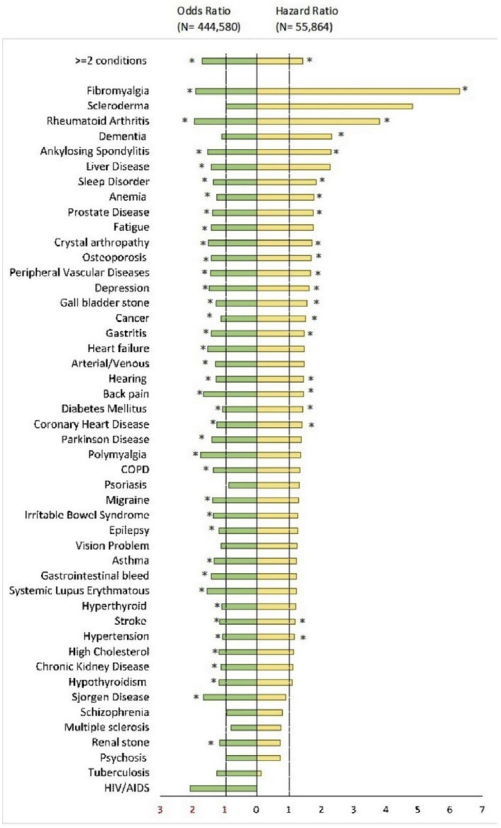
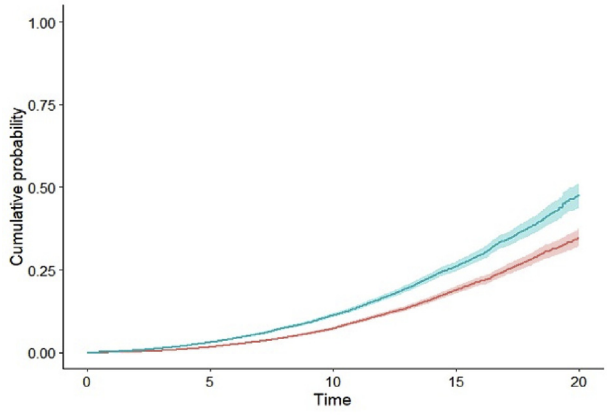
Conclusions: The burden of comorbidity is higher in people with OA, both at and after the initial diagnosis, than people without OA. The temporal association reported merits further investigation with regard to causality.

Figure 1 Comparison of Odds Ratios and Hazard Ratios for comorbidities before and after OA diagnosis



P value <0.05; COPD-Chronic obstructive pulmonary diseases

Figure 2 Cumulative probabilities of having two or more comorbidities in OA patients and matched controls without OA



Red line- Non-Osteoarthritis; Blue line- Osteoarthritis; Shaded area represents 95% CI

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ADVERSE EVENTS ASSOCIATED WITH ANALGESICS USED FOR OSTEOARTHRITIS PAIN: ANALYSIS OF POST-MARKETING DATA

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Purpose: Several pharmacological interventions are available for treating patients with osteoarthritis (OA) pain. Whilst each of these therapies is associated with potential adverse events (AEs), those risks have not been comprehensively quantified in the real-world setting. Real-world data for AEs associated with OA analgesics may be useful to patients and healthcare providers to better assess treatment risk when considered within the context of an individual's medical history and existing comorbidities. The aim of this study was to analyze post-marketing data for AEs associated with analgesics most commonly used for OA pain.

Methods: Data were obtained from the US Food and Drug Administration Adverse Event Reporting System (FAERS) database between January 1, 2001, and June 30, 2019. We identified the known labeled risks associated with nonsteroidal anti-inflammatory drugs (NSAIDs), Drug Enforcement Administration (DEA) class II/III opioids, tramadol, and acetaminophen from the boxed warning, warnings, precautions, and adverse reactions sections of the drug labels for these agents. Based on this research, lists of custom Medical Dictionary for Regulatory Activities query searches were developed to identify AE cases. Cumulative case counts on primary suspect outcomes (i.e., cases in which the reporter listed the specified drug as the primary suspect cause associated with the AE) were calculated, and all cases were required to have OA as a reported condition. The reporting odds ratio (ROR) approach was used to compute a measure akin to the odds ratio to quantify the strength of the association between the specific aforementioned analgesic classes and AEs reported in a post-marketing safety database such as FAERS. RORs were calculated by dividing the odds of a specific AE occurring with the specific analgesic used for OA pain by the odds of that AE occurring with all drug classes (non-stratified) or only drug classes with OA as a reported condition (stratified). RORs greater than 1 indicated an elevated association between the specific drug class and the AE compared with the other drug classes, whereas RORs below 1 indicated lack of such an association. The limits of the 95% confidence intervals of ROR were obtained via an approximation of the normal distribution. The lower limit of this distribution (ROR05) was calculated and reported for both the non-stratified and stratified RORs, providing 95% certainty that the true mean of the population was at or above the number reported.

Results: During the study period in the FAERS database, the cumulative primary suspect case counts, with OA being a reported condition, were as follows: 7,128 for NSAIDs, 938 for DEA class II/III opioids, 296 for tramadol, and 149 for acetaminophen. For primary suspect AE cases overall, non-stratified ROR05s were greater than 1 (indicative of higher odds of AEs compared with the other drug classes) for 13 of the 16 expected safety issues for NSAIDs, 7 of the 18 for DEA class II/III opioids, 4 of the 18 for tramadol, and 1 of the 16 for acetaminophen (tables 1 and 2). ROR05s were the highest for gastrointestinal (GI) ulceration/perforation (9.67), GI bleeding (8.24), and myocardial infarction (3.09) for NSAIDs; withdrawal symptoms (9.43), sedation (4.58), and drug abuse/dependence (2.13) for DEA class II/III opioids; withdrawal symptoms (2.92), GI obstruction (1.73), and drug overdose (1.22) for tramadol; and hepatotoxicity (7.37) for acetaminophen. Stratified ROR05 results showed similar trends but with different magnitudes. For primary suspect AE cases, when comparing to other drugs with OA as a reported condition, stratified ROR05s for NSAIDs were 2.72 for GI ulceration/perforation and 2.28 for GI bleeding. For DEA class II/III opioids, stratified ROR05s were 10.79 for withdrawal symptoms, 6.38 for sedation, and 2.56 for drug abuse/dependence. For tramadol, an association was demonstrated for seizures (1.42) when comparing to other drug classes with OA as a reported condition, which was not apparent in the non-stratified results. For acetaminophen, the stratified ROR05 was 6.58 for hepatotoxicity. Of all studied primary suspect cases with OA as a reported condition, serious AE cases (defined as death, life-threatening AEs, hospitalization, disability/permanent damage, congenital anomalies/birth defects, AEs requiring intervention to prevent permanent impairment/damage, or other serious AEs) comprised 55.7% (83/149) of all studied AEs with acetaminophen, 63.8% (598/938) with DEA class II/III opioids, 75.4%, (5,371/7,128) with NSAIDs, and 90.5% (268/296) with tramadol.

Conclusions: This study provides a comprehensive and quantitative evaluation of the safety issues with drugs used to treat patients with OA pain in the real-world setting. The results of our study demonstrate that the most commonly used OA analgesics are associated with elevated risks for certain AEs compared with the other drug classes, underscoring the need for new and safer

therapies for OA pain. These data will help patients and healthcare providers to better assess the benefit-risk profiles of these analgesics before incorporating them into treatment regimens. This study was limited by the lack of control for other confounding factors and the potential for use of multiple medications in individual patients. Further research is required to evaluate the downstream effects of the studied AEs (e.g., medical costs) and to benchmark these AEs against the safety profiles for the evaluated analgesics reported in randomized clinical trials.

Table 1. Non-stratified ROR05s for NSAIDs and acetaminophen with OA as a reported condition compared with all drugs classes*

Known labeled risks	NSAIDs	Acetaminophen
GI ulceration/perforation	9.67	–
GI bleeding	8.24	0.19
Myocardial infarction	3.09	–
Anemia	2.98	–
Bleeding events	2.84	0.75
Venous thromboembolism	2.09	0.06
Stroke	1.97	0.14
Renal failure	1.88	0.43
Hyperkalemia	1.83	–
Hypertension	1.82	0.15
Cardiac failure	1.58	–
Serious skin reactions	1.75	0.16
Anaphylactic reaction	1.73	0.50
Hepatotoxicity	0.77	7.37
Disseminated intravascular coagulation	0.55	–
Hematological toxicity	0.41	0.32

*Non-stratified ROR was calculated by dividing the odds of a specific AE occurring with the specific analgesic used for OA pain by the odds of that AE occurring with all other drug classes. The ROR05 provided 95% certainty that the true mean of the population was at or above the number reported. ROR greater than 1 indicated an elevated association between the specific drug class and the AE.

Table 2. Non-stratified ROR05s for DEA class II/III opioids and tramadol with OA as a reported condition compared with all drugs classes*

Known labeled risks	DEA class II/III opioids	Tramadol
Withdrawal symptoms	9.43	2.92
Sedation	4.58	–
Drug abuse/dependence	2.13	0.57
Respiratory depression	2.04	0.36
Drug overdose	1.88	1.22
Coma	1.74	1.21
Respiratory failure	1.73	0.61
Breathing abnormalities	0.96	0.61
Seizures	0.66	0.93
Serotonin syndrome	0.58	0.52
Diverticulitis	0.39	0.34
Bradycardia/bradyarrhythmia	0.32	0.33
Hypotension	0.20	–
GI obstruction	0.19	1.73
Difficulty swallowing	0.10	0.09
Accidental ingestion/exposure	–	–
Hyperamylasemia	–	–
Spasm of the sphincter of Oddi	–	–

*Non-stratified ROR was calculated by dividing the odds of a specific AE occurring with the specific analgesic used for OA pain by the odds of that AE occurring with all other drug classes. The ROR05 provided 95% certainty that the true mean of the population was at or above the number reported. ROR greater than 1 indicated an elevated association between the specific drug class and the AE.

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IDENTIFYING MOLECULAR SIGNATURES UNDERLYING KNEE OSTEOARTHRITIS THROUGH TRANSCRIPTOMICS

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Purpose: Osteoarthritis (OA) is a pervasive, lifelong disorder targeting joints, and is a leading cause of mobility-disability worldwide. Yet, there are no successful pharmacological approaches that can stop its progression. This substantial unmet need can be attributed to the complex and poorly understood molecular mechanisms which initiate and drive this disease. Total RNA sequencing is a powerful technique which enables the identification of active genes driving disease progression, as well as non-coding epigenetic changes that influence whether gene changes result in functional changes. Due to the heterogeneity in OA, it is increasingly viewed as a disease with different sub-types or phenotypes which may influence approaches to diagnoses and therapy.
Methods: We have used our large-scale knee OA patient biobank (n=750) to perform total RNA sequencing (Illumina Truseq-Stranded Total RNA, NextSeq550) on synovium samples from 50 late stage (Kellgren-Lawrence Grade 3/4) radiographic knee OA patients. We have developed separate bioinformatic pipelines for mRNA, long non-coding RNA and circular RNA. We have also collected substantive anthropometric, pain and functional data in order to elucidate relationships between clinical variables and molecular signatures.
Results: RNA extracted from synovium had an average RIN of 8.6±0.72, and RNA sequencing metrics indicate an average Q30 of over 90% indicating 99.9% base-call accuracy. After filtering, 19,857 genes were expressed in synovium. Sex, BMI (normal, overweight, obese), synovial inflammation, 1 year response to surgical intervention (WOMAC MCID, patient response), as well as baseline pain (WOMAC pain, stiffness, function) distinguished a number of differentially expressed genes. Multivariate analysis further indicated that subsets of genes can be distinguished by synovial inflammation, and responder status after adjusting for other factors. Unsupervised cluster analysis indicates that molecular signatures between patients cannot be distinguished by clinical variables alone, and these variables themselves do not self-segregate patient clusters.
Conclusions: Transcriptomics of late-stage OA synovial tissue indicates a number of differentially regulated genes by demographic and clinical variables. Phenotyping of these patients indicates that clinical variables alone cannot distinguish sub-groups, but combinations of these variables with molecular signatures or molecular signature independent of clinical phenotype may be able to distinguish patient sub-groups. Future directions include incorporation of long non-coding and circular RNA molecular signatures to form a comprehensive molecular profile of each patient, as well as RNA sequencing of other joint tissues within the same cohort.

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IS THE PARADOXICAL INCREASE OF CARTILAGE THICKNESS IN CTGF NULL MICE DUE TO COMPENSATION BY ACTIVIN A

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Purpose: Previously we identified connective tissue growth factor (CTGF) by proteomic analysis of the pericellular matrix (PCM), and showed that, like other PCM bound proteins, it was released upon cartilage injury. Postnatal, pan tissue deletion of CTGF in adult mice resulted in thicker knee cartilage which protected the mouse from osteoarthritis. This appeared to contradict the predicted phenotype, as we also showed that CTGF was covalently bound to latent TGFβ (transforming growth factor beta) and controlled the bioavailability of TGFβ (an anabolic factor) in cartilage. As loss of CTGF in vivo also caused a paradoxical increase in canonical Smad2 signalling, we hypothesised that another Smad2 activating ligand may be compensating for CTGF/TGFβ loss. The role for activin A was explored.
Methods: $Ctgf^{fl/fl}$ and $Inhba^{fl/fl}$ mice were acquired under MTA, courtesy of Andrew Leask and Marty Matzuk respectively. The mice were crossed with Ubi-Cre/ER^{T2} line (Jackson Laboratories) to generate $Ctgf^{fl/fl}$;Ubi-Cre/ER^{T2}, $Inhba^{fl/fl}$;Ubi-Cre/ER^{T2} and $Ctgf^{fl/fl}$;$Inhba^{fl/fl}$;UbiCre/ER^{T2} lines. Genetic deletion was induced at 4 weeks of age through daily injections of tamoxifen (50 mg/kg) intraperitoneally on three consecutive days. RT-PCR and western blot was used to confirm efficiency of deletion. Mice were culled at 6 weeks and auricular cartilage biopsy punches (4 mm diameter) were taken from the posterior distal ear region, embedded in paraffin and sectioned. Slides were imaged and cartilage thickness was measured using FIJI image processing package. For RNA