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Sex- and age-related modifiers of operant behavior and the risk of opioid addiction in patients with chronic pain

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Chronic pain is a complex biopsychosocial phenomenon that integrates somatic, psycho-emotional, and behavioral components. An important characteristic of chronic pain is its persistence for more than three months; over time, it ceases to be merely a symptom and transforms into an independent pathological condition with its own behavioral dynamics. One of the key complications of chronic pain is the development of operant behavior, which increases the risk of therapy ineffectiveness and the emergence of opioid analgesic addiction. Age and sex factors may play a modifying role in the development of such behavioral patterns, influencing clinical prognosis and therapeutic strategies.
The objective: **to determine the role of sex and age as modifying factors in the formation of operant behavior and the risk of opioid addiction among patients with different types of chronic pain. To investigate the relationship between pain type (primary, secondary, mixed), behavioral patterns of patients, and the scores on the Diagnosis, Intractability, Risk, Efficacy (DIRE) scale, with the aim of improving personalized pain management strategies and determining the appropriateness of initiating or continuing opioid analgesia.**
Materials and methods**. A total of 302 patients aged 18–70 years with chronic primary, secondary, and mixed pain completed the study program. The diagnosis of mental and psychosomatic disorders was performed according to the International Classification of Diseases, 11th Revision (ICD-11) criteria. Based on the aetiopathogenetic mechanisms of pain and the clinical-psychopathological characteristics defined by ICD-11, all participants were divided into 5 groups: PPP 1 – Primary psychogenic pain; PPP 2 – Psychophysiological pain; PPP 3 – Mixed primary psychogenic and psychophysiological pain; SMP – Secondary mixed pain; SOP – Secondary organic pain. The DIRE scale was used to assess the risk of operant behavior formation and to predict the appropriateness of opioid analgesia. Statistical analysis was performed using the χ^2 test, Kruskal–Wallis test, and Dunn's multiple comparison test.**
Results**. The difference in the frequency of operant behavior risk between men and women was not statistically significant; however, aetiopathogenetic stratification by groups revealed significant differences. In Group PPP 1, men showed a markedly higher risk of operant behavior development and opioid therapy addiction – almost 1.5 times higher than women ($\chi^2 = 8.35$, $p = 0.003$). In Group PPP 3, the risk of operant behavior formation and probable opioid analgesia addiction was maximal in men (100%) compared with women (76.7%) ($\chi^2 = 5.82$, $p = 0.015$). In Groups PPP 2 and SMP, sex differences did not reach statistical significance. In Group SOP, most patients, regardless of gender, had the lowest risk of developing addiction to opioid analgesia. In the total sample ($p = 0.572$), no association was found between age and risk, but subgroup analysis (age categories) showed that PPP 1 and PPP 3 demonstrated a pronounced tendency toward risk-related behavior among younger patients (under 29 years). The only statistically significant age-risk relationship was observed in PPP 1 ($p = 0.035$). Older patients with SOP and SMP had the highest DIRE scores and the lowest risk of operant behavior formation.**
Conclusions**. Sex and age are significant modifying factors in the development of operant behavior and the risk of opioid addiction among patients with chronic pain. The most vulnerable group comprises young men with primary psychogenic and mixed pain, who require proactive psychotherapeutic, psychoeducational, and preventive interventions to reduce the risk of operant behavior. The identified patterns have practical implications for forming personalized analgesic strategies and for substantiating indications for the initiation or continuation of opioid therapy.**
Keywords: *chronic pain, operant behavior, illness behaviour, DIRE, opioids, age, sex, addiction risk.*

Статеві та вікові модифікатори оперантної поведінки й ризику опіоїдної залежності у пацієнтів із хронічним болем

А. Е. Асанова

Хронічний біль є складним біопсихосоціальним феноменом, який поєднує соматичні, психоемоційні та поведінкові компоненти. Важливою характеристикою хронічного болю є його тривалість понад 3 міс.; з часом він перестає бути лише симптомом і трансформується в самостійне патологічне явище з власною поведінковою динамікою. Одним із ключових ускладнень хронічного болю є формування оперантної поведінки, що підвищує ризик неефективності терапії та розвитку залежності від опіоїдних анальгетиків. Вікові й статеві чинники можуть відігравати модифікуючу роль у розвитку таких поведінкових патернів, визначаючи клінічний прогноз і терапевтичну тактику.
Мета дослідження: визначення ролі статі та віку як модифікуючих чинників формування оперантної поведінки й ризику розвитку опіоїдної залежності у пацієнтів із різними типами хронічного болю, а також аналіз взаємозв'язку між типом болю (первинний, вторинний, змішаний), поведінковими патернами пацієнтів та показниками шкали Diagnosis, Intractability, Risk, Efficacy (DIRE) з метою вдосконалення персоналізованих стратегій знеболення та визначення доцільності призначення або продовження опіоїдної анальгезії.

Матеріали та методи. Повністю програму дослідження завершили 302 пацієнти віком 18–70 років із хронічним первинним, вторинним та змішаним болем. Діагностика психічних та психосоматичних розладів проводилась відповідно до критеріїв Міжнародної класифікації хвороб 11-го перегляду (МКХ-11). За етіопатогенетичними механізмами виникнення болю та клініко-психопатологічними характеристиками відповідно до критеріїв МКХ-11 усі пацієнти були розподілені на 5 груп: ППБ-1 – первинний психічний біль; ПФБ-2 – психофізіологічний біль; ППБ-3 – змішаний первинний психічний біль та психофізіологічний; ВЗБ – вторинний змішаний біль; ВОБ – вторинний органічний біль. Для оцінки ризику формування оперантної поведінки та прогнозування доцільності опіоїдної анальгезії застосовували шкалу DIRE. Статистичний аналіз здійснювали з використанням χ^2-критерію, тесту Крускала – Уолліса та тесту Дана для множинних порівнянь.

