ORIGINAL RESEARCH

CYP2D6 genotype can help to predict effectiveness and safety during opioid treatment for chronic low back pain: results from a retrospective study in an Italian cohort

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Background: Opioids are widely used for chronic low back pain (CLBP); however, it is still unclear how to predict their effectiveness and safety. Codeine, tramadol and oxycodone are metabolized by CYP/CYP450 2D6 (CYP2D6), a highly polymorphic enzyme linked to allele-specific related differences in metabolic activity.

Purpose: *CYP2D6* genetic polymorphisms could potentially help to predict the effectiveness and safety of opioid-based drugs in clinical practice, especially in the treatment of CLBP.

Patients and methods: A cohort of 224 Italian patients with CLBP treated with codeine or oxycodone was retrospectively evaluated to determine whether adverse reactions and effectiveness were related to *CYP2D6* single-nucleotide polymorphisms. *CYP2D6* genotyping was performed using the xTAG® CYP2D6 Kit v3 (Luminex) to determine *CYP2D6* metabolizer phenotype (poor, intermediate, rapid and ultrarapid). Subjects from the cohort were categorized into two groups according to the occurrence of side effects (Case) or benefit (Control) after chronic analgesic treatment. The impact of *CYP2D6* polymorphism on treatment outcome was tested at the metabolizer phenotype, diplotype and haplotype levels.

Results: *CYP2D6* polymorphism was significantly associated with opioid treatment outcome (Omnibus P=0.018, for both global haplotype and diplotype distribution test). *CYP2D6**6 and *9 carriers, alleles characterized by a reduced (*9) or absent (*6) enzymatic activity, were significantly (P<0.05) associated with therapeutic failure. *CYP2D6* ultrarapid metabolizers (*CYP2D6**2N patients) showed an increased risk of side effects, as would be predicted. Despite their low frequency, *CYP2D6* *1/*11, *4/*6 and *41/* 2N diplotypes showed significant (P<0.05) associations of efficacy and side effects with chronic opioid treatment.

Conclusion: Our results showed that reduced CYP2D6 activity is correlated with lack of therapeutic effect. We found that the pharmacogenetic analysis of *CYP2D6* could be helpful in foreseeing the safety and effectiveness of codeine or oxycodone treatment in CLBP.

Keywords: polymorphisms, pharmacogenetics, codeine, oxycodone, analgesic drugs, personalized medicine

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Introduction

Chronic low back pain (CLBP) is a common disease difficult to manage due to its complex pathogenesis.[1] Several prognostic factors, such as demographic (sex, age and cultural/educational environment),[2] occupational (type of work activity)[3] and psychological (anxiety, pain catastrophizing and depression),[4] have been claimed as important determinants of CLBP. Given the inflammatory nature of CLBP, several

studies have evaluated biomarkers related to inflammatory response, rather than those related to disk degeneration.[5] Indeed, the combination of age, leptin and MCP-1 predicted 61% of the risk of LBP duration, suggesting these analytes as promising biomarkers for the diagnosis of acute low back pain (LBP) and its risk to become chronic.[6] During the last years, the scientific community has witnessed the mounting interest in genomics and pharmacogenetics as possible tools to predict both the risk to develop CLBP and the effectiveness and safety of pharmacological treatments.[7–10] Moreover, some patients experience pain processing disorders and they may be also at risk for opioid addiction.[11,12] Recently, it has been suggested that pharmacokinetic and pharmacodynamic evaluation of drugs could be helpful in improving the effectiveness[13] and in preventing, at the same time, the onset of tolerance and hyperalgesia.[14] Hence, personalized medicine is one of the most promising solutions to maximize the effectiveness and reduce the risk of side effect in patients' treatment.[15]

Most of the drugs, especially opioids used for chronic pain therapy, are being metabolized by the hepatic enzyme CYP/CYP450 2D6 (*CYP2D6*, located on chromosome 22q13.2, OMIM*124030).[16] Indeed, the genetic polymorphism of cytochrome 450 (P450) determines interindividual variability in the metabolism of many drugs, with relevant implications in terms of efficacy and safety, and significantly affecting the pharmacokinetics of about 50% of the drugs in clinical use.[17–20]

Among opioids, codeine and oxycodone are the most prescribed drugs being activated by CYP2D6.[21–24] Based on the extent of CYP2D6 substrate metabolism, the population can be categorized into four different groups: extensive metabolizers (EMs), intermediate metabolizers (IMs), poor metabolizers (PMs) and ultrarapid metabolizers (UMs).[25]

