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Systematic Review on Atypical Antipsychotic Drugs Induced Hyperprolactinemia and Its Clinical Approach in Special Conditions

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ABSTRACT:
A mental illness known as psychosis is typified by a detachment from reality. Psychