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A statistical analysis of pain relief after surgical operations

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Abstract

Objectives: Administering pain relief measures requires information about development of post-operative pain. Such information can be obtained from studying the patients' perception of pain. The aim of this study is to develop a statistical model that predicts the level of pain in different periods after the operation and the time effects of analgesics. The results can be used for an effective and timely application of pain medications.
Methods: This paper applies an ordered response model to a sample of 392 observations from 49 patients undergoing orthopedic surgeries. The patients' subjective pain levels have been recorded for several intervals up to 24 h after their respective operations. The adopted statistical model accounts for the unobserved heterogeneity among patients through random coefficients. Such heterogeneity could be due to differences in patients' perception of pain as well as their health status and sensitivity.
Results: The analysis indicates that post-operative pain gradually increases over time but with a slightly diminishing rate. The results suggest that analgesics are quite effective in containing the development of pain. However, the analgesic effects manifest gradually, at a rate more or less similar to that of post-operative pain.
Conclusion: Highlighting the importance of pain from both clinical and economic perspectives, the analysis indicates that a timely application of analgesics is crucial for an effective pain relief after surgical operations. In particular, the results indicate that the optimal time of administering analgesics is immediately after the operation. The main policy implication of this finding is that preemptive measures of pain relief could be most effective and should be favored to similar analgesic treatments after the manifestation of pain. The results also show that the post-operative pain risks differ significantly across individual cases, which suggests that case-specific clinical assessments supersede any statistical analysis. The proposed statistical model can be used to identify high-risk categories and explore the variations across different analgesic types.
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Keywords: Post-surgical pain; Analgesia; Statistical analysis; Ordered response models

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1. Introduction

National health organizations throughout the world recognize pain[1] relief as a primordial medical objective [2]. Neglecting treatment of pain might lead to chronic pain, longer treatments and future complications [3–6]. Inadequate management of pain not only decreases the quality of life but could create a considerable financial burden on the health care system [7,8]. An increasingly important category of pain treatment regarding both financial costs and pain intensity is related to pain resulting from surgical operations [9]. There is a great body of medical literature that studies the post-operative acute pain [9–12]. These studies highlight the necessity to develop an effective strategy for pain management by identifying the high-risk patients and the optimal methods of prevention and relief. Although many studies have addressed the assessment and management of post-operative pain, only a few studies have used a systematic statistical modeling of pain development. In particular, the development of pain and analgesia with time has not been studied.[2] Statistical modeling of pain development allows a better understanding of the variation among patient groups regarding various risk factors and different treatment methods. Moreover, considering the pain development and analgesic effect as functions of time helps identify the optimal timing of pain treatment. This is especially important as it can be used to assess early relief measures and pre-emptive analgesia. Such measures have been subject to a number of studies, but the empirical evidence reported so far, has not been conclusive [12,14,15].

This paper proposes a ordered response statistical model that predicts the perceived levels of post-operative pain as a function of the time after surgery, the time after the analgesic therapy and patient characteristics. The adopted methodology has a novelty in that the non-linear effects of time and the unobserved heterogeneity among patients can be taken into account through random coefficients. Such heterogeneity is especially important for virtually all pain measures are based on subjective perceptions that vary among individuals. The proposed model can be used to identify the effects of patient and treatment characteristics on pain relief. Moreover, the estimation of separate time effects for post-surgical pain and analgesic relief can be used to identify the optimal timing of the treatment.

The model has been applied to 392 post-operative pain records after orthopedic operations from 49 patients. The analysis shows that the timing of the analgesics has an important effect on the pain outcome. The results suggest that the optimal timing is immediately after the operation, thus provide empirical evidence for the effectiveness of pre-emptive treatment of pain. Moreover, the results provide some information about the pattern of pain variations among different age and gender groups.

The rest of the paper is organized as follows: Section 2 provides a description of the methods together with the main features of the statistical model. The data and the estimation results are reported in Section 3. Section 4 concludes the paper with a discussion of the main findings and suggestions for further research.

2. Materials and methods

Apart from external indicators in certain cases, the pain intensity can only be measured on an individual basis using self-report pain scales [11]. A wide variety of pain scales have been used in the literature. The most widely used one-dimensional assessment scales,[3] include visual analogue scale [16,17], verbal rating scale [18], verbal assessment scale [19], and face expression scale [20]. The difficulties encountered in the design and administration of these measurements, have been discussed elsewhere [20]. Valid measures can be obtained by asking simple and clear questions that allow all patients to report correctly their level of pain. Statistical modeling of pain levels allows a better account of unobserved variations among individuals

[1] International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1].

