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CHAPTER 6

Screening Models For Neuroleptic Drug-Induced Hyperprolactinemia: A Mini-Review

Prashant Tiwari[1,*], Sunil Kumar Dubey[2], Shweta Shrivastava[1] and Pratap Kumar Sahu[3]

[1] *School of Pharmacy, School of Health and Allied Sciences, ARKA JAIN University, Jamshedpur - 832102, India*

[2] *Institute of Pharmacy, Birla Institute of Technology and Science, Pilani, Rajasthan - 333031, India*

[3] *Department of Pharmacology, School of Pharmaceutical Sciences, Siksha O Anusandhan (Deemed to be University), Bhubaneswar - 751029, India*

Abstract: Schizophrenia is a thought disorder characterized by hallucinations, delusions, and disorganized thinking. It affects 1% of the world population. Neuroleptics are the drugs used in the treatment of schizophrenia. Besides extrapyramidal side effects, hyperprolactinemia is a major side effect with neuroleptics like haloperidol, risperidone, *etc*. Hyperprolactinemia results in gynecomastia (male), galactorrhoea, oligomenorrhoea, and amenorrhoea (female) which leads to sexual dysfunction and infertility. Dopamine receptor agonists like cabergoline, bromocriptine, *etc* are used in the treatment of hyperprolactinemia. However, these drugs may aggravate the symptoms of schizophrenia. So, there is a need for the discovery of drugs that can be used against neuroleptic drug-induced hyperprolactinemia. Lack of suitable animal models for the evaluation of new drugs against neuroleptic drug-induced hyperprolactinemia is a major concern. In this chapter, reviews on neuroleptic drug-induced hyperprolactinemia and the available animal models for the screening of hyperprolactinemia are included.

Keywords: Animal Model, Hyperprolactinemia, Neuroleptic, Schizophrenia.

INTRODUCTION

Schizophrenia is a thought disorder characterized by unusual behavior and the inability to understand and accept the truth. **People with schizophrenia also experience other mental disorders** such as anxiety, depression, *etc*. [1 - 4]. Its symptoms include positive symptoms (delusions, hallucinations), negative symptoms (withdrawal from society, flattening of emotional response), cognitive

* **Corresponding author Prashant Tiwari**: School of Pharmacy, School of Health and Allied Sciences, ARKA JAIN University, Jamshedpur, India; Tel: +91-7828865022; E-mail: dr.prashant@arkajainuniversity.ac.in

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impairments, and affective dysregulation [5 - 7]. The prevalence of schizophrenia is about 1% of the world population. Americans show a high prevalence of around 1.2% [8].

The drugs used to control schizophrenia are antipsychotics or neuroleptics or major tranquilizers [9]. Positive symptoms respond well to conventional antipsychotic medications. However, negative symptoms and cognitive impairments show a negligible response towards antipsychotics [5 - 7]. First-generation antipsychotics are also known as typical antipsychotics. They came into insight and use in the 1950s. Few examples are chlorpromazine, haloperidol, *etc*. They act by blocking dopamine (D2) receptors. Second-generation drugs are known as atypical antipsychotics. The first atypical antipsychotic, clozapine, was discovered in the 1960s and introduced clinically in the 1970s [10]. They act by blocking serotonin receptors in addition to dopamine receptors [11].

Antipsychotic drugs are associated with a range of side effects in most patients. The most troublesome side effects are neurologically known as extrapyramidal side effects (EPS). The typical antipsychotics are more associated with EPS which includes drug-induced Parkinsonism, akathisia, and tardive dyskinesia, *etc*. The atypical antipsychotics show fewer EPS while producing an increased risk of agranulocytosis, seizures, and weight gain1 [2 - 14].

However, both typical, as well as atypical antipsychotics, increases prolactin levels by 10-fold or more than pretreatment values. Approximately 60% of women and 40% of men treated with a prolactin-raising antipsychotic had a prolactin level above the upper limit of the normal range. Hyperprolactinemia results in gynecomastia (male), galactorrhoea, oligomenorrhoea, and amenorrhoea (female) which leads to sexual dysfunction and infertility [15 - 17].

