GENETIC VARIABILITY OF PHARMACOKINETICS AND PHARMACODYNAMICS OF ANALGESICS (LAYERED MEDICINE) - PART II

MONICA NEAMȚU, ALEXANDRU VASINCU, DANIELA ABABEI*, OANA ARCAN, DELIA BULEA, RĂZVAN NICOLAE RUSU, VERONICA BILD

Received: 2nd of April 2019 / Revised: 20th of May 2019
Accepted: 23rd of June 2019 / Published: 20th of September 2018

Keywords: analgesics, single nucleotide polymorphism, pharmacogenomics

Abstract: Pain therapy, the most widely spread disorder, tends more as other diseases, to administration of drug molecules targeted to the affected tissue at the right dose, or to the patient or patient groups (personalized medicine). A decisive determinant of this strategy is the genetic one, which is to some extent the basis of the variability of pharmacokinetic and pharmacodynamic response to analgesics in the patient population. The differences in action and response to analgesics are due in these cases to hyperfunctional or nonfunctional uni-nucleotide gene polymorphisms encoding enzyme-modified transport proteins or receptors involved in the biotransformation and dynamics of analgesics. Genomic testing increases therapeutic efficacy and avoids adverse effects especially in patients with long-term therapies.

INTRODUCTION

Pain, especially chronic, affects a large number of patients and can become itself by its persistence a self-contained disease with significant costs to society and varying degrees of disability for patients with professional, social, and family consequences. Population studies conducted in the United States have shown that the number of prescriptions for painful sufferings in 20 years (1991-2011) has risen dramatically from 76 million to 219 million (Reuben, 2015). The approach over the past two decades to combat both chronic and acute pain on genetic basis, justifies the hopes of the effectiveness of this type of therapy and the reduction of costs allocated by the population and the state for analgesics. One of the open pathways for this is represented by the therapeutic transfer of viral or non-viral vectors, RNA or DNA segments encoding antinociceptive factors involved in the natural pain control mechanism (endogenous opioids, neurotransmitters, neurotrophins, growth factors, immunomodulators) which injected into target tissues or peripheral tissues, are conveyed by natural transport systems in the neurons and glia of the spinal nerve networks responsible for pain (Goins, 2012; Kibaly, 2016). The second therapeutical pathway on genetic basis is personalized therapy not only of chronic and acute pain but also of other diseases in which it has proved effective (diabetes, cancer, hypertension, tuberculosis, etc.). Successful treatment of pain or other suffering in certain patient groups, with certain drug molecules and in personalized doses, is part of the new concept of layered or personalized medicine (genomic medicine). Initially, pharmacogenetics deciphered individual allele-based pathological abnormalities of perceptions for painful sensitivity due to presence of some restricted gene polymorphisms (specific and typically rare in the population such as certain familial hereditary diseases). Then, as the genotyping acquisitions proceeded, the localization and other genes continued to decrypt the causes of variability in the patient's response to different classes of analgesics, from optimal response to those of unexplained failure of the same therapies with the same doses. Personalization of genotyping means the separation of patients on well-tailored therapeutic groups based on the results of genetic tests, regarding the identification and evaluation of interindividual allelic variability of single nucleotide polymorphisms (SNP) polymorphisms present in genes. This is reflected in patients' response to medication. Personalized medicine is important both for effective pain therapy in adults and the pediatric population (Schiavone, 2017). In addition to the known rarely genetic major defects family inherited, referred above, genetic influences in the population with painful disorders contribute synergistically or antagonistically to the phenotypic expression of the response to analgesic therapy. Research shows that although in the mass of the population a frequent situation is the mutual canceling of polymorphisms and genetic effects, the frequency of the *functional* mutant gene variants involved in the pharmacokinetics and pharmacodynamics of analgesics is still between 10-50% (Lotsch, 2009). This makes that the genetic differences with an impact on patients' response to analgesics, especially first-line drugs like opioids, to be increasingly taken into account when choosing a strategy for analgesic therapy, a motivated option otherwise by observations from medical practice. It is known, for example, that the success rate for morphine is only 65% at the same dose and affection (Mogil, 1999). The lack of favorable response to opioids for the other 35% of patients is based on both genetic and cumulative contribution of epigenetic factors, both of which being still insufficiently investigated and evaluated. It is also proven that the human population is divided into morphino-sensitive and morphino-insensitive individuals (Buchsbaum, 1977) and that there is a demonstrated

concordance between the rate of identical pain-related features in monozygotic as opposed to dizygotic brothers (Martin, 1997). On the other hand, other examples show that, depending on the target receptors, men's analgesia is *mu*-opioid (men respond better to *mu*-receptor opioids), whereas in women analgesia is *kappa*-opioid, and stress analgesia is mediated in men by glutamate and in women through non-glutamic mechanism. Taking into account the differences, the administration of the targeted drug to the affected individual and tissue ("magic bullet") and no adverse effects is no longer far away. Blakey (2011) affirmation remains valid: "Each prescription written constitutes an excursion into the unknown that is fundamental to the balance of risk or benefit in medicine. Will the patient respond fully, partially or not at all? Will there be unacceptable or even life-threatening adverse effects? ". It is true that for the time being, only relatively small groups of patients can benefit from genetically guided therapy, but the basis for expanding this concept is now being opened by decoding the human genome, reducing the cost of DNA sequencing associated with increasing the number of accessible genetic tests that can select the appropriate drug molecule in the appropriate patient at the appropriate doses and times. One of the most widely used predictive pharmacological tests (first approved in the US and the EU) is *AmpliChip CYP450* on DNA microarrays with rapid scanning of thousands of markers that identify the polymorphisms of the CYP2D6 and CYP2C19 genes, principally responsible for metabolic liver enzymes, with an important modulating role of drug response (Covic, 2012).

GENETIC MODULATION OF ANALGESICS PHARMACOKINETICS

The pharmacokinetics of analgesics includes a sequence of treatments to which all the drug substances in the body are subjected: absorption (bioavailability), biotransformation (metabolism), transport, distribution and excretion of the administered substances (Goodman Gilman, 1992).

INFLUENCE OF THE GENETIC FACTOR IN THE ANALGESICS METABOLISATION

A crucial process with significant impact in the treatment of pain is the *metabolisation of analgesics* that is performed in two phases (I and II). Phase I involves oxidation, reduction and hydrolysis, processes that can result in inactive, weakly active or more active metabolites than the primary drug. In the phase II, are taken place combinations/conjugations of the metabolites with a substrate (glucuronoconjugation, glutamino- and sulfoconjugation, acetylation or methylation) are carried out in the presence of catalytic enzymes: N-acetyltransferase, UDP-glucuronosyltransferase (GGT) and glutathion S-transferase (GSTs). Analgesic drugs commonly used in medical practice include *opioid* substances (morphine and morphinomimetics) and *non-opioid* substances. The most commonly used of these are antiepileptic/non-steroidal anti-inflammatory NSAIDs. Their action is inhibitory to cyclooxygenase-COX enzyme synthesizing prostaglandin (PG) enzymes with algic and/or inflammatory activity (especially PG2). NSAIDs commonly used are *non-selective* COX or with reduced selective inhibitors (diclofenac), COX-1 *selective* inhibitors (ibuprofen, naproxen, acetyl salicylic acid, indomethacin) and *selective* COX-2 inhibitors (celecoxib, parecoxib, etoricoxib). Non-opioid analgesics include also serotonin (triptans) and neuroleptics (co-analgesics) agonists such as anticonvulsants and antidepressants. Many substances used in pharmacological therapeutics and implicitly in pain therapy are metabolised in Phase I by oxidation by cytochrome P450 hemoprotein enzymes superfamily, which determined the focus of pharmacogenomics research on genes responsible for P450 synthesis. Some of the enzymes in this family process oxidative the molecules involved in pain mechanisms, both endogenous molecules synthesized by the body such as pain mediators (substance P, serotonin, histamine, cytokines, bradykinins, prostaglandin E2) or pain suppressors (own opioids) and also exogenes (analgesic and co-analgesic drugs). For the synthesis of these protein-enzymes are responsible 57 functional cytochrome P (CYP) genes and 58 non-functional CYP genes (Muralidharan, 2011). Mutations by single nucleotide polymorphism (SNP) substitutions or deletions occurring in the genes responsible for the synthesis of P450 enzymes induce changes in metabolism (biotransformations) of administered analgesics. Thus, the decrease in enzyme metabolism of analgesics prolongs their effects by prolonging their duration of action and delaying elimination from the body (eg NSAIDs). Other analgesic drugs (codeine, tramadol, metamizole, parecoxib, tilidine) increase their action over the pain even through catabolites resulting from metabolisation. Genomic polymorphic variants with a proven and currently proven role in drug metabolism are those responsible for the synthesis of CYP1A2, **CYP2D6**, CYP2C9, CYP3A4, CYP2E1, CYP2A6 enzymes. The genes responsible for the synthesis of mentioned enzymes may have each their own distinct sub-variants. For example, the synthetizing CYP2D6 gene of the metabolizing enzyme CYP2D6 has over 80 polymorphic sub-variants corresponding to extended varieties of enzymatically expressed phenotypes among the population. Numerous DNA sequencing meta-analyzes associated with clinical data have eventually led to the acceptance of the possible classification of SNP polymorphisms in carrier populations among various populations of the globe in 4 groups depending on the metabolic effects of the synthesized enzymes. It has been agreed to choose as the metabolic behavioral prototype the

