Nonresponse to high-dose bupropion for depression in a patient carrying *CYP2B6**6 and *CYP2C19**17 variants: a case report

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We report the case of a patient with major depression treated with high-dose bupropion due to prior detected subtherapeutic blood concentrations at standard dosing. Pharmacogenetic panel testing identified the patient as a carrier of the *CYP2B6**6 allele, which has been associated with reduced bupropion metabolism and decreased concentrations of the pharmacologically active metabolite hydroxybupropion. Interestingly, we also found the patient to be homozygous for the *CYP2C19**17 allele, predicting an ultra rapid metabolizer phenotype. We propose a combined effect of the detected *CYP2C19* and *CYP2B6* genetic variants on bupropion metabolism. This case underlines the potential benefit of pre-emptive pharmacogenotyping but also the yet still fragmentary evidence making precise pharmacogenotype guided antidepressant selection and dosing challenging.

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Depressive disorders show interindividual courses of disease but often proceed in recurrent episodes. In fact, half of the affected patients suffer from at least one further episode after the first one [1] and up to 20 % even develop a chronic course of depression [2]. Consequently, the need for effective treatment is high. However, about 50% of treated unipolar depressive patients do not experience remission under a first-line antidepressant treatment [1]. Furthermore, clinical treatment response in an acute depressive episode can only be assessed after several weeks of drug exposure [3], potentially making finding an effective treatment time consuming and exhausting for the patient.

One of the compounds used in antidepressant therapy is the selective noradrenaline and dopamine reuptake inhibitor bupropion. Besides, its use as an antidepressant, bupropion is also approved for supportive therapy in smoking cessation. Furthermore, it is considered a probe substrate for *CYP2B6* and is part of various phenotyping assays including the widely used Geneva cocktail [4].

The parent compound bupropion is extensively metabolized giving rise to three major metabolites namely hydroxy-, threohydro- and erythrohydrobupropion, which are all pharmacologically active [5]. Hydroxy- and threohydrobupropion are considered to play an important role in the antidepressant effect of bupropion [5]. However, the aforementioned hydroxybupropion is the most active metabolite, exhibiting 50% of the parent molecule's pharmacologic effect [6]. Hydroxybupropion is a product of cytochrome P450 mediated hydroxylation, predominantly catalyzed by *CYP2B6* [7]. The stereoisomers threohydro- and erythrohydrobupropion are both formed by the carbonyl reductases HSD11B1 and the aldo-keto reductase AKR7 in the liver and intestine [8]. The aforementioned Phase I metabolites are then further glucuronidated or excreted directly via urine [9,10].

Besides these very well described steps in the metabolism of bupropion, there has recently been data published, proposing a relevant contribution of *CYP2C19* in hydroxylation at the 4' benzo position of bupropion,

Figure 1. Illustration of the major steps in Phase I bupropion metabolism.

threo- and erythrohydrobupropion [11,12]. Hitherto, neither an antidepressant effect nor pharmacologic activity in general has been described for 4'-hydroxybupropion. However, the formation of the stereoisomers 4'-hydroxythreo- and 4'-hydroxyerythrohydrobupropion via CYP2C19 was shown to be a major elimination pathway for the underlying active metabolites threo- and erythrohydrobupropion [11] (Figure 1).

Together with bupropion, current therapeutic drug monitoring (TDM) guidelines recommend assessment of the CYP2B6 product hydroxybupropion, as its serum concentration was found to be predictive for clinical response to bupropion in a psychiatric setting [13,14]. Moreover, bupropion's chemical instability is a relevant limitation for its use in TDM. Hence, TDM reference values of bupropion are primarily based on hydroxybupropion with only minor contribution of bupropion (850–1500 ng/ml) [13].

Case report

We herein report the case of a male, 38-year old patient, diagnosed with a recurrent depressive disorder (ICD-10 F33). He admitted himself to our hospital in December 2019 due to an acute deterioration of the current depressive episode with intercurrent visual and acoustic hallucinations. However, psychotic symptoms could not be clinically confirmed during the course of the hospitalization. He was diagnosed with a currently moderate depressive episode (ICD-10 F33.1) under treatment with a combination of bupropion (1050 mg/d), lithium (36.5 mmol/d) and trazodone (200 mg/d) at admission. Notably, the recommended maximum daily dosage of bupropion in depression treatment according to Swiss summary of product characteristics is 300 mg. Upon request, the prescribing outpatient psychiatrist explained to have performed this unusual dose escalation due to clinical ineffectiveness under regular doses of bupropion and based on TDM data (Table 1). Importantly, the patient has a medication history with inefficacy of various antidepressant pharmacotherapies since the age of 22. According to the patient, the so far unsuccessful antidepressant treatment attempts included escitalopram, sertraline, paroxetine, duloxetine, clomipramine, agomelatine, moclobemide, venlafaxine, fluvoxamine, fluoxetine, mirtazapine and reboxetine.