[2] To our knowledge there is only one recent study [13] that proposed a combined scoring system based on age, sex, type of surgery, extent of preoperative pain, and level of anxiety in order to predict the severity of early postoperative pain. That paper however, does not analyse the pattern of development of pain with time.

[3] One-dimensional pain scales are mainly aimed at measuring pain intensity. Their advantage is in their simplicity and their main limitation is that they do not account for other important factors, including those that may exacerbate/reduce pain as well as potential physiological damages and cognitive and behavioral changes.

in terms of pain perception as well as the potential reporting errors.

No matter the type of measurement scale, the pain data can be represented as ordered categorical variables. Ordered discrete choice models are commonly used for modeling categorical response variables that represent groups of continuous variables with an explicit ordering, such as income groups. The application of these models can be extended to categorical variables that have an "assessed" order, such as the pain intensity or "the extent of pain relief after treatment" [21].

In this paper we use an ordered logit model [22,23].[4] In this model it is assumed that the individual choices are based on a latent variable, which is considered as a measure of the individual's random utility. This latent variable is defined as a function of explanatory variables. In the context of this study, the latent variable y^*_{it} is defined as the pain level of patient i at period t. The latent variable y^*_{it} is assumed to be a continuous additive function of a vector of time-variant factors denoted by X_{it}, and of a vector of patient's characteristics represented by Z_i. Vector X_{it} includes, for instance, the time period after the operation and the number of hours after the application of analgesics. Vector Z_i can also include the type and characteristics of the applied analgesics.

Considering the additive stochastic term the latent pain level can be written as

$$y^*_{it} = \alpha + X_{it}\beta + Z_i\gamma + \varepsilon_{it}, \tag{1}$$

where subscripts i and t, respectively, represent the patient and the number of hours after the operation; α, β and γ are the parameter vectors to be estimated; ε_{it} is an *iid* stochastic error term representing the unobserved factors. We assume that patients translate their continuous pain level (latent to the analyst) to a finite number of pain levels (J) revealed in the survey. The probability of choosing pain level j is defined as

$$\Pr(y_{it} = j) = \Pr(\mu_{j-1} < y^*_{it} \leq \mu_j); \quad -\infty = \mu_0 < \mu_1 < \ldots < \mu_J = +\infty, \quad j \in \{1, 2, \ldots, J\}, \tag{2}$$

[4] Recently, this kind of models have been used in a RAND study assessing patients' use and preferences for information about the technical and interpersonal quality of care delivered by individual physicians [24,25]. To our knowledge, there is no previous example of application of these models in the context of post-operation pain.

where y_{it} is the discrete response variable, that is patient i's pain level, t hours after operation; and μ_j's are the threshold parameters. Assuming a logistic probability distribution for the error term ε_{it}, the above probability can be written as

$$\Pr(y_{it} = j) = \frac{1}{1 + \exp(-\mu_j + \alpha + X_{it}\beta + Z_i\gamma)} - \frac{1}{1 + \exp(-\mu_{j-1} + \alpha + X_{it}\beta + Z_i\gamma)} \tag{3}$$

that can be estimated using the maximum likelihood estimation method.

In the above model it is assumed that all individual patients use a similar measure of pain. This is a restrictive assumption in that individuals differ with respect to their sensitivity facing pain. Moreover, the patients' perception of pain could vary depending on their expectations regarding the gravity of their operation. For instance a patient with a complex operation could complain less than a similar patient who had a relatively simple operation but who suffers the same level of pain. This restrictive assumption can be partly relaxed by considering that the intercept parameter α varies across different individuals. Moreover, the effect of independent variables X_{it} could also vary across individual cases. For instance, the development of pain after the operation and the effect of analgesics depend on the type and complexity of the operation as well as other unobserved patient characteristics. Such unobserved heterogeneity can be partly accounted for by randomizing coefficient vector β across patients.

