Pharmacogenetics and Analgesic Effects of Antidepressants in Chronic Pain Management

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Abstract and Introduction

Abstract

Antidepressants are widely administered to chronic pain patients, but there is large interindividual variability in their efficacy and adverse effect rates that may be attributed to genetic factors. Studies have attempted to determine the impact of genetic polymorphisms in enzymes and transporters that are involved in antidepressant pharmacokinetics, for example, cytochrome P450 and P-gp. The impacts of genetic polymorphisms in the targets of antidepressants, such as the serotonin receptor or transporter, the noradrenaline transporter and the COMT and monoamine oxydase enzymes, have also been described. This manuscript discusses the current knowledge of the influence of genetic factors on the plasma concentrations, efficacy and adverse effects of the major antidepressants used in pain management.

Introduction

The management of chronic pain is a major issue in clinical practice. Several non-opioid based therapies can be useful for managing pain. The current evidence-based guidelines recommend the use of antidepressants, particularly tricyclics and serotonin-noradrenaline reuptake inhibitor antidepressants (SNRIs), for the treatment of various types of chronic pain, including neuropathic pain,[1,2] musculoskeletal pain, such as low back pain, central pain syndrome and fibromyalgia.[3,4]

Chronic pain and depression are closely linked and are part of the most frequent reasons to seek medical care. The prevalence of chronic pain is high in the general population and ranges from 2 to 60% depending on the reference definition.[5,6] Between 40 and 60% of patients with chronic pain also experience depression.[7–9] The link between depression and chronic pain may be psychological, but it may also be biological due to common pathways. Because the biological mechanism for depression relies mostly on the dysregulation of the neurotransmitters serotonin (5-HT), noradrenaline (NA) and dopamine, NA and 5-HT have also been implicated in the pathophysiology of chronic pain.

Thus, antidepressants are not only used in pain management because depression is often a comorbidity of chronic pain. Experimental and clinical data suggest that antidepressants have analgesic effects that differ from their classical action on mood. Indeed, studies have shown that analgesia is often achieved with lower doses than those required for depression and that the effect onset may be faster than that obtained in depression. For example, in diabetic polyneuropathy, 60 mg of duloxetine demonstrated an improvement in the 24-h average pain severity score with a rapid onset of action with separation from the placebo beginning at 1 week.[10] Moreover, the analgesic effect may be present without an effect on mood.

This effect seems independent of the antidepressant effect. The antinociceptive activity of antidepressants is demonstrated in a large amount of preclinical[11] and clinical[12] experimental studies. Ongeha *et al*.[13] clearly revealed this analgesic effect in nondepressed pain patients, in their meta-analysis of 39 placebo-controlled studies.

However, the precise analgesic mechanism of action of antidepressant drugs remains debated. The commonly accepted hypothesis is a central action mediated by descending pain control pathways via an inhibition of the presynaptic reuptake of noradrenaline and serotonin,[14,15] but effects at the peripheral site, that are independent from the mood effect, have also been described: particularly the blockade of sodium channel.

The efficacy of the tricyclic antidepressants amitriptyline, clomipramine, imipramine, desipramine, nortriptyline and doxepin on the treatment of chronic and neuropathic pain has been demonstrated in numerous studies.[16–21] However, new antidepressants are also effective for other chronic pain conditions and are increasingly used in chronic pain patients because of their improved tolerability. These belong to the group of SNRIs, for example, venlafaxine, duloxetine and milnacipran,[22,23] and the atypical antidepressant group, such as bupropion[24] and mirtazapine.[25] The superiority of tricyclics, particularly clomipramine and amitriptyline, in the management of pain may be explained by their additional action on sodium channels blockade,[26–29] which is an action that SNRIs do not exhibit. Venlafaxine has a similar chemical structure to the opioid derivative tramadol, has the tertiary amine functional group necessary for μ-opioid receptor recognition, and may indeed act also partly as an agonist to the μ-opioid receptor.[30] This type of opioidergic profile may explain their efficacy for pain management. The analgesic efficacy of selective serotonin reuptake inhibitors (SSRIs) remains undoubtedly less important.