The frequencies of CYP2D6 metabolizer phenotypes in Caucasians are: PMs, 5%–10%; IMs, 10%–15%; EMs, 65%–80% and UMs, 5%–10%.[17,26–28]

As ultrarapid CYP2D6 metabolizer's patients would need higher drug doses, they are more at risk to develop not only more side effects[19] but also lower drug's dosages in the meantime lower dosage.[29]

Morlock and Braunstein have underlined the positive pharmacoeconomic impact of a pharmacogenetics-based treatment in patients with chronic pain.[30] Nevertheless, there is no clear evidence of the role of widespread genetic analysis in patients with chronic pain.

In this retrospective study, we investigated how *CYP2D6* genotyping could be helpful in predicting the effectiveness and side effects in a cohort of CLBP Italian patients clinically treated with codeine/acetaminophen or oxycodone.

Patients and methods
Subjects
The patients were enrolled in the PainOMICS study, a large multicenter study funded by the European Community in the Seventh Framework Program (FP7) – THEME (HEALTH.2013.2.2.1-5 – understanding and controlling pain) to evaluate the genomics, glycomics and activomics of biomarkers related to pain. The protocol[7] has been approved by the Ethical Committee at the University of Parma and all the participating clinical centers. It has been registered on clinicaltrials.gov (NCT02037789). All patients enrolled have signed a written informed consent.

Inclusion and exclusion criteria of PainOMICS project have been previously published.[7] In the present study, we considered all CLBP patients whose physicians had decided to prescribe codeine/acetaminophen or oxycodone for pain treatment, and categorized the patients showing side effects and no pain relief from the opioid treatment as "Case" and those patients who reported pain relief with opioid treatment without side effects as "Control". We excluded all patients with possible drug–drug interaction (DDI) with ongoing treatments.[13,31]

As the primary endpoint, we evaluated the correlation between pharmacokinetic *CYP2D6* pattern and the effectiveness/safety of codeine/acetaminophen or oxycodone in the visit after the first prescription. We considered the treatment effective if it had led to a reduction of at least 30% of pain, evaluated by the Brief Pain Inventory. As a safety measure, we registered the onset of severe side effects (nausea, vomiting, dizziness) that would determine the patients' decision to withdraw from the treatment.

Patients were stratified into two groups according to the genetic factors that may contribute to variability in drug response and that can help maximize the likelihood of efficacious treatment by minimizing the adverse drug reactions (ADRs):[32,33] patients showing effectiveness of the drug and no severe side effects and patients showing no effectiveness of the drug and/or severe side effects that prejudice the treatment continuation.

Patients enrolled were also stratified into four groups according to their corresponding *CYP2D6* metabolizing phenotype.[17,26–28]

Pharmacogenetic analysis
Blood sample collection and analysis were performed according to the previously determined personalized standard operat-

ing procedures.[34] *CYP2D6* genotyping was performed using the xTAG® CYP2D6 Kit v3 (Luminex). Briefly, genomic DNA, extracted from whole blood and collected in vacutainer with EDTA, was purified with a DNA purification Kit (cod. AS1010; Promega) using an automatic system Maxwell16 (Promega). Genomic DNAs were quantified using a Nano-Drop ND-1000 spectrophotometer, adjusting the concentration of each sample in the range of 24–1,800 ng. The xTAG CYP2D6 Kit v3 detects a comprehensive panel of functional *CYP2D6* nucleotide variants, including gene rearrangements associated with the deletion (*5) and duplication genotypes. The assay incorporates multiplex PCR and multiplex Allele-Specific Primer Extension with Luminex's Universal Tag sorting system on the Luminex® 100/200™ xMAP® platform based on the principles of flow cytometry which integrates key xMAP detection components such as lasers, optics, fluidics and high-speed digital signal processors. The test automatically determines the diplotype of each sample (Table 1).

Results have been reported with the xTAG Data Analysis Software (TDAS CYP2D6, applies algorithms to the mean fluorescence intensity values produced[57] by each sample to generate automated genotyping calls for each mutation easy). Data acquisition protocols for Luminex IS and xPONENT3.1 software were designed for protocol-based data acquisition with robust data regression analysis. Each run included at least one DNase/RNase-free water controls (TDAS automatically assigns the last sample the primary negative) and commercially available *CYP2D6* controls as positive controls. The assignment of *CYP2D6* genotypes to each metabolizer phenotype was carried out according to Table S1, as reported in the Luminex xTAG CYP2D6 Kit.

