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Perceived Failure of Acetaminophen and NSAIDs in Migraine: A Narrative Review of Medication Overuse, Chronification, and Pharmacogenomic Evidence

Ritisha Mukerjee
ritishamukerjee09@gmail.com

ABSTRACT

A perceived loss of analgesic effectiveness does not necessarily indicate true pharmacological tolerance. It may instead reflect medication overuse, migraine chronification and altered pain processing or psychological factors, which have different mechanisms and clinical implications. This review aims to distinguish perceived analgesic tolerance from true tolerance, MOH, and migraine chronification, while examining variability in analgesic response. It is focused on acetaminophen or paracetamol and NSAIDs, particularly UGT, SULT and CYP pathways involved in metabolism. PubMed- indexed literature was analysed which included clinical, neuroimaging, pharmacological, pharmacogenomic and guideline evidence. Studies addressing MOH, migraine chronification, pain processing, analgesic metabolism and genetic variation were taken into consideration. The evidence indicated that perceived analgesic failure cannot directly be attributed to tolerance. Medication overuse and migraine chronification are linked to altered pain processing and brain connectivity, while variation in UGT, SULT and CYP can influence acetaminophen metabolism and CYP2C9 variation affects selected NSAIDs. Perceived analgesic failure should not automatically be considered as pharmacological tolerance. Pharmacogenomics may explain some variation in analgesic metabolism, but evidence remains insufficient for routine personalised therapy. Unsupervised dose escalation should therefore be avoided, particularly when headaches become increasingly frequent.

KEYWORDS: *Analgesic tolerance, Acetaminophen, Non-steroidal anti-inflammatory drugs, Migraine chronification, Medication-overuse headache, Pharmacogenomics, Drug metabolism.*

INTRODUCTION

Headache disorders, particularly migraine are among the leading causes of disabilities worldwide. Migraine severely reduces productivity and the quality of life. As a result, many people rely on over the counter (OTC) painkillers such as acetaminophen and NSAIDS for symptom relief. Consequently, the frequent and unsupervised use of analgesics has become increasingly common. Many patients believe that the painkillers have “stopped working” or that they have developed a "tolerance". This perceived loss of effectiveness often leads to over dosage or more frequent medication without medical guidance. Migraine affects approximately 15% of the global population, while medication overuse headache affects 1-2% of

the global population making it one of the most common chronic headache disorders. [1] [2]It has been observed that self-medication with OTC analgesics is increasing worldwide due to their easy availability.From a national standpoint India has one of the largest populations affected by headache disorders. Migraine prevalence in India is estimated at 14-25%, depending on region and study. [3] OTC analgesics are easily accessible and self-medication is widespread because of affordability, convenience and limited awareness. Consequently, medication overuse- headache remains under diagnosed and often mistaken for worsening migraine.

Acetaminophen (paracetamol) is an analgesic and antipyretic that relieves pain and reduces fever, whereas NSAIDs (e.g. ibuprofen, naproxen, aspirin, diclofenac) reduces pain, inflammation, and fever by inhibiting cyclooxygenase (COX) enzymes and prostaglandin synthesis. Acetaminophen and NSAIDs are commonly used to treat headaches, migraine attacks, fever, musculoskeletal pain, osteoarthritis, dental pain, dysmenorrhea, postoperative pain, and minor injuries. Their effectiveness and favourable safety profile as recommended does make them first-line treatments for many acute painful conditions. [4] These medicines are available over the counter because they have established efficacy and acceptable safety when used according to recommended doses. Their availability enables individuals to manage common, short term conditions such as pain and fever without requiring a prescription. Over the counter availability improves access to treatment , encourages self-care for minor illnesses, lowers health care costs, and decreases burden on health care services by allowing patients to manage uncomplicated conditions independently. Although self-medication offers convenience, prolonged or inappropriate use may delay diagnosis of underlying diseases, increase the risk of adverse drug reactions, drug interactions, incorrect dosing, and medication overuse. Long term use of analgesics can contribute to medication overuse -headache in susceptible individuals. [5] Many OTC cold, flu and pain medicines contain Acetaminophen and NSAIDs, patients often unknowingly take multiple products with the same active ingredient, increasing the risk of accidental overdose particularly with Acetaminophen. [6] People with recurrent migraine often rely on acute pain medicines for symptom relief. Frequent use can create a cycle of medication overuse, increasing the risk of medication overuse headache (MOH) and migraine chronification. [7]

When patients say that a painkiller has stopped working, they usually mean that their usual analgesic no longer provides adequate headache relief leading them to take medication more frequently. However this perceived loss of effectiveness may reflect medication-overuse headache and migraine chronification rather than the true drug tolerance.[8] [9] As migraine attacks become more frequent and pain relief becomes less consistent, patients might assume that their body has become more accustomed to the medication. However recurring use of acute headache medicines can itself contribute to MOH, creating a cycle of increasing headache frequency and medication use.[10] True pharmacological response is a biological process in which repeated exposure to drugs causes reduced physiological response, meaning progressively higher doses are required to achieve the same therapeutic effect. However, clinical evidence suggests that a perceived loss of analgesic efficacy is often caused by factors other than true tolerance.[11] True pharmacological tolerance results from biological adaptation to a drug whereas perceived reduction in effectiveness may occur because of medication overuse headache, migraine progression or other

clinical factors without the drug itself becoming less active. Medication-overuse headache, migraine chronification and increased amount of headaches can reduce the apparent effectiveness of acute analgesics, even when true pharmacological tolerance has not developed. As headache frequency increases patients often use acute medications more frequently which increases the risk of medication-overuse headache and further head chronification making acute treatments appear less effective over time.[7]

Delayed administration or use of an inadequate dose may reduce the effectiveness of acute migraine treatment, as analgesics are generally more effective when taken early in the migraine attack and at an appropriate therapeutic dose. This may lead the individual to believe that the medication has "stopped working" when the issue is suboptimal treatment timing or dosing. [12] During a migraine attack, delayed gastric emptying can slow the absorption of oral analgesics such as NSAIDS reducing or delaying pain relief. In addition, individual differences in drug metabolism can alter drug concentrations and contribute to variability in analgesic response between patients. [13]

Reduced analgesic effectiveness in patients with chronic migraine is often caused by medication overuse headache (MOH) and migraine chronification rather than true pharmacological tolerance. Neuroimaging studies demonstrate structural and functional brain changes associated with medication overuse while pain coping studies indicate that psychological factors further may contribute to perceived treatment failure. Migraine chronification is the progression of episodic migraine into a more persistent form characterised by increasing headache frequency and reduced symptom free periods. It is associated with alterations in brain structure, functional connectivity and pain processing. Frequent use of acute headache medication, together with altered pain processing and functional brain network disruption, may promote transition from episodic migraine to chronic migraine. Medication overuse has been associated with structural and functional brain abnormalities linked to chronification. [14] Patients with chronic migraine experience headaches more frequently with fewer headache free intervals. Those with multimorbidity have greater disability, poorer quality of life and an increased likelihood of relapse, limiting opportunities for recovery. [15] Medication overuse headache is a secondary headache disorder that occurs in patients with a preexisting primary headache disorder due to the regular overuse of acute or symptomatic headache medication for more than three months. It typically presents as headaches occurring on 15 or more days per month with migraine features on at least 8 days per month, and often improves after the overused medication is withdrawn. [16] Frequent analgesic use is associated with reduced grey matter volume, impaired white matter integrity, abnormal salience network activity and altered functional connectivity, suggesting that medication overuse contributes to migraine chronification and worsening headache.[17] Chronic migraine is a primary headache disorder characterized by frequent migraine attacks, whereas Medication overuse headache (MOH) is a secondary headache disorder caused by the regular overuse of acute headache medications. However, medication overuse can contribute to migraine chronification. [18] Patients with chronic migraine often use acute headache medications more frequently, increasing the risk of medication overuse. As a result, a person can simultaneously meet diagnostic criteria for both chronic migraine and MOH. Migraine chronification is the progression from episodic to chronic migraine (headache on ≥15 days/month for >3 months [18]), whereas MOH is a secondary

headache disorder defined by regular overuse of acute medication [16]. The two often coexist, and both are associated with altered pain processing and functional brain-network changes [9,10,14,17]. These concepts are defined in detail in the sections that follow.

METHODS

A literature search was conducted using Pubmed databases in August 2026 to identify studies relevant to interindividual variability in acetaminophen analgesic response, pharmacological tolerance,medication-overuse headache (MOH), migraine chronification and the pharmacogenomics of analgesic metabolism. The search was limited to literature published within the preceding 10 years. Search terms included a combination of *analgesic response, acetaminophen, paracetamol, medication-overuse headache , pharmacological tolerance, chronic migraine, pharmacogenomics, UGT, SULT, CYP enzymes, glutathione, and hepatotoxicity*.Studies were considered for inclusion if they addressed acetaminophen metabolism , genetic variation in drug-metabolising pathways , analgesic effectiveness , medication overuse , migraine chronification, or the clinical utility of pharmacogenomic testing. Relevant original research articles and review articles were considered. Studies were excluded if they fell outside the publication period or did not address the reviews's research focus.The selected literature was analysed thematically , with findings organised into pharmacokinetic variation, pharmacological tolerance, medication- overuse headache, migraine chronification and pharmacogenomic clinical utility. Particular attention was paid to distinguishing evidence of altered drug metabolism , drug exposure, or toxicity risk from evidence of differences in actual analgesic effectiveness.

PHARMACOLOGICAL TOLERANCE AND PERCEIVED ANALGESIC FAILURE

Pharmacological tolerance is an acquired reduction in response after repeated drug exposure. Its concerns reduced sensitivity to a drug at comparable exposure; pharmacokinetic tolerance concerns exposure-related adaptation, such as increased clearance during repeated use. In contrast, a pre-existing genetic difference in metabolism is interindividual pharmacokinetic variability and does not, by itself, demonstrate acquired tolerance. [19] Demonstrating tolerance requires evidence of a declining response over time while accounting for dose, adherence, drug exposure and changes in the underlying disorder. The opioid and general pharmacology references cited here explain the concept but do not establish tolerance to acetaminophen or NSAIDs in migraine. The evidence assembled in this review does not establish clinically meaningful acquired tolerance to these non-opioid analgesics as the explanation for perceived treatment failure. This limitation should not be interpreted as proof that tolerance can never occur. [20] [21] Perceived painkiller tolerance is the patient's experience that an analgesic no longer provides sufficient relief. It is suggested that this apparent loss of effectiveness can occur alongside medication overuse, migraine chronification, altered pain processing, abnormal brain connectivity and psychological factors such as catastrophizing, rather than necessarily representing true drug tolerance. Analgesic treatment may appear to fail when migraine becomes more frequent, pain processing becomes altered, or medication is used repeatedly. Patients may respond by increasing acute medication use, which can contribute to MOH and further migraine chronification. "Perceived analgesic failure" is used here to

describe a patient-reported reduction in relief without presuming its cause. The following sections consider medication-overuse headache, migraine chronification and pharmacokinetic variability separately. [7]. Neuroimaging studies have also identified structural and functional brain changes associated with medication overuse [10]

MEDICATION-OVERUSE HEADACHE

Medication overuse headache is a secondary headache disorder occurring in people with a pre-existing headache disorder who regularly overuse acute headache medication. Under ICHD-3, diagnosis requires headache on the ≥15 days/month, regular medication overuse for >3 months, and a pre-existing headache disorder. The medication- specific overuse threshold is ≥15 days/month for simple analgesics such as acetaminophen/NSAIDs and ≥10 days/month for triptans, opioids or combination analgesics.[16] MOH develops in patients who already have a primary headache disorder, such as migraine. Because chronic migraine involves frequent headaches while MOH involves excessive use of acute medication both conditions can occur in the same patient [7] [9]. Frequent use of acute medication can become associated with increased headache frequency and altered pain processing meaning patients may experience less satisfaction and consequently use medication more often. Certain studies found altered salience processing, brain connectivity and structural abnormalities in CM-MOH providing possible explanations for this perceived reduction in treatment effectiveness. [9] [17] [14] Several biological and behavioral mechanisms have been proposed in MOH , including altered pattern processing, abnormal salience network and triple network connectivity, structural brain changes and psychological factors such as pain catastrophizing and reduced pain acceptance. Increased habenula- salience network connectivity has also been associated with longer medication overuse, suggesting the involvement of addiction related neural pathways. However, the interaction between these neurological, psychological and behavioral mechanisms remains complex, and the pathophysiology of MOH is not yet fully understood.[9] [14] [10]
MOH is a headache disorder associated with excessive use of acute medication, whereas pharmacological tolerance reduces drug response after repeated exposure. Physical dependence involves physiological adaptation producing withdrawal symptoms when a drug is stopped, while addiction involves compulsive drug seeking and continued use despite harm. The study investigating habenula-salience connectivity in chronic migraine with medication-overuse headache, found neural changes resembling addiction related processes in CM- MOH, but this does not mean that MOH is equivalent to addiction.[14]

MIGRAINE CHRONIFICATION

Episodic migraine can develop into chronic migraine as headache frequency increases and pain processing mechanisms become altered. Frequent acute medication use altered brain structure and activity abnormal functional connectivity and psychological factors such as pain catastrophizing has been associated with chronic migraine and medication overuse.[8] [10]
Altered central pain processing can increase sensitivity to normally non-painful or mildly painful stimuli and contribute to greater pain severity and allodynia. In CM-MOH abnormal activity in the salience matrix and altered brain connectivity have been reported which may make acute medication appear less

effective and could therefore be interpreted by patients as developing analgesic tolerance.[10] [19] Migraine chronification and MOH can reinforce one another. Increasing headache frequency may lead to more frequent acute medication use while medication overuse is associated with further headache chronification and changes in pain processing networks. However these conditions should not automatically be interpreted as pharmacological tolerance because the observed changes involve headache frequency, medication use and altered neural processing, rather than demonstrated loss of drug effect at equivalent drug exposure.[9] [10] [14]

ACETAMINOPHEN RESPONSE AND METABOLISM

This section distinguishes four levels of evidence: enzyme activity in vitro, drug exposure or clearance in humans, toxicity risk, and analgesic effectiveness. Evidence at the first three levels does not establish the fourth (Table 1). Individual analgesic response can vary because of differences in pain biology, drug pharmacokinetics, genetics, and other patient factors. Thus, poor response does not by itself demonstrate rapid metabolism or pharmacological tolerance; genetic variation can affect drug disposition while differences in pain processing in pain processing can independently affect perceived analgesia. [22] [23] Most acetaminophen is metabolised by glucuronidation and sulfation before elimination. Human liver studies identify UGT1A1, UGT1A6 and UGT1A9 as important acetaminophen-glucuronidating enzymes, with UGT1A9 contribution substantially over clinically relevant concentrations. Genetic variation in UGT1A6 and UGT1A9 has been associated with differences in glucuronidation activity or clearance. [24] [25] Sulfation is a major phase two pathway for acetaminophen elimination. Studies have identified SULT1A1, SULT1A3/4 and SULT1E1 as enzymes capable of catalyzing acetaminophen sulfation. SULT1A1 genetic variants produce differences in enzyme activity toward acetaminophen in vitro providing evidence that SULT variation can influence its metabolism, although clinical consequences remain uncertain. [26] [27] A small production of acetaminophen undergoes oxidation primarily through CYP2E1 producing reactive metabolite NAPQI. NAPQI is normally detoxified by conjugation with glutathione (GSH). During overdose normal conjugation pathways become overwhelmed and GSH can become depleted allowing NAPQI to damage liver proteins and contribute to hepatotoxicity. [28] [29] Investigated variants include UGT1A6 variants such as S7A, T181A and R184S, UGT1A9 rs3832043, and UGT1A-region variants including rs10929303, rs1042640 and rs8330. SULT research includes **SULT1A1*1, *2 and 3*, while CYP research has examined CYP2E1 variants. Glutathione related studies have investigated GSTT1, GSTM1 and GSTP1 variants. Evidence demonstrates effect on enzyme activity, acetaminophen metabolism , or toxicity risk, but findings are not yet sufficiently consistent to establish reliable individual treatment predictions. [30] Currently no strong evidence supports routine pharmacogenomic testing to guide acetaminophen dosing or analgesic response. Although genetic associations with acetaminophen metabolism and toxicity have been reported, pharmacogenomic evidence for analgesics remain inconsistent and clinical utility has not yet sufficiently been established. Reviews emphasize that lack of robust evidence for improved clinical outcomes limits implementation of pharmacogenomic testing. [22] [31]

Level of evidence	Acetaminophen	NSAIDs
Enzyme activity (in vitro)	UGT1A1/1A6/1A9 glucuronidation [24]; SULT1A1 variants alter sulfation [26,27]	n/a
Drug exposure or clearance in humans	UGT1A9 variation and glucuronidation in neonates [25]	CYP2C9 genotype and exposure to selected NSAIDs [32]
Toxicity risk	NAPQI/glutathione pathway [28,29]; candidate SNP associations with hepatotoxicity, inconsistent [30]	Higher exposure in reduced-function CYP2C9 carriers [32]
Analgesic response (pain relief)	No consistent genotype–response association in the cited reviews [22,23,31]	Not established in the cited literature
Clinical utility	Routine testing not supported [22,30,31]	CPIC dosing guidance for selected drugs [32]

Table 1. Levels of Evidence for Pharmacogenomic Influences on Acetaminophen and NSAID Metabolism, Toxicity Risk, and Analgesic Response.

