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Chapter

Pharmacogenetics and Tramadol-Related Fatalities

Sanaa M. Aly, Jean-Michel Gaulier and Delphine Allorge

Abstract

Tramadol (TR) is a widely prescribed pain killer because of its relatively safe profile among opioids. Nevertheless, intoxication can occur and overdose can lead to fatal outcomes. Surprisingly, in some fatalities for which death is attributable to TR alone, *postmortem* blood concentration levels overlap with the therapeutic concentration range. These fatal cases might be explained by pharmacokinetic and pharmacodynamic properties of TR that are known to be both enantioselective and influenced by genes. Indeed pharmacogenetics (PG) is of great importance in this issue as it has the ability to elucidate the genetic variation contributing to drug absorption, distribution, metabolism, excretion, and response so that adverse drug reactions, toxicity, and even death can be avoided. The aim of this chapter is to present this issue.

Keywords: tramadol, pharmacogenetics, toxicology, *post-mortem* investigation, molecular autopsy

1. Introduction

There is large interindividual variability in drug response and toxicity, as well as in drug concentrations after administration of the same dosage [1]. The genetic makeup could be the reason of variation in drug response among individuals [2]. In general, genetic factors are estimated to account for 15–30% of interindividual differences in drug response, but for certain drugs, this can be as high as 95% [1].

The genetic variations contribute to absorption, distribution, metabolism, excretion, response, and adverse drug reactions, which could be explored by pharmacogenetics (PG). PG could also characterize differential enzyme activity (e.g., the cytochrome P450 system) informing appropriate drug dosage on the individual (personalized medicine) and population levels. The advancement of genetic modalities will enable more accurate predictions of drug-related death determinations and contribute to the growing not only in forensic toxicology context but also in clinical settings [2].

The main application of molecular autopsy involves investigation of drug-related deaths by exploiting several molecular techniques, especially those of genetic nature [3].

The PG use as an adjunct for molecular autopsy would add to the understanding of potential genetic contribution to metabolism of certain drug (such as tramadol), thus enabling and improving the practice of *antemortem* drug therapy [4].

Tramadol (TR) is a worldwide used pain killer drug. Since TR was marketed, it has been widely prescribed because of its relatively safe profile among opioids. Nevertheless, intoxication can occur and overdose can lead to fatal outcomes. Surprisingly, in some fatalities for which death is attributable to TR alone, *postmortem* blood concentration levels overlap with the therapeutic concentration range (0.1–0.8 mg/L) [5–8]. These fatal cases might be explained by pharmacokinetic and pharmacodynamic properties of TR that are known to be influenced mainly by the CYP2D6 phenotype.

1.1 Tramadol (TR)

TR is a synthetic centrally acting analgesic drug worldwide used for the treatment of moderate to severe pain [9, 10]. TR is used as a pain killer in different types of pain such as osteoarthritic, endodontic or dental, chronic cancer, acute renal, neuropathic, and postoperative pain. It is also used in case of acute myocardial infarction, postoperative shivering in lower abdominal surgery, Brugada syndrome, and morphine allergy [11].

However, several precautions should be taken before TR prescription. It should not be administrated below the age of 16 years, and some forms as Ultram should be administrated above the age of 18 years. TR should not be prescribed during pregnancy, in case of lactating and expecting mothers, person with epilepsy, mental illness or suicide attempt, heart or respiratory problems, stomach or intestinal blockage, liver, kidney, or metabolic disease, TR sensitivity, addiction to drug or alcohol, intake of some drugs as sedatives, tranquilizers, narcotics, 2 weeks intake of monoamine oxidase inhibitor (MAOI), methylene blue injection, antibiotics, antifungal, and anti-HIV medications [11].