CYP2D6 gene responsible for expression of the following variants of enzymatic phenotypes: a) *poor* metabolic action (PM) enzymes due to the presence of 2 deficiency alleles with deficit in analgesic hydroxylation; b) *intermediary* action (IM) with a non-functional allele; c) *extensive* action (EM) with a functional allele and d) *ultrafast* action (UM) with two functional alleles. The existence and level of action of citocrom P450 in the patients mass with pain has a particular clinical and therapeutic significance since the predominant coding of one or other of the enzymatic variants enumerated above depends on the variability of the degree of pain abolition at the same usual dosage of the analgesic substance. Substances carrying allelic variants that synthesize weakly-metabolizing (PM) enzymes may, for example, exhibit low oxidative processing, persistent high plasma concentrations of the administered analgesic and slow elimination with good analgesic effect but which can induce by the high levels also undesirable consequences (eg. adverse effects, sometimes risky). On the contrary, the individuals at the other extremity, with duplications or gene multiplications in the UM metabolisation position type, can induce a rapid hepatic metabolisation of the analgesic substance, resulting in sub-therapeutic, inefficient plasma levels. The CYP2D6 prototype gene influences the pharmacokinetics of a large number of drug substances, approximately 25% of commonly used drugs, including opioid, anti-emetic, antiarrhythmic, antipsychotic (Zhou, 2009). At the same time, the distribution of over 100 known functional gene variants of the above-mentioned CYP450 enzymes is important. From this point of view, there are significant differences in the frequency of variant carriers depending on their belonging to different *ethnic groups*, which should be taken into account in the medical practice in order to obtain the maximum therapeutic efficiency, while avoiding the risk of toxic accidents. Thus, a significant percentage of the Arabian and Ethiopian populations (29%) are carriers SNP polymorphic variants of the UM CYP2D6 gene type, whereas 7-10% of the Caucasian populations are affected by the presence of the autosomal recessive character of the CYP2D6 non-functional allele, while in Asians their presence is only 0.5%. Other examples are offered by the CYP2D4 variant, which has a frequency of 20% in Caucasians but is absent in the Chinese. Also, CYP2D6*-10 is specific to Asians, and CYP2D6*-45 and 46 variants are characteristic of African populations (Stamer, 2010). On the other hand, interindividual genetic variability also involves other types of related changes in patient behavior towards certain drug molecules. For example, in carriers with functional deficiency of the CYP2D6 gene with poor enzyme variant (PM), the beneficial effect of protection against opioid dependence is proven (Tyndale, 1997).

MODULATION OF METABOLIC PHASES I AND II OF OPIOID ANALGESICS (CODEINE, TRAMADOL, MORPHINE)

