RESEARCH LETTER

Pain treatment and risk associated with the use of analgesics on admission to the internal medicine ward: a prospective observational study

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Introduction Pain is one of the most common symptoms in hospitalized patients. Among the individuals admitted to internal medicine wards (IMWs), its prevalence may exceed 60%.[1-3] Numerous patients experience pain for months before hospitalization; however, they are frequently not provided with adequate pain treatment.[3]

IMW patients comprise a complex population of mostly elderly individuals with chronic comorbidities, frequent multiple organ failure, poor cognitive status, and common polypharmacy; therefore, they are vulnerable to adverse drug reactions. The use of analgesics raises the risk of potentially serious adverse effects, some of which may have a negative impact on the course of chronic diseases.

Despite the high prevalence of pain in hospitalized patients, both undertreatment and inadequate therapy are significant health issues. Research on these topics remains scarce. The aim of this study was to evaluate pain characteristics as well as the effectiveness and safety of pharmacotherapy for pain among patients admitted to the IMW. We also sought to analyze the most common errors and risk of drug-drug interactions (DDIs) as well as drug-disease interactions associated with pain treatment.

Patients and methods We assessed 280 individuals consecutively admitted to the IMW of the H. Cegielski Medical Centre in Poznań, Poland between May 2019 and October 2020, and attended to by the first author (AS). Only the patients who reported pain on admission (n = 111 [39.6%]) were included in further analysis.

On admission, pain was evaluated using the Polish versions of the Brief Pain Inventory and Douleur Neuropathique 4,[4] supplemented with a questionnaire regarding pain exacerbations designed by the authors. The Numeric Rating Scale (NRS; range, 0–10) was applied to rate the pain intensity. The Edmonton Symptom Assessment System adapted to the Verbal Rating Scales was used to evaluate other symptoms.[5] Pharmacotherapy of pain and nonpharmacologic pain therapies were recorded. Information regarding the physicians responsible for pain treatment, consultations with specialists in pain management, use of prescription and over-the-counter (OTC) drugs, and knowledge about pain as well as the implemented therapy was also collected. The efficacy of prehospital pain treatment was assessed based on the decrease in pain intensity, using 4 ranges: less than 25%, 25% to 49%, 50% to 74%, and 75% to 100%. Pain intensity reduction on the NRS by at least 50% was defined as a substantial improvement in pain control.[6] Appropriate pain therapy was predefined according to product characteristics and pain management recommendations, including: 1) correct formulations, routes of administration, and doses, 2) use of coanalgesics and adjuvants preventing the adverse effects of analgesics, and 3) avoidance of coadministration of drugs with antagonizing clinical effects (eg, spasmolytics with prokinetics) or medications that raise the risk of significant DDIs or drug-disease interactions.[7] DDIs were assessed according to the Lexicomp Drug Interactions Checker.[7] DDIs graded as moderate and major were determined, and the following recommendations were analyzed: C (monitor therapy), D (consider therapy modification), and X (avoid combination).

Approval of the Bioethical Committee of the Poznan University of Medical Sciences

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(472/19) was obtained. The study was performed in accordance with the 1964 Declaration of Helsinki and the recommendations of Good Clinical Practice.

Statistical analysis All statistical analyses were performed using the STATISTICA v. 13.0 software package (StatSoft Polska Sp. z o.o., Kraków, Poland). Categorical variables were presented as numbers and percentages, and quantitative variables as medians with interquartile ranges (IQRs). Comparison of the NRS values between the groups with appropriate and inappropriate pain therapy was conducted with the Mann–Whitney test, since the NRS scores were not normally distributed. Odds ratios (ORs) were calculated to compare proportions between the 2 groups. The level of significance was set at P below 0.05.

Results

Patient characteristics and pain pattern The study group comprised 111 patients (63 women) who reported pain on admission to the IMW. The age of the patients ranged from 23 to 94 years (median [IQR], 68 [60–77] years). The median (IQR) number of chronic diseases per patient in the study group was 3 (2–5), and renal impairment (defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2) was present in over 10% of the patients. The 3 most common causes of hospitalization were congestive heart failure, urinary tract infection, and anemia. More than one-third of the study population had been hospitalized in an IMW at least once within the previous 5 years (median [IQR] number of hospitalizations, 1 [1-2]).

