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# Preventive Prescribing of Laxatives for Opioid-induced Constipation Using Electronic Clinical Rule Implementation by Cinical Pharmacists

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## Abstract

**Objective:** The objective of this study was: (1) to develop and validate an electronic clinical rule for 'Opioid-Laxative Use' and to implement this rule in clinical pharmacy practice; (2) to improve guideline compliance by using this refined clinical rule; and (3) to investigate if opioid-induced constipation (OIC) can be reduced in hospitalised patients by the application of this clinical rule.

**Methods:** Interventions using clinical rule alerts were performed between June and September 2009. We compared guideline compliance before and after the intervention to determine the difference. Interventions consisted of telephone consultations by a clinical pharmacist advising physicians to add a laxative to opioid therapy. Patient files were matched to a historical control group using an opioid without a laxative to examine the difference between intervention- and control patients in the presence of OIC.

**Results:** Prospective validation of the rule resulted in several refinements. In the intervention period, 140 alerts were generated, 60 of which (43%) led to co-prescription of a laxative. Therefore, guideline compliance increased from 70% to 83%. A significant difference in OIC was found between the intervention group (12%) and the control group (56%).

**Conclusions:** This study showed that pharmacy intervention based on an electronic clinical rule for ´Opioid-Laxative Use´ led to more adequate co-prescription of opioids and laxatives. This led to a better compliance with the guideline as well as a better outcome, as measured by the significant decrease in the prevalence of OIC.

**Keywords:** Gastrointestinal tract; Computerised physician order entry; Opioid-induced constipation; Clinical decision support systems

## Introduction

While opioids are the cornerstone of pain management for moderate to severe cancer pain and chronic non-cancer pain, the use of opioids is commonly associated with opioid-induced bowel dysfunction, which has a serious impact on patients' quality of life. The gastrointestinal (GI) tract is an important site of opioid-related adverse effects due to the presence of opioid receptors, whose activation by exogenous opioids disrupts GI motility and secretion, thereby inhibiting normal bowel function [1]. These adverse events include a range of different gastrointestinal symptoms, including straining, hard stools, incomplete evacuation, abdominal distension, bloating, increased gastroesophageal reflux and constipation [2].

Constipation is the most common and often most debilitating adverse event while using opioids, with a reported incidence of 41% in patients with chronic non-cancer pain treated with morphine [3]. Pappagallo found that 80% of patients receiving opioids required at least one treatment for constipation, while 58% needed two or more treatments [4]. In another study surveying 2,055 patients using opioids for non-cancer pain, 57% reported having constipation associated with opioid treatment [5]. Of these patients, 33% considered constipation to be the most bothersome adverse event associated with their opioid treatment.

Reducing or avoiding opioid-induced constipation (OIC) is an important objective for improving the management of patients with chronic pain. Opioid dose reduction or discontinuation of opioid therapy negatively affects pain management and severely impairs patients' quality of life [1]. Therefore, preventing the occurrence of OIC remains the best treatment. First, guidelines generally recommend non-pharmacological interventions, such as increasing dietary fibre and fluid intake and encouraging mobility. However, these interventions are usually insufficient to prevent or treat OIC, and most patients receiving long-term opioid therapy require pharmacological intervention. Several types of pharmacological agents are available for treating OIC, including stool softeners, bowel stimulants and bulk laxatives, which are all grouped as laxatives in this paper.

It is widely advised to start a laxative concurrently with opioids before OIC can occur. However, a study which assessed laxative prescription in patients receiving a strong opioid for the first time showed that only 37% of patients started taking laxatives within 5 days of starting opioid therapy [6-8]. In community practice in the Netherlands, a laxative is prescribed for only 15-50% of patients starting opioids [9].

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Retrospective research in the Catharina Hospital in Eindhoven in 2008 showed that co-prescription of a laxative was omitted at the start of therapy in 67% of clinical patients receiving opioids [9,10]. A study by Bouvy et al. showed that pharmacy intervention can lead to better opioid and laxative combination therapy in the community setting [6].