1.2 Epidemiological data

The changes in opioid consumption have been described worldwide. In Europe, they were characterized by an increasing use of TR. Between 2006 and 2015 in France, TR (alone or in combination use) were the second most commonly used mild opioids. There was an increased consumption of TR over the 10-year period (+62%) in France. In recent reports, France ranked third place for mild opioid consumption, with TR (alone or in combination use) being one of the most used substance (48%). In other European countries, TR is also the most commonly used mild opioids in Germany, Italy, Spain, and Denmark (98, 82, 78, and 85%, respectively) [12].

In the same time, there is a particular concern about the rise of nonmedical use of analgesics, especially opioids. Much has been written about the opioid crisis in the USA, but a similar crisis engulfing the Middle East, North, and West Africa is receiving little attention [13]. Therefore, drug world report 2018 mentioned the critical challenge in some countries in Africa and other regions needing to grips with the TR crisis [14, 15].

The 2017 report of the National Survey of Substance Abuse in Egypt was subsequently presented to the WHO which revealed that the abuse of TR is still a national concern in Egypt despite it became a schedule IV controlled substance since 2012. This may be because of wide-scale abuse of this analgesic. In the 2012/2013 survey, 7.6% of the general population abused drugs: of these 31.5% reported misuse of TR [16].

Because TR is widely used either as licit or illicit drug, FDA has only approved the medical use by prescription. Although TR has become a schedule IV controlled substance in the USA since 2014, this did not hinder legitimate access. In 2014, there

was a total of 43.7 million, 39.8 million, and 36.5 million TR prescriptions dispensed in the USA in 2016, 2017, and 2018, respectively [17].

1.3 Adverse reactions

The WHO Global Database reports of suspected adverse drug were studied to investigate TR. There has been a sudden increase in reports (nearly 5-fold) for TR: from 200 reports in 2013 to 800 in 2018 [9].

In overdose, the multiple systematic symptoms are reflecting the multimodal activity of TR. Acute adverse effects associated with TR are like those of other weak opioids. Common side effects include dizziness, nausea, constipation, and headache. TR overdose presented with multiple systematic symptoms ranging from cardiovascular toxicity to significant neurologic toxicity including lethargy, nausea, tachycardia, agitation, seizures, coma, hypertension, and respiratory depression [9].

The smallest amount of TR associated with a seizure was 200 mg occurred within 6 hours after ingestion. The mechanism underlying TR toxicity has been closely related to both opioid and MAOI activity [18]. The enhanced risk of seizure was attributed to the increased risk from serotoninergic toxicity due to the expected prolonged half-life of the ingested parent compound resulting in slower drug metabolism [19]. Both TR and M1 inhibit the reuptake of serotonin and noradrenaline. Hence, the concomitant use of serotonergic drugs such as serotonin reuptake inhibitors and MAOIs, increase the risk of adverse events, including seizure and serotonin syndrome.

The parent drug of TR causes sedation (but does not impair ventilation) and the M1 metabolite causes both sedation and respiratory depression [now termed opioid-induced ventilatory impairment (OIVI)] which is responsive to naloxone [20]. Both monoaminergic and opioid mechanisms contribute to this effect. In a case series study of TR overdose, respiratory depression occurs only in severe cases of overdose with very high doses [9, 21].

On the other hand, other work suggested that poor metabolizers (PMs) of TR tend to experience more adverse effects of the drug. The results showed that intermediate metabolizers (IMs) were found to have a statistically higher incidence of adverse drug reactions (dizziness, headache, nausea, sweating, and dry mouth) when compared with the groups that metabolize TR faster [ultra-rapid metabolizers (UMs) and extensive metabolizers (EMs)]. Other studies found no difference in term of adverse events such as nausea and vomiting between patients with the CYP2D6 UMs, PMs, IMs, and EMs [22].

Regarding the chronicity, the main problem observed was the significant increase in comorbid anxiety, depressive, and obsessive-compulsive symptoms while there was no increase in psychotic symptoms [9].

Concerning dependence potential, the International Narcotics Control Board reported in 2018 widespread misconceptions regarding TR among the general population in North Africa and the Middle East. Some consider TR to be a mood enhancer that increases sexual stamina and/or boosts energy during work. However, mood elevation is often reported and leads to the consumption of higher doses of the drug, psychological or physical dependence, and increased risk of overdose [9, 23].

The development of physical dependence to TR is dose-related, and administrations of supra-therapeutic doses lead to a similar dependence profile to morphine, whereas the risk of physical dependence is lower than prototypic opioids when low-dose TR is used over an extended period. However, these are not exclusively related to its opioid effects and may reflect withdrawal from catecholamine and serotonin receptors and present as atypical sequelae [9].

1.4 TR-related fatalities

In a report about a young Caucasian female admitted to hospital with refractory cardiac arrest and high levels of both TR and M1, the genetic analysis revealed the patient had a duplicated wild-type allele, indicative of a CYP2D6 UM phenotype. The event was specifically ascribed to the inhibition of noradrenaline reuptake and excessive blood adrenaline levels following binge-type ingestion of TR (to gain a "high") that led to strong myocardial stunning [24].

In France, the number of deaths related to TR toxicity increased from 32 in 2013 to 49 in 2017. TR was the first most commonly cause of death due to analgesics [25]. In Egypt, about 18% of fatalities are related to TR in the national poison center. TR was the second most commonly cause of death among cases attended in the poison center in 2012 [26].

2. Pharmacology

TR is a complex drug that is administered as a racemate with the (+)- and (−)-enantiomers of the parent compound and related metabolites showing various pharmacological effects. It is metabolized by polymorphic enzymes including CYP2D6 and CYP3A4 to its more potent metabolites particularly *O*-desmethyltramadol (ODT, M1) as well as *N,O*-didesmethyltramadol (NODT, M5) [9, 10].

2.1 Pharmacokinetics

TR is marketed as the hydrochloride salt. It is available in a variety of pharmaceutical formulations for oral, sublingual, intranasal, rectal, intravenous, subcutaneous, and intramuscular administration. It is also available in combination with acetaminophen, immediate-release and extended-release formulations. Tablets and capsules are the most commonly used and easily available formulations. The recommended daily dose is in the range of 100–400 mg. The maximum dose should not exceed 400 mg/day [9].

After oral administration, TR is rapidly absorbed (with a time lag of 30 min for capsules). The bioavailability of TR is around 70% after single-dose administration, but increases to 90–100% after repeated administration as a result of the saturation of the hepatic first pass effect [9, 27]. TR sustained release capsules had identical bioavailability to TR immediate-release capsules with lower peak concentrations and less fluctuation in plasma concentrations [9].

The analgesic potency of TR itself is about 10% that of morphine following parenteral administration but more potent if administered orally because of the activity of M1. The production of analgesia is consistent with M1 formation, which commences an hour postadministration and peaks 2–3 h later [9].

The TR volume of distribution has been reported to be 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The plasma binding of TR is approximately 20% [28]. TR crosses the blood-placental barrier and a very small amount of the drug is excreted in breast milk [29]. TR is mainly excreted through the kidneys, the remaining being excreted in feces [30]. About 60% of TR dose is excreted as metabolites, meanwhile 30% is excreted in the urine as unchanged drug.

The elimination half-lives range of racemic TR and M1 have been reported to be about 5–7 h [31]. The longer elimination time of TR in case of overdose (about 9.24 h) gives an indication about the capacity limited of TR metabolism, which is dependent upon the rate of metabolism by the P450 enzymatic system [9].

2.2 Pharmacodynamics

TR acts in a multimodal fashion to bring about analgesia that involves the µ-opioid receptor system, the noradrenergic system, and the serotonergic system. TR has some affinity for the µ-opioid receptor, whereas the active hepatic metabolite, M1 has high relative greater affinity for the µ-opioid receptor [32]. The affinity of morphine for this same receptor is approximately 10–100 times greater than M1 and 300 times greater than TR. TR is approximately 10-fold less potent than codeine. A weak agonistic TR effect was revealed at the δ-opioid receptors, and a weaker TR affinity was shown at κ-opioid receptors. TR acts by other mechanisms on the central nervous system including monoaminergic activity through weak noradrenaline and serotonin reuptake inhibition to prevent pain transmission [33].

