

## **PHARMACEUTICAL MEDICINE**

### **SUPPLEMENTAL MATERIAL**

#### **Clinical Presentations of Drug-Induced Hyperprolactinaemia: A Literature Review**

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**Table S1a** Embase search strategy (via OvidSP)

Number	Search terms	Results (18 March 2021)
1	(prolactin\$ or hyperprolactinaemia\$ or hyperprolactinemia\$).ti,ab.	56,526
2	exp drug induced disease/ or (drug-induced or medication-induced or medicine-induced or therapy-induced or drug complication\$ or therapy complication\$ or drug disease or drug injur\$ or medication injur\$ or medicine injury\$ or drug-related disease or medicine-related disease or therapy-related disease or iatrogenic drug\$).tw. or adverse drug reaction.fs.	1,332,950
3	1 and 2	3,583
4	3 not ((exp animal/ or nonhuman/) not exp human/)	3,457
5	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	916,730
6	case reports/ or case study/ or case report\$.jx. or case report\$.jw.	151,291
7	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	3,346,142
8	review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and "treatment comparison")).ti,ab.	2,540,575
9	or/5-8	6,753,483
10	4 not 9	2,400
11	10 not conference abstract.pt.	2,333
12	limit 11 to English language	2,036

Note: Searches were calibrated to capture records mentioning HPL in either the title or abstract. This allowed the retrieval of studies more likely to provide relevant data on HPL beyond its occurrence as a result of treatment interventions, thus aiding the balance of scientific sensibility and precision according to the nature of the research question under consideration. It is conceivable that the use of controlled vocabulary for HPL and PRL blood levels ('exp hyperprolactinemia" and 'exp prolactin blood level/') could have retrieved additional interventional studies. However, in the context of the current review, interventional studies were not anticipated to provide detailed information on the consequences of HPL. This rationale follows guidance provided in Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions.[1]

*HPL* hyperprolactinaemia, *PRL* prolactin

**Table S1b** MEDLINE and MEDLINE In-Process search strategy (via OvidSP)

Number	Search terms	Results (18 March 2021)
1	(prolactin\$ or hyperprolactinaemia\$ or hyperprolactinemia\$).ti,ab.	46,931
2	exp "Drug-Related Side Effects and Adverse Reactions"/ or (drug-induced or medication-induced or medicine-induced or therapy-induced or drug complication\$ or therapy complication\$ or drug disease or drug injur\$ or medication injur\$ or medicine injury\$ or drug-related disease or medicine-related disease or therapy-related disease or iatrogenic drug\$).tw. or adverse effects.fs.	1,867,354
3	1 and 2	3,358
4	3 not (exp animals/ not exp humans/)	3,091
5	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	823,373
6	case reports/ or case study/ or case report\$.jw.	2,191,203
7	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	3,076,613
8	review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and "treatment comparison")).ti,ab.	2,599,167
9	or/5-8	8,067,879
10	4 not 9	1,991
11	limit 10 to English language	1,789

Note: Searches were calibrated to capture records mentioning HPL in either the title or abstract. This allowed the retrieval of studies more likely to provide relevant data on HPL beyond its occurrence as a result of treatment interventions, thus aiding the balance of scientific sensibility and precision according to the nature of the research question under consideration. It is conceivable that the use of controlled vocabulary for HPL and PRL blood levels ('exp hyperprolactinemia" and 'exp prolactin blood level/') could have picked additional interventional studies. However, in the context of the current review, interventional studies were not anticipated to provide detailed information on the consequences of HPL. This rationale follows guidance provided in Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions.[1]

*HPL* hyperprolactinaemia, *PRL* prolactin

**Table S2** Study characteristics

Author, year	Study design	Geographic location	Study setting	Sample size <sup>a</sup> (N)	Patients with drug-induced HPL <sup>b</sup> (n)	Study years (range)	Study duration/ observation period	Definition of HPL
<b>Clinical trials</b>								
Kelly, 2006[2]	RCT	US	NR	27	13	NR	12 weeks	PRL > 18 ng/mL
Man, 2016[3]	RCT	China	NR	99	99	2013–2014	NR	PRL > 24 ng/mL
Yuan, 2008[4]	RCT, crossover	China	NR	20	20	2004–2005	NR	Males: PRL ≥ 20 ng/mL; females: PRL ≥ 25 ng/mL
Shim, 2007[5]	RCT	South Korea	NR	56	54	NR	8 weeks	Males: PRL > 20 ng/mL; females: PRL > 24 ng/mL
Atmaca, 2002[6]	RCT	Turkey	Inpatients and outpatients	35	2	2000 (October to December)	6 weeks	Males: PRL ≥ 15 ng/mL; females: PRL ≥ 20 ng/mL
Yoon, 2016[7]	RCT	South Korea	Inpatients and outpatients	42	42	NR	8 weeks	Males: PRL > 20 ng/mL; females: PRL > 24 ng/mL
Karaman, 1993[8]	RCT	Turkey	NR	37	21	1987–1991	NR	PRL ≥ 20 ng/mL
Kinon, 2006[9]	RCT	US	Inpatients and outpatients	54	54	NR	4 months	Males: PRL > 18.8 ng/mL; females: PRL > 24.2 ng/mL
Lee, 2010[10]	RCT	South Korea	Outpatients	60	60	NR	8 weeks	Males: PRL > 20 ng/mL; females: PRL > 25 ng/mL
Perez-Iglesias, 2012[11]	RCT	Spain	NR	141	n = 64 at 3 months; n = 28 at 1 year	2002–2005	1 year	Males: PRL > 17.7 ng/mL; females: PRL > 29.2 ng/mL
Qiao, 2016[12]	RCT	China	Inpatients	60	60	2012–2014	8 weeks	PRL ≥ 496 mIU/L
Cavallaro, 2004[13]	Non-randomised uncontrolled trial	Italy	Outpatients	19	19	2002–2003	8 weeks	Males: PRL > 18 ng/mL; females: > 29 ng/mL
Lee, 2006a[14]	Non-randomised uncontrolled trial	South Korea	Outpatients	7	7	2004–2005	8 weeks	PRL > 19.7 ng/mL

Author, year	Study design	Geographic location	Study setting	Sample size <sup>a</sup> (N)	Patients with drug-induced HPL <sup>b</sup> (n)	Study years (range)	Study duration/ observation period	Definition of HPL
Lu, 2008[15]	Non-randomised uncontrolled trial	Taiwan	NR	23	20	NR	NR	PRL > 25 ng/mL
Savitz, 2015[16]	Non-randomised uncontrolled trial	Multiple countries	Outpatients	400	220	2007–2012	2 years	NR
Trives, 2013[17]	Non-randomised uncontrolled trial	Spain	Outpatients	13	13	NR	3 months	Increase in serum PRL levels, defined as 2 x ULN, or less than 2 x ULN if relevant clinical signs existed
Ranjbar, 2015[18]	Non-randomised controlled trial (before-and-after clinical trial)	Iran	Outpatients	30	30	2013–2014	3 months	NR
Andersen, 1982[19]	Non-randomised uncontrolled trial	Denmark	NR	13	13	NR	NR	NR (description of individual serum PRL levels in tables and figures shows that all patients developed HPL induced by the treatment intervention)
Düring, 2019[20]	Non-randomised uncontrolled trial	Denmark	Inpatients and outpatients	56	36	NR	6 weeks	Males: PRL > 0.4 IU/L; females: PRL > 0.6 IU/L
Mir, 2008[21]	Non-randomised uncontrolled trial	UK	Outpatients	27	27	NR	26 weeks	Males: PRL > 410 mU/L; females: PRL > 510 mU/L
<b>Observational studies</b>								
Ahuja, 2008[22]	Case report	NR	NR	12	12	NR	NR	NR
Alosaimi, 2018[23]	Cross-sectional	Saudi Arabia	Inpatients and outpatients	997	442	2012–2014	NR	Males: PRL > 20 ng/mL; females: PRL > 25 ng/mL
Atluri, 2018[24]	Retrospective	South India	Outpatients	40	30	2017 (January to December)	NR	PRL > 25 ng/mL

