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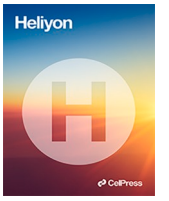

Research article

Novel insights into post-marketing AEs associated with leuprorelin: A comprehensive analysis utilizing the FAERS database

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ABSTRACT

Purpose: This research focused on meticulously tracking and identifying adverse reactions associated with leuprorelin, a drug prescribed for conditions such as prostate cancer, endometriosis, uterine fibroids, and early-onset puberty. The main objective was to enhance patient safety and offer informed guidance on the appropriate use of this treatment.

Methods: From the first quarter of 2004 to the fourth quarter of 2023, a comprehensive analysis was conducted on a significant number of adverse event reports (AERs) from the FDA Adverse Event Reporting System (FAERS) database. Data mining with dismutation analysis was conducted to quantify signals associated with adverse events (AEs) related to leuprorelin, utilizing powerful algorithms such as ROR, PRR, BCPNN, and EBGM.

Results: A total of 102 positive reaction terms (PT) spanning 24 System Organ Classes (SOCs) were identified from an analysis of 60,709 reports associated with leuprorelin use. Notably, several previously unrecognized adverse reactions were uncovered, including Artificial Menopause, Ovarian Adhesion, Follicular Cystitis, Intercepted product preparation error, among others. These findings underscore the importance of exercising additional vigilance regarding the potential adverse effects of leuprorelin, such as Abscess Sterile, Injection site granuloma, Intercepted medication error, and Bulbospinal muscular atrophy congenital.

Conclusions: This research has successfully uncovered new and unforeseen signals associated with adverse drug reactions (ADRs) following leuprorelin administration. The study provides valuable insights into the intricate connection between ADRs and leuprorelin usage. The results underscore the crucial significance of continuous surveillance and meticulous monitoring to promptly

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identify and manage AEs, ultimately enhancing patient safety and well-being while undergoing leuprorelin therapy.

1. Introduction

Leuprorelin acetate, a synthetic nonapeptide, is a potent gonadotropin releasing hormone (GnRH) agonist commonly used in various clinical settings. It is utilized for the treatment of conditions such as prostate cancer, endometriosis, uterine fibroids, central precocious puberty, and in vitro fertilization techniques [1]. Initially introduced in 1985 as an alternative to surgical castration and estrogen therapy for prostate cancer [2,3], leuprorelin acetate has since become a well-established treatment option for endometriosis, uterine fibroids, and central precocious puberty (CPP) [4–7]. These conditions pose significant global burdens, with prostate cancer affecting approximately 10 million men worldwide [8]. Prostate cancer is the second most common cancer and the fifth leading cause of cancer death in the world [9]. Endometriosis impacting 10 % of women of reproductive age (approximately 190 million women globally), and uterine fibroids accounting for over 75 % of women worldwide [10,11]. And the incidence of CPP may be as high as 1 in 5000, whereas a more modest definition estimates an incidence of 1 in 10,000 [12].

Leuprorelin acetate initially induces a notable increase in the secretion and serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary, accompanied by elevated sexual steroid levels within three days of treatment initiation. However, upon continued administration, this GnRH agonist suppresses the pituitary-gonadal axis by downregulating gonadotropin receptors, desensitizing gonadotropin-producing cells, and reducing circulating levels of LH, FSH, and sex hormones within two to four weeks. These downregulation mechanisms are essential for the drug's clinical applications in gynecology and other fields [1]. Despite its extensive usage, there are sporadic reports of rare adverse reactions when leuprorelin is used alone or in combination with other medications, highlighting gaps in our knowledge of its safety profile. Further research and analysis of leuprorelin's safety in practical, real-world scenarios are warranted.

Our study focused on conducting a detailed analysis of adverse effects associated with leuprorelin using real-world data from the FDA Adverse Event Reporting System (FAERS). We employed four different algorithms for adverse reaction signal strength analysis: Reported Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Empirical Bayesian Geometric Mean (EBGM). Our study can effectively detect and manage adverse reactions of leuprolide, so as to improve patient medication safety.

2. Materials and methods

2.1. Data source

Considering the date leuprorelin was introduced to the market, this research extracted American Standard Code for Information Interchange (ASCII) report files from the FAERS database, covering the period from Q1 2004 to Q4 2023. The analysis was conducted using R software version 4.3.2. (Fig. 1).

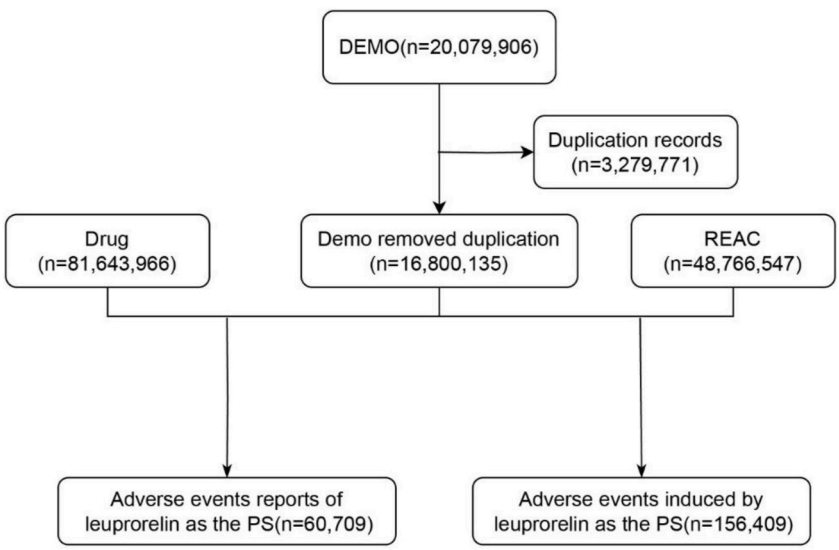

Fig. 1. The flow diagram of selecting leuprorelin -related AEs from FAERS database. (**DEMO, demographic and administrative information; DRUG, drug Information; REAC, preferred terminology for adverse drug reactions; PS, primary suspect drug**).