During the first 7 days of hospitalization bupropion dosage was steadily reduced to 300 mg per day. Resulting in subtherapeutic trough serum levels after reaching steady state (Table 1). Importantly, there was no evidence neither for a lack of adherence nor for drug–drug interactions explaining the low steady state serum concentration.

Table 1. Collected trough serum levels of total bupropion + hydroxybupropion with relevant therapeutic reference range of 850–1500 ng/ml, analyzed applying high-performance liquid chromatography-mass spectrometry/mass spectrometry.

Collection date	Bupropion dosage (mg/d)	Trough serum level (ng/ml)	Setting
07 November 2019	400	412	Outpatient
28 November 2019	1050	1003	Outpatient
17 December 2019	300	396	Inpatient

Table 2. Selected results of panel-pharmacogenotyping and phenotype interpretation.

Gene	Variant	Genotype	Predicted phenotype
<i>CYP1A2</i>	rs762881 g.75041917C>A (in *1F)	A/A	Increased inducibility (UM)
<i>CYP2B6</i>	rs3745274 c.516G>T (in *6)	G/T	Reduced function (IM)
<i>CYP2C19</i>	rs12248560 g.4195C>T (in *17)	T/T	Increased function (UM)
<i>CYP2D6</i>	rs3892097 c.506-1G>A (in *4)	G/A	Reduced function (IM)
<i>CYP2D6</i>	rs1065852 c.100C>T (in *4 and *10)	C/T	Reduced function (IM)
<i>ABCB1</i>	rs2032583 c.2685 + 49T>C	T/T	Wild type

IM: Intermediate metabolizer; UM: Ultra rapid metabolizer.

Meanwhile, adequate lithium serum levels (0.97 mmol/l, therapeutic reference range: 0.6–1.0 mmol/l) and normal range of hepatic – and kidney function laboratory values were detected (e.g., serum creatinine, total bilirubin, ALAT and ASAT).

Due to the patient's medication history with 16 years of difficulties in therapeutic management and the known involvement of *CYP2B6* in metabolism of bupropion, a pharmacogenetic consultation by clinical pharmacists of the hospital was conducted after written informed consent of the patient. This intervention is part of an observational study approved by the local ethics committee. Panel-pharmacogenotyping was conducted applying the commercial service Stratipharma[®] offered by humatrix AG (Pfungstadt, Germany). In their laboratory, the polymorphisms are determined applying real-time PCR using the automated Life Technologies QuantStudio 12 k flex (Thermo Fisher, MA, USA) with the respective optimized and commercially available chemistry. Interpretation of the genotype identified the patient as *CYP2C19* ultra rapid metabolizer (UM; *17 homozygous) and *CYP2D6* intermediate metabolizer (IM; *4 heterozygous), while also exhibiting the genotypes resulting in reduced function of *CYP2B6* (*6 heterozygous) and increased inducibility of *CYP1A2* (*1F homozygous). Furthermore, the patient shows no variation at the analyzed *ABCB1* gene locus (Table 2). Especially the present *CYP2C19* predicted ultra rapid metabolizer phenotype could very likely be an important cause for many of the previously ineffective antidepressant therapies (i.e., escitalopram, sertraline, moclobemide and clomipramine). Additional genetic markers might also have played a role in the patient's history of antidepressant therapy failure, including *CYP1A2**1F (i.e., agomelatine and duloxetine) and *ABCB1* wild type (i.e., escitalopram and venlafaxine).

Based on the patient's medication history, his genetic profile and the known contribution of *CYP1A2*, *CYP2C19* and *CYP2D6* to the metabolism as well as *ABCB1* to the transport of various antidepressants, the following substances would have been recommended to be used in this patient: trazodone or mianserin. However, due to the long history of antidepressant treatment resistance and chronification of the depressive disorder, the patient refused further adaption of the antidepressant pharmacotherapy and was referred to a clinic specialized in electroconvulsive therapy for further treatment.

Discussion

Considering that both cytochromes *CYP2B6* and *CYP2C19*, which are extensively involved in bupropion metabolism, are highly polymorphic, one might expect a relevant impact of genetic variability on interindividual differences of pharmacokinetics and eventually response to bupropion.

