Original Research Article

Hospital Pharmacy
1–8

DOI: 10.1177/00185787261474381
journals.sagepub.com/home/hpx
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When the Law Changes Therapy: Interrupted Time-Series Analysis of the Regulatory Impact on Intravenous Analgesic Consumption in 2 Italian Orthopaedic Hospitals (2021-2024)

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Abstract

Objectives: Tramadol is a centrally acting weak opioid widely used for moderate postoperative pain in orthopaedic surgery, so its regulatory status is directly relevant to hospital pharmacists. In November 2022 the Italian Ministry of Health reclassified tramadol as a controlled substance under Section A of Presidential Decree 309/1990. Its effect on surgical-hospital prescribing has not been systematically described. We quantified the change in consumption and expenditure of intravenous (IV) tramadol and of the IV non-steroidal anti-inflammatory drugs (NSAIDs) used as alternatives in 2 Italian orthopaedic IRCCS hospitals.

Methods: Retrospective 2-centre drug-utilisation study (Hospital A: 9100 procedures/year; Hospital B: 13 500/year) covering January 2021 to December 2024. Monthly dispensing and cost of IV tramadol, ketorolac, ketoprofen lysine and ibuprofen were extracted from the pharmaceutical management system. Use was expressed as Defined Daily Doses (DDDs) per 100 procedures. Pre- and post-policy periods were compared with a single-group interrupted time-series analysis using segmented linear regression with calendar-month indicators and Newey-West standard errors.

Results: Mean annual IV tramadol dispensing fell from 953 to 259 units at Hospital A (−72.8%) and from 2011 to 617 at Hospital B (−69.3%). Segmented regression showed immediate level changes for IV tramadol of $\beta_2 = -1.45$ at Hospital A ($P < .001$) and −2.60 at Hospital B ($P < .001$); expressed relative to the model-predicted pre-policy level at the intervention, these correspond to immediate reductions of approximately 57% and 63%. For IV ketorolac, level changes were +2.41 ($P = .012$) and +12.68 ($P < .001$). Aggregate IV-analgesic expenditure per 100 procedures rose from €18.96 to €25.99 at Hospital A (+37%) and from €47.20 to €412.73 at Hospital B (+774%); this between-centre difference was driven by Hospital B's high-cost ready-to-use IV ibuprofen bag, which accounted for about 93% of total post-policy expenditure and 99% of the increase at that centre.

Conclusions: The reclassification coincided with a marked reduction in IV tramadol use and a parallel rise in IV NSAID use. The rise in pharmacy expenditure was driven less by the regulatory shift than by the local formulary choice that accompanied it.

Keywords

tramadol, controlled substances, drug utilisation, defined daily dose, interrupted time series, orthopaedic surgery, postoperative pain, NSAIDs, pharmacoeconomics

Introduction

Tramadol is a centrally acting analgesic with a dual mechanism of action, weak μ-opioid receptor agonism combined with inhibition of serotonin and noradrenaline reuptake, long considered a workhorse of moderate postoperative analgesia, particularly in orthopaedic and trauma surgery. Its perceived safety relative to strong opioids contributed to widespread use in Europe over the past 2 decades, even as concerns about misuse, dependence and serotonergic toxicity grew.[2-4]

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In Italy, this trajectory changed on 17 November 2022, when the Ministry of Health amended Presidential Decree 309/1990 (DPR 309/90) and moved tramadol-containing medicinal products into the regime applicable to controlled substances.[1] From that date, prescriptions have been subject to entry in the narcotics register, dedicated prescription forms, secured storage and tighter dispensing oversight. The clinical indications were left unchanged, but the additional administrative requirements were expected to influence prescriber behaviour.

Comparable measures elsewhere have produced sizeable, and at times unintended, shifts in prescribing. In Denmark, the combination of media attention and risk-minimisation actions in 2017 to 2018 was followed by a marked decline in tramadol use, without a clear compensatory rise in stronger opioids.[2,3] In the United Kingdom, the reclassification of tramadol as a Schedule 3 controlled drug in June 2014 triggered a comparable contraction in primary-care and hospital prescribing.[5-7] In the United States, the rescheduling of hydrocodone combination products from Schedule III to Schedule II in October 2014 reduced surgical opioid prescribing in the year that followed,[8] and earlier opioid-prescribing guidance from the Centers for Disease Control and Prevention has been associated with parallel changes in prescribing patterns.[9]

Real-world data describing how the November 2022 Italian reclassification has reshaped postoperative analgesic prescribing in surgical hospitals are still scarce. Orthopaedic surgery is a particularly informative setting because postoperative pain is consistent in intensity, treatment is largely protocolised and IV tramadol historically held a defined place in multimodal regimens. The aim of the present study was therefore to quantify, using interrupted time-series methodology and DDD-based normalised metrics, the change in dispensing and acquisition cost of IV tramadol and of the IV NSAIDs commonly used as alternatives, ketorolac, ketoprofen lysine and ibuprofen, in the orthopaedic operating rooms of 2 Italian IRCCS hospitals during the 4 years that span the regulatory change.