In metabolic phase I, codeine (methylmorphine) is strongly transformed by cytochrome P450 CYP2D6 isoenzyme into codeine-6-glucuronide intermediate products + nor-codeine (together with 83% from codeine) and morphine-6-glucuronide-M6G (6%). The analgesic effect of codeine is given by the M6G metabolite which has a 200-fold higher affinity for opioid miu receptors compared to morphine. The CYP2D6 enzyme is known to have many functional isoforms corresponding to the polymorphic gene variants which respond by their synthesis and functionally evidenced by the metabolic enzyme decrease, increase or metabolic-enzymatic inactivity on codeine. Thus, enriched gene-type polymorphic enriched versions of EM for CYP2D6 may present exaggerated effects at common doses of codeine, with predisposition to intoxication or even life-threatening by potentiating the side effects of the M6G metabolite (eg depression of breathing) being reported deaths in this way (Ciskowski, 2009). A high SNP gene variability is from this point of view the Caucasian populations in which treatment of pain with 60 mg of codeine that should reduce pain intensity by 50% finishes in 1 of 7 patients with failure or toxicity (Lotsch, 2009). Moreover, in such cases, adverse reactions may precipitate in genetically uninvestigated patients to who are filled opioids with non-opioid analgesics or in individuals with associated deficiencies in the excretion of metabolites (eg renal impairment). Other isoforms with metabolic action on codeine are CYP3A and UGT2B7. A codeine-like behavior is presented by tramadol (an opioid metabolised by the CYP2D6 enzyme), by its O-desmethyl-tramadol derivative (O-DSMT) derivative, which in turn has an affinity for the *miu* opioid receptors of 200 times higher than tramadol (Stamer 2003, 2007). Patients carrying PM variants with poor enzyme activity on the tramadol substrate (eg CYP2D6*10 homozygous Chinese) require high doses to achieve the analgesic effect (at risk for adverse effects in undetected genetically patients), unlike those who are carriers of at least one wild allele (Wang, 2006). Also, in carriers of gene-rich variants with extensive metabolism, the increase of O-DSMT favors the risk of side effects. Regarding the phase II metabolisation of analgesics represented by conjugation, an increasing interest has been shown since 1990 on the UGT enzyme (uridine diphospho- glucuronosyl-transferase) with the UGT2B7 isoform (from UGT-A1-10, UGT2B-4, 7,10,11,15,17,28 family). The isoform UGT2B7 is a special enzyme that has demonstrated strong glucuronidation actions of analgesic drugs such as morphine, codeine, buprenorphine, fluribiprofen, nonsteroidal anti-inflammatory drugs and anticonvulsants. It catabolizes morphine in two compounds with opposite effects: morphine-6-glucuronide (M6G) with analgesic effects (and with a 42-fold more expanding than morphine variability coeficient) and morphine-3-glucuronide (M3G-70%) with antianalgesic, excitatory effects. Various gene polymorphisms (SNPs) of the UGT2B7 gene in the nontranslational region induce morphine-derived metabolite alterations, e.g., M6G decrease, while UGT2B7*2/2 variant combined with the CYP2D6 enzyme has reversed effects.

CONTRIBUTION OF GENE VARIABILITY IN THE METABOLISM OF NON-OPIOID ANALGESICS

In pain-relieving analgesic pharmacology, not only opioids, but also non-opioid drugs have an important place to combat chronic pain, post-surgery pain, or frequently associated with opioids in the treatment of acute postoperative pain, or in addition to opioid medication in major surgery. They complete the analgesic action, reduce the side effects of opioids by reducing their doses and reduce the risk of opioid addiction. There is a certain genetic influence on the effectiveness of non-opioid analgesics, a class of drugs that include: synthetic NSAIDs and some neuroleptics, antiemetics, antiarrhythmics or serotonin reuptake inhibitors. Thus, NSAIDs contribute to pain relief by inhibiting CYP2C9, CYP2C8 and CYP2C19 genes responsible for the formation of catabolic enzymes. Contributions of genetics to modification of inhibitory actions on genes and enzymes were first suggested by highlighting in some experimental animals, but also in some patients, a high degree of sensitivity to NSAIDs or paracetamol, while others, on the contrary, found the presence of increased resistance to this therapy. In recent years, it has been shown that response differences are due to the variability of action (gene-dependent) of metabolizing enzymes on the drug substrate. For example, it is now known that the synthesis of enzymes which metabolise synthesis NSAIDs (diclofenac, ibuprofen, naproxen, piroxicam, celecoxib, parecoxib, etoricoxib, valdecoxib) significantly responds to the CYP2C9 gene (33 sub-variants), CYP2C8 and CYP2C19. The existence to polymorphic genic variants carriers of gene CYP2C9 PM type (metabolic / enzymatic weak effect on NSAIDs) allows to CYP2C9*3 homozygotes slowing down the elimination of the analgesic (COX-1 and 2 inhibitors) and consequently increase of their concentration in plasma over 2 fold compared to CYP2C9*1/1 wild-type carriers (Tang, 2001; Stamer, 2007). Delayed excretion of NSAIDs in CYP2C9*3 allele carriers is associated with an increase in pharmacodynamic activity with significant clinical effects but which not exclude careful monitoring of the risk of adverse effects on these substances. Catabolism of other substances used to combat pain in association with opioids (with the advantage of lowering their dosages especially in the treatment of chronic pain) such as co-analgesics represented by adjuvants neuroleptics such as antidepressants (dextromorphan, trimipramine or paroxetine), antipsychotics (haloperidol), antiemetics (metoclopramide) or antiarrhythmics (amiodarone) are made by enzymes synthesized under the control of the CYP2D6 gene, which also controls opioid metabolism. For example, carriers of the CYP2D6 polymorphic (SNP) gene variant with a reduced degree of synthesis (PM type) of the metabolizing isoenzyme exhibit high exposure to the drug by slowing metabolism associated with a risk of adverse reactions. In contrast, duplicates of the CYP2D6 gene with ultra-fast enzyme metabolism (UM type) of antidepressants or antipsychotics can result in ineffective sub-therapeutic concentrations (Kirchheiner-2003, 2004). Antidepressants used in the treatment of chronic pain are substrates for other genes by the enzymes they synthesize, such as the CYP2C19 and ABCB1 genes.