Результати. Встановлено, що загальна різниця у частоті ризику формування оперантної поведінки між чоловіками та жінками не є достовірною, однак при стратифікації за етіопатогенетичними групами виявлено статистично значущі відмінності. У групі ППБ-1 спостерігалося істотне переважання чоловіків із підвищеним ризиком формування оперантної поведінки та залежності від опіоїдної терапії – майже у 1,5 раза вище, ніж у жінок ($\chi^2 = 8{,}35$, $p = 0{,}003$). У групі ППБ-3 ризик формування оперантної поведінки та ймовірної залежності від опіоїдної анальгезії був максимальним у чоловіків (100%), тоді як у жінок становив 76,7% ($\chi^2 = 5{,}82$, $p = 0{,}015$). У групах ПФБ-2 та ВЗБ статеві відмінності не досягли статистичної значущості. У групі ВОБ більшість пацієнтів незалежно від статі мали найнижчі ризики формування залежності від опіоїдної анальгезії. У загальній вибірці ($p = 0{,}572$) зв'язку між віком і ризиком не виявлено, однак у підгруповому аналізі (вікові категорії) групи ППБ-1 та ППБ-3 демонстрували виражену схильність до ризикової поведінки саме серед молодших пацієнтів (віком до 29 років). Єдина статистично значуща залежність між віком і ризиком виявлена у групі ППБ-1 ($p = 0{,}035$). Пацієнти старшого віку у групах ВОБ та ВЗБ мали найвищі бали за шкалою DIRE та найнижчі ризики формування оперантної поведінки.

Висновки. Стать і вік є значущими модифікуючими факторами формування оперантної поведінки та ризику опіоїдної залежності у пацієнтів із хронічним болем. Особливо вразливою групою є молоді чоловіки з первинно-психічним та змішаним болем, які потребують проактивних психотерапевтичних, психоосвітніх і превентивних заходів для зниження ризику розвитку оперантної поведінки. Виявлені закономірності мають практичне значення для формування персоналізованих стратегій знеболення та обґрунтування показань до призначення або продовження опіоїдної терапії.

Ключові слова: *хронічний біль, оперантна поведінка, хвороблива поведінка, DIRE, опіоїди, вік, стать, ризик залежності.*

Chronic pain is a complex biopsychosocial phenomenon that goes far beyond a purely physiological sensation. It is formed as a result of the interaction of biological, emotional, cognitive, and behavioral mechanisms and has the property of persisting even after the disappearance of the primary damaging factor or even arising without the presence of the primary factor [1]. An important characteristic of chronic pain is that it lasts more than 3 months and, over time, ceases to be just a symptom and transforms into an independent pathological phenomenon with its own behavioral dynamics. One of the key mechanisms sustaining this process is operant (illness) behavior – a form of behavior that is not directed towards recovery and which emerges and becomes reinforced as a result of the consequences that follow its performance [2].

Usually, some patients gradually adapt to the pain: reduce their excessive focus on it, perceive pain as part of everyday life and maintain their usual level of activity. At the same time, a substantial proportion of patients with chronic pain disorders and syndromes develop the opposite dynamic – they become excessively dependent on external support, catastrophise their pain, perceive themselves as severely ill, and require constant attention from those around them and from healthcare professionals [3]. This leads to the development of restrictive behavior with a gradual decrease in physical and social activity [4, 5].

The operant mechanism works as follows: if an action is followed by a result (reward or elimination of discomfort), the probability of repeating this action increases significantly [6]. Positive reinforcement occurs when a positive stimulus is added after an action, increasing its repetition. Negative reinforcement consists of eliminating or reducing an unwanted stimulus after an action, which also increases the likelihood of repetition. Avoidant behavior, which often accompanies chronic pain, is a type of negative reinforcement aimed at preventing the stimulus [7]. Accordingly, patients with chronic pain disorders and syndromes often exhibit operant behavior patterns such as avoidance, passivity, focus on pain, and catastrophizing [8, 9]. Operant reinforcement can also be used to induce and intensify pain sensations in healthy individuals, confirming the role of reinforcement in modulating pain behavior [6]. This demonstrates that operant behavior not only shapes the response to pain but may also be one of the key mechanisms underlying chronic pain syndrome.

It should be noted that the interaction of biological and psychological mechanisms with social factors is an important component in understanding differences in the choice of behavioral strategies. For example, biopsychosocial differences between men and women affect the perception of pain, the choice of strategies to overcome it, and the response to treatment. This finding highlights the importance of considering not only clinical factors but also age- and sex-related characteristics in developing individualized approaches aimed at improving the quality of care for patients with chronic pain disorders and syndromes [10].

Studies have found that hormonal and neuroimmune characteristics can shape a predisposition to certain behavioral strategies, such as avoidance, active coping, or seeking help [11]. In a study by A. K. Baker et al. (2022), men with chronic pain had less activity in the brain structures associated with reward anticipation compared to men without pain. This suggests that positive reinforcement, which motivates action, works less effectively in men and no such changes were observed in women, indicating differences between the sexes in neurobiological responses to pain [12].

Gender differences also manifest themselves in the psychosocial dimension. Women are more prone to catastrophizing, while men demonstrate a higher level of pain

control, i.e., greater self-efficacy [7]. Recent studies by L. H. L. Le et al. (2024) have shown that catastrophizing can alter the relationship of pain, emotional stress, and behavioral responses, particularly avoidance of activities [13]. Women and men use different coping strategies for pain: women more often prefer methods that focus on emotions and attention, seek social support, while men prefer strategies aimed at solving the problem, as well as behavioral distraction from pain [14]. It is worth noting that men are also more likely to use alcohol to relieve pain and reduce stress [15]. Meanwhile, women are more likely to seek medical help and report higher intensity pain, prolonged pain, and greater sensitivity to pain compared to men [16, 17].

In addition, social factors further influence behavioral responses to pain, its processing, and perception. Support from others can play both a positive and negative role. Attention and support from a partner can intensify pain in patients with chronic pain, accompanied by an increase in the subjective assessment of pain intensity, as well as an active response of the brain to pain stimuli [18]. At the same time, gender discrimination can also affect health and behavior, particularly coping strategies [19]. Men are more often encouraged to continue being active despite pain, while women are encouraged to take care of themselves and rest [20].