CYP2D6 haplotype frequencies in the population analyzed were compared to the ones reported in the literature (Table 2).

Statistical analysis

Demographic variables were reported as mean±SD. Associations between the three assigned phenotype groups (poor, intermediate to extensive and ultrarapid) and outcomes (poor pain control, adverse reaction or either) were assessed using chi-squared tests for categorical variables.

CYP2D6 diplotype and haplotype frequencies were tested using UNPHASEDv. 3.1.7[65] under an additive model and adjusting for sex and age at sampling. We set the statistical significance for the haplotype-based analyses at a global *P*-value of <0.05. Analyses excluded haplotypes with a frequency <1%.

Results

One thousand patients were enrolled in the University Parma's Pain Center for PainOMICS study between June 2014 and February 2016.

Two hundred and twenty-four Italian patients (22.4% of PainOMICS Project participants), 78 males and 146 females, with a mean age 66.8 years (±14.3), were selected since they had been treated with one of the two drugs considered (109 patients treated with codeine/acetaminophen and 115 with oxycodone). Thirteen patients were excluded for possible DDI,[66] while 15 patients were excluded because of genotyping failure. Hence, a total of 196 patients (66 males and 130 females) were analyzed.

Ninety-seven and 99 patients had been treated with codeine/acetaminophen and oxycodone or oxycodone/naloxone, respectively.

Twenty-seven (13.8%) patients showed side effects/or no pain relief from opioid treatment (Case) and 169 patients (86.2%) reported pain relief with opioid treatment (Control), as shown in Figure 1.

Approximately 15% of the Italian population considered in the two groups receive one or more prescriptions in addition to the opioid.

Demographic and clinical characteristics of the volunteers enrolled are summarized in Table 3.

The EM phenotype was the most frequent in both Case and Control groups, representing 78% and 80%, respectively, of the group studied; the IM/PM (reduced metabolic activity) phenotype frequencies were 15% and 17%, and the UM (increased metabolic activity) accounted for 7% and 3% of the studied groups (Figure 2).

Distribution of *CYP2D6* metabolizer phenotypes in the two groups studied according to sex showed no significant differences (Case, Fisher's exact test *P*=0.304; Control, Fisher's exact test *P*=0.302), as shown in Table 4.

CYP2D6 haplotype and diplotype distributions displayed significant differences in the "Case" *and* "Control" groups (Omnibus *P*=0.018, for both global haplotype and diplotype distribution test) (S1). *CYP2D6**6 (PM) and *9 (IM) haplotypes were significantly overrepresented in the Case group (Table 5). At the diplotype level, CYP2D6*1/*11 (EM), *4/*6 (PM), and *41/*2N (UM) were individually associated with an increased risk of treatment failure and toxic effect (Table 6).

The major frequency of haplotypes *6 (6%) and *9 (6%) in the group of the cases with side effects and without benefit (Case) in respect to the group with benefit (Control) is actu-

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Table 2 Allelic frequency in the Caucasian population

Genotype or allele	Phenotype	Observed (predicted) frequency (%)	Reference
*1/*1	WT	53.3 (55.0)	^Scordo et al, 2004[63]
*1/*3 (*4, *5, *6)	PM	35.0 (32.7)	
*3/*4, *4/*4, *4/*5	IM	3.4 (4.2)	
*1/*2×2	UM	8.3 (8.1)	
*1	WT	22–32	Cavallari et al, 2011[19]
*2	EM	22	
*4, *5	PM	22–28	
*10, *17, *29, *41	IM	1–12	
*2 n, *Xn	UM	1–5	
*1	WT	33–37	#Haufroid and Hantson, 2015[64]
*2	EM	22–33	
*3, *4, *5, *6	PM	15–35	
*9, *10, *17, *41	IM	2–16	
N/R	PM	30–100	§Ting and Schug, 2016[15]
N/R	IM	10–20	
N/R	UM	8–43	

Notes: ^Calculated according to the Hardy–Weinberg equation in Italian population; §reported after a proportional correction of a factor 10 in order to uniform the data; #EU Caucasian.
Abbreviations: EM, extensive metabolizer; IM, intermediate metabolizer; N/R, not reported; PM, poor metabolizer; UM, ultrarapid metabolizer; WT, wild type.