GENETIC INFLUENCE OF THE ANALGESICS TRANSPORT

An important role in the pharmacokinetics of analgesics is represented by the drug-carrier molecules family in brain regions with key roles in the central mechanisms of pain. Most transporters are glycoproteins that modulate the hemato-encephalic and neuronal transmembrane passage, and finally the intracellular concentration of the therapeutic molecules. One of the most well-known transporters group is the ABC family with 7 subfamilies and 49 members (Muralidharan, 2011; Mercer, 2011), the most studied transporter being B1 glycoprotein P (P-gp). The P-gp transporter is encoded by the ABC B1 gene and acts as a transmembrane pump for the active transport of some drug molecules, implicitly analgesic. It has over 50 mutational SNP variants with numerous polymorphisms (by insertions / deletions) identified in the ABC B1 gene that increase or decrease the concentration of analgesics in the brain by their transport with variable velocity through the blood-brain barrier. In this way, for example, modifications of the polymorphic encoded SNP positions of the ABCB1 gene shows in both animal and clinical experiments in cancer patients treated with morphine, significant associations with the variability of analgesia and the reduction of adverse effects (Fujita, 2010). The P-gp transporter mediates the effects of opioids and antidepressants through its structural functional variants genetically coded. It has thus been shown in heroin-dependent patients undergoing methadone replacement therapy that the doses may be reduced to carrier of ABCB1-2435 C>T variants that decrease the expression of the P-gp transporter resulting in slowing of the methadone flow out of the brain . The transport also modulates in this way methadone-induced analgesia, as evidence of increased anti-antalgic effects following the pharmacological blockade of the P-gp transporter (Coller, 2006; Lotsch, 2009; Mercer, 2011). SNP gene variants responsible for carrier synthesis modulate the variability of patient response to other molecules also involved in analgesic mechanisms, for example the SLC6A2 and SLC6A4 genes for noradrenaline and serotonin.