Meanwhile, actions that lead to social support or reduced pain (positive reinforcement) are more likely to be repeated in the future, even if they do not promote recovery. For example, avoiding physical activity due to the expectation of pain reduces discomfort in the short term (negative reinforcement), but in the long term reinforces operant behavior and leads to "psychological" and possibly physical disability [21].

Such mechanisms are consistent with the operant model and explain cause-and-effect relationships. In addition, studies show that in women, fear and avoidance are associated with increased pain intensity, while in men this association has not been found [16]. However, at the same pain intensity, women report higher levels of activity, pain acceptance, and social support. Men, on the other hand, have greater fear of movement, poorer psycho-emotional state, and lower activity levels [22]. A study by M. Racine et al. (2019), which assessed gender differences in patients with chronic pain undergoing an interdisciplinary treatment program, found that men have a higher level of fear of movement, while women are more prone to overexertion. Importantly, both groups showed improvement in psychoemotional state and physical function after treatment, but women reported a more pronounced reduction in pain intensity [23].

One of the methods used in the treatment of chronic pain remains opioid analgesia, which is often prescribed for chronic pain management; however, its long-term use is associated with a risk of addiction [24]. Studies show that the same operant reinforcement processes that maintain chronic pain behavior also play a role in the development of opioid abuse risk. Avoidance, seeking relief, and obtaining short-term rewards become behavioral mechanisms that reinforce both pain and the tendency to use opioid drugs in an uncontrolled manner [25].

In general, the prevalence of opioid addiction does not show significant gender differences. Although the prevalence of opioid addiction is similar in both sexes, the behavioral characteristics of abuse differ. Women are more likely to report excessive or uncontrolled use of opioids [26]. Operant reinforcement explains why opioid use behavior becomes entrenched, as positive reinforcement is associated with feelings of reward, which increases the likelihood of repeated use. Negative reinforcement forms a habit by reducing discomfort and stress, which reinforces use for relief [27]. The prevalence of opioid addiction is associated not only with biological mechanisms, but also with social and behavioral factors. Women are more likely to receive prescriptions for opioids for pain management, take them for longer periods of time, and often in higher doses, which increases the risk of abuse. In men, opioid abuse is more often associated with risky behavior, external and social stimuli that encourage continued use [28].

It is important to note that painful behavior in chronic pain also has its own age-related characteristics, which can be influenced by family reactions, emotional regulation, and central sensitization mechanisms. Young patients have greater neurobiological vulnerability and behavioral characteristics that increase the risk of operant opioid reinforcement of pain and subsequent drug addiction [29, 30].

Chronic pain in adolescence is associated with an increased risk of prescription drug abuse in adulthood, highlighting the importance of early prevention and non-pharmacological strategies in young patients [31, 32].

In an American study by H. Han et al. (2013), young patients had significantly higher levels of opioid dose increases than older patients. At the same time, women increased their doses less often than men, although the result was not statistically significant [33]. The presence of depressive or anxiety disorders and the comorbid use of other psychoactive substances significantly increases the risk of developing opioid addiction in young people aged 11 to 25 [34, 35]. In another American study, Y. F. Kuo (2019) investigated mortality in patients aged 21 to 64 due to prescription opioid abuse. In this group, patients who died from opioid overdose were more likely to be male, more likely to have mental disorders (depression, anxiety, bipolar disorder, post-traumatic stress disorder (PTSD), substance use disorders) and chronic pain. The average age often correlated with occupational injuries, opioid prescriptions after surgery, and socioeconomic factors that increased the duration of treatment [36].

Thus, studying the age and gender characteristics of operant behavior formation in patients with chronic pain disorders and syndromes is of great clinical importance, and allows not only to more accurately predict the risks of pain chronicity and opioid addiction, but also to develop personalized treatment strategies with an emphasis on behavioral mechanisms that support pain syndrome.

The objective of this study was to determine the role of gender and age as modifying factors in the formation of operant behavior and the risk of developing opioid addiction in patients with various types of chronic pain; to investigate the relationship of pain type (primary, secondary,

mixed), patient behavior patterns, and the Diagnosis, Intractability, Risk, Efficacy (DIRE) scale scores in order to improve personalized pain management strategies and determine the appropriateness of prescribing or continuing opioid analgesia.

MATERIALS AND METHODS

General characteristics of the study group

To achieve the goal, 340 outpatients with chronic pain disorders and syndromes were screened. All patients were examined for compliance with the inclusion/exclusion criteria. The final study included 302 individuals with chronic primary, secondary, and mixed pain disorders lasting more than 3 months. The age of the study cohort ranged from 18 to 70 years.

The diagnosis of primary chronic pain disorders was established only after excluding secondary causes of pain.

Chronic secondary pain included: chronic postoperative pain (MG30.21) or post-traumatic pain (MG30.20); chronic neuropathic pain (MG30.5); chronic secondary musculoskeletal pain (MG30.3); chronic secondary visceral pain (MG30.4); chronic secondary headache or orofacial pain (MG30.6).

Chronic primary pain included the following: chronic primary visceral pain (MG30.00); chronic widespread pain (MG30.01); chronic primary musculoskeletal pain (MG30.02); chronic primary headache or orofacial pain (MG30.3); and complex regional pain syndrome (MG30.04).

Inclusion criteria:

1. Adult outpatients aged 18 to 70 years.
2. Presence of chronic pain > 3 months classified under International Classification of Diseases, 11th Revision (ICD-11) category MG30 (Chronic pain), including primary, secondary, or mixed variants.
3. Ability to undergo a standardized clinical, psychological and psychiatric examination.
4. Voluntary informed consent to participate in the study, obtained in accordance with the Helsinki Declaration.