TR is administered as a racemate, with the (+)- and (−)-enantiomers of the parent compound and their respective metabolites displaying different effects to achieve synergistic pain relief. The (+)-enantiomer of TR is most potent in serotonin reuptake inhibition, while (−)-enantiomer is a noradrenaline reuptake inhibitor. The (+)-enantiomer of the M1 has the highest affinity and potency up on the µ-opioid receptors. It also exerts most of the opioid effects. The (+)-ODT is the most potent stereoisomer in relieving pain as well as in causing adverse effects [10].

TR is mainly metabolized by two pathways: *N*- and *O*-demethylation (phase I reactions) and conjugation (phase-II reactions). There are at least 11 known metabolites of TR (M1–M5). The metabolites *N*-desmethyltramadol (M2), M3 and M4 of TR have negligible affinity for the human µ-opioid receptor. The *O*-demethylation of TR to M1 is catalyzed by cytochrome P450 (CYP) 2D6, whereas *N*-demethylation to M2 is catalyzed by CYP2B6 and CYP3A4 (**Figure 1**) [9]. M1, the active metabolite of TR, is metabolized through glucuronidation in the liver, mostly via UGT2B7 and UDP glucuronosyltransferase 1–8 (UGT1A8) [22].

2.3 Pharmacogenetics (PG)

2.3.1 Definitions

PG is the inherited variation study in relation to drug response. Its goal is to develop novel ways to minimize toxicity and maximize drug efficacy for the patient [34]. PG is an important innovation in clinical medicine as a result of progression of genomic science to determine the correct drug with the correct dose as a specific treatment with the use of genetic information [35]. Personalized medicine has the potential to select the most appropriate drug for certain patients, to predict optimal dosage for a drug, and to develop cost-effective treatments. Individualized response to treatment may be attributed to biological (for example age, sex, nature of disease), behavioral (for example smoking, drug interactions), or genetic factors (for example genetic variants of pharmacogenes) [34].