On admission, most patients experienced 1 pain type. Thirty-three individuals (29.7%) suffered from more than 1 type of pain or from pain localized at more than 1 site. Sixty-six persons (59.5%) suffered from at least 1 type of chronic pain, with a median (IQR) duration of 4 (1–10) years, while 44 patients (40.5%) experienced only acute pain. The most prevalent was pain associated with osteoarthritis as well as with cancer and noncancer diseases of the gastrointestinal tract or urinary system. According to the underlying pathophysiology, the most common types of pain were musculoskeletal, visceral, and neuropathic (67.6%, 40.5%, and 9%, respectively). The median (IQR) intensity of the average and worst pain on the day before the admission was 3 (3–5) and 7 (6–9) points, respectively, which indicates mild-to-moderate suffering during the preceding 24 hours in the whole study group. Severe exacerbations of pain occurred in 63 patients (56.8%).

Pain treatment On admission, the patients reported concomitant use of up to 21 drugs (median [IQR], 7 [4–10] drugs). A total of 95 individuals (85.6%) took analgesics (range, 1–4; median [IQR], 1 [1–2] drugs), whereas 16 patients (14.4%) did not use any analgesics before the admission to the IMW. Nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, and tramadol were used the most frequently, by 55%, 40.5%, and 27.9% of the patients, respectively. Opioids placed on the third step of the World Health Organization analgesic ladder (mostly buprenorphine and oxycodone) were taken by 18 persons (16.2%). Coanalgesics (predominantly drotaverin) were prescribed to 21 patients (18.9%). Pregabalin was used by 3 patients (2.7%) with neuropathic pain.

The majority of the patients (50.5%) took drugs prescribed by a single physician, mostly a general practitioner, less commonly an orthopedist, neurologist, or specialist in pain management or palliative medicine. More than a half of the study group (n = 59) used OTC drugs (taken exclusively or concomitantly with the prescribed ones). Furthermore, 9 persons (8.1%) used analgesics without recommendation of a physician. Almost one-third of the patients (n = 31) with chronic pain reported using nonpharmacologic methods of pain management (mostly physiotherapy) in the past. Invasive methods of pain treatment were not implemented in any of the patients. Over 90% of the study group declared knowing (at least partly) the cause of the experienced pain and indications for the taken analgesics. Among the 95 persons receiving analgesics, 82 took them on their own, while 13 required assistance. In the assessment of the treatment outcome, only 61 patients (55%) reported substantial improvement in pain control, while in 7 cases (6.3%), the pain intensity was reduced by less than 25%.

Eight individuals (13.1%) taking NSAIDs and 17 (39.5%) taking opioids reported adverse effects of such therapy (including stomach pain, skin reactions, and hypertension related to NSAID use, and drowsiness, nausea / vomiting, constipation, and hypotension due to opioids). A total of 3 serious adverse reactions due to analgesic use in the past were reported: anaphylactic shock caused by metamizole, angioedema following ketoprofen use, and tramadol-induced seizures. None of the patients reported any DDIs.

Inappropriate pain therapy Treatment evaluation on admission revealed errors associated with pain management in 75 patients (67.6% of the entire study group) out of 95 in whom treatment was implemented before the admission (TABLE 1), including over 40% of patients with more than 1 error. Overall, the predominating errors were related to the lack of short-acting analgesic use for pain exacerbations and inadequate adjuvant treatment. Inappropriateness associated with NSAIDs comprised concurrent usage of more than 1 drug (12 patients, including 4 who took 3 NSAIDs concomitantly), exceeding the maximal recommended doses (7 patients using 300–400 mg/day of ketoprofen, 300 mg/day of diclofenac, or 30 mg/day of meloxicam), inadequate indications (eg, visceral pain; 10 patients), NSAID use despite contraindications (3 patients), and the lack of an adjuvant agent to prevent gastrointestinal complications (15 patients). The concomitant use of more than 1 NSAID represented the majority of

TABLE 1 Errors in pain pharmacotherapy on admission among 111 patients and reasons for analgesic modification in 105 patients hospitalized for more than 3 days

Parameter		Value
Therapy inappropriateness (n = 111)		
Any error or lack of any treatment		91 (82)
Lack of adequate analgesics	Lack of any treatment	16 (14.4)
	Lack of adequate rescue medication for pain exacerbations	55 (49.5)
	Lack of coanalgesics for neuropathic pain	7 (6.3)
Lack of adjuvants to prevent adverse effects of analgesics	Lack of PPIs in patients using NSAIDs, despite indications[a]	15 (13.5)
	Lack of antiemetics at opioid initiation	2 (1.8)
	Lack of laxatives in patients taking opioids	36 (32.4)
Duplicates[b]		19 (17.1)
Inadequate dosage, drug formulations, or route of administration	Too high initial dose	10 (9)
	Dose exceeding the maximally recommended (NSAIDs)	7 (6.3)
	Administration at intervals exceeding the duration of analgesia	15 (13.5)
	Incorrect drug formulation	2 (1.8)
	Incorrect route of administration	3 (2.7)
Use of analgesics without adequate indications[c]		10 (9)
Use of analgesics despite contraindications[d]		3 (2.7)
Category X drug combinations[e]	NSAID + NSAID or metamizole	12 (10.8)
	Metamizole + carbamazepine	1 (0.9)
	Opioid + opioid[f]	3 (2.7)
Therapy modification (n = 105)		
Any modification		84 (80)
Recommendation of short-acting analgesics for pain exacerbation		55 (52.4)
Initiation of adjuvants to prevent adverse effects of analgesics	PPIs in NSAID therapy	15 (14.3)
	Antiemetics at opioid initiation	2 (1.9)
	Laxatives prophylactically with opioids	36 (34.3)
NSAID cessation		52 (49.5)
Introduction of weak opioids		12 (11.4)
Analgesic dosage increase		11 (10.5)
Introduction of coanalgesics for neuropathic pain		7 (6.7)
Introduction of paracetamol		6 (5.7)
Introduction of strong opioids		5 (4.8)
Analgesic discontinuation (causative treatment possible)		1 (1)