COMPARATIVE SUMMARY

Pharmacodynamic tolerance is a reduced response to a drug despite continued exposure. Pharmacokinetic changes involve altered drug exposure because of changes in absorption or metabolism.Perceived analgesic tolerance is the patient's experience of reduced pain relief, which can result from worsening migraine or altered pain processing. MOH is a headache disorder associated with regular overuse of headache medication.[11] [16] Pharmacodynamic tolerance generally develops following repeated drug exposure following repeated drug exposure. Pharmacokinetic changes require altered absorption or metabolism and therefore do not necessarily require repeated drug exposure. Perceived tolerance does not require true pharmacological tolerance while MOH specifically requires regular medication overuse for more than 3 months.[11] [16] Pharmacodynamic tolerance, pharmacokinetic changes and perceived tolerance are not defined by medication-use frequency. MOH is different because its diagnosis incorporates regular medication overuse, with thresholds depending on the medication class.[16] Pharmacodynamic tolerance and pharmacokinetic changes are not defined by headache frequency. Perceived tolerance is also not a diagnostic headache condition. MOH however requires headache occurring on ≥15 days/month for >3 months, alongside medication overuse. [16] Pharmacological tolerance and pharmacokinetic changes can occur in patients with migraine but are not defined by migraine. Perceived analgesic tolerance can occur during chronic migraine. MOH can coexist with chronic migraine, as demonstrated by the CM-MOH groups examined in neuroimaging literature.[9] Genetic testing cannot diagnose pharmacological tolerance, perceived tolerance or MOH. Genetic variation can influence acetaminophen metabolism through pathways such as UGT, SULT and CYP, but current evidence is insufficient for genetic testing to reliably predict analgesic response or diagnose these conditions. Increasing analgesic use may provide temporary system release but can increase the risk of medication overuse and MOH is susceptible to patients. Greater acute medication frequency has also been associated with structural and functional brain changes in CM-MOH.[9] [10] Pharmacodynamic tolerance

requires evidence of reduced drug response despite comparable drug exposure Pharmacokinetic changes require pharmacokinetic evidence showing altered drug exposure. Perceived tolerance requires clinical assessment of patients' treatment response and alternative explanations. MOH requires clinical headache and medication use history meeting the ICHD-3 rather than genetic and or laboratory testing.

	True (pharmacodynamic) tolerance	**Pharmacokinetic change**	**Perceived tolerance**	**MOH**
Definition	Reduced drug response despite continued exposure	Altered exposure from changed absorption or metabolism	Patient's experience of inadequate relief	Secondary headache disorder from regular overuse of acute medication (ICHD-3 8.2)
Needs repeated exposure	Generally yes	No	No	Yes (>3 months)
Defined by medication-use frequency	No	No	No	Yes (thresholds by drug class)
Defined by headache frequency	No	No	No	Yes (≥15 days/month)
Established by	Reduced response at comparable exposure	Pharmacokinetic evidence	Clinical assessment of response and alternative explanations	Headache and medication-use history meeting ICHD-3
Can coexist with chronic migraine	Can occur, not defined by it	Can occur, not defined by it	Can occur during chronic migraine	Yes (CM-MOH) [9]

Table 2. Comparison of True Pharmacodynamic Tolerance, Pharmacokinetic Change, Perceived Analgesic Tolerance, and Medication-Overuse Headache.

CLINICAL AND PUBLIC-HEALTH IMPLICATIONS

When patients perceive that analgesics is becoming less effective, they may increase the dose or frequency of medication rather than recognising the worsening migraine or MOH. This can reinforce medication overuse and contribute to further headache chronification.[7] [9] Pharmacists and clinicians can identify frequent analgesic use , headache frequency, and potential medication duplication, educate

patients about appropriate acute medication use and recognize possible MOH early. This is important because patients with CM-MOH can experience greater disability and poorer quality of life. [15][7] Pharmacogenomics has a current clinical role for selected NSAIDs metabolised by CYP2C9, particularly celecoxib, where CYP2C9 genotype can influence drug exposure and dosing recommendations. However, pharmacogenic guidance is not established for all NSAIDs so its clinical use remains drug specific.[32] Preliminary genetic associations may be mistaken for clinically validated predictors. This can lead to unnecessary testing, inappropriate treatment charges, false reassurance or inaccurate assumptions about analgesic response or toxicity, because many reported associations have not been sufficiently validated for clinical decision making. [22] [30]