[31,32]

Successful pain management has to provide adequate analgesia without excessive adverse effects. The management of pain with antidepressants is complicated by the large interindividual response variability to therapy. No response, a partial response and an unbearable side effect have been reported following the same conventional drug dosing, which may affect the treatment adherence.

The high frequency of poor adherence in chronic pain conditions was confirmed in a recent prospective study[33] and a meta-analysis[34] that investigated medication adherence in patients with chronic, nonmalignant pain. These studies determined that nonadherence to medication is common in 40–60% and 30% of patients, respectively. Another study demonstrated that patient adherence to a newly initiated antidepressant treatment varied significantly across the medical conditions for which it was prescribed. The duloxetine adherence rate was thus lower in patients with chronic pain conditions (29.9%) than in patients with major depressive disorder (37.3%).[35]

Poor adherence is likely the most important factor contributing to treatment failure, but factors such as age, gender, co-medication, smoking habits, treatment duration and/or inadequate dosages[36,37] and genetic variations should also be considered. Because genetic factors appear to be the most stable and predictable elements, a pharmacogenetic approach may aid the individualization of treatment.

During recent years, the possible influence of a set of genetic polymorphisms and the response to antidepressants in the treatment of depression were examined in genome-wide association studies (GWAS)[38–40] and clinical studies.[41–51] They include the CYP superfamily, the P-gp, the COMT, the MAO, the serotonin transporter, the noradrenaline transporter and variants in the serotonin receptors.

Because tricyclic antidepressants and SNRIs are now an integral part in the management of chronic and neuropathic pain, this paper discusses the potential role of these polymorphisms in the specific context of pain management.

Method

Relevant articles in the PubMed and EMBASE databases were identified using the following keywords: 'pain', 'neuropathy', 'depression', 'antidepressants', 'resistance' and/or 'pharmacogenetics.' We limited our search to English language studies published in peer-reviewed journals. Additional publications were identified from review articles.[52–73]

Discussion

Several genes are involved in the interindividual variability of the antidepressant response. The best characterized genes encode drug-metabolizing enzymes and drug transporters, such as the CYP superfamily and P-gp. Additionally, few studies have investigated genes involved in antidepressant pharmacodynamics, for example, the serotonin receptor, serotonin transporter, noradrenaline transporter, COMT, MAO and sodium channels.

Polymorphisms Involved in Drug Pharmacokinetics

The majority of the data originated from studies performed in patients treated for depression, and generalization to the pain context was not always possible. Like for antidepressants used for depression, several studies have also indicated a relation between the pain-relieving effect and the serum drug concentration of antidepressants, particularly of tricyclic antidepressants.[18,74–75]

Assuming this relationship, some hypothesis may be discussed.

Cytochrome P450 Enzymes. The CYP superfamily is a large group of enzymes responsible for the oxidation and reduction of 80% of all prescribed drugs. The primary CYP enzymes involved in the antidepressant drug metabolism are CYP1A2, CYP2D6 and CYP2C19[76] (). Bupropion is metabolized by CYP2ref-6. The metabolic pathways of the most commonly used antidepressants are presented in , and the drugs that are used as analgesics are indicated.[77] Genetic changes in CYP genes can result in alterations in enzyme activities.

Table 1. Antidepressant metabolic pathways.