Exclusion criteria:

1. Psychotic disorders.
2. Severe cognitive impairments that make psychological testing impossible, active suicidal behavior.
3. Severe, unstable somatic conditions: heart failure, liver or kidney failure, cancer.
4. Opioid addiction or uncontrolled use of other psychoactive substances.
5. Significant sensory impairments or the presence of implanted medical devices (e.g., pacemakers, neurostimulators).
6. Patients who refused to participate or withdrew from the study before the end of the main observation period.
7. Confirmed, suspected, or planned pregnancy during the screening examination.
8. Women who are breastfeeding.
9. Surgery planned during the screening assessment.
10. Severe or complete loss of working capacity.
11. Patients with severe chronic pain syndromes within the following disorders were not included in the study: central neuropathic pain (autoimmune, vascular (post-stroke), neurodegenerative, inflammatory); peripheral neuropathic pain (infectious, genetic, autoimmune, toxic (chemotherapeutic), ischemic (peripheral vascular disorders, diabetes), metabolic (amyloidosis, disorders caused by nutrient deficiency)); nociceptive (liver cirrhosis, ischemic heart disease); obstructive (urolithiasis, cholelithiasis), acute peptic ulcer; cancer pain; burns.

The study approved by the local bioethics committee.

Psychiatric examination: primary and comorbid mental disorders were diagnosed by a psychiatrist in accordance with ICD-11. The examination included screening for: depressive disorder, anxiety disorder, anxiety-depressive disorder, panic disorder, PTSD, body distress disorder (somatoform disorder).

Based on the etiopathogenetic mechanisms of pain (primary, secondary, mixed) and clinical and psychopathological characteristics according to ICD-11, all patients with chronic pain disorders and syndromes were divided into 5 groups:

- PPP 1 – Primary psychogenic pain – 64 patients with pain symptoms in the structure of non-psychotic mental disorders;
- PPP 2 – Psychophysiological pain – 58 patients with primary chronic pain without mental disorders;
- PPP 3 – Mixed primary psychogenic and psychophysiological pain – 60 patients with a combination of mental disorders and primary chronic pain;
- SMP – Secondary mixed pain – 58 patients with secondary pain disorders and comorbid mental syndromes;
- SOP – Secondary organic pain – 62 patients without mental disorders.

In addition, all patients underwent an examination using a “chronic pain examination chart”, which included socio-demographic characteristics (gender, age, marital status, education, financial status, place of residence, employment), clinical (somatic comorbidity, specific characteristics associated with chronic pain) indicators, and were also assessed using the DIRE scale. This publication will focus on the gender and age characteristics of operant behavior formation in chronic pain.

The DIRE scale is a validated clinical tool for predicting the appropriateness and effectiveness of long-term opioid analgesia in patients with chronic non-cancer pain, as well as for assessing the risk of developing operant pain behavior.

The methodology includes an analysis of four main factors: D – Diagnosis, I – Intractability, R – Risk, E – Efficacy. The risk factor is broken down into four subcategories: mental health, substance abuse, patient credibility (reliability in treatment), and level of social support. Each parameter is assessed on a Likert scale from 1 to 3 points: 1 point – unfavorable situation for prescribing opioids, 3 points – favorable situation for therapy. The total DIRE score ranges from 7 to 21. A score of 14 or higher indicates a higher chance of successful, controlled opioid therapy and a low risk of operant behavior. 7–13 points – high probability of developing painful (dysfunctional) behavior and complications, making long-term opioid therapy inadvisable [37].

Statistical data processing

Statistical analysis was performed using StatPlus 7.0 (AnalystSoft Inc., USA) and RStudio version 2025.05.1+513

(Posit Software, PBC) software. The Shapiro–Wilk test was used to check the primary data for normal distribution. For variables that did not meet the normal distribution, the nonparametric Kruskal–Wallis test was used, followed by a posteriori multiple comparison using Dunn's test. Frequencies were analyzed using the χ^2 criterion, and when the expected value was < 5, Fisher's exact criterion was used.

RESULTS AND DISCUSSION

The study included 302 patients with chronic pain, including 153 men (50.6%) and 149 women (49.4%). The vast majority of respondents lived in cities (n = 260; 86.1%), while significantly fewer lived in rural areas (n = 42; 13.9%). The average age of patients was 36.40 ± 0.67 years (Me [IQR] = 35 [26–45]). Marital status: married – 124 (41.1%), unmarried – 132 (43.7%), divorced – 46 (15.2%).

In terms of education, most respondents had higher education (n = 225; 74.5%), while n = 77 (25.5%) had secondary education. The professional employment of patients was distributed as follows: employed – 217 (71.8%), unemployed – 71 (23.6%), military personnel – 14 (4.6%).

In terms of satisfaction with their financial situation, most patients reported satisfaction – 162 (53.6%); 112 (37.1%) were dissatisfied, while 28 (9.3%) were completely dissatisfied.

The relationship between the risk of operant behavior and the risk of opioid addiction in patients with chronic pain, depending on age.

302 patients with chronic pain disorders and syndromes were divided into 3 age categories: patients ≤ 29 years (n = 110), patients aged 30–39 years (n = 94), and patients ≥ 40 years (n = 98) (Table 1). The structure of age groups had some peculiarities (Fig. 1). Thus, in the Group PPP 3, 55% were patients ≤ 29 years of age, while in the Group SMP only 17.2%, and *vice versa*, the distribution in the category ≥ 40 years of age was 11.7% vs 55.2%. That is, young people ≤ 29 years predominated in the Group PPP 3, while patients ≥ 40 years constituted the majority in the Group SMP. This age distribution is fully consistent with the clinical nature of pain syndromes and their pathogenetic mechanisms.

The risk of operant behavior and addiction was determined in each age category using Fisher's exact criterion, and it was found that the largest number of patients with a predicted (probable) risk were in Groups PPP 1 and PPP 3, followed by Groups PPP 2 and SMP, with only 2 patients identified in the Group SOP (2 women, aged ≥ 40, unemployed, living in the city, dissatisfied with their financial situation, married). At the same time, according to the results of statistical analysis (Fisher's exact test), the relationship between the frequency of distribution of individuals in age categories and the risk factor was established only in the Group PPP 1 (p = 0.035), although in the Group PPP 3 (p = 0.872) the frequency of predicted risk was higher. This can be explained by the fact that, given the significant difference in the distribution between the number of patients with and without risk factors in the Group PPP 3 (almost 9:1), the sensitivity of the statistical method decreases.