Data are presented as number (percentage) of patients.

a Patients who require chronic continuation of nonselective NSAIDs and are at a higher risk of developing gastrointestinal complications (including previous events, age>65 years, or concomitant use of aspirin or steroids)

b The use of >1 drug of the same pharmacologic class without indications

c NSAIDs in visceral pain

d NSAIDs in ulcer disease or bleeding from the gastrointestinal tract

e "Avoid combination" recommendation according to the Lexicomp Drug Interaction Checker

f Concomitant use of opioids placed on the second and third steps of the WHO analgesic ladder

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PPIs, proton pump inhibitors; WHO, World Health Organization

the DDIs that should be avoided (rated X according to the Lexicomp Drug Interactions Checker). Errors in opioid use included mostly lack of a rescue medication, inappropriate intervals between subsequent doses, and the lack of adjuvants to prevent constipation.

Individuals with errors in analgesic pharmacotherapy (including all classes of analgesics) suffered more severe pain "at its worst" during the day preceding the admission (median NRS, 8 points vs 6.5 points in the patients with appropriate therapy; $P = 0.02$). They were also at an almost 3-fold higher risk of experiencing severe (NRS >6) pain "at its worst" (OR, 2.611; 95% CI, 1.063–6.413) than the individuals with adequate pain management. The patients with errors

related to NSAID use suffered from more severe worst pain during the previous day as compared with those with appropriate NSAID use (median NRS, 8 vs 7 points; $P = 0.004$).

Potential drug-drug and drug-disease interactions of analgesics The analysis of the pharmacotherapy showed 231 potentially clinically significant DDIs of analgesics and coanalgesics in 63 patients (56.8%), which comprised over 40% of potential DDIs regarding all drugs taken by the patients. A total of 145 potential DDIs (62.8%) concerning analgesics and coanalgesics were associated with NSAID use, and 59 (25.5%) with opioid use. Most potential DDIs of NSAIDs were related to their concomitant use with drugs indicated in cardiovascular diseases (eg, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 36 patients, β-blockers in 35, antiplatelets and anticoagulants in 29, and diuretics in 25 patients). The potential DDIs of opioids were predominantly connected with simultaneous usage of central nervous system (CNS) depressants and diuretics (in 23 and 15 individuals, respectively). Only 1 potential DDI (0.4%) of paracetamol (with acenocoumarol) was identified. Fifty-four potential DDIs of analgesics and coanalgesics in 33 patients (29.7%) met the criteria of major interactions, and 24 DDIs in 15 individuals (13.5%) had a Lexicomp Drug Interaction Checker risk rating of X (avoid combination).

In 54 individuals (48.6%), NSAID use may have exacerbated chronic diseases, such as hypertension (in 35 individuals, including 5 who used 2 or 3 NSAIDs concurrently), coronary heart disease (5 patients), congestive heart failure (4 patients), and chronic kidney disease (5 patients). NSAIDs were also used by 3 individuals with gastric ulcer disease and bleeding in the upper gastrointestinal tract.

Pain treatment modifications Among the 111 analyzed patients, 6 were discharged within 3 days and were not further assessed. In 21 patients (20%), analgesic treatment was continued unchanged, but in 84 cases (80%), some modifications needed to be introduced following the initial assessment (TABLE 1).

Discussion In the present study, we demonstrate that patients admitted to the IMW often suffer from moderate or severe pain. Many of them do not receive effective treatment despite experiencing chronic pain for at least a few years. In the current analysis, only in 55% of the patients did the treatment implemented before the admission lead to substantial improvement in pain control (≥50% reduction in pain intensity), while almost 15% did not use analgesics at all, which is particularly worrying in the case of people with chronic pain.[1,6,8,9] Moreover, many patients took analgesics associated with an increased risk of adverse drug reactions and ones that could have worsened the course of their chronic diseases. All these findings confirm the still widespread incidence of inadequate pain treatment among patients admitted to the IMWs.