2.3.2 PG strengths

Personalized medicine has the finality of improving drug safety and efficacy. PG application in clinical practice promises more effective decision-making in relation to diagnostic testing, individualized drug selection, and dosing. This depends on the genetic variations that affect the observed differences in drug response which can be classified into two groups: pharmacokinetic and pharmacodynamic. The genes that influence the pharmacokinetic properties of a drug influence the drug absorption, distribution, metabolism, and excretion. The genes that affect the pharmacodynamic of a drug influence the mechanism of the drug's target and how
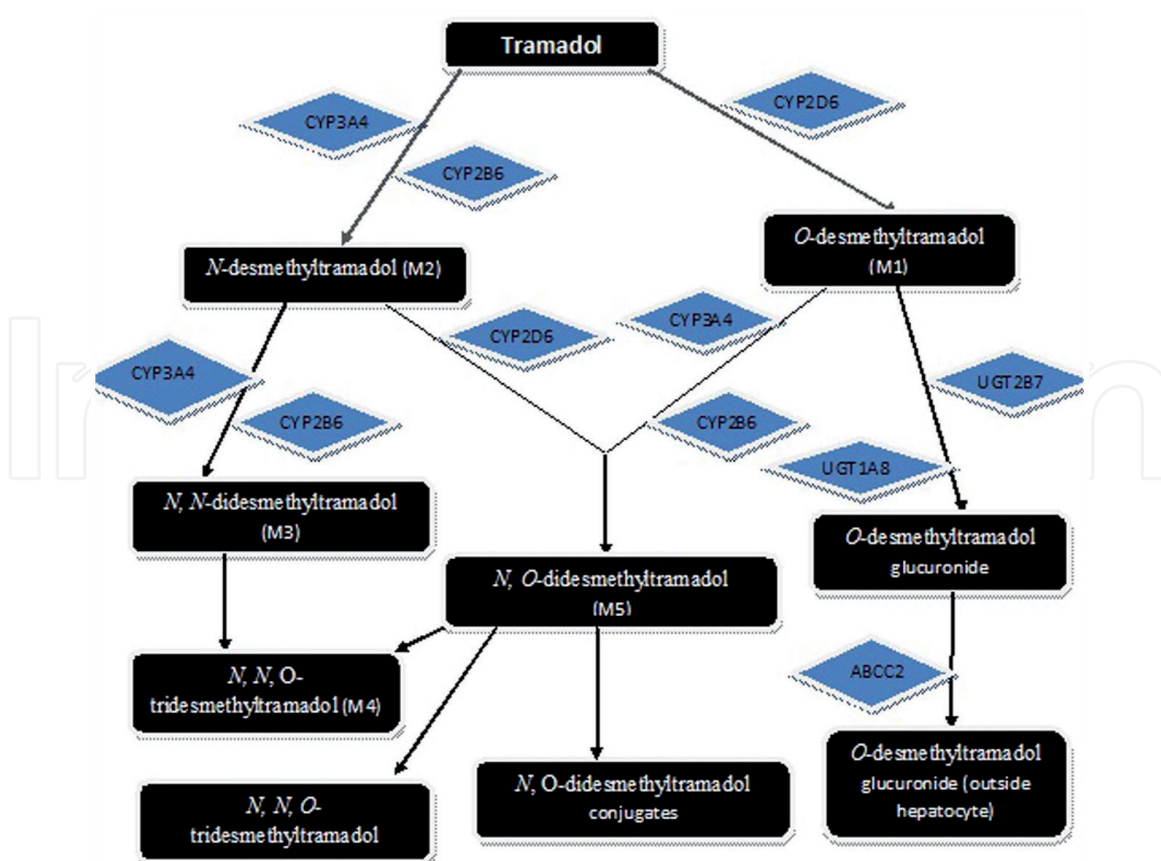
Figure 1.
Tramadol metabolism.

it affects the body. The risk-benefit balance of a drug can be evaluated based on PG effects on safety, efficacy, or both. Thus, prior analysis of a patient's genotype may be used to guide clinical decision because the patient may benefit from an alternative drug or reduction in dose of a standard therapy. PG has the potential to reduce the costs (pharmacoeconomy) associated with inappropriate drug or severe adverse drug reactions that require hospitalization [34].

2.3.3 PG limitations

There are several limitations of PG that invariably makes genetic-guided therapies unfavorable in comparison with the standard health care. One of these limitations is the cost of PG test as the additional expense of the genetic test has to be borne as an extra expenditure by the patient, or by healthcare coverage provided by insurance. The second common limitation is the speed of getting genetic test result as the speedy generation of the PG test result is as important as of the genetic information results itself. Imperfect understanding of genetic determinants of drug response is one of the common limitations which in turn affects physician and patient confidence to genetic test [35].

2.3.4 Opportunities for growth of PG

The landscape of PG testing is rapidly evolving. There are several factors that have great impacts on PG development and increase its utility such as accumulations of PG data, the continuity of technological innovations with more accessibility, and costs continuing to drop [35, 36]. Work has been done to suggest that genetic variations may be studied in oral fluid [33]. Oral fluid tests may encourage

healthcare professionals to use pharmacogenetic tools more often. Moreover, one of the PG-guided clinical trial principle is to improve and accelerate drug development by correlating genetic patient profile with treatment outcomes in early clinical trial phase, and subsequently extending Phase III only to individuals having the genetic predispositions linked to the safe and effective use of the tested drugs [35].

2.3.5 Uses of PG

PG can enhance patient care by applying treatments tailored to genetic make-up and decreasing the risk of severe adverse effects. In 2019, there are 132 PG dosing guidelines for 99 drugs and PG information is included in 309 drug labels. Recently, the genotyping has become more accessible. Next generation sequencing is a cost-effective choice to genotype samples at many PG loci simultaneously [37], and guidelines are available from organizations such as Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group [36].