To ensure data integrity, redundant reports were eliminated and only the most recent report per case date was retained. Drug name standardization was carried out using the Medex_UIMA_1.8.3 system. Reports pinpointing leuprorelin as the main substance associated with adverse drug event (ADE) signals were extracted. Additionally, this study employed the 'Medical Dictionary for Regulatory Activities' (MedDRA) to standardize and localize AE terminology in the Preferred Terms (PTs) format. Adverse drug reaction reports sharing the same PTs were consolidated, with PTs categorized by their respective System Organ Classes (SOCs) [13].

2.2. Statistical analysis

In this study, four disproportionality analysis methods were utilized for data mining purposes: ROR [14], PRR [15], BCPNN [16], and EBGM [17]. ROR is effective in reducing biases associated with events that have a limited number of reports, while PRR is known for its higher specificity compared to ROR. BCPNN excels in synthesizing and cross-verifying data from multiple sources. By integrating ROR, PRR, BCPNN, and EBGM, this research capitalizes on the unique strengths of each method, expanding the detection and validation capabilities. This comprehensive approach aids in identifying safety signals more accurately, reducing false positives through mutual verification, and improving the detection of rare adverse reactions by adjusting thresholds and variability. These methods all utilize a disproportionality measure based on a 2 x 2 table, as illustrated in Table 1. The specific formulas for the four methods used in this study can be found in Supplementary Table S1.

3. Results

3.1. Basic information of AE reports

Over the course of the study, we collected a total of 16,800,135 unique AERs from the FAERS database, among which 60,709 were specifically associated with leuprorelin (Fig. 1). The demographic characteristics of leuprorelin-associated AEs are described in Table 2. In the dataset of leuprorelin-linked AEs that we analyzed, there was a noticeable gender disparity: 65.82 % of the reports involved males, while females accounted for only 24.82 %. Additionally, the highest incidence of AEs was observed in patients over 65, who made up 31.45 % of the reports. From 2004 to 2023, there was a noticeable increase in AERs related to Leuprorelin. Consumers were the predominant reporters, contributing 34,116 cases (56.20 %), followed by pharmacists with 11,665 cases (19.21 %), and physicians with 8,945 cases (14.73 %). There were 15,716 cases reported in the United States (28.83 %). The most common serious medical events reported, aside for unspecified ones, included deaths, which accounted for 30.12 % (10,856 cases), hospitalizations at 24.57 % (8,855 cases), and disability conditions at 2.21 % (795 cases). AEs were most frequently reported within 7 days or after more than 60 days following treatment, making up 21.37 % and 20.87 % of cases, respectively. The leading indications for leuprorelin usage included prostate cancer (37,236 cases, 61.84 %), unspecified reasons (8,968 cases, 14.9 %), endometriosis (6,589 cases, 10.94 %), uterine leiomyoma (1,987 cases, 3.3 %), and precocious puberty (1,468 cases, 2.44 %). These findings are in line with FDA-approved indications and provide crucial insights into leuprorelin AE reporting patterns, helping to assess the drug's safety profile and clinical effectiveness.

3.2. Risk signal mining results

When leuprorelin was identified as the main suspect in AE signals, screening using methods like ROR, PRR, BCPNN, and EBGM ultimately highlighted AE signals across 24 SOCs. The outcomes of the study suggested that AEs most closely associated with the use of leuprorelin predominantly occur within the realms of general disorders, general disorders and administration site conditions (n = 34,532, ROR 1.28, PRR 1.22 IC 0.28, EBGM 1.22), injury, poisoning and procedural complications (n = 21,435, ROR 1.53, PRR 1.46, IC 0.54, EBGM 1.46), and nervous system disorders (n = 11,060, ROR 0.78, PRR 0.79, IC -0.34, EBGM 0.79). Utilizing the ROR method to gauge signal intensity, the top three categories identified were reproductive system and breast disorders with 7,036 cases (ROR 5.41, PRR 5.21, IC 2.36, EBGM 5.14), followed by vascular disorders with 10,772 cases (ROR 3.19, PRR 3.04, IC 1.59, EBGM 3.02), and neoplasms benign, malignant and unspecified (incl cysts and polyps) with 7,493 cases (ROR 1.73, PRR 1.70, IC 0.76, EBGM 1.69), in that order. The first two systems satisfied all four algorithmic requirements. Additionally, this study identified several other frequently occurring AEs, such as Infections and infestations, and Ear and labyrinth disorders, besides those explicitly mentioned in the drug insert. These AEs need clinical attention. There are no warnings or precautions given in leuprorelin's instructions regarding pregnancy, puerperium, and perinatal conditions. See Table 3 for details.

Table 1
Four grid table.

	Target ADEs	Non-target ADEs	Total
Leuprorelin	a	b	a + b
Non- leuprorelin	c	d	c + d
Total	a + c	b + d	N = a + b + c + d

Notes: a, number of reports containing both the target drug and target adverse drug reaction; b, number of reports containing other adverse drug reaction of the target drug; c, number of reports containing the target adverse drug reaction of other drugs; d, number of reports containing other drugs and other adverse drug reactions.

Table 2
Clinical characteristics of reports with leuprorelin from the FAERS database (2004 Q1–2023 Q4).