Group PPP 2 has no correlation between age and risk (p = 0.741) and the distribution is almost the same, only ≥ 40 years does the number of patients at risk increase (66.7%). No correlation between age and risk was found in Groups SMP (p = 0.251) and SOP (p = 0.496).

That is why there is no dependence of factors in the general sample of examined patients (p = 0.572), and the characteristics of patients in each group indicate that Groups PPP 1 and PPP 3 have a connection between the risk of operant behavior and probable addiction to opioid analgesia in younger patients. The relative distribution of patients (%) by age category and diagnosed risk of probable addiction to opioid analgesia and operant behavior (based on the DIRE scale) in patients with chronic pain is shown in Fig. 1.

Table 1

Distribution of patients with chronic pain by age categories and risk of operant behavior and probable addiction to opioid analgesia (based on the DIRE scale), abs. (%)

Pain Group	DIRE score, R	Age category, years			Total
		≤ 29	30–39	≥ 40	
PPP 1	7–13	11 (45.8)	17 (80.9)	14 (73.6)	42 (65.6)
	≥ 14	13 (54.2)	4 (19.1)	5 (26.4)	22 (34.4)
PPP 2	7–13	14 (56.0)	11 (52.4)	8 (66.7)	33 (56.9)
	≥ 14	11 (44.0)	10 (47.6)	4 (33.3)	25 (32.5)
PPP 3	7–13	**28 (84.8)**	18 (90.0)	6 (85.7)	**52 (86.7)**
	≥ 14	**5 (15.2)**	2 (10.0)	1 (14.3)	8 (13.3)
SMP	7–13	3 (30.0)	3 (18.7)	**14 (43.7)**	20 (34.4)
	≥ 14	7 (70.0)	13 (81.3)	**18 (56.3)**	38 (65.6)
SOP	7–13	0 (0)	0 (0)	2 (7.2)	2 (3.2)
	≥ 14	18 (100.0)	16 (100.0)	26 (92.8)	**60 (96.8)**
Total	7–13	56 (50.9)	49 (52.1)	44 (44.9)	149 (49.3)
	≥ 14	54 (49.1)	45 (47.9)	54 (55.1)	153 (50.7)

Notes: Group PPP 1 – Primary psychogenic pain; Group PPP 2 – Psychophysiological pain; Group PPP 3 – Mixed primary psychogenic and psychophysiological pain; Group SMP – Secondary mixed pain; Group SOP – Secondary organic pain; DIRE: D – Diagnosis, I – Intractability, R – Risk, E – Efficacy.

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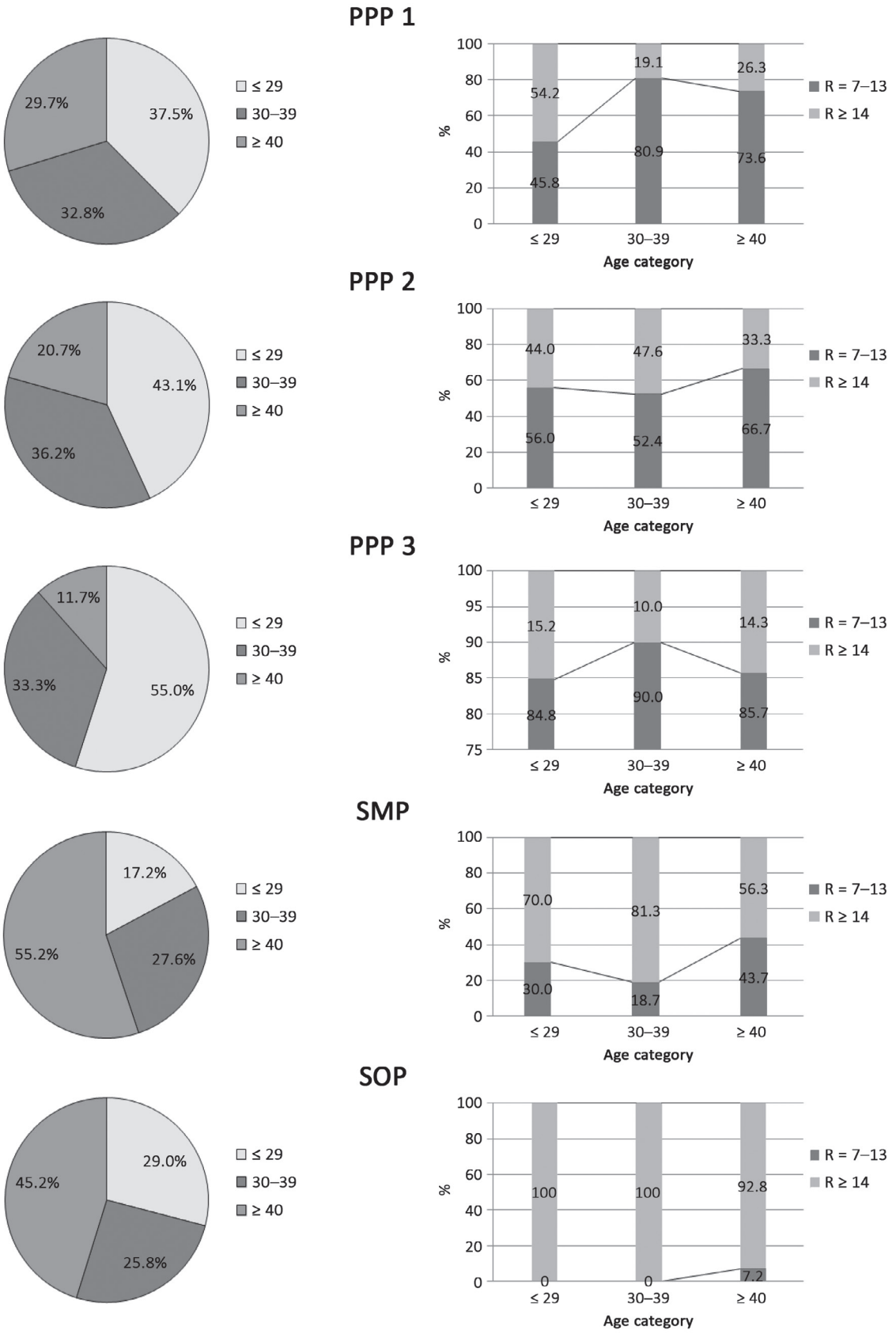

