

# Real-World Pharmacovigilance Analysis of Adverse Events Associated with Liposomal Bupivacaine and Bupivacaine

Dong Xu Chen<sup>1,2,\*</sup>, Xuan Ming Chen<sup>3,\*</sup>, Shou Ming Chen<sup>1,2</sup>, Yi Da Wang<sup>3</sup>

<sup>1</sup>Department of Anesthesiology, West China Second Hospital, Sichuan University, Chengdu, People's Republic of China; <sup>2</sup>Key Laboratory of Birth Defects and Related Diseases of Women and Children, Sichuan University, Ministry of Education, Chengdu, People's Republic of China; <sup>3</sup>Key Laboratory of Bioresource and Eco-Environment of Ministry of Education, College of Life Science, Sichuan University, Chengdu, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Yi Da Wang, Key Laboratory of Bioresource and Eco-Environment of Ministry of Education, College of Life Science, Sichuan University, Chengdu, People's Republic of China, Email scu\_wyd@foxmail.com; Shou Ming Chen, Department of Anesthesiology, West China Second Hospital, Sichuan University, Chengdu, People's Republic of China, Email 761858401@qq.com

**Purpose:** Liposomal bupivacaine, a novel formulation of bupivacaine, is increasingly employed for the long-lasting pain relief. The primary goal of this study was to conduct a thorough safety evaluation of liposomal bupivacaine and bupivacaine.

**Patients and Methods:** This study analyzed adverse events (AEs) associated with liposomal bupivacaine and bupivacaine using the FDA Adverse Event Reporting System (FAERS) database from Q1 2004 to Q2 2024. Reports were screened for signal detection, focusing on the onset time and disproportionality analysis to identify positive safety signals. We evaluated the AEs associated with liposomal bupivacaine and bupivacaine. Then, we further categorized them according to the Important Medical Event Terms List (IME list).

**Results:** The analysis revealed 8,023 AE reports in total. Liposomal bupivacaine had 58 positive safety signals, 24 of which were off-label and listed in the IME list. These signals were primarily associated with cardiac (eg, cardiogenic shock), gastrointestinal (eg, paralytic ileus), and neurological disorders. Bupivacaine generated 107 safety signals, with 49 being off-label but also on the IME list. These signals mainly affected the fetus (eg, fetal bradycardia), respiratory system (eg, respiratory depression), and nervous system (eg, neurotoxicity).

**Conclusion:** This study identified unexpected AEs associated with liposomal bupivacaine and bupivacaine. Physicians must exercise particular caution when administering liposomal bupivacaine due to its associated risks. Monitoring for delayed analgesia-related AEs may enhance the safe use of this medication for pain management.

**Keywords:** FAERS database, liposomal bupivacaine, bupivacaine, postoperative pain, adverse reactions

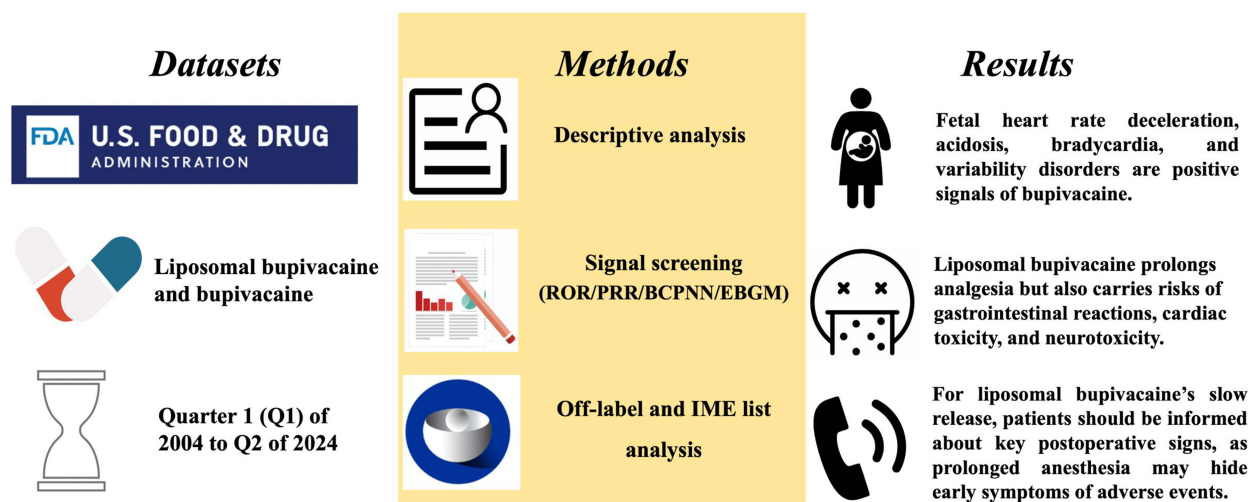
## Introduction

Acute postoperative pain is a significant clinical challenge, with a high incidence among surgical patients.<sup>1</sup> Inadequate pain control not only increases patient discomfort but also contributes to a range of postoperative complications, including delayed recovery and an increased risk of chronic postoperative pain.<sup>2,3</sup> Effective management of postoperative pain is critical to enhancing patient outcomes and reducing healthcare costs. Traditionally, opioid analgesics have been the cornerstone of postoperative pain control.<sup>4</sup> However, the use of opioids is associated with a broad spectrum of side effects, such as respiratory depression, immune system depression, and an increased risk of opioid dependence.<sup>5</sup> Moreover, higher opioid dosage did not necessarily provide a proportionate increase in analgesic efficacy, conversely, previous studies have observed a lower quality of early recovery in these conditions.<sup>6,7</sup>

There has been a growing interest in the use of local anesthetics for postoperative pain control. Local anesthetics offer a safer alternative by providing site-specific analgesia with fewer systemic side effects.<sup>8</sup> At present, bupivacaine has been widely used due to its potent and long-acting effects. However, even bupivacaine, despite its extended duration compared to other agents like lidocaine, has limitations: its relatively short duration of action when administered as a single injection for

## Graphical Abstract

## A real-world pharmacovigilance study of liposomal bupivacaine and bupivacaine



postoperative pain management. This necessitates repeated dosing or continuous infusion, which can be logistically challenging and increases the risk of complications, such as local anesthetic systemic toxicity (LAST).<sup>9</sup> Despite extensive research on prolonging local anesthetic efficacy through adjuvants like dexamethasone and dexmedetomidine, duration remains limited to under 6 hours.<sup>10</sup> Therefore, the search for long-acting local anesthetics is still an important topic.

To address these issues, liposomal formulations of local anesthetics have been developed. This novel formulation extends the duration of bupivacaine's analgesic effect, providing sustained pain relief for up to 72 hours with a single administration.<sup>11</sup> The liposomal delivery system allows for a gradual release of bupivacaine, maintaining therapeutic drug levels over an extended period.<sup>12</sup> This prolonged action reduces the need for repeated dosing or continuous infusion, thus minimizing the risk of LAST and improving patient compliance. Studies have demonstrated its superiority over traditional bupivacaine in improving pain relief and reducing opioid consumption compared to those receiving non-liposomal bupivacaine.<sup>13,14</sup> Additionally, liposomal bupivacaine has been associated with fewer opioid-related side effects, further improving the overall patient's satisfaction. Importantly, the extended duration of action aligns with the typical timeline of acute postoperative pain, which tends to peak within the first 48–72 hours after surgery.<sup>15</sup> This makes liposomal bupivacaine an ideal option for managing moderate-to-severe pain during this critical period.

However, despite its potential benefits, safety concerns have been raised regarding liposomal bupivacaine. The US Food and Drug Administration (FDA) has issued warnings about the risk of cardiac and neurotoxicity associated with bupivacaine, including its liposomal formulation. For example, toxic effects of bupivacaine have been documented at plasma concentrations as low as 800 ng/mL, despite early subjective central nervous system (CNS) symptoms typically being reported at higher concentrations ranging from 2500 to 4000 ng/mL.<sup>16</sup> The issues raised emphasize why ongoing drug safety monitoring remains critical for clarifying potential dangers connected with this specialized delivery mechanism. Given that an expanding patient population now receives this lipid-encapsulated anesthetic compound, combined with relatively restricted study groups during development phases, it becomes crucial to evaluate its safety characteristics in actual healthcare environments following commercial release.

Our analysis drew upon adverse event records maintained in FDA Adverse Event Reporting System (FAERS) to identify potential warning signals and evaluate real-world safety profiles for both conventional and liposome-formulated versions of bupivacaine. The primary objective was to provide insights that could guide responsible clinical usage protocols and administration strategies.

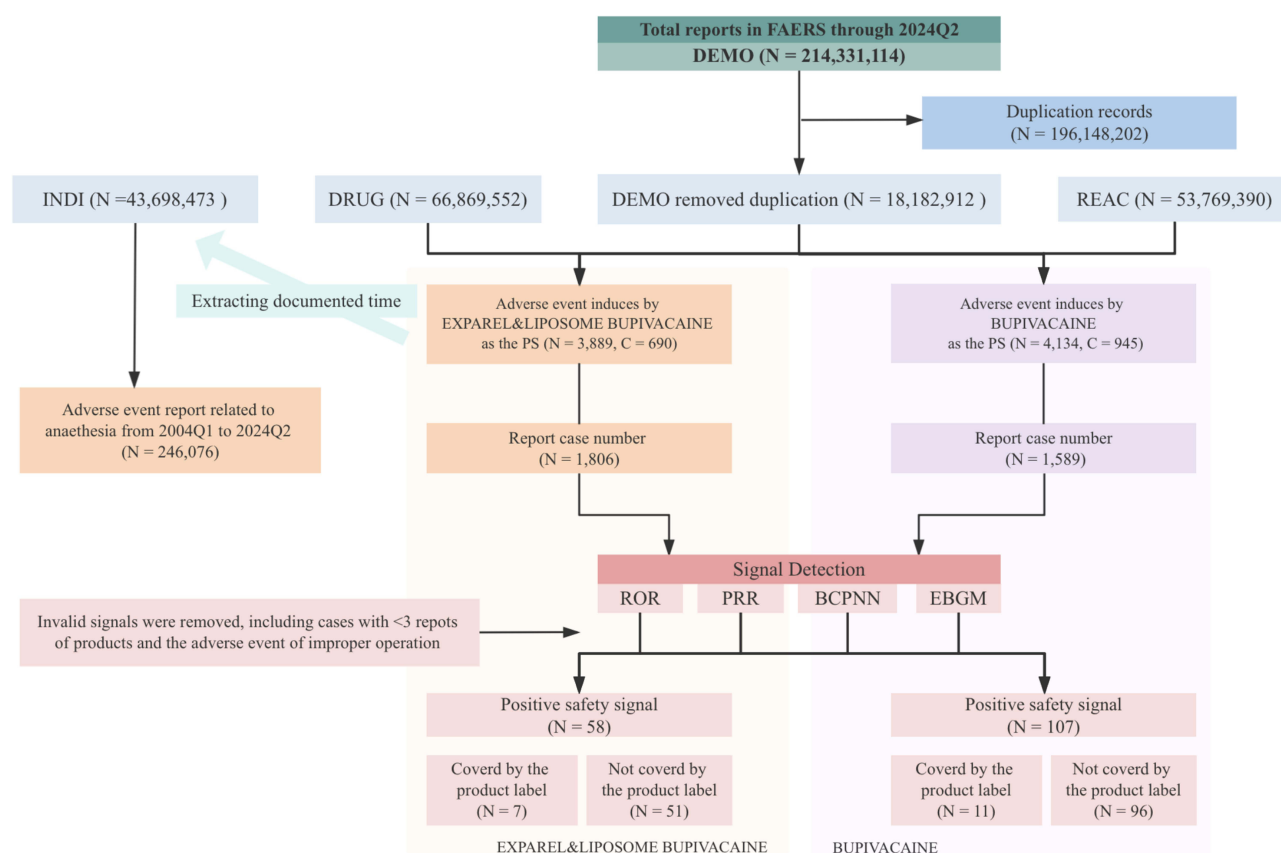
## Materials and Methods

### Study Design and Data Source

The FDA's adverse event (AE) monitoring system serves as a vital component in the post-approval monitoring of unwanted medication reactions and pharmaceutical administration mistakes.<sup>17</sup> This comprehensive repository combines information from two primary sources: approximately 5% originates from the Safety Information and Adverse Event Reporting Program, while the Pharmacovigilance System contributes the remaining 95%. Researchers can freely access this collection to detect and examine patterns indicating disproportionate documentation of negative medication outcomes, thereby helping establish connections between specific pharmaceutical agents and undesirable clinical manifestations.<sup>18,19</sup> Selection of the investigation period was determined by data accessibility and medication availability factors. When this research commenced, information through the second quarter of 2024 had been made public by regulatory authorities. Ethical committee approval was deemed unnecessary for this investigation since it utilized anonymized data already available in the public domain.

### Cases and Drugs Definition

Potential drug-induced adverse effects undergo systematic categorization using MedDRA<sup>®</sup> designated preferred terms (PTs). This classification protocol implements a structured arrangement in which these designated terms advance through progressive tiers of Higher-Level Terms and Grouping Terms, eventually being allocated to System Organ Classes reflecting their physiological origins, bodily locations, or therapeutic domains. The FDA's surveillance database further employs distinctive coding mechanisms to signify each medication's role in documented incidents. To ensure comprehensive analytical validity, our investigation incorporated various classification markers for the pharmaceutical agents under examination. The designation "PS" was strategically utilized to identify compounds reported as the principal contributors to adverse outcomes, thereby strengthening methodological robustness (Figure 1). When conducting our



**Figure 1** Flowchart depicting the study process.

**Note:** N represents the number of adverse events, and C represents the type of adverse events.

comparative risk profile analysis between standard and lipid-encapsulated formulations following regulatory approval, we extracted relevant information from the American Standard Code for Information Interchange (ASCII)-formatted records within the FAERS information repository, encompassing a twenty-year period beginning with the initial quarter of 2004 and extending through the second quarter of 2024.