Factors	Available case number, n	Case proportion, %
Gender		
female	14,966	24.65
male	39,956	65.82
unkown	5,787	9.53
Age		
<18	1,592	2.62
18~65	10,215	16.83
≥65	19,095	31.45
unknow	29,807	49.10
Reporter(Top five)		
Consumer	34,116	56.20
Pharmacist	11,665	19.21
Physician	8,945	14.73
Other health-professional	4,395	7.24
unkown	1,561	2.57
Reported countries(Top five)		
United States	15,716	28.83
Canada	13,348	24.48
other	9,260	16.99
Netherlands	5,350	9.81
Australia	4,109	7.54
Route(Top five)		
other	24,448	40.29
subcutaneous	24,279	40.02
intramuscular	11,626	19.16
transplacental	98	0.16
parenteral	78	0.13
Outcomes		
other serious	14,688	40.76
death	10,856	30.12
hospitalization	8,855	24.57
disability	795	2.21
life threatening	643	1.78
required intervention to Prevent Permanent Impairment/Damage	162	0.45
Year		
2004	171	0.28
2005	110	0.18
2006	133	0.22
2007	162	0.27
2008	527	0.87
2009	1,115	1.84
2010	1,518	2.50
2011	1,694	2.79
2012	1,166	1.92
2013	2,360	3.89
2014	3,589	5.91
2015	4,124	6.79
2016	4,203	6.92
2017	3,205	5.28
2018	3,073	5.06
2019	3,924	6.46
2020	5,737	9.45
2021	6,395	10.53
2022	7,494	12.34
2023	10,009	16.49
Adverse event occurrence time - medication date (days)		
<7	9,741	21.37
7~28	1,259	2.76
28~60	1,074	2.36
≥60	9,515	20.87
unknow	24,001	52.65
Indications		
prostate cancer	37,236	61.84
product used for unknown indication	8,968	14.9
endometriosis	6,589	10.94
uterine leiomyoma	1,987	3.3
precocious puberty	1,468	2.44
bulbospinal muscular atrophy congenital	526	0.87

(*continued on next page*)

Table 2 (*continued*)

Factors	Available case number, n	Case proportion, %
breast cancer	722	1.21
drug use for unknown indication	215	0.36
gender dysphoria	177	0.29
menorrhagia	131	0.22

To further elucidate the adverse effects of leuprorelin in different medical conditions, we conducted specific analyses according to different diseases, and focused on the AEs of leuprorelin in the treatment of prostate cancer. Signal strengths of reports of leuprorelin in treatment of prostate cancer at the SOC level are described in Table 4. The top three SOCs ranked by case numbers were general disorders and administration site conditions (n = 22,569, ROR 1.6, PRR 1.44 IC 0.53, EBGM 1.44), injury, poisoning and procedural complications (n = 13,649, ROR 1.81, PRR 1.68, IC 0.75, EBGM 1.68), and vascular disorders (n = 6,134, ROR 3.29, PRR 3.12, IC 1.64, EBGM 3.11). Utilizing the ROR method to gauge signal intensity, the top three categories identified were vascular disorders with 6,134 cases (ROR 3.29, PRR 3.12, IC 1.64, EBGM 3.11), followed by neoplasms benign, malignant and unspecified (incl cysts and polyps) with 5,886 cases (ROR 2.52, PRR 2.41, IC 1.27, EBGM 2.41), and injury, poisoning and procedural complications with 13,649 cases

Table 3
The signal strength of ADEs of leuprorelin at the SOC level.

System organ class	Case Reports	ROR (95 % CI)	PRR (95 % CI)	χ^2	IC(IC025)	EBGM (EBGM05)
general disorders and administration site conditions	34532	1.28(1.26, 1.29)	1.22(1.22, 1.22)	1626.59	0.28(0.27)	1.22(1.2)
injury, poisoning and procedural complications	21435	1.53(1.51, 1.56)	1.46(1.43, 1.49)	3425.22	0.54(0.52)	1.46(1.44)
nervous system disorders	11060	0.78(0.76, 0.79)	0.79(0.77, 0.81)	669.34	−0.34 (-0.37)	0.79(0.78)
vascular disorders	10772	3.19(3.13, 3.25)	3.04(2.98, 3.1)	14927.77	1.59(1.57)	3.02(2.97)
musculoskeletal and connective tissue disorders	10437	1.22(1.2, 1.24)	1.21(1.19, 1.23)	386.02	0.27(0.24)	1.2(1.18)
investigations	9657	0.95(0.93, 0.96)	0.95(0.93, 0.97)	28.75	−0.08 (-0.11)	0.95(0.93)
psychiatric disorders	8535	0.9(0.88, 0.92)	0.9(0.88, 0.92)	95.76	−0.15 (-0.18)	0.9(0.89)
gastrointestinal disorders	8133	0.56(0.55, 0.57)	0.58(0.57, 0.59)	2695.58	−0.78 (-0.81)	0.58(0.57)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	7493	1.73(1.69, 1.77)	1.7(1.67, 1.73)	2193.64	0.76(0.73)	1.69(1.66)
reproductive system and breast disorders	7036	5.41(5.28, 5.54)	5.21(5.11, 5.31)	23746.91	2.36(2.33)	5.14(5.04)
skin and subcutaneous tissue disorders	5257	0.59(0.57, 0.6)	0.6(0.59, 0.61)	1469.22	−0.73 (-0.77)	0.6(0.59)
infections and infestations	4784	0.55(0.53, 0.56)	0.56(0.55, 0.57)	1744.4	−0.83 (-0.88)	0.56(0.55)
renal and urinary disorders	3590	1.19(1.15, 1.23)	1.18(1.13, 1.23)	102.14	0.24(0.19)	1.18(1.15)
respiratory, thoracic and mediastinal disorders	3587	0.45(0.43, 0.46)	0.46(0.44, 0.48)	2401.5	−1.12 (-1.17)	0.46(0.45)
cardiac disorders	2602	0.58(0.56, 0.6)	0.59(0.57, 0.61)	777.65	−0.77 (-0.82)	0.59(0.57)
metabolism and nutrition disorders	2429	0.68(0.66, 0.71)	0.69(0.66, 0.72)	346.7	−0.53 (-0.59)	0.69(0.67)
eye disorders	1408	0.43(0.4, 0.45)	0.43(0.41, 0.46)	1074.9	−1.21 (-1.29)	0.43(0.41)
blood and lymphatic system disorders	1179	0.42(0.4, 0.45)	0.42(0.4, 0.45)	933.21	−1.23 (-1.31)	0.43(0.41)
hepatobiliary disorders	662	0.44(0.41, 0.48)	0.44(0.41, 0.48)	466.36	−1.17 (-1.28)	0.44(0.42)
immune system disorders	436	0.24(0.22, 0.26)	0.24(0.22, 0.26)	1049.41	−2.05 (-2.18)	0.24(0.22)
ear and labyrinth disorders	424	0.6(0.54, 0.66)	0.6(0.54, 0.66)	113.78	−0.74 (-0.87)	0.6(0.55)
endocrine disorders	410	1(0.91, 1.1)	1(0.91, 1.1)	0	0(-0.14)	1(0.92)
pregnancy, puerperium and perinatal conditions	409	0.57(0.52, 0.63)	0.57(0.52, 0.63)	132.21	−0.81 (-0.95)	0.57(0.53)
congenital, familial and genetic disorders	142	0.28(0.23, 0.33)	0.28(0.24, 0.33)	267.8	−1.85 (-2.08)	0.28(0.24)