Antidepressants	Cytochrome
Agomelatine	1A2, 2C9, 2C19
Amitriptyline†	1A2, 2C9, 2C19, 2D6, 3A
Bupropion†	2B6

Citalopram	2C19, 2D6, 3A
Duloxetine†	1A2, 2D6
Fluoxetine	2C9, 2C19, 2D6, 3A
Fluvoxamine	1A2, 2D6
Imipramine†	1A2, 2C19, 2D6, 3A
Maprotiline†	2D6
Mirtazapine†	1A2, 2D6, 3A
Paroxetine	2D6
Reboxetine	3A
Sertraline	2B6, 2C9, 2C19, 2D6, 3A
Trazodone	2D6, 3A
Trimipramine†	2C9, 2C19, 2D6
Venlafaxine†	2D6, 3A

†Antidepressants used for the treatment of chronic pain at the University Hospitals of Geneva [78].

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Bupropion†	2B6
Citalopram	2C19, 2D6, 3A
Duloxetine†	1A2, 2D6
Fluoxetine	2C9, 2C19, 2D6, 3A
Fluvoxamine	1A2, 2D6
Imipramine†	1A2, 2C19, 2D6, 3A
Maprotiline†	2D6
Mirtazapine†	1A2, 2D6, 3A
Paroxetine	2D6
Reboxetine	3A
Sertraline	2B6, 2C9, 2C19, 2D6, 3A
Trazodone	2D6, 3A
Trimipramine†	2C9, 2C19, 2D6
Venlafaxine†	2D6, 3A

†Antidepressants used for the treatment of chronic pain at the University Hospitals of Geneva [78].

The CYP2D6 system has been extensively studied and is the best characterized to date. The gene encoding CYP2D6 is highly polymorphic, with up to 80 allelic variants currently described.[79] These variants result in differences in enzyme activity ranging from 1 to 200%, which determine its metabolizer status.[61,77] Four phenotypes can be identified: 'ultrarapid metabolizer' (UM), 'extensive metabolizer' (EM), 'intermediate metabolizer' (IM) and 'poor metabolizer' (PM).[77,79–80] The prevalence of CYP2D6 PM, in other words, complete enzyme deficiency, is estimated to be 5–10%[77] in Caucasian populations but is rare – 3% – in other ethnic populations. IMs, which have reduced enzymatic activity, account for 10–15% [77] of Caucasians but up to 50% of Asians. EMs, with normal enzymatic activity, account for 60–70% of Caucasians. UMs, which exhibit increased metabolism, account only for 1–10% of Caucasians but potentially up to 30% of Northern African and Arabian populations.[79,81] Genetic variations of CYP2D6 have been consistently demonstrated to influence the plasma level

concentrations of antidepressants with large variations, up to 30–40-fold with similar doses.[45] Because the drug–plasma concentrations influence the response of antidepressants and the occurrence of side effects, antidepressants have been found to exhibit variable efficacy and tolerability. Multiple data have demonstrated that adverse events are related to phenotype differences because more frequent adverse events are found in PMs, even at the usual recommended dosages and the PM genotype is more common in patients reporting tricyclic antidepressant adverse effects.[45–46,82] For efficacy, some data have demonstrated that UM patients present reduced antidepressant efficacy when the drugs are used to treat depression; however, this has not been confirmed in the large STAR*D study population.[83–85] Because CYP2D6 is involved in the endogenous morphine synthesis pathway and because it has been shown that poor metabolizers of CP2D6 may be less tolerant to some pain stimuli, such as tonic pain, than extensive metabolizers independent of analgesic treatment,[86] the findings suggest that the CYP2D6 gene may be a candidate for modulation of the pain sensitivity threshold.[87]

Genetic variations associated with the EM, PM and UM phenotypes have also been described for CYP2C19.[88] The frequency of the PM phenotype is approximately 2–5% in Caucasian populations and approximately 20% in Asian populations.[88] The different phenotypes are also associated with variable plasma concentrations[60,89] and occurrence of side effects.[90] Studies have demonstrated that the plasma concentrations of the antidepressant substrates of CYP2C19 are reduced in UM patients[60] whereas gene deletion (PM) may be associated with a sixfold increase in concentration.[89]