## Descriptive Analysis

After screening, the characteristics of reports involving liposomal bupivacaine and bupivacaine encompassed sex, age, age group, country, outcome, the latest year of FDA acceptance, report type, and other clinical characteristics. Significant adverse outcomes documented in these reports included critical medical emergencies requiring hospital admission, functional impairment, and fatal incidents. The onset time of AEs was acquired by subtracting the recorded initiation of therapeutic intervention.

## Signal Screening and Statistical Analysis

Within pharmaceutical safety oversight, disproportionate reporting analysis functions as a key methodological framework for identifying potential correlations between reported AEs and individual therapeutic compounds ([Table S1](#)).<sup>20</sup> This approach operates on the premise that a connection between a drug and specific AEs would manifest as a higher observed frequency than expected, resulting in a disproportional ratio. Safety concerns are flagged when this statistical measure exceeds its predetermined critical threshold. The research examined complete FAERS repository contents utilizing four established analytical procedures to recognize significant safety alerts ([Figure 1](#) and [Table S2](#)): reporting odds ratio (ROR),<sup>21,22</sup> proportional reporting ratio (PRR),<sup>23</sup> Bayesian confidence propagation neural network (BCPNN),<sup>24</sup> and Empirical Bayesian Geometric Mean (EBGM).<sup>25</sup> For enhanced analytical credibility, a strong and valid association with the target drug was only considered when all four methodological approaches in identifying significant safety indicators for the investigated clinical manifestation.

Implementing the confidence interval's lower limit in conjunction with establishing minimum frequency requirements for medication-reaction combinations serves as an effective filtering mechanism to minimize erroneous positive signal detection. This methodological approach is particularly valuable when evaluating associations characterized by minimal observed or anticipated occurrence rates.<sup>26</sup> However, due to the lack of a universally accepted threshold criterion, we implemented widely used criteria for identifying safety signals in post-marketing research.<sup>21–23,25,27</sup>

Our investigation further examined unanticipated preferred terms not mentioned in the regulatory approval documents for the study medication, potentially indicating previously unrecognized risks associated with its use. Additionally, we categorized preferred terms according to the most current iteration (26.1) of the 'Important Medical Events' compilation developed by the EudraVigilance Expert Working Group. The essential qualification for inclusion in the IME listing is the manifestation of a significant adverse event or reaction. This definition encompasses any adverse medical occurrence, irrespective of dosage administered, that results in mortality creates a life-endangering circumstance, requires hospital admission or extends an ongoing hospitalization period, or produces lasting or substantial functional limitation or incapacity.

Data management and analysis were performed using the packages openxlsx, dplyr, scales, survminer, forestplot, ggplotify, forestploter, grid, patchwork, data.table, ggplot2, ggrepel, readr, pheatmap, extrafont, calibrate, Cairo, ggalluvial, RColorBrewer, plotly, reticulate, ProcessX, webshot, htmlwidgets, tidyverse, gtable, ggpubr of the "R" software (version 4.2.2).

## Results

### Descriptive Analysis

FAERS encompassed 21,433,114 documented incidents through 2024's second quarter. Documented adverse clinical manifestations related to liposomal bupivacaine and bupivacaine spanned from 2004Q1 to 2024Q2, comprising 8023 AE reports attributed to liposomal bupivacaine (3889), and bupivacaine (4134) as the PS, covering 690 (liposomal bupivacaine) and 945 (bupivacaine) AE categories.

Throughout the twenty-year surveillance period spanning from the first quarter of 2004 through the second quarter of 2024, a total of 3,395 incident reports identified liposomal bupivacaine and bupivacaine as PS ([Table 1](#)). Gender distribution analysis

**Table 1** Characteristics of Reports Associated with Bupivacaine and Liposome Bupivacaine from 2004Q1–2024Q2. Healthcare Professionals Including Reporters Such as Physicians and Pharmacists; Nonhealthcare Professionals Including Reporters Such as Consumer and Lawyer

Variables	Total	Liposome Bupivacaine	Bupivacaine
<b>Case</b>	N=3395	N=1806	N=1589
<b>Age (year)</b>			
<18	100 (3.0%)	23 (1.3%)	77 (4.8%)
18–64	371 (11.0%)	346 (19.2%)	25 (1.6%)
65–85	948 (28.0%)	167 (9.2%)	781 (49.2%)
>85	286 (8.4%)	5 (0.3%)	281 (17.7%)
Missing	1690 (49.6%)	1265 (70.0%)	425 (26.7%)
<b>Sex</b>			
Female	1437 (42.3%)	575 (31.8%)	862 (54.2%)
Male	803 (23.7%)	294 (16.3%)	509 (32.0%)
Missing	1155 (34.0%)	937 (51.9%)	218 (13.7%)
<b>Weight (Kg)</b>			
<50	87 (2.6%)	21 (1.2%)	66 (4.2%)
>100	95 (2.8%)	48 (2.7%)	47 (3.0%)
50–100	522 (15.3%)	195 (10.8%)	327 (20.6%)
Missing	2691 (79.3%)	1542 (85.4%)	1149 (72.3%)
<b>Reporter</b>			
Healthcare professional	2856 (84.1%)	1390 (77.0%)	1466 (92.3%)
Nonhealthcare professional	466 (13.7%)	394 (21.8%)	72 (4.5%)
Missing	72 (2.2%)	22 (1.2%)	51 (3.2%)
<b>Country</b>			
United States	2434 (71.7%)	1754 (97.1%)	680 (42.8%)
Other countries	868 (25.6%)	27 (1.5%)	841 (52.9%)
Country not specified	93 (2.7%)	25 (1.4%)	68 (4.3%)
<b>Outcome</b>			
Death	106 (3.1%)	50 (2.8%)	56 (3.5%)
Disability	93 (2.7%)	11 (0.6%)	82 (5.2%)
Hospitalization	626 (18.4%)	328 (18.2%)	298 (18.8%)
Life-threatening	218 (6.4%)	43 (2.4%)	175 (11.0%)
Other serious illness	1067 (31.4%)	362 (20.0%)	705 (44.4%)
Required intervention to prevent / permanent impairment / damage	30 (0.9%)	4 (0.2%)	26 (1.6%)
Congenital anomalies	1 (0.0%)	0 (0.0%)	1 (0.1%)
Missing	1044 (30.8%)	798 (44.2%)	246 (15.5%)

**Abbreviations:** LAST, local anesthetic systemic toxicity; FAERS, FDA Adverse Event Reporting System; ADRs, adverse drug reactions; AEs, adverse events; PTs, Preferred Terms; MedDRA, Medical Dictionary for Regulatory Activities; ASCII, American Standard Code for Information Interchange; ROR, reporting odds ratio; PRR, proportional reporting ratio; BCPNN, Bayesian confidence propagation neural network; EBGM, Empirical Bayesian Geometric Mean; ePT, expected PT.