Table 4
The signal strength of ADEs of leuprorelin in treatment of prostate cancer at the SOC level.

System organ class	Case Reports	ROR (95 % CI)	PRR (95 % CI)	χ^2	IC(IC025)	EBGM (EBGM05)
general disorders and administration site conditions	22569	1.6(1.57, 1.62)	1.44(1.41, 1.47)	3709.02	0.53(0.5)	1.44(1.42)
injury, poisoning and procedural complications	13649	1.81(1.78, 1.85)	1.68(1.65, 1.71)	4178.01	0.75(0.72)	1.68(1.66)
vascular disorders	6134	3.29(3.2, 3.37)	3.12(3.06, 3.18)	9020.41	1.64(1.6)	3.11(3.05)
investigations	5897	1.05(1.03, 1.08)	1.05(1.03, 1.07)	14.61	0.07(0.03)	1.05(1.03)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	5886	2.52(2.45, 2.59)	2.41(2.36, 2.46)	4998.38	1.27(1.23)	2.41(2.36)
nervous system disorders	4836	0.6(0.59, 0.62)	0.63(0.62, 0.64)	1181.97	−0.67 (-0.72)	0.63(0.61)
musculoskeletal and connective tissue disorders	4813	1.01(0.98, 1.04)	1.01(0.99, 1.03)	0.2	0.01(-0.03)	1.01(0.98)
gastrointestinal disorders	3243	0.4(0.38, 0.41)	0.42(0.4, 0.44)	2855.95	−1.25(-1.3)	0.42(0.41)
infections and infestations	2992	0.62(0.6, 0.65)	0.64(0.62, 0.67)	663.13	−0.65 (-0.71)	0.64(0.62)
psychiatric disorders	2846	0.53(0.51, 0.55)	0.54(0.52, 0.56)	1151.75	−0.88 (-0.93)	0.55(0.53)
renal and urinary disorders	2723	1.64(1.58, 1.71)	1.62(1.56, 1.68)	664.91	0.7(0.64)	1.62(1.57)
skin and subcutaneous tissue disorders	2186	0.44(0.42, 0.46)	0.45(0.43, 0.47)	1528.01	−1.14(-1.2)	0.45(0.44)
respiratory, thoracic and mediastinal disorders	2186	0.49(0.47, 0.52)	0.51(0.49, 0.53)	1100.26	−0.98 (-1.04)	0.51(0.49)
cardiac disorders	1871	0.76(0.73, 0.8)	0.76(0.73, 0.79)	138.91	−0.39 (-0.45)	0.77(0.74)
metabolism and nutrition disorders	1358	0.69(0.66, 0.73)	0.7(0.66, 0.74)	180.56	−0.52 (-0.59)	0.7(0.67)
reproductive system and breast disorders	1003	1.33(1.25, 1.42)	1.33(1.25, 1.41)	81.76	0.41(0.32)	1.33(1.26)
blood and lymphatic system disorders	668	0.43(0.4, 0.47)	0.44(0.41, 0.48)	494.72	−1.19(-1.3)	0.44(0.41)
eye disorders	583	0.32(0.29, 0.35)	0.32(0.3, 0.35)	839.87	−1.62 (-1.74)	0.32(0.3)
hepatobiliary disorders	404	0.49(0.44, 0.54)	0.49(0.44, 0.54)	215.65	−1.03 (-1.17)	0.49(0.45)
ear and labyrinth disorders	189	0.48(0.42, 0.56)	0.48(0.42, 0.55)	104.26	−1.05 (-1.25)	0.48(0.43)
endocrine disorders	144	0.63(0.54, 0.75)	0.64(0.55, 0.75)	30.13	−0.65 (-0.89)	0.64(0.55)
immune system disorders	136	0.14(0.11, 0.16)	0.14(0.12, 0.17)	750.6	−2.87 (-3.11)	0.14(0.12)
congenital, familial and genetic disorders	39	0.14(0.1, 0.19)	0.14(0.1, 0.19)	210.35	−2.85(-3.3)	0.14(0.11)

(ROR 1.81, PRR 1.68, IC 0.75, EBGM 1.68), in that order. The first systems satisfied all four algorithmic requirements. Moreover, signal strengths of reports of leuprorelin in treatment of endometriosis, uterine fibroids and precocious puberty at the SOC level are described detailedly in Supplementary Tables S2, 3, 4.

After a comprehensive analysis, 102 essential PTs that met the criteria of all four algorithms were identified and ranked using the ROR technique, highlighting the top 30 terms. The findings revealed that PTs exhibiting the strongest signals included bulbospinal muscular atrophy congenital (n = 26, ROR 1346.97, PRR 1346.75, IC 7.98, EBGM 253.33), intercepted product preparation error (n = 5202, ROR 814.15, PRR 787.11, IC 7.8, EBGM 223.53) and blood testosterone normal (n = 5, ROR 777, PRR 776.97, IC 7.8, EBGM 222.71).

The study results were compared with the instructions for use of leuprorelin to identify potential new adverse reactions. These included artificial menopause, ovarian adhesion, follicular cystitis, intercepted product preparation errors, metastases to the penis, and bulbospinal muscular atrophy congenital. Refer to Table 5 for more details. Leuprorelin users should be especially vigilant for potential adverse reactions such as abscess sterile, injection site granuloma, and intercepted medication errors.

In order to analyze the AEs associated with leuprorelin in the treatment of prostate cancer, a total of 100 significant PTs that met the criteria of all four algorithms were identified and ranked using the ROR technique, highlighting the top 30 PTs. The results revealed that PTs exhibiting the strongest signals included intercepted medication error (n = 3721, ROR 620.05, PRR 593.98, IC 8.18, EBGM 289.6), prostatic specific antigen abnormal (n = 294, ROR 318.58, PRR 317.49, IC 7.67, EBGM 203.46) and follicular cystitis (n = 3, ROR 241.6, PRR 241.59, IC 7.4, EBGM 169.41). The top three PTs ranked by case numbers were hot flush (n = 4,937, ROR 54.2, PRR 51.16 IC 5.55, EBGM 46.98), intercepted product preparation error (n = 3,721, ROR 620.05, PRR 593.38, IC 8.18, EBGM 289.6), and

Table 5
The top 30 signal strength of AEs of leuprorelin ranked by ROR at the PTs level.

SOC	PTs	Case reports	ROR (95 % CI)	PRR (95 % CI)	χ2	IC (IC025)	EBGM (EBGM05)
investigations	blood testosterone normal	5	777(150.74, 4004.99)	776.97 (149.76, 4031.13)	1107.1	7.8 (6.27)	222.71 (56.47)
investigations	prostatic specific antigen abnormal	343	225.86 (196.54, 259.57)	225.37 (196.48, 258.51)	44412.77	7.03 (6.85)	131.06 (116.66)
investigations	blood testosterone abnormal	332	172.05 (150.45, 196.74)	171.68 (149.67, 196.93)	36290.58	6.79 (6.61)	110.95 (99.17)
investigations	blood luteinising hormone abnormal	13	144.31(74.75, 278.6)	144.29(74.1, 280.96)	1263.36	6.63 (5.75)	98.86 (57.01)
investigations	laparoscopy	47	95.5(68.87, 132.43)	95.47(68.42, 133.22)	3361.14	6.2 (5.74)	73.27 (55.74)
investigations	prostatic specific antigen decreased	66	85.86(65.37, 112.77)	85.82(65.23, 112.92)	4335.87	6.08 (5.69)	67.47 (53.71)
investigations	blood testosterone increased	373	80.19(71.56, 89.87)	80(71.12, 89.98)	23143.3	6(5.84)	63.83 (58.03)
investigations	blood follicle stimulating hormone abnormal	12	79.36(42.1, 149.59)	79.35(42.38, 148.57)	739.54	5.99 (5.12)	63.41 (37.31)
investigations	prostatic specific antigen	8	73.13(33.85, 157.98)	73.13(34.05, 157.06)	460.72	5.89 (4.86)	59.39 (31.18)
investigations	prostatic specific antigen increased	1898	60.02(57.13, 63.05)	59.3(57.02, 61.67)	91381.06	5.64 (5.57)	49.96 (47.94)
reproductive system and breast disorders	artificial menopause	22	106.85(65.82, 173.44)	106.83(65.45, 174.38)	1716.5	6.32 (5.65)	79.76 (53.18)
reproductive system and breast disorders	endometriosis	853	82.6(76.58, 89.08)	82.15(75.96, 88.85)	54088.07	6.03 (5.92)	65.19 (61.19)
reproductive system and breast disorders	ovarian adhesion	12	69.07(36.95, 129.11)	69.06(36.88, 129.31)	658.59	5.82 (4.97)	56.69 (33.59)
reproductive system and breast disorders	menopause delayed	3	62.16(17.99, 214.72)	62.16(18.08, 213.69)	150.43	5.7 (4.14)	51.96 (18.42)
reproductive system and breast disorders	bilateral breast buds	4	59.2(20.32, 172.46)	59.2(20.14, 173.98)	192.24	5.64 (4.26)	49.89 (20.39)
general disorders and administration site conditions	injection site abscess sterile	45	333.08 (218.73, 507.22)	332.99 (220.64, 502.56)	7190.5	7.33 (6.82)	161.27 (113.43)
general disorders and administration site conditions	abscess sterile	59	291.17 (204.13, 415.31)	291.06 (204.53, 414.19)	8806.86	7.24 (6.79)	150.78 (112.02)
general disorders and administration site conditions	administration site ulcer	4	77.7(25.98, 232.42)	77.7(25.93, 232.86)	242.27	5.96 (4.56)	62.36 (24.93)
general disorders and administration site conditions	injection site granuloma	30	64.76(43.7, 95.97)	64.75(43.75, 95.83)	1558.26	5.75 (5.2)	53.76 (38.68)
renal and urinary disorders	follicular cystitis	3	133.2(34.44, 515.11)	133.2(34.45, 515.04)	275.53	6.55 (4.9)	93.54 (30.16)
renal and urinary disorders	urinary tract toxicity	7	114.51(48.14, 272.39)	114.5(48.34, 271.23)	575.53	6.39 (5.25)	83.94 (40.65)
renal and urinary disorders	urethral intrinsic sphincter deficiency	5	62.16(23.8, 162.38)	62.16(23.79, 162.41)	250.72	5.7 (4.44)	51.96 (23.27)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	metastases to penis	3	116.55(30.92, 439.32)	116.55(30.74, 441.92)	249.94	6.41 (4.78)	85.03 (28.02)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	prostate cancer metastatic	716	102.73(94.4, 111.8)	102.26(94.55, 110.6)	54023.56	6.27 (6.15)	77.19 (71.92)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	metastatic salivary gland cancer	6	88.8(35.84, 220.02)	88.8(36.05, 218.76)	405.1	6.11 (4.92)	69.29 (32.43)
injury, poisoning and procedural complications	intercepted product preparation error	5202	814.15 (773.42, 857.03)	787.11 (742.16, 834.78)	1156295.78	7.8 (7.75)	223.53 (214.13)
injury, poisoning and procedural complications	radiation induced fatigue	3	186.48(44.56, 780.31)	186.47(44.59, 779.83)	345.9	6.87 (5.17)	116.92 (35.3)

