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Proton pump inhibitors therapy and risk of hyperprolactinemia with associated sexual disorders

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Proton pump inhibitors (PPIs) are the most widely prescribed medications in the world. According to numerous studies, PPIs have been linked to hyperprolactinemia, which can lead to a variety of sexual and reproductive issues. This review summarizes the effects of numerous PPIs on the blood prolactin levels and associated sexual dysfunctions, which have an effect on the patient's life quality and fertility. The study is taken into account all the available resources till January 31, 2021. Out of total 364, only 27 relevant resources were involved in this review. In certain studies, short-term PPIs use has been shown to have little or no effect on the blood prolactin and other reproductive hormones levels. PPIs have been linked to the development of hyperprolactinemia in several case studies with varying degrees of the blood prolactin levels increase seen in individuals taking PPI alone or in combination with medications, like prokinetics. The relative risk of the sexual consequences development, such as gynecomastia, has been documented using lansoprazole and omeprazole in various cohort studies. On the other hand, other bits of data are insufficient to establish a definite relationship that can turn a possibility into certainty. The majority of the literature data is comprising of double-blind, randomized, crossover studies, case reports, and adverse drug reaction incidents reported to various pharmacovigilance centers. To investigate this link, high-quality studies in patients taking PPIs for a longer time period are needed. We conclude this article with a comprehensive discussion of the hyperprolactinemia clinical implications and the PPIs' function.

Key words: proton pump inhibitors, hyperprolactinemia, reproductive symptoms, sexual dysfunction, omeprazole, gynecomastia, galactorrhea, erectile dysfunction

Proton pump inhibitors

The proton pump inhibitors (PPIs) are common and increasing medications that are prescribed in different acid-related disorders. These PPIs inhibit the secretion of gastric acid by specific inhibition of the H+/K+ATPase via a covalent bonding to a cysteine residue of the proton pump in the gastric parietal cells (Sachs et al. 2006). Due to the covalent bonding, their inhibitory effects for acid secretion last much longer than their half-life. This inhibitory effect enables healing of the peptic ulcers, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, Barrott's esophagitis, and eradication of Helicobacter pylori in combined therapy (Shin and Sachs 2008). The PPIs also provide prophylactically a potent gastric acid inhibition in the management of the non-steroidal anti-inflammatory drugs, NSAID-associated ulcers, and stress-related ulcers (Brett 2004; Scheiman 2013). The PPIs include omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole, and dexlansoprazole.

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There is an increasing trend towards the use of PPIs in the last two decades in both hospital and primary care settings, whereas their use is still rising. There is multiple evidence of an inappropriate use of PPIs in hospital settings as it is indicated in studies from several countries including Nederland (van Vliet et al. 2008), Italy (Pasina et al. 2011), Ireland (Mat Saad et al. 2005), the USA (Nardino et al. 2000; Mazer-Amirshahi et al. 2014), Australia (Naunton et al. 2018), India (Mathew et al. 2015), and Singapore (Akram et al. 2014). The inappropriate use of PPIs has also been established in different studies in Pakistan (Naqvi et al. 2014). In one Pakistan study, Shafi et al. (2011) have concluded that 51% of the enrolled patients using PPIs were with no definite indication. The PPIs were prescribed over 2/3 (64%) of the studied patients, by either unqualified practitioners or bought over the counter, without licensed indications.

Hyperprolactinemia

Hyperprolactinemia is a common clinical condition, in which the serum prolactin levels are persistently elevated: beyond 25 ng/ml for non-pregnant women, up to 210 ng/ml for pregnant women, and 20 ng/ml for men. In addition, marked interindividual differences in prolactin levels have been recognized. Serum prolactin often exhibits up to four times of the circadian variation with maximal concentration during sleep (Biswas and Rodeck 1976; Peuskens et al. 2014; Alosaimi et al. 2018). Hyperprolactinemia can occur at any age, but it more frequently occurs in the middle-aged and elderly individuals (Touitou and Haus 2004).

Etiology. There are numerous causes that contribute to the high prolactin levels. Prolactin secretion is regulated by a delicate mechanism as shown in Figure 1. Due to the complex regulation of the prolactin synthesis, hyperprolactinemia can be divided into three main types: physiological, pathological, and pharmacological (Holt 2008). The physiological hyperprolactinemia can occur from normal physiological processes, such as pregnancy, lactation, stress, and anxiety-related high secretion of prolactin, physical activity, sexual activity, and sleep. Physiological hyperprolactinemia is usually mild or moderate. The pathological hyperprolactinemia can be caused by the hypothalamic pituitary gland as well as non-pituitary-hypothalamic disorders. The former mainly includes pituitary adenomas, mixed pituitary adenomas, gliomas, acromegaly, and pituitary talk disruption. Among the pituitary tumors, the

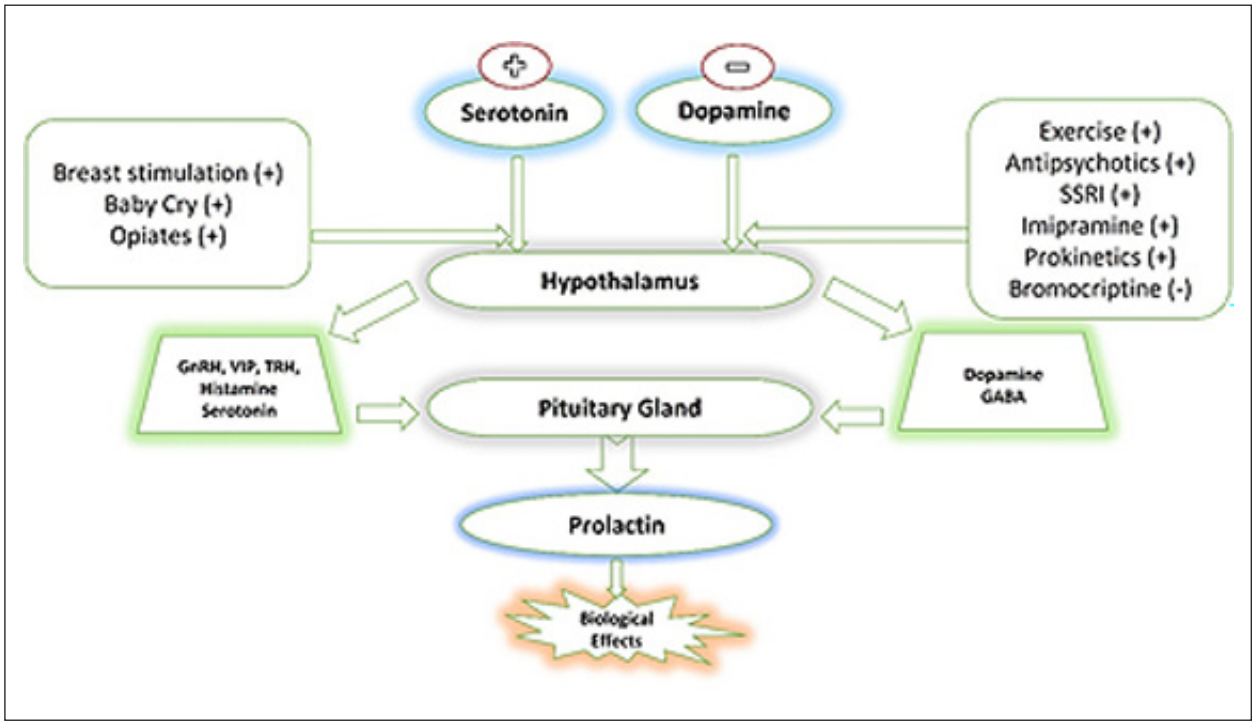

Figure 1. Mechanisms involved in drug-induced prolactin secretion. It is indicated that the prolactin secretion is regulated by delicate mechanisms.

prolactin-secreting adenomas are more common in the hyperprolactinemia cause. The latter type includes cirrhosis, central nervous system disorders, chronic renal failure, and hypothyroidism. In addition to the above, hyperprolactinemia can also be caused by unidentified reasons. These conditions are known as an idiopathic hyperprolactinemia (Chahal and Schlechte 2008; Bushe et al. 2010; Capozzi et al. 2015; Alosaimi et al. 2018).

The third important cause of hyperprolactinemia is the intake of drugs, known as pharmacologic hyperprolactinemia. Table 1 depicts the main medications causing prolactin level induction. The reasons for the modest hyperprolactinemia caused by drugs are variable. Some drugs cause blockade of the central dopaminergic system. These drugs include antipsychotics, antiemetics, and some antidepressants. The incidence of antipsychotics-induced hyperprolactinemia is high as compared to other medications. The hyperprolactinemic effect of the antipsychotics is mediated through the D2 receptors in the hypothalamic tuberoinfundibular system and the anterior pituitary lactotrophs (Marken et al. 1992; Verhelst and Abs 2003; La Torre and Falorni 2007). Morphine and its analogs also stimulate the secretion of prolactin through opiate receptors in the hypothalamus (Van Vugt and Meites 1980). Some antidepressants, such as imipramine, desipramine, and amitriptyline, increase prolactin level by increasing the availability of serotonin and blocking its reuptake (Haddad and Wieck 2000; La Torre and Falorni 2007). Histamine stimulatory effects have also been shown. These are mediated through H2 receptors (Knigge 1990).

Symptoms. The biological effects in pathological hyperprolactinemia are similar to those seen in a high serum prolactin during the postpartum period. Such effects include the inhibition of the gonadotropin-releasing hormone release, gonadal dysfunction, and the promotion of the milk formation. Due to this reason, the human reproductive system is more often affected and the hypogonadotropic hypogonadism is the usual consequence of the high prolactin levels in both genders (Milenkovic et al. 1994; Mah and Webster 2002; Verhelst and Abs 2003). The clinical conditions appearance differs with age, sex, and the degree of the prolactin excess. In premenopausal women, the symptoms related to hypogonadism are often seen in all patients ranging from sterility, loss of libido or painful intercourse, irregular menstruation, amenorrhea or oligomenorrhea, galactorrhea, and decreased bone mass. Primary amenorrhea is the first symptom in the prepubertal patients. Galactorrhea may be seen either spontaneously or after nipple stimulation; however, many premenopausal women with high serum prolactin do not exhibit this phenomenon (Bahamondes et al. 1985; Sartorio et al. 2000; Verhelst and Abs 2003; Majumdar and Mangal 2013).

Absence or disappearance of menstrual cycle is only the sign that has been observed with high prolactin levels in the post-menopausal women and may accompanied with other atypical symptoms. Galactorrhea is not common in the postmenopausal women due to low estrogen levels and the prolonged hypoestrogenism may result in an osteopenia (Boyd et al. 1977; Verhelst and Abs 2003). In addition, hyperprolactinemia in women may represent signs of

Table 1
Drugs capable of hyperprolactinemia induction

S: No	Class	Drugs
1	Antipsychotics	Phenothiazine, Butyrophenone (Haloperidol), Thioxanthones, Risperidone, Paliperidone, quetiapine, Olanzapine, Amisulpride, Molindone, Zotepine
2	Antidepressants	Imipramine, Desipramine, Amitriptyline, Amoxapine, Clomipramine, Fluoxetine, Paroxetine, Citalopram, Fluvoxamine, Sertraline, Pergoline, Tranylcypromine, Clorgyline
3	Other psychotropics	Buspirone, Alprazolam
4	Antiemetics Prokinetics	Metoclopramide, Domperidone
5	Antihypertensive	α methyldopa, Reserpine, Verapamil
6	H2 receptor blocker	Cimetidine, Ranitidine
7	Opiates	Morphine, Spiradoline, Methadone, Amphetamine, Fenfluramine
8	Others	Physostigmine, Protease Inhibitors, Estrogens

Data are summarized from following studies: La Torre and Falorni (2007); Marken et al. (1992); Molitch (2005); Verhelst and Abs (2003); Voicu et al. (2013).

chronic hyperandrogenisms, such as hirsutism and acne due to high secretion of dehydroepiandrosterone from the adrenals (Boyd et al. 1977; Biller 1999). In men, hyperprolactinemia can incite decreased sex drive, erectile dysfunctions, infertility, weight gain, and osteoporosis. Gynecomastia and galactorrhea may also be less frequently present in men. The patient may present diminished energy and reduced muscle mass (Luciano 1999; Verhelst and Abs 2003; Shibli-Rahhal and Schlechte 2009; Majumdar and Mangal 2013). In the case of pituitary tumors, in addition to common endocrinological symptoms (Verhelst and Abs 2003; Majumdar and Mangal 2013), the hyperprolactinemia may present pressure symptoms including headache, visual defects, seizures, etc.

Hyperprolactinemia and sexual dysfunction. High prolactin levels are associated with an impaired sexuality or sexual dysfunction in both men and women. Even the drug-induced sexual dysfunction comprises a list containing the majority of the drugs with high potential for increasing prolactin levels (Conaglen and Conaglen 2013). Hyperprolactinemia, a well-defined hypothalamic-pituitary disorder, has developed in a lack or marked decrease in sexual desire, lubrication problems, and orgasm (Lundberg and Hulter 1991). In the study of Kadioglu et al. (2005), a statistically lower value of the female sexual function index (FSFI) score has been observed for all phases of the female sexual functions, such as desire, lubrication, arousal, satisfaction, orgasm, and pain during the intercourse, in the hyperprolactinemic women using FSFI questionnaire. Similar finding has also been observed in a recent study conducted on women with mild hyperprolactinemia (Krysiak et al. 2018). In the studies conducted on the cotton-top tamarin females, Snowdon and Ziegler (2015) have demonstrated that prolactin level is significantly associated with the sexual behavior. In other studies, it has been reported that high prolactin level lowers the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and that estradiol leads to an inhibition of the hypothalamic-pituitary-gonadal (HPG) axis. In females, the level of hyperprolactinemia correlated with the degree of suppression of HPG-axis and hypogonadal state (Smith et al. 2002; Kishimoto et al. 2008) and consequently with sexual side effects (Knegtering et al. 2008).