revealed 42.3% female subjects (N = 1,437) and 23.7% male subjects (N = 803). Body mass documentation was substantially incomplete, with 79.3% (N = 2,691) of cases lacking weight measurements; among documented cases, 15.3% fell within the 50–100 kg range (N = 522), 2.8% exceeded 100 kg (N = 95), and 2.6% weighed below 50 kg (N = 87). Age demographic analysis indicated 3.0% pediatric cases under 18 years (N = 100), 11.0% adults aged 18–64 years (N = 371), 28.0% older adults aged 65–85 years (N = 948), and 8.4% elderly individuals exceeding 80 years (N = 286). Report sources predominantly comprised healthcare practitioners (84.1%, N = 2,856), with non-clinical reporters including consumers and legal representatives constituting 13.7% (N = 466). Geographically, the United States accounted for the majority of submissions (71.7%, N =

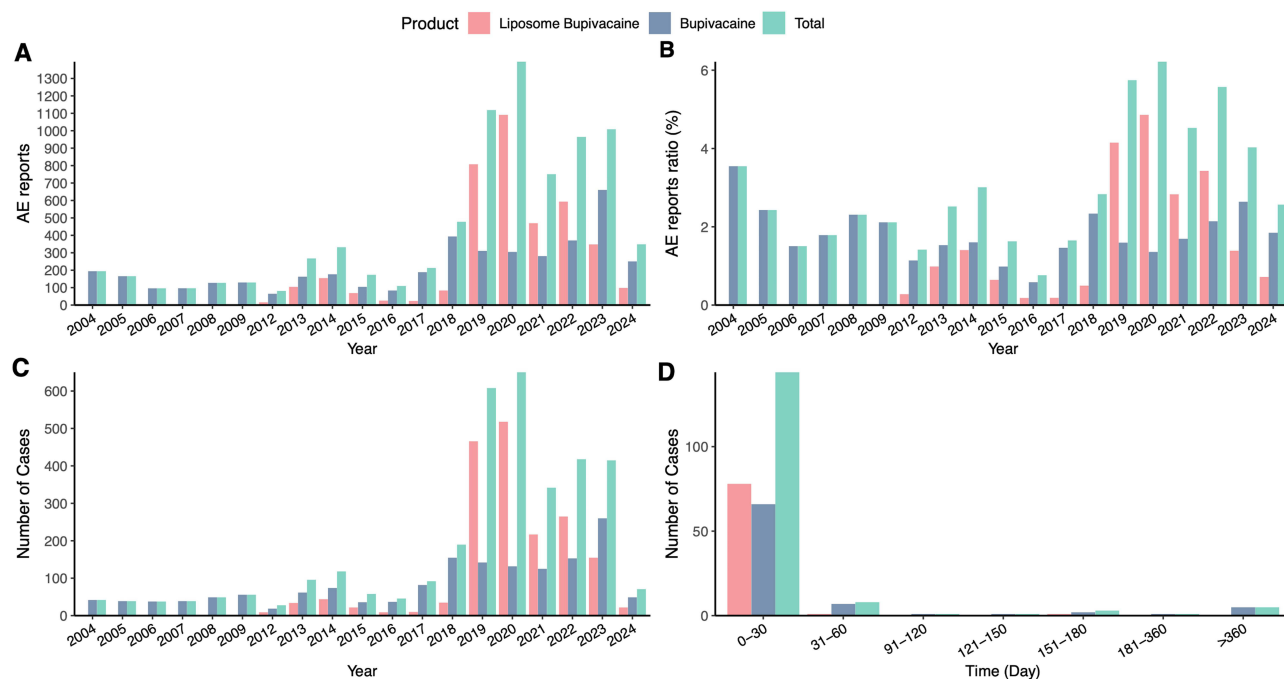
2,434), followed by international jurisdictions (25.6%,  $N = 868$ ), while 2.7% ( $N = 93$ ) lacked geographical specification. As for the outcome, most reports (31.4%,  $N = 1067$ ) showed other serious illness, 18.4% ( $N = 626$ ) concluded with hospitalization, 6.4% ( $N = 1067$ ) were life-threatening, 3.1% ( $N = 106$ ) were death and 2.7% ( $N = 93$ ) were disability. The above information is further grouped based on liposomes and non-liposomes, which is presented in [Table 1](#).

[Figure 2A](#) presents the yearly AE report trends for liposomal bupivacaine and bupivacaine from Q1 2004 to Q2 2024. Initially, the number of AEs reported only by bupivacaine from 2004 to 2009 was always less than 200. After 2012, liposomal bupivacaine-related AEs were reported and increased year by year with small fluctuations. The proportion of bupivacaine decreased year by year before 2009 and began to rise after the appearance of liposomal bupivacaine in 2012 and reached the peak of 6% in 2020 ([Figure 2B](#) and [C](#)). After that, they are in a relatively stable state of about 5%. The AEs of liposomal bupivacaine mainly occurred within 30 days, while the AEs of bupivacaine mainly occurred in the range of 0–30 days, and a small number of AEs occurred after 30 days ([Figure 2D](#)).

## Adverse Events Associated with Liposomal Bupivacaine

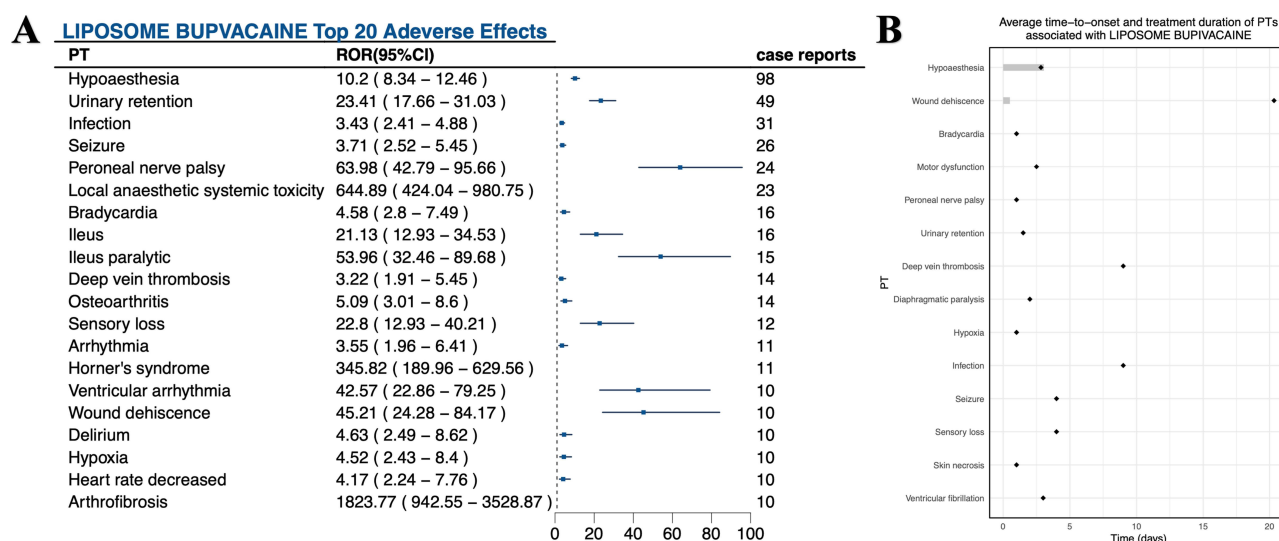
The FAERS repository documented 690 distinct adverse event classifications associated with liposomal bupivacaine administration. Following the implementation of signal detection protocols, 632 classifications were excluded from further analysis, specifically those with insufficient reporting frequency (fewer than 3 documented instances). Ultimately, 58 positive signals were identified ([Figure S1](#)). Results revealed that liposomal bupivacaine involved adverse reactions mainly concentrated in cardiac disorders, nervous system disorders, injury, poisoning and procedural complications, general disorders and administration site conditions and respiratory, thoracic and mediastinal disorders. Some adverse reactions, such as bradycardia, ventricular tachycardia, hypoaesthesia, paresis, hypoxia, apnoea, and urinary retention, are classified as ePT (expected PT, as documented in the official FDA specification, [Table S3](#)).

