Adverse Events Associated with Analgesics Used for Osteoarthritis Pain: Analysis of Post-Marketing Data

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Introduction

- Osteoarthritis (OA) is a chronic, degenerative joint disease affecting approximately 300 million adults worldwide[1]
- Pain is the principal reason why patients with OA seek medical attention[2]
- Analgesics for managing OA pain include acetaminophen (paracetamol), nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, and opioids[3]
- Randomized controlled trials (RCTs) with OA analgesics often exclude patient subgroups encountered in clinical practice (e.g., those with comorbidities or using analgesic polypharmacy) and may have inadequate follow-up times to monitor long-term safety
- Therefore, there is a need to assess adverse event (AE) risks associated with OA analgesics in the real-world setting

Study Objective

- To assess AE risks associated with the most commonly used analgesic classes (acetaminophen, NSAIDs, tramadol, and opioids) for OA pain in the United States

Methods

Study Design and Data Source

- This retrospective, observational study included AE cases that were obtained from the US Food and Drug Administration Adverse Event Reporting System (FAERS)[4] database between January 1, 2001, and June 30, 2019
- The FAERS database contains post-marketing AE reports
- Study agents included all approved formulations (prescribed or over-the-counter [OTC]) of acetaminophen, NSAIDs, tramadol, and Drug Enforcement Administration (DEA) class II/III opioids (**Table 1**)

Table 1 Study Drugs[a]

Class	Drugs
Acetaminophen	Acetaminophen (paracetamol)
NSAIDs	Aspirin, celecoxib, diclofenac, diclofenac plus misoprostol, etodolac, ibuprofen, indomethacin, ketoprofen, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac
Tramadol	Tramadol, tramadol plus acetaminophen
DEA class II/III opioids	Benzhydrocodone plus acetaminophen, codeine plus acetaminophen, fentanyl, hydrocodone, hydrocodone plus acetaminophen, hydrocodone plus ibuprofen, hydromorphone, morphine, oxycodone, oxycodone plus acetaminophen, oxycodone plus aspirin, oxycodone plus ibuprofen, tapentadol

[a]Used in patients with OA as a reported condition.

Identification of AE Cases

- AE risks were identified from the drug labels
  - 16 risks identified for NSAIDs were applied to acetaminophen and NSAIDs
  - 18 risks identified for opioids were applied to tramadol and opioids
- AE reports voluntarily submitted to FAERS by healthcare professionals, consumers, and drug manufacturers were evaluated
- Cases were narrowed for the following Medical Dictionary for Regulatory Activities preferred terms: “osteoarthritis,” “interspinous osteoarthritis,” “nodal osteoarthritis,” “rapidly progressive osteoarthritis,” and “spinal osteoarthritis”
- Primary suspect cases (i.e., those in which the reporter listed the specified drug as the primary suspect cause associated with the AE) were identified
- Duplicate cases were excluded

Statistical Analysis

- The strength of the association between the specific analgesic class and the AE was quantified using reporting odds ratios (RORs)[5,6]
- RORs were computed using a 2 × 2 contingency table for each given drug (X) and AE (Y) (**Table 2**)
- RORs were calculated for the specific analgesic used for OA pain versus all drugs for any diagnosis (non-stratified analysis) and versus drugs with OA as a reported condition (stratified analysis)
- A significant elevated association occurred if the lower limit of the ROR 95% confidence interval (CI) was >1

Table 2 ROR Calculation (2 × 2 Contingency Table)[a]

	Adverse Event (Y)	Not Adverse Event (Y)	Total	Formula
Drug (X)	*a*	*b*	*a* + *b*	$ROR = \frac{a/b}{c/d}$
Not Drug (X)	*c*	*d*	*c* + *d*	
Total	*a* + *c*	*b* + *d*	*a* + *b* + *c* + *d*	

[a]The number of reports with the drug with the AE is shown as *a* (events in exposed), the number of reports with the drug without the AE is shown as *b* (non-events in exposed), the number of reports with other drugs with the same AE is shown as *c* (events in non-exposed), and the number of reports with other drugs without the AE is shown as *d* (non-events in non-exposed). An ROR <1.0 indicates that the odds of AE reports for drug X are lower relative to the odds of AE reports in the comparator group of drugs and is not necessarily an inference of any protective effect.

