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Gender difference in long-term use of opioids among Taiwan officially registered patients with chronic noncancer pain

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Abstract

Research regarding sex or gender difference in chronic pain proliferated in this decade. This study was to analyze gender difference in Taiwan patients receiving long-term opioids for chronic noncancer pain.

An observational cross-sectional survey was conducted among the registered outpatients by the Taiwan Food and Drug Administration. Participants completed a self-report questionnaire, including the Taiwanese version of Brief Pain Inventory and enquiry regarding sexual activities, depressive symptoms, and misuse behaviors.

In total, 68 female and 142 male patients were analyzed. Both pain intensity and daily function interference reduced comparably (around 50%) between women and men after taking opioids in the past 1 week. The opioid-related adverse effects, including constipation, decreased sexual desire and satisfaction, and misuse behaviors were not significantly different. Women were exceedingly diagnosed with depression (67.7% vs 49.3%, $P = .012$) and had a higher mean depressive symptom score in the past 1 month, especially among those age <40 years (23.3 vs 11.9, $P = .009$), as compared with men. In addition, women had a lower mean self-rated health score (37.9 vs 44.3, $P = .047$). The mean morphine equivalent dose was significantly lower in women (131.6 vs 198.2 mg/day, $P = .008$), which was not correlated with their depressive scores.

Gender differences in the effectiveness and adverse effects of long-term opioids were not found among Taiwan registered outpatients with chronic noncancer pain. However, more female patients inclined to have a coexisting depression diagnosis, depressive symptoms, and a lower perceived health score, needing regular screening and closer monitoring.

Abbreviations: CNCP = chronic noncancer pain, MED = morphine equivalent dose.

Keywords: chronic pain, difference, gender, noncancer, opioid

1. Introduction

This decade has witnessed substantial literatures regarding sex or gender differences in their responses to experimental pain perception,[1] biopsychosocial factors,[2] and pharmacological or nonpharmacological pain interventions.[3] The emerging evidence implicates biological sex hormones as key factors influencing pain sensitivity, while psychosocial and environmental processes may explain gender differences in pain expression,[2] such as increased pain sensitivity and risk for clinical pain among women.[3]

By now, several population-based epidemiological studies have demonstrated greater pain prevalence among women relative to men.[4–9] Women are more likely to experience a variety of chronic pain syndromes and tend to report more severe pain, at a higher frequency, and in a greater number of body regions,[2,9] resulting in a lower self-report health and functioning status.[8] However, men with chronic noncancer pain (CNCP) are more likely to receive opioids than women [6,10] and are at higher risk than women for escalation to high-dose opioid therapy and death from opioid-related causes.[11]

Long-term use of opioids has been strictly regulated in Taiwan since 1996.[12] Each CNCP patient should be assessed by the hospital's opioid committee and finally approved by the Taiwan Food and Drug Administration. The duration of each opioid prescription is limited and the long-term opioid therapy should be re-evaluated and recorded for surveillance at least every 4 months. The physicians must report the patients with aberrant behaviors to the hospital's opioid committee for discontinuing the opioid treatment.[12]

Consistent with a 55% increase of opioid consumption in Taiwan from 2002 to 2007,[13] the registered CNCP outpatients escalated from 114 in 2001 [14] to 328 in 2010.[15] We had interviewed 210 CNCP patients in 2010 [15] and this study further analyzed the gender difference among them regarding the concurrent perceptions of pain relief and adverse effects by

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chronic opioid therapy, including daily function, depression, sexual activity, and drug misuse behaviors.

2. Methods

2.1. Participants

With the approval of the Taiwan Food and Drug Administration in January 2010, all of the registered CNCP patients were included.[15] According to the official patient list with omitted Chinese first names, the study interviewers visited the outpatient departments and requested the treating physicians to identify the patients and their conditions. A total of 210 (64.0%) of the 328 registered CNCP patients signed the written informed consent approved by the hospital institutional review board (TSGHIRB-098-05-254) and completed the Chinese language questionnaire by themselves or with verbal help from the interviewer.[15] The questionnaire included the Taiwanese version of Brief Pain Inventory,[16] the Chinese version of Beck Depression Inventory,[14] aberrant behaviors associated with prescription opioid misuse, self-reported impacts on sexual function (desire, frequency, capability, and satisfaction), and use of complementary and alternative medicine (CAM).[15] The opioid prescriptions were verified by the treating physicians and converted to a daily oral morphine equivalent dose (MED), with a so-called watchful dose as 200 mg per day which suggests a careful reassessment.[17] The secondary analysis of gender difference among these 210 patients was conducted in this study.

2.2. Statistical analysis

The results of the questionnaire were entered into SPSS version 17 (SPSS, Chicago, IL). The demographic data were presented as patient number (%) or mean ± SD. Gender difference in pain severity (0–10), daily function interference scores by pain (0–10), total depressive scores (0–63), and self-rated health score (0–100) were analyzed by using *t*-test or Mann–Whitney *U* test. Gender impact on opioid adverse effects, depression diagnosis, misuse behaviors, and use of CAM were examined as categorical variables by using the χ^2 test or Fisher's exact test. In addition, *t*-test and Mann–Whitney *U* test were used again to compare the MEDs between different genders among patients with side effects, sexual interference, and depression. In all cases, a *P* value $< .05$ was considered statistically significant.

3. Results

Among 210 (64.0%) of 328 registered outpatients, 68 (54.8%) of 124 women and 142 (69.6%) of 204 men completed the questionnaires. Table 1 presents comparable demographic data between women and men, including work status, pain treatment experience, suicidal ideation, and mean durations of chronic pain (median 84 vs 108 months) and opioid treatment (median 48 vs 60 months). Up to 72.1% of women and 79.6% of men became workless due to chronic pain, however, without significance. More women ever had a diagnosis of depression (67.6 vs 49.3%, $P = .012$), with an odds ratio 2.15 (95% confidential interval 1.17–3.94), as compared with men. Women reported significantly higher depressive scores summed by more depressive symptoms, especially among those aged under 40 (mean 23.3 vs 11.9, $P = .009$, maximal score 63). Consistently, women perceived a lower mean health score than men (37.9 vs 44.3, $P = .047$, maximal score 100).

As shown in Table 2, women had a lower mean MED than men did (131.6 vs 198.2 mg/day, $P = .008$), and less women received high-dose opioids that surpassed the watchful dose of 200 mg/day (19.7 vs 37.5%, $P = .011$). The leading 3 diagnoses of chronic pain were chronic pancreatitis, spinal cord injury and neuralgia. All 7 patients diagnosed with fibromyalgia were female. There were no significant differences in daily MEDs for each diagnosis among women and men. The highest 3 MEDs were 1100, 910, and 740 mg/day in 3 men with chronic pancreatitis, neuralgia, and spinal cord injury, respectively. The high doses came mainly from fentanyl patch (300 μg/h) plus sustained-release oral morphine 30 and 60 mg.

Figure 1 depicts comparable pain scores and interference with daily function after taking opioids in the past week. In addition, the opioid-related side effects and depressed sexual issues were compared in Table 3. Constipation, dry mouth, and nausea-vomiting were the leading side effects. Despite taking lower opioid doses, women were not less or more likely to suffer the side effects and decreases of sexual capability, frequency, and satisfaction. All 95% confidential intervals overstrode 1.0.

As demonstrated in Table 4, opioid misuse and aberrant behaviors were not significantly different between women and men. Only 2 (1.0%) men reported that they had ever, but seldom, borrowed pain medication from someone else. Relative to men, women did not have a greater risk to visit an emergency department for a pain-related complaint (odds ratio 1.48, 95% confidential interval 0.67–3.27, $P = .335$).

4. Discussion

This country-wide survey first demonstrated gender difference among the Taiwan registered patients receiving long-term opioids for chronic noncancer pain. The experience of the other pain management and the impact of long-term opioids on either effectiveness or adverse effects were comparable between women and men. However, more female patients had a coexisting depression diagnosis, more depressive symptoms, and a lower perceived health score.