PROLACTIN

Prolactin is a lactogenic hormone secreted from the pituitary gland in the brain. The main action of prolactin is to maintain lactation through which there is a stimulation of the mammary gland to secrete milk. When prolactin serum concentration increased during pregnancy causes enlargement of mammary glands, then milk production starts. It happens because of a decrease in the progesterone level during pregnancy [18]. Prolactin has a key role in the regulation of the immune system, pancreatic development, affects adipose tissue, and the body metabolism [19]. The secretion of the prolactin hormone is managed by endocrine neurons at the base of the forebrain. Prolactin is regulated by dopamine. Elevated serum prolactin levels can cause an irregular menstrual cycle and galactorrhoea in females [20, 21].

Prolactin Receptor

Prolactin is a member of class 1 cytokine receptors. Prolactin receptor has a wide tissue distribution including mammary glands, uterus, placenta, adrenal gland, gonads as well as liver, kidney, heart, lung, skin, lymphoid cells, and brain. Prolactin receptor is a tyrosine kinase linked receptor. Prolactin acts as a cytokine. Different actions have been reported for prolactin in various tissues. Human prolactin is present on chromosome 5 and consists of nine coding exons and two noncoding exons [22]. However, regulation of prolactin levels occurs at transcription and post-transcriptional levels. It has come into notice that prolactin degradation may be helpful for the inhibition of breast cell transformation [23, 24]. Further, binding of prolactin receptor may cause dimerization with [BPB1] another prolactin receptor which leads to activate non-receptor tyrosine kinase that recruits the Janus kinase, single transducer and activators of transcription proteins which ultimately activates mitogen-activated protein kinase (MAPK) and Src kinase. This results in the activation of Janus kinase 2, a tyrosine kinase that initiates the JAK-STAT pathway which ultimately activates mitogen-activated protein kinase (MAPK) and Src kinase [25 - 27].

Normal Prolactin Level

The prolactin level is measured in nanograms per milliliter (ng/mL). Normal levels in human beings are: females- less than 25 ng/mL, males- less than 17 ng/mL [28]. Serum prolactin level is sometimes given as nanomole per liter [29]. The normal serum prolactin levels in men and women vary between <20 µg/L and <25 µg/L. The normal plasma level in male rats are 8 to 33 ng/mL and female rats is 43 to 977 ng/mL [30].

HYPERPROLACTINEMIA

Hyperprolactinemia is a condition of elevated serum prolactin [31]. Pituitary Society (PS) suggested that PRL values up to 100 mg/L (2000 mU/L) may be due to antipsychotic drugs, whereas macroprolactinomas are typically associated with levels >25 mg/L (>5000 mg/L) [32]. Moreover, PRL level in non-functioning pituitary adenomas is almost always <100 mg/L (<2000 mg/L) [29]. Pituitary tumors account for 50% of cases of hyperprolactinemia which seeks its proper investigation in the absence of drug-induced hyperprolactinemia [33, 34].

Drug-Induced Hyperprolactinemia

Neuroleptic drug use is a common and severe cause of hyperprolactinemia. Disturbance in prolactin levels is one of the most common endocrine disorders [35]. However, some of the pathological causes such as prolactin associated

pituitary tumors is accountable for elevated serum prolactin levels. There are a number of antipsychotics drugs like alprazolam, moclobemide, amitriptyline, haloperidol, Compazine, risperidone, chlorpromazine, perphenazine, sulpiride, metoclopramide, *etc* is responsible for increased serum prolactin level [36]. Drugs that are the most common cause of hyperprolactinemia are listed in Table (**1** and **2**). When serum prolactin levels elevated, there is an immediate need to discontinue the treatment until the prolactin level return to its normal value [37, 38]. Hyperprolactinemia causes inhibition of the hypothalamus secretion of gonadotropin-releasing hormone which in turn results in the release of gonads sex hormone by inhibiting the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [39 - 43].

Table 1. Causative agents for hyperprolactinemia[15].