The impact of *CYP2B6* polymorphisms on bupropion pharmacokinetics has been studied before, associating *CYP2B6**6 allele carriers with reduced bupropion metabolism and decreased hydroxybupropion serum concentrations [15–17]. The pharmacogenomics knowledge for personalized medicine database rates this drug–gene interaction with moderate evidence and likely functional significance (level 2A) [18]. On the other hand, there is so far only

limited evidence linking *CYP2C19* genetic variation to altered bupropion pharmacokinetics. Hitherto, only a limited number of studies have been published, investigating the effect of *CYP2C19* polymorphisms on bupropion pharmacokinetics and therapeutic effectiveness [19,20]. The most conclusive study that was able to differentiate between metabolizer phenotypes, showed an impact of the predicted reduced activity variant (*CYP2C19**2) on bupropion, threohydro- and erythrohydrobupropion blood concentrations. However, in this trial the *17 variant did not reach statistical significance due to under-representation in a study population of 42 healthy volunteers undergoing smoking cessation [19]. Nevertheless, as mentioned before several studies were able to provide evidence for the impact of *CYP2C19* on bupropion pharmacokinetics [11,12], supporting the hypothesis that *CYP2C19* genetic variation might play a role in modulating bupropion metabolism.

The predicted *CYP2C19* ultra rapid metabolizer status, overall, potentially causes increased metabolic degradation of the active substance via *CYP2C19*. Furthermore, the predicted reduced *CYP2B6* activity might even enhance the alternative elimination pathway via *CYP2C19*. In conclusion, we attribute the striking subtherapeutic bupropion serum levels and observed unsatisfactory therapy response to a combined effect of the detected *CYP2C19* and *CYP2B6* genetic variants. Notably, we are reporting the case of a single patient in clinical routine care. Accordingly, this certainly limits the conclusions that can be or should be drawn from the observation. Another limitation is that due to the routine care setting, where a psychiatrist not linked to our clinic has also taken part in the patient's treatment, we are restricted to the data we are reporting. Importantly, we do not have access to any further blood samples, which could be used to determine the levels of any of the bupropion metabolites to strengthen our hypothesis.

There is yet more research needed to fully understand the possibly combined impact of *CYP2B6* and *CYP2C19* genotypes on bupropion metabolism and therapeutic response in depression therapy. According to pharmacogenomics knowledge for personalized medicine database, the average frequency of both *CYP2B6**6 and *CYP2C19**17 alleles is over 20 % in the European population [18], which emphasizes the potential clinical importance of these variants. Currently there are no guidelines available for genotype guided dosing and selection of bupropion.

It may be speculated, that with an early-panel pharmacogenotyping the patient may have been treated more adequately in terms of compound selection and dosing. However, there is still not enough evidence to formulate precise and definite recommendations for drug and dose selection in antidepressant pharmacotherapy. This case shows the need to perform further prospective studies to examine the use of pre-emptive pharmacogenotyping and thereof driven therapeutic recommendations.

Executive summary

Case report

- A male, 38-year old patient, diagnosed with a recurrent depressive disorder (ICD-10 F33), suffering from a moderate depressive episode (ICD-10 F33.1) at clinic admission.
- The patient shows a long history of unsatisfactory response to various antidepressants.
- Detection of subtherapeutic bupropion serum levels under recommended maximum daily dosage.

Selected results of panel-pharmacogenotyping

- *CYP2B6**6/*1 (reduced function and intermediate metabolizer), *CYP2C19**17/*17 (increased function and ultra rapid metabolizer).

Discussion

- The role of *CYP2B6* and *CYP2C19* in bupropion pharmacokinetics is well described.
- The evidence showing an impact of genetic variation on bupropion pharmacokinetics is still limited, especially for *CYP2C19*.
- We propose a combined effect of the detected *CYP2C19* and *CYP2B6* genetic variants on bupropion metabolism.

Conclusion

- There might be a potential benefit in early panel-pharmacogenotyping for antidepressant selection and dosing.
- The evidence to allow precise antidepressant selection and dosing based on results from pharmacogenotyping is still fragmentary.

Author contributions

CK Stäuble, ML Lampert, KE Hersberger and HE Meyer zu Schwabedissen were involved in the study design. CK Stäuble, ML Lampert and HE Meyer zu Schwabedissen were responsible for the interpretation of the genotyping data. T Mikoteit and M Hatzinger were responsible for the psychiatric clinical assessments. CK Stäuble wrote a first version of the manuscript and T Mikoteit,

M Hatzinger, ML Lampert, KE Hersberger and HE Meyer zu Schwabedissen contributed additional content and were responsible for critical revision.

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No writing assistance was involved in the preparation of the manuscript.

Ethical conduct of research

The local ethics committee approved the underlying observational study (2019-01452).

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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