Women are more likely to report severe pain and chronic pain in multiple geographic regions,[4–9] in addition to Taiwan [18] and China.[19] After receiving chronic opioid therapy, women perceived more unfavorable pain and a lower function status than did men (59% vs 42%).[5] However, women had lower odds of being prescribed chronic opioid therapy (odds ratio 0.67, 95% CI 0.58–0.78),[10] but greater odds of receiving physical therapy (OR 1.40, 95% CI 1.18–1.65) [10] and guideline-recommended psychotherapy, rehabilitation therapy, and pharmacy reconciliation.[4] The Taiwan Food and Drug Administration summarized all of the registered patients between 2003 and 2012,[20] with a ratio of women/men as 0.62 (246/398). In this study, the women/men ratio was 0.61 (124/204) from 328 registered patients in 2010. Generally, women and man in this study had comparable demographic data, experience of pain treatment, opioid effectiveness, and side effects. Therefore, to facilitate multidisciplinary pain treatment for Taiwan women, or to eliminate the factors deterring women from receiving long-term opioids would provide more adequate pain management for the under-estimated women suffering chronic pain in Taiwan.

Depression is prevalent in people living with chronic pain.[21] The patients with opioid analgesic use of more than 90 days had an increased risk of a new depression diagnosis (hazard ratio from 1.35 to 2.05 in 3 patient populations), as compared with those with opioid use of less than 30 days in a retrospective

Table 1

Demographic data and depressive status.

Gender	Women (n = 68)	Men (n = 142)	*P* value
Pain duration, month	107.4 ± 71.4 (24–372)	115.4 ± 69.7 (24–360)	.440[†]
Opioid therapy, month	61.2 ± 46.7 (12–240)	64.9 ± 44.7 (12–240)	.584[†]
Pain reduction after taking opioids, %	48.4 ± 18.3 (10–100)	49.8 ± 20.3 (0–100)	.618[†]
Physician interviewing time, minute	12.1 ± 6.7 (3–40)	12.3 ± 7.8 (3–70)	.858[†]
Age, year	53.0 ± 15.6 (25–88)	48.6 ± 13.9 (21–89)	.038[†]
< 80	61 (89.7%)	135 (95.1%)	.152[‡]
≥ 80	7 (10.3%)	7 (4.9%)	
Marital status			
Married	30 (44.1%)	76 (53.5%)	.202[c]
Single	38 (55.9%)	66 (46.5%)	
Work status (%), n = 62/135			
Full-time work	6 (9.7%)	27 (20.0%)	.060[c]
Part-time work	8 (12.9%)	9 (6.7%)	
Retired	15 (24.2%)	19 (14.1%)	
Unemployed	33 (53.2%)	80 (59.3%)	
Workless due to pain, n = 43/98			
Yes	31 (72.1%)	78 (79.6%)	.328[c]
No	12 (27.9%)	20 (20.4%)	
Ever received nerve block			
Yes	25 (36.8%)	51 (35.9%)	.905[§]
No	43 (63.2%)	91 (64.1%)	
Ever received complementary and alternative medicine			
Yes	40 (58.8%)	78 (54.9%)	.595[§]
No	28 (41.2%)	64 (45.1%)	
Ever visited traditional Chinese medicine doctors			
Yes	38 (55.9%)	74 (52.1%)	.608[§]
No	30 (44.1%)	68 (47.9%)	
Ever took Chinese herbal remedies			
Yes	37 (54.4%)	58 (40.8%)	.065[§]
No	31 (45.6%)	84 (59.2%)	
Ever receiving acupuncture			
Yes	24 (35.3%)	43 (30.3%)	.466[§]
No	44 (64.7%)	99 (69.7%)	
Ever receiving massage			
Yes	10 (14.7%)	33 (23.2%)	.152[§]
No	58 (85.3%)	109 (76.8%)	
Ever receiving chiropractic			
Yes	13 (19.1%)	28 (19.7%)	.918[§]
No	55 (80.9%)	114 (80.3%)	
Depression diagnosed before chronic pain			
Yes	6 (8.8%)	3 (2.1%)	.061[‡]
No	62 (91.2%)	139 (97.9%)	
Depression diagnosed after chronic pain			
Yes	46 (67.6%)	70 (49.3%)	.012[§]
No	22 (32.4%)	72 (50.7%)	
Suicidal ideation			
Never	35 (51.5%)	84 (59.2%)	.293[§]
Ever	33 (48.5%)	58 (40.8%)	
Beck Depression Inventory score, 0–63	19.8 ± 13.1 (1–50)	15.1 ± 11.7 (1–57)	.009[‖]
Age 20–39	23.3 ± 14.0 (6–44)	11.9 ± 7.7 (3–35)	.009[‖]
Age 40–64	19.8 ± 13.4 (1–50)	15.9 ± 12.8 (1–57)	.116[†]
Age 65–79	14.0 ± 8.9 (5–26)	19.2 ± 12.0 (2–39)	.347[†]
Age ≥ 80	19.3 ± 12.6 (3–39)	16.9 ± 12.8 (1–36)	.728[†]
Self-rated health score, 0–100	37.9 ± 23.2 (0–80)	44.3 ± 20.8 (0–80)	.047[†]
Age 20–39	44.2 ± 27.5 (0–80)	46.7 ± 21.2 (0–80)	.913[‖]
Age 40–64	41.0 ± 21.1 (0–80)	45.0 ± 20.2 (10–80)	.302[†]
Age 65–79	27.9 ± 22.3 (10–75)	39.5 ± 25.7 (10–80)	.348[†]
Age ≥ 80	18.6 ± 18.6 (10–60)	30.0 ± 16.3 (10–50)	.246[†]

