Cohort Study

Pediatric Hip Disease Increases the Risk for Opioid Use in Adulthood: Long-term Burden of Pain and Depression

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Background: Legg-Calvé-Perthes disease (LCPD) and slipped capital femoral epiphysis (SCFE) can result in painful deformation of the hip joint with impaired range of motion and early development of secondary osteoarthritis. It has not been investigated whether having LCPD or SCFE is associated with increased use of pain or antidepressant drug prescriptions later in life.

Objective: With this study, we aimed to investigate if patients with a history of LCPD or SCFE have an increased risk of prescription analgesic or antidepressant drugs in adulthood compared with matched controls.

Study Design: The included patients were identified by the Swedish Patient Register and matched for age, gender, and residency with 10 control individuals not exposed to any of the mentioned pediatric hip diseases, by the Swedish National Population Register.

Setting: This was a nationwide, registry-based cohort study which included 1,292 patients diagnosed with LCPD at age 2-15 years and 1,613 patients diagnosed with SCFE at age 5-16 years and > 17 years from 2005 through 2011.

Methods: Prescription data of first-line analgesic drugs (acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids), or first-line antidepressant drugs (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants) were derived from the Swedish Prescribed Drugs Register. Conditional logistic regression models were fitted to estimate the relative risk for the prescription in exposed compared with unexposed individuals. Adjustment was performed for gender and birth year.

Results: In the group with an LCPD diagnosis, the adjusted odds ratio for analgesic prescriptions overall was 1.3 (95% CI, 1.2-1.5). For patients with an SCFE diagnosis, the adjusted odds ratio for analgesic prescriptions overall was 1.4 (95% CI, 1.3-1.6). Among patients with an LCPD diagnosis, the adjusted odds ratio for antidepressant prescriptions overall was 1.0 (95% CI, 0.8–1.2). For patients with an SCFE diagnosis, the adjusted odds ratio was 1.2 (95% CI, 1.1-1.4).

Limitations: As with all register studies, there are known associated biases such as selection, detection, and observational bias as well as the uncertain quality of input data. Further, the Swedish Prescribed Drugs Register only includes drugs that were prescribed by a physician and dispensed at a pharmacy. This is also a factor that may lead to underestimating the use of acetaminophen and nonsteroidal anti-inflammatory drugs, as these drugs can be acquired "over the counter."

Conclusion: During childhood, patients with LCPD or SCFE seem to suffer long-term pain and have an increased risk of requiring analgesic medication in adulthood, including opioids. It is important to assess the causes, type, and severity of pain to optimize pain management to counteract possible overuse in these patients. Seemingly, patients with LCPD do not have an increased risk for antidepressant drug therapy in adulthood whereas we did see an increased risk for that in patients with previous SCFE compared with the general population.

Key words: Pediatric hip disease, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, pain, chronic pain, depression, medication, drugs, opioids

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Long-term pain places a great burden on an individual level and on society. Pain management is costly and pain itself is often associated with social disabilities and decreased well-being (1). It is of utmost importance that patients that are at risk for chronic pain are detected and addressed at an early stage to prevent long-term complications and the potential misuse of analgesic drugs (2). Overprescribing and overconsumption of opioids in pain management have serious public health implications and have attracted attention in the US and Europe (3-5). The prevalence of chronic pain in Europe is estimated to be between 12% and 30% (6). Patients with chronic pain are known to have a poorer quality of life. In addition to pain, the risk of developing depression is increased in pediatric and adult patients with painful chronic diseases (7,8).

Legg-Calvé-Perthes disease (LCPD) and slipped capital femoral epiphysiolysis (SCFE) are pediatric hip diseases associated with pain during the course of the disease. In adulthood, an increased risk of premature secondary hip osteoarthritis (OA) has been described (9). Common symptoms of secondary OA are pain and stiffness deriving from the hip joint; this, in turn, can lead to total hip arthroplasty surgery (10,11). Patients with a history of pediatric hip disease and secondary OA generally undergo total hip arthroplasty surgery at a younger age than patients with primary OA (12). However, until total hip arthroplasty surgery is performed, a period of pain precedes it (13) and commonly analgesic prescriptions are initiated earlier than nonpharmacological interventions (14).