[Figure 3A](#) displays the ROR findings for the twenty most prevalent AEs, demonstrating the comparative likelihood of reporting specific events versus all other events for liposomal bupivacaine relative to other pharmaceuticals documented in the FAERS database. The most frequently documented events at the PT level included seizure ( $N = 26$ ), peroneal nerve palsy ( $N = 24$ ), LAST ( $N = 23$ ), ileus ( $N = 16$ ), paralytic ileus ( $N = 15$ ), deep vein thrombosis ( $N = 14$ ), sensory loss ( $N = 12$ ),



**Figure 2** Comprehensive analysis of target drugs' data. **(A)** Frequency of target drugs' AEs in the FAERS database (2004Q1 - 2024Q2). **(B)** AE ratio for target drugs versus the total AE reports (2004Q1 - 2024Q2). **(C)** Number of target drugs' cases in the FAERS database (2004Q1 - 2024Q2). **(D)** The frequency of AEs occurred in different time periods (2004Q1 - 2024Q2).





**Figure 3 (A)** The reporting odds ratios of the top 20 AEs related to liposomal bupivacaine. **(B)** Reported time-to-onset analysis and duration of treatment of the top 20 AEs with liposomal bupivacaine.

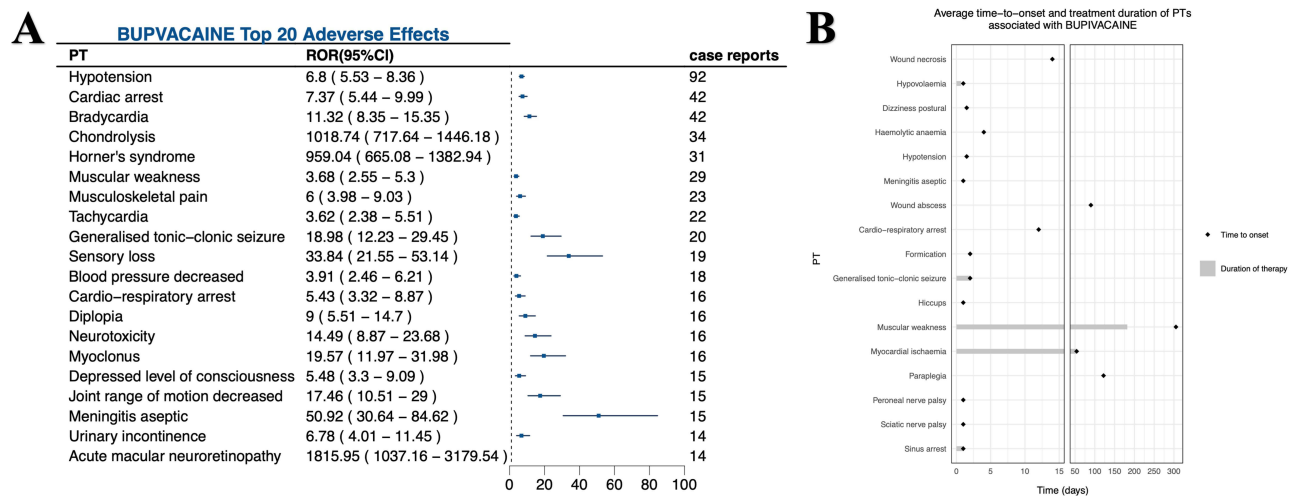
arrhythmia (N = 11), and decreased heart rate (N = 10). Multiple disproportionality metrics—ROR (3.71/63.98/644.89/4.63), PRR (3.69/63.59/641.08/4.62), EBGM05 (3.69/63.3/612.71/4.62), and IC025 (1.88/5.98/9.26/2.21)—revealed substantially elevated AE reporting frequencies for seizure, peroneal nerve palsy, and LAST. EBGM05 exceeding 2 and IC025 greater than 0, representing the lower boundaries of 95% confidence intervals for EBGM and IC respectively, constitute standard thresholds in statistical signal identification methodology (Table S4). Comparable patterns were evident across additional AEs including Horner's syndrome, osteoarthritis, wound dehiscence, and arthrofibrosis—with ROR, PRR, EBGM05, and IC025 values suggesting statistically significant signal intensity. When classified according to system organ classes, these twenty predominant events were distributed across categories including gastrointestinal disorders, "injury, poisoning and procedural", "musculoskeletal and connective tissue disorders", and "cardiac disorders"

The total number of effective cases was 133, and the onset time was analyzed. It should be noted that some cases only have the time for treatment, while others only have the time for AEs to occur (Figure 3B). Hypoaesthesia occurs during drug use; however, most of the adverse reactions occurred within 10 days of administration, and one case of wound dehiscence was identified 20 days after administration.

## Adverse Events Associated with Bupivacaine

Analysis of the FAERS pharmacovigilance database revealed 945 unique adverse reaction classifications linked to bupivacaine administration. Through application of signal evaluation criteria, 838 classification categories were subsequently removed from analytical consideration, specifically those demonstrating minimal reporting frequency (less than three documented instances). Ultimately, 107 positive signals were identified (Figure S2). Results revealed that non-liposomal bupivacaine involved adverse reactions mainly concentrated in nervous system disorders, cardiac disorders, respiratory, thoracic and mediastinal disorders, musculoskeletal and connective tissue disorders, eye disorders and vascular disorders. Some adverse reactions, such as paralysis, cardiac arrest, bradycardia, ventricular fibrillation, ventricular tachycardia, respiratory arrest, apnoea, chondrolysis, hypotension, urinary retention and hypovolemia, are classified as ePT (e-Table 3).