GENETIC MODULATION OF PHARMACODYNAMIC ACTION OF ANALGESICS

The biochemical and physiological effects, as well as the mechanisms of action of the analgesics, are part of their pharmacodynamics and are influenced by the variability of genotypes in the population mass as well as the pharmacokinetic processes mentioned above. The decisive factor of the pharmacodynamics of analgesics depends on the ability and their effectiveness of coupling to neurons receptors in the spinal and cerebral target areas, with a role in pain perception. Poor binding on membrane receptors or low number of active receptors induce poor and unsatisfactory therapeutic effects on pain. Receptors, as protein structures, are genetically encoded, in the first line of the analgesic efficacy being the opioid receptors: miu, delta, kappa, epsilon and the orphan receptor FQ (nociceptin). All of mentioned opioid receptors manifest their actions by modulating G protein (pGm) in their structure, in this case the inhibiting variant of protein G (Gi) with the reduction of AMPc formation. The OPRM1 gene responsible for the encoding of the opioid miu receptor is highly SNP polymorphic, mutant variants being due either to alteration of the extracellular receptor domains or to the intracellular neurons (Shabalina, 2009). In the first case, was identify the decrease of the extracellular glycosylation site of the protein-miu receptor (replacement aspartate with asparagine at position 40) with reduction of the analgesic effects of the opioids (see note I). In the second case, is better known the OPRM1 mutant gene variant which affects the 3rd intracellular loop of the receptor followed by cascade events: decrease in G protein binding capacity, decrease in receptor signaling capacity and decrease in therapeutic effects or even inefficiency of the analgesic. This mutation affects precisely those cerebral neuronal areas densely populated by miu opioid receptors involved in natural pain control and stimulation of reward behavior, associated in the same time with important participations in the mechanisms of perception and pain feeling: the somatosensory cortical area I and II, the anterior cingulated cortex, the posterior islet cortex and the *accumbens* nucleus. The patient carriers of OPRM1 gene mutation need to reduce or suppress pain high doses of opioid analgesics: morphine, M6G, alfentanil, methadone (Oertel, 2009). The alteration of the pharmacodynamic intimate mechanism is related to two key factors of miu neuronal receptor function: (1) G-protein - kinase receptors (GRK) on surface neuronal membrane regulating Gi protein by phosphorylation and 2) protein G - K^+ rectifying channels (GIRK), couples factors being primary post-synaptic effectors in central nervous system neurons. In the first case (GRK), mutant coding of modulators signal proteins arrestin *beta*-1 and 2 block the action of the Gi protein by inducing desensitization (lack of activation) of the phosphorylated miu opioid receptor (Ferguson, 1996). In the second case (GIRK), normally the GIRK ionic channels present in the heart (involved in the mechanism of cardiac pain), spinal cord, cerebral zones activated by coupling with the G protein opens, followed by an influx of K^+ ions from the extracellular space in the cytoplasm, activating in turn the miu opioid receptors that induce analgesia by blocking the transmission of pain. In contrast, in carriers of ion channels genetically modified GIRK, mutations in the intracellular domain of GIRK decrease their sensitivity for the Gi receptor protein. Under these conditions, the binding of the Gi protein to a neuronal receptor ligand (the ligands may be for miu receptors and nociceptin FQ receptors or for muscarinic receptors, adrenergic alpha2, serotonin 1A, cannabinoid, adenosine 1A), results in the reduction of K^+ inside the cell, to which is added the depression of N-type Ca^{2+} channels, which ultimately induces opioid receptor desensitization (Nishizawa, 2014). GIRK1 channels (encoded by the KCVJ3 gene) participate in opioid analgesia (Marker, 2004), and GIRK2 channels (CKNJ6 gene) contribute to modulation of opioid-induced tolerance (Saland, 2008). GIRK1,2 and GIRK3 (encoded by the KCNJ9 gene) strongly modulate painful sensitivity, gene *knockout* mice developing hyperalgesia (Marker, 2004; Smith, 2008). The GIRK2 and GIRK6 ion channels are involved in inflammation and allodynia by lowering the excitability threshold and increasing pain sensitivity (Eijkelkamp, 2009). Two of the SNP mutant variants (Cs2835859) of the CKNJ6 and KCNJ9 genes have recently been identified as being responsible for the analgesic and pain sensitivity associated with the predisposition for nicotine, alcohol and cocaine dependence and can serve as useful markers in medical practice (Nishizawa, 2014). Desensitization of neuronal opioid receptors promotes the occurrence and installation of pain, primarily being targeted bulbar neurons from *locus coeruleus* area and cerebrospinal gray substance from the brainstem, major inhibitory areas in ascending pain transmission through spinal tangles to the thalamus and cortical areas somato-sensitive and vegetative projection of painful sensitivity pathways.