As mentioned earlier, the major P450 enzyme activities involved in drug metabolism are influenced by genetic variations. Thus, it is not surprising that the currently available examples of the beneficial use of PG in the interpretation of forensic toxicology data predominantly concern drugs that are extensively metabolized by P450s. Many cases exhibited severe intoxication or even death can be attributed to genetic variations in drug-metabolizing enzymes leading to toxic concentrations of either the parent drug or metabolite(s) in the body. Therapeutic opioids (as codeine, TR, oxycodone, hydrocodone, ethylmorphine, and methadone), selective serotonin reuptake inhibitors (as fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram), and tricyclic antidepressants are commonly implicated in severe adverse effects, as well as drug-related deaths because of certain genetic polymorphisms which affect the drug metabolism [38].

2.3.6 PG and TR

The CYP2D6 enzyme is accountable for the formation of M1 (**Figure 1**). Individuals may be classified as PM, IM, EM, or UM according to the metabolic activity of the CYP2D6 enzyme, determined by either phenotyping or predicted from genotyping (**Table 1**) [10]. CYP2D6 genotype data are commonly arranged into star (*) alleles. The intermediate (extensive/normal commonly divided into fast [NM-F] and slow [NM-S] subgroups) [39]. Individuals with two functional CYP2D6 alleles or one functional and one decreased functional allele were classified as EM. Individuals with one nonfunctional allele and one functional or decreased functional allele are identified as IM [10]. A carrier of two reduced function is also considered IM [22]. Individuals with two nonfunctional alleles as PMs. UMs were defined as individuals with CYP2D6 multiplications, resulting in at least three functional CYP2D6 alleles [10].

Different pharmacological effects can therefore be expected depending on an individual's CYP2D6 phenotype. Both pharmacological properties (opioidergic and monoaminergic) of the drug may also be modified because of modulation of P450 enzymatic activity by genetic polymorphisms and/or drug interactions. The opioidergic properties will be very clear in UM, meanwhile the monoaminergic antidepressant activity will be very clear in PM [40].

The PM, in comparison to EM, have an increased exposure to (+)- and (−)-TR combined with a reduced formation of especially (+)-ODT but also of (−)-ODT. UM, on the contrary, are expected to form higher amounts of (+)-ODT than EM and to be more prone to opioid- related adverse effects. Comparisons between EM and UM are, however, sparse in scientific literature [10]. PMs are experiencing better pain relief

Phenotype	Genotype (allele)		
	Fully functioning	**Defective functioning (decreased, reduced)**	**Nonfunctioning (dysfunction-inactive)**
UM	≥3	0	0
EM			
EM1s (heterozygous wild-type)	1	1	0
EM2s (homozygous wild-type)	2	0	0
IM	1	2/1	1/ 1
PM	0	0	2
Examples	*1	*9, *10, *17(Z)	*3, *4, *5, *6, *14

UM, ultra-rapid metabolizer; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

Table 1.
CYP2D6 phenotypes in relation to their genotypes.

than IMs who may experience insufficient relief. UMs are being more likely to experience adverse effects from TR because of the more rapid release of M1 [9].

Apart from M1, there are two additional primary TR metabolites, M2 and M5. M2 is an inactive metabolite which its formation is mediated by presence of two enzymes (CYP2B6 and CYP3A4), while M5 has some opioid effects and its metabolic route is less assured. However, all three enzymes (CYP2D6, CYP2B6, and CYP3A4) are involved in TR metabolism (**Figure 1**) [10].

The CYP2B6 gene is highly polymorphic as well as CYP2D6, but the relevance of CYP2B6 polymorphisms in TR has been less studied. Many CYP3A4 polymorphisms have been identified, although it is not well associated with the phenotypical variability. The CYP3A4*22 allele is associated with reduction of the enzymatic activity. Recent study tried to explain if the interindividual differences in enantioselective metabolic profiles could be explained by CYP2D6, CYP2B6, and/or CYP3A4 genotype. This item hypothesized that interindividual differences are better explained by the combined genotype of all three enzymes involved in the metabolism of the drug, rather than by CYP2D6 itself [10].