In the study population, pain presented a diverse etiology and pathophysiology, predominantly musculoskeletal and visceral, due to cancerous or noncancerous diseases. All the specific pain characteristics require an individually tailored therapy based on high-quality evidence. The most prevalent analgesics used in the study population were NSAIDs. This observation is noteworthy, as there are limited indications for the use of this class of analgesics in the treatment of pain other than inflammatory, and there is a relevant risk of serious adverse drug reactions associated with their use.[10] The predominant use of NSAIDs seems to be related to their appearance as potent analgesics in media advertisements and their common availability without prescription. In the study group, more than a half of the patients admitted to taking OTC drugs. Another OTC analgesic, paracetamol, which is recommended in the treatment of mild-to-moderate pain of various etiologies due to its safety profile, was taken less frequently.[11,12] Unsatisfactory pain relief in a significant number of patients clearly indicated the need for implementing opioids in some of them and optimizing adjuvant treatment. Limitation of opioid use in pain treatment is well recognized, and possibly resulted from physician resistance to prescribe these drugs due to the fear of life-threatening adverse effects or addiction.[13]

The analysis of analgesic treatment showed a surprisingly high number of errors in pain pharmacotherapy as well as a lack of treatment in a significant number of individuals. Associations between treatment errors and pain severity were also demonstrated.

The most common inappropriateness of pain pharmacotherapy (lack of short-acting analgesics for pain exacerbations and inadequate adjuvant treatment) indicated possible errors in physician prescription practices, not enough attention paid to pain treatment, or patient misunderstanding of the doctor's recommendations. Importantly, the number of errors in pain pharmacotherapy contrasted with patient self-declared knowledge regarding the drugs they were taking. This clearly indicates the need for better communication with patients and caregivers, as well as for their education.

Analgesics are one of the drug classes associated with the highest risk of drug-related problems in hospitalized patients.[3,14] The risk is particularly relevant in view of advanced age, multimorbidity, and polypharmacy characterizing this population. In our study population, analgesics and coanalgesics were associated with over 40% of estimated potential DDIs, with the highest risk related to NSAID usage. Importantly, these agents can cause serious interactions when combined with drugs used to treat many internal diseases, for example, hypertension. Their application in patients with cardiovascular diseases (eg,

heart failure, ischemic heart disease) should be avoided; however, in the present study, a considerable number of patients with these diseases were exposed to NSAIDs. Alternative analgesics and measures of pain treatment should be considered in this patient group. The risk of opioid-related DDIs should be reduced by limiting the concomitant use (if possible) and dosages of drugs with CNS depressant effects (eg, hypnotics or antipsychotics).

Overall, some modifications of pain therapy were needed in 4 out of 5 patients. In line with the current recommendations,[12] NSAIDs were withdrawn in over 80% of the patients who used them on admission, and the treatment was switched to safer options. Among the introduced drugs, opioids may raise the greatest concern, as already mentioned above. However, when titrated carefully and supplemented with medications to prevent their common adverse effects (such as laxatives), they may be a safe option for the management of pain of at least moderate intensity. Long-term opioid treatment requires supervision of a physician experienced in pain management.

It is worth noting that opioids may affect functioning of the internal organs, especially the digestive tract, as well as the endocrine, respiratory, and cardiovascular systems. Individual opioids differ regarding the risk of such complications.[15,16] These properties have to be considered when opioids are prescribed to patients with internal diseases. In the current study, opioids that are known to have a smaller impact on the respiratory system (eg, tramadol and buprenorphine as compared with morphine and fentanyl) and the digestive tract (tramadol and buprenorphine as compared with morphine), and whose pharmacokinetic properties are less affected by renal impairment (buprenorphine as compared with morphine) were predominantly used.[15,17,18]

Conlusions Inadequate treatment of pain remains an essential clinical problem for persons admitted to IMWs. Well-chosen analgesic therapy may effectively lower the intensity of pain; however, at the cost of potential adverse effects. On the other hand, inappropriate pain treatment may lead to poorer pain control, increased risk of DDIs, and exacerbations of chronic illnesses (especially when NSAIDs are used).

The vast majority of the study participants needed modification of pain management during the hospitalization to minimize the intensity of suffering and decrease the risk associated with the treatment. Pharmacotherapy of pain in patients with internal diseases requires special competence and caution, especially when implementation of NSAIDs is considered. Physicians, but also patients, require additional education in pain management for analgesia to become more effective and safer, particularly in view of the growing number of individuals with multimorbidity and polypharmacy.

ARTICLE INFORMATION

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