Materials and methods

This literature review was completed on three freely available biomedical literature databases; i.e., PubMed, ScienceDirect, and Google scholar. This research collects data that are related to the effects of PPIs treatment inducing hyperprolactinemia and related sexual problems from 1978 to January 2021. Initially 364 articles were selected. Later, 337 articles were excluded and only 27 articles were considered to be relevant for this study. The data search was done using the following key words. "Proton pump inhibitors, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and hyperprolactinemia, effect on prolactin, endocrine hormones, hormonal imbalance, endocrine effects, sexual dysfunction, erectile dysfunction, gynecomastia, galactorrhea, male semen, ejaculation, irregular menses, amenorrhea, oligomenorrhea, breast pain, breast enlargement, and reproductive disorders".

Abstracts and citations were identified from all the three databases and analyzed for the relevance to the question. An additional search was also conducted for the references (papers) not identified in the primary search. The search was not limited to a single language. We also searched for adverse drug reaction (ADR) relevant to the question in two online available pharmacovigilance databases including European pharmacovigilance Centre and WHO global pharmacovigilance database.

Results and discussion

The literature search identified 364 relevant references and after comprehensive evaluation 27 were selected for this study as shown in Figure 2. Since its introduction to the clinical use, PPIs have gained considerable interest in reducing the gastric symptoms. However, the safety of PPIs has been unheeded since their clinical approval, especially in the long-lasting therapies. The endocrine effects, after the use of different PPIs, have been a question for the researchers even before approving the first of their members; i.e., omeprazole, in the clinical settings. Most of the studies conducted in this linking are composed of double-blind, randomized, cross-over, retrospective cohort studies, case reports, and ADR events reported to various pharmacovigilance databases.

A detailed search was made on two online available Pharmacovigilance databases for ADR reports, received in connection with all PPIs. The number of ADRs reported to the European pharmacovigilance Centre in association with PPIs use are represented in Table 2. The table also contains the ADR reported particularly for hyperprolactinemia. The largest ADR has been reported for lansoprazole with a total of 9 till January 2021 in connection with hyperprolactinemia

