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REVIEW ARTICLE

A Review on Safety and Public Health Implications of Use of Over-the-Counter Pain Medication

Vivian Ukamaka Nwokedi*[1], Cletus Okechukwu Ogadah[2], Bankole Israel Adeyemi[3], Iregbu John Kelenna[4], Felix Jessica Chioma[4], Emeka Onyebuchi Enechukwu[5], Oreoluwa Ayomide Adeyemo[6], Vincent Barrah[7], Precious Esong Sone[8]

[1] *PG Scholar, Department of Clinical Pharmacy, Faculty of Pharmacy, University of Benin, Benin City, Nigeria*
[2] *PG Scholar, Department of Epidemiology and Evidence-Based Medicine First Moscow State Medical University, Sechenov, Russia*
[3] *Director, Ondo State Primary Health Care Development Agency, Akure, Nigeria*
[4] *PG Scholar, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria*
[5] *PG Scholar, Department of Data, Inequality and Society, Edinburgh Futures Institute, The University of Edinburgh, Scotland, United Kingdom*
[6] *PG Scholar, Department of Chemistry and Biochemistry, University of Toledo, Ohio, United States*
[7] *PG Scholar, Department of Public Health, Chicago State University, Chicago, Illinois, United States*
[8] *PG Scholar, Department of Healthcare Management, East Carolina University, Greenville, North Carolina, United States*

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Abstract: Over-the-counter (OTC) pain medications are widely accessible category of pharmaceuticals used for managing mild to moderate pain. While these medications offer significant therapeutic benefits, their increasing misuse poses substantial public health challenges worldwide. Current epidemiological data indicates concerning trends in OTC medication misuse, with acetaminophen toxicity accounting for 46% of acute liver failure cases in the United States and 40-70% in Europe and Great Britain. The primary focus is on two major classes of OTC pain medications: nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Their mechanisms of action, particularly through cyclooxygenase enzyme inhibition and prostaglandin synthesis modulation, directly influence their safety profiles. Misuse patterns encompass various behaviors, including self-medication, dosage exceedance, and inappropriate combination with other medications. The health consequences range from gastrointestinal complications and hepatotoxicity to cardiovascular and renal impairment. Recent regulatory measures and healthcare initiatives have attempted to address these challenges through restricted packaging, enhanced labeling requirements, and educational interventions. Nevertheless, the persistent gap between public perception of OTC medication safety and actual risk profiles necessitates continued attention to policy development and implementation of preventive methods.

Keywords: Acetaminophen; Toxicity; Drug Safety; Medication Misuse; Non-Prescription Analgesics; Pain Management.

1. Introduction

Pain medication accessibility has transformed significantly over recent decades, with over-the-counter (OTC) medications becoming increasingly prevalent in global healthcare systems. These medications, while providing essential therapeutic benefits, present complex challenges in their utilization and safety profiles [1, 2]. The proliferation of OTC pain medications reflects broader shifts in healthcare delivery, emphasizing patient autonomy and self-care practices [3]. The distinction between prescription and non-prescription medications historically served as a regulatory framework to ensure medication safety. However, the current landscape of OTC pain medication usage suggests a more nuanced reality, where accessibility does not always align with appropriate utilization [4]. Recent epidemiological data indicates that approximately 60 million Americans consume acetaminophen weekly, often unaware of its presence in combination products [5]. The scope of OTC medication misuse encompasses various patterns, from inadvertent overdosing to deliberate misuse for non-therapeutic purposes [6]. Global statistics reveal concerning trends, with the World Health Organization reporting that over 50% of medications are prescribed, dispensed, or sold inappropriately [7]. This situation becomes more complex with OTC medications, where professional oversight is limited or absent [8]. Pharmacological advances have expanded the range of available OTC pain medications, yet this progress brings new challenges in ensuring safe usage [9]. The economic implications of OTC medication misuse manifest through increased healthcare utilization, particularly in emergency departments and specialized care units [10]. Annual statistics indicate approximately 56,000 emergency department visits and 2,600 hospitalizations in the United States alone related to acetaminophen overdose [11]

* Corresponding author: Vivian Ukamaka Nwokedi

2. Pharmacological Classification

2.1. Nonsteroidal Anti-Inflammatory Drugs

2.1.1. Chemical Classification

NSAIDs constitute a remarkably diverse group of therapeutic agents that can be categorized into several distinct chemical classes. The propionic acid derivatives, including widely used medications like ibuprofen and naproxen, form a major category characterized by their specific molecular structure. The acetic acid derivatives, prominently represented by diclofenac, comprise another significant class. Salicylates, with aspirin being the most notable example, represent one of the oldest and most established NSAID classes. These chemical classifications are not merely taxonomic distinctions - they directly influence how these drugs behave in the body, affecting their absorption rates, distribution patterns, and elimination profiles. The unique structural characteristics of each class contribute to differences in their therapeutic window, duration of action, and potential for adverse effects [12].