Assuming that α and β are normal random variables, the model in Eq. (1) can be written as

$$y^*_{it} = \alpha_i + X_{it}\beta_i + Z_i\gamma + \varepsilon_{it}, \quad \alpha_i \sim N(\alpha, \sigma^2_\alpha), \quad \beta_i \sim N(\beta, \sigma^2_\beta) \tag{4}$$

and Eq. (3) is changed by substituting α and β with α_i and β_i, respectively, resulting in:

$$\Pr(y_{it} = j) = \frac{1}{1 + \exp(-\mu_j + \alpha_i + X_{it}\beta_i + Z_i\gamma)} - \frac{1}{1 + \exp(-\mu_{j-1} + \alpha_i + X_{it}\beta_i + Z_i\gamma)}. \tag{5}$$

As the likelihood function does not have a closed form solution, the model with random coefficients can only be estimated using the maximum simulated likelihood method, by approximating the likelihood function with Monte Carlo simulation technique that is integrating the conditional likelihood with random draws for the random coefficients.[5]

In this paper, we consider both the simple model with constant parameters as in (1) and the alternative model with random coefficients as expressed in (4). The patient characteristics included in the model (Z_i) are gender, age categories, a dummy variable indicating whether more than one analgesic have been used, and an indicator controlling for the quality of care as perceived by the patient. The time-variant explanatory variables (X_{it}) include the number of hours after the operation and the number of hours elapsed after the analgesic as well as their respective squares. Considering this specification, the adopted model is based on the assumption that after controlling for observed patient characteristics and stochastic errors, the evolution of pain level (y^*) follows a quadratic function of the following form:

$$y_t^* = y_0^* + \theta_1 t + \theta_2 t^2 + \omega_1 s + \omega_2 s^2 \qquad (6)$$

where $\theta_1, \theta_2, \omega_1$ and ω_2 are the parameters to estimate; y_t^* and y_0^* are, respectively, the pain level at t and the initial pain level at $t = 0$ (right after the operation); and s is the time elapsed after the analgesic (or after the most recent analgesic for patients with several analgesics). Note that in the random coefficient model explained above, the pain function (6) is assumed to be patient-specific, that is parameters $\theta_1, \theta_2, \omega_1$ and ω_2 vary across individual cases.

The above statistical models have been applied to 392 records from a sample of 49 inpatient orthopedic surgeries performed during 2002 and 2003, in Buccheri La Ferla hospital in Palermo, Italy. The initial data set includes observations from 60 patients that cannot be considered a random sample as they represent a selection of orthopedic surgeries that are considered as "routine" interventions at that hospital, including surgeries on femur, arm and ankle as well as knee and hip prostheses. Among the available observations we excluded those from 11 patients whose observations were not complete in order to keep a balanced data set.[6] All the patients had given their consent before the survey. The data were collected using regular interviews coordinated by two physicians. Observations were performed over 3 h intervals during the first 24 h following the operation, resulting in eight observations for each case. The survey coordinators decided to focus on the first 24 h, considered as the most critical period with the highest incidence of complication and assistance requests. The 3 h intervals have been chosen, because the involved physicians wanted to explore the short-term effects and the variation of pain with time. Shorter intervals and longer follow-up periods were considered too burdensome and costly.

The pain level was recorded using a verbal rating scale (VRS) in five levels: level 0 corresponds to no pain at all, at rest or in movement; level 1 indicates no pain at rest, but slight pain while moving; level 2 represents slight pain at rest and high pain in movement; level 3 indicates high pain at rest and intolerable pain when moving; and finally, level 4 means intolerable pain even at rest. In each interview the respondents were provided with a simple explanation of the five categories and are asked to choose the one that best describes their pain intensity.

While VRS measures provide a quick and simple method of pain assessment for acute pain, the reported levels could be affected by the differences in patients' age, language, educational and cognitive status [17]. However, some of these differences are taken into account through the random coefficients used in the statistical model. In addition to simplicity, the VRS measures have the advantage of developing a "confidential" relationship between the patient and the interviewer, immediately following the surgery, hence a better assessment of pain.

Most of the interviews have been conducted by the survey coordinators or in their presence. Each one of the questionnaires was checked after the completion of the corresponding interviews. Several nurses instructed by the survey coordinators have assisted in conducting the interviews. In general, we could expect certain

[5] We used the pseudo-random Halton procedure that is proved to be more efficient than truly random draws [26,27]. Using LIMDEP software [28] we considered several numbers of draws. The results were not sensitive to the number of draws with about 1000 draws.