Antipsychotics	Typical	Atypical
	Haloperidol Chlorpromazine, Thioridazine, Thiothixene	Risperidone, Amisulpride Molindone, Zotepine
	Typical Antipsychotics Phenothiazines: Chlorpromazine, Fluphenazine, Thioridazine Butyrophenones: Haloperidol, Droperidol, Penfluridol, Trifluperidol. Thioxanthene: Flupenthixol, Chlorprothixene, Cyclopethanol, Thiothixene **Atypical Antipsychotics** Dibenzothiazepines:Clozapine, Olanzapine Dibenzoxazepine: Loxapine Dihydroindolone:Molindone Diphenyl Butylpyridine:Pimozide, Penfluridol Benzamide:Sulpiride Benzisoxazole:Risperidone	

Clinical Hyperprolactinemia

Hyperprolactinemia is reported in schizophrenic patients taking neuroleptic drugs. Risperidone 10 mg/day for a period of 8 weeks showed a significant increase in serum prolactin levels [48, 49]. Risperidone and clozapine-induced hyperprolactinemia in outpatients with schizophrenia [50]. Sulpiride 150mg/day for 10 days sulpiride causes hyperprolactinemia. Amisulpride (50–800 mg/day for 13to 50 days) was found to significantly increase plasma prolactin [51]. Similar results were observed in Korean patients when treated with 300 mg/day of amisulpride [52]. Levosulpiride also develops serum prolactin levels of > 200 ng/mL [53]. Patients receiving haloperidol at a dose of 10-20 mg for a period of 60 weeks showed a significant increase in prolactin concentration (30 and 50 ng/ml).In another study, Olanzapine moderately elevates PRL *i.e.* 1-4 ng/ml, haloperidol significantly increased PRL *i.e.* 17 ng/ml whereas, risperidone

strongly increase PRL *i.e.* 45-80 ng/ml [54].

Table 2. Causes of Hyperprolactinemia [44 - 47].

Physiologic hypersecretion	Coitus, Pregnancy, Lactation, Chest wall stimulation Sleep, Stress, Lunch or Dinner, Lactation, and Mammary stimulus.
Pathological hypersecretion	Infiltrative disorders, Non-functioning pituitary tumors, Empty sella syndrome, Hypothyroidism, and during renal failure.
Pituitary hypersecretion	Prolactinoma, Acromegaly and Laron syndrome.
Pituitary diseases	Functioning adenomas, Non-functioning adenomas, and Abnormal stalk.
Hypothalamic-pituitary stalk damage	Craniopharyngioma, Irradiation, Inflammation, Trauma and Suprasellar surgery.
Systemic disorders	Hypothyroidism, Cranial radiation.

Treatment of Hyperprolactinemia

Dopamine agonist like bromocriptine is the choice of treatment for hyperprolactinemia. These drugs decrease serum prolactin concentrations and decrease the size of most lactotroph adenomas [55]. Generally, cabergoline is the drug of the second choice but in some, cases cabergoline is the unlike preferable drug due to its safety and efficacy than bromocriptine (cause nausea like cabergoline) [56 - 61].

Quinagolide (CV 205-502) is a non-ergot dopamine agonist [62 - 64]. Quinagolide works in a similar way towards decreasing the serum prolactin level and adenoma size as cabergoline [64]. The development of key side effects in patients such as postural hypotension, nausea, mental fogginess which are witnessed with the use of dopamine agonist drug can be prevented by the use of its small dose of haloperidol (1, 2, and 5 mg/kg/day)and sulpiride (20 and 40 mg/kg/day) and administering it with food or during bedtime [65, 66].

Neuroleptic drug-induced hyperprolactinemia can also be countered by use of dopamine agonists. However, this may lead to compromising the efficacy of neuroleptics because of the role of dopamine in the pathophysiology of schizophrenia [67]. So, there is a need to develop drugs for neuroleptic drug-induced hyperprolactinemia which should not affect dopaminergic function as a neurotransmitters released by neuronal cells to send a signals to other nerve cells.The brain includes several distinct dopamine pathways, one of which plays a major role in the motivational component of reward-motivated behavior. Screening with animal models is the first step in the drug discovery process [68]. As per available literature few animal models are available to evaluate

hyperprolactinemia produced by neuroleptic drugs. These animal models have many limitations.