2.1.2. Mechanism of Action

NSAIDs exert their therapeutic effects through a well-characterized biochemical pathway centered on the inhibition of cyclooxygenase enzymes. These crucial enzymes, particularly COX-1 and COX-2, play vital roles in the biosynthesis of prostaglandins - important signaling molecules involved in inflammation, pain, and fever. COX-1 is constitutively expressed in most tissues and maintains physiological functions, while COX-2 is primarily induced during inflammatory responses. NSAIDs effectively reduce prostaglandin synthesis by inhibiting these enzymes, leading to their therapeutic effects. However, this same mechanism also explains their potential adverse effects, particularly on the gastrointestinal system and renal function [13].

2.2. Acetaminophen (Paracetamol)

2.2.1. Molecular Basis of Action

Acetaminophen exhibits a unique pharmacological profile that distinguishes it from conventional NSAIDs. Its primary mechanism involves the selective inhibition of COX-3, a variant of cyclooxygenase found predominantly in the central nervous system. This centrally-mediated action explains its effectiveness in pain management and fever reduction. Unlike traditional NSAIDs, acetaminophen demonstrates minimal peripheral anti-inflammatory activity, making it particularly suitable for situations where anti-inflammatory effects are not desired or could be detrimental. This selective central action contributes to its favorable safety profile when used at recommended doses [14]. The drug's ability to provide effective pain relief and fever reduction without significant anti-inflammatory effects has made it a unique and valuable therapeutic option, distinct from the traditional NSAID class [15].

2.2.2. Metabolic Pathways

The metabolic processing of acetaminophen involves sophisticated hepatic pathways that are critical for both its therapeutic efficacy and safety profile. Under normal therapeutic conditions, the majority of the drug (approximately 90%) undergoes phase II conjugation reactions. The primary pathways involve glucuronidation, catalyzed by UDP-glucuronosyltransferases, and sulfation, mediated by sulfotransferase enzymes. These conjugation processes render the drug more water-soluble and facilitate its excretion. A smaller but significant portion of acetaminophen undergoes oxidative metabolism through the cytochrome P450 system, particularly CYP2E1, resulting in the formation of N-acetyl-p-benzoquinone imine (NAPQI). This reactive metabolite is normally detoxified by glutathione conjugation, but can accumulate to toxic levels when glutathione stores are depleted, such as in overdose situations [16].

2.3. Combination Therapy

2.3.1. Rationale

Modern pain management protocols increasingly recognize the value of combination therapy as a sophisticated approach to pain control. This strategy leverages the distinct mechanisms of action of different analgesics to achieve optimal therapeutic outcomes. By combining medications that work through different pathways, clinicians can often achieve greater pain relief at lower doses of individual components. This approach not only enhances therapeutic efficacy but also potentially reduces the risk of dose-dependent adverse effects associated with higher doses of single agents. The synergistic interactions between different analgesics can lead to a total therapeutic effect that exceeds the sum of individual drug effects, a phenomenon particularly valuable in managing complex pain conditions. This rationale has been supported by numerous clinical studies demonstrating superior pain control with combination therapies compared to single-drug approaches [17].

2.3.2. Common Combinations

The combination of acetaminophen with various NSAIDs represents a particularly effective approach, utilizing complementary mechanisms of action - acetaminophen's central pain-modulating effects and NSAIDs' peripheral anti-inflammatory properties.

Acetaminophen-caffeine combinations have gained prominence due to caffeine's ability to enhance analgesic efficacy through multiple mechanisms, including improved drug absorption and independent pain-modulating effects. Multi-ingredient formulations have been developed for specific pain conditions, taking into account the unique pathophysiology of different pain types. These may include combinations targeting tension headaches, migraine, or musculoskeletal pain, often incorporating additional active ingredients such as muscle relaxants or decongestants. The selection of specific combinations is guided by the nature of pain, patient characteristics, and the desired therapeutic outcome [18].