CYP1A2 plays an important role in duloxetine metabolism. There are pronounced interindividual differences in the CYP1A2 activity in humans[91,92] with 15 SNPs having been described in the gene encoding CYP1A2. Furthermore, the most important factor for the variability of CYP1A2 activity is its inducement by the polyaromatic hydrocarbons present in cigarette smoke,[93] which is related to genetic polymorphisms. For example, the -164C>A polymorphism (*CYP1A2*1F*) in intron 1 confers a high inducibility of CYP1A2 in smokers.[94] Smoking may cause a 50% reduction in the duloxetine plasma concentrations.[95] The influence of these differences in CYP1A2 activity on duloxetine efficacy or tolerance has not been examined in pain management.

Finally, CYP2ref-6 is involved in the metabolism of bupropion. Due to the existence of extensive genetic polymorphism, its activity is also highly variable in the population.

CYP2ref-6 is one of the most polymorphic CYP genes in humans with over 100 described SNPs.[96] The most common allelic variant *CYP2ref-6*6* results in reduced enzyme activity. It is present in 28% of Caucasians and up to 40% of Africans and Chinese. Although the clinical relevance of these mutations in the treatment of chronic pain with bupropion is not known, clinical significance of CYP2ref-6 variants has been implicated in smoking cessation in response to bupropion.[97–100]

Genetic variations of these cytochromes have been consistently demonstrated to influence the plasma level concentrations of antidepressants and the drug–plasma concentrations to influence the response and side effect occurrence.

Because of the well-established data on CYP, the dosage recommendations for 'antidepressive' dosages based on the CYP2D6 and CYP2C19 phenotype/genotype have been developed[70,101] and are easily accessible at the PharmGKB website.[102] These are summarized in . Admittedly, a reasonable treatment approach is the use of a lower starting dose with dosage adjustments based on the clinical response and plasma concentration in PM individuals and the exclusion of the molecule for UM individuals. The validity of these approaches has not been systematically tested in clinical situations in which antidepressants are used as pain killers, but we can reasonably assume that the use of a lower starting dose with dosage adjustments is suitable for a PM individual, even if very low doses of tricyclic doses are used. For UM subjects, the low dosage warrants the use of the enzyme substrate.

Table 2. Dosage guidelines for amitriptyline and, by analogy, tricyclics according to the CYP2C19 and CYP2D6 phenotype.

CPY2C19	CYP2D6			
	UM	**EM**	**IM**	**PM**
UM	• Avoid use of tricyclic drugs • If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments	• Avoid use of tricyclic drugs • If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments	• Avoid use of tricyclic drugs • If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments	• Avoid use of tricyclic drugs • If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments
EM	• Avoid use of tricyclic drugs • If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments	• Initiate therapy with recommended starting dose	• Consider a 25% reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments	• Avoid use of tricyclic drugs • If a tricyclic is warranted, consider a 50% reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

IM	• Avoid use of tricyclic drugs • If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments	• Initiate therapy with the recommended starting dose	• Consider a 25% reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments	• Avoid use of tricyclic drugs • If a tricyclic is warranted, consider a 50% reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments
PM	• Avoid the use of tricyclic drugs • If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments	• Decrease the usual dose by 50% and adjust according to therapeutic monitoring	• Avoid the use of tricyclic drugs • If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustment	• Avoid the use of tricyclic drugs • If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments

EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer; UM: Ultrarapid metabolizer.
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P-gp. P-gp is a plasma membrane transporter encoded by the human ATP-binding cassette *ABCref-1* gene, which is expressed in various human tissues, including the placenta, GI tract, kidney and the luminal membranes of endothelial cells in the blood–brain barrier.[103,104] The function of P-gp is to export drugs from cells against a concentration gradient. The absence or inhibition of P-gp function can result in increased exposure to drugs.[105,106] To date, 30 *ABCref-1* genetic polymorphisms have been described,[107] and this high number of polymorphisms may explain the interindividual variability in the expression and function of P-gp. For example, *ABCB*1-knockout mice, which lack the drug-transporting P-gp at the blood–brain barrier, have higher brain concentrations of P-gp substrates. Evidence from several experiments with knockout mice lacking functional P-gp demonstrates that this pump has a significant impact on the analgesic effect of some opioids. In rats treated with a string P-gp inhibitor, a single intravenous morphine injection has a prolonged antinociceptive effect.[108] The previous studies on humans suggest that patients with a lower expression of P-gp require lower doses of morphine and are at greater risk of adverse effects.[109–111] Similarly, the proportion of patients presenting with somnolence and confusion was greater in patients whose P-gp expression was lower.[112] A number of antidepressants are substrates of P-gp ()[113–115] and a series of studies have investigated the influence of functional polymorphisms of P-gp on the antidepressant drug plasma levels, clinical response and side effect profile and report contradictory findings.[41,49,60,71,116–117] No link between these mutations and antidepressant efficacy or tolerability has been demonstrated to date in depressed or chronic pain patients. But it is reasonable to believe that an increased CNS exposure to antidepressants, due to a low P-gp activity would increase the risk of adverse effects, like it has been described for other psychotropic drugs such as the above discussed example of morphine. Exploring P-gp activity should be discussed when CNS adverse effects are intense at a small dosage.

Table 3. Antidepressant substrates of P-gp.

Antidepressants	P-gp
Agomelatine	
Amitriptyline†	x
Bupropion†	
Citalopram	x
Duloxetine†	
Fluoxetine	
Fluvoxamine	
Imipramine†	x
Maprotiline	
Mirtazapine†	
Paroxetine	
Reboxetine	
Sertraline	
Trazodone	

Trimipramine†	x
Venlafaxine†	x

†Antidepressants used for the treatment of chronic pain at the University Hospitals of Geneva [78].

Polymorphisms Involved in Antidepressant Targets

The analgesic properties of antidepressants have been suggested to result from the inhibition of amine, noradrenaline and serotonin reuptake in the CNS, which consequentially leads to increased activity of the antinociceptive descending pathways. The antidepressants may also have an analgesic effect through their action on sodium channel receptors of the primary afferent neurons.

COMT is one of the principal catecholamine metabolic enzymes and acts as a key modulator of dopaminergic and adrenergic/noradrenergic neurotransmission, which are the neurotransmitters implicated in the pathophysiology of chronic pain, but likely also other endogenous substrates. The association between *COMT* gene variations and pain sensitivity has been reported in various studies. As for CYP2D6, *COMT* is also a candidate gene that may influence sensitivity to pain and thereby pain management.

The best-described COMT allelic variant is the 158 G>A (*rs4680*) polymorphism, which results in the Val158Met substitution. The Met/Met variant is associated with fourfold lower COMT activity[118] (Val/Val: Important activity; Val/Met: Intermediate activity; Met/Met: Low activity). The frequencies of the Val/Val, Val/Met and Met/Met genotypes are 21, 47 and 32%, respectively. The lower activity allele results in higher synaptic monoamine concentrations, particularly dopamine levels, ultimately increasing the dopaminergic stimulation of postsynaptic neurons. Dopamine is known to participate in the brain reward system by facilitating the release of enkephalin.[119] However, although a reduction in pain sensitivity may be expected in these patients, it has been demonstrated that Met/Met subjects have a lower tolerance, exhibit more pronounced responses to experimentally induced pain[119] and have an increased sensitivity to pain, specifically non-neuropathic chronic pain.[120,121] Studies performed in fibromyalgia patients demonstrated that Met/Met individuals are also significantly more sensitive to thermal and pressure pain stimuli.[122,123]