Results

Primary Suspect AE Case Counts With OA Analgesics

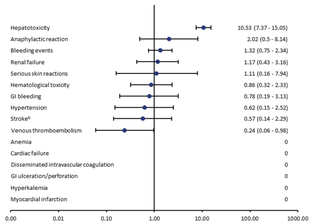
- Cumulative primary suspect case counts in AE reports with OA being the reported condition were greatest for NSAIDs (n = 7,128), followed by DEA class II/III opioids (n = 938), tramadol (n = 296), and acetaminophen (n = 149)

AE Risks Associated With Acetaminophen

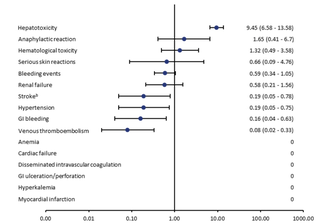
- Hepatotoxicity was the only AE among the 16 labeled AEs that had a significantly elevated risk associated with acetaminophen in comparison with all drugs (**Figure 1A**) and with drugs used for OA (**Figure 1B**)

Figure 1 AE Risks Associated With Acetaminophen

A. ROR (95% CI) for acetaminophen used for OA pain versus all drugs for any diagnosis (non-stratified analysis)[a]



B. ROR (95% CI) for acetaminophen used for OA pain versus drugs with OA as a reported condition (stratified analysis)[a]



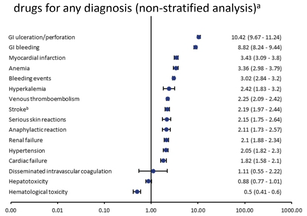
[a]An ROR >1.0 indicates that the odds of AE reports for drug X are higher relative to the odds of AE reports in the comparator group of drugs.
[b]Includes hemorrhagic stroke, ischemic stroke, and transient ischemic attack.

AE Risks Associated With NSAIDs

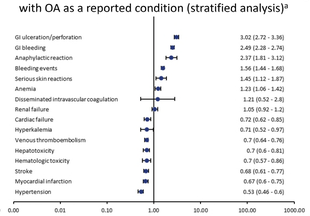
- Risks for 13 of the 16 labeled AEs were significantly elevated with NSAIDs in comparison with all drugs (**Figure 2A**)
  - Risks were elevated for gastrointestinal (GI) ulceration/perforation, GI bleeding, myocardial infarction, anemia, bleeding events, hyperkalemia, venous thromboembolism, stroke, serious skin reactions, anaphylactic reaction, renal failure, hypertension, and cardiac failure
- Risks for 6 of the 16 labeled AEs were significantly elevated for NSAIDs in comparison with drugs used for OA (**Figure 2B**)
  - Risks were elevated for GI ulceration/perforation, GI bleeding, anaphylactic reaction, bleeding events, serious skin reactions, and anemia
  - Cardiovascular AE risks were not elevated in the comparison with drugs used for OA, possibly because patients with OA, who are typically older, may have had underlying cardiovascular risks

Figure 2 AE Risks Associated With NSAIDs

A. ROR (95% CI) for NSAIDs used for OA pain versus all drugs for any diagnosis (non-stratified analysis)[a]



B. ROR (95% CI) for NSAIDs used for OA pain versus drugs with OA as a reported condition (stratified analysis)[a]



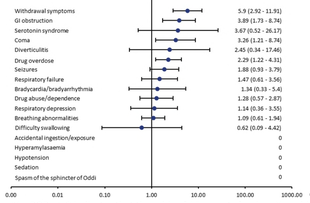
[a]An ROR >1.0 indicates that the odds of AE reports for drug X are higher relative to the odds of AE reports in the comparator group of drugs.
[b]Includes hemorrhagic stroke, ischemic stroke, and transient ischemic attack.