Conclusion

Nowadays medicine is going toward a "patient-centered" and "personalized" approach in which omics represent an important pillar to characterize each patient both for diagnostic and for therapeutic purposes.[67,68] The principle of "one size fits all"[69] is not applicable in clinical practice; drugs' metabolism and interaction with other drugs have to be always considered. Hence, genomics could be helpful in stratifying subgroups of patients in whom treatments are potentially more effective, improving the therapeutic index of drugs in pain therapy.[70] Nowadays precision medicine is a great opportunity with a revolutionary impact on the "health system", especially in terms of effectiveness, safety, ethics and cost savings.[30] Genomics is also promising in improving safety by reducing ADRs. ADRs and treatment failures represent a significant albeit avoidable expenditure even today, in terms of both cost and quality of life, as they are one of the leading causes of morbidity and mortality in health care. An estimated 2.2

million serious ADRs occur yearly in the US, resulting in >100,000 deaths.[71] Pharmacogenetics approach may help to choose the most appropriate drug and dosage for a specific patient, maximizing the therapeutic efficacy and improving the drug safety.[72,73]

Many of the pain killers currently used, such as opioids and antidepressant drugs, are metabolized by CYP2D6 enzyme. Polymorphisms of the *CYP2D6* gene may potentially induce clinically important effects across a wide range of therapeutic areas.[74,75] Identification of patient *CYP2D6* genotypes could help clinicians to tailor drug treatment by selection of appropriate therapies minimizing ADRs. Studies of genetic polymorphisms linked to pain syndromes and medication metabolism herald a fresh therapeutic approach based on genotype with targeted analgesia and fewer side effects.[76,77] Furthermore, pharmacoeconomics analysis showed how pharmacogenetic analysis prior to starting a specific pain treatment can reduce the direct and indirect therapeutic costs.[30]

In our study, we evaluated if and how CYP2D6 pharmacogenetic analysis could be helpful in predicting the effectiveness and safety of codeine or oxycodone treatment in CLBP Italian cohort.

In our cohort, we observed that >10% of patients, who were initially treated with codeine or oxycodone, stopped the treatment due to the occurrence of side effects and/or because of no improvement in pain relief. Codeine and oxycodone are frequently prescribed as a drug for treatment of chronic severe pain that cannot be treated with other pharmacological or invasive treatment. Nevertheless, a scarce analgesic effect may be expected in 5%–10% of Caucasian people who have PM phenotype.[61] In fact, prodrugs such as codeine, which must be metabolized by CYP2D6 to morphine to provide analgesia, are often not effective in these patients.[62]

On the other hand, UMs have higher quantities of expressed enzymes because of gene duplication (allele *2N) with production of higher plasma concentration of active drug. In our cohort, we confirmed that UM patients complain more frequently of side effects compared to normal metabolizer patients (7% vs 2.96%). It has to be underlined that these results are concordant both in codeine and in oxycodone treatments, even though they have two different metabolic ways: codeine is an inactive prodrug with active metabolites (morphine), while oxycodone is an active drug with active metabolites. Our results showed, concordantly with previous studies, that in both treatments, an increased metabolism (*2N) exposes patients to more toxic effects. On the other
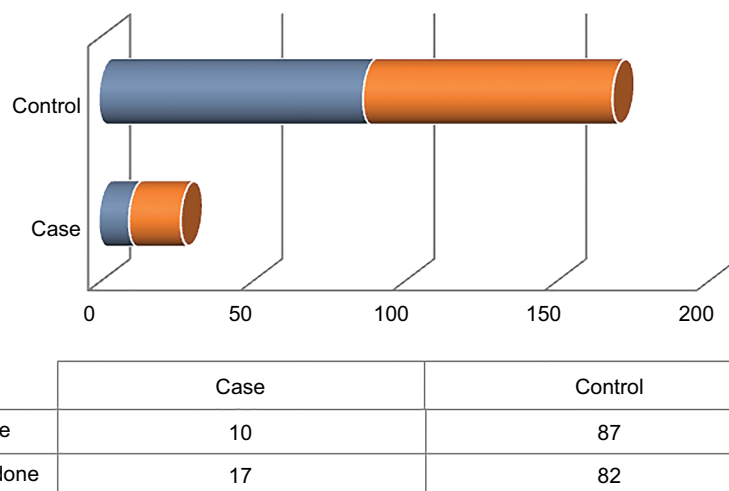
	Case	Control
■ Codeine	10	87
■ Oxycodone	17	82

Figure 1 Patients chronically treated with codeine or oxycodone for the low back pain in each group selected to investigate the onset of the side effects and lack of benefit.

Table 3 Demographic and clinical characteristics of the two groups selected during enrollment of Italian volunteers of the retrospective study in the PainOMICS project

Characteristics of patients		Case (no benefit with side effects)				Control (benefit without side effects)				Total cohort			
		n	M	SD	%	n	M	SD	%	n	M	SD	%
Age			68.7	13.1			66.5	14.5			6.8	14.3	
Sex	Male	7			28.13	59			34.9	66			35.1
	Female	20			71.9	110			65.1	130			64.9
Weight (kg)			73.1	14.6			74.7	14.4			74.5	14.4	
Height (cm)			163.5	8.5			165.9	8.9			165.5	8.8	
BMI			27.3	4.7			27.1	5			27.2	4.9	
Smoker		8			29.6	46			27.2	54			27.6
Pain generator	Radiculopathy	8			33.3	69			41.1	77			40
	Stenosis	4			13.3	11			6.3	15			7.3
	Sacroiliac joint	4			13.3	14			8.4	18			9.1
	Widespread Degeneration	6			23.3	31			18.4	37			19.1
	Zygapophyseal/ facet joint	5			16.7	44			25.8	49			24.5
Pathophysiology of pain	Spinal stenosis				12.9				4.7				5.9
	Facet joint pain				16.1				25.8				24.4
	Sacroiliac joint pain				12.9				8.9				9.5
	Radicular pain				35.5				42.6				41.6
	Widespread pain				22.6				17.9				18.6
Total score of pain detected			12.6	6.2			12.6	7.2			12.6	7	
Opioid	Codeine	10			37	87			51.5	97			49.5
	Oxycodone	17			63	82			48.5	99			50.5
Other drugs	No				87.1				82.8				83.4
	Yes				12.9				17.2				16.6

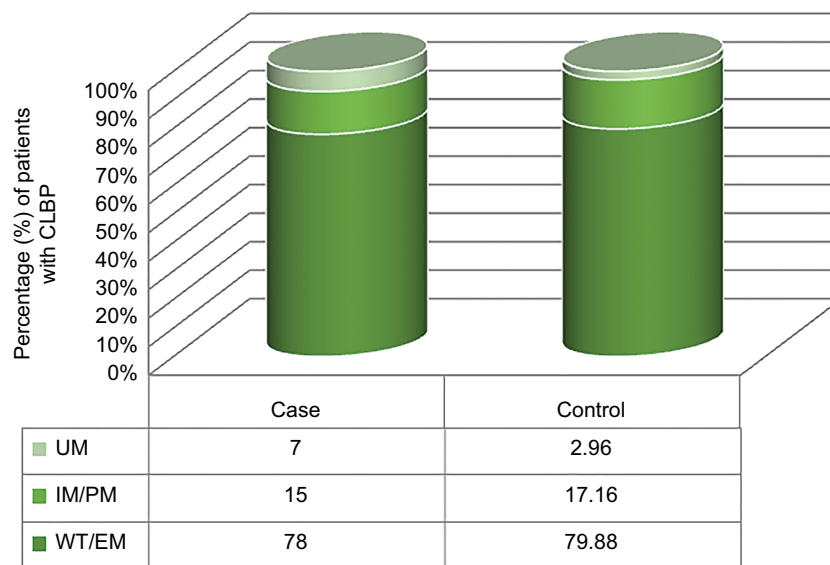**Abbreviation:** BMI, body mass index.

Figure 2 Phenotype of patients (in percentage) chronically treated with opioids for the low back pain and split into two groups (Case = side effects without benefit; Control = benefit without side effects) in order to investigate the pharmacokinetics of codeine and oxycodone excluding DDI issues.
Abbreviations: CLBP, chronic low back pain; DDI, drug–drug interaction; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

Table 4 Distribution of *CYP2D6* metabolizer phenotypes in the two groups studied according to sex

	WT/EM	IM/PM	UM	Total
Males	55 (83.3%)	10 (15.2%)	1 (1.5%)	66
Case	6 (85.7%)	–	1 (14.3%)	7
Control	49 (83.1%)	10 (17.0%)		59
Females	101 (77.7%)	23 (17.7%)	6 (4.6%)	130
Case	15 (75.0%)	4 (20.0%)	1 (5.0%)	20
Control	86 (78.2%)	19 (17.3%)	5 (4.6%)	110
Total	156 (79.6%)	33 (16.8%)	7 (3.6%)	196

Note: No significant differences between sexes were found (Case, Fisher's exact test $P=0.304$; Control, Fisher's exact test $P=0.302$).
Abbreviations: EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

hand, we found a result discordant with previous studies,[78,79] which was that IMs and PMs reported higher effectiveness. This apparently paradoxical ambiguity in our results could be attributed to the significant allele frequency (6%) in*6 (PM) and *9 (IM) compared to the Control (0% and 1%, respectively) in which although a greater number of patients presented with a slow metabolism, the beneficial effect was still present. This result is an evidence that the alleles *6 and *9 seem to be responsible for the lack of therapeutic effect in the Case group, which was not observed in the Control group despite having the most number of representing PMs.

To our knowledge, our study represents the first study about the pharmacogenetic usefulness of screening CYP2D6 in a well-phenotyped, large cohort of Italian patients with CLBP (Figure 3), where patients with already existing pos-sible DDIs have been excluded. It is mandatory to acknowledge the limitations and biases of the present work.

The sample size was extremely small, since only 27 out of 224 patients ended up in the "Case" group. Notwithstanding, the association testing of *CYP2D6* haplotype and diplotypes showed global significant differences according to "the no benefit/benefit status". Replication studies using larger cohorts are clearly warranted to extend and confirm the present results.

Our major bias could be related to the "not appropriate" drug selection by the physician, but we are confident that this possible bias cannot be considered as all the patients have been enrolled from the same center and have been seen by a few physicians who have same therapeutic approach. Another bias is related to the retrospective design of the study. Even though we have excluded possible DDI, we could not follow-up the patients prospectively looking at possible drug adjustments or better definition of no effect/side effect. A prospective study that could overcome this bias through a better definition of people who are candidates to these treatments is needed, as already suggested by Lloyd et al.[80]

We confirmed that pharmacogenetics has the potential to improve pain management by predicting the individual response to a specific analgesic before initiation of therapy and, therefore, to streamline the way physicians prescribe medications to the individual.[15] *CYP2D6* genetic polymorphism analysis might represent a helpful support for the clinicians in the optimization of pharmacological therapies, as also suggested by Linares et al in a small study.[81]

Table 5 CYP2D6 haplotype distribution in the two groups studied (Case and Control) and their association with the no benefit/benefit status

Allele	Case (frequency)	Control (frequency)	OR	95% Lo	95% Hi	χ^2	P-value	Common (frequency >1%)
*1	20 (37%)	129 (38%)	1.000	1.000	1.000	0.092	0.761	+
*4	7 (13%)	66 (20%)	0.730	0.291	1.831	1.157	0.282	+
*2	9 (17%)	61 (18%)	0.973	0.415	2.282	0.077	0.782	+
*41	6 (11%)	38 (11%)	1.045	0.387	2.817	0.001	0.971	+
*35	3 (6%)	20 (6%)	0.921	0.248	3.429	0.040	0.841	+
*5	1 (2%)	8 (2%)	0.678	0.079	5.829	0.159	0.690	+
*9	**3 (6%)**	**4 (1%)**	**5.760**	**1.111**	**29.870**	**5.358**	**0.021**	+
*10	0 (%)	4 (1%)	0.000	0.000	0.000	0.744	0.389	+
*2N	2 (4%)	3 (1%)	4.795	0.710	32.380	3.142	0.076	+
*1N	0 (%)	2 (1%)	0.000	0.000	0.000	0.000	1.000	
*6	**3 (6%)**	**1 (0%)**	**81.340**	**3.356**	**1,971.000**	**19.400**	**0.011**	+
*15	0 (%)	1 (0%)	0.000	0.000	0.000	0.000	1.000	
*35	0 (%)	1 (0%)	0.000	0.000	0.000	0.000	1.000	

Notes: The significant results are reported in bold and shading.