Author, year	Study design	Geographic location	Study setting	Sample size <sup>a</sup> (N)	Patients with drug-induced HPL <sup>b</sup> (n)	Study years (range)	Study duration/ observation period	Definition of HPL
Barszcz, 2007[25]	Case series	Poland	NR	25	25	NR	3 months	PRL > 23.5 ng/mL
Chen, 2010[26]	Prospective	Taiwan	Outpatients	26	24	NR	8 weeks	Males: PRL > 17.7 ng/mL; females: PRL > 29.2 ng/mL
Emsley, 2008[27]	Prospective	South Africa	Inpatients	50	18	2004–2006	24 months	NR
Furuhjelm, 1980[28]	Case series	Sweden	Outpatients	17	7	1976	NR	PRL > 25 ug/L
Holzer, 2006[29]	Case report	Switzerland	NR	5	5	2003–2004	NR	NR
Kalkavoura, 2013[30]	Prospective	Greece	Outpatients	83	80	NR	6 months	Males: PRL > 20 ng/ml; females: PRL > 25 ng/ml
Kopecek, 2006[31]	Cross-sectional	Czech Republic	Inpatients	12	11	NR	NR	Males: PRL > 381 mIU/mL; females: > 513 mIU/mL
Kotan, 2011[32]	Prospective	Turkey	Outpatients	21	18	NR	24 weeks	NR
Kulshreshtha, 2017[33]	Retrospective	India	Outpatients	128	39	2010–2014	NR	PRL > 25 ng/mL
Lankford, 1981[34]	Cross-sectional	US	NR	10	9	NR	NR	PRL > 30 ng/mL
Lee, 2005[35]	Case series	South Korea	Outpatients	16	14	2001–2002	6 months	PRL > 25 ng/mL
Lee, 2006b[36]	Prospective	South Korea	Inpatients	27	9	NR	12 weeks	NR
Leonard, 1989[37]	Retrospective	Canada	Outpatients	66	10	1978–1987	NR	PRL > 15 ng/mL
Margari, 2015[38]	Prospective	Italy	Outpatients	34	13	2010–2013	Mean: 5.5 (range 3–12) months	Males: PRL > 20 ng/mL; females: > 25 ng/mL
Matsuoka, 1986[39]	Case series	Japan	Inpatients	35	19	NR	8 weeks	PRL > 30 ng/mL
Melkersson, 1999[40]	Retrospective	Sweden	NR	28	9	NR	NR	PRL reference value < 15 ng/mL
Melkersson, 2005[41]	Cross-sectional	Sweden	Outpatients	75	23	NR	NR	Males and females after menopause: PRL ≥ 10 ng/mL;

Author, year	Study design	Geographic location	Study setting	Sample size <sup>a</sup> (N)	Patients with drug-induced HPL <sup>b</sup> (n)	Study years (range)	Study duration/ observation period	Definition of HPL
Park, 2016[42]	Cross-sectional	South Korea	Inpatients	245	94	2011–2013	NR	females pre-menopause: PRL $\geq$ 20 ng/mL Excess PRL levels: mild ( $\leq$ 50 ng/mL) moderate (51–75 ng/mL) severe (76–100 ng/mL) extreme ( $>$ 100 ng/mL)
Pollock, 1998[43]	Case report	UK	NR	8	8	NR	18 months	PRL $>$ 500 mU/L
Roke, 2012[44]	Retrospective	Netherlands	Outpatients	98	24	2006–2009	NR	PRL above the 97.5th percentile based on normative data for age and sex
Seppala, 1977[45]	Case series	Finland	Outpatients	123	10	1976	NR	PRL $>$ 30 ng/mL
Smith, 1992[46]	Case series	US	Outpatients	6	6	1987–1988	NR	PRL $\geq$ 25 ng/mL
Trenque, 2011[47]	Case/non-case study in a pharmacovigilance database	France	NR	11,863	187	1985–2009	NR	NR (The introduction section states that "HPL is defined as an elevated level of serum PRL, in the absence of such conditions as pregnancy or lactation, and is caused by an increase in PRL secretion from the pituitary gland.")
Venetikou, 2008[48]	Cross-sectional	Greece	NR	165	6	NR	NR	Elevated PRL
Vilar, 2008[49]	Retrospective	Brazil	NR	1,234	180	2000–2006	NR	NR (normal values were males: PRL $<$ 18 ng/mL and females: PRL $<$ 30 ng/mL)
Yunilainen, 2018[50]	Cross-sectional	Russia	NR	244	120	2011–2012	NR	NR (normal values were males: PRL 73–380 mU/L and females: PRL 64–395 mU/L. [HPL was taken as a bioactive PRL level of greater than the ULN])

Author, year	Study design	Geographic location	Study setting	Sample size <sup>a</sup> (N)	Patients with drug-induced HPL <sup>b</sup> (n)	Study years (range)	Study duration/ observation period	Definition of HPL
Zhang, 2018[51]	Cross-sectional	China	Inpatients	118	66	2017–2018	NR	Males: PRL ≥ 20 ng/mL; females PRL ≥ 25 ng/mL

<sup>a</sup> Patients randomised (if trials) or recruited (if observational studies)

<sup>b</sup> Patients diagnosed with drug-induced HPL

HPL hyperprolactinaemia, NR not reported, PRL prolactin, RCT randomised controlled trial, ULN upper limit of normal

**Table S3** Patients characteristics

Author, year	N at baseline	Analysis population	Groups/subgroups	Patients with drug-induced HPL <sup>a</sup> (n)	Age, years, [mean (SD)] <sup>b</sup>	Sex (females) [n (%)]	Race/ethnicity [n (%)]	Serum PRL levels [mean (SD)] <sup>b</sup>
<b>Clinical trials</b>								
Andersen, 1982[19]	6	Drug-induced HPL	Females assigned to metoclopramide; menstruating <sup>c</sup>	6	Median NR (range 21–33)	6 (100)	NR	Median NR (range 19–64) ng/mL
	7		Females assigned to metoclopramide; post-menopausal females <sup>c</sup>	7	Median NR (range 51–62)	7 (100)	NR	NR
Atmaca, 2002[6]	17	Overall population	Randomised to haloperidol <sup>d</sup>	2	30 (11)	17 (100)	NR	16 (4) ng/mL
Cavallaro, 2004[13]	19	Drug-induced HPL	Drug-induced HPL assigned to cabergoline after baseline enrolment <sup>c</sup>	19	34 (6)	13 (69)	NR	87 (52) ng/mL
Düring, 2019[20]	56	Overall population	Assigned to amisulpride <sup>d</sup>	36	25 (7)	17 (48)	NR	99 (42) ng/mL
Karaman, 1993[8]	37	Overall population	Randomised to bromocriptine vs placebo after baseline enrolment <sup>d</sup>	21	Group bromocriptine: 26 (5); group placebo: 25 (5)	37 (100)	NR	Hyperprolactinaemia group (n = 21): 72 (23) ng/mL



Author, year	N at baseline	Analysis population	Groups/subgroups	Patients with drug-induced HPL <sup>a</sup> (n)	Age, years, [mean (SD)] <sup>b</sup>	Sex (females) [n (%)]	Race/ethnicity [n (%)]	Serum PRL levels [mean (SD)] <sup>b</sup>
Kelly, 2006[2]	12	Overall population	Randomised to risperidone <sup>d</sup>	12	47 (10)	3 (25)	Black 6 (50)	NR
	9		Randomised to fluphenazine <sup>d</sup>	1	46 (10)	1 (12)	Black 5 (56)	NR
Kinon, 2006[9]	27	Drug-induced HPL	Drug-induced HPL randomised to olanzapine after baseline enrolment <sup>c</sup>	27	40 (11)	14 (52)	Multiple: White 13 (48); African 11 (41); Asian 0 (0); East Asian 2 (7); Hispanic 1 (4)	NR
			Drug-induced HPL randomised to remain on previous antipsychotic medication after baseline enrolment <sup>c</sup>	27	39 (9)	14 (52)	Multiple: White 15 (56); African 7 (26); Asian 1 (4); East Asian 2 (7); Hispanic 2 (7)	NR
Lee, 2006a[14]	7	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	7	35 (8)	7 (100)	NR	168 (58) ng/mL
Lee, 2010[10]	60	Drug-induced HPL	Drug-induced HPL randomised to bromocriptine vs placebo after baseline enrolment <sup>c</sup>	60	38 (7)	60 (100)	NR	Group randomised to bromocriptine 2.5 mg (n = 14): 126.21 (57.41) ng/mL; group randomised to bromocriptine 5 mg (n = 13): 114.08 (41.23) ng/mL; group randomised to bromocriptine 10 mg (n = 11): 148.12 (51.17) ng/mL; group randomised to placebo (n = 10): 94.07 (68.98) ng/mL
Lu, 2008[15]	20	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	20	32 (10)	20 (100)	NR	97 (69) ng/mL
Man, 2016[3]	99	Drug-induced HPL	Drug-induced HPL randomised to peony-	99	30 (8)	99 (100)	NR	111 (50) ng/mL