Table 1. Common Over-the-Counter Analgesics

Drug Class	Examples	Maximum Daily Dose	Contraindications	Common Adverse Effects	Drug Interactions
NSAIDs	Ibuprofen	2400 mg	Active GI bleeding, severe renal impairment	GI upset, bleeding risk	Anticoagulants, antihypertensives
	Naproxen	1250 mg	Pregnancy (3rd trimester)	Increased BP, edema	SSRIs, corticosteroids
	Aspirin	4000 mg	Bleeding disorders	Tinnitus, GI bleeding	Methotrexate, warfarin
Acetaminophen	Paracetamol	4000 mg	Severe liver disease	Hepatotoxicity (overdose)	Alcohol, isoniazid
Combination Products	Acetaminophen + Caffeine	Varies by formulation	Multiple organ dysfunction	Combined risk profile	Multiple potential interactions

3. Implications of Misuse

3.1. Gastrointestinal effects

The gastrointestinal complications associated with NSAID use stem from their fundamental mechanism of action on prostaglandin synthesis. NSAIDs significantly impair the stomach's natural defense mechanisms by inhibiting prostaglandin production. This disruption manifests in multiple ways: reduced mucus secretion, decreased bicarbonate production, impaired mucosal blood flow, and increased acid secretion [19]. The spectrum of resulting gastrointestinal injury is broad and clinically significant. Mild manifestations include dyspepsia, heartburn, and nausea, while severe complications can develop into potentially life-threatening conditions such as gastric ulceration, hemorrhage, and intestinal perforation. The risk is particularly pronounced in chronic NSAID users, with epidemiological data demonstrating a five-fold increase in serious gastrointestinal complications compared to non-users. This elevated risk becomes even more significant in elderly patients, those with a history of peptic ulcer disease, or individuals taking multiple NSAIDs concurrently. The cumulative nature of this risk emphasizes the importance of careful patient monitoring and appropriate gastroprotective strategies [20].

3.2. Hepatotoxicity

The mechanism of acetaminophen-induced hepatotoxicity represents a complex cascade of biochemical events centered around the accumulation of its toxic metabolite, NAPQI. Under normal conditions, NAPQI is efficiently neutralized by cellular glutathione. However, when glutathione stores become depleted, usually due to excessive acetaminophen doses, NAPQI accumulates to toxic levels. This accumulation triggers a series of detrimental cellular events, including oxidative stress, protein modification, and mitochondrial dysfunction [21]. The risk of hepatotoxicity is significantly influenced by several factors. Chronic alcohol consumption depletes glutathione stores and induces CYP2E1, thereby increasing NAPQI formation. Malnutrition compromises glutathione synthesis, while certain medications can either enhance acetaminophen metabolism or compete for detoxification pathways. Prevention strategies emphasize public education about proper dosing, recognition of acetaminophen in combination products, and awareness of early warning signs. Healthcare providers focus on risk assessment, patient education, and prompt intervention when toxicity is suspected [22].

3.3. Cardiovascular Effects

The cardiovascular implications of both NSAIDs and acetaminophen use represent a significant clinical concern, particularly in vulnerable populations. These medications can influence cardiovascular function through multiple mechanisms. NSAIDs affect prostaglandin-mediated blood pressure regulation, potentially leading to hypertension or exacerbating existing hypertensive conditions. They also impact platelet function, which can alter blood clotting mechanisms and potentially increase the risk of both bleeding and thrombotic events. The cardiovascular effects of acetaminophen, while generally milder, still warrant consideration, particularly in long-term use. The elderly population faces particularly elevated risks due to age-related changes in drug metabolism and the higher prevalence of cardiovascular conditions. Patients with pre-existing cardiovascular diseases require especially careful monitoring and individualized approach to analgesic selection [24].