(*continued on next page*)

Table 5 (*continued*)

SOC	PTs	Case reports	ROR (95 % CI)	PRR (95 % CI)	χ2	IC (IC025)	EBGM (EBGM05)
injury, poisoning and procedural complications	intercepted medication error	1111	107.76 (100.64, 115.38)	107(100.89, 113.48)	86793.35	6.32 (6.22)	79.85 (75.41)
infections and infestations	tracheobronchitis bacterial	3	62.16(17.99, 214.72)	62.16(18.08, 213.69)	150.43	5.7 (4.14)	51.96 (18.42)
endocrine disorders	pituitary apoplexy	24	81.98(52.28, 128.54)	81.97(52.22, 128.66)	1518.9	6.02 (5.4)	65.07 (44.66)
congenital, familial and genetic disorders	bulbospinal muscular atrophy congenital	26	1346.97 (554.41, 3272.58)	1346.75 (557.49, 3253.38)	6555.67	7.98 (7.25)	253.33 (120.53)
investigations	blood testosterone normal	5	777(150.74, 4004.99)	776.97 (149.76, 4031.13)	1107.1	7.8 (6.27)	222.71 (56.47)

prostatic specific antigen increased (n = 1,605, ROR 90.01, PRR 88.36, IC 6.26, EBGM 76.52). Further details can be found in Table 6. Additionally, the signal strengths of reports on the use of leuprorelin in the treatment of endometriosis, uterine fibroids, and precocious puberty at the PTs level are elaborated in Supplementary Tables S5, S6, and S7.

4. Discussion

Leuprorelin post-marketing AEs were thoroughly analyzed using the FAERS database for the first time in pharmacovigilance. The main objective of the study was to comprehensively characterize, describe, and analyze the AEs associated with leuprorelin reported to date. This research would yield valuable and accurate insights into the safety profile of leuprorelin in clinical practice.

The proportion of adverse reactions of leuprolide in patients aged 65 and older (31.45 %) was higher compared to those under 65 years old. This could be attributed to the drug's common use in treating prostate cancer, which is more prevalent in elderly patients. The other reasons also caused more adverse reactions occurred in male patients. Due to a larger user base, American and Canadian AEs were significantly higher than those seen in other countries. This trend might be explained by a variety of factors such as an increase in population size, more willingness to report incidents, early market entry, and the quick expansion of approved uses.

In our research, the most frequently observed and notable AEs at the SOC level—including general disorders and administration site conditions, disorders of the nervous system, vascular disorders, and musculoskeletal and connective tissue disorders—aligned with safety data reported in drug labeling and from clinical trials. Within the PTs related to general disorders and administration site conditions, the three most frequently reported PTs were abscess sterile [18,19], injection site granuloma [20] and administration site ulcer [21]. Local AEs associated with leuprorelin acetate were found in 5 %–15 % of patients [22,23]. Johnson, Stephanie R et al. identified a sterile abscess in the long-acting treatment of Central Precocious Puberty (CPP) with leuprorelin, but the underlying mechanism remains unclear [24]. Sterile abscess formation has also been reported in 1.5 %–3 % of all patients receiving this treatment [25,26]. Shiota et al. reported a 4.2 % incidence rate of leuprorelin acetate granuloma [27]. Additionally, Ian Janes, W C et al. noted that leuprorelin acetate could result in injection site ulceration and skin necrosis [28]. The unique formulation and method of administration(subcutaneous, intramuscular, etc.) of the drug may contribute to such adverse effects, highlighting the importance of recognizing this rare adverse event for clinicians.

Another SOC identified was "injury, poisoning and procedural complications," which included issues such as medication administration errors and medication use problems. This highlights the essential requirement for standardized drug administration protocols when utilizing leuprorelin in clinical settings. Additionally, there were frequent reports of reproductive system and breast disorders, aligning with the drug's known adverse effects, emphasizing the importance of recognizing established risks. The AEs signals identified in this study covered the majority of events outlined in the leuprorelin instructions, including severe conditions like pituitary apoplexy and ulcers at the administration site. The occurrence of these relevant AEs require attention and necessitate prompt intervention.

Furthermore, our analysis revealed several critical AE signals previously undocumented. These novel AE signals included injection site granuloma, follicular cystitis, bulbospinal muscular atrophy congenital, artificial menopause, progression of cancer (metastases to penis, prostate cancer metastatic, metastatic salivary gland cancer) etc. The development of sterile abscesses and granulomas was likely a response to the polymers used in delivering long-acting gonadotropin-releasing hormone agonists, akin to a foreign body reaction as seen with absorbable sutures. It is also plausible that these reactions were triggered by gonadotropin-releasing hormone agonist peptides [25,29,30]. Prolonged use of leuprorelin could result in significant hypoestrogenic side effects, leading to artificial amenorrhea and other adverse reactions [31]. Moreover, a prospective, non-interventional study declared that there were serious AEs such as metastatic prostate cancer and tumor progression (i.e., metastasis) after treatment with leuprorelin, which warranted our vigilance [32]. Merseburger, A.S. and Roesch, M.C. also observed the same phenomenon [33]. Additional adverse reactions, such as follicular cystitis, ovarian adhesion, bacterial tracheobronchitis, and congenital bulbospinal muscular atrophy, which have not yet been reported, could also result from direct drug toxicity or allergic responses. Further research is necessary to fully understand the specific mechanisms involved. Therefore, close monitoring of patients receiving leuprorelin is essential, including regular tumor marker assessments, blood routine examinations, skin tests, and pathological examinations. Timely symptomatic interventions should be implemented if necessary.

