study, bupropion was genotoxic in the comet assay at concentrations of  $\geq 25 \mu\text{M}$  whereas higher concentrations were needed to induce significant results in terms of SCE (200  $\mu\text{M}$ ) or micronuclei (MN, 300 and 400  $\mu\text{M}$ ):

Regarding the CBMN assay it is important to note that the exposure to bupropion at the beginning of the culture or at 24 h resulted in negative MN results, although impaired cell division was clearly observed (i.e. nuclear division index reduction). Concentration-dependent positive results were only achieved when the authors used a different protocol, with the exposure to bupropion at 44 h, leading to the conclusion that this drug is a weak MN inducer in human lymphocytes, requiring specific experimental conditions for the observation of positive genotoxicity results.

The clastogenic effects of bupropion hydrochloride in adult male albino mice were evaluated by Roshdy and Fyad (2010) using a 14-d oral treatment protocol (0.2 and 0.4 mg/kg/d). The authors reported abnormal sperm head shapes as well as structural and numeric chromosome aberrations in spermatocytes. This genotoxicity pattern was also observed in the cytogenetic evaluation of bone marrow cells, leading the authors to conclude that bupropion hydrochloride is considered mutagenic and therefore should be subjected to careful medical supervision. Other authors using the same animal model, reported that the seeds of the Fennel plant and anethole reduced the clastogenic effects of bupropion hydrochloride (Hassan et al. 2011).

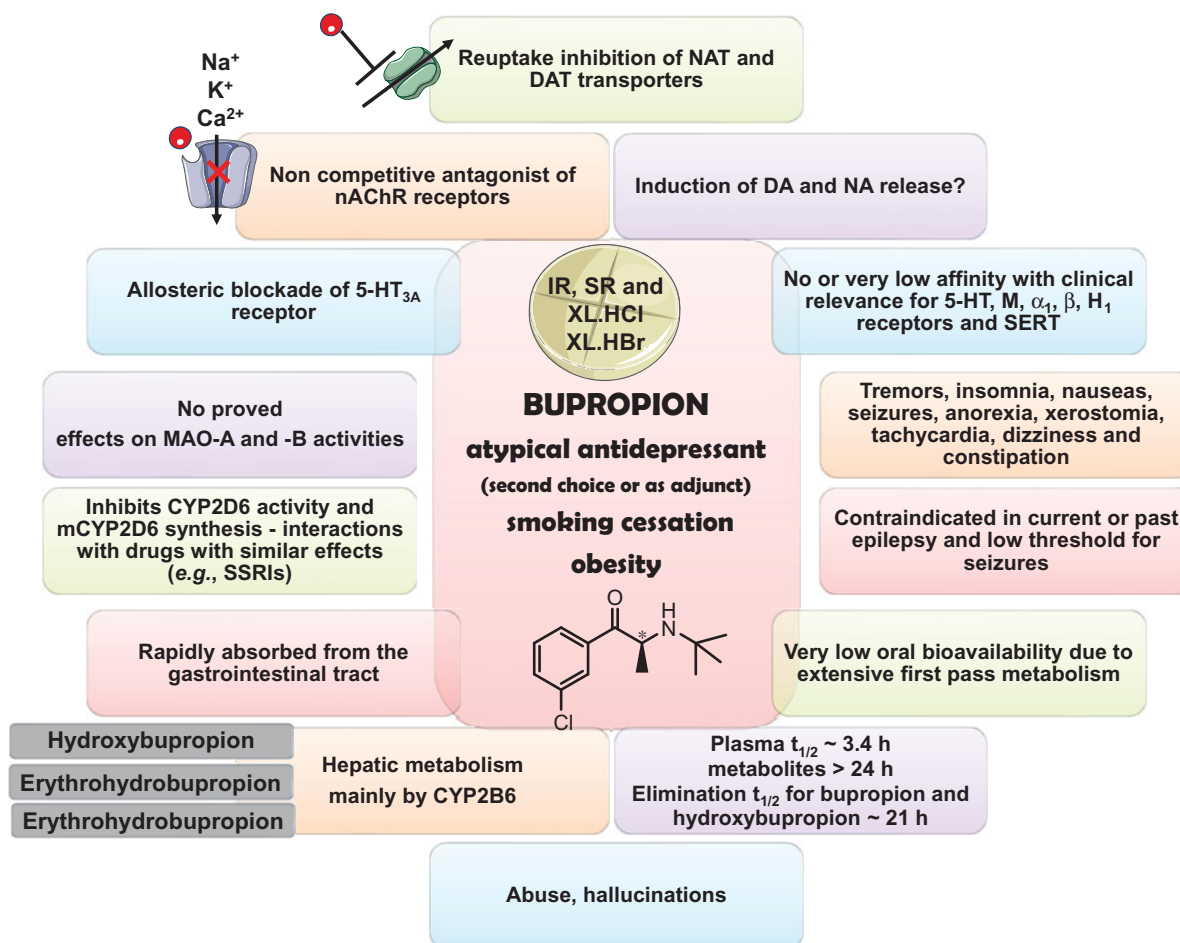
### **2-Bromo-3-chloropropiophenone (BCP): the case of a bupropion mutagenic impurity**

The presence of mutagenic impurities in drug substances represents a major concern of public health. The ICH M7(R1) guideline addresses this topic in order to limit the carcinogenic risk of impurities (ICH. 2017). Meng et al. (2013) evaluated the genotoxic effects of 2-bromo-3'-chloropropiophenone (BCP) in the Ames test (*Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537) and in the *in vitro* MN assay (TK6 human lymphoblastoid cells, flow cytometry), with and without S9 metabolic activation. This study is considered pertinent since BCP is an intermediate chemical in the synthesis of bupropion, being recognized as a relevant impurity present in bupropion hydrochloride. According to the US Pharmacopeia, the limit of BCP is 0.1%, which can represent exposure levels of 150 or 300 µg/d (for prescribed doses of 150 and 300 mg, respectively), much higher than the limit of 1.5 µg/d. This value corresponds to the Threshold of Toxicological Concern (TTC)-based acceptable daily intake for mutagenic impurities in pharmaceuticals (ICH 2017). The results from the study of Meng et al. (2013) revealed that BCP is clearly mutagenic in the presence of S9 increasing the background frequency rate in 22- and 145-folds for strains TA100 and TA153, respectively.