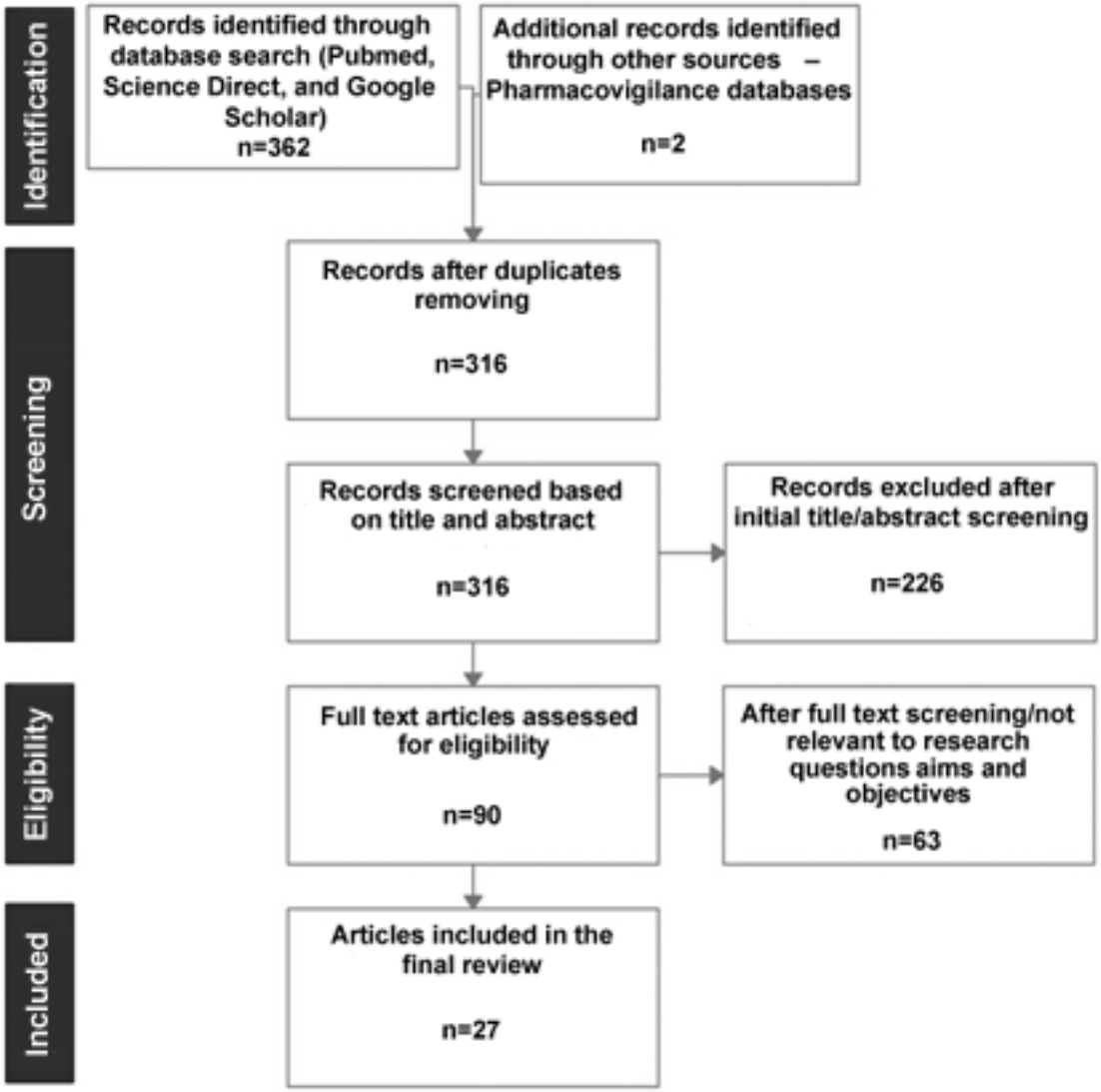

Figure 2. The picture reveals that the literature search identified 364 relevant references and after comprehensive evaluation only 23 reminded relevant for this study. PRISMA flow diagram for systematic review related to hyperprolactinemia related to proton pump inhibitor (PPI) use.

followed by omeprazole and esomeprazole with 7 and 6 hyperprolactinemic cases, respectively. Pantoprazole received 1 and rabeprazole 2 ADR reports for hyperprolactinemia. Among reproductive disorders, a large number of cases have been reported for gynecomastia and erectile dysfunction in association with omeprazole. For gynecomastia itself, a maximum number of cases has been reported for all PPIs molecules (Eudravigilance 2021).

The hyperprolactinemia and reproductive/sexual disorders listed on the global pharmacovigilance database (VigiAccess®) maintained by Uppsala Monitoring Centre are shown in table 3 till Jan 2021. A maximum number of cases has been reported for omeprazole in all individual categories of ADR. About 56 cases have been recorded for hyperprolactinemia in people using PPIs. As listed for the European database, gynecomastia and erectile dysfunction are major ADRs reported globally in users of PPIs (VigiAccess 2021).

The detailed information about the individual ADR reports is not available and no information is available for the screening of prolactin in all ADR mentioned in the Tables 2 and 3. The data have been compiled as one of the major signs and symptoms of high plasma prolactin secretion. Gynecomastia

Table 2
Adverse drug reaction (ADR) events reported to European Database of Suspected ADR

Disorders	Omeprazole	Esomeprazole	Pantoprazole	Lansoprazole	Dexlansoprazole	Rabeprazole
Hyperprolactinemia	07	06	01	09	–	02
Gynecomastia	104	45	48	45	01	11
Galactorrhea	15	09	03	11		03
Breast pain	15	19	14	03	01	02
Breast Enlargement	16	12	04	05	01	01
Sexual dysfunction	03	03	01	–	–	–
Amenorrhea	07	05	02	04	02	02
Menstruation Irregular	07	03	–	01	–	–
Menstrual Disorder	05	07	04	–	–	01
Dysmenorrhea	03	02	02	–	–	01
Menopausal Symptoms	02	02	01	–	–	–
Erectile Dysfunction	52	23	27	14	–	04

Table 3
Adverse drug reaction (ADR) events reported to global pharmacovigilance database

Disorders	Omeprazole	Esomeprazole	Pantoprazole	Lansoprazole	Dexlansoprazole	Rabeprazole
Hyperprolactinemia	23	13	06	13	–	04
Gynecomastia	439	114	97	123	02	38
Galactorrhea	46	38	13	30	0	29
Breast pain	93	56	35	36	04	28
Breast Enlargement	63	28	16	18	01	05
Sexual dysfunction	34	09	07	06	–	–
Amenorrhea	21	07	06	05	01	05
Menstruation Irregular	17	09	03	03	01	09
Menstrual Disorder	24	12	02	04	01	07
Dysmenorrhea	05	02	03	04	01	02
Oligomenorrhoea	–	–	–	–	–	01
Menopausal Symptoms	06	07	01	01	–	–
Dyspareunia	–	01	–	01	–	–
Erectile Dysfunction	264	70	64	62	–	25
Ejaculatory disorders	06	02	01	04	–	01
Male Infertility	08	03	–	02	–	01

represents a leading adverse reaction reported with PPI treatment, which may have different etiologies. The involvement of hyperprolactinemia in the pathogenesis of gynecomastia could be justified as a secondary cause of hypogonadism. Though the prolactin receptors being found in the male breast tissues, they may be co-expressed and cross regulated with growth hormones and progesterone receptor. Besides, male hypogonadism, an alternative pathway has also been proposed that high prolactin level may stimulate the breast tissue growth from excessive progesterone receptor activation (Ferreira et al. 2008; Galdiero et al. 2012; Maggi et al. 2013; Bravo et al. 2015; Sansone et al. 2017). Similarly, the exact role of the hyperprolactinemia in the pathophysiology of erectile dysfunction is not known; however, after testosterone, prolactin is the alternate endocrine hormone suspected to play a role in the male sexual

problems (Soran and Wu 2005). Overall, it is quite evident from the ADR reports that PPI may contribute to the development of sexual disturbances of varying capacities.