ICHD-3 defines MOH as headache on ≥15 days/month in a patient with a pre-existing headache disorder, with regular overuse for >3 months of one or more acute medications. The overuse threshold is ≥15 days/month for simple analgesics, including acetaminophen and NSAIDs, and ≥10 days/month for ergots, triptans, opioids, combination analgesics or multiple drug classes [16]. The European Academy of Neurology guideline identifies education and counselling as the first step in managing MOH, with withdrawal of the overused medication and preventive treatment for patients in whom education is insufficient [33]. Consistent with these documents, patients who find that an analgesic is no longer adequate should not escalate the dose or frequency beyond the product label or the prescriber's instructions. They should record headache and medication days and seek clinical assessment, particularly when acute-medication use approaches these thresholds.

RESEARCH GAPS AND FUTURE DIRECTIONS

Perceived analgesic tolerance is inconsistently defined because a patient's report that a painkiller has become less effective may reflect worsening migraine, altered pain processing, inadequate treatment or medication overuse, rather than true pharmacological tolerance. Future studies should separately measure analgesic response, headache frequency, medication use frequency, dose, adherence and drug exposure to distinguish these mechanisms. [7] [8] [9] Longitudinal studies should record headache days or months, migraine days or months, headache severity, acute medication type / dose / frequency, timing of administration, adherence, preventive treatment, medication overuse status, analgesic blood concentrations and relevant UGT/CYP genetic variants. These measures would allow changes in headache burden to be separated from changes in drug exposure and medication use.[7] [9] [22] Clinical actionability would require replication of genotype- drug response associations in large, diverse patient populations, demonstration that genotype guided treatment improves analgesic efficacy or safety and evidence that genetic testing produces better clinical outcomes than standard treatment. Current evidence on acetaminophen pharmacogenomics is not sufficiently consistent to support routine personalised dosing. [22] [30] Although CPIC provides CYP2C9 guidance for selected NSAIDs evidence remains limited for many other NSAIDs and for clinical outcomes beyond pharmacokinetic differences. Larger prospective studies are needed to determine whether genotype guided NSAID selection actually improves analgesia and reduces adverse effects.[32] The relationship between medication overuse and migraine chronification appears to be bidirectional: increasing migraine frequency can lead to greater use of acute medication , while medication overuse may further encourage headache chronification.The 7T MRI

findings linking acute medication frequency and with brain abnormalities in CM-MOH support an association between medication overuse and headache chronification, but they do not by themselves establish which occurs first.[9] [10] Public health interventions can focus on patient education about medication-use limits clearer OTC labelling, pharmacist counselling , identification of duplicate active ingredients, an early recognition of frequent headache and medication overuse. Improving awareness may help prevent inappropriate dose escalation and reduce progression toward MOH. [7] [15]

CONCLUSION

A perceived reduction in analgesic effectiveness does not by itself demonstrate pharmacological tolerance. In patients with recurrent migraine reduced relief may instead reflect increasing headache frequency, medication overuse, altered pain processing, or other clinical factors. Reduced analgesic effectiveness may reflect medication overuse headache, migraine chronification, altered pain processing, and psychological factors such as pain catastrophizing. Neuroimaging studies have identified altered brain structure as well as connectivity in CM-MOH, while pain coping researchers have identified greater catastrophizing and reduced pain acceptance. Genetic variation in UGT, SULT and CYP pathways can influence acetaminophen metabolism while CYP2C9 variation can affect the pharmacokinetics of selected NSAIDs. However genotype response associations for acetaminophen remain insufficiently validated for routine personalised dosing, and NSAID pharmacogenomic guidance remains limited to selected drugs such as celecoxib. Patients should not assume that reduced pain relief means they have developed drug tolerance or simply increase the dose or frequency themselves. Increasing acute medication can contribute to medication overuse and migraine chronification; frequent headaches and analgesic use should instead prompt assessment by a healthcare professional.

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Mentor: Nirupma Singh
Email:nirupmajadaun21@gmail.com
Affiliation:Department of Biological Sciences and Engineering, Netaji Subhas University of Technology (Formerly NSIT), Dwarka, Delhi, India.

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