Methods

Setting and Design

This was a retrospective, 2-centre, drug-utilisation study with an interrupted time-series design conducted at IRCCS Galeazzi-Sant'Ambrogio Hospital (Hospital A) and at the San Siro site of IRCCS Istituto Ortopedico Galeazzi (Hospital B), both in Milan, Italy. Both centres are tertiary referral hospitals dedicated to orthopaedic and musculoskeletal surgery and operate within the same pharmacy governance framework. Hospital A performs approximately 9100 orthopaedic procedures per year, Hospital B approximately 13 500; both show the elective-surgery seasonal pattern characteristic of Italian hospitals, with an August trough (about 50% reduction in monthly volume), a December dip (about 30%) and peaks in March to June and September to November. The study is reported according to the STROBE statement.

The observation period covered 48 consecutive calendar months (1 January 2021-31 December 2024). The interruption was set at the transition between October and November 2022, corresponding to the entry into force of the Ministerial Decree relocating tramadol within Section A of DPR 309/1990 on 17 November 2022.[1] In the primary model, calendar time was coded 1 to 48 (January 2021 = 1); the intervention indicator was set to 0 for the 22 months up to and including October 2022 and to 1 from November 2022 onwards, and the time-after-intervention term counted post-policy months (November 2022 = 1). November 2022 was therefore classified as the first post-policy month, generating 22 pre-policy and 26 post-policy months at each centre. Because the decree took effect mid-month, November 2022 is a partially exposed month; its coding was tested directly in a pre-specified sensitivity analysis in which November 2022 was treated as a transition month and excluded, with December 2022 as the first fully post-policy month (Supplementary Table S3). No major change occurred in surgical activity, case-mix or institutional analgesic protocols during the study period, with the exception of the addition of IV ibuprofen 400 mg (100 mL ready-to-use bag) to the Hospital B formulary in late 2022 as a non-opioid alternative; this formulary change is explicitly addressed in the sensitivity analysis.

Data Sources and Variables

Monthly dispensing and acquisition cost data for IV tramadol (100 mg/2 mL vial), IV ketorolac (30 mg/1 mL vial), IV ketoprofen lysine (Atrosilene® 160 mg/2 mL vial, 100 mg of ketoprofen base) and IV ibuprofen 400 mg (Hospital B only) were extracted from the in-house pharmaceutical management system. The unit of measurement was the number of units dispensed to the orthopaedic operating-room cost centres each month; dispensed quantities are used throughout as a proxy for consumption, on the understanding that they may differ from quantities actually administered because of ward stock movements, returns, transfers and wastage (addressed in the Limitations). Dispensed units were converted into Defined Daily Doses (DDDs) using the 2024 WHO/ATC index[10]: 0.3 g for tramadol (N02AX02, parenteral), 30 mg for ketorolac (M01AB15, parenteral), 0.15 g for ketoprofen (M01AE03, parenteral) and 1.2 g for ibuprofen (M01AE01, parenteral). To control for surgical workload, monthly DDDs were normalised to the number of procedures performed in the same month at each centre and expressed as DDDs per 100 procedures. Acquisition cost was expressed in Euros at the unit price actually paid (€0.20 for tramadol, €0.18 for ketorolac, €0.27 for ketoprofen lysine and €6.33 for IV ibuprofen 400 mg) and additionally normalised as cost per 100 procedures and as incremental cost per surgical patient. No patient-level data were extracted.

Statistical Analysis

The pre-specified primary analysis was a single-group interrupted time-series with segmented linear regression of monthly DDDs per 100 procedures against time, fitted separately for IV tramadol and IV ketorolac at each centre according to the model:

$$Y_t = \beta_0 + \beta_1 \cdot time + \beta_2 \cdot intervention + \beta_3 \cdot time - after - intervention + \Sigma\gamma_k \cdot M_k + \varepsilon_t$$

where β_0 is the baseline level, β_1 the pre-policy trend, β_2 the immediate level change at the policy date, β_3 the change in slope thereafter and γ_k 11 calendar-month indicators (M_k) included to absorb seasonality. Calendar time was coded in months since the start of the series (January 2021 = 1). The intervention was coded as described above, and the post-intervention slope was obtained as $\beta_1 + \beta_3$. January was used as the reference month for the calendar-month indicators. Immediate relative effects were expressed as β_2 divided by the model-predicted (seasonally adjusted) pre-policy level at the intervention, rather than by the baseline level at the start of the series.

Autocorrelation was assessed with the Durbin-Watson statistic and addressed by Newey-West heteroscedasticity- and autocorrelation-consistent standard errors with a 4-month lag. The lag was chosen a priori using the standard data-driven rule $L = 4 \cdot (T/100)^{2/9}$, which for $T = 48$ monthly observations yields 3.4 and was rounded up to 4; this window also spans within-quarter autocorrelation compatible with the quarterly structure of elective-surgery scheduling. Robustness to this choice was verified by re-estimating the models with lags of 1 to 6 months (Supplementary Table S2). Three pre-specified sensitivity analyses were performed: (i) repeating the regression on monthly units rather than DDDs per 100 procedures; (ii) restricting the analysis to the central months of the calendar year and (iii) excluding the 4 months either side of the November 2022 cut-off. Full model output (all coefficients, standard errors and 95% confidence intervals, including the 11 calendar-month indicators, the post-intervention slopes and the immediate relative reductions with confidence intervals) and residual diagnostics (autocorrelation function, Ljung-Box and Breusch-Godfrey tests, tests for residual seasonality and assessment of influential observations) are provided in Supplementary Tables S1 to S4. Statistical significance was set at $P < .05$. Analyses were performed with Python 3.11 (statsmodels 0.14, pandas 2.0).

Ethical Considerations

The study used aggregate, fully anonymised drug-consumption and surgical-volume data routinely collected for hospital management. Under Italian regulations on observational research conducted on aggregate administrative data, formal ethics committee approval was not required. The study was performed in accordance with the Declaration of Helsinki.

Results

Trends in Dispensing

Between 2021 and 2024 a consistent, parallel pattern emerged at the 2 centres. At Hospital A, mean annual IV tramadol dispensing fell from 953 units in the pre-policy 2-year period to 259 units in the post-policy period (−72.8%); IV ketorolac rose from 6687 to 8521 units/year (+27.4%) and IV ketoprofen lysine from 1226 to 2781 units/year (+126.8%). At Hospital B, IV tramadol decreased from 2011 to 617 units/year (−69.3%), IV ketorolac rose from 15 575 to 19 963 units/year (+28.2%) and IV ibuprofen 400 mg, newly introduced in late 2022, rose from 511 to 8206 units/year. The expected seasonal pattern in surgical activity was clearly visible in the monthly time series and was absorbed by the calendar-month indicators included in the regression.

Expressed as DDDs per 100 orthopaedic procedures (Table 1), IV tramadol use fell from 3.49 to 0.96 at Hospital A (−72.5%) and from 4.91 to 1.52 at Hospital B (−69.0%). IV ketorolac rose from 73.5 to 94.8 DDDs per 100 procedures at Hospital A (+29%) and from 114.1 to 148.0 at Hospital B (+30%); IV ketoprofen lysine, prescribed only at Hospital A, rose from 9.0 to 20.6 (+128%); IV ibuprofen 400 mg at Hospital B rose from a residual 1.25 to 20.3. These annual figures are calendar-year (2021-2022 vs 2023-2024) comparisons and are not identical to the interrupted time-series pre-/post-policy windows, which classify November and December 2022 as post-policy (see Table 1 footnote).

Interrupted Time-Series Analysis

Segmented regression on the 48 monthly observations (22 pre-policy, 26 post-policy), with calendar-month indicators and Newey-West standard errors, confirmed an abrupt, statistically significant fall in IV tramadol use at the time of the policy at both centres (Table 2 and Figure 1). At Hospital A, $\beta_0 = 4.65$ DDDs per 100 procedures, $\beta_1 = -.092$ per month ($P < .001$), $\beta_2 = -1.45$ ($P < .001$) and $\beta_3 = +.073$ per month ($P < .001$). At Hospital B, $\beta_0 = 5.88$, $\beta_1 = -.077$ per month ($P < .001$), $\beta_2 = -2.60$ ($P < .001$) and $\beta_3 = +.065$ per month ($P < .001$). Because IV tramadol use was already declining before the policy, the immediate relative effect was expressed relative to the model-predicted pre-policy level at the intervention rather than to the baseline level at the start of the series. The predicted (seasonally adjusted) level immediately before the intervention was 2.53 DDDs per 100 procedures at Hospital A and 4.11 at Hospital B; the immediate level changes therefore correspond to relative reductions of approximately 57% at Hospital A and 63% at Hospital B (95% confidence intervals in Supplementary Table S1), larger than the values obtained when the start-of-series baseline is used as the denominator.