Fig. 1. Relative distribution of patients (%) by age categories and diagnosed risk of operant behavior and probable opioid addiction (based on the DIRE scale) among patients with chronic pain

Notes: Group PPP 1 – Primary psychogenic pain; Group PPP 2 – Psychophysiological pain; Group PPP 3 – Mixed primary psychogenic and psychophysiological pain; Group SMP – Secondary mixed pain; Group SOP – Secondary organic pain; R – risk of operant behavior and addiction to opioid analgesia.

Table 2

Frequency of risk diagnosis of operant behavior and probable addiction to opioid analgesia in patients with chronic pain, abs. (%)

Gender	Risk, score	Total number of patients (n = 302)	Pain Group				
			PPP 1 (n = 64)	PPP 2 (n = 58)	PPP 3 (n = 60)	SMP (n = 58)	SOP (n = 62)
Men (n = 153)	"+" 7–13	82 (53.6)	25 (86.2)	17 (54.8)	30 (100)	10 (34.5)	0 (0)
	"–" ≥ 14	71 (46.4)	4 (13.8)	14 (45.2)	0 (0)	19 (65.5)	34 (100)
Women (n = 149)	"+" 7–13	68 (45.6)	17 (48.6)	16 (59.3)	23 (76.7)	10 (34.5)	2 (7.1)
	"–" ≥ 14	81 (54.4)	18 (51.4)	11 (40.7)	7 (23.3)	19 (65.5)	26 (92.9)
p-value		0.1663*	0.001**	0.837**	0.010**	1.0**	0.199**

Notes: Group PPP 1 – Primary psychogenic pain; Group PPP 2 – Psychophysiological pain; Group PPP 3 – Mixed primary psychogenic and psychophysiological pain; Group SMP – Secondary mixed pain; Group SOP – Secondary organic pain; * – calculation based on the χ^2 criterion; ** – calculation based on Fisher's exact criterion.

The relationship between the risk of operant behavior and long-term use of opioid analgesia in patients with chronic pain, depending on gender.

The difference in the frequency of risk of opioid analgesia addiction (criterion for distribution of DIRE scale values of 13 points, risk of 7–13 points) was studied (Table 2). Analysis of the results in the general sample of patients using the χ^2 criterion indicates that the difference in the risk frequency of operant behavior formation and the risk of opioid analgesia addiction between men and women is not significant ($\chi^2 = 1.19$, $p = 0.166$). However, the distribution of patients into groups and the analysis of results using Fisher's exact test showed a difference among groups. Thus, in the Group PPP 1, there was a significant predominance of the relative number of men at risk of operant behavior, almost 1.5 times ($\chi^2 = 8.35$, $p = 0.001$). In the Group PPP 3, all men were at risk of operant behavior development and sensitivity to opioid analgesia, and 76.7% ($\chi^2 = 5.82$, $p = 0.01$) in the women. In the Groups PPP 2, SMP, and SOP, no differences in the frequency of diagnosis of sensitivity risk between gender categories were found. In the Group SMP, the distribution between categories of patients with and without risk was almost equal, and in gender terms, equal. Finally, in the Group SOP, the characteristics of patients were the opposite, namely, the vast majority of patients did not have a risk of operant behavior and opioid addiction, so it is more appropriate to prescribe opioid analgesia.

The criterion for dividing into "risk+" and "risk–" groups is a DIRE score ≥ 14, as indicated in a similar study (7–13; 14–21 points) [38].

Studying the role of the gender factor in diagnosing the risk of operant behavior formation and probable addiction to opioid analgesia in patients with chronic pain disorders and syndromes on the DIRE scale requires not only routine calculation of the total score on the scale, but also taking into account the frequency of detection of sensitivity risk to avoid losing an objective assessment of the study results. The assessment of the questionnaire results is useful for personalized treatment, but for a complete and comprehensive study of this psychiatric problem, taking into account socio-demographic factors, attention should be paid to the population factor of the study.

The assessment of the total DIRE scale score according to the Kruskal–Wallis criterion showed a statistically significant difference ($H = 143.2$; $p < 0.001$). Further multiple comparisons showed a significant difference between Groups SMP and PPP 1 ($p = 0.0001$), the score in the Group SOP was significantly higher than in all comparison groups ($p < 0.001$), and the score in the Group PPP 3 was significantly lower than in the other groups (in the pair SOP vs PPP 3, $p = 0.02$). No difference was found between the compared Groups PPP 1 and PPP 2 ($p = 0.24$) or between the Groups PPP 2 and SMP ($p = 0.12$). No differences were found based on gender.

However, the Group SOP scored higher, and most patients were assessed as having the lowest risk for long-term prescription or continuation of opioid analgesia and the development of operant behavior. Patients in the Group PPP 3 are at risk for opioid use and operant behavior formation. Patients in the Groups PPP 1 and PPP 2 had the same number of points, but men in the Group PPP 1 were more likely than women to be in the risk group.