CONCLUSIONS

The pharmacokinetic and pharmacodynamic advantages of analgesic pain therapy based on pharmacogenomic molecular mechanisms are primarily due to the increase in efficiency by individualization treatment under the conditions of dose reduction, the ideal of any drug therapy (it is known that "in the usual classical treatment, patients take biger doses for smaller effects "- Stamer, 2007). In addition, is followed the avoidance of adverse side effects and toxicity (100,000/year deaths in the USA by adverse effects), reducing the risk of addiction, avoiding the

loss of time to maximize efficacy doses and appropriate drug associations, avoiding polypragmasia and drug interactions which can amplify (or block) the metabolic effects of enzymes and especially the occurrence of adverse effects in particular in fragile individuals such as elderly with multiple sufferings and associated therapies or young children. Since the phenotype of pain and response to treatment are also influenced by epigenetic factors (environmental factors, lifestyle, diseases and associated medications), in the near future, it will be more accurately highlighted how and where these factors induce subtle changes summed up in the genome of individuals. Today the recent acquisitions, as well as the benefits of pharmacogenomics, widen the possibility of applying these data and results to pain management strategies in order to maximize the efficiency gains on this basis. It is true that there are complex difficulties due to the redundancy and pleiotropism characteristic of the biological systems, which require time to solve and that the therapy of acute and chronic pain can not yet be personalized satisfactorily (depending on the patient's genotype) for large populations. Many times, only the accentuated adverse effects or the failure of the therapy can direct the physician's prediction to a genetic motivation. But predictive analgesic therapy, guided and genetically individualized, remains for the very near future the most effective strategic option for well-defined patient groups.

REFERENCES

Blakey JD, Hall IP. (2011): *Current progress in pharmacogenetics*, British Journal of Clinical Pharmacology, 71,6:824-831

Buchsbaum MS, Davis GC, Bunney VE Jr. (1977): Nature , London, 270: 620-622, pmid: 339 110 (*CrossRef, PubMed, Google Scholar)*

Ciskowski C, Madadi P, Phillips MS, Lawres AE, Koren G.(2009): *Codeine, ultrarapid metabolism genotype and post-operative death*, New England J.Med. 361(8):827-828

Coller JK, Barrat DT, Dahlen K, Loennechen MH. et al.(2006): *ABCB1 genetic variability and metadone dosage requirements in opioid-dependent individuals*, Clin.Pharmacol.Therap.80:682-690

Covic M.(2012): *Farmacogenomica: o speranță pentru medicina personalizată*, Rev.Viața medicală, 16(1162)

Eijkelkamp N, Heijnen KJ, Elsenbruch S, Holtman G. Et al. (2009): *G-protein coupled receptor kinase 6 control post-inflamatory visceral hyperalgesia*, Brain Behav. Immun. 23:18-26

Fergusson SS, Barak LS, Zhang J, Caron MG. (1996): *G-protein- coupled receptor regulation: role of G-protein-coupled receptor kinases and arrestins*, Canadian Journ.Physiol.Pharm.,74:1095-1110

Fujita K, Ando Y, Yamamoto W, Miya T. et al. (2010): *Association of UGTB2B7 and ABCB1 genotypes with morphine-induced adverse drug reaction in Japanese pacients with cancer,* Cancer Chemotherapy Pharmacology. 65:251-258

Goins WF,Cohen JB, Glorioso JC.(2012): *Gene therapy for the treatment of chronic peripheral nervous system pain* , Neurobiology of Disease, 48:55-270

Goodman Gilman A, Rall TW, Nies As, Taylor P (1992): The pharmacological Basis of Therapeutics, vol.I, VIII Edition, Mc Graw-Hill International Edit, *Medical Series*, pg.3 și 33

Kibaly C, Loh HH, Law P-Y.(2010): *A Mechanisms Approach to the Development of gene Therapy for Chronic Pain*, International Review of Cell and Molecular Biology, vol.327, ISSN 1937-6448

Kirchheiner J, Niccken K, Bauer M, Wong M-L, Licinio J. et al.(2004)- *Pharmacogenetics of antidepressants and antipsichotics: the contribution of the allelic variation to the phenotype af drug response* , Mol.Psichiatry 9: 442-473

Kirchheiner J, Sasse J,Maineke I, Roots I et al.(2003): *Trimipramine pharmacogenetics after intravenous and oral administration in carriers of CYP2D6 fenotypes predicting poor, exiensive and ultrahigh activity*, Pharmacogenetics,13:721-728

Lotsch J, Geisslinger G, Tegeder I. (2009)-*Genetic modulation of the pharmacological treatment of pain,* Pharmacology and Therapeutics 124:168-184

Marker CL, Stoffel M, Wickman K. (2004): *Spinal G-protein-gated K+ channels formed by GIRK1 and GIRK-2 subunits modulate thermal nociception and contribute to morphine analgesia*, Journ.Neurosci.24, 2806-2812