The slope changes were positive but did not reverse the underlying decline: the post-intervention slope, obtained as $\beta_1 + \beta_3$, remained slightly negative at both centres (−0.019

Table 1. Mean Annual Dispensing of Intravenous Tramadol and Intravenous NSAIDs at the 2 Participating IRCCS Centres, Expressed as Units Dispensed and as Defined Daily Doses per 100 Orthopaedic Procedures, Compared by Calendar-Year Period (2021-2022 vs 2023-2024).

Drug	Mean units/y 2021-2022	Mean units/y 2023-2024	DDDs/100 proc. 2021-2022	DDDs/100 proc. 2023-2024	% Change
Hospital A, IV tramadol 100 mg	953	259	3.49	0.96	−72.8%
Hospital A, IV ketorolac 30 mg	6687	8521	73.5	94.8	+27.4%
Hospital A, IV ketoprofen lysine 100 mg[a]	1226	2781	9.0	20.6	+126.8%
Hospital B, IV tramadol 100 mg	2011	617	4.91	1.52	−69.3%
Hospital B, IV ketorolac 30 mg	15 575	19 963	114.1	148.0	+28.2%
Hospital B, IV ibuprofen 400 mg[b]	511	8206	1.25	20.3	+1524%

Abbreviations: DDD, Defined Daily Dose; IV, intravenous; NSAID, non-steroidal anti-inflammatory drug.
The 2021 to 2022 and 2023 to 2024 columns are calendar-year means and do not correspond exactly to the interrupted time-series pre-/post-policy windows, which classify November and December 2022 as post-policy. Values for these 2 months therefore fall in the 2021 to 2022 calendar-year column but in the post-policy window of the regression; this is most relevant for IV ibuprofen 400 mg, which was introduced at Hospital B in late 2022 and had essentially no genuine pre-policy use.
[a]Atrosilene® 160 mg/2 mL ampoule, ketoprofen base content 100 mg/vial.
[b]IV ibuprofen 400 mg (100 mL ready-to-use bag) was introduced at Hospital B in late 2022. Surgical workload denominators (annual mean): 9100 procedures at Hospital A and 13 500 procedures at Hospital B.

Table 2. Segmented Linear Regression Coefficients (Interrupted Time-Series) for IV Tramadol and IV Ketorolac, Expressed as Defined Daily Doses per 100 Orthopaedic Procedures per Month, Around the November 2022 Reclassification of Tramadol. Post-Intervention Slope Is $\beta_1 + \beta_3$. Standard Errors and 95% Confidence Intervals for All Coefficients Are Reported in Supplementary Table S1.

Series (DDDs/100 proc., monthly)	β_0	β_1/month	β_2 (level)	β_3/month	Post slope $\beta_1 + \beta_3$	P (β_2)/R^2
IV tramadol, Hospital A	4.65	−.092	−1.45	+.073	−.019	<.001/0.944
IV tramadol, Hospital B	5.88	−.077	−2.60	+.065	−.012	<.001/0.952
IV ketorolac, Hospital A	65.54	+.698	+2.41	+.153 (NS)	+.851	.012/0.983
IV ketorolac, Hospital B	104.31	+.751	+12.68	+.198 (NS)	+.949	<.001/0.989

Abbreviations: DDD, Defined Daily Dose; IV, intravenous; NS: not statistically significant.
The model included 11 calendar-month indicators (January as reference month) to absorb seasonality and Newey-West standard errors with a 4-month lag to address residual autocorrelation. β_0 = baseline level; β_1 = pre-policy trend; β_2 = immediate level change at the policy date; β_3 = change in slope after the policy. The post-intervention slope ($\beta_1 + \beta_3$) remained negative for IV tramadol at both centres, indicating a continued but slower decline; the β_3 terms for IV ketorolac were NS.

DDDs per 100 procedures per month at Hospital A and −0.012 at Hospital B), indicating that IV tramadol use continued to fall after the policy, although far more slowly than before, rather than rebounding. Model fit was high ($R^2 = 0.944$ at Hospital A and 0.952 at Hospital B), and the Durbin-Watson statistic (1.98-2.05) was compatible with the absence of first-order residual autocorrelation; formal residual diagnostics are reported in Supplementary Table S4.