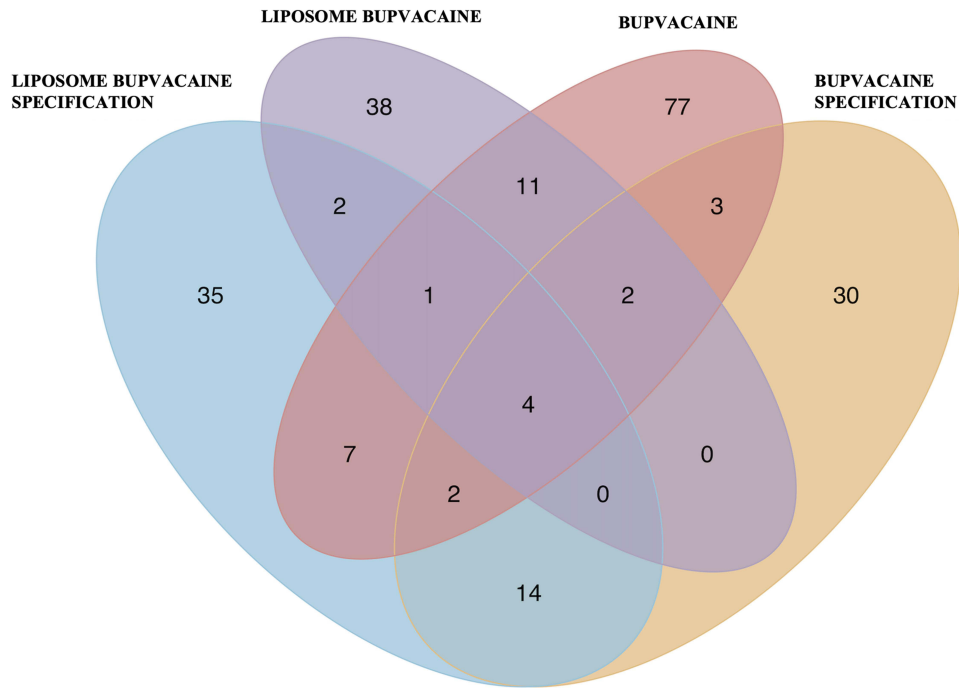
Horner's syndrome (N = 31), muscular weakness (N = 29), musculoskeletal pain (N = 23), generalized tonic-clonic seizure (N = 20), sensory loss (N = 19), cardio-respiratory arrest (N = 16), diplopia (N = 16), neurotoxicity (N = 16), myoclonus (N = 16), depressed level of consciousness (N = 15), joint range of motion decreased (N = 15), meningitis aseptic (N = 15), and acute macular neuroretinopathy (N = 14) represented the most commonly documented occurrences within the PT level (Figure 4A). Diverse statistical analytical frameworks including ROR (33.84/14.49/5.48), PRR (33.69/14.44/5.46), EBGM05 (33.61/14.42/5.46), and IC025 (5.07/3.85/2.45) indicated significantly elevated AE reporting for sensory loss, neurotoxicity



**Figure 4 (A)** The reporting odds ratios of the top 20 AEs related to bupivacaine. **(B)** Reported time-to-onset analysis and duration of treatment of the top 20 AEs with bupivacaine.

and depressed level of consciousness. Similar patterns were found in Horner’s syndrome, muscular weakness, musculoskeletal pain, myoclonus, diplopia, and acute macular neuroretinopathy (Table S4). The top 20 events were classified into categories such as “cardiac disorders”, “musculoskeletal and connective”, “nervous system disorders” and “eye disorders”.

The total number of effective cases was 45, and the onset time was analyzed (Figure 4B). Generalized tonic-clonic seizure, myocardial ischemia, and sinus arrest occurs during drug use. Most of the adverse reactions occurred within 15 days of administration, and a few occurred after 50 days of administration, such as wound abscess. Muscular weakness, myocardial ischemia and paraplegia, especially muscular weakness occurred 300 days after dosing.



**Figure 5** Venn diagram of liposomal bupivacaine, bupivacaine, liposomal bupivacaine specification and bupivacaine specification.



## Off-Label and IME List Analysis

The AEs between liposomal bupivacaine and bupivacaine had many commonalities and specificities (Figures 5 and S3). Liposomal bupivacaine and bupivacaine have 11 off-label intersections and 38, 77 AEs, respectively (details are presented in Table S5). Further screening based on the IME list revealed 8 off-label positive signals between liposomal bupivacaine and bupivacaine, 16 for liposomal bupivacaine and 41 for bupivacaine. The commonality between liposomal bupivacaine specification and liposomal bupivacaine is found mainly in neurological and cardiovascular symptoms. Liposomal bupivacaine is characterized by a broader range of conditions affecting multiple systems, including neurological symptoms, cardiovascular complications, respiratory and digestive dysfunction. The overlap between bupivacaine specification and bupivacaine is primarily observed in neurological, cardiovascular, and gastrointestinal systems. Bupivacaine emphasizes additional fetal-related conditions (foetal heart rate deceleration, bradycardia, or baseline foetal heart rate variability disorder) and respiratory complications (respiratory distress, diaphragm paralysis, respiratory depression). Additionally, psychiatric disorders and skin tissue disorders were solely identified in liposomal bupivacaine (Figure S3), while eye disorders, hepatobiliary disorders, immune system disorders, perinatal conditions, ear and labyrinth disorders, and pregnancy, puerperium and blood and lymphatic system disorders were exclusively found in bupivacaine. Both groups share a wide range of symptoms affecting the nervous and cardiovascular systems, but their respective focuses differ significantly in terms of the specific systems they affect.

## Discussion

Our findings validate previously established safety concerns from both clinical trials and observational research. AEs shared by the liposomal and non-liposomal bupivacaine, such as bradycardia, urinary retention, ventricular tachycardia, apnoea, etc., were more common. However, we have also identified novel potential ADR signals that are not delineated in the specification and warrant further assessment, such as foetal acidosis, respiratory distress and neurotoxicity of bupivacaine, while for liposomes, they include impaired gastric emptying and cardiogenic shock. In addition, liposomal bupivacaine prolongs analgesia, while carries risks of gastrointestinal reaction, cardiac and neurotoxicity compared with bupivacaine, so routine follow-up after local anesthetic use needs to be extended simultaneously to ensure the safety risks associated with delayed effects, and patients might be educated to recognize AEs signs about liposomal bupivacaine.