Rudaz et al. showed that enantiomer ratios of all four compounds in urine changed over time in one individual administered 100 mg TR [41]. The largest increase in enantiomer ratio was observed for M2 in CYP2D6 EM and IM, rising from about two to almost seven during 24 h following drug intake. Homozygosity of CYP2B6*5 and *6 indicated a reduced enzyme function, although further studies are required to confirm it. The significance of CYP2B6 polymorphisms in TR pharmacokinetics has not been carefully investigated. The same study concluded that consideration for the time is important when you assess enantiomer ratios as it might possibly be used to distinguish a recent TR intake from a past one [10].

Of additional relevance is the significant interethnic differences in CYP2D6 allele frequencies demonstrated across many countries [9]. For example, the CYP2D6*1 seems to be the most prevalent in studied groups from Egyptians. In contrast, CYP2D6*4, CYP2D6*10 and CYP2D6*DUP showed minor occurrence [42].

Chronic treatment with TR induced hepatotoxicity in all patients with duplicated or normal function (CYP2D6*DUP or *1) allele in UMs and EMs displayed higher blood levels of M1, but in none of the patients with impaired or reduced functioning allele *4 or *10 [42].

3. Detection of TR

3.1 Techniques

Toxicological analysis of TR is based on chemical spot tests, immunoassays, mass spectrometry, and chromatography.

- Preliminary urine multidrug screen tests as well as automated immunoassay systems which are commonly used with a 0.3 mg/L cut-off value [43].

- Gas chromatography-mass spectrometry (GC-MS) can be used to analyze blood samples for detection of TR and its metabolites. Blood concentrations are ranging from 0.03 to 22.59 mg/L, from 0.02 to 1.84 mg/L and from 0.01 to 2.08 mg/L for TR, M1, and M2, respectively [9, 44].

- Liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was developed for the quantitation of TR and its main metabolites in hair. The Lower detected Limits were in the range 0.010–0.030 ng/mg hair. The TR, M1, and M2 concentrations were markedly lower in the nonabuse cases (3.3–20.1 ng/mg, 0.3–1.9 ng/mg, 0.5–4.3 ng/mg, respectively) compared to the abuse cases (63.4–107 ng/mg, 3.8–6.3 ng/mg, 24.9–45.7 ng/mg hair, respectively); also the M2/M1 ratio differed significantly. Hair has become an important biomarker owing to the possibility of detecting target analytes for periods >1 month [45].

- Liquid chromatography coupled to fluorescence detection was also used for TR and its main metabolites M1 and M2 and M5 simultaneous determinations in human plasma, oral fluid, and urine. The lower limit of detection was 2.5 ng/mL for all compounds. The assay was applied to assess the pharmacokinetics of TR and its main metabolites following administration of a single oral dose (100 mg) TR to healthy volunteers [46]. Maltodextrin-modified capillary electrophoresis method was reported to detect the stereoisomers of TR for a single-run chiral separation of TR with detection limit of 2 mg/L. This method was approved to measure the concentration of drug in plasma samples, urine, and tablets [47].

- HPLC (linear dual column-MS/MS) was successfully used on oral fluid for the simultaneous detection of TR and its metabolite (M1, M2, and M5) [33].

3.2 Interpretations of toxicological and genetic analyses

Different studies tried to correlate concentrations of TR and its metabolites with different genotyping of CYP2D6. The best correlation was obtained for M2/M1 ratio and PM. The M2/M1 ratio in PM is almost above 7 [48].

Levo et al. calculated the TR/M1 and TR/M2. When the number of functional alleles increased, the median TR/M1 decreased. They also showed that median TR/M2 also correlated with the number of functional alleles, but in the reverse direction, as can be expected based on the complementary nature of two pathways [49].