For IV ketorolac, the picture was the mirror image of tramadol. At Hospital A, $\beta_0 = 65.54$ DDDs per 100 procedures, $\beta_1 = +.70$ per month ($P < .001$), $\beta_2 = +2.41$ ($P = .012$) and $\beta_3 = +.15$ per month (non-significant). At Hospital B, $\beta_0 = 104.31$, $\beta_1 = +.75$ per month ($P < .001$), $\beta_2 = +12.68$ ($P < .001$) and $\beta_3 = +.20$ per month ($P = .20$). Model R^2 was 0.983 at Hospital A and 0.989 at Hospital B. The November 2022 step increases corresponded to +3.7% at Hospital A and +12.2% at Hospital B, on top of an established positive trend of approximately 0.7 DDDs per 100 procedures per month at both centres. Because the slope-change coefficients for IV ketorolac were not statistically significant at either centre, the data indicate a significant immediate upward step in IV ketorolac use around the policy superimposed on a pre-existing upward trend, rather than a statistically demonstrable acceleration of that trend.

Sensitivity Analyses

The 3 pre-specified sensitivity analyses produced concordant results. Repeating the segmented regression on raw monthly units rather than DDDs per 100 procedures yielded coefficients of identical direction and significance ($\beta_2 = -83.86$ units/month at Hospital B; $P < .001$). Restricting the analysis to the central months of the calendar year produced a level-change estimate at Hospital B of $\beta_2 = -2.35$ ($P < .001$), within 10% of the primary analysis. Excluding the 4 months either side of the cut-off yielded $\beta_2 = -2.58$ ($P < .001$), almost identical to the primary estimate, supporting robustness to short-term anticipation and transition effects. Treating November 2022 as a transition month and taking December 2022 as the first fully post-policy month left the immediate

