Opioid Reduction at the Population Level: The Leap from Randomized Controlled Trial to Real World Effectiveness

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Background: In 2018, the Charles Neer award recognized a randomized clinical trial for demonstrating a significant reduction in the number of narcotic naïve patients who subsequently became chronic opioid users following rotator cuff surgery (1). In parallel, several small RCTs demonstrated that the implementation of multimodal prescribing protocols (e.g., acetaminophen, non-steroidal anti-inflammatories) in addition to narcotic prescriptions reduced opioid use after arthroscopic surgery (2). While RCTs are the "gold standard" for evaluating safety and efficacy of new therapeutic agents, the results may not accurately represent the populations encountered in clinical practice due to the strict inclusion and exclusion criteria, rigorous quality standards, intense monitoring and most notably - patient volunteerism, (3). Internal validity is often achieved at the expense of external validity (generalizability). In contrast, real-world evidence - derived through sources outside the typical research setting – plays a critical role in evaluating the effectiveness of interventions across broader populations and under routine clinical conditions. The value of real-world data is increasingly recognized by regulatory bodies including the US Food and Drug Administration (FDA) and is being utilized to inform payers, clinicians and patients. The objective of this study was to evaluate the effectiveness of a combined pre-operative education and opioid prescribing protocol in reducing the number of chronic opioid users after surgery and the volume of opioids dispensed using a real-world pre-post intervention study.

Materials & Methods: This was a retrospective, pre-post intervention cohort study. All adult opioid-naïve patients who underwent outpatient shoulder surgery at a single sports medicine orthopaedic institution between 2013 and 2022 were included. Patients who had surgery between 2013 and 2018 comprised the **pre-intervention group**, during which time patients did not receive formal opioid education, and surgeons prescribed analgesics at their discretion (varying dosages, durations, and combinations of acetaminophen, ibuprofen, oxycodone, hydromorphone, codeine, and tramadol). In 2019, a standardized protocol was introduced at the institutional level, marking the beginning of the **post-intervention group** (2019–2022). The protocol consisted of a previously validated opioid education protocol combined with a standardized multimodal postoperative analgesic prescription. Under the standardized protocol, patients were instructed to take scheduled oral acetaminophen and ibuprofen for five days with opioids reserved for breakthrough pain as needed. Tramadol was selected as the protocol's narcotic as it had been rarely utilized at the institution prior to 2019 and could serve as a surrogate measure of surgeon compliance. The primary outcome was dispensed morphine milligram equivalents (MME) per patient, calculated using prescriptions filled in the first 180 post-operative days. A validated regional data repository tracking all narcotic prescriptions from any source (e.g., surgeon, primary care, emergency, etc.) was cross-referenced with the study cohort. T-tests were used to compare continuous variables between time periods, and Chi-square tests were used for categorical data. Relative risk (RR) and number needed to treat (NNT) to prevent one chronic opioid user were also calculated.

Results: A total of 4,176 opioid naïve patients who underwent outpatient shoulder surgery were identified of which 3,163 were pre-intervention and 1,013 were post-intervention (Table 1). Post-intervention, surgeon compliance to the prescription protocol (i.e., tramadol prescribed) was high at 79.6%. There was a 31% reduction in the overall amount of narcotics dispensed post-intervention (417.0 vs 287.8 MME; $p<0.001$) with 10.3% of patients not filling their narcotic prescription. There was a 47% RR reduction in the proportion of patients chronically utilizing opioids >180 days after surgery (5.8 vs 3.1%; $p<0.001$) and the NNT was 37 patients (95% CI, 23-86).

Conclusion/Discussion: The institution-wide implementation of a previously validated opioid education protocol combined with a standardized multimodal prescribing protocol resulted in a significant reduction in the volume of opioids dispensed and the proportion of patients who became chronic opioid users. This real-world study supports the scalability and compliance of such protocols to provide meaningful population level improvements to mitigate the opioid crisis.

[1]Cheesman Q, DeFrance M, Stenson J, et al. The effect of preoperative education on opioid consumption in patients undergoing arthroscopic rotator cuff repair: a prospective, randomized clinical trial-2-year follow-up. *J Shoulder Elbow Surg*. 2020;29(9):1743-1750. doi:10.1016/j.jse.2020.04.036

[2]Gazendam A, Ekhtiari S, Horner NS, et al. Effect of a Postoperative Multimodal Opioid-Sparing Protocol vs Standard Opioid Prescribing on Postoperative Opioid Consumption After Knee or Shoulder Arthroscopy. *JAMA*. 2022;328(13):1326-1335. doi:10.1001/jama.2022.16844

[3]Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. Adv Ther. 2018 Nov;35(11):1763-1774. doi: 10.1007/s12325-018-0805-y. Epub 2018 Oct 24. PMID: 30357570; PMCID: PMC6223979.

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Table 1. Patient characteristics and study outcomes.

Variable	Pre-intervention	Post-intervention	p-value
N	3,163	1,013	0.28
Mean age (95% CI)	49.2 (48.7, 49.6)	51.6 (50.6, 52.5)	<0.001
Sex (% Male)	72.4	69.0	0.04
Mental health diagnosis (%)	25.2	29.5	0.01
Patients filling tramadol prescription (%) *surrogate for surgeon compliance with intervention (standardized multimodal protocol)	6.4	79.6	<0.001
Patients not filling any opioid prescription (%)	8.5	10.3	0.13
Narcotics dispensed (MME/patient; 95% CI)	417.0 (402.6, 431.3)	287.7 (272.4, 303.0)	<0.001
Patients filling opioid prescription >180 days (%)	5.8	3.1	<0.001