There is a contradiction about specific dose, timing, duration, and selection of animals either male or female. Few available preclinical models of drug-induced hyperprolactinemia are discussed here.

PRE-CLINICAL SCREENING MODELS FOR HYPERPROLACTINEMIA

Most animal models of hyperprolactinemia use antipsychotic drugs. Hyperprolactinemia can also be induced by metoclopramide and prolactin. The various pre-clinical animal models for screening of hyperprolactinemia have been tabulated in brief in Table **3**.

Prolactin Model

Rehman *et al*, injected 5 mg rat prolactin subcutaneously (SQ) daily for 1 week in two divided doses for induction of hyperprolactinemia and they found an elevated level of prolactin (500 ng/ml) in the treated group as compared to control (20 ng/ml) [69].

Haloperidol (HPL) Model

Savita *et al* showed that intraperitoneal administration of haloperidol for 16 days at doses level (1, 2 and 5 mg/kg/day) significantly produced hyperprolactinemia in female albino rats. The drugs were administered once daily. On the 17th day, all animals were sacrificed and blood was drawn from the tail vein for measurement of PRL [70, 71]. This study has a limitation that only female rats were used and they have not specified the optimal dose level for induction of hyperprolactinemia caused by haloperidol. Again, out of the three doses, they should have suggested (5 mg/kg/day) dose. We have induced hyperprolactinemia using haloperidol 5 mg/kg/day for 16 days and successfully evaluated effect of *Butea monosperma*(200 mg/kg/day/p.o. and 400 mg/kg/day/p.o.) and *Tinospora cordifolia*(200 mg/kg/day/p.o. and 400 mg/kg/day/p.o.) on hyperprolactinemia [72, 73].

Metoclopramide (MCP) Model

Metoclopramide (MCP) (24 mg/kg thrice daily for 5 days, 75 mg/kg twice daily for 15 days and 150 mg/kg daily for 10 days i.p.) can be used as a screening model to induce hyperprolactinemia [55, 74]. Several studies used different doses and different durations. The albino rats were given intraperitoneally MCP 150 mg/kg daily, for 10 days. Thereafter at the day 14, blood was drawn from the tail vein for the measurement of PRL. It was observed that at least 80% elevation of

serum PRL concentrations was found in the drug-treated group as compared to the control group [75]. Intraperitoneal injection of MCP (75 mg/kg, twice daily) was given for 15 days to albino rats, and on the 15th day after the treatment, the blood sample was collected from the orbit vein. It was noticed that there was a significant increase in serum PRL levels [76]. Hyperprolactinemia was induced after the daily administration of metoclopramide dihydrochloride (24 mg/kg body wt., 3 times a day) for 5 days. The levels of the serum prolactin were significantly greater ($p<0.01$) than normal animals. In addition, for the evaluation of serum prolactin level, the albino mice were used for the study [77]. One study also used estrogen and progesterone in addition to MCP to induce hyperprolactinemia. Metoclopramide hydrochloride injection (50 mg/kg) was administered for 5 days. After that estradiol was injected for twenty-five days then progesterone was administered for five days and at the end, the PRL in Wistar rats' serum were measured and there was hyperprolactinemia [78].

Sulpiride Model

Administration of sulpiride at a dose of 20 mg/kg intraperitoneally for a period of 28 days in rats showed a remarkable rise in PRL [79]. Similarly, administration of sulpiride daily intraperitoneally at a dose of 40 mg/kg in male Wistar rats for 30 and 60 days significantly increases plasma PRL levels [80]. We have induced hyperprolactinemia using sulpiride 20 mg/kg/day for 28 days and successfully evaluated effect of the *Butea monosperma* (200 mg/kg/day/p.o. and 400 mg/kg/day/p.o.) and *Tinospora cordifolia* (200 mg/kg/day/p.o. and 400 mg/kg/day/p.o.) on hyperprolactinemia [72, 73].