Table 6 CYP2D6 diplotype distribution in the two groups (Case and Control) evaluated and their association with the status "no benefit or benefit" and "side effects or not"

Genotype	Case (frequency)	Control (frequency)	OR	95% Lo	95% Hi	χ^2	P-value	Common (frequency >1%)
*1/*1	5 (19%)	28 (17%)	1	1	1	1.682e-05	0.997	+
*1/*4	0 (0%)	21 (12%)	0	0	0	3.757	0.053	+
*1/*2	2 (7%)	24 (14%)	0.4782	0.08255	2.771	1.023	0.312	+
*1/*41	1 (4%)	12 (7%)	0.5818	0.05916	5.721	0.3729	0.541	+
*1/*35	1 (4%)	9 (5%)	0.6507	0.06512	6.503	0.1576	0.691	+
*1/*5	1 (4%)	2 (1%)	2.888	0.2018	41.33	0.6081	0.436	+
*1/*9	2 (7%)	2 (1%)	6.921	0.6521	73.46	2.734	0.098	+
*1/*2N	1 (4%)	2 (1%)	2.236	0.1576	31.73	0.7267	0.394	+
*1/10	0 (0%)	1 (1%)	0	0	0	0	1.000	
*1/11	**2 (7%)**	**0 (0%)**	**5.977e+163**	**1.69e+152**	**2.114e+175**	**12.43**	**0.000**	+
*4/*4	1 (4%)	8 (5%)	0.7348	0.07269	7.428	0.1092	0.741	+
*2/*4	3 (11%)	12 (7%)	1.91	0.3676	9.93	0.5443	0.461	+
*4/*41	1 (4%)	10 (6%)	0.5659	0.05744	5.575	0.2826	0.595	+
*4/*35	0 (0%)	4 (2%)	0	0	0	0.6435	0.422	+
*4/*5	0 (0%)	1 (1%)	0	0	0	0	1.000	
*4/*10	0 (0%)	1 (1%)	0	0	0	0	1.000	
*4/*6	**1 (4%)**	**1 (1%)**	**25.66**	**0.2941**	2.239	**4.656**	**0.031**	+
*2/*2	1 (4%)	7 (4%)	0.8332	0.08038	8.636	0.08367	0.772	+
*2/*41	2 (7%)	7 (4%)	1.729	0.2649	11.29	0.4101	0.522	+
*2/*9	0 (0%)	1 (1%)	8.357e-07	8.357e-07	8.357e-07	0	1.000	
*2/*10	0 (0%)	1 (1%)	0	0	0	0	1.000	
*2/*9	0 (0%)	1 (1%)	0	0	0	0	1.000	
*2/*15	0 (0%)	1 (1%)	0	0	0	0	1.000	
*41/*41	0 (0%)	1 (1%)	0	0	0	0	1.000	
*41/*35	0 (0%)	3 (2%)	0	0	0	0.5801	0.446	+
*41/*5	0 (0%)	2 (1%)	0	0	0	0.3935	0.531	+
*41/*9	1 (4%)	1 (1%)	9.136	0.3764	221.8	2.495	0.114	+
*41/*2N	**1 (4%)**	**0 (0%)**	**5.904e+97**	**7.661e+91**	**4.55e+103**	**6.176**	**0.013**	+
*41/*1N	0 (0%)	1 (1%)	0	0	0	0	1.000	
*35/*35	1 (4%)	1 (1%)	3.485	0.1627	74.63	0.888	0.346	+
*5/*35	0 (0%)	1 (1%)	0	0	0	0	1.000	
*35/*3	0 (0%)	1 (1%)	0	0	0	0	1.000	
*5/*10	0 (0%)	2 (1%)	0	0	0	0.4365	0.509	+

Notes: The significant results are reported in bold and shading.
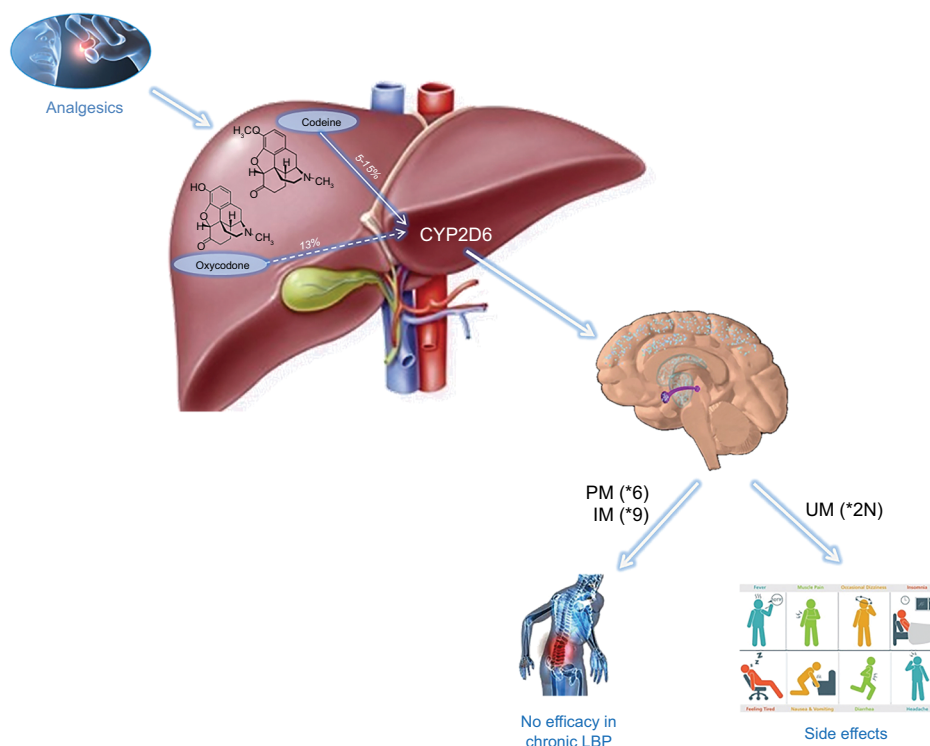
Figure 3 Cartoon to summarize the results.
Notes: The alleles *6 and *9 seem to be mainly responsible for the lack of therapeutic effect during chronic treatment with opioids. *2N is responsible of side effects.
Abbreviations: IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