In patients with LCPD, a higher risk for depression and a lower health-related quality of life has been described (15,16), but whether or not this contributes to a higher pain perception is unknown. In contrast, in adult patients with a history of SCFE, the risk for depression is the same as in the general population (17). Few studies address the course of pain in these patients later in life when the patients are confronted with the possible sequelae of the disease (18,19). This study aimed to evaluate the burden of LCPD and SCFE expressed in the use of pain and antidepressant drugs later in life.

We sought to find out the following: Do patients with a history of LCPD or SCFE have an overall increased risk for an analgesic drug prescription in adulthood compared with matched controls? Do patients with a history of LCPD or SCFE have an overall increased risk for an antidepressant drug prescription in adulthood compared with matched controls? Is there an increased risk for a long-term prescription (> 12 months) of analgesics and antidepressants in this cohort compared with matched controls?

Methods

Study Design and Setting

Pain is an individual experience and therefore difficult to compare objectively. An analysis of analgesic drugs prescriptions is, therefore, more objective. The latter requires a patient's personal engagement to contact the health care system followed by an examination by a physician who then decides together with the patient about the necessity of a pain drug prescription. Antidepressant drug therapy also requires a physician's assessment for diagnosis and prescription. The recommended first-line drugs for pain management in Sweden are acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. The recommended first-line drugs for depression management in Sweden are selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and tricyclic antidepressant (TCA). These drugs are therefore investigated in this study.

In Sweden, all citizens registered in the Swedish National Population Registry receive a personal identity number. This facilitates collecting data at an individual level in other national registries. The Swedish Patient Register was used to identify all patients from 1964 (when the register started) through 2011 with a diagnosis of LCPD (ICD-7: 732.04, ICD-8: 722.11, ICD-9: 732B, ICD-10: M91.1 and M91.2) and SCFE (ICD-7: 732.03, ICD-8: 722.10, ICD-9: 732C, ICD-10: M93.0). For each patient, 10 controls were matched by utilizing the Swedish National Population Registry.

Selected matching variables were the date of birth, gender, region of residence, and being alive at the time of an LCPD or SCFE diagnosis. Any prescription of analgesic drugs or antidepressant drugs linked to the patients and their matched controls during adulthood were retrieved from the Swedish prescribed drug register (SPDR). This register started in 2005 and contains all prescribed drugs in Sweden dispensed at pharmacies.

Study Patients

The process of selecting the final study population from the initial dataset is illustrated for patients with LCPD (Fig. 1) and patients with SCFE (Fig. 2). After taking into account the age restriction described above,

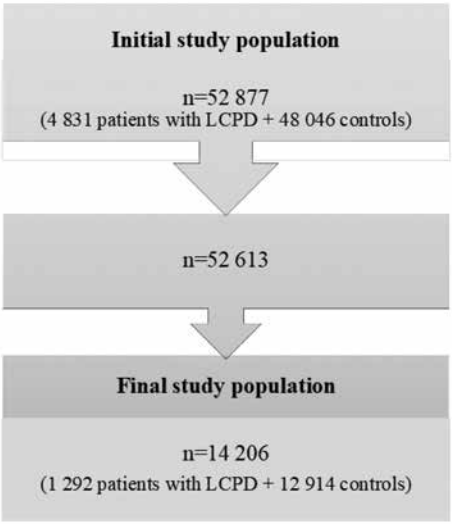

Fig. 1. *Method of selection of study population with an LCPD diagnosis and their controls. The Swedish Patient Register (SPR) was used to identify all patients from 1964 (when the SPR started) through 2011 with a diagnosis of LCPD.*

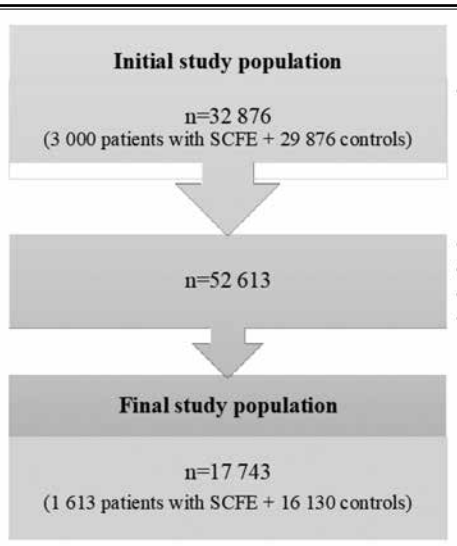

Fig. 2. *Method of selection of study population with an SCFE diagnosis and their controls. The Swedish Patient Register (SPR) was used to identify all patients from 1964 (when the SPR started) through 2011 with a diagnosis of SCFE.*

the mean age at LCPD onset was 7 years (range 2–16) and for SCFE onset the mean age was 13 years (range 5-16) (Fig. 3). The characteristics of the final study population are shown in Table 1.