However, it has been shown that cancer patients carrying the Met/Met mutation require significantly lower daily morphine than heterozygous and noncarriers[124,125] and that the Met/Met genotype is associated with higher regional density of μ-opioid receptors.[119] Another study demonstrated differences in the morphine side effects, such as drowsiness, confusion and hallucinations, associated with certain *COMT* variants, which influenced how well the patients tolerated morphine.[112] Experimental evidence points to a link with CNS endogenous opioid dysfunction. The enhanced monoaminergic activity may upregulate opioid receptors by decreasing the level of endorphin, and the abnormal endogenous control of nociceptive pain pathways could lead to an overexcitability of the dorsal neurons in the spinal cord, a decrease in nociceptive thresholds and an increase in spontaneous pain. Although the results remain conflicting, it has been shown that a polymorphism in the *COMT* gene, namely, Val158Met, influences pain sensitivity in human experimental pain and the efficacy of morphine in cancer pain treatment. Due to the role of COMT as modulators of the intrasynaptic catecholamine concentrations, a potential role of the *COMT* gene in the antidepressant response is supported. The influence of the Met/Met variant on the therapeutic efficacy of antidepressants has been studied only in patients with depression but not in pain. The results are contradictory, some of the studies showing a weaker and slower response in Met/Met patients,[43,126] some the contrary.[127,128] However, all these studies indicate a possible role of the *COMT* gene in the response to antidepressants.

Regarding other candidate genes, several studies have demonstrated the existence of numbers of polymorphisms of the *MAO*, serotonin transporter and receptors and noradrenaline transporter genes. The clinical consequence of these mutations on antidepressant treatment when used for depression is not clear. The main polymorphisms and their impact on enzyme function are listed in . Given that one of the putative mechanisms of action of antidepressants in the treatment of pain involves a balanced increase in noradrenaline and serotonin transmission, we can assume that a decrease in the expression of the *MAO* and/or noradrenaline transporter (*SLC6A2*) leads to a higher efficacy but also a higher risk of the monoaminergic side effects. Because the antidepressant analgesic effect relies not only on monoaminergic transmission and because there are multiple determinants of pain, the clinical relevance of this assumption should be formally further assessed. The evidence for the efficacy of SSRIs in the treatment of pain is anecdotal, suggesting that the dual reuptake inhibition of both monoamines is necessary for the analgesic activity of antidepressants. The influence of gene mutations of the serotonin transporter and receptors, which are well described in the setting of depressive disorders, should therefore have less impact in the context of pain management.

Table 4. Polymorphisms of enzymes involved in antidepressant pharmacodynamics.

Protein	Function	Main SNP	Enzymatic activity	Clinical impact	Ref.
Monoamine	Serotonin and	*VNTR* polymorphism of the	L: associated with increased expression and	Conflicting results, no	[129–132]

oxidase (MAO)	noradrenaline metabolism	promoter region (S and L)	activity of MAO up to 10×	proven associations	
Serotonin transporter (SERT)	Regulation of the concentration of serotonin in the synaptic cleft by the presynaptic reuptake level	Promoter *(5-HTTLPR)* (S and L)	S: associated with increased transcription and serotonin reuptake (up to 2- to 2.5-times)	L: better response to fluvoxamine, fluoxetine, paroxetine, mirtazapine, sertraline, escitalopram and citalopram treatments	[51,57,133]
				Homozygotes SS: more side effects with fluoxetine, citalopram and escitalopram treatments	
		VNTR of intron 2 (*STIN2*)		Conflicting results, no proven associations	[134–137]
Noradrenaline transporter SLC6A2	Regulation of the concentration of noradrenaline in the synaptic cleft by presynaptic reuptake	Several polymorphisms		Conflicting results, no proven associations	[132,138–140]
Serotonin receptor 5HT1A	Postsynaptic + presynaptic localization modulation of serotonin release	G>C 1019 promoter C1019G (*rs6295*)		G>C: Poorer response to fluvoxamine, fluoxetine and citalopram treatment, no proven associations	[42,132,139–142]
Serotonin receptor 5HT2A	Postsynaptic localization modulation of serotonin release	T>C 102 (*rs6313*) A>G 1438 (*rs6311*)		No proven associations No proven associations	[78,132,143–144]

L: Long form; S: Short form.