The data were presented as n (%) or mean ± SD (range).

[*] Single status, including never married, separated, divorced, and widowed.

[†] *P* values were estimated by Student's *t*-test.

[‡] *P* values were estimated by Fisher's exact test.

[§] *P* values were estimated by chi-square test.

[‖] *P* values were estimated by Mann–Whitney U test.

Table 2

Opioid dosage and diagnosis of chronic noncancer pain.

Gender	Women (n = 68)			Men (n = 142)			*P* value
	Mean ± SD	(Range)	Median	Mean ± SD	(Range)	Median	
Morphine equivalent dose (MED), mg/day (n = 66/136)*	131.6 ± 94.8	(4.5–380)	120	198.2 ± 176.4	(10–1100)	180	0.008†
Age < 80 years, n = 59/129	135.6 ± 94.1	(9–380)	120	200.7 ± 179.5	(10–1100)	180	0.021†
Age ≥ 80 years, n = 7/7	98.5 ± 102.1	(4.5–270)	40	150.0 ± 101.0	(30–300)	120	0.361‡
< 200 mg/day, n = 138	53 (80.3%)			85 (62.50%)			0.011§
≥ 200 mg/day, n = 64	13 (19.7%)			51 (37.50%)			
Diagnosis for chronic pain							
Chronic pancreatitis, n = 4/40	135.0 ± 71.4	(60–210)	135	195.2 ± 192.9	(10–1100)	150	0.543‡
Spinal cord injury, n = 16/28	176.3 ± 108.5	(30–380)	180	217.0 ± 198.5	(20–740)	180	0.454‡
Neuralgia, n = 9/18	115.3 ± 53.6	(18–180)	120	182.8 ± 205.6	(10–910)	125	0.347‡
Failed back surgery syndrome, n = 7/13	85.0 ± 44.2	(30–120)	105	189.2 ± 141.2	(30–480)	180	0.112†
Fibromyalgia, n = 7/0	115.4 ± 78.5	(18–270)	100	–	–	–	–

The data were presented as n (%) or mean ± SD (range).

MED = morphine equivalent dose.

* There were 8 patients receiving weak opioids that had not been converted into MEDs (nalbuphine 1, tramadol 2, buprenorphine 4 and combined tramadol and buprenorphine 1).

† *P* values were estimated by Mann–Whitney *U* test.

‡ *P* values were estimated by Student's *t*-test.

§ *P* values were estimated by chi-square test.

survey.[22] However, another prospective observational cohort study did not observe an increase of depressive symptoms following the 12-month opioid use for chronic pain.[23] It is noteworthy that two-thirds of our female patients had a diagnosis of depression after chronic pain, especially among those age < 40. Among chronic opioid users, young and middle-aged women (< 65 years) were at particularly higher risk of unfavorable global pain status (66% of women vs 40% of men among those aged 21 to 44 years; 59% vs 39% in those aged 45 to 64).[5] Consequently, suicidal ideation is a risk factor in this population that it must be assumed some proportion of drug overdose by intended suicide, not just by temporarily relieving their pain.[21] When possible, clinicians should avoid rapid dose escalation, which may be a proxy for loss of control or undetected abuse known to be associated with depression.[24] Over 40% of our patients ever had suicidal ideation, without gender difference. In Taiwan, prescription opioid abuse and overdose-related death have not yet become public health issues. According to the Taiwan official opioid regulation,[12] physicians should refer each CNCP patient to an initial psychiatric consultation, which should encompass the patient's psychiatric status, any comorbid psychiatric disorders, history of drug abuse, and social psychological function, followed by psychiatric re-assessment at least every 6 months.[25] Further prospective and longitudinal surveys in Taiwan are needed to determine the opioid prescription-related mortality that we did not obtain in this cross-sectional survey.