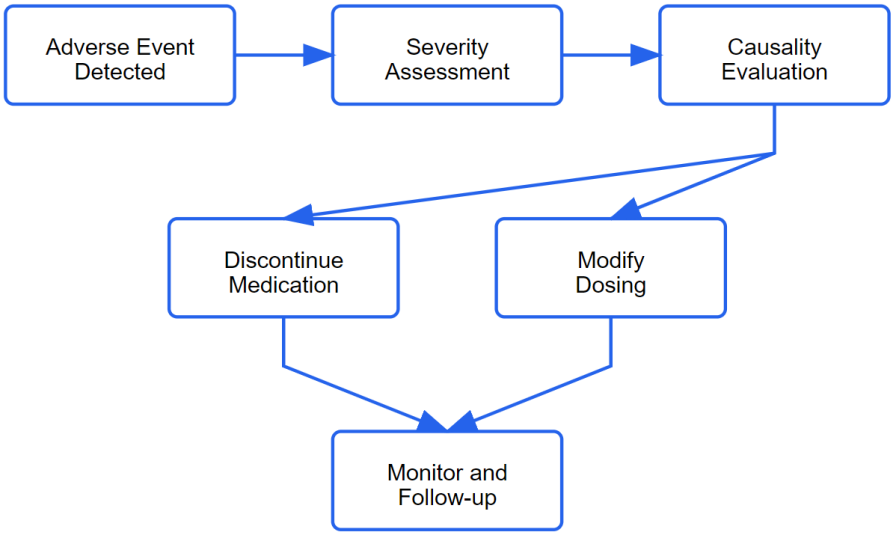

Figure 1. Management of Adverse Effects

3.4. Renal Toxicity

3.4.1. Pathophysiological Mechanisms

The nephrotoxic effects of OTC analgesics involve complex pathophysiological mechanisms that can significantly impact renal function. NSAIDs' interference with prostaglandin synthesis affects critical aspects of renal physiology, particularly the maintenance of renal blood flow and glomerular filtration rate. Under normal conditions, prostaglandins serve as essential mediators of renal vasodilation, helping maintain adequate renal perfusion, especially during periods of physiological stress [25]. The disruption of this protective mechanism can have serious consequences, particularly in vulnerable populations. Volume depletion, whether from dehydration, heart failure, or other causes, makes the kidney especially dependent on prostaglandin-mediated vasodilation. In such states, NSAID use can precipitate significant renal dysfunction. Moreover, patients with pre-existing cardiovascular conditions face heightened risk due to the delicate balance between cardiac output and renal perfusion. The combination of altered renal hemodynamics and direct tubular toxicity can create a perfect storm for kidney injury, especially in settings of polypharmacy or concurrent medical conditions [26].

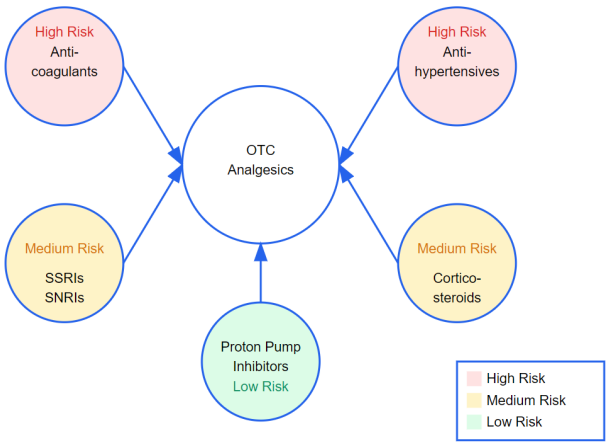

Figure 2. Drug Interactions with Common OTC analgesics

3.4.2. Clinical Presentation

The spectrum of renal manifestations associated with OTC analgesic use ranges from subtle to severe, with both acute and chronic consequences. In the early stages, patients may develop clinically silent electrolyte imbalances, particularly affecting sodium and potassium homeostasis. These disturbances can progress to more severe manifestations of acute kidney injury, characterized by rising creatinine levels and declining urine output. The development of interstitial nephritis represents a serious complication, often presenting with systemic symptoms including fever, rash, and eosinophilia. Papillary necrosis, a particularly severe form of renal

injury, can occur with chronic use, leading to permanent kidney damage. Contemporary epidemiological research has revealed concerning trends, demonstrating that regular NSAID users face approximately double the risk of developing chronic kidney disease compared to non-users [27].

4. Impact on Public Health

4.1. Economic Burden

The financial impact of OTC analgesic complications represents a substantial strain on healthcare systems and society at large. The direct medical costs associated with managing these complications encompass a wide spectrum of healthcare services, from emergency department interventions to extended hospitalization periods. In the United States, acetaminophen-related hospitalizations alone impose a staggering financial burden exceeding $1 billion annually, reflecting the significant resources required for managing overdoses, hepatotoxicity, and related complications [28]. Apart from direct medical expenses, the economic impact extends into multiple societal domains. Workplace productivity losses emerge as a major contributor, accounting for approximately 40% of the total economic burden. This encompasses both absenteeism and reduced workplace efficiency among affected individuals. The calculation of disability-adjusted life years (DALYs) reveals the substantial impact on quality of life and functional capacity [29].