AE Risks Associated With Tramadol

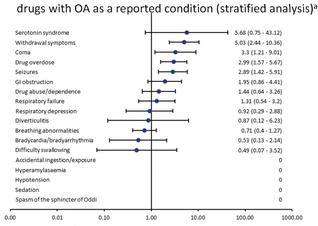
- Risks for 4 of the 18 labeled AEs were significantly elevated with tramadol in comparison with all drugs (**Figure 3A**)
  - Risks were elevated for withdrawal symptoms, GI obstruction, coma, and drug overdose
- Risks for 4 of the 18 labeled AEs were significantly elevated with tramadol in comparison with drugs used for OA (**Figure 3B**)
  - Risks were elevated for withdrawal symptoms, coma, drug overdose, and seizures

Figure 3 AE Risks Associated With Tramadol

A. ROR (95% CI) for tramadol used for OA pain versus all drugs for any diagnosis (non-stratified analysis)[a]



B. ROR (95% CI) for tramadol used for OA pain versus drugs with OA as a reported condition (stratified analysis)[a]



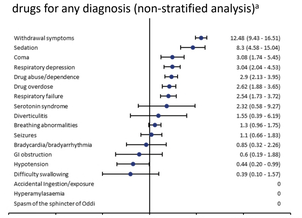
[a]An ROR >1.0 indicates that the odds of AE reports for drug X are higher relative to the odds of AE reports in the comparator group of drugs.

AE Risks Associated With Opioids

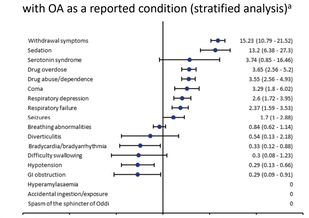
- Risks for 7 of the 18 labeled AEs were significantly elevated with opioids in comparison with all drugs (**Figure 4A**)
  - Risks were elevated for withdrawal symptoms, sedation, coma, respiratory depression, drug abuse/dependence, drug overdose, and respiratory failure
- These same 7 labeled AEs had elevated risks with opioids in comparison with drugs used for OA (**Figure 4B**)
  - However, the risk magnitudes were generally higher in the comparison with drugs used for OA (**Figure 4B**) than in the comparison with all drugs (**Figure 4A**), suggesting that opioids present greater AE risks in patients with OA
  - The risk for GI obstruction was significantly reduced in the comparison with drugs used for OA, possibly because patients with OA, who are typically older, may have been using therapy for constipation

Figure 4 AE Risks Associated With Opioids

A. ROR (95% CI) for opioids used for OA pain versus all drugs for any diagnosis (non-stratified analysis)[a]



B. ROR (95% CI) for opioids used for OA pain versus drugs with OA as a reported condition (stratified analysis)[a]



[a]An ROR >1.0 indicates that the odds of AE reports for drug X are higher relative to the odds of AE reports in the comparator group of drugs.

Study Limitations

- Denominator not representative of the general population (only represented patients who had AEs from the medication)
- Lack of control for confounding factors
- Lack of information on the use of multiple medications, OTC versus prescription analgesics, non-selective versus selective NSAIDs, therapies that may have decreased AE risk (e.g., proton pump inhibitors), and acute versus chronic analgesic treatment
- Inability to extrapolate results to other geographic regions and to establish a causal relationship between an AE and a drug in the FAERS database

Summary

- This retrospective, observational study using real-world data demonstrated significantly elevated AE risks with OA analgesics in the United States, including risks for potentially serious/life-threatening AEs (e.g., hepatotoxicity with acetaminophen; GI ulceration/perforation and bleeding with NSAIDs; and withdrawal symptoms, coma, and drug overdose with tramadol and opioids)
- These risks were consistent with the known safety profiles from RCTs
- Higher risk magnitudes with opioids versus drugs used for OA than with opioids versus all drugs suggest that opioids present greater risks in patients with OA than in those with any diagnosis
- The identified AE risks should be considered when selecting OA analgesics, especially in patients with comorbidities and using analgesic polypharmacy
- These risks highlight the need for innovative and safer agents for managing OA pain

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Disclosures

Raveendhara R. Bannuru reports personal fees for consultancy from Regeneron Pharmaceuticals, Inc.; Mo Dimbil is an employee of Advera Health Analytics, a consulting firm that received payment from Teva Pharmaceutical Industries Ltd. and Regeneron Pharmaceuticals, Inc., to conduct this research; Wenhui Wei and Clotilde Huyghues-Despointes are employees of Regeneron Pharmaceuticals, Inc.; Susan Colilla, Joanne E. Nettleship, and Ravi Iyer are employees of Teva Pharmaceutical Industries Ltd.

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