Different types of studies have been conducted in relevance to various PPIs for their potential to cause any endocrine effects, i.e., the potential for disrupting hormonal levels summarized in Table 4. None of the randomized, double-blind, and cross-over studies, has shown clinically significant variations in hormonal concentrations after PPIs therapy. In the study of Dammann et al. (1994), no statistically significant changes in the placebo and pantoprazole treated groups have been observed, yet. The maximum value for the prolactin measurement has been raised in pantoprazole treated group suggesting that some of the subjects have developed increased prolactin levels. The majority of the randomized, double-blind, and cross-over studies have been conducted on endocrine effects with a short-term PPI therapy comprising of 1–2 weeks. Only one study (Meikle et al. 1994) has been conducted on moderate-term

Table 4
Studies report for endocrine effects with proton pump inhibitors (PPIs) use

PPIs/Drug	Study Design	Dose duration	Hyperprolactinemia or other endocrine irregularities	Year	References
Omeprazole	8 healthy men aged 19–29 years with drug or placebo administration in a randomized, crossover, double blinded study	60 mg once daily for 7 days	No hormonal differences between omeprazole and placebo treated volunteers	1987	MacGilchrist et al. 1987
Lansoprazole	32 men with drug or placebo administration in a randomized double-blind parallel study	60 mg once daily for 8 weeks	No statistically significant difference in hormone concentration claimed by the author	1994	Meikle et al. 1994
Rabeprazole	12 healthy male volunteers aged 26–31 in a single center, double blind, two period, randomized cross-over study	20 mg once daily oral dose for 14 days	No statistically significant difference in endocrine hormones concentration claimed by the author	1999	Dammann et al. 1999
Omeprazole	43 male patients aged 18–47 years	20 mg once daily oral dose for 45 days with clarithromycin 500 mg and metronidazole 500 mg twice daily for initial 10 days	There was significant difference in the mean serum level of testosterone between patients in the post therapy stage and controls while other insignificant differences for prolactin, FSH, LH and E2		Thanoon and Mahmood 2011
Cimetidine Misoprostol Omeprazole Ranitidine	81535 men aged 25–84 from 1st January 1989 to 15 September 1992 registered with 478 practices in UK in open cohort study with nested case control analysis	All subjects received at least one prescription for cimetidine, misoprostol, omeprazole, or ranitidine in study period.	Relative risk of gynecomastia (endocrine disorder) for omeprazole was 0.6 (0.1–3.3)	1994	Garcia Rodriguez and Jick 1994
Lansoprazole	Animal studies on male Sprague-Dawley rats	Animals were given the drug with 150mg/kg/day or vehicle for 14 days.	Significant reduction in both plasma and testicular testosterone levels while no significant changes in other hormones.	2003	Coulson et al. 2003
Any PPI	A retrospective cohort study using PharmaMetrics Plus™ health claim database	A total of 220791 of new PPI users from 2006 to 2016.	389 cases of Gynecomastia were diagnosed. No other hormonal data record was studied.	2019	He et al. 2019
Omeprazole	8 healthy males volunteers in double-blind randomized cross-over study	60 mg /day and identical placebo for 8 days. Endocrine function was assessed on day 7.	No alteration in basal level of any endocrine hormones. A significant impairment of the cortisol response to exogenous ACTH.	1986	Howden et al. 1986

Table 4
Continued ...

PPIs/Drug	Study Design	Dose duration	Hyperprolactinemia or other endocrine irregularities	Year	References
Lansoprazole	A retrospective study of 175 men aged 18–89 years during the period of January 1993 to June 2000 presented with breast enlargement and managed by a single surgeon.	True gynecomastia was diagnosed in about 127 patients.	Out of 127 patients, 11 patients were using Lansoprazole and 5 patients have hyperprolactinemia. Rest of the patients have other causes.	2003	Daniels and Layer 2003
Pantoprazole	12 healthy male volunteers aged 20–33 in a double blind, two period, randomized cross-over study	40 mg once daily oral dose or placebo for 2 weeks	No alteration in endocrine hormones levels in both groups.	1994	Dammann et al. 1994
Lansoprazole	12 healthy male volunteers aged 23–29 in a double blind, randomized, three-way cross-over study	30 mg or 60 mg once daily dose or placebo for 7 days. Three 7 days dosing was done with 2 weeks wash out period.	No clinically relevant influence on endocrine hormones was observed.	1993	Dammann et al. 1993
Omeprazole	8 healthy volunteers	30 mg daily for 28 days	On 29th day the basal levels of endocrine hormones remained unchanged.	1984	Muller et al. 1984
	Cross sectional study at tertiary care hospital of	74 patient data were collected who were presented to endocrinology department for hyperprolactinemia from June 2015 to May 2016	26 out of 74 cases were drug induced among which 50% was PPI induced with or with prokinetics.	2016	Mohanty et al. 2016