Author, year	N at baseline	Analysis population	Groups/subgroups	Patients with drug-induced HPL <sup>a</sup> (n)	Age, years, [mean (SD)] <sup>b</sup>	Sex (females) [n (%)]	Race/ethnicity [n (%)]	Serum PRL levels [mean (SD)] <sup>b</sup>
			glycyrrhiza decoction vs placebo after baseline enrolment <sup>c</sup>					
Mir, 2008[21]	27	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	27	28 (8)	13 (48)	White 16 (60); Black 7 (26); Asian 3 (11); Mixed 1 (4)	Median NR (range 28–56) ng/mL
Perez-Iglesias, 2012[11]	110	Overall population	Overall population <sup>d</sup>	28	28 (8)	43 (40)	NR	NR
Qiao, 2016[12]	30	Drug-induced HPL	Drug-induced HPL randomised to aripiprazole adjunctive treatment after baseline enrolment <sup>c</sup>	30	35 (7)	30 (100)	Han Chinese 30 (100)	102 (38) ng/mL
			Drug-induced HPL randomised to non-adjunctive treatment after baseline enrolment <sup>c</sup>	30	33 (7)	30 (100)	Han Chinese 30 (100)	123 (73) ng/mL
Ranjbar, 2015[18]	30	Drug-induced HPL	Drug-induced HPL assigned to aripiprazole after baseline enrolment <sup>c</sup>	30	31 (7)	30 (100)	NR	NR
Savitz, 2015[16]	400	Overall population	Overall population <sup>d</sup>	220	16 (2)	157 (39)	Multiple: American Indian or Alaskan native 1 (< 1); White 256 (66); Black 27 (7); Asian 106 (27); Other 1 (< 1)	NR
Shim, 2007[5]	26	Drug-induced HPL	Drug-induced HPL randomised to aripiprazole after baseline enrolment <sup>c</sup>	26	39 (6)	15 (58)	NR	NR
	28		Drug-induced HPL randomised to placebo after baseline enrolment <sup>c</sup>	28	41 (5)	17 (61)	NR	NR

Author, year	N at baseline	Analysis population	Groups/subgroups	Patients with drug-induced HPL <sup>a</sup> (n)	Age, years, [mean (SD)] <sup>b</sup>	Sex (females) [n (%)]	Race/ethnicity [n (%)]	Serum PRL levels [mean (SD)] <sup>b</sup>
Trives, 2013[17]	13	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	13	44 (13)	8 (62)	White 13 (100)	Median 84 (range 44–99) ng/mL
Yoon, 2016[7]	10	Drug-induced HPL	Drug-induced HPL (PRL < 50 ng/mL) <sup>c</sup>	10	37 (7)	1 (10)	NR	32 (10) ng/mL
	32		Drug-induced HPL (PRL ≥ 50 ng/mL) <sup>c</sup>	32	Group addition of aripiprazole: 35 (7); group switching to aripiprazole: 35 (8)	28 (88)	NR	Group randomised to addition of aripiprazole: 113 (22) ng/mL; group switching to aripiprazole: 112 (60) ng/mL
Yuan, 2008[4]	10	Drug-induced HPL	Drug-induced HPL randomised to peony-glycyrrhiza decoction after baseline enrolment <sup>c</sup>	10	32 (8)	10 (100)	NR	105 (38) ng/mL
			Drug-induced HPL randomised to bromocriptine after baseline enrolment <sup>c</sup>	10	30 (7)	10 (100)	NR	130 (29) ng/mL
<b>Observational studies</b>								
Ahuja, 2008[22]	12	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	12	Median NR (range 29–71)	12 (100)	NR	NR
Alosaimi, 2018[23]	442	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	442	37 (13)	186 (42)	NR	NR
Atluri, 2018[24]	15	Drug-induced HPL	Drug-induced HPL (levosulpiride)	15	33 (9)	15 (100)	NR	144 (54) ng/mL
	2		Drug-induced HPL (ranitidine)	2	NR	NR	NR	NR
	13		Drug-induced HPL (domperidone)	13	31 (5)	13 (100)	NR	122 (56) ng/mL
Barszcz, 2007[25]	25	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	25	26 (NR)	25 (100)	NR	69 (43) ng/mL

Author, year	N at baseline	Analysis population	Groups/subgroups	Patients with drug-induced HPL <sup>a</sup> (n)	Age, years, [mean (SD)] <sup>b</sup>	Sex (females) [n (%)]	Race/ethnicity [n (%)]	Serum PRL levels [mean (SD)] <sup>b</sup>
Chen, 2010[26]	15	Drug-induced HPL	Drug-induced HPL assigned to adjunctive aripiprazole after baseline enrolment (risperidone)	15	39 (9)	10 (67)	Taiwanese 15 (100)	77 (51) ng/mL
	5		Drug-induced HPL assigned to adjunctive aripiprazole after baseline enrolment (amisulpride)	5	31 (10)	5 (100)	Taiwanese 5 (100)	145 (55) ng/mL
	4		Drug-induced HPL assigned to adjunctive aripiprazole after baseline enrolment (sulpiride)	4	43 (7)	2 (50)	Taiwanese 4 (100)	71 (49) ng/mL
Furuhjelm, 1980[28]	7	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	7	36 (7)	8 (100)	NR	Median NR (range 45–≥ 200) ng/mL
Holzer, 2006[29]	5	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	5	Median NR (range 18–14)	2 (40)	NR	Median 59 (range 25–80) ng/mL
Kalkavoura, 2013[30]	80	Drug-induced HPL	Drug-induced HPL	80	44 (10)	44 (55)	NR	NR
Kopecek, 2006[31]	11	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	11	Median NR (range 18–63)	8 (73)	NR	Median NR (range males: 505–1,318; females: 887–4,250) mIU/mL
Kotan, 2011[32]	18	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	18	35 (9)	7 (39)	NR	NR
Kulshreshtha, 2017[33]	39	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	39	37 (10)	39 (100)	NR	121 (81) ng/mL
Lankford, 1981[34]	10	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	9	NR	9 (100)	NR	117 (19) ng/mL
Lee, 2005[35]	14	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	14	NR	14 (100)	NR	120 (48) ng/mL
Lee, 2006b[36]	9	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	9	NR	7 (78)	NR	104 (24) ng/mL
Leonard, 1989[37]	10	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	10	NR	0 (0)	NR	24 (NR) ng/mL
Margari, 2015[38]	13	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	13	NR	8 (62)	White: 13 (100)	64 (33) ng/mL

Author, year	N at baseline	Analysis population	Groups/subgroups	Patients with drug-induced HPL <sup>a</sup> (n)	Age, years, [mean (SD)] <sup>b</sup>	Sex (females) [n (%)]	Race/ethnicity [n (%)]	Serum PRL levels [mean (SD)] <sup>b</sup>
Pollock, 1998[43]	8	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	8	Median NR (range 24–48)	8 (100)	NR	Median NR (range 169–343) ng/mL
Seppala, 1977[45]	10	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	10	NR	10 (100)	NR	NR
Smith, 1992[46]	6	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	6	33 (NR)	6 (100)	NR	78 (NR) ng/mL
Trenque, 2011[47]	187	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	187	40 (14)	133 (72)	NR	NR
Venetikou, 2008[48]	6	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	6	NR	0 (0)	NR	NR
Vilar, 2008[49]	180	Drug-induced HPL	Drug-induced HPL <sup>c</sup>	180	40 (11)	108 (60)	NR	105 (73) ng/mL

<sup>a</sup> Patients diagnosed with drug-induced HPL

<sup>b</sup> Unless otherwise specified

<sup>c</sup> Overall set of participants enrolled in the study who were diagnosed with drug-induced HPL, regardless of treatment status

<sup>d</sup> Overall set of participants enrolled in the study, regardless of the drug-induced HPL status

*ASEX* Arizona Sexual Experience Scale, *HPL* hyperprolactinaemia, *PRL* prolactin, *SD* standard deviation

**Table S4** Characteristics of patients with drug-induced HPL

Author, year	Groups/subgroups	Patients with drug-induced HPL <sup>a</sup> (n)	Diagnosis	ICD/DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
<b>Clinical trials</b>									
Andersen, 1982[19]	Assigned to metoclopramide; menstruating females	6	NR	NR	Metoclopramide	D2 antagonists	Monotherapy	30 mg/day	18 days
	Assigned to metoclopramide; post-menopausal females	7	NR	NR	Metoclopramide	D2 antagonists	Monotherapy	Group IV (4 women): 10 mg/day, IV; group IV; group oral (3 women): 30	Group A: 1 day [IV]; group B: 15 days [oral]

Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
Atmaca, 2002[6]	Randomised to haloperidol <sup>c</sup>	2	Schizophrenia	DSM-IV	Haloperidol	Antipsychotics	Monotherapy	mg/day, oral 10 mg/day	6 weeks
Cavallaro, 2004[13]	Drug-induced HPL assigned to cabergoline after baseline enrolment <sup>c</sup>	19	Schizophrenia	DSM-IV	Risperidone	Antipsychotics	Monotherapy	Mean: 3.1 mg/day	At least 6 months
Düring, 2019[20]	Assigned to amisulpride	36	Schizophrenia or schizoaffective disorder	ICD-10	Amisulpride	Antipsychotics	Monotherapy	Mean: 279 mg/day	6 weeks
Karaman, 1993[8]	Drug-induced HPL randomised to bromocriptine vs placebo after baseline enrolment <sup>c</sup>	21	NR	NR	NR	Oral contraceptives	NR	NR	NR
Kelly, 2006[2]	Randomised to risperidone	12	Treatment- resistant schizophrenia	DSM-IV	Risperidone	Antipsychotics	Monotherapy	4 mg/day (fixed dose)	12 weeks
	Randomised to fluphenazine <sup>c</sup>	1	Treatment- resistant schizophrenia	DSM-IV	Fluphenazine	Antipsychotics	Monotherapy	12.5 mg/day [fixed dose]	12 weeks
Kinon, 2006[9]	Drug-induced HPL randomised to olanzapine after baseline enrolment <sup>c</sup>	27	Schizophrenia or schizoaffective disorder	DSM-IV	Risperidone, conventional antipsychotics	Antipsychotics	Monotherapy	NR	Mean (SD): 11.9 (8.4) years
	Drug-induced HPL randomised to remain on current antipsychotic								Mean (SD): 12.5 (7.8) years

Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
	medication after baseline enrolment <sup>c</sup>								
Lee, 2006a[14]	Drug-induced HPL	7	Schizophrenia	DSM-IV	Amisulpride, risperidone	Antipsychotics	Monotherapy	Amisulpride 200–800 mg/day, Risperidone 6 mg/day	At least 8 weeks
Lee, 2010[10]	Drug-induced HPL randomised to bromocriptine vs placebo after baseline enrolment <sup>c</sup>	60	Schizophrenia	DSM-IV	Haloperidol, risperidone, trifluoperazine, chlorpromazine, thioridazine, nemonapride, and olanzapine	Antipsychotics	Polytherapy	Haloperidol 5–40 mg, risperidone 2–10 mg, trifluoperazine 10–60 mg, chlorpromazine 200– 300 mg, thioridazine 200–300 mg, nemonapride 20–40 mg, olanzapine 15 mg [dose schedule NR]	1 year
Lu, 2008[15]	Drug-induced HPL assigned to aripiprazole after baseline enrolment <sup>c</sup>	20	Schizophrenia or schizoaffective disorder	DSM-IV	Sulpiride, risperidone	Antipsychotics	Monotherapy	Sulpiride 400–800 mg/day, risperidone 1.5–6 mg/day	Mean (SD): 16.8 (13.4) months

Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
Man, 2016[3]	Drug-induced HPL randomised to peony- glycyrrhiza decoction vs placebo after baseline enrolment <sup>c</sup>	99	Schizophrenia or schizoaffective disorder	ICD-10	Risperidone, paliperidone, sulpride and amisulpride, olanzapine, ziprasidone, and quetiapine	Antipsychotics	Mixed	NR	At least 3 months
Mir, 2008[21]	Drug-induced HPL assigned to aripiprazole after baseline enrolment <sup>c</sup>	27	Schizophrenia, schizoaffective, bipolar affective disorder, psychotic depression, drug- induced affective psychosis	NR	Risperidone, olanzapine, amisulpride, quetiapine, zuclopenthixol, clozapine	Antipsychotics	Mixed	Risperidone (2–25 mg IM every 15 days), olanzapine (5–20 mg), amisulpride (150–600 mg), quetiapine (150–600 mg), zuclopenthi xol (250 mg), clozapine (50 mg) [dose schedule NR]	NR
Perez-Iglesias, 2012[11]	Randomised to haloperidol, olanzapine, or risperidone	28	Schizophrenia spectrum disorders	DSM-IV	Haloperidol, olanzapine, and risperidone	Antipsychotics	Monotherapy	NR	1 year
Qiao, 2016[12]	Drug-induced HPL randomised to aripiprazole adjunctive vs non- adjunctive	60	Schizophrenia	DSM-IV	Risperidone, paliperidone	Antipsychotics	Monotherapy	Risperidone and paliperidon e: 1 mg/day and	4 weeks



Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
	treatment after baseline enrolment							3 mg/day respectively , start dose; dosage titrated to 6– 12mg/day for the first 2 weeks. After the third week, 3–6 mg/day and 6-12 mg/day, respectively	
Ranjbar, 2015[18]	Drug-induced HPL assigned to aripiprazole after baseline enrolment <sup>c</sup>	30	Schizophrenia, delusional disorder, or refractory obsessive- compulsive disorder	NR	Risperidone	Antipsychotics	Monotherapy	6 mg/kg	2 months
Savitz, 2015[16]	Assigned to paliperidone	220	Schizophrenia	DSM-IV	Paliperidone	Antipsychotics	Polytherapy	1.5–12 mg/day	2 years
Shim, 2007[5]	Drug-induced HPL randomised to aripiprazole after baseline enrolment <sup>c</sup>	26	Schizophrenia	DSM-IV	Haloperidol	Antipsychotics	Monotherapy	Mean (SD): 20.7 (12.6) mg/day	At least 3 months
	Drug-induced HPL randomised to placebo after baseline enrolment <sup>c</sup>	28						Mean (SD): 24.8 (14.2) mg/day	

Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
Trives, 2013[17]	Drug-induced HPL assigned to aripiprazole after baseline enrolment <sup>c</sup>	13	Schizophrenia, unspecified psychoses, schizoaffective disorder, delusional disorder	NR	Risperidone (long-acting injection)	Antipsychotics	Mixed	25–37.5 mg/day	Median: 51 (14–57) months
Yoon, 2016[7]	Drug-induced HPL and serum PRL level < 50 ng/mL randomised to aripiprazole- addition (adding aripiprazole to previous antipsychotics) after baseline enrolment <sup>c</sup>	10	Schizophrenia or other another psychotic spectrum disorder	DSM-IV	Paliperidone, risperidone, quetiapine, haloperidol, blonanserin, sulpiride, and clozapine	Antipsychotics	NR	NR	At least 1 month
	Drug-induced HPL and serum prolactin level ≥ 50 ng/mL randomised to aripiprazole- addition (adding aripiprazole to previous antipsychotics) or switching (switching previous antipsychotics to aripiprazole) after baseline enrolment <sup>c</sup>	32	Schizophrenia or other another psychotic spectrum disorder	DSM-IV	Paliperidone, risperidone, quetiapine, haloperidol, blonanserin, sulpiride, and clozapine	Antipsychotics	NR	NR	At least 1 month
Yuan, 2008[4]	Drug-induced HPL randomised	10	Schizophrenia	ICD-10	Risperidone	Antipsychotics	NR	Mean (SD): 3.3 (1.0)	

Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
	to peony- glycyrrhiza decoction after baseline enrolment <sup>c</sup>							mg/day [maintenan ce dose]	At least 6 months
	Drug-induced HPL randomised to bromocriptine after baseline enrolment <sup>c</sup>							Mean (SD): 4.1 (1.1) mg/day [maintenan ce dose]	
<b>Observational studies</b>									
Ahuja, 2008[22]	NA	12	Schizophrenia, schizoaffective disorder, bipolar affective disorder	ICD-10	Haloperidol, risperidone, amisulpride, olanzapine	Antipsychotics	Mixed	NR	NR
Alosaimi, 2018[23]	NA	442	Primary disorders: psychotic, bipolar, depressive, and anxiety; personality disorders, secondary psychiatric disorders, multiple disorders and others	NR	NR	Antipsychotics, antidepressants, mood stabilisers, and antianxiety medications	NR	NR	NR
Atluri, 2018[24]	Levosulpiride	15	NR	NR	Levosulpiride	D2 antagonists	NR	NR	Mean (SD): 76.23 (126.1) days; median (range): 30 (5–480) days
	Ranitidine	2			Ranitidine	H2 antagonists			NR
	Domperidone	13			Domperidone	D2 antagonists			Mean (SD): 22.66 (17.16) days;

Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
Barszcz, 2007[25]	NA	25	Schizophrenia, schizoaffective disorder, organic paranoic disorders	NR	NR	Antipsychotics	Mixed	NR	Median (range): 15 (2–60) days At least 6 months
Chen, 2010[26]	Drug-induced HPL assigned to aripiprazole- addition after baseline enrolment (risperidone) <sup>c</sup>	15	Schizophrenia, schizoaffective disorder, or bipolar disorder	DSM-IV	Risperidone	Antipsychotics	Monotherapy	Mean (SD): 4.7 (2.3) mg/day	Mean (SD): 34.9 (34.9) weeks
	Drug-induced HPL assigned to aripiprazole- addition after baseline enrolment (amisulpride) <sup>c</sup>	5			Amisulpride			Mean (SD): 460 (260.8) mg/day	Mean (SD): 18.3 (18.3) weeks
	Drug-induced HPL assigned to aripiprazole- addition after baseline enrolment (sulpiride) <sup>c</sup>	4			Sulpiride			Mean (SD): 612.5 (469.7) mg/day	Mean (SD): 69.7 (72.2) weeks
Emsley, 2008[27]	NA	18	Schizophrenia, schizophreniform disorder or schizoaffective disorder	DSM-IV	Risperidone (long-acting injection)	Antipsychotics	Polytherapy	12.5 mg–50 mg every 2 weeks	2 years
Furuhjelm, 1980[28]	NA	7	NR	NR	NR	Oral contraceptives	Monotherapy	NR	NR

Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
Holzer, 2006[29]	NA	5	Obsessive- compulsive disorder, schizophrenia, schizoaffective disorder, and severe depression with psychotic symptoms	ICD-10	Risperidone	Antipsychotics	Polytherapy	0.04 and 0.1 mg/kg/dose s	NR
Kalkavoura, 2013[30]	NA	80	Schizophrenia	DSM-IV	Risperidone, amisulpride, and haloperidol (most common ones)	Antipsychotics	Mixed	Mean (SD): risperidone 4.8 (2.2), risperidone long acting 48.6 9 (4.1), amisulpride 816.6 (216.7), haloperidol 33.4 (18.5) mg	At least 5 years
Kopecek, 2006[31]	NA	11	Severe depressive episode without psychotic symptoms, recurrent depressive disorder with current moderate symptoms, panic disorder, mixed anxiety depression, borderline personality disorder, obsessive compulsive	ICD-10	Risperidone	Antipsychotics	Mixed	Median: 1.25 mg/day	Median: 15.5 days

Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
			disorder, post-traumatic stress disorder, adjustment disorder depressive type						
Kotan, 2011[32]	NA	18	Schizophrenia	DSM-IV	Amisulpride	Antipsychotics	Monotherapy	800 mg/day	24 weeks
Kulshreshtha, 2017[33]	NA	39	NR	NR	Domperidone, levosulpiride, itopride; risperidone, ziprasidone, amisulpride, pimozide, amitriptyline, paroxetine, ethinylestradiol	Prokinetics, antipsychotics and antidepressants, oestrogens	NR	NR	NR
Lankford, 1981[34]	NA	9	NR	NR	Thiothixene, fluphenazine, chlorpromazine, trifluoperazine, mesoridazine, perphenazine	Antipsychotics	Monotherapy	NR	Range: 2–18 years
Lee, 2005[35]	NA	14	Schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder	DSM-IV	Risperidone	Antipsychotics	Mixed	2–8 mg/day [maximum doses], 0.5–8 mg/day [maintenance doses]	Range: 3–60 months
Lee, 2006b[36]	NA	9	Schizophrenia, paranoid type, schizoaffective disorder, bipolar type	DSM-IV	Risperidone	Antipsychotics	Monotherapy	2–4 mg/day	12 weeks

Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
Leonard, 1989[37]	NA	10	NR	NR	NR	NR	NR	NR	NR
Margari, 2015[38]	NA	13	Early-onset schizophrenia spectrum psychosis, no- early-onset schizophrenia spectrum psychosis (autism spectrum disorders, tic disorders, and disruptive behaviour disorders)	DSM-IV	Risperidone	Antipsychotics	Monotherapy	Mean: 1.2 mg/day	Mean: 5.5 (range 3–12) months
Matsuoka, 1986[39]	NA	19	Schizophrenia and non-schizophrenic	DSM-III	NR	Antipsychotics	NR	NR	NR
Melkersson, 1999[40]	NA	9	Schizophrenia	DSM-III- R	Chlorpromazine, zuclopenthixol, haloperidol, thioridazine, pimozide, levomepromazine , perphenazine	Antipsychotics	Mixed	Median (range): 255 (40– 1,620) mg/day [expressed as chlorproma zine equivalents ]	For at least 6 months
Melkersson, 2005[41]	Olanzapine	7	Schizophrenia, schizophreniform disorder or schizoaffective disorder	DSM-IV	Olanzapine	Antipsychotics	Monotherapy	Median (range): 10 (5–20) mg/day	Median (range): 0.9 (0.2–5.5) years
	Risperidone	16	Schizophrenia, schizophreniform		Risperidone			Median (range): 3	Median (range): 1.0

Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
			disorder or schizoaffective disorder					(1–8) mg/day	(0.2–8.8) years
Park, 2016[42]	Aripiprazole	4	Schizophrenia, bipolar disorder, psychotic depression, schizoaffective disorder	DSM-IV	Aripiprazole	Antipsychotics	Monotherapy	Mean (SD): 15.21 (9.62) mg/day	For at least 2 weeks
	Blonanserin	15	Schizophrenia, bipolar disorder, psychotic depression, psychotic disorder		Blonanserin			Mean (SD): 12.7 (6.27) mg/day	
	Olanzapine	12	Schizophrenia, bipolar disorder, psychotic depression		Olanzapine			Mean (SD): 13.69 (6.68) mg/day	
	Paliperidone	22	Schizophrenia, bipolar disorder, schizoaffective disorder		Paliperidone			Mean (SD): 7.03 (3.63) mg/day	
	Quetiapine	7	Schizophrenia, bipolar disorder, psychotic depression, schizoaffective disorder		Quetiapine			Mean (SD): 361.96 (308.7) mg/day	
	Risperidone	34	Schizophrenia, bipolar disorder, psychotic depression, schizoaffective disorder, brief		Risperidone			Mean (SD): 4.52 (3.45) mg/day	



Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
Pollock, 1998[43]	NA	8	psychotic disorder, psychotic disorder NR	NR	Each patient took different drug: haloperidol; sulpiride, thioridazine, fluoxetine, procyclidine; venlafaxine, sulpiride, chlorpromazine; fluvoxamine thioridazine; sertraline, sulpiride, chlorpromazine procyclidine; flupenthixol decanoate; thioridazine thyroxine; thioridazine	Antipsychotics	Mixed	NR	Range: 1–3 years
Roke, 2012[44]	Risperidone	24	Primary diagnoses of autism spectrum disorders or disruptive behaviour disorders	NR	Risperidone	Antipsychotics	Monotherapy	Mean (SD; range): 1.5 (0.9; 0.25– 4) mg/day	Mean (SD; range): 53 (27.8; 16– 126) months
Seppala, 1977[45]	NA	10	NR	NR	NR	Oral contraceptives	NR	NR	NR
Smith, 1992[46]	NA	6	Psychiatric diagnosis	NR	NR	Antipsychotics	NR	NR	NR
Trenque, 2011[47]	NA	187	NR	NR	Citalopram, escitalopram, fluoxetine,	Antidepressants	Mixed	NR	NR

Author, year	Groups/ subgroups	Patients with drug- induced HPL <sup>a</sup> (n)	Diagnosis	ICD/ DMS	Treatment known or suspected to have induced HPL (drug)	Treatment known or suspected to have induced HPL (class)	Monotherapy/ polytherapy	Dose (total dose/day) <sup>b</sup>	Treatment duration mean (SD) <sup>b</sup>
Venetikou, 2008[48]	NA	6	NR	NR	NR	Antihypertensives, antipsychotics, and antidepressants	NR	NR	NR
Vilar, 2008[49]	NA	180	NR	NR	NR	Anxiolytics, H2 antagonists, antihypertensives, prokinetics, antidepressants, antipsychotics	Mixed	NR	NR
Yunilainen, 2018[50]	NA	120	Schizophrenia, acute polymorphic psychotic disorder with symptoms of schizophrenia, affective disorders, mental retardation with behavioural impairment	NR	NR	Antipsychotics	NR	NR	NR
Zhang, 2018[51]	Sexual dysfunction <sup>d</sup>	56 10	Schizophrenia	DSM-V	Clozapine, risperidone, olanzapine, aripiprazole	Antipsychotics	NR	NR	NR

<sup>a</sup> Patients diagnosed with drug-induced HPL

<sup>b</sup> Unless otherwise specified

<sup>c</sup> Patients with drug-induced HPL were enrolled and randomised/allocated to treatment of the HPL condition. Data on characteristics and clinical symptoms of drug-induced HPL were collected from baseline data (before patients received treatment to control the HPL)

<sup>d</sup> Sexual dysfunction defined as a total ASEX total score of  $\geq 19$ , and any item with a score of  $\geq 5$  or any three items with a score of  $\geq 4$

*DSM* Diagnostic and Statistical Manual of Mental Disorders, *HPL* hyperprolactinaemia, *ICD-10* International Classification of Diseases, 10<sup>th</sup> Revision, *IM* intramuscular, *IV* intravenous, *NR* not reported, *SD* standard deviation

**Table S5** Other clinical presentations

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
<b>Clinical trials</b>						
Amenorrhoea and decreased libido	Antipsychotics	19	11 (58)	NR	NA	Cavallaro, 2004[13]
Amenorrhoea, decreased libido, and galactorrhoea			2 (11)			
<b>Observational studies</b>						
Amenorrhoea and galactorrhoea	Anxiolytics, H2-antihistamines, antihypertensives, prokinetics, antidepressants, antipsychotics	108	8 (8)	NR	Females	Vilar, 2008[49]
	Antipsychotics	18	1 (6)	NR	NA	Emsley, 2008[27]
Galactorrhoea and/or oligomenorrhoea	Antipsychotics	9	9 (100)	NR	NA	Lankford, 1981[34]
Hypogonadism	Anxiolytics, H2-antihistamines, antihypertensives, prokinetics, antidepressants, antipsychotics	72	49.968 (70)	NR	Males	Vilar, 2008[49]
Muscle rigidity	Antipsychotics	11	1 (10)	NR	NA	Kopecek, 2006[31]
Oligomenorrhoea and galactorrhoea	Antipsychotics	14	2 (14)	NR	Females	Melkersson, 2005[41]
PRL-associated symptoms <sup>b</sup>	Antipsychotics	94	87 (93)	NR	NA	Park, 2016[42]
Weight gain	Antipsychotics	8	1 (13)	NR	NA	Pollock, 1998[43]

<sup>a</sup> Patients diagnosed with drug-induced HPL

<sup>b</sup> Amenorrhoea, oligomenorrhoea, menorrhagia, irregular menstruation, mastalgia [breast pain], gynaecomastia, decreased sexual drive, impotence, and orgasmic dysfunction  
*HPL* hyperprolactinaemia, *NA* not applicable, *NR* not reported, *PRL* prolactin

**Table S6** Breast and lactation disorders reported by the included studies

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
<b>Clinical trials</b>						
Breast discharge	Antipsychotics	221	1 (1)	NR	NA	Savitz, 2015[16]
Breast pain						
Breast tenderness	Antipsychotics	99	1 (2)	NR	NA	Man, 2016[3]
Galactorrhoea	Dopamine antagonists	6	1 (17)	Mean: 1 week	Menstruating females	Andersen, 1982[19]
	Antipsychotics	2	2 (12)	Range: 3–4 weeks	NA	Atmaca, 2002[6]
	Antipsychotics	36	13 (37)	NR	NA	Düring, 2019[20]
	Oral contraceptives	21	13 (62)	NR	NA	Karaman, 1993[8]
	Antipsychotics	54	9 (17)	NR	NA	Kinon, 2006[9]
	Antipsychotics	7	3 (43)	NR	NA	Lee, 2006a[14]
	Antipsychotics	60	2 (4)	NR	NA	Lee, 2010[10]
	Antipsychotics	20	3 (15)	NR	NA	Lu, 2008[15]
	Antipsychotics	99	13 (14)	NR	NA	Man, 2016[3]
	Antipsychotics	30	2 (7)	Mean: 2 months	NA	Ranjbar, 2015[18]
	Antipsychotics	221	16 (8)	NR	NA	Savitz, 2015[16]
	Antipsychotics	26	2 (8)	NR	NA	Shim, 2007[5]
	Antipsychotics	20	5 (25)	NR	NA	Yuan, 2008[4]
	Galactorrhoea and gynaecomastia	Antipsychotics	12	1 (9)	NR	NA
Gynaecomastia	Antipsychotics	36	12 (34)	NR	NA	Düring, 2019[20]
	Antipsychotics	1	1 (100)	NR	NA	Kelly, 2006[2]
	Antipsychotics	54	7 (13)	NR	NA	Kinon, 2006[9]
	Antipsychotics	30	3 (10)	Mean: 2 months	NA	Ranjbar, 2015[18]
	Antipsychotics	221	6 (3)	NR	NA	Savitz, 2015[16]
	Antipsychotics	13	2 (16)	NR	NA	Trives, 2013[17]

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
Lactating	Antipsychotics	60	2 (4)	Mean: 4 weeks	NA	Qiao, 2016[12]
Mastalgia (breast pain)	Antipsychotics	13	3 (24)	NR	NA	Trives, 2013[17]
<b>Observational studies</b>						
Galactorrhoea	Antipsychotics, antidepressants, mood stabilisers, and antianxiety medications	442	23 (6)	NR	NA	Alosaimi, 2018[23]
	Dopamine antagonists	28	23 (82)	NR	NA	Atluri, 2018[24]
	H2-antihistamines	2	2 (100)			
	Antipsychotics	25	12 (48)	NR	NA	Barszcz, 2007[25]
	Antipsychotics	18	1 (6)	NR	NA	Emsley, 2008[27]
	Oral contraceptives	7	1 (15)	NR	NA	Furuhjelm, 1980[28]
	Antipsychotics	5	2 (40)	NR	NA	Holzer, 2006[29]
	Antipsychotics	11	2 (19)	NR	NA	Kopecek, 2006[31]
	Prokinetics, antipsychotics and antidepressants, oestrogens	39	33 (85)	NR	NA	Kulshreshtha, 2017[33]
	Antipsychotics	14	4 (29)	NR	NA	Lee, 2005[35]
	Antipsychotics	9	2 (23)	Mean: 6 months	NA	Lee, 2006b[36]
	Antipsychotics	13	1 (8)	NR	NA	Margari, 2015[38]
	Antipsychotics	19	13 (69)	NR	NA	Matsuoka, 1986[39]
	Antipsychotics	9	1 (12)	NR	Females	Melkersson, 1999[40]
	Oral contraceptives	10	5 (50)	NR	NA	Seppala, 1977[45]
	Antipsychotics	6	2 (34)	NR	NA	Smith, 1992[46]
	Antidepressants	187	102 (55)	NR	NA	Trenque, 2011[47]
		180	25 (14)	NR	NA	Vilar, 2008[49]

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
Gynaecomastia	Anxiolytics, H2-antihistamines, antihypertensives, prokinetics, antidepressants, antipsychotics	108	21 (20)		Females	
		72	4 (6)		Males	
	Antipsychotics	80	51 (63)	NR	Females	Yunilainen, 2018[50]
	Antipsychotics	8	5 (63)	NR	NA	Pollock, 1998[43]
	Antipsychotics, antidepressants, mood stabilisers, and antianxiety medications	442	18 (5)	NR	NA	Alosaimi, 2018[23]
	Antipsychotics	5	3 (60)	NR	NA	Holzer, 2006[29]
	Antipsychotics	56	3 (6)	NR	NA	Park, 2016[42]
	Antipsychotics	24	8 (34)	NR	NA	Roke, 2012[44]
	Antidepressants	187	54 (29)	NR	NA	Trenque, 2011[47]
	Antipsychotics	40	10 (25)	NR	Males	Yunilainen, 2018[50]
Mastalgia (breast pain)	Antidepressants	187	21 (12)	NR	NA	Trenque, 2011[47]

<sup>a</sup> Patients diagnosed with drug-induced HPL  
*HPL* hyperprolactinaemia, *NA* not applicable, *NR* not reported

**Table S7** Female genital system disorders reported by the included studies

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
<b>Observational studies</b>						
Vaginal dryness during intercourse	Antipsychotics	80	42 (53) 15 (19)	NR	Females (PRSexDQ scale) Females (UKU)	Yunilainen, 2018[50]

<sup>a</sup> Patients diagnosed with drug-induced HPL

*HPL* hyperprolactinaemia, *NR* not reported, *PRSexDQ* Psychotropic-Related Sexual Dysfunction Questionnaire, *UKU* Udvalg for Kliniske Undersøgelser Side Effects Rating Scale for neuroleptics (task force for clinical investigations)

**Table S8** Hair and skin abnormalities reported by the included studies

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
<b>Clinical trials</b>						
Facial acne and hirsutism	Antipsychotics	99	2 (3)	NR	NA	Man, 2016[3]
Facial acne and hirsutism	Antipsychotics	20	1 (5)	NR	NA	Yuan, 2008[4]

<sup>a</sup> Patients diagnosed with drug-induced HPL

*HPL* hyperprolactinemia, *NA* not applicable, *NR* not reported



**Table S9** Infertility reported by the included studies

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
<b>Clinical trials</b>						
Anovulation	Dopamine antagonists	6	2 (34)	Mean: 1 week	NA	Andersen, 1982[19]
<b>Observational studies</b>						
Infertility	Dopamine antagonists	13	4 (31)	NR	NA	Atluri, 2018[24]
Infertility <sup>b</sup>	Oral contraceptives	7	2 (29)	NR	NA	Furuhjelm, 1980[28]
Oligospermia	Antipsychotics	7	1 (15)	NR	Males	Melkersson, 2005[41]

<sup>a</sup> Patients diagnosed with drug-induced HPL

<sup>b</sup> Reported as a long-term complication

*HPL* hyperprolactinemia, *NA* not applicable, *NR* not reported

**Table S10** Menstrual cycle bleeding disorders reported by the included studies

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
<b>Clinical trials</b>						
Abnormal menstrual duration (oligomenorrhoea and/or amenorrhoea)	Antipsychotics	20	20 (100)	NR	NA	Yuan, 2008[4]
Abnormal menstruation	Antipsychotics	99	53 (54)	NR	NA	Man, 2016[3]
Amenorrhoea	Antipsychotics	36	9 (25)	NR	NA	Düring, 2019[20]
	Oral contraceptives	21	21 (100)	NR	NA	Karaman, 1993[8]
	Antipsychotics	12	2 (17)	NR	NA	Kelly, 2006[2]
	Antipsychotics	7	7 (100)	NR	NA	Lee, 2006a[14]
	Antipsychotics	60	48 (80)	NR	NA	Lee, 2010[10]
	Antipsychotics	20	9 (45)	NR	NA	Lu, 2008[15]
	Antipsychotics	99	42 (43)	NR	NA	Man, 2016[3]
	Antipsychotics	75	8 (11)	NR	NA	Savitz, 2015[16]
	Antipsychotics	26	6 (23)	NR	NA	Shim, 2007[5]
	Antipsychotics	42	13 (31)	NR	NA	Yoon, 2016[7]
	Change in menstruation	Antipsychotics	27	5 (19)	NR	Females
Menorrhagia	Antipsychotics	36	1 (3)	NR	NA	Düring, 2019[20]
Menstrual cycle changes	Antipsychotics	30	30 (100)	Mean: 2 months	NA	Ranjbar, 2015[18]
Menstrual irregularities	Antipsychotics	54	7 (13)	NR	NA	Kinon, 2006[9]
Menstruation irregular	Antipsychotics	75	3 (4)	NR	NA	Savitz, 2015[16]
Oligo/amenorrhoea	Antipsychotics	13	6 (47)	NR	NA	Trives, 2013[17]
Oligomenorrhoea	Antipsychotics	20	11 (55)	NR	NA	Lu, 2008[15]
	Antipsychotics	26	5 (20)	NR	NA	Shim, 2007[5]
	Antipsychotics	42	6 (15)	NR	NA	Yoon, 2016[7]
Premenstrual tension	Antipsychotics	13	1 (8)	NR	NA	Trives, 2013[17]

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
<b>Observational studies</b>						
Abnormal menstruation, such as amenorrhoea and irregular menstrual cycles	Antipsychotics	10	10 (100)	NR	Females	Park, 2016[42]
Amenorrhoea	Antipsychotics	14	14 (100)	Mean: 12 months	NA	Lee, 2005[35]
	Dopamine antagonists, antipsychotics and antidepressants, oestrogens	39	4 (11)	NR	NA	Kulshreshtha, 2017[33]
	Antipsychotics	19	13 (69)	NR	NA	Matsuoka, 1986[39]
	Antipsychotics	12	11 (92)	NR	NA	Ahuja, 2008[22]
	Antipsychotics	18	1 (6)	NR	NA	Emsley, 2008[27]
	Oral contraceptives	7	7 (100)	NR	NA	Furuhjelm, 1980[28]
	Antipsychotics	44	42 (96)	NR	Females	Kalkavoura, 2013[30]
	Antipsychotics	18	1 (6)	NR	NA	Kotan, 2011[32]
	Antipsychotics	9	3 (34)	NR	Females	Melkersson, 2005[41]
	Anxiolytics, H2-antihistamines, antihypertensives, prokinetics, antidepressants, antipsychotics	108	16 (15)	NR	Females	Vilar, 2008[49]
	Antipsychotics	80	8 (10)	NR	Females (UKU)	Yunilainen, 2018[50]
	Antipsychotics	11	1 (10)	NR	NA	Kopecek, 2006[31]
	Antidepressants	187	21 (12)	NR	NA	Trenque, 2011[47]
	Oral contraceptives	10	10 (100)	NR	NA	Seppala, 1977[45]
Antipsychotics	8	6 (75)	NR	NA	Pollock, 1998[43]	
Amenorrhoea (absence of menstruation for 6 months or longer)	Antipsychotics	6	3 (50)	Mean: 4 months	NA	Smith, 1992[46]
Amenorrhoea and delayed menses	Antipsychotics	18	1 (6)	NR	NA	Emsley, 2008[27]
Dysmenorrhoea	Antipsychotics	80	3.2 (4)	NR	Females (UKU)	Yunilainen, 2018[50]

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
	Antipsychotics	25	20 (80)	NR	NA	Barszcz, 2007[25]
Menstrual abnormalities (e.g., oligomenorrhoea or amenorrhoea)	Antipsychotics	9	7 (78)	Mean: 6 months	NA	Lee, 2006b[36]
Menstrual cycle impairments	Antipsychotics	80	43.2 (54)	NR	NA (UKU)	Yunilainen, 2018[50]
Menstrual disturbances	Antipsychotics	7	5 (72)	NR	Females	Melkersson, 1999[40]
Menstrual irregularities	Antipsychotics, antidepressants, mood stabilisers, and antianxiety medications	442	56 (13)	NR	NA	Alosaimi, 2018[23]
	Antipsychotics	13	1 (8)	NR	NA	Margari, 2015[38]
	Antipsychotics	18	2 (12)	NR	NA	Kotan, 2011[32]
Oligomenorrhoea	NR	13	1 (8)	NR	NA	Atluri, 2018[24]
	Prokinetics, antipsychotics and antidepressants, oestrogens	39	14 (36)	NR	NA	Kulshreshtha, 2017[33]
	Antipsychotics	9	1 (12)	NR	Females	Melkersson, 2005[41]
	Anxiolytics, H2-antihistamines, antihypertensives, prokinetics, antidepressants, antipsychotics	108	20.952 (20)	NR	Females	Vilar, 2008[49]
	Antipsychotics	80	28.8 (36)	NR	Females (UKU)	Yunilainen, 2018[50]
Oligomenorrhoea (menstrual intervals between 35 and 180 days)	Antipsychotics	6	3 (50)	Mean: 4 months	NA	Smith, 1992[46]
Oligomenorrhoea or amenorrhoea	Antipsychotics	24	11 (46)	NR	NA	Chen, 2010[26]
Oligomenorrhoea	Antipsychotics	8	1 (13)	NR	NA	Pollock, 1998[43]
Polymenorrhagia	Antipsychotics	80	2.4 (3)	NR	Females (UKU)	Yunilainen, 2018[50]

<sup>a</sup> Patients diagnosed with drug-induced HPL

HPL hyperprolactinaemia, NR not reported, PRSexDQ Psychotropic-Related Sexual Dysfunction Questionnaire, UKU Udvalg for Kliniske Undersøgelser Side Effects Rating Scale for neuroleptics (task force for clinical investigations)

**Table S11** Sexual dysfunction as reported by the included studies

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
<b>Clinical trials</b>						
Decreased desire	Antipsychotics	36	13 (37)	NR	NA	Düring, 2019[20]
Decreased libido	Antipsychotics	99	1 (2)	NR	NA	Man, 2016[3]
	Antipsychotics	221	1 (1)	NR	NA	Savitz, 2015[16]
	Antipsychotics	13	10 (77)	NR	NA	Trives, 2013[17]
Decreased lubrication	Antipsychotics	36	3 (9)	NR	NA	Düring, 2019[20]
Delayed ejaculation	Antipsychotics	27	4 (15)	NR	NA	Mir, 2008[21]
Ejaculatory dysfunction	Antipsychotics	36	4 (12)	NR	NA	Düring, 2019[20]
Erectile difficulties	Antipsychotics	27	6 (23)	NR	NA	Mir, 2008[21]
	Antipsychotics	36	4 (12)	NR	NA	Düring, 2019[20]
Erectile dysfunction	Antipsychotics	146	1 (1)	NR	Males	Savitz, 2015[16]
	Antipsychotics	19	6 (32)	NR	NA	Cavallaro, 2004[13]
Erectile dysfunction and decreased libido	Antipsychotics	19	6 (32)	NR	NA	Cavallaro, 2004[13]
Impotence	Antipsychotics	13	2 (16)	NR	NA	Trives, 2013[17]
Increased desire	Antipsychotics	36	6 (17)	NR	NA	Düring, 2019[20]
Loss of libido	Antipsychotics	27	10 (38)	NR	NA	Mir, 2008[21]
Orgasmic difficulties	Antipsychotics	27	6 (23)	NR	NA	
Orgasmic dysfunction	Antipsychotics	36	3 (9)	NR	NA	Düring, 2019[20]
Problems of sexual arousal	Antipsychotics	27	6 (23)	NR	NA	Mir, 2008[21]
Reduction in ejaculation volume/intensity	Antipsychotics	27	4 (15)	NR	NA	
Sexual ADRs	Antipsychotics	28	11 (39)	Mean: 1 year	NA	Perez-Iglesias, 2012[11]
Sexual dysfunction	Antipsychotics	30	9 (30)	Mean: 2 months	NA	Ranjbar, 2015[18]
	Antipsychotics	42	23 (55)	NR	NA	Yoon, 2016[7]
<b>Observational studies</b>						

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
Anorgasmia	Antipsychotics	18	2 (12)	NR	NA	Kotan, 2011[32]
Decreased libido	Antipsychotics	7	1 (15)	NR	Males	Melkersson, 2005[41]
	Antipsychotics, antidepressants, mood stabilisers, and antianxiety medications	442	75 (17)	NR	NA	Alosaimi, 2018[23]
	Antipsychotics	18	2 (12)	NR	NA	Kotan, 2011[32]
	Antipsychotics	120	67.2 (56)	NR	NA (PRSexDQ scale)	Yunilainen, 2018[50]
	Antipsychotics	120	62.4 (52)	NR	NA (UKU)	
	Antipsychotics	80	49.6 (62)	NR	Females (PRSexDQ scale)	
	Antipsychotics	80	44 (55)	NR	Females (UKU)	
	Antipsychotics	40	18.4 (46)	NR	Males (UKU)	
Degraded quality of life due to sexual impairments	Antipsychotics	80	44.8 (56)	NR	Females (PRSexDQ scale)	Yunilainen, 2018[50]
	Antipsychotics	120	61.2 (51)	NR	NA (PRSexDQ scale)	
	Antipsychotics	40	16 (40)	NR	Males (UKU)	
Delayed onset of orgasms	Antipsychotics	80	39.2 (49)	NR	Females (PRSexDQ scale)	Yunilainen, 2018[50]
	Antipsychotics	40	10.8 (27)	NR	Males (UKU)	
	Antipsychotics	120	50.4 (42)	NR	NA (PRSexDQ scale)	
Difficulty achieving orgasm	Antipsychotics	120	69.6 (58)	NR	NA (PRSexDQ scale)	Yunilainen, 2018[50]
	Antipsychotics	80	52 (65)	NR	Females (PRSexDQ scale)	
Erectile dysfunction	Antipsychotics	40	16 (40)	NR	Males (UKU)	
	Antipsychotics	9	2 (23)	Mean: 6 months	NA	Lee, 2006b[36]
	NR	10	10 (100)	NR	Males	Leonard, 1989[37]
	Antihypertensives, antipsychotics, and antidepressants	6	6 (100)	NR	Males	Venetikou, 2008[48]

Symptom or long-term complication	Treatment known or suspected to have induced HPL (class)	Patients with drug-induced HPL, <sup>a</sup> (n)	Patients with symptoms, n (%)	Time since start of drug until symptom	Groups at baseline/subgroup populations	Author, year
Impaired erection	Antipsychotics	40	9.6 (24)	NR	Males (UKU)	Yunilainen, 2018[50]
Impaired orgasm	Antipsychotics	80	38 (48)	NR	Females (UKU)	Yunilainen, 2018[50]
	Antipsychotics	120	51.6 (43)	NR	NA (UKU)	
Impotence	Antipsychotics	7	1 (15)	NR	Males	Melkersson, 2005[41]
Increased libido	Antipsychotics	120	25.2 (21)	NR	NA (UKU)	Yunilainen, 2018[50]
	Antipsychotics	80	16 (20)	NR	Females (UKU)	
Sexual disorders, mainly ejaculation disorders	Antidepressants	187	7 (4)	NR	NA	Trenque, 2011[47]
Sexual dysfunction	Antipsychotics	19	6 (32)	NR	NA	Matsuoka, 1986[39]
	Antipsychotics	24	5 (21)	NR	NA	Roke, 2012[44]
Sexual dysfunction, ASEX total score of $\geq 19$ , and any item with a score of $\geq 5$ or any three items with a score of $\geq 4$	Antipsychotics	56	56 (100)	NR	Patients with sexual dysfunction	Zhang, 2018[51]

<sup>a</sup> Patients diagnosed with drug-induced HPL

*ASEX* Arizona Sexual Experience, *HPL* hyperprolactinaemia, *NR* not reported, *PRSexDQ* Psychotropic-Related Sexual Dysfunction Questionnaire, *UKU* Udvalg for Kliniske Undersøgelser Side Effects Rating Scale for neuroleptics (task force for clinical investigations)

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