Statistical Analysis, Study Size

Follow-up continued through December 31, 2011, emigration or death, whichever occurred first. Means (SD) were used to describe continuous variables; the χ^2 test was used to assess categorical data. Statistical significance was set at $P < 0.05$. Conditional logistic regression models were fitted to estimate the risk with 95% CI for the prescription of analgesic drugs (NSAIDs, acetaminophen, and opioids) and antidepressant drugs (SSRI, SNRI, and TCA), in exposed compared with unexposed individuals by using the SPDR. To consider that the risk assessments represent patients with long-term pain, we examined the risk for prescriptions with a duration longer than 12 months, in a subgroup analysis. All statistical analyses were performed using R statistical software, version 4.1.2, and R studio, version 1.4.1717 (R Foundation).

Results

Prescriptions of Analgesic Drugs in Patients With a History of LCPD and SCFE

Patients with a history of LCPD had an adjusted 1.3-fold higher risk odds ratio (OR) for analgesic drug prescriptions (95% CI, 1.2-1.5) compared to age and

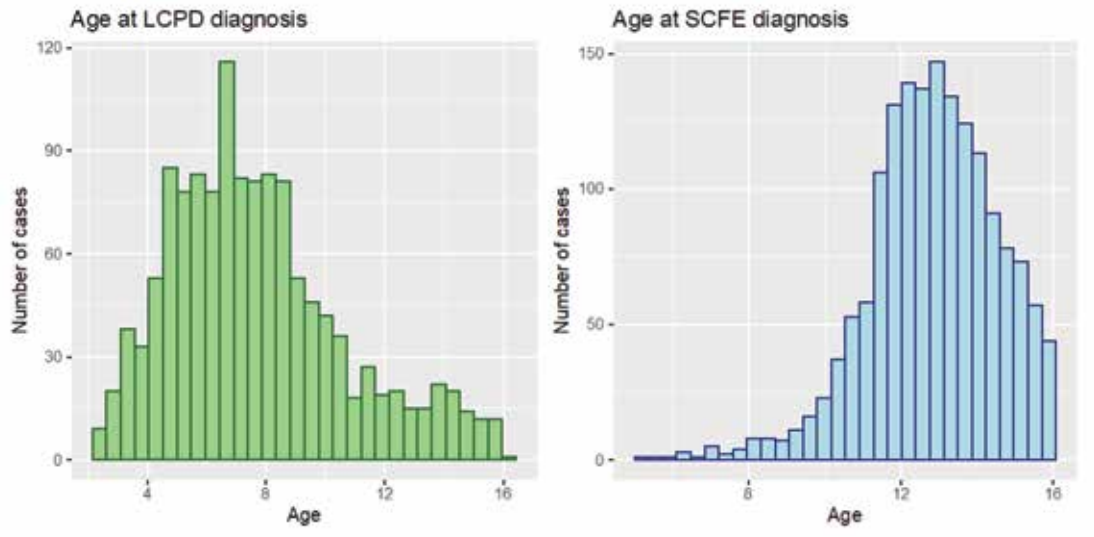

Fig. 3. *Mean age at LCPD diagnosis was 7.3 years (range 2.1-15.8 years). Mean age at SCFE diagnosis 12.6 years (range 5.3–16.0 years).*

Table 1. *Population of patients with LCPD or SCFE and age-and gender-matched controls. Ratio 1:10.*