4.2. Risk Patterns

The distribution of risks associated with OTC analgesic misuse reveals distinct patterns across different demographic groups, each presenting unique challenges for prevention and intervention strategies. The elderly population exhibits particular vulnerability to adverse effects, with physiological changes in drug metabolism, reduced renal function, and multiple comorbidities contributing to increased risk. Their susceptibility to gastrointestinal and renal complications is notably higher, often complicated by polypharmacy and age-related changes in drug clearance [30]. In contrast, younger adult populations show different risk patterns, characterized by higher rates of intentional misuse, often related to self-medication practices or recreational use. The complex interplay of socioeconomic factors significantly influences OTC analgesic use patterns and associated risks. Access to healthcare services, varying levels of health literacy, and disparities in healthcare availability create distinct risk profiles across different socioeconomic groups. Educational background, income levels, and healthcare access barriers play crucial roles in determining both the likelihood of misuse and the severity of resulting complications [31].

5. OTC Misuse Prevention and Mitigation

5.1. Institutional Strategies

The implementation of regulatory measures and packaging modifications has yielded significant results in mitigating OTC analgesic misuse. Quantity limitations represent a critical intervention, restricting the amount of medication available in a single purchase. This approach effectively reduces the potential for acute overdose by limiting immediate access to large quantities. Blister packaging requirements serve multiple protective functions: they create a physical barrier that slows consumption, provide an obvious visual cue of medication quantity consumed, and introduce a moment of deliberation before each dose is accessed. The empirical evidence supporting these interventions is compelling, with data showing a substantial 43% reduction in acetaminophen-related mortality following the introduction of these packaging restrictions [32, 33].

Table 2. Risk Factors and Prevention Strategies for OTC Analgesic-Related Adverse Events

Adverse Effects	Risk Factors	Prevention Techniques	Monitoring Parameters
Gastrointestinal	Age >65 years, H. pylori infection, concurrent anticoagulation	PPI co-prescription, lowest effective dose	Hemoglobin, stool occult blood
Hepatic	Alcohol use, malnutrition, concurrent hepatotoxic medications	Dose limitation, alcohol abstinence	Liver function tests
Renal	Existing CKD, diabetes, hypertension	Regular renal function monitoring, hydration	Serum creatinine, eGFR
Cardiovascular	Hypertension, heart failure, CAD	BP monitoring, alternative pain management	Blood pressure, edema
Special Populations	Pregnancy, elderly, pediatric	Age-appropriate dosing, increased monitoring	Population-specific parameters

5.2. Healthcare Provider Initiatives

Community pharmacists play a vital role in promoting safe OTC analgesic use through direct patient interaction and clinical oversight. Their role extends beyond dispensing to include comprehensive medication counseling, risk assessment, and early intervention in potentially problematic usage patterns. Structured intervention programs, implemented through pharmacy networks, have demonstrated measurable success in improving appropriate medication use. These programs typically incorporate standardized assessment tools, patient education protocols, and follow-up monitoring [34]. The effectiveness of these initiatives is further enhanced through continuing medical education programs focused on OTC analgesic safety. These educational efforts ensure healthcare providers maintain current knowledge of best practices, emerging safety concerns, and optimal prescribing strategies, ultimately leading to more effective patient guidance and improved outcomes [35].

5.3. Public Education

The dissemination of safety information through multiple channels represents a crucial component of comprehensive OTC analgesic risk management. Digital platforms offer unprecedented reach and accessibility, while traditional media channels ensure coverage across diverse demographic groups. Evidence supports the effectiveness of multimedia educational approaches in enhancing medication literacy, particularly when content is tailored to specific audience needs and preferences [36]. Early intervention programs targeting younger populations have shown particular promise. [37].

5.4. Technological Innovations

Advanced technological solutions offer new possibilities for monitoring and managing OTC analgesic use. Electronic tracking systems provide capabilities for monitoring purchase patterns and potential misuse at both individual and population levels. These systems enable real-time surveillance and early detection of concerning usage trends, allowing for timely intervention [38]. Mobile applications and smart device integration represent emerging tools for supporting safe medication use. The combination of electronic compliance monitoring and automated dosing reminders shows promising results in preventing accidental overdose through improved adherence to recommended dosing schedules and enhanced user awareness of cumulative intake [39].