[6] With the exception of one case that did not have any analgesic, all these patients had a continuous epidural or femoral analgesic. Given that continuous analgesia is generally rare in the studied hospital we also esteemed that those cases might have had certain unusual conditions and should not be pooled with the rest of the data.

variation across the interviewers. Unfortunately we do not have any information to identify the specific interviewer for each observation. However, to the extent that the inter-rater variation is uncorrelated with the explanatory variables, it should be captured by the stochastic error term and would not bias the results of our analysis.

In addition to pain assessments, the questionnaires included patient's name, age and sex as well as type of surgery and the time of analgesic treatments. Patients were also asked about how they evaluate the quality of the medical care they had received into three levels (poor, good and very good).

The patients in the sample have been treated with one of the following analgesics: Diclofenac, Meperidine, Paracetamol, Benzodiazepine and Ketorolac. These analgesics are very commonly used in the treatment of post-surgical pain, do not have severe contraindications and are usually available at the hospital's pharmacy. The type of analgesic is unique for each patient and has been selected based on the type of the operation as well as the patient's medical condition. We assume that these analgesics have a similar appeasement effect. Given that different analgesic types might have completely different time-effects, the above assumption may be restrictive. However, since the random coefficients vary across individual patients, they could capture these differences to the extent that the time effects can be modeled with the same functional form for all the included analgesic types.

3. Results

The final sample consisted of 24 male and 25 female patients. The patients' age varied from 15 to 86 years old for men and 22–89 for women with a median value of 67 for both male and female patients. Table 1 summarizes reported values for pain intensity monitored at 3 h intervals after the operation. As this table indicates, most patients did not declare any pain immediately after the surgery, which is probably due to the effects of anesthesia. Table 1 also lists the number of administered analgesics over time. Overall, 60 analgesics were administered to the patients in the sample, most of which have been performed about 12–18 h after the operation.

As it is seen in the table, the reported pain was often limited to level 2 that is, slight pain at rest and high pain at movement. The peak level of pain (as shown by the highest number of patients declaring a level of pain higher than 1) appeared in the time interval from 6 to 12 h after the surgery. Number of patients declaring a level of pain higher than 2 increased from 10 to 15 in these time intervals. Pain rose for some patients 18 h after the surgery with four patients declaring intolerable pain (level 4) and asking for further analgesics. In order to avoid the problem of small sample, the maximum pain values (level 4), that are limited to 2.6% of the observations, were stacked to the next lower level (level 3).

A descriptive summary of the variables included in the model is provided in Table 2. T_SURG is the number of hours after the operation and T_ANAL is the number of hours after the administration of the most recent analgesic. Patients' subjective assessment about the quality of care has been described in three categories: poor, good and very good. While most patients rated the provided care as good, only two graded the quality as very good. We constructed a dummy variable (POOR) representing the five patients who described the quality level as poor. The variables also include

Table 1
Distribution of patients by pain level and time after surgery

Level of pain	Hours after surgery							
	3 h	6 h	9 h	12 h	15 h	18 h	21 h	24 h
0	39	38	28	23	23	24	23	22
1	9	9	11	14	11	13	14	16
2	1	2	6	7	6	5	4	10
3	0	0	2	3	8	5	4	1
4	0	0	2	2	1	2	4	0
Total number of patients	49	49	49	49	49	49	49	49
Number of administered analgesics	1	1	7	27	8	5	10	1

Table 2
Descriptive statistics (392 observations from 49 patients)

	Mean	S.D.	Minimum	Maximum
Level of pain	0.717	0.97	0	3
T_SURG	13.50	6.88	3	24
T_ANAL	6.29	4.41	3	24
REPEAT	0.163	0.37	0	1
MALE	0.490	0.5	0	1
Age	59.6	20.5	15	89
Age 30–39	0.082	0.27	0	1
Age 40–49	0.122	0.32	0	1
Age 50–59	0.102	0.30	0	1
Age 60–69	0.143	0.35	0	1
Age 70–79	0.245	0.43	0	1
Age ≥80	0.184	0.38	0	1
POOR	0.102	0.30	0	1

T2_SURG and T2_ANAL respectively denoting the time squares and dummy variable REPEAT representing patients who have received more than one analgesic during the sample period.

The estimation results are listed in Table 3. Comparing the estimated coefficients across the two models show significant differences between corresponding coefficients, suggesting that ignoring the unobserved heterogeneity could create significant biases in the estimated parameters. As it can be seen in the table, in the model with random parameters, the significant variations in the coefficients of the time variables suggest that the development of pain and the effect of analgesics vary from case to case.