	LCPD (n = 1,292)	Control (n = 12,914)	SCFE (n = 1,613)	Control (n = 16,130)
Gender				
Women (%)	253 (20)	2,530 (20)	603 (37)	6,030 (37)
Men (%)	1,039 (80)	10,384 (80)	1,010 (63)	10,100 (63)
Mean follow-up time (range)	36 (9–62)		40 (6–60)	
Mean age at follow-up (range)	37.3 (25.0–62.3)		38.9 (25.0–63.7)	

gender-matched controls. Details of the unadjusted and adjusted risks for the prescriptions of the different analgesic drugs are shown in Table 2. Stratification for gender showed slightly higher risks for pain drug prescriptions in women (acetaminophen and opioid drugs) than in men compared to their respectively matched controls (Table 3a). In patients with a history of LCPD, 37% had analgesic drug prescriptions for more than 12 months, compared to 28% of the matched control individuals. The overall adjusted risk for a long-term prescription (> 12 months) of analgesics was 1.5 (95% CI, 1.3–1.8).

Patients with a history of SCFE had an adjusted 1.5-fold higher risk OR for analgesic drug prescriptions (95% CI, 1.3-1.6) compared to age and gender-matched controls. In detail, the unadjusted and adjusted risks for the prescriptions of the different analgesic drugs are shown in Table 2. Stratification for gender showed a higher risk for pain drug prescriptions in women than in men, compared to their respectively matched controls (Table 3b). In patients with a history of SCFE, 45% had analgesic drug prescriptions for > 12 months, compared to 31% of the matched controls. We found an increased overall adjusted risk of 1.8 (95% CI, 1.6–2.1) for a long-term prescription (> 12 months) of analgesics.

Prescriptions of Antidepressant Drugs in Patients With a History of LCPD and SCFE

In patients with a history of LCPD, we found no increase in the risk for an antidepressant drug prescription compared to their age and gender-matched controls. In Table 2, the OR for each antidepressant drug group is presented. Stratification for gender did not reveal any gender-specific risk changes (Table 3a). Twelve percent of patients with previous LCPD and 15% of the control population had prescriptions for antidepressant therapy for more than one year. We found a slightly decreased OR 0.8 (95% CI, 0.6–1) for long-term prescriptions.

For patients with a history of SCFE, the adjusted overall risk for the prescription of antidepressant drugs was 1.2 (95% CI, 1.1-1.4) compared to their age- and

Table 2. *Adjusted odds ratio for a drug prescription in patients with LCPD or SCFE in adulthood.*

	LCPD				SCFE			
	Crude		Adjusted*		Crude		Adjusted*	
	OR	CI (95%)	OR*	CI (95%)	OR	CI (95%)	OR	CI (95%)
Analgesic	1.3	1.2–1.5	1.3	1.2–1.5	1.4	1.3–1.6	1.5	1.3–1.6
NSAID	1.3	1.1–1.4	1.3	1.1–1.4	1.4	1.2–1.5	1.3	1.2–1.5
Acetaminophen	1.6	1.4–1.8	1.6	1.4–1.8	1.9	1.7–2.1	1.9	1.7–2.2
Opioids	1.6	1.4–1.8	1.6	1.4–1.8	1.7	1.6–1.9	1.8	1.6–2.0
Antidepressant	1.0	0.8–1.2	1.0	0.8–1.2	1.2	1.1–1.4	1.2	1.1–1.4
SSRI	1.0	0.8–1.2	1.0	0.8–1.2	1.2	1.0–1.4	1.2	1.0–1.4
SNRI	1.1	0.8–1.4	1.1	0.8–1.4	1.0	0.7–1.3	1.0	0.7–1.3
TCA	1.1	0.7–1.6	1.1	0.7–1.6	1.4	1.0–1.9	1.4	1.0–1.9

*Adjusted for birth year and gender

Table 3a. *Adjusted odds ratio for a drug prescription in patients with LCPD in adulthood, stratified for gender.*