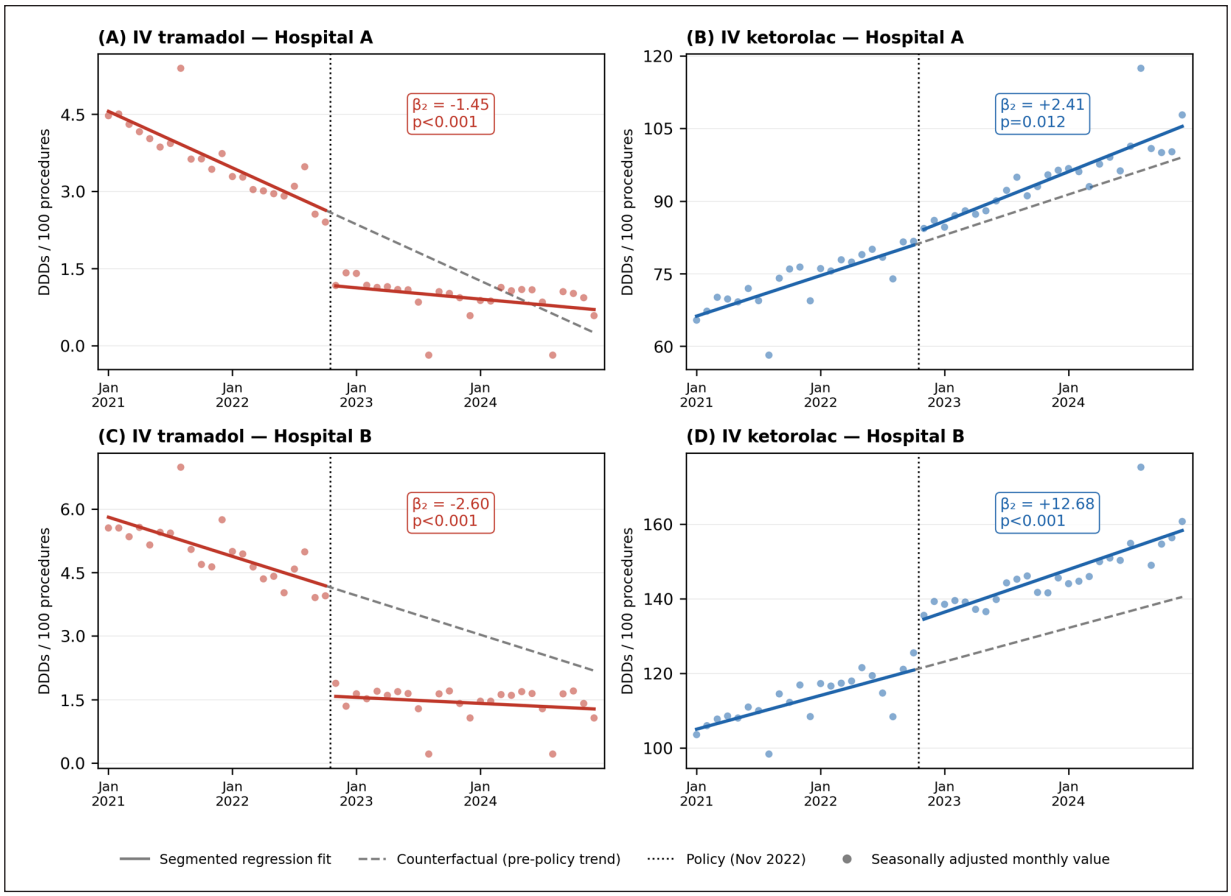

Figure 1. Interrupted time-series analysis of intravenous tramadol and intravenous ketorolac use at the 2 participating IRCCS centres, January 2021 to December 2024: (A) Hospital A, IV tramadol, (B) Hospital A, IV ketorolac, (C) Hospital B, IV tramadol and (D) Hospital B, IV ketorolac. Each panel plots monthly consumption expressed as DDDs per 100 orthopaedic procedures, after subtraction of the calendar-month component estimated by the segmented-regression model (ie, seasonally adjusted values). The vertical dotted line marks 17 November 2022, the date on which tramadol was reclassified under Section A of Presidential Decree 309/1990. Solid coloured lines show the segmented-regression fit (red for IV tramadol, blue for IV ketorolac), drawn separately over the pre-policy and post-policy periods. The dashed grey line shows the counterfactual trajectory, obtained by extending the pre-policy linear trend ($\beta_0 + \beta_1 \cdot$time) into the post-policy period. The annotation in each panel reports the immediate level change at the policy date (β_2) and the corresponding *P* value, estimated by ordinary least squares with Newey-West heteroscedasticity- and autocorrelation-consistent standard errors (4-month lag). The full set of regression coefficients is reported in Table 2.
DDDs, Defined Daily Doses.

level change for IV tramadol essentially unchanged in direction and significance (Supplementary Table S3).

Trends in Expenditure

Annual pharmaceutical expenditure for tramadol fell sharply at both centres, by approximately 73% at Hospital A and 69% at Hospital B, mirroring the contraction in volume. Conversely, expenditure on the considered IV NSAIDs increased substantially. When the 4 IV agents were aggregated and normalised to surgical workload, the cost per 100 orthopaedic procedures rose from €18.96 to €25.99 at Hospital A (+37%) and from €47.20 to €412.73 at Hospital B (+774%). On a per-patient basis, the incremental analgesic cost was €0.07 per surgical patient at Hospital A and €3.66 per surgical patient at Hospital B.

The dramatic difference between the 2 centres deserves explicit decomposition. At Hospital B, IV ibuprofen 400 mg expenditure alone rose from approximately €3200/year to approximately €52 000/year. On the reported unit volumes and acquisition prices, IV ibuprofen accounted for approximately 93% of total post-policy IV-analgesic expenditure at Hospital B and for approximately 99% of the increase in IV-analgesic expenditure from the pre-policy to the post-policy period. In a counterfactual "NSAID substitution only" scenario, in which the 8206 ready-to-use IV ibuprofen bags dispensed post-policy at Hospital B were instead replaced one-for-one by vial-based ketorolac (€0.18 per vial) while all other volumes were held at their observed values, total post-policy IV-analgesic expenditure at Hospital B would have fallen close to, and marginally below, the pre-policy baseline (approximately €5200 vs €6440 per year), corresponding to

an incremental cost of essentially zero, of the order of a few euro-cents per surgical patient, rather than the observed €3.66. The exact counterfactual value depends on the substitution assumption adopted (comparator agent, vial-vs-bag equivalence and whether the observed rise in ketorolac is retained); the quantities, prices and denominator used here are reported in full in Supplementary Table S5 so that readers can reproduce the calculation. The disproportionate budget impact at Hospital B is therefore primarily a consequence of the formulary choice that accompanied the regulatory change, specifically, the introduction of a ready-to-use IV bag at a per-unit cost roughly thirty times higher than vial-based alternatives, rather than of the regulatory change itself.

Discussion

In the 4 years that span the November 2022 Italian reclassification of tramadol, the 2 IRCCS orthopaedic hospitals showed a substantial, sustained and statistically significant shift away from IV tramadol and towards IV NSAIDs. The interrupted time-series identified an abrupt change centred on the regulatory deadline, with level changes of −1.45 DDDs per 100 procedures at Hospital A ($P < .001$; baseline 4.65) and −2.60 at Hospital B ($P < .001$; baseline 5.88), immediate relative reductions of approximately 57% and 63% relative to the model-predicted pre-policy level at the intervention, on top of an already declining pre-policy trend. The mirror-image rises in IV ketorolac, with level increases of +2.41 at Hospital A and +12.68 at Hospital B, complete a temporal pattern consistent with opioid-to-NSAID substitution among the measured agents. The magnitude of the change is in line with responses observed in healthcare systems that have undertaken comparable interventions[2-9] and, although the uncontrolled design precludes a formal causal claim, is unlikely to reflect background secular trends alone, given its temporal coincidence with the regulatory deadline, its consistency across 2 centres of different volume, and its survival in all sensitivity analyses.

Three points deserve emphasis. First, the use of DDDs per 100 procedures as the primary metric, rather than units dispensed, allowed comparison across centres of different size and removed the distortion introduced by surgical workload and variable vial potency; the explicit modelling of August and December dips via calendar-month indicators further controlled for elective-surgery seasonality. The high model fit ($R^2 = 0.944$-0.989) reflects the strong deterministic time trend and the 11 calendar-month indicators and is expected in such a model; it does not by itself establish correct specification. Model adequacy was therefore assessed through residual diagnostics rather than R^2 alone, with Durbin-Watson values close to 2 and the additional autocorrelation, seasonality and influence checks reported in Supplementary Table S4. Second, the segmented regression made it possible to disentangle the immediate "shock" effect of the policy (β_2) from the longer-term trend (β_3) and the pre-policy trajectory (β_1). The negative pre-policy slope of IV tramadol at both centres is itself instructive: the regulatory measure did not act on a stable use pattern but coincided with a further steepening of an already-declining trajectory, possibly reflecting growing clinician awareness of the safety concerns associated with tramadol.[2,3] The positive pre-policy slope of IV ketorolac suggests that some substitution was already in progress before the regulatory deadline. Third, and most importantly for hospital pharmacists, the cost decomposition demonstrates that the headline rise in expenditure at Hospital B is almost entirely attributable to the parallel introduction of IV ibuprofen 400 mg as a ready-to-use bag, not to the regulatory shift itself. Hospital A, which did not introduce IV ibuprofen, absorbed the policy with a marginal cost increase of approximately 7 cents per surgical patient.

From a pharmacological standpoint (Table 3), the substitution of tramadol with ketorolac, ketoprofen lysine or ibuprofen represents a transition from a centrally acting analgesic with multimodal activity to peripherally acting cyclo-oxygenase inhibitors. The IV NSAIDs that have replaced tramadol act via inhibition of prostaglandin synthesis and provide effective control of inflammatory pain, but they lack the central component, exhibit a ceiling effect, and carry well-recognised gastrointestinal, renal and cardiovascular risks. They are therefore less suitable for patients with peptic ulcer disease, advanced kidney disease, decompensated heart failure or established cardiovascular disease, comorbidities common in the elderly orthopaedic population.[11] The shift documented here may therefore deliver meaningful safety benefits at the population level (reduced opioid exposure, lower risk of dependence and serotonergic interactions) while exposing a different subgroup of patients to NSAID-related complications, and the net clinical balance ultimately depends on appropriate case-by-case selection.

The economic dimension deserves particular attention from a hospital pharmacist's perspective. The 2 centres faced the same regulatory shock and responded with substantially the same reduction in IV tramadol use, but the budget consequences differed by an order of magnitude, €0.07 versus €3.66 per surgical patient, entirely as a function of the formulary alternative chosen. IV ibuprofen 400 mg supplied as a 100 mL ready-to-use bag costs approximately thirty times more per unit than vial-based alternatives, and even a modest replacement rate translates into a sizeable budget impact across a high-volume surgical population. This is not an argument against ready-to-use formulations, which carry advantages in preparation time, sterility risk and nursing workload not captured by acquisition cost; it is an argument for explicit, transparent costing whenever a regulatory measure narrows the available analgesic options.

Multimodal analgesia represents a clinically attractive way to limit reliance on a single class. Combinations of paracetamol with ibuprofen or other NSAIDs have shown additive analgesic activity with opioid-sparing effects[12] and may help bridge effective postoperative pain control with the need to contain

Table 3. Pharmacological Profile of the Analgesic Agents Considered.

Drug	Mechanism of action	Site of action	Main risks
Tramadol	μ-opioid agonist + SNRI	Central	Sedation, nausea, dependence, serotonin toxicity
Ketorolac	Non-selective COX inhibitor	Peripheral	GI bleeding, renal impairment, CV risk
Ketoprofen	Non-selective COX inhibitor	Peripheral	Similar to ketorolac
Ibuprofen	Non-selective COX inhibitor	Peripheral	GI, renal, CV (lower with short-term IV use)

Abbreviations: COX, cyclo-oxygenase; CV, cardiovascular; GI, gastrointestinal; IV, intravenous; SNRI, serotonin-noradrenaline reuptake inhibitor.

both opioid and NSAID exposure. The pattern observed here is consistent with regulatory deprescribing phenomena described elsewhere,[8,9] suggesting that the change reflects a generalisable response of prescribers to administrative friction rather than a primarily clinical re-evaluation of tramadol.

Limitations

First, the dataset consists of aggregate dispensing data and does not allow patient-level analysis of indications, doses, pain scores, length of stay, adverse events or readmissions; outcome studies remain a priority for future research. Dispensed units are used as a proxy for consumption; because they may differ from the quantities actually administered as a result of ward stock accumulation, returns, transfers and wastage, and because dispensing and inventory procedures may themselves have changed around the reclassification, the absolute levels should be interpreted as dispensing rather than true consumption, although these factors are unlikely to account for the abrupt, policy-timed and internally consistent change observed across 2 centres. Second, the design is a single-group, uncontrolled interrupted time-series and cannot formally establish that the reclassification itself caused the observed changes: both hospitals were exposed to the same national policy within the same pharmacy governance framework, so neither can serve as an unaffected control, and concurrent formulary, clinical, supply or administrative changes cannot be excluded. Third, the introduction of IV ibuprofen 400 mg at Hospital B in late 2022 is a structural confounder for the cost analysis at that centre, addressed through explicit decomposition and counterfactual costing. Fourth, the substitution signal rests on a temporal association among the 4 measured agents; the analysis does not capture patient-level treatment changes or the full range of alternative analgesics (other opioids, non-IV formulations, paracetamol, regional anaesthesia and other multimodal strategies), and formal interrupted time-series models were fitted only for tramadol and ketorolac. Fifth, only 2 IRCCS centres in northern Italy are represented, and results may not be fully generalisable. Sixth, the cost analysis reflects acquisition prices rather than full process costs.

Conclusions

The November 2022 reclassification of tramadol as a controlled substance under DPR 309/90 was followed by a marked, statistically significant and immediate reduction in IV tramadol consumption, described by interrupted time-series analysis on monthly DDDs per 100 procedures, with level changes of −1.45 at Hospital A ($P < .001$) and −2.60 at Hospital B ($P < .001$), and by a parallel rise in IV NSAID use, with concordant findings across both centres and all sensitivity analyses. The associated rise in pharmacy expenditure was driven less by the regulatory shift itself than by the local formulary choice that accompanied it, with the parallel introduction of IV ibuprofen 400 mg accounting for over 90% of the post-policy cost increase at Hospital B. These temporal associations are consistent with administrative restrictions on a specific drug rapidly reshaping clinical prescribing patterns, and underline the importance of pairing regulatory measures with clinical guidance, multimodal protocols, prescribing surveillance and explicit consideration of the per-procedure cost impact. Patient-level studies are needed to determine whether the new analgesic mix delivers comparable pain control and an acceptable safety profile, particularly in older orthopaedic patients in whom NSAID-related risks are highest.

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Ethical Considerations

The study used only aggregate, fully anonymised drug-consumption and surgical-volume data routinely collected for hospital pharmacy management. Under Italian regulations on observational studies on aggregate administrative data, formal ethics committee approval was not required. The study was performed in accordance with the principles of the Declaration of Helsinki.

Author Contributions

Conceptualisation, B.C.; methodology, L.G. and C.B.; formal analysis, L.G. and B.C.; data curation, B.F., D.P. and F.P.; validation, B.F., D.P. and C.B.; writing—original draft preparation, G.O., F.P. and B.A.M.; writing—review and editing, B.C., L.G., B.F., G.O., D.P., C.B. and F.P.; methodological supervision, C.B.; supervision, B.C. and F.P. All authors have read and agreed to the published version of the manuscript.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

The aggregated data that support the findings of this study are available from the corresponding author upon reasonable request, subject to the data-sharing policies of the participating hospitals. The Python script used for the segmented regression and figure generation is available on request.

Supplemental Material

Supplemental material for this article is available online.

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