The results of the DIRE scale assessment were analyzed taking into account the gender factor. The application of the nonparametric Kruskal–Wallis test showed the presence of intergroup differences ($H = 163.3$; $df = 9$; $p < 0.001$), and subsequent analysis using the post hoc Dunn test with multiple comparisons made it possible to identify groups that differed from each other (Fig. 2). Thus, the results for men in the Group SOP differed significantly from those for men in all comparison groups ($p < 0.001$), namely, the score on the scale was higher. Men in the Group SMP had significantly higher scores on the scale compared to the Groups PPP 1 and PPP 3 ($p < 0.001$). In the pair of the Groups PPP 2 and PPP 3, the values in the latter were significantly lower ($p = 0.002$). In the women's groups, the difference was more pronounced, but the overall trend was similar to that of the male respondents. Significantly higher DIRE scores were found in women in the Group SOP, and the lowest in the Group PPP 3 (a significant difference was found in the comparison pairs PPP 1 vs SOP – $p < 0.001$; SOP vs PPP 3 – $p < 0.001$). No statistically significant differences were found within the comparison groups between men and women. That is, the lowest DIRE scores were found in patients in the Group PPP 3, among whom men were more likely to be at risk of opioid use and operant behavior formation.

At the same time, the highest scores were in the Group SOP, and almost all of them had lower risks, i.e., they were potential candidates for prescription and relatively long-term opioid analgesia. Given the lack of statistical differences between the Groups SMP and SOP, their results can be considered "close" in terms of clinical significance.

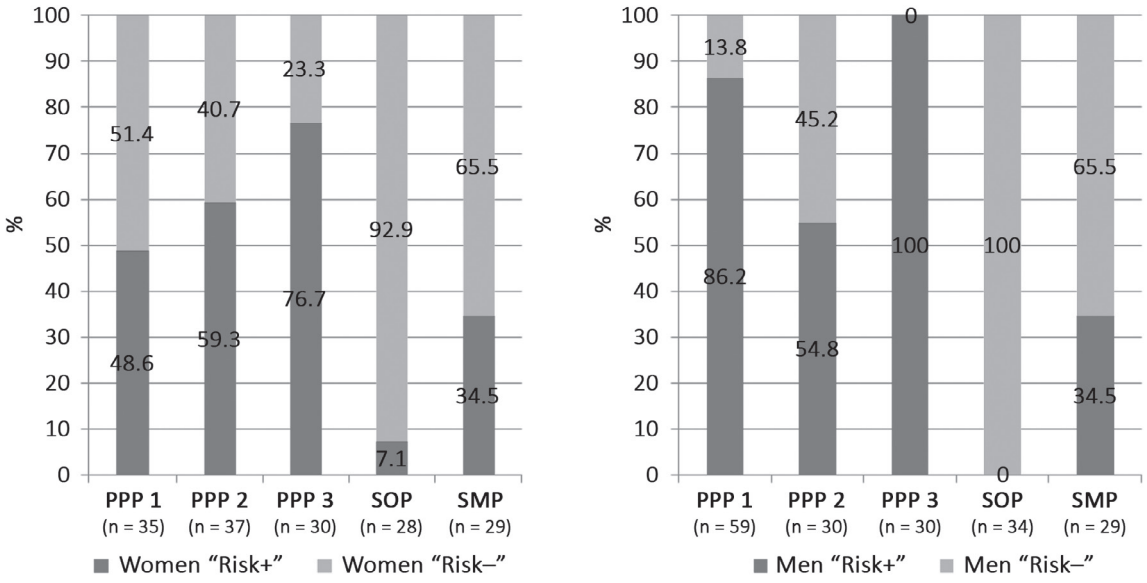

Fig. 2. Distribution of women and men by risk factor for operant behavior and opioid use

Notes: Group PPP 1 – Primary psychogenic pain; Group PPP 2 – Psychophysiological pain; Group PPP 3 – Mixed primary psychogenic and psychophysiological pain; Group SMP – Secondary mixed pain; Group SOP – Secondary organic pain; "Risk+" – higher risk of operant behavior and addiction to opioid analgesia; "Risk–" – lower risk of operant behavior and addiction to opioid analgesia.

In the Group PPP 1, there was a significant predominance of men with an increased risk of developing operant behavior and probable addiction to opioid therapy – almost 1.5 times higher than in women (χ^2 = 8.35, p = 0.003). This may reflect a more pronounced behavioral reactivity of men in response to pain. In our opinion, this may indicate that men with primary psychological pain are typically emotionally rigid, prone to affect denial, and overestimate pharmacological agents as a tool for pain control. Such a cognitive attitude may create fertile ground for the formation of operant behavior patterns (e.g., more frequent use of analgesics, self-increased doses, search for secondary benefits). Individual reviews and meta-analyses also indicate gender differences in response to opioids and behavioral responses to pain, which may explain the more "externalizing" (dependent) strategy in some men [39].

In the Group PPP 3, the risk of developing operant behavior and probable addiction to opioid analgesia was highest in men (100%), while in women it was 76.7% (χ^2 = 5.82, p = 0.015). This fact confirms that the combination of psychogenic and physiological mechanisms of pain creates a critical risk zone where emotional dysregulation is combined with somatic mechanisms of pain reinforcement.

In men, behavioral compensation mechanisms are likely to be activated (due to the need to "control" symptoms), which may lead to an increase in the frequency of medication use. In women, this tendency is somewhat milder, possibly due to more pronounced emotional reflection and the search for social support, which reduce the risks of operant behavior formation. Thus, gender modifies the behavioral response to pain, but only in the context of certain psychophysiological conditions, which is reflected in validated screening tools for assessing the risks of opioid addiction in patients with chronic pain disorders [40].

The Groups PPP 2, SMP, and SOP. In the Groups PPP 2 and SMP, gender differences did not reach statistical significance. The result may indicate that when somatic or stress-associated mechanisms dominate, the behavioral responses of men and women may become equalized. At the same time, in the Group SOP, most patients, regardless of gender, had the lowest risks of developing addiction to opioid analgesia, which corresponds to clinical patterns: with a clear organic basis for pain, emotional and behavioral mechanisms are less pronounced, and compliance with therapy is more stable. For secondary (organic/mixed) forms, the risk of opioid problems is determined primarily by clinical-somatic and organizational factors (dose, duration, comorbidities), rather than gender, as reflected in current guidelines/reviews [41].