The literature reported the value of M1/M2 ratio in case of massive TR intoxication. A quick death has been expected in case of M1/M2 is more than 1 [50].

The metabolic profiles of CYP2D6 PM showed large area under curve (AUCs) of the M2 enantiomers with low corresponding values of the M1 and M5 enantiomers. The (+)-enantiomers of M1 and M5 were affected to a larger extent than the

(−)-enantiomers. The observed reduced levels of the M5 enantiomers were expected. M5 is formed from both M1 and M2. Since PMs only form low amounts of M1 due to the abolished (canceled) function of CYP2D6, the amounts of the M2 enantiomers will accumulate. Another metabolic profile of CYP2D6 IM showed the AUCs of both the M2 and M5 enantiomers exceeded the ones of the M1 enantiomers [10].

The general hypothesis in literature regarding adverse effects following TR administration is that the frequency and intensity is related to the concentrations of (+)-M1. The higher the concentration of (+)-M1, the higher the risk of side effects and toxicity. In Haage et al. study, the individual experiencing most drug reaction symptoms (both fainting and vomiting during the experimental day) was the one with the second lowest maximal concentration and AUC of (+)-M1 in the 100 mg dosage group [10].

A recent work reported that the TR/M1 ratio may not accurately reflect the rate of TR *O*-demethylation in clinical patients. This study accounted that due to (i) *postmortem* redistribution (PMR) phenomenon, and (ii) various interval and/or time between TR administration and death. In addition, TR is metabolized by multiple enzymes (e.g., TR and/or its metabolites are metabolized by CYP2D6, CYP3A4, CYP2B6, UGT1A8, or ABCC2) (**Figure 1**) and may be metabolized at different rates based on body size, liver function, chronicity of TR, general opioid, and/or other drug use [39]. Surprisingly, the first abovementioned cause is not accurate as PMR is not a problem in case of interpretation of fatalities related to TR. Indeed, many studies revealed that cardiac-to-femoral blood ratios obtained for TR and M1 are close to 1 [51–54].

It is suggested that the monogenic model likely introduces error, particularly for samples at the extremes of CYP2D6 activity; a prediction using multiple genes may reduce these discrepancies although this comparison has not been performed. The forensic community has not yet leveraged the power of machine learning for such studies. However, the forensic DNA community has begun developing methods of individualizing humans [39].

4. Conclusion

This chapter about PG and TR highlights important related issues including pharmacological and genetic aspects of TR. It clarified the interindividual variability in response and toxicity to TR in order to support the use of genetic screening to predict individual responses to pain medications and the risk of adverse events. This in turn will encourage the use of PG as part of clinical practice for TR. Finally, novel machine learning approaches using multigenic model can comprehensively analyze genotype-phenotype relationships that hold significant promise for application to predict response to TR, which may contribute to the relatively high rate of TR-related fatalities.

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Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

EMs or NMs	Extensive or normal metabolizers
GC-MS	Gas chromatography-mass spectrometry
IMs	Intermediate metabolizers
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
M1 or ODT	*O*-desmethyltramadol
M2	*N*-desmethyltramadol
M5 or NODT	*N,O*-didesmethyltramadol
MAOI	Monoamino oxidase inhibitors
NM-F	Fast normal metabolizers
NM-S	Slow normal metabolizers
OIVI	Opioid-induced ventilatory impairment
PG	Pharmacogenetics
PMs	Poor metabolizers
TR	Tramadol
UMs	Ultra-rapid metabolizers

Author details

Sanaa M. Aly[1,2*], Jean-Michel Gaulier[2,3] and Delphine Allorge[2,3]

1 Forensic Medicine and Clinical Toxicology Department, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

2 CHU Lille, Unité Fonctionnelle de Toxicologie, Lille, France

3 Université de Lille, ULR 4483 – IMPECS – IMPact de l'Environnement Chimique sur la Santé Humaine, Lille, France

*Address all correspondence to: sasydayem@hotmail.com

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