	Women				Men			
	Crude		Adjusted*		Crude		Adjusted*	
	OR	CI (95%)	OR*	CI (95%)	OR	CI (95%)	OR	CI (95%)
Analgesic	1.5	1.2–2.0	1.5	1.2–2.0	1.3	1.1–1.4	1.3	1.1–1.4
NSAID	1.4	1.1–1.8	1.4	1.1–1.8	1.3	1.1–1.4	1.3	1.1–1.4
Acetaminophen	1.9	1.4–2.6	1.9	1.5–2.6	1.5	1.3–1.7	1.5	1.3–1.7
Opioids	2.1	1.6–2.7	2.1	1.6–2.7	1.4	1.2–1.7	1.4	1.2–1.7
Antidepressant	1.1	0.8–1.5	1.1	0.8–1.5	0.9	0.8–1.1	0.9	0.8–1.1
SSRI	1.2	0.8–1.6	1.2	0.8–1.6	1.1	0.7–1.1	0.9	0.7–1.1
SNRI	1.0	0.6–1.8	1.0	0.6–1.8	1.1	0.7–1.5	1.1	0.7–1.5
TCA	1.2	0.6–2.3	1.2	0.6–2.3	1.0	0.6–1.7	1.0	0.6–1.7

*Adjusted for birth year.

Table 3b. *Adjusted odds ratio for a drug prescription in patients with SCFE in adulthood, stratified for gender.*

	Women				Men			
	Crude		Adjusted*		Crude		Adjusted*	
	OR	CI (95%)	OR*	CI (95%)	OR	CI (95%)	OR	CI (95%)
Analgesic	1.9	1.6–2.2	1.9	1.6–2.2	1.3	1.1–1.4	1.3	1.1–1.4
NSAID	1.7	1.4–2.0	1.7	1.5–2.0	1.2	1.1–1.4	1.2	1.1–1.4
Acetaminophen	2.1	1.8–2.6	2.2	1.8–2.6	1.8	1.5–2.1	1.8	1.5–2.1
Opioids	1.9	1.6–2.2	1.9	1.6–2.3	1.6	1.4–1.9	1.7	1.4–1.9
Antidepressant	1.2	1.0–1.5	1.2	1.0–1.5	1.2	1.0–1.4	1.2	1.0–1.4
SSRI	1.2	0.9–1.4	1.2	0.9–1.4	1.2	1.0–1.5	1.2	1.0–1.5
SNRI	1.0	0.6–1.4	1.0	0.6–1.4	1.0	0.7–1.5	1.0	0.7–1.5
TCA	1.5	1.0–2.1	1.5	1.0–2.1	1.3	0.7–2.1	1.3	0.7–2.1

*Adjusted for birth year.

gender-matched controls. Detailed results are shown in Table 2. Stratification for gender revealed a slightly higher risk for antidepressant drug prescriptions in women than in men compared to their matched controls, respectively (Table 3b). Seventeen percent of patients with previous SCFE and 15% of the control population had prescriptions for antidepressant therapy for more than one year. We found similar risks for long-term prescriptions of antidepressant drug therapy for more than one year (OR 1.1; 95% CI, 0.9–1.3).

Discussion

Our study shows that patients with a history of LCPD and SCFE have a higher risk for analgesic drug prescription in adulthood compared to their controls. Patients with a history of LCPD had no increased risk for antidepressant drug prescription, but an increased risk for antidepressant drug prescription was noticed in patients with a history of SCFE, compared to their matched controls. However, this increase was not statistically significant when looking at the prescriptions of antidepressants lasting longer than one year.

Background and Rationale

These findings are important, giving awareness to this patient group that is at risk for developing long-term pain and depression. Chronic pain often demands analgesic therapy, which is an important part of the therapy for this condition. However, any initiation of analgesics, in particular opioids, should be well monitored and planned to avoid potential misuse, overuse, and the potentially lethal consequences of these drugs.

For many patients with chronic pain, possible co-existing depression is often overlooked, and therefore they might never get a clinical diagnosis of depression. Only about one-third of patients with depressive symptoms acquire antidepressant treatment (20). To optimize proper and timely pain management it is important to assess the exact causes, type, and severity of pain and address the psychological aspects in this patient group. This is to help these patients improve their physical, mental, and social functioning.

The association between depression and inferior outcomes of joint arthroplasties, such as the increased risk of complications and increased utilization of health careresources is well known (21,22). This is in agreement with other studies that investigated patients affected by both psychological and physical diseases, and found that they are at higher risk for morbidity and are linked to increased health care resource utilization, as well as poorer quality of life and poorer outcomes (23). Putting this knowledge into context, we can grasp the importance of taking care of the patient group with a history of LCPD or SCFE in a timely manner and introduce proper pain management.