Opioids can suppress gonadal hormone production, resulting in low testosterone levels, reduced libido, decreased sexual capability, and even infertility in both men and women.[26,27] Long-term use of opioids in women exhibited clinically associated reproductive dysfunction, including decreased libido (61%–100%) and altered menstrual cycle (amenorrhea, 23%–71%).[28] A cross-sectional survey using the National Health and Nutrition Examination Survey program in the United States revealed both men and women with opioid exposure in the past

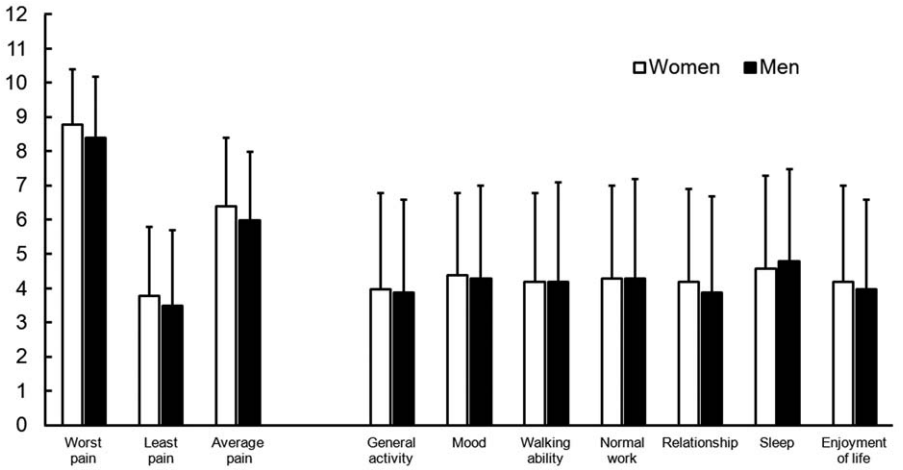

Figure 1. No observed gender differences in pain intensity and interference with daily function after taking opioids in the past 1 week.

Table 3

Side effects and sexual interference after taking opioids in the past 1 week.

	Women (n = 68)		Men (n = 142)		*P* value	OR (95% CI)
	n (%)	MED	n (%)	MED	(MED)	(Women/Men)
Side effects						
Constipation, n = 98	30 (44.1%)	157.1 ± 111.5	68 (47.9%)	215.2 ± 183.8	0.113*	0.86 (0.48–1.54)
Dry mouth, n = 38	12 (17.6%)	118.7 ± 97.2	26 (18.3%)	232.8 ± 171.4	0.039*	0.96 (0.45–2.03)
Nausea or vomiting, n = 26	9 (13.2%)	40.0 ± 37.6	17 (12.0%)	297.6 ± 259.7	0.002*	1.12 (0.47–2.67)
Drowsiness, n = 21	10 (14.7%)	127.6 ± 94.7	11 (7.7%)	213.6 ± 127.5	0.098*	2.05 (0.83–5.10)
Sweating, n = 10	3 (4.4%)	90.0 ± 52.0	7 (4.9%)	193.3 ± 120.4	0.209*	0.89 (0.22–3.55)
Itching, n = 10	5 (7.4%)	126.3 ± 160.2	5 (3.5%)	226.0 ± 109.5	0.302*	2.18 (0.61–7.78)
Sexual interference						
Decreased desire, n = 146	48 (70.6%)	132.7 ± 97.4	98 (69.0%)	202.9 ± 181.5	0.015*	1.08 (0.57–2.03)
Among those with sexual activity, n = 39/94						
Decreased capability, n = 77	23 (59.0%)	133.6 ± 92.6	54 (57.4%)	246.1 ± 230.2	0.035†	1.07 (0.50–2.27)
Decreased frequency, n = 84	25 (64.1)	128.1 ± 91.3	59 (62.8%)	235.0 ± 223.3	0.030†	1.06 (0.49–2.30)
Decreased satisfaction, n = 77	23 (59.0)	124.5 ± 92.0	54 (57.4%)	230.1 ± 221.0	0.031†	1.07 (0.50–2.27)

The data were presented as n (%) or mean ± SD for MED, morphine equivalent dose, mg/day.
MED = morphine equivalent dose.
* *P* values were estimated by Student's *t*-test.
† *P* values were estimated by Mann–Whitney *U* test.