Martin N, Boomsma D, Machin G (1997): *A twin-pronged attack on complex traits*, Nat.Genet., 17: 387-392 (CrossRef, Pubmed, Google Scholar)

Mercer S, CoopA.(2011): *Opioid Analgesics and P-glycoprotein Eflux Transporters: Apotential Systems-LevelContribution to Analgesic Tolerance*, Curr Top Med Chem, 11(9):1157-1164
Mogil JS (1999): The genetic mediation of individual differences in sensitivity to pain and its inhibition, Proc.Natl.Acad.Sci. USA, 96 (14) 7744-7751 (https://doi.org/10.1073/.pnas.96.14.7744)
Muralidharan A, Smith TM. (2011): *Pain, analgesia and genetics*, Journ.of Pharmacy and Pharmacology, 63:1387-1400
Nishizawa D, Fukuda K, Kasai S, Ogai Y, Hasegawa J et al.(2014): *Association Between KCNJ6 (GIRK2) Gene Polymorphism rs 2835859 and Post-operative Analgesia, Pain sensitivity and Nicotin Dependence*, Journal of Pharmacological Sciences, 126:253-263
Oertel BG, Kettner M, ScholichK, Renne C, Roskam B et al. (2009): *A common human opioid receptor variant diminishes the receptor signaling efficacy in brain regions processing the sensory information of pain*, Journ.Biol.Chem. 284:6530-6535
Saland Lc, Chavez JB, Lee DC, Garcia RR, Caldwell KK. (2008): *Chronic ethanol exposure increases the association of hippocampal mu-opioid receptors with G-protein –receptor kinase 2*, Alcohol, 42: 493-497
Schiavone S, Neri M, Pomara C, Riezzo I. et al.(2017): *Personalized medicine in the Paediatric Population: the Balance Between Pharmacogenethics Progress and Bioethics*, Current Pharmaceutical Biotechnology, 18,3:253-262
Shabalina SA, Zaykin DV, Gris P, Ogurtsov AY et al. (2oo9): *Expansion of the human mu-opioid receptor gene arhitecture: novel functional variants*, Human Molecular Genetics, 18, 6:1037-1051
Smith SB, Marker CL, Perry C, Liao G. Et al. (2008*): Quantitative trait locus and computational mapping identifies Kcnj9 (GIRK3) as a candidate gene affecting analgesia from multiple drug classes*, Pharmacogenetics and Genomics, 18:231-241
Stamer UM, Lehnen K, Hothker F, Bayerer B, Wolf S. et al.(2003): *Impact of CYP2D6 genotype on postoperative tramadol analgesia*, Pain, 105:232-238
Stamer UM, Stuber F (2007)-*The pharmacogenetics of analgesia*, Expert Opin.Pharmacotherapy, 8(14): 2235-2245
Stamer UM, Zhang L, Stuber F.(2010): *Personalized therapy in pain management: where do stand?*, Pharmacogenomics, 11(6):843-864
Tang C, Shou M, Rushmore TH, Mei Q et al. (2001): In vitro metabolism of celecoxib, a cyclooxygenase 2-inhibitor by allelic variant forms of human liver microsomal cytochrome P450 2C9: correlation with CYP2C9 genotype and in vivo pharmacokinetics, Pharmacogenetics, 11: 223-235
Tyndale RF, Droll KP, Sellers EM (1997): *Genetically deficient CYP2D6 metabolism provides protection against orale opiate dependence*, Pharmacogenetics, 7(5):375-379
Wang GX, Zhang H, He FF, Fang XM. (2006): *Effect of the CYP2D6*10 C188T polymorphism on postoperativ tramadol analgesia in a Chinese population*, European Journal of Clinical Pharmacology.,62(11):927-931
Zhou SF.(2009): *Polymorphism of human cyrochrome P450 2D6 and its clinical significance(Part II)*, Clinical Pharmacokinet.,48:761-804
CYP ALLELE Nomenclature Commitee (*http://www.cypalleles .ki.se)*
www.ncbi.nlm.nih.gov/SNP

Affiliation:
University of Medicine and Pharmacy "Gr.T.Popa" Iasi
Faculty of Pharmacy, Department of Pharmacodynamics and Clinical Pharmacy
* dana.ababei@gmail.com