Liposomal bupivacaine and conventional bupivacaine share an identical pharmacodynamic profile: these anesthetic agents achieve their clinical effects through direct interaction with voltage-gated sodium channels, consequently diminishing sodium ion transmembrane permeability and inhibiting neural impulse transmission. This inhibitory mechanism demonstrates dual dependency on both temporal factors and membrane potential, ultimately elevating the threshold required for action potential initiation, attenuating electrical signal propagation throughout neural pathways, and potentially inducing comprehensive functional neural blockade. While bupivacaine provides effective analgesia for several hours, its effect diminishes relatively quickly. Liposomal bupivacaine, on the other hand, provides extended analgesia over several days due to its slow-release formulation. Local anesthetic injections, such as bupivacaine, might possess potential cardiac toxicity (ie, cardiac arrest) and neurotoxicity (ie, seizures).<sup>28</sup> The CNS exhibits greater vulnerability to local anesthetic toxicity relative to cardiovascular structures. Initial CNS toxicity manifestations present as excitatory phenomena resulting from preferential inhibition of central inhibitory pathways, characterized by shivering, muscular fasciculations, and tremors, potentially escalating to generalized tonic-clonic seizure activity. With progressive elevation of local anesthetic plasma concentrations, comprehensive blockade of both inhibitory and excitatory neural pathways occurs, precipitating generalized CNS depression. Cardiovascular toxicity from local anesthetics demonstrates a characteristic biphasic response pattern: the initial phase, coinciding with central nervous system excitation, features sympathetic nervous system activation producing tachycardia and hypertension that may temporarily mask the direct myocardial depressant properties of the anesthetic agent. This initial phase subsequently transitions to cardiac rhythm disturbances and pronounced contractile dysfunction that ultimately supersede sympathetic stimulation as plasma concentrations continue to increase, potentially progressing to complete cardiovascular collapse.<sup>29</sup> Additionally, several reports regarding related myotoxicity have emerged.<sup>30</sup> Consequently, it is rational that with novel delayed formulations of local anesthetics, particularly bupivacaine, the risk of this toxicity could escalate. This complicates postoperative monitoring, particularly in outpatient settings, where follow-up may not be as rigorous. Regarding slow-release

for liposomal bupivacaine, patients may experience AEs after being discharged, making it harder to promptly address complications. Educate patients to monitor for postoperative complications such as hematoma and infection. Prolonged anesthesia may delay symptom awareness, making early detection crucial.

Liposomal bupivacaine demonstrates improved safety profiles compared to conventional bupivacaine. Animal studies in rabbits required twice the dose of liposomal formulation to induce seizures and ventricular arrhythmias.<sup>31</sup> Human trials with supraphysiological doses (300–750 mg) showed no clinically significant QTc prolongation and low incidence of tachy/bradycardia, exceeding the FDA-approved 266 mg maximum.<sup>32</sup> Despite these differences, both formulations are associated with potential ADRs, primarily affecting the cardiovascular and nervous systems. Bupivacaine's high lipid solubility enables blood–brain barrier penetration, increasing risks of neuro/cardiotoxicity at elevated doses. Its potassium channel blockade may trigger severe arrhythmias and cardiovascular collapse in overdose scenarios. Common adverse effects of bupivacaine include bradycardia, hypotension, and seizures were identified in the current study. Liposomal bupivacaine shares these risks but is associated with fewer instances of systemic toxicity due to its gradual release. However, it is linked to some delayed adverse events, including prolonged numbness, motor deficits, and, in rare cases, delayed cardiovascular reactions. Both drugs have been reported to cause off-label adverse reactions when used outside their approved indications, emphasizing the need for strict adherence to dosing guidelines.

The AEs of bupivacaine on the fetus is another important consideration, given our discovery that foetal heart rate deceleration abnormality, acidosis, bradycardia, and baseline foetal heart rate variability disorder are fetal related positive signals. In severe cases, fetal distress may occur, necessitating immediate medical intervention or emergency delivery. Liposomal bupivacaine is absolutely contraindicated for obstetric paracervical blocks due to documented fetal bradycardia and death. This restriction aligns with animal studies demonstrating embryogenic toxicity during critical developmental phases.<sup>33</sup> The risk of adverse effects in the fetus further underscores the need for careful dosing and monitoring during the administration of bupivacaine in obstetric procedures.

This study highlights pharmacosurveillance's unique strengths in complementing pivotal trials: access to diverse global populations typically excluded from pre-marketing studies and comprehensive monitoring of all event types. However, this study also has inevitable limitations. First, this study relied on post-marketing surveillance databases, ie, FAERS database. The FAERS database's voluntary reporting system may introduce data limitations, including underreporting, duplication, incompleteness, and notoriety bias, potentially affecting study outcomes. For example, in this study, the outcome of AEs for liposomal bupivacaine was unknown in 30.8% and bupivacaine in 44.2%, which may bias the analysis of results. Second, the FAERS database lacks detailed patient-level covariates, such as comorbidities, concomitant medications, the type of anesthesia, and surgical procedures. These missing data make it challenging to control for potential confounders that may influence the occurrence of ADRs. Third, FAERS cannot definitively establish causality between bupivacaine, liposomal bupivacaine, and reported AEs. In addition, this study only demonstrated and discussed the two drugs without a comparative analysis. Moreover, levobupivacaine was not included in this discussion due to its small number of entries in the FAERS database, PS only 40 cases. Another limitation is the potential for bias in data interpretation, as the study does not account for variations in clinical practice or off-label uses of these anesthetics, which may influence the incidence and types of adverse events observed.

## Conclusion

This study validates previously established safety concerns for liposomal and conventional bupivacaine while identifying novel ADR signals requiring further investigation, such as impaired gastric emptying and cardiogenic shock for liposomal bupivacaine. Although liposomal bupivacaine provides prolonged analgesia, it carries risks of delayed AEs, including gastrointestinal, cardiac, and neurological toxicities. These risks emphasize the necessity for extended postoperative monitoring, particularly in outpatient settings, where delayed complications may go unnoticed. Additionally, patient education on recognizing signs of AEs, especially for liposomal formulations, is critical to ensure timely medical intervention. Both formulations require cautious use and monitoring, highlighting the need for ongoing pharmacosurveillance to ensure safe clinical application.

## Ethical Approval Statement

This study utilized data from a publicly available, open-source database. According to the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (effective February 18, 2023, China), research involving publicly available datasets is exempt from additional ethical review by an Institutional Review Board (IRB) or ethics committee (Article 32, Items 1 and 2).

## Acknowledgment

The authors thank the FDA Adverse Event Reporting System (FAERS).

## Author Contributions

Dong Xu Chen and Xuan Ming Chen contributed to execution, data acquisition, analysis, interpretation, and drafting of the manuscript. Yi Da Wang and Shou Ming Chen contributed to conception, study design, revising or critically reviewing the manuscript and final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted and take responsibility for all aspects of the work.

## Funding

This study was supported by the Science and Technology Department of Sichuan Province (No. 2024NSFSC1679 to Dong Xu Chen) and Chengdu Science and Technology Department - Technological Innovation R&D Project (General Project. No. 2024-YF05-00339-SN to Dong Xu Chen).

## Disclosure

The authors declare no competing interests.