After conducting research on age-related patterns associated with the possible risk of operant behavior formation and the advisability of using opioid analgesia, the following results were obtained: in the general sample (p = 0.572), no connection between age and risk was found, but in the subgroup analysis (age categories), the Groups PPP 1 and PPP 3 showed a pronounced tendency toward risky behavior among younger patients (≤ 29 years). This means that the age factor acts as a trigger only when the pain is psychogenic in origin – that is, when behavioral mechanisms and affective reactions prevail over somatic ones. In other words, a general pattern can be observed: "the type of pain is more important than age"; age is not an independent predictor of risk, but it enhances the influence of psychopathological factors in patients with certain types of pain [42].

The Group PPP 1: affective sensitivity as a risk determinant. The only statistically significant correlation between age and risk was found in the Group PPP 1 (p = 0.035). This indicates that young patients with primary mental disorders (depression, anxiety, somatoform disorders) are particularly prone to developing addiction to opioid analgesia and operant behavior, even with a relatively short history of pain. The results are consistent with the M. Escorial study (2024), according to which younger age is considered one of the

leading risk factors for abuse, but the effect is exacerbated by the presence of mental disorders, high doses, and social vulnerability [43]. Clinically, this is explained by the fact that at a young age, pain and anxiety are often integrated into a single phenomenon, and opioids may be viewed by the patient not as analgesics, but as a means of stabilizing their emotional state.

The Group PPP 3: behavioral generalization. In this group, the risk frequency was the highest (9:1), but without statistical significance ($p = 0.872$) due to the "ceiling" effect: almost all patients already have a high level of risk, so age differences are leveled out. Here, age ceases to be a modifier, since operant behavior is already an established behavioral pattern regardless of age. Experimental and clinical studies confirm that operant mechanisms (reinforcement/avoidance) can significantly modulate the pain experience and maintain the symptom regardless of age when the pattern is already established [44]. Clinically, this indicates that PPP 3 is the most "behaviorally inert" group of patients, in which the risk of addiction can develop as an automated strategy for overcoming pain. Patients are often unaware of the risk, demonstrating a high level of psychological rationalization ("I need it, otherwise I can't work/sleep") and low motivation to change. A combination of cognitive-behavioral therapy and careful monitoring of pharmacotherapy may be appropriate here, as behavioral patterns are persistent and do not correct themselves spontaneously with age.

The Groups PPP 2, SMP and SOP: absence of age-related addiction. In the Group PPP 2, the distribution was almost uniform ($p = 0.741$); however, after the age of 40, an increase in risk was observed (66.7%), which is likely associated with the accumulation of psychosomatic disturbances and depletion of nervous system resources rather than behavioral factors.

Regarding the Groups SMP and SOP, the absence of statistical differences ($p > 0.25$) confirms that in these cohorts, the risk of operant behavior is determined by the organic component of pain, not by age. Patients in these groups demonstrate a high level of self-control and low affective reactivity.

In somatic forms of pain, age has a neutral or even protective role, whereas the primary determinant of risk is the quality of medical supervision and the adequacy of the analgesic strategy. This is why the risk of developing addiction and operant behavior is lower in older patients compared with younger ones.

CONCLUSIONS

1. Gender is not a universal predictor of operant behavior risk, but it does influence its severity in certain types of pain. The greatest gender differences are observed in primary psychogenic (PPP 1) and mixed primary psychogenic and psychophysiological (PPP 3) chronic pain, where men show a higher propensity for painful behavior and pharmacological forms of addiction.

2. In men, the risk of developing operant behavior and the risk of probable opioid addiction is more often associated with cognitive patterns of control and denial of affect, while in women it is associated with affective lability, somatization, and the need for social reinforcement.

3. In secondary forms of chronic pain (SMP, SOP), gender does not significantly affect risk, confirming the dominance of organic or mixed pathogenesis over the psychogenic component. The Group SOP is the most appropriate group for prescribing opioid analgesia with the lowest risk of operant behavior formation. The Group SMP has a lower risk of operant behavior formation, but combines psychoemotional disorders at the subclinical level in its structure; therefore, it also requires special attention.

Men with psychogenic or psychophysiological forms of chronic pain (PPP 1, PPP 3) are a priority risk group for the development of operant behavior and probable opioid abuse. Addiction is emotional-compensatory or cognitive-protective in nature; therefore, for patients in these groups, it is advisable to use multimodal programs with the mandatory inclusion of cognitive-behavioral therapy, psychoeducation on tolerance and pain control with a reduction in medication reinforcement, especially with regard to opioid analgesia.

4. The age distribution is not random, but reflects the pathogenetic nature of pain syndromes: psychogenic forms – younger, organic – older. Younger age (≤ 29 years) is associated with a higher risk of opioid analgesia addiction and the formation of operant behavior, which is explained by emotional instability, impulsivity, and the absence of established coping strategies. Middle age (30–39 years) is characterized by transitional risks – psychophysiological mechanisms begin to prevail over psychogenic ones, but stress reactivity remains high. Older age (≥ 40 years) predominates in patients with secondary (organic) forms of pain, where the risk of addiction is minimal, and the prescription and possible long-term opioid therapy may be clinically justified with adequate monitoring.

5. In young patients of the Group PPP 1, with primary psychogenic disorders in which pain syndromes are present (depressive, anxiety, somatoform disorders, PTSD), an emotionally dependent model of drug use may develop – that is, "opioid as an antidepressant" rather than "opioid as an analgesic". Therefore, in younger patients with primary psychogenic pain disorders (PPP 1), it is essential to identify the latent emotional motivation behind medication intake, since addiction develops at the level of affective reinforcement, not pharmacological tolerance.

Thus, it can be concluded that age and sex act as clinical modifying factors of operant behavior, but not as primary causes of risk. The obtained data emphasize the importance of an individualized approach to opioid analgesia, one that considers not only the type of pain but also the gender, age, and psychological features of the patient's behavioral reactivity.

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