5.5. Policy Development

The movement toward standardized OTC analgesic regulations reflects growing recognition of the need for consistent safety measures across jurisdictions. These efforts aim to establish uniform standards for packaging, labeling, and quantity restrictions, enhancing global medication safety through harmonized approaches [40]. The development of collaborative frameworks facilitates the sharing of best practices and surveillance data among regulatory bodies and healthcare systems. A particularly significant advancement involves the integration of OTC medication monitoring within electronic health records systems. This integration supports medication management by providing healthcare providers with complete medication profiles, including both prescription and OTC medications. Such systems enable better detection of potential drug interactions and cumulative dose concerns, leading to more effective patient care and reduced adverse events [41].

Table 3. Global Regulatory Guidelines to OTC Analgesic Control (2020-2024)

Region	Pack Size Restrictions	Required Warnings	Sales Restrictions	Monitoring Systems
United States	No federal limits	FDA-mandated liver warnings	Behind-counter (selected products)	PDMP for combination products
European Union	Varies by country (8-100 tablets)	Harmonized labeling requirements	Pharmacy-only status common	National monitoring databases
Australia	100 tablet limit	Extensive warning labels	Schedule 2/3 classifications	Real-time monitoring
United Kingdom	32 tablet limit (pharmacy)	Prominent liver/overdose warnings	Location restrictions	Yellow Card system
Canada	No specific limits	Bilingual warnings required	NAPRA scheduling	Provincial monitoring

5.6. Clinical Recommendations

5.6.1. Risk Assessment

Validated risk assessment instruments serve as essential tools in the systematic evaluation of OTC analgesic use patterns and potential misuse. These instruments incorporate multiple risk factors, including medication use history, concurrent medical conditions, and psychosocial factors, to generate comprehensive risk profiles. Regular screening implementation has demonstrated particular value in high-risk populations, such as elderly patients, those with chronic pain conditions, and individuals with a history of substance use [42]. The effectiveness of these screening tools is enhanced through structured follow-up protocols specifically

designed for chronic OTC analgesic users. These protocols establish regular monitoring intervals, define specific assessment parameters, and provide clear intervention thresholds [43].

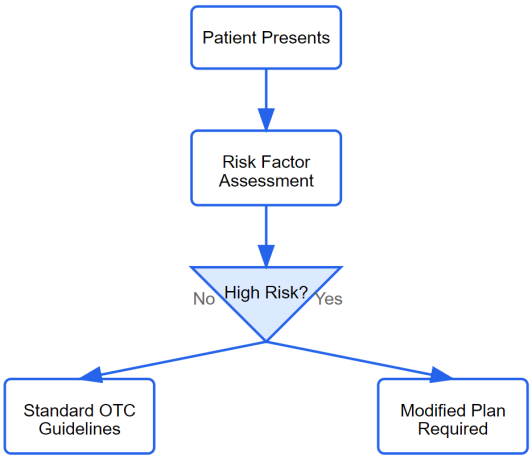

Figure 3. Safety Assessment Algorithm for OTC Analgesic

5.7. Alternative Pain Management Interventions

The use of non-pharmacological pain management techniques represents a crucial component of comprehensive pain care, offering evidence-based alternatives or complements to OTC analgesics. Physical therapy interventions demonstrate significant efficacy in managing various pain conditions through targeted exercise programs, manual therapy techniques, and modality-based treatments. Cognitive behavioral approaches provide valuable tools for pain management, addressing both the physical and psychological aspects of pain experience. These approaches include pain coping strategies, stress management techniques, and behavioral modification methods that have shown substantial evidence of effectiveness [44]. The field of complementary therapies has also yielded several evidence-supported interventions that can be valuable additions to pain management protocols. These may include acupuncture, mindfulness-based stress reduction, and therapeutic massage, all of which have demonstrated efficacy in specific pain conditions. The usage of these complementary techniques provides healthcare providers with an expanded toolkit for managing pain, potentially reducing reliance on pharmacological interventions and their associated risks [45].

6. Conclusion

The strategies to avoid misuse of OTC analgesics requires balanced approaches to maintaining medication accessibility while ensuring public safety. Medication-related adverse effects highlight the importance of coordinated responses from healthcare providers, regulatory bodies, and public health systems. Implementation of evidence-based interventions, coupled with technological innovations, offers promising directions for improving medication safety. The economic and public health implications of OTC analgesic misuse show the necessity for continued research, policy development, and educational initiatives.

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