MANAGEMENT OF HYPERPROLACTINEMIA

Dopamine agonist like bromocriptine is the choice of treatment for hyperprolactinemia. These drugs decrease serum prolactin concentrations and decrease the size of most lactotroph adenomas [81]. Cabergoline is the drug of the first choice as it is safe and efficacious. Bromocriptine is the drug of second choice [82 - 86]. Bromocriptine is an ergot derivative. It is more likely to cause nausea than cabergoline [87].

Quinagolide (CV 205-502) is a non-ergot dopamine agonist [88, 89]. Quinagolide works in a similar way towards decreasing the serum prolactin level and adenoma size as cabergoline [90]. The development of key side effects in patients such as postural hypotension, nausea, mental fogginess which are witnessed with the use of dopamine agonist drugs can be prevented by the use of its small dose and administering it with food or during bedtime [91, 92].

Neuroleptic drug-induced hyperprolactinemia can also be countered by use of

dopamine agonists. However, this may lead to compromising the efficacy of neuroleptics because of the impact of dopamine in the pathophysiology of schizophrenia [93]. So, there is a need to develop drugs for neuroleptic drug-induced hyperprolactinemia which should not affect dopaminergic function. Screening with animal models is the first step in the drug discovery process [94].

Table 3. Animal models for pre-clinical screening study [69 - 80].

Animal Model	Drug	Dose	Rout of Drug Administration	Duration
Albino Rats	Prolactin	5 mg/kg/day	Subcutaneous (sq.)	1 week
Albino Rats	Haloperidol	1, 2 & 5 mg/kg/day	Intraperitonial (i.p)	16 days
Albino Mice	Metoclopramide	24 mg/kg	Intraperitonial (i.p)	Thrice daily for 5 days
Albino Rats	Metoclopramide	75 mg/kg	Intraperitonial (i.p)	Twice daily for 15 days
Albino Rats	Metoclopramide	150 mg/kg/day	Intraperitonial (i.p)	10 days
Wistar rats	Metoclopramide	50 mg/kg/day	Intraperitonial (i.p)	5 days
Wistar rats	Sulpiride	20, 40 mg/kg/day	Intraperitonial (i.p)	28 days
Wistar rats	Sulpiride	20, 40 mg/kg/day	Intraperitonial (i.p)	30 & 60 days

Surgical Treatment of Prolactin

There are limited dopaminergic drugs available to subside the adverse event of neuroleptic drugs. Currently, dopaminergic drugs are the choice of treatment for the symptoms of prolactin, but presently hyperprolactinemic symptoms can also be reduced by the surgery. However, the success rate of clinical surgery is very poor and even sometimes very critical to operating the prolactinoma patients. Moreover, some of the studies revealed that now a days hyperprolactinemia may occur within four years after the surgery. One of the studies suggested that transsphenoidal surgery (TS) may be proposed as conclusive therapy. This therapy may especially give patients with intrasellar tumors caused by prolactinoma at the pituitary gland. Transsphenoidal surgery subsides the reverse clinical symptoms, reduce high prolactin level, and normalize tumor size in patients with pituitary prolactinoma [95].

In addition, about 70 prolactinaemic patients with pituitary prolactinoma were diagnosed, but the success rate of the surgery depends upon the diameter, size of the adenoma, and prolactin level in blood serum. However, assessment of these two parameters may give a comprehensive conclusion as well as the prediction of endocrine results [96]. Another study exhibited that around 184 causes of male

prolactinoma were examined and the following parameters were observed such as hormone levels, imaging features, clinical manifestations (dysfunction, headache, and visual disturbance), pathology results, preoperative treatments, surgical outcomes, *etc*. Bromocriptine sensitivity tests were conducted for all patients. Finding of the study (decreased prolactin level and increased dopamine level)indicate that in male prolactinoma patients, pituitary diameter and increased prolactin levels were reduced significantly [97]. Considering the facts, there are limited surgical tools available to subside the prolactinoma associated with hyperprolactinemia. Hence, there is a need to develop more precise surgical gears and other alternatives to overcome the adverse events associated with the neuroleptic drug.