To our knowledge, no research has been performed on pharmacy intervention to improve opioid and laxative combination therapy in a hospital setting, and the effects on clinical outcomes have not been studied. In clinical practice, problems like OIC may potentially be prevented with the help of electronic clinical decision support systems (CDSSs). These systems are computer-based information systems which integrate clinical information and patient information to support decision making in patient care [11]. For example, clinical information on drugs or laboratory values can be used to generate alerts when a patient is not treated according to the guidelines. This information from guidelines and protocols can be translated into clinical rules: decision support algorithms, which are integrated in the CDSS. In the Catharina Hospital, research on clinical rules started in 1998. Since then, many clinical rules have been developed and implemented in clinical practice: for example, the clinical rule 'NSAIDs and Prophylactic Gastro-Protection' or the clinical rule 'Renal Impairement' [10].

The objective of the present study consists of three parts:

- to develop and validate a clinical rule for 'Opioid-Laxative Use' and to implement this rule in clinical pharmacy practice;
- to improve guideline compliance by using this refined clinical rule;
- and to investigate if opioid-induced constipation can be reduced in hospitalised patients by the application of this clinical rule.

## Methods

### Study site

This study was conducted in the Catharina Hospital in Eindhoven, The Netherlands, which is a 600-bed university-affiliated hospital. The hospital uses an electronic health record (EHR) (CS-EZIS, Chipsoft BV, Amsterdam) with integrated computerised physician order entry (CPOE). In this system, most patient data (medication, laboratory data, therapy, microbiology, diagnosis, etc.) are recorded. The integrated CPOE includes basic drug-oriented decision support, such as drug-drug interactions and drug-dose checking, based on the nationally established electronic drug database (WinAp, G-standard, Den Haag, The Netherlands) [12]. Since 2004, the Department of Pharmacy at the Catharina Hospital has been involved in the development of a strategy for designing and validating clinical rules by means of an advanced clinical decision support system–the CDSS Gaston (Medecs BV, Eindhoven).

### Decision support system

In this study, the CDSS Gaston was used. This system, which is commercially available worldwide, was developed in 1998 at the Technical University Eindhoven in collaboration with our hospital. Technical assistance during our research was supplied by Medecs BV. The CDSS Gaston is linked to our EHR, which allows the electronic data stored in the EHR to be used in clinical rules [13,14]. The CDSS consists of two modules: (1) a guideline editor for developing electronic guidelines and (2) a guideline execution engine. The editor is a user-friendly environment, in which clinical rules are built as flowcharts. The steps in the flowchart contain the selection definitions based on the parameters that are available in the EHR. The engine is used for retro- and prospective database research and prospective alerting.

### Clinical rule 'Opioid-Laxative Use'

In 2008, the clinical rule for ´Opioid-Laxative Use´ was developed according to a strategy designed in our hospital. This strategy is based on the Plan-Do-Check-Act cycle and includes an expert team that optimises the quality and clinical relevance of clinical rules [10]. The 'Opioid-Laxative Use' rule was specifically selected for development based on a national study that identified high-risk patients with medication-related problems leading to hospital admission [15].

The first draft of the clinical rule was designed to generate an alert when a patient uses an opioid without a laxative. This clinical rule was designed and retrospectively validated in a previous study. Patients were included if a new prescription for a drug from the category ´opioid analgesics´ had been made in the previous 24 hours. Piritramide and sufentanyl are mostly used for a short post-surgery period. Therefore, these drugs were only included in the rule if they were used for more than 72 hours. The clinical rule was prospectively validated according to the development strategy to fine-tune the clinical rule so that it leads only to relevant alerts [10]. The adaptations made to the clinical rule are shown in Figure 1 and described in the Results section.

### Site setup and participants

The development of the clinical rule was carried out by the *research team*, consisting of a pharmacist who built the clinical rule, a hospital pharmacist/clinical pharmacologist and a research pharmacist experienced in decision support. Time investment for this rule was three months full time (spread over six months) for the pharmacist and one hour a week for six months for the other two members of the research team. Furthermore, the clinical relevance was monitored by an *expert team* that consisted of two specialised physicians (an anaesthesiologist and an oncologist) and an experienced hospital pharmacist, all of them experts on pain management.

From June until September 2009, the clinical rule ´Opioid-Laxative Use´ was implemented in daily hospital practice (intervention phase). This clinical rule included all patients admitted to the hospital except for intensive care patients. If a patient met all criteria defined in the clinical rule, an alert was generated.

Once a day at noon, an (Excel) list of alerts was generated by the CDSS and placed on the electronic pharmacy desktop. The relevance of each alert was first evaluated by a hospital pharmacist, who then consulted the physician on duty by telephone to discuss the recommendation. Subsequently, the physician decided whether or not to follow the recommendation. In our hospital, we recommended that the physician start macrogol, as it was the laxative of first choice. Also, the physician was asked why a laxative had not been co-prescribed with the opioid initially.

### Outcome values

The main outcome value in this study was the percentage of patients having OIC. During the intervention phase from June 2009 until September 2009, the first 50 consecutive patients with a successful intervention were collected. A successful intervention was defined as the start of a prescription for a laxative within 24 hours after the hospital pharmacist consulted the physician. These 50 patients were matched to 50 controls collected in the period January 2009 until June 2009 (control phase), in which the clinical rule had not been used. These control patients were selected for using an opioid without a

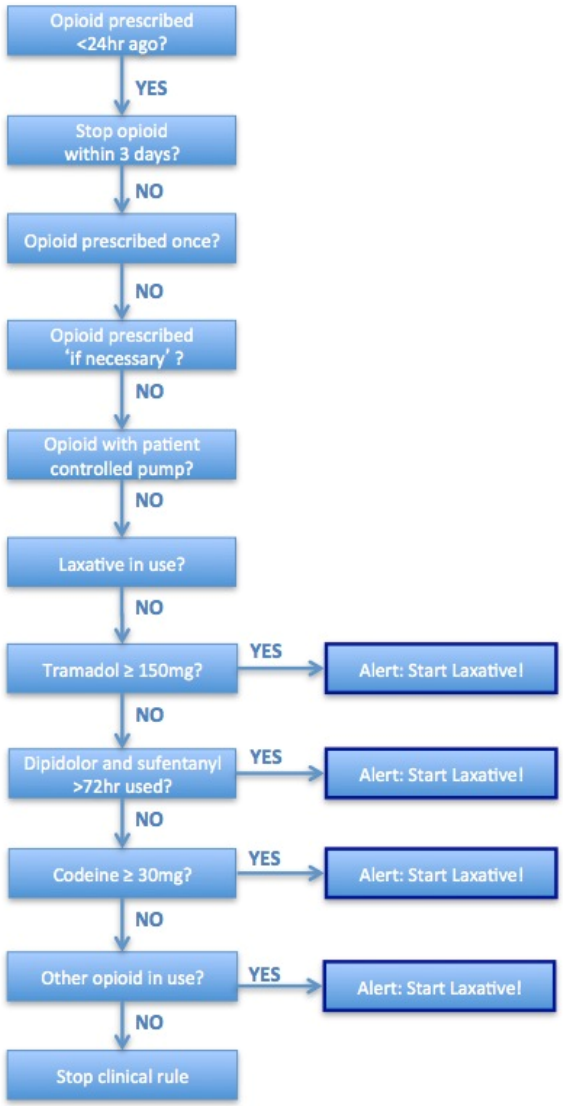


**Figure 1:** Schematic flowchart of the clinical rule for ´Opioid-Laxative Use´.

prescription for a laxative. Patients were matched for sex, age (± 10 years), opioid and department (surgery vs. non-surgery). To assess the presence of OIC, all patient files were investigated by three independent researchers. In case of uncertainty, the patient file was evaluated by all three researchers. OIC was scored binomially as a combined outcome parameter: no defecation for 3 or more days and/or a notification of constipation in the patient file and/or the start of a laxative during treatment with opioids. We also evaluated the combined use of an opioid and laxative at the moment of discharge from the hospital.

Secondly, the percentage of guideline compliance was measured before and after the intervention phase and the results were compared to determine the difference. According to the guideline, every patient using an opioid needs a co-prescription of a laxative. The percentage of patients using opioids and a co-prescription of a laxative was measured in the control phase as well as in the intervention phase.

This study was approved by the independent Medical Research Ethics Committee of the Catharina Hospital, indicating that the Medical Research Involving Human Subjects Act does not apply for this study.

PSS (Version 19) was used to analyse the results using an ANOVA test for continuous variables and a two-sided chi-square test for categorical variables at a significance level of $\alpha=0.05$ and $1-\beta=0.80$.

## Results

### Refinement of the clinical rule 'Opioid-Laxative Use'

Prospective validation of the clinical rule using the validation strategy with the expert team led to the following refinements:

• Patients using opioids as a component of self-manufactured products of our hospital pharmacy were included.

• Patients using stool hardeners (e.g loperamide) were excluded.

• Patients using an opioid planned to stop within 3 days were excluded.

• Patients using opioids in a patient-controlled analgesia pump who used an opioid only once or only when necessary were excluded.

• Patients using the weak opioids tramadol or codeine in a dosage equal to or below 150 mg a day or 30 mg a day respectively were excluded. This choice was based on the registered doses for pain management.

Figure 1 shows the final schematic flowchart of the clinical rule. The expert team found that all alerts generated by the CDSS during prospective validation were clinically relevant, expressed as a positive predictive value of 100% [10].

### Guideline compliance

The first draft of the clinical rule for ´Opioid-Laxative Use´ showed that 67% of the patients using opioids had no co-prescription of a laxative [10]. Refinement through the validation strategy (Plan-Do-Check-Act) showed that the clinical rule could be adjusted to select only patients who actually need intervention according to the expert team. The refined rule was tested retrospectively on 50 patients from the control group and this showed that for 30% of the patients using opioids, a laxative was omitted. This percentage of non-compliance with the rule could be further reduced to 17% by pharmacy intervention using the alerts generated by the CDSS.

### Intervention study

During 100 days of intervention, 140 alerts were generated by the CDSS. First the physicians were asked why a laxative had not yet been prescribed; in most cases the laxative had been forgotten (Figure 2a). Secondly, the advice to start a laxative was given, which in 43% of the cases (60/140) led to a successful intervention (Figure 2b). For 57% of patients, consultation did not lead to an intervention. Fourteen patients (10%) had already been discharged at the time of intervention. For 44 patients, the physician made the deliberate choice not to prescribe a laxative, and for 22 patients, the physician forgot the prescription after consultation by telephone (Figure 2). Reasons for deliberately not starting a laxative were that patients were receiving terminal care with opioids (28 times), patients had diarrhoea (eight times), patients had already used the opioid without a laxative and without OIC before admission (five times), and the physician was not persuaded to start a laxative before OIC occurred (three times).

Of the 60 patients with a successful intervention, 10 were excluded

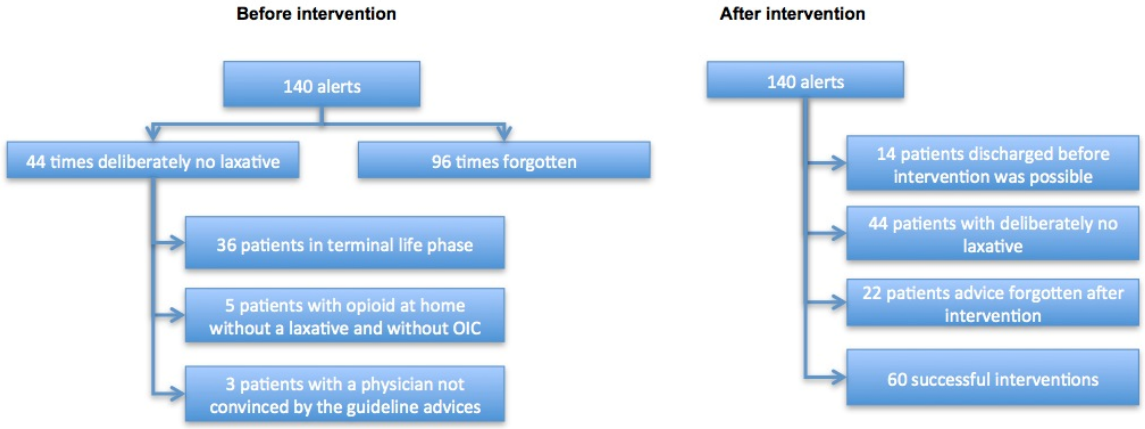


**Figure 2:** Schematic representation of the physicians' reasons why a laxative had not been added before intervention and the results after intervention.

| | Interventions (n=50) | Controls (n=50) | P-value |
|---|---|---|---|
| Average age (yr ± SD) | 65.7 (±2.0) | 65.6 (±11.2) | n.s. |
| Gender male/female | 26/24 | 26/24 | n.s. |
| Non-surgery vs. surgery department | 32 vs.18 | 33 vs.17 | n.s. |
| Constipation developed during stay | 6 | 28 | <0.001 |
| Opioid use <5 days | 15 | 12 | n.s. |
| Laxative prescribed within 5 days | 50 | 16 | <0.001 |
| Discharged with opioid, with laxative | 27 | 13 | 0.04 |
| Discharged with opioid, without laxative | 5 | 22 | <0.001 |
| Discharged without opioid, with laxative | 4 | 2 | n.s. |
| Discharged without opioid, without laxative | 14 | 15 | n.s. |

n.s.=not significant

**Table 1:** General study characteristics and results of the intervention study.

for having an incomplete patient record. Therefore, 50 patients with a successful intervention and a complete dossier were matched to 50 controls with a complete dossier showing the defecation status during admission.