Abbreviations: E2 – estradiol; FSH – follicle-stimulating hormone; LH – luteinizing hormone; PPIs – proton pump inhibitors.

lansoprazole therapy. The effects of long-term use of PPIs on endocrine hormones, particularly prolactin, are lacking. The study conducted by Meikle et al. (1994) has mentioned the prolactin measurements in methodology and summary, but the results section with data for prolactin are lacking and neither of authors had discussed it. In some studies, changes in serum testosterone levels after PPI therapy have been reported with no changes in other hormones levels (Coulson et al. 2003; Thanoon and Mahmood 2011). Most of the studies conducted have been confined to the male gender only, therefore, engendering a question of PPI's relevancy with the endocrine hormones in females.

Very few retrospective cohort studies have been conducted so far about the endocrine effects after PPI therapy. One study has reported a relative small risk of gynecomastia developing and only omeprazole along with other H2 receptor antagonists (H2RAs) and misoprostol have been studied in this cohort study (Garcia Rodriguez et al. 1994). In the study of He et al. (2019), gynecomastia has been reported in 0.2% of cases. No hormonal data have been considered in this study. Similarly, in the retrospective study of Daniels and Layer (2003), a total of 127 cases of true gynecomastia have been considered out of 175 male patients, in which 11 patients were treated with lansoprazole and 5 patients had hyperprolactinemia. Retrospective cohort studies have also confined to the male patients only and mostly one PPI molecule has been considered. No other hormonal data have been found until now. In the context of PPIs and hyperprolactinemia, various case reports have been reported. They are summarized in Table 5.

The most prominent feature of patients in all the hyperprolactinemia cases was galactorrhea, which is one of the preliminary symptoms when prolactin level is raised. Most of the patients with hyperprolactinemia were young adults. The time for the onset of symptoms was diverse ranging from few days to a year. Some clinical cases of PPI inducing gynecomastia, impotence, irregular menses, and galactorrhea have also been reported with prolactin levels of normal ranges (Convens et al. 1991; Lindquist and Edwards 1992; Rosenshein et al. 2004; Patrascu et al. 2015). This suggests a highly complex system in

Table 5
Case studies reported for hyperprolactinemia after proton pump inhibitors (PPI) therapy

PPI molecule (dose)	Patient's case	Concomitant drug	Prolactin (ng/ml)	Features	Onset time	Year	Reference
Lansoprazole (15 mg per day)	A 21-year-old male diagnosed with duodenitis	Nil	32.9	Galactorrhea	1 year	2004	Prieto et al. 2004
Omeprazole (20 mg twice daily)	13-year-old girl for dyspeptic symptoms	Nil	288	Galactorrhea	4 days	2010	Jabbar et al. 2010
Esomeprazole (40 mg once daily)	32-year-old female with complaints of post-prandial reflex and epigastric pain	Nil	276	Galactorrhea	7 days	2015	Pipaliya et al. 2016
Esomeprazole (20 mf once daily)	22-year-old female with GERD	Levosulpiride (75 mg once daily)	40	Galactorrhea and breast heaviness	10 days	2017	Rajgadhi et al. 2017
Lansoprazole (15 mg once daily)	17-year-old girl with no specific history consulted the emergency room for bilateral galactorrhea	She was on contraception by intrauterine device with progestin for a year.	92	Galactorrhea	1 week	2017	Duwicquet et al. 2017
Pantoprazole (40 mg daily for 4 weeks then 20 mg daily)	45-year-old male with postprandial retrosternal heartburn at night	Salmeterol	No hormonal profiling	Erectile dysfunction and decrease in libido	5 weeks	2000	Amoros 2000
Rabeprazole (20 mg daily)	35-year-old female with the complaints of diarrhea and dyspepsia	Metronidazole Domperidone Magaldrate and Simethicone	No hormonal profiling	Bilateral Galactorrhea	3 days	2015	Patrascu et al. 2015
Omeprazole (20 mg bid for several years to 40 mg bid since last 3 months)	A 26-years old female presented galactorrhea after her kidney transplant.	Metoclopramide Nortriptyline Tacrolimus Prednisone Amlodipine	140	Galactorrhea	3 months	2020	Prikis et al. 2020

Nil= No other concomitant drug used.

the development of sexual symptoms in both the normal and the excess of prolactin secretion. The reason for PPI-induced sexual disorder with normal prolactin levels could be another endocrine abnormality. However, in all cases, the patient prolactin level has been returned to normal values or has improved or regained the quality after the discontinuation of PPIs.