## References

- Gerbershagen HJ, Aduckathil S, van Wijck AJM, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology*. 2013;118(4):934–944. doi:10.1097/ALN.0b013e31828866b3
- Pirie K, Traer E, Finnis D, Myles PS, Riedel B. Current approaches to acute postoperative pain management after major abdominal surgery: a narrative review and future directions. *Br J Anaesth*. 2022;129(3):378–393. doi:10.1016/j.bja.2022.05.029
- Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367(9522):1618–1625. doi:10.1016/S0140-6736(06)68700-X
- Frieden TR, Houry D. Reducing the risks of relief—the CDC Opioid-prescribing guideline. *N Engl J Med*. 2016;374(16):1501–1504. doi:10.1056/NEJMp1515917
- Manchikanti L, Abdi S, Atluri S, et al. American society of interventional pain physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: part 2—guidance. *Pain Physician*. 2012;15(3 Suppl):S67–116.
- LF C, MS A, C D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clin J Pain*. 2008;24.
- Kleeman-Forsthuber L, Pollet A, Johnson RM, Boyle J, Jennings JM, Dennis DA. Evaluation of low-dose versus high-dose opioid pathway in opioid-naïve patients after total knee arthroplasty. *Arthroplasty Today*. 2022;14:81–85. doi:10.1016/j.artd.2021.11.019
- Saied NN, Helwani MA, Weavind LM, Shi Y, Shotwell MS, Pandharipande PP. Effect of anaesthesia type on postoperative mortality and morbidities: a matched analysis of the NSQIP database. *Br J Anaesth*. 2017;118(1):105–111. doi:10.1093/bja/aew383
- Macfarlane AJR, Gitman M, Bornstein KJ, El-Boghdady K, Weinberg G. Updates in our understanding of local anaesthetic systemic toxicity: a narrative review. *Anaesthesia*. 2021;76(Suppl 1):27–39. doi:10.1111/anae.15282
- Xuan C, Yan W, Wang D, et al. The facilitatory effects of adjuvant pharmaceuticals to prolong the duration of local anesthetic for peripheral nerve block: a systematic review and network meta-analysis. *Anesth Analg*. 2021;133(3):620–629. doi:10.1213/ANE.0000000000005640
- Zadrazil M, Marhofer P, Opfermann P, et al. Liposomal bupivacaine for peripheral nerve blockade: a randomized, controlled, crossover, triple-blinded pharmacodynamic study in volunteers. *Anesthesiology*. 2024;141(1):24–31. doi:10.1097/ALN.0000000000004988
- Viscusi E, Gimbel JS, Pollack RA, Hu J, Lee G-C. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in bunionectomy: Phase III results from the randomized EPOCH 1 study. *Reg Anesth Pain Med*. 2019.
- Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. *Dis Colon Rectum*. 2011;54(12):1552–1559. doi:10.1097/DCR.0b013e318232d4c1
- Golf M, Daniels SE, Onel E. A Phase 3, randomized, placebo-controlled trial of DepoFoam® bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. *Adv Ther*. 2011;28(9):776–788. doi:10.1007/s12325-011-0052-y
- Small C, Laycock HJC. Acute postoperative pain management. *Br J Surg*. 2020;107.
- Administration USF and D. EXPAREL (bupivacaine liposome injectable suspension). 2018.
- Jing Y, Liu J, Ye Y, et al. Multi-omics prediction of immune-related adverse events during checkpoint immunotherapy. *Nat Commun*. 2020;11(1):4946. doi:10.1038/s41467-020-18742-9

18. Raschi E, Fusaroli M, Giunchi V, et al. Adrenal insufficiency with anticancer tyrosine kinase inhibitors targeting vascular endothelial growth factor receptor: analysis of the FDA adverse event reporting system. *Cancers*. **2022**;15(1):14. doi:10.3390/cancers15010014
19. Xia S, Gong H, Zhao Y, et al. Tumor lysis syndrome associated with monoclonal antibodies in patients with multiple myeloma: a pharmacovigilance study based on the FAERS database. *Clin Pharmacol Ther*. **2023**;114(1):211–219. doi:10.1002/cpt.2920
20. Caster O, Aoki Y, Gattepaille LM, Grundmark B. Disproportionality analysis for pharmacovigilance signal detection in small databases or subsets: recommendations for limiting false-positive associations. *Drug Saf*. **2020**;43(5):479–487. doi:10.1007/s40264-020-00911-w
21. Yan Y-D, Zhao Y, Zhang C, et al. Toxicity spectrum of immunotherapy in advanced lung cancer: a safety analysis from clinical trials and a pharmacovigilance system. *EClinicalMedicine*. **2022**;50:101535. doi:10.1016/j.eclinm.2022.101535
22. Zhou C, Peng S, Lin A, et al. Psychiatric disorders associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA adverse event reporting system (FAERS) database. *EClinicalMedicine*. **2023**;59:101967. doi:10.1016/j.eclinm.2023.101967
23. Zhu H, Qu Y, Du Z, et al. Mining and analysis of adverse event signals of cariprazine based on the real-world data of FAERS database. *J Affect Disord*. **2024**;347:45–50. doi:10.1016/j.jad.2023.11.076
24. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol*. **1998**;54(4):315–321. doi:10.1007/s002280050466
25. Chen C, Ding L, Fu F, Xiao J. Updated insights on dementia-related risk of sacubitril/valsartan: a real-world pharmacovigilance analysis. *CNS Neurosci Ther*. **2023**;29(9):2548–2554. doi:10.1111/cns.14195
26. Practical aspects of signal detection in pharmacovigilance: report of CIOMS working group VIII. **2010**.
27. Zhai Y, Ye X, Hu F, et al. Endocrine toxicity of immune checkpoint inhibitors: a real-world study leveraging US Food and Drug Administration adverse events reporting system. *J Immunother Cancer*. **2019**;7.
28. White JL, Durieux ME. Clinical pharmacology of local anesthetics. *Anesthesiol Clin North America*. **2005**;23(1):73–84. doi:10.1016/j.atc.2004.11.005
29. Casati A, Putzu M. Bupivacaine, levobupivacaine and ropivacaine: are they clinically different?. *Best Pract Res Clin Anaesthesiol*. **2005**;19(2):247–268. doi:10.1016/j.bpa.2004.12.003
30. Zink W, Seif C, Bohl JRE, et al. The acute myotoxic effects of bupivacaine and ropivacaine after continuous peripheral nerve blockades. *Anesth Analg*. **2003**;97(4):1173–1179. doi:10.1213/01.ANE.0000080610.14265.C8
31. Reactions A, Interactions D, Forms D, Pacira Pharmaceuticals Inc. *Exparel (Bupivacaine Liposomal Injectable Suspension) [Prescribing Information]*. San Diego, CA: Pacira Pharm Inc; **2012**.
32. Naseem A, Harada T, Wang D, et al. Bupivacaine extended release liposome injection does not prolong QTc interval in a thorough QT/QTc study in healthy volunteers. *J Clin Pharmacol*. **2012**;52(9):1441–1447. doi:10.1177/0091270011419853
33. Sorenson E, Chesnut C. Liposomal bupivacaine: a review and applications to dermatologic surgery. *Dermatol Surg*. **2019**;45(1):68–73. doi:10.1097/DSS.0000000000001628

## Journal of Pain Research

### Publish your work in this journal

The Journal of Pain Research is an international, peer reviewed, open access, online journal that welcomes laboratory and clinical findings in the fields of pain research and the prevention and management of pain. Original research, reviews, symposium reports, hypothesis formation and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-pain-research-journal>

**Dovepress**  
Taylor & Francis Group