Table 6
The top 30 signal strength of AEs of leuprorelin in treatment of prostate cancer ranked by ROR at the PTs level.

SOC	PTs	Case reports	ROR (95 % CI)	PRR (95 % CI)	$\chi 2$	IC (IC025)	EBGM (EBGM05)
injury, poisoning and procedural complications	intercepted product preparation error	3721	620.05 (591.86, 649.59)	593.38 (570.57, 617.1)	1072213.82	8.18 (8.12)	289.6 (278.54)
injury, poisoning and procedural complications	intercepted medication error	904	149.96 (139.32, 161.41)	148.4(137.21, 160.5)	104778.65	6.88 (6.77)	117.68 (110.66)
injury, poisoning and procedural complications	radiation associated haemorrhage	6	96.64(40.65, 229.77)	96.64(40.8, 228.92)	484.78	6.37 (5.21)	82.64 (40.04)
injury, poisoning and procedural complications	cystitis radiation	17	69.96(42.26, 115.82)	69.95(42.02, 116.44)	1027.85	5.96 (5.26)	62.34 (40.89)
injury, poisoning and procedural complications	radiation proctitis	16	69.93(41.59, 117.57)	69.92(41.19, 118.69)	966.99	5.96 (5.24)	62.31 (40.34)
investigations	prostatic specific antigen abnormal	294	318.58 (276.11, 367.58)	317.49 (276.79, 364.18)	59337.8	7.67 (7.48)	203.46 (180.51)
investigations	blood testosterone abnormal	223	177.51 (152.69, 206.36)	177.05 (151.36, 207.11)	29708.21	7.08 (6.87)	134.97 (118.99)
investigations	blood testosterone increased	279	102.26(90, 116.18)	101.93(90.62, 114.65)	23614.16	6.43 (6.25)	86.47 (77.71)
investigations	prostatic specific antigen decreased	46	100.17(73.2, 137.08)	100.12(73.17, 137)	3833.18	6.41 (5.97)	85.17 (65.51)
investigations	prostatic specific antigen increased	1605	90.01(85.36, 94.91)	88.36(83.31, 93.71)	119865.34	6.26 (6.18)	76.52(73.2)
renal and urinary disorders	follicular cystitis	3	241.6(62.47, 934.33)	241.59(62.48, 934.15)	503.15	7.4 (5.75)	169.41 (54.63)
renal and urinary disorders	urinary tract toxicity	7	207.7(87.31, 494.09)	207.68(87.67, 491.96)	1052.18	7.25 (6.11)	152.04 (73.63)
renal and urinary disorders	bladder stenosis	6	52.85(22.89, 122.04)	52.85(22.75, 122.76)	279.04	5.6 (4.48)	48.4(24.03)
reproductive system and breast disorders	reproductive toxicity	5	100.67(38.87, 260.72)	100.66(38.53, 263)	418.61	6.42 (5.17)	85.56 (38.59)
reproductive system and breast disorders	testicular atrophy	60	50.82(39.02, 66.19)	50.79(39.37, 65.53)	2686.32	5.54 (5.17)	46.67 (37.41)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	metastases to penis	3	211.4(56.08, 796.87)	211.39(55.75, 801.52)	456.87	7.27 (5.63)	154.01 (50.74)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	prostate cancer metastatic	667	170.3(156.14, 185.73)	168.99 (156.25, 182.77)	85700.56	7.03 (6.9)	130.24 (121.12)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	hormone-refractory prostate cancer	116	85.26(70.13, 103.65)	85.14(69.99, 103.58)	8380.49	6.21 (5.93)	74.1(62.93)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	anaplastic meningioma	3	84.56(25.13, 284.57)	84.56(25.08, 285.05)	215.4	6.2 (4.68)	73.66 (26.68)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	neuroendocrine carcinoma of prostate	4	64.43(22.9, 181.28)	64.42(22.8, 182.04)	224.14	5.86 (4.51)	57.92 (24.37)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	prostate cancer recurrent	45	57.29(42.16, 77.86)	57.26(41.85, 78.35)	2258.22	5.7 (5.27)	52.07 (40.29)
infections and infestations	tracheobronchitis bacterial	3	112.75(32.64, 389.47)	112.74(32.8, 387.57)	276.88	6.56(5)	94.12 (33.36)
general disorders and administration site conditions	administration site ulcer	3	99.48(29.15, 339.47)	99.48(28.94, 341.98)	248.6	6.4 (4.86)	84.71 (30.33)
general disorders and administration site conditions	injection site abscess sterile	12	90.21(49.04, 165.92)	90.19(49.12, 165.59)	912.47	6.28 (5.44)	77.89 (46.78)
general disorders and administration site conditions	injection site granuloma	23	85.89(55.38, 133.19)	85.86(55.79, 132.15)	1674.14	6.22 (5.61)	74.65 (51.71)
general disorders and administration site conditions	terminal state	572	62.21(57.05, 67.84)	61.81(57.15, 66.85)	30841.22	5.8 (5.68)	55.8(51.9)
gastrointestinal disorders	abdominal fat apron	10	90.93(46.63, 177.34)	90.92(46.69, 177.04)	765.81	6.29 (5.38)	78.43 (44.85)
endocrine disorders	pituitary apoplexy	15	84.57(49.15, 145.52)	84.56(48.85, 146.39)	1076.99	6.2 (5.45)	73.66 (46.77)

(*continued on next page*)

Table 6 (*continued*)