This literature review has collected the available data for PPIs relation in inducing hyperprolactinemia and associated sexual disturbances in patients to January 2021. In this context, the exact mechanism is not clear; however, there may several hypotheses for PPI's role in inducing changes in the serum prolactin levels. It has been described that PPIs can cross the blood-brain barrier and reach various parts of the brain, thereby a central stimulation of prolactin secretion can be assumed (Ortiz-Guerrero et al. 2018). One mechanism may be the inhibition of the dopamine receptors D2 (DRD2). The involvement of the DRD2 in the induction of hyperprolactinemia has been well studied and documented (Hansen 2006). The PPIs may act as a weak or partial inhibitor of DRD2. The prolactin levels mentioned in the case reports have suggest high strength inhibition of the DRD2 by PPI thereby, a genetic linkage or other unknown reason may be involved to justify the high prolactin secretion. Another possibility might be the interference of PPI with

other dopamine receptors like D1, D3, and D4 that has also a defined role in inducing prolactin secretion and controlling related sexual function (Schnell et al. 1999; Ben-Jonathan and Hugo 2015). Prolactin secretion through the serotonergic pathway could be another possibility of PPI-induced hyperprolactinemia. The significance of the serotonergic receptors and their role in prolactin secretion and adjustment of sexual behavior are also well studied aspects (Hall et al. 1983; Stobie and Shin 1983). The opioid pathway system and its interaction with prolactin secretion may be another alternative mechanism for PPI-induced stimulation as it has been shown by Butelman and Kreek (2001), who have suggested that prolactin release is a valid biomarker for the kappa-opioid receptor agonists to modulate DRD2 like receptor functions. Thus, there are several agents involved in the regulation of prolactin secretion and this regulation is controlled via the delicate balance between stimulation and inhibition of prolactin secretion. Prolactin releasing factors are directly involved in the stimulation of prolactin secretion, while prolactin inhibitory factors, in contrast, are involved directly in the inhibition of prolactin secretion. The PPIs may be assumed to be linked at some level with this balance system of prolactin secretion (Ben-Jonathan 2001).

Apart from the central stimulation, PPIs may have a role in a decreasing prolactin clearance that potentially increases the plasma levels. The use of PPIs is associated with an increased risk of both acute kidney injury and chronic kidney disease (Hart et al. 2019). This could lead to a delay in the prolactin clearance.

Considering the sexual impairment and associated reproductive problems with using PPIs, there may be a decrease in the serum testosterone level, as shown by Coulson et al. (2003), which may be responsible for the sexual impairment and other reproductive complications. In addition, high prolactin may impair the pulsatile release of LH that results in a decrease in testosterone levels (Buvat et al. 1985). Dopamine is the main neurotransmitter involved in the stimulation of sexual behavior in most animals. The study conducted by (Drago et al. 1981) has suggested that increased prolactin release may explain the initial stimulatory effect of hyperprolactinemia on rat sexual functions. The second time, the downregulation of the dopamine receptor, due to excessive stimulation, would explain the subsequent inhibitory effect. In another study, the high prolactin decreased FSH, LH, and estradiol levels leading to an inhibition of the HPG axis. In females, the level of hyperprolactinemia correlated with the degree of suppression of the HPG axis and the hypogonadal states (Smith et al. 2002; Kishimoto et al. 2008).

The findings of Paick et al. (2006) have suggested the direct involvement of prolactin in the sexual activity in men with erectile dysfunction. Moreover, the sexual impairment and other reproductive disorders caused by the PPIs could be a result of indirect actions. The PPIs have been shown to interfere with vitamin B12 and minerals particularly serum magnesium and iron levels resulting in vitamin B12 deficiency and hypomagnesemia (Heidelbaugh 2013; Urbas et al. 2016). Vitamin B12 and hypomagnesemia are some of the profound causes of sexual abnormalities and infertility issues in both men and women (Bennett 2001; Omu et al. 2001; Toprak et al. 2017; Tian 2018).

The PPI safety profile has never been doubted before, but several data, being published in recent years, displayed alarming complications including vitamins and minerals deficiency, risk of fractures, pneumonia, *Clostridium difficile* infection, chronic kidney diseases, and dementia. These emerging data have led to subsequent investigations to assess these potential risks in a patient exposed to a long-term PPI therapy (Eusebi et al. 2017; Jaynes and Kumar 2018). Such type of studies needs to be conducted in a variety of populations to answer a detailed question about the nature of PPI responsible for such health effects as well as the characteristics of the susceptible population.

Conclusion

The available evidence is mainly confined to the short-term PPI therapy that suggests the possibility of PPIs to contribute to the development of various sexual and reproductive disorders including elevation of serum prolactin. However, to draw a clear relation with prolactin levels, the available literature is inadequate. It is evident that PPIs are now used widely for longer duration in both ambulatory and bedridden patients. The hormonal effects and evaluation of the sexual and reproductive problems with long-term use of PPIs have not been studied, but the risk of developing such an effect still exists. Therefore, more comprehensive quality studies are needed to delineate the association of PPIs and prolactin levels in patients using it for a longer duration.

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