The results suggest that male patients show lower pain levels compared to female cases. This result is consistent with the previous studies suggesting significant differences in pain perception between male and female cases [29]. More importantly, the positive effect of time after surgery suggests that the pain increases with time within the 24 h period recorded in the data. The negative coefficient of the square term indicates however, that post-operative pain increases at a decreasing rate. On the other hand, the negative and significant effect of time after the analgesics suggests that these interventions are effective in lowering pain, but that their effects appear gradually. Here, the second order effect is positive, suggesting that the appeasing effect diminishes with time.

The variation of pain among age groups does not show any clear pattern. This may suggest that age variables capture other unobserved differences across patients. Given the limited number of patients in the sample and the relatively high variation within each age

Table 3
Estimation results

	Model with constant parameters	Model with random parameters	
	Coefficient	Coefficient's Mean	Coefficient's Std. Dev.
T_SURG	0.489** (0.088)	0.643** (0.0704)	0.0956** (0.0077)
T2_SURG	−0.0109** (0.0031)	−0.0182** (0.0024)	0.00006 (0.0003)
T_ANAL	−0.473** (0.117)	−0.468** (0.0896)	0.2029** (0.017)
T2_ANAL	0.0182** (0.0052)	0.0147** (0.0040)	0.00007 (0.0008)
REPEAT	0.903** (0.315)	0.0188 (0.258)	
MALE	−0.839** (0.225)	−1.264** (0.194)	
Age 30–39	0.334 (0.577)	1.209* (0.497)	
Age 40–49	1.748** (0.492)	4.174** (0.457)	
Age 50–59	1.913** (0.511)	4.168** (0.470)	
Age 60–69	0.969* (0.499)	1.115* (0.445)	
Age 70–79	0.937* (0.450)	2.079** (0.397)	
Age ≥80	1.806** (0.4549)	3.266** (0.407)	
POOR	2.077** (0.400)	2.545** (0.320)	
Constant	−3.556** (0.707)	−5.522** (0.591)	1.129** (0.102)
Threshold parameters			
μ_1	1.682** (0.141)	2.635** (0.128)	
μ_2	3.014** (0.220)	4.329** (0.199)	

Standard errors are given in brackets. The dependent variable is the level of pain in four categories from 0 to 3.
* Significant at 5%.
** Significant at 1%.

Table 4
Marginal effects estimated at the sample mean

	$Y=0$	$Y=1$	$Y=2$	$Y=3$
Simple ordered logit model				
T_SURG	−.1200	.0667	.0362	.0170
T2_SURG	.0027	−.0015	−.0008	−.0004
T_ANAL	.1161	−.0646	−.0351	−.0165
T2_ANAL	−.0045	.0025	.0013	.0006
REPEAT	−.2219	.0988	.0805	.0426
MALE	.2030	−.1112	−.0621	−.0297
Age 30–39	−.0830	.0426	.0271	.0133
Age 40–49	−.3983	.1040	.1757	.1187
Age 50–59	−.4237	.0865	.1944	.1428
Age 60–69	−.2373	.1014	.0882	.0476
Age 70–79	−.2299	.1076	.0806	.0417
Age ≥80	−.4153	.1247	.1761	.1145
POOR	−.4494	.0739	.2101	.1654
Random coefficient ordered logit model				
T_SURG	−.1439	.1219	.0176	.0043
T2_SURG	.0036	−.0031	−.0004	−.0001
T_ANAL	.1048	−.0889	−.0128	−.0031
T2_ANAL	−.0033	.0028	.0004	.0001
REPEAT	−.0042	.0036	.0005	.0001
MALE	.2755	−.2307	−.0360	−.0088
Age 30–39	−.2915	.2236	.0539	.0140
Age 40–49	−.7177	.1511	.3627	.2038
Age 50–59	−.7054	.1216	.3669	.2169
Age 60–69	−.2672	.2105	.0452	.0115
Age 70–79	−.4757	.3476	.1008	.0273
Age ≥80	−.6613	.3359	.2407	.0846
POOR	−.5513	.3141	.1803	.0569

group, the present data cannot provide reliable information about the age effects. The results also indicate a positive effect for repeated analgesics but this effect is not statistically significant in the random-coefficient model. The positive effect in the first model can be explained by the higher severity of the case where repeated analgesics were applied, which is partly captured by the random coefficients in the second model. The results also suggest a negative correlation between subjective quality and the pain level: it is possible that the psychological factors linked to medical care have conditioned the perception of pain.