SOC	PTs	Case reports	ROR (95 % CI)	PRR (95 % CI)	χ2	IC (IC025)	EBGM (EBGM05)
endocrine disorders	pituitary haemorrhage	24	48.68(32.08, 73.87)	48.67(32.25, 73.45)	1031.44	5.49 (4.9)	44.88 (31.66)
vascular disorders	hot flush	4937	54.2(52.6, 55.85)	51.16(50.17, 52.17)	222857.7	5.55 (5.51)	46.98 (45.82)

What's more, similar to the findings regarding leuprorelin related AER, the most frequently observed and notable AEs for SOC levels in leuprorelin treatment for prostate cancer included: general disorders and administration site conditions, injury, poisoning and procedural complications and vascular disorders. To be specific, these AEs include intercepted product preparation error, hot flush, prostatic specific antigen increased, which were found with high frequency and high signal intensity. We realize that high frequency of PTs may be caused by objective factors such as underlying diseases or medication usage methods. However, the signal intensity calculated by ROR shows a statistical correlation between the drug and adverse reactions. Therefore, signal strength can reduce bias and should be more worthy of attention as a more objective indicator for AEs research.

Although clinical trials and guidelines have documented AEs such as dizziness, sweats, nausea, gastroenteritis, decreased libido, tremor, weight gain, flatulence, and cardiovascular diseases, our extensive data analysis from the FAERS database did not show significant signals for these specific AEs. Unlike clinical trials, reporting in FAERS is voluntary and often sporadic, potentially leading to adverse reactions being inadequately documented. Minor adverse reactions may be easily missed during the reporting process, resulting in an underrepresentation of these events. However, we should still pay attention to the supplementary significance of new adverse reactions identified by the FAERS database to clinical practice.

Safety studies of leuprorelin have predominantly consisted of meta-analyses or short-term clinical trials with limitations such as small sample sizes and short follow-up periods, hindering a comprehensive analysis of adverse effects [34–38]. Our study represents a significant advancement by compiling the largest dataset of leuprorelin-related cases to date, encompassing 60,709 reported cases and 156,409 adverse events. Our study included detailed assessments of the timing and severity of adverse events, providing a valuable perspective on leuprorelin's safety profile. Furthermore, this comprehensive analysis not only confirmed previously recognized adverse reactions but also uncovered several significant, previously unreported adverse events, which complemented the management of ADRs during clinical use of leuprorelin. And we should add these positive signals to the management of adverse drug reactions during clinical use of leuprorelin.

It's important to recognize a few limitations that need careful consideration: 1) The FAERS database operates as a voluntary reporting system, potentially leading to incomplete or inaccurate data from various countries and healthcare providers. For instance, healthcare professionals might over-report rare AEs, whereas those with minimal patient impact could be underreported.2) In disproportionality analyses, rare AEs associated with leuprorelin may not reach statistical significance due to their infrequency, leaving unidentified some safety signals. 3)Determining whether AEs are specifically due to leuprorelin is challenging, particularly with the potential confounding effects of other concurrent medications. 4)Given that FAERS is solely maintained by the U.S Food and Drug Administration, which may lead to some of the data has certain deviation, such as the United States found that may arise more AERs. Besides, when adverse events occur, a comprehensive evaluation of the patient's primary disease and its progression, drug/food interactions, timing of symptom onset, and dose correlation is necessary.5) It is crucial to emphasize that disproportionality analysis solely enables the identification of statistical significance based on signal strength and does not offer conclusive evidence of causality. These points underscore the complexity of interpreting real-world data and the need for meticulous analysis to ensure accurate safety assessments.

5. Conclusion

Leuprorelin is a widely used drug known for its effectiveness in various therapeutic applications. However, its side effects require careful consideration. This study conducted a comprehensive analysis of the adverse events (AEs) associated with leuprorelin, revealing a wide range of AEs connected to its usage. Our detailed investigation uncovered several unexpected and uncommon adverse drug reactions (ADRs), including injection site granuloma and induced menopause. These findings emphasize the crucial role of leuprorelin's information leaflet in offering clinical guidance and underscore the necessity for further exploration of its biological mechanisms and clinical impacts. It is essential for healthcare providers and patients to consistently assess the risks linked to its usage and adjust treatment plans as needed.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All analyses were based on data of the FDA Adverse Event Reporting System (FAERS) database, which was approved by the ethics review board of the National Center for Health Statistics. The detailed information located on the FAERS website.

Consent for publication

Not applicable.

Ethics statement

Not applicable.

Availability of data and materials

Data included in article/supp. material/referenced in article. The survey data are publicly available on the Internet for data users and researchers throughout the world https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers.

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CRediT authorship contribution statement

Huawei Han: Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Xinping Bu:** Methodology, Formal analysis, Conceptualization. **Xinzhe Wang:** Resources, Methodology, Formal analysis, Conceptualization. **Shuai Chen:** Software, Data curation. **Ningsheng Tian:** Software, Investigation, Data curation. **Jie Jin:** Supervision, Resources, Project administration. **Qian Feng:** Software, Data curation. **Bo Ma:** Software, Data curation. **Jiasong Teng:** Writing – original draft, Visualization, Validation, Supervision. **Zhiwei Li:** Writing – review & editing, Writing – original draft, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

ADEs	adverse drug events
AEs	adverse events
AERs	adverse event reports
ASCII	the American Standard Code for Information Interchange
BCPNN	Bayesian confidence propagation neural network
CPP	Central Precocious Puberty
DEMO	demographic and administrative information
DRUG	drug Information
EBGM	empirical Bayes geometric mean
FAERS	FDA Adverse Event Reporting System
MedDRA	Medical Dictionary for Regulatory Activities
PRR	proportional reporting ratios
PS	primary suspect drug
PTs	preferred terms
REAC	preferred terminology for adverse drug reactions
ROR	reporting odds ratios
SOCs	System Organ Classes

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34969.

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