However, while the pharmacokinetic consequences of polymorphic metabolism are relatively well characterized for many drugs, the documentation of its importance with respect to therapeutic response and dosing remains scanty.[15] Added to this is the fact that our study is the first attempt to apply the pharmacokinetic knowledge to opioids for the chronic treatment of LBP. Further studies are required to assess the clinical significance of these differences in the treatment outcome and optimal dosage of drugs metabolized by these polymorphic enzymes. It is of potential clinical importance to be able to identify individuals who have altered pharmacokinetics for CYP2D6 substrates as appropriate dosage strategies for these drugs can be adopted and ADRs can be avoided.

The principle that a good therapy is based on a good diagnostic determines, therefore, a wide field of action for the precision of personalized medicine, not only in relation to diagnostic innovations introduced by "omics", but also in the rediscovery of the traditional quality and accuracy of analytical and biological variability of the value of the study.

The success of treatment is also closely linked to the precocity of therapeutic intervention because the health expenditure increases exponentially with the progress of the disease. Prevention is, therefore, a considerable resource for health systems. This way you can minimize the "cost-toxic" treatment by improving the quality of life of patients and optimize the management of available financial resources.

Data sharing statement

The authors intend to share, only for research purposes, individual deidentified genetic and clinical data after 1 year of the publication of the paper. The data will be accessible for 3 years and it will be possible to have access only through an official request sent to the corresponding author of the paper.

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Author contributions

CD conceived this current study, conducted the pharmacogenetic analysis and wrote the manuscript. During the patients' enrollment and sample analysis, MA was the Principal Investigator of the granted European project "PainOMICS" and Clinician Director of the Anesthesia, Critical Care and Pain Medicine Unit in the Pain Therapy Center of University Hospital of Parma. VN elaborated the statistical results. SDA checked the clinical information on patients' treatment by matching them with pharmacogenetic results. MA and RVS improved the experimental design and the manuscript. EB and AM are the supervisors of the project activity in the University of Parma. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Phenotypes set for the various combinations of CYP2D6 alleles detected by xTAG CYP2D6 Kit v3

	*1	*2	*3	*4	*5	*6	*7	*8	*9	*10	*11	*15	*17	*29	*35	*41
*1	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM
*2		EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM
*3			PM	PM	PM	PM	PM	PM	IM	IM	PM	PM	IM	IM	EM	IM
*4				PM	PM	PM	PM	PM	IM	IM	PM	PM	IM	IM	EM	IM
*5					PM	PM	PM	PM	IM	IM	PM	PM	IM	IM	EM	IM
*6						PM	PM	PM	IM	IM	PM	PM	IM	IM	EM	IM
*7							PM	PM	IM	IM	PM	PM	IM	IM	EM	IM
*8								PM	IM	IM	PM	PM	IM	IM	EM	IM
*9									IM	IM	IM	IM	IM	IM	EM	IM
*10										IM	IM	IM	IM	IM	EM	IM
*11											PM	PM	IM	IM	EM	IM
*15												PM	IM	IM	EM	IM
*17													IM	IM	EM	IM
*29														IM	EM	IM
*35															EM	EM
*41																IM

Abbreviations: EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.