Shortcomings in the Management of Hyperprolactinemia

The treatment outcome desired in hyperprolactinemia is to reduce the prolactin level. There is also a need to reduce tumor mass and prevent further disease proliferation. Dopamine agonists play a chief role in the management of hyperprolactinemia. The drugs acting on the dopamine receptor (D_2) in the pituitary gland (lactotroph cells) leads to downregulating the release of prolactin level [98, 99]. Dopamine agonists including apomorphine, pergolide, ropinirole, bromocriptine, cabergoline,quinagolide *etc* are used as a first-line therapy with keen objective to reduce hyperprolactinemia [100].

In pregnancy and the hyperprolactinaemic woman, dopaminergic agonist therapy should be withdrawn to avoid any possible teratogenic risk. Bromocriptine has been found to be safer in pregnancy. However, cabergoline and quinagolide are still limited use due to their adverse effect profile [101 - 103]. Further, in case of hyperprolactinemia, women's are intolerant to dopamine agonist due to hormonal and pregnancy associated side effect rather oestrogen-replacement therapy may be given to prevent further osteoporosis [104]. There is a need of regular management of prolactin level who use oral contraceptives [105]. However, in most cases olanzapine may be given because of lesser side effect on prolactin secretion [106, 107].

Ideal Drug for Management of Hyperprolactinemic

Among the existing drugs bromocriptine is used to reduce the prolactin level in 80-90% of patient with hyperprolactinemia [108 - 110]. However, about 60% of patients develop severe adverse events which included abdominal pain, dyspepsia, dizziness, headache and postural hypotension which limits their use [111]. Various studies have been done which suggested that bromocriptine in long term use causes intolerance and resistance [112, 113]. Cabergoline is also a preferable choice to reduce the hyperprolactinemia because of its better tolerability than

bromocriptine [114, 115]. Presently quinagolide is alternative drug because of its effectiveness and safe therapeutic potential.

Resistance is an abbreviated term related to treatment failure during the continuation of treatment. Nonetheless, resistance to the dopamine receptor results in the failure of the reduction of the prolactin level [116]. So, in this connection, a recent study revealed that nearly 20% hyperprolactinemic patients and 30% macroprolactinoma patients treated with bromocriptine failed to reduce the prolactin level whereas 10%-20% of patients treated with cabergoline were better in condition [117, 118]. Because of the limited therapeutic utility of dopamine agonists, there is a need to look forward to the alternate therapy to minimize the side effect of neuroleptic drugs. So, the medicinal plants such as *B. monosperma* and *T. cordifolia* may be a suitable alternative in the management of hyperprolactinemia.

CONCLUSION

Hyperprolactinemia is a major side effect associated with neuroleptic drugs used in the treatment of schizophrenia. Use of dopaminergic agonists for the treatment of neuroleptic drug-induced hyperprolactinemia may compromise the efficacy of neuroleptic drugs. So, there is a need to develop drugs for neuroleptic drug-induced hyperprolactinemia which should not affect dopaminergic function. Screening with animal models is the first step in the drug discovery process. Lack of suitable animal models for evaluation of neuroleptic drug-induced hyperprolactinemia may be one of the reasons for the non-availability of suitable drugs.

Available animal models use prolactin (5 mg/kg/day for 1 week), haloperidol (1, 2 & 5 mg/kg/day for 16 days), metoclopramide (24 mg/kg for five days, 75 mg/kg for 15 days, 150 mg/kg/day for 10 days and 50 mg/kg/day for 5 days) and sulpiride (20, 40 mg/kg/day for 28 days and 20, 40 mg/kg/day for 30 and 60 days). These animal models are associated with ambiguity with respect to the dose of chemicals, sex of animals, *etc*. So, we suggest that there is a need to develop new models or validate available preclinical models to counter the neuroleptic drug-induced hyperprolactinemia. These animal models may also encourage research on other complications associated with antipsychotic drugs.

ABBREVIATIONS

(EPS) Extrapyramidal side effects

(MAPK) Mitogen-activated protein kinase

(PRL) Prolactin

(FSH) Follicle-stimulating hormone

(LH) Luteinizing hormone

(HPL) Haloperidol

(MCP) Metoclopramide

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors confirm that the contents of this chapter have no conflict of interest.

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