Voltage-gated sodium channels are multimeric complexes encoded by multiples genes. They are key regulators of the membrane potential in excitable tissues, such as sensory neurons. Nine isoforms of voltage-gated sodium channels (Nav 1.1–Nav 1.9) have been identified. The cellular and tissue expressions of individual isoforms are quite specific. Subunit Nav 1.7 is preferentially expressed in nociceptive neurons and plays a major role in nociception and neuropathic pain. It is encoded by the *SCN9A* gene. A large number of polymorphisms have already been discovered.[145,146] Studies in mice have emphasized their role in neuropathic, inflammatory, mechanical and thermal acute pain thresholds.[147,148] In humans, mutations in the *SNC9A* gene cause overexpression and hyperexcitability of Nav 1.7. It has been implicated in several painful states, such as idiopathic erythermalgia and paroxysmal extreme pain disorder.[149,150] Conversely, a null mutation of Nav 1.7 induces the loss of channel function and a lack of propagation of nociceptive signals. It is linked to a rare condition, namely, the congenital insensitivity to pain syndrome, in which normal individuals have impaired perception of pain.[151,152] As stated above, part of the analgesic effect of tricyclic antidepressants is due to the blockade of this sodium channel; many tricyclics, including fluoxetine and paroxetine, inhibit Nav 1.7 with different potencies. These all interact, predominantly in a state- and use-dependent manner, with the inactivated state of the channel. It has been shown that the potencies of amitriptyline, nortriptyline, imipramine, desipramine and maprotiline to block the inactivated state are in the range of the therapeutic plasma concentrations used for the treatment of neuropathic pain, whereas SSRI are blockers only in supratherapeutic dosages.[11] The link between the overexpression of Nav 1.7 and the variability of the response to treatment with amitriptyline has not been clearly demonstrated, but a relationship between the level of expression of the *SNC9A* gene and the effect of amitriptyline may be postulated.

Future Perspective

The effect of antidepressants or analgesics exhibits highly variable interindividual efficacy or tolerability. Because half of the patients treated for chronic pain are not relieved and a substantial proportion exhibit side effects that lead to treatment discontinuation, the exploration of the reason of this variability should be more systematically conducted in clinical practice. Antidepressants interact with several molecular targets, and as such, their ability to relieve pain may not be attributable to a single molecular mechanism. The identification of genetic biomarkers that can predict the antidepressant treatment response and genetically guide the prescription of drugs could definitively improve clinical practice.

Many antidepressants have dose- and concentration-response curves developed for their application to treat depression. Therapeutic drug monitoring is the first step for monitoring a treatment. In patient requiring long-term treatment, genotypic or phenotypic tests have added value, particularly in exploring the origin of a low concentration and to rule out the adherence issue.

During the past years, the ability to test for polymorphisms, particularly in cytochromes, has become more accessible, inexpensive and usable in clinical practice, and these are guidelines that link the results to therapeutic recommendations. Tests are also easily available for P-gp and COMT, although these are more rarely performed. All of the tests should be routinely discussed with a clinical pharmacologist in cases of exaggerated response as well as in cases of nonresponse. If a genetic variant is identified, the predicted clinical consequences should be assessed, and clinical adjustments, such as modifying the dose, modifying the dosing schedule or changing the medication, should be considered. Even if the current dosage adjustment guidelines for antidepressants, which were developed from data collected in depressed patients, in other words, who receive higher drug doses than those prescribed for pain treatment, are thus not directly applicable to patients with chronic pain, they can help guide the treatment adaptation. The pharmacogenetics of antidepressants in the context of pain management remains a field with a high amount of missing information. There are other candidate genes, particularly the genes encoding MAO, the sodium channels and the noradrenaline transporter, whose genetic variability may also be translated to individual variations in the treatment response. However, for these other genes, further studies are needed before the pharmacogenetics can be integrated into an individualized prescription.