In the matched control group without intervention, 28 patients (56%) developed OIC compared to six patients (12%) in the intervention group (Table 1). This result is statistically significant ($p<0.001$). Also, the two groups showed a significant difference in the number of patients discharged with an active opioid prescription.

## Discussion

This study validated and refined the clinical rule for ´Opioid-Laxative Use´ and investigated the effect of the refined rule on guideline compliance after implementation in daily hospital practice. It demonstrated that this clinical rule can be optimised to select only those patients who need a laxative prescription in combination with their opioid therapy. Also, it showed that implementation of this rule led to a significant decrease in the prevalence of opioid-induced constipation. A key strength of this study was that, to our knowledge, it was the first to investigate clinical outcomes of adding a laxative to opioid therapy. Despite the fact that this advice is widely given in current guidelines and is mandatory according to Dutch Health Authority, we did not find other studies reporting on a reduction of OIC after increasing guideline compliance.

Before implementation of the clinical rule, 30% of the patients using opioids had no co-prescription of a laxative. By applying the clinical rule to our admitted patients, guideline non-compliance was reduced to 17%. Although this was an improvement in guideline compliance, we found that the follow-up of the interventions remained low (43%). However, in many cases the physician had a valid reason for not prescribing a laxative: for example, for patients with diarrhoea or in a terminal phase of life. For 22 patients the intervention was forgotten, so there is still room for improvement. Further research is needed to find a solution for increasing guideline and alert compliance.

Prospective validation is an important step in the development of a clinical rule [10,16,17]. Despite the consultation of an expert team in the earlier phases of validation, many changes were still required to optimise the clinical rule during prospective validation. This confirms that structured development and validation of clinical rules are crucial before widespread implementation in clinical practice [10,16,17]. In the near future, the rule will be further optimised: for instance, when data on the bowel elimination (e.g., diarrhoea) of patients have been added to the EHR.

The importance of adding a laxative to opioid therapy is evident. Constipation occurred even in the intervention group, which reinforces the recommendation to add a laxative in opioid therapy. However, little is known about which opioid leads to OIC most often and whether or not this is a dosage-related side effect. For this reason, the content of the rule is partly based on expert opinion rather than on evidence from literature. Further literature research might clarify this issue [18].

Several types of pharmacologic agents are used to treat opioid-induced constipation, including osmotic or lubricant laxatives, stimulant laxatives and prokinetics. Newer studies in this area suggest that the effects of these ´older´ therapies are non-specific and generally unpredictable, often generating diarrhoea or cramps. In our study, these newer therapies were not included, as they were not available in our hospital during the study period.

This study showed a significant effect on OIC in a relatively small group of patients. A larger number of patients is needed to address the difference in effect in relation to different opioids, sex or age differences or differences between hospital departments.

This study showed that pharmacy intervention is a suitable method

for implementing a clinical rule in daily practice. However, this method was not compared with other possible alerting methods. Currently, we are investigating the options to make the co-prescription of the laxative more transparent. We found that it was not always clear to the physicians that the laxative was started only for prevention of OIC. For example, this study showed that three patients in the intervention group were discharged with a prescription for a laxative but not for an opioid. A solution could be the development of pre-defined combination prescriptions that are easy for a physician to prescribe. An important subject for further investigation will be how to integrate these new and promising systems into clinical workflow.

## Conclusion

This study showed that pharmacy intervention based on an electronic clinical rule for ´Opioid-Laxative Use´ led to better co-prescription of opioids and laxatives. This led to a better compliance with the guideline as well as a better outcome, as measured by the significant decrease in the prevalence of OIC. Therefore, we conclude that the use of this electronic rule increases medication safety. As a co-prescription is not always indicated, the addition of a laxative to opioid therapy should always be prescribed in consultation with the physician.

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### Ethical Standards

All human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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