From in-patient care during childhood, at pediatric orthopedic centers where the diagnosis of LCPD or SCFE are initially treated, these patients often do not return to orthopedic centers until they have symptoms of secondary OA and are referred for potential total hip arthroplasty surgery in adulthood. Since there is a transition over time in patient-responsible health care institutions, it is important that all medical professionals that may encounter this patient category pay attention to early signs of pain and depression. This is to prevent adverse events associated with chronic pain and to avoid the overuse of opioids in the young adult population.

Limitations

As with all register studies there are known associated biases such as selection, detection, and observational bias, as well as the uncertain quality of input data, although the quality of the SPDR is generally good (24). Unfortunately, the SPDR was first established in 2005. This might underestimate the risks for drug prescriptions, but this applies to both patients and controls. Further, the SPDR only includes drugs that were prescribed by a physician and dispensed at a pharmacy. This also is a factor that may lead to an underestimation of the use of acetaminophen and NSAIDs, as these drugs can be acquired over-the-counter.

Moreover, the collected data include only prescribed drugs through the end of 2011; one can argue these this data are not up to date. But the treatment regimen for LCPD and SCFE has not changed greatly since 2011 and the use of analgesics, in particular opioids, has increased in general in Sweden (25,26), suggesting that our results might present a lower risk for analgesic prescription and use than the reality.

The results of this study can also be affected by a potential surveillance bias. The patients in our study have often had close contact with the health care system since childhood when they were diagnosed with LCPD or SCFE. This in turn may have resulted in the initiation of pain management earlier than in the control group.

Adjusting for all matching variables is said to avoid bias when further confounders are present (27,28). However, in this study, we were not able to adjust for the matching variable "place of residence" because this variable is not available in the dataset. The fact that we could not adjust for all matching variables is not expected to significantly affect our results, as the geographic pattern of the diagnoses LCPD and SCFE are considered evenly distributed nationally.

Analgesics Drug Prescriptions

We noted an increased risk for analgesic drug prescriptions of the most common drugs for the treatment of nociceptive pain (acetaminophen, NSAIDs, and opi-

oids) in both patient groups compared to the general population. This increase persisted even after selectively looking at patients that had prescriptions for a longer period (> 12 months). This suggests an increased risk for long-term pain in adulthood following pediatric hip disease earlier in life; this is possibly related to the degenerative changes in the hip joint known to be associated with these conditions.

The fact that we see an increased risk for an analgesic drug prescription in these patient categories suggests a higher level of pain for them compared with an age- and gender-matched control group. But it is also conceivable that this is an effect of a well-monitored health status due to continual contact with health care since childhood.

Antidepressant Drug Prescription

This study found no increased risk for antidepressant therapy in adulthood succeeding LCPD in childhood compared to age- and gender-matched controls. Among patients with previous SCFE, we found a statistically significant increase in the risk for SSRI and TCA prescriptions in adulthood compared to age-and gender-matched controls. However, no increase in the risk for SNRI was detected. The increased risk for an SSRI prescription was expected as this is one of the first-line drugs for the treatment of depression. In contrast, the increased risk for TCA was unexpected as it has been used to manage neuropathic pain (29,30). However, patients with a history of pediatric hip disease are more likely to suffer from the nociceptive type of pain rather than neuropathic. Thus, it is more likely that the prescriptions of TCA we saw in this study were targeted at depression. Still, the exact reason for the increased risk of TCA prescriptions in patients with previous SCFE is unknown.

Conclusion

Patients with LCPD or SCFE during childhood seem to suffer long-term pain and have an increased risk of prescriptions for analgesic drugs in adulthood, including opioids. Patients who had LCPD do not have an increased risk for antidepressant drug therapy in adulthood, whereas we did see an increased risk in patients with previous SCFE compared with the general population. It is important to assess pain's causes, type, and severity to optimize pain management to counteract possible misuse or overuse in these patients.

Further research is needed to investigate if different treatment approaches in association with the disease's severity or proactive treatment of the sequelae of pediatric hip disease can reduce the analgesic prescription risk and its burden on LCPD and SCFE patients.

Significance

The information from this study can be used in the physician-patient meeting and assist in the planning of pain-managing strategies, as well as help patients in their coping process.

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