30 days had a higher odds ratio (1.40) of low testosterone levels than those unexposed,[29] especially among those over 70 years (OR 1.70), as compared with those between 17 and 45 years. Meanwhile, men with chronic opioid therapy are at higher risk (hazard ratio 1.44) than women for escalation to high-dose opioid therapy in a Canadian cohort study.[11] Similarly, our male patients had a higher mean daily dose and were more likely to receive high-dose opioids that surpassed the watchful dose of 200 mg per day, despite comparable sexual function interference than women. Further prospective surveys are needed to discover the suppression of testosterone and estrogen levels and its relationship with opioid doses in the Taiwan CNCP patients.

This uncontrolled and nonblinded study has several limitations, some of which have been discussed in the earlier publication.[15] Some more limitations should be considered in this gender study. First, the ratio of women/men respondents is only 48%. The higher rates of depression diagnosis in these women may predispose them to a more unfavorable opioid effectiveness and more adverse effects. Second, the secondary analysis in this study was limited to the variables contained in the original questionnaires, which did not enquire about the psychosocial factors that correlate with the diagnosis of depression in women and the details of medication adherence. Third, these self-report data were subject to recall bias as well.

Table 4

Prescription opioid misuse behaviors.

Gender	Women (n = 68)	Men (n = 142)	*P* value†	OR (95% CI)
Using pain medicine for symptoms than for pain (e.g., to help sleep, improve mood, or relieve stress)				
Often or sometimes	20 (29.4%)	34 (23.9%)	0.396	1.32 (0.69–2.53)
Seldom or never	48 (70.6%)	108 (76.1%)		1.00
Taking your medications differently from how they are prescribed				
Often or sometimes	28 (41.2%)	60 (42.3%)	0.882	0.96 (0.53–1.72)
Seldom or never	40 (58.8%)	82 (57.7%)		1.00
Taking more of your medication than prescribed				
Often or sometimes	13 (19.1%)	31 (21.8%)	0.651	0.85 (0.41–1.75)
Seldom or Never	55 (80.9%)	111 (78.2%)		1.00
Borrowing pain medication from someone else				
Often or sometimes	0 (0.0%)	0 (0.0%)	–	–
Seldom or never	68 (100.0%)	142 (100.0%)		1.00
Visiting the emergency room for more pain medication				
Often or sometimes	12 (17.6%)	18 (12.7%)	0.335	1.48 (0.67–3.27)
Seldom or never	56 (82.4%)	124 (87.3%)		1.00
Ever lost your opioid medication twice or more times				
Yes	5 (7.4%)	7 (4.9%)	0.530‡	1.53 (0.47–5.01)
No	63 (92.6%)	135 (95.1%)		1.00
Ever obtained opioids from others out of the hospital				
Yes	2 (2.9%)	8 (5.6%)	0.505‡	*0.51 (0.11–2.46)*
No	66 (97.1%)	134 (94.4%)		*1.00*

The data were presented as n (%).
† *P* values were estimated by Chi-square test.
‡ *P* values were estimated by Fisher's exact test.

The effectiveness might be overrepresented by high utilizers of care, while the intolerable side effects and aberrant behaviors might have been under-reported on account of a total of non-respondent rate 36% of all CNCP patients. Consequently, those with severe depressive symptoms would be unrevealed among the nonrespondent women (45.2%) and men (30.4%). From a clinical point of view, the statistically significant difference in depression diagnosis did not influence their effectiveness and major side effects of opioid therapy between genders.

This cross-sectional survey analyzed the gender difference among the Taiwan officially registered and surveilled outpatients with chronic noncancer pain and revealed comparable effectiveness and adverse effects of long-term opioids. Notably, more female patients inclined to have a coexisting depression diagnosis, more depressive symptoms, and a lower perceived health score. Routine screening and closer monitoring for depression are needed.

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