These approaches are the first steps toward individualized prescription medicine, particularly in an area where many objective tests are not available to help guiding the treatment. Pharmacogenetic testing may allow fewer medication-related side effects, an improved selection of medication and a reduction in the burden and cost of chronic pain.

Sidebar

Executive Summary

Use of antidepressants in chronic pain management

- The current evidence-based guidelines recommend the use of antidepressants, particularly tricyclics and serotonin-noradrenaline reuptake inhibitors, for the treatment of various types of chronic pain.
- The analgesic properties of antidepressants have been suggested to result from the inhibition of amine, noradrenaline and serotonin reuptake in the CNS, which leads to increased activity of the antinociceptive descending pathways, but effects at the peripheral site, that are independent from the effect on the mood, have also been described.

Important interindividual variability in antidepressant drug response

- The management of pain with antidepressants has been found to exhibit variable efficacy and tolerability, that may be attributed to genetic factors.
- Numerous studies and reviews have described the influence of pharmacogenetics on the efficacy and tolerance of antidepressants in the treatment of depression. We now discuss the potential role of these polymorphisms in the specific context of pain management.

Polymorphisms involved in drug pharmacokinetics

- Antidepressant drugs are mainly metabolized through the cytochrome P450 superfamily.
- *CYP2D6* is highly polymorphic, with up to 80 allelic variants described. Genetic variations of *CYP2D6* have been demonstrated to influence the plasma level concentrations of antidepressants. More frequent adverse events are found in PM and data suggest that UM patients present reduced efficacy.
- Genetic variations have also been described for CYP2C19 and the different phenotypes are also associated with variable plasma concentrations and occurrence of side effects.
- Because of the well-established data on CYP2D6 and CYP2C19 showing the link between the genetic variations, the drug–plasma concentrations, the response of antidepressants and the occurrence of side effects, dosage recommendations based on the CYP2D6 and CYP2C19 phenotype/genotype have been done for 'antidepressive' dosages and can be extrapolated for 'analgesic' dosages.

P-gp

- A number of antidepressants are substrates of P-gp. To date, no link between mutations of *ABCref-1* gene and antidepressant efficacy or tolerability has been demonstrated. It is reasonable to believe that an increased CNS exposure to antidepressants, due to a low P-gp activity, would increase the risk of adverse effects.

Polymorphisms involved in antidepressant targets

- COMT is one of the principal key modulator of dopaminergic and adrenergic/noradrenergic neurotransmission, suggesting a possible role of the *COMT* gene in the response to antidepressants. The association between *COMT* gene variations and pain sensitivity has been reported in various studies but the influence on the therapeutic efficacy of antidepressants remains contradictory.

- Part of the analgesic effect of tricyclic antidepressants is due to the blockade of the voltage-gated sodium channels key regulators of the membrane potential in excitable tissues, such as sensory neurons. A link between the overexpression of the subtype Nav 1.7 and the variability of the response to treatment with amitriptyline is postulated.

Future perspective

- Because half of the patients treated for chronic pain are not relieved and a substantial proportion exhibits side effects that lead to treatment discontinuation, the exploration of the reason of this variability should be more systematically conducted.

- The identification of genetic biomarkers that can predict the antidepressant treatment response and genetically guide the prescription of drugs could definitively improve clinical practice.

- Genotypic and phenotypic tests have become more accessible and are the first steps toward individualized prescription medicine, particularly in an area where many objective tests are not available to help guide the treatment.

- However antidepressants interact with several molecular targets and the pharmacogenetics of antidepressants in the context of pain management remains a field with a high amount of missing information.

- Further studies are needed before the pharmacogenetics can be integrated into an individualized prescription.

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