Without S9, and for the other Ames strains no increase was observed. An increase in the MN frequency up to ~5-fold was also observed (with and without S9) and BCP revealed to possess aneugenic potential. The authors suggested that the genotoxicity of BCP was mediated by the formation of ROS and reactive metabolites.

### **Conclusion and future perspectives**

Since its introduction in the market in 1989, bupropion has been proposed for several clinical conditions, namely depression and in the treatment of smoking cessation aid. However, with over 40 million patients worldwide prescribed with bupropion (Fava et al. 2005), understanding the possible causes of intersubject complex pharmacokinetic and pharmacodynamic variability is critical to assure safety and efficacy. Figure 3 highlights major clinical, pharmacokinetic and pharmacodynamic aspects of bupropion. Bupropion is a synthetic cathinone that exerts its effects through inhibition of dopamine, noradrenaline reuptake and inhibition of nicotinic receptors (Damaj et al. 2004; Shalabi et al. 2017). Bupropion is cleared via oxidation by cytochrome P450 to hydroxybupropion and 4'-hydroxybupropion and via reduction by 11β-HSD-1 and aldo-ketoreductase to threohydrobupropion and erythrohydrobupropion. All four metabolites undergo glucuronidation, and threo- and erythrohydrobupropion are also hydroxylated to threo-4'-hydroxy- and erythro-4'-hydroxy-hydrobupropion (Gufford et al. 2016; Sager et al. 2016a, 2016b, 2017). The metabolic polymorphic pathway of bupropion is considered crucial to explain the interindividual and interspecies variability in dose-response. Indeed, bupropion exerts antidepressant effects in a mouse model (Musso et al. 1993), which metabolizes bupropion mainly to hydroxybupropion, but it is incapable of exerting that effect in rat models (Welch et al. 1987), which metabolizes bupropion mainly by side-chain cleavage. Hydroxybupropion was thought to be the major active metabolite since the early published reports, being thus extensively studied. However, information available about the pharmacological effects of threohydrobupropion and erythrohydrobupropion, the two other active metabolites of bupropion is scarce. Therefore, dosing bupropion and its metabolites and genotyping metabolizing enzymes and pharmacological targets (Swan et al. 2005; Swan et al. 2007; Choi and Shin 2015) might have a role in the future to evaluate the patient's response to bupropion. Given bupropion instability in biological



**Figure 3.** Pharmacokinetic and pharmacodynamic aspects of bupropion. nAChRs: nicotinic acetylcholine receptors; DA: dopamine; NA: noradrenaline; CYP2B6: cytochrome P450; 5-HT<sub>3A</sub>R: 5-hydroxytryptamine type 3A receptor; SSRIs: selective serotonin reuptake inhibitor; IR: immediate release; SR: sustained release; XL: extended release; SERT: serotonin transporter.

samples (Laizure and DeVane 1985), toxicological analysis must target both bupropion and its major metabolites. It is also important to be aware of the chiral inversion of bupropion stereoisomers that may confound some *in vitro* to *in vivo* extrapolations. However, this artifact proved to have a minor influence in altering *in vivo* bupropion *R/S* ratios dependent on the CYP2B6 activity (Sager et al. 2016b). Due to the bioactive enantiomer's differences, a stereoselective bioanalytical method for bupropion, hydroxybupropion, erythrohydrobupropion, and threohydrobupropion was recently validated (Teitelbaum et al. 2016a, 2016b). Further studies concerning bupropion HBr are also needed to clarify the implication in the bromism, a toxic syndrome characterized by neurologic, psychiatric and dermatologic adverse effects, when high amounts of bromide are ingested (Bowers and Onoroski 1990; Shader 2009).

Finally, more research on bupropion, its metabolites and analogs is aimed to evaluate their clinical

significance and safety profiles, including their genotoxicity potential and *postmortem* redistribution behavior. In addition, although oral administration of bupropion is thought to have low abuse potential, recreational use of bupropion through other routes, such as nasal insufflation and intravenous administration of crushed tablets is increasing (Hilliard et al. 2013; Stall et al. 2014; Schifano and Chiappini 2018), being this a worrying issue. Bupropion abuse is often encountered in individuals with a history of drug abuse and/or without easy access to other psychostimulants (e.g. incarcerated individuals). Therefore, it becomes crucial for clinicians to be aware of the abuse potential of this drug and to give close attention to possible red-flags that might suggest a patient is abusing bupropion.

### Disclosure statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment,

consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received, or pending or royalties. No writing assistance was utilized in the production of this manuscript.

## Funding

This work was supported by grants from CESPÚ (TramTap-CESPU-2016, Chronic-TramTap\_CESPU\_2017 and TraTapMDMA-CESPU-2018) and Fundação para a Ciência e a Tecnologia (UID/DTP/04138/2013).

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