Because of the non-linearity of the model, the relative effect of different factors can only be analyzed using the marginal effects. The estimated marginal effects at the sample mean are provided in Table 4. These estimates measure the change in the probability of a given pain level due to a one-unit increase in the corresponding explanatory variable. For instance, according to the random coefficient model, compared to female patients, the maless are 27.6% more likely to report no pain (level 0) and 23.1% less likely to report minor pain (level 1).

In general, the results in the table suggest that the marginal effect of virtually all the variables has a lower magnitude for high levels of pain. This might suggest that in lower pain levels, a larger fraction of variation in pain can be explained by the explanatory variables. Particularly, this pattern in analgesic time effects can be considered as suggestive evidence that analgesics can be less effective when pain is strong.

The estimated marginal effects of times after surgery (T_SURG) and analgesics (T_ANAL) for moderate pain levels (Table 4) indicate that the effect of the latter variable is on average about two thirds of the former in absolute value, whereas the coefficients of the corresponding square terms are more or less similar. This implies that the appeasing effect of the analgesics after 3 h is approximately equal to the pain increase suggesting that analgesia will be most effective if it is administered as early as possible that is, immediately after the operation or possibly even a few hours prior to the operation.

4. Discussion

This paper proposed an ordered discrete choice model to analyze the development of post-operative pain. The evolution of pain has been considered using two time variables measuring, respectively, the time after the operation and the hours elapsed after the administration of the analgesics. The model can account for some of the unobserved factors, especially those related to differences in pain perception among patients. Using data from a sample of orthopedic patients it has been shown that the proposed model can be used to obtain plausible and meaningful estimates of the effects of various factors such as time and patient characteristics.

The reported empirical analysis has a few shortcomings that could be considered with caution before extending the results to other contexts. First, the data used in this study was limited to a relatively small sample of patients and to a short period (24 h) after the surgical interventions. Secondly, considering that the time effects on pain could strongly depend upon the intervention and the analgesic type, assuming a similar quadratic functional form might be restrictive. Refining the model to account for such variations would require more data. Finally, as a one-dimensional measure of perceived intensity the pain scale used in this study ignores other important clinical factors and undesired consequences. However, it should be noted that the above limitations are mainly related to the available data rather than the adopted methodology. In fact the proposed framework can be used for other pain scales and is readily extensible for modeling different coefficients or functional forms for various analgesics.[7]

The results indicate that the perception of pain and the analgesic effects might vary considerably across individuals. Such unobserved heterogeneity can be partly taken into account using random coefficient models. While confirming a significant appeasing effect for the applied analgesics, the analysis shows that time has a crucial effect in the development of the post-operative pain as well as the analgesic effects: both these effects appear gradually but at a slightly decreasing rate. The results also suggest that analgesics are most effective if they are administered preemptively and as early as possible after the operation.

A conclusive evaluation of the proposed methodology will require further research especially in the application of the model in other data and larger samples. In particular with sufficiently large data the adopted model can be used to identify the treatment effect of different analgesics on various patient groups as well as the effect of various risk factors in the evolution of post-surgical pain. Such analyses can be used for a more effective allocation of resources among different cases.

The results of this study have two clear implications that could be used both at the hospital level and by policy makers. First, the effect of analgesia is a function of time and an effective management of pain relief depends upon an optimal timing. In particular in cases where undesired long-term effects are not important or can be controlled, early preemptive analgesia is more effective than later relief measures upon manifestation of pain. Of course this result should be considered in relation with the scope and time horizon covered in the data. Secondly, the considerable variation of pain development and analgesic effects among individual cases suggest that an effective analgesia requires a case-specific clinical assessment that cannot be replaced by statistical analyses such as the one presented in this paper. However, while policy makers as well as health policy researchers can greatly benefit from communication with medical experts in identifying the sources of variations across individual cases, physicians and micro-level decision makers can use the results of statistical analyses as a general guidance in combination with clinical assessments, in order to increase the effectiveness of pain relief measures.

[7] For instance, as one of the referees suggested, the time effects might be influenced by the analgesic's pharmacokinetic properties such as half-life. These inter-relationships can be easily explored using the proposed statistical model by including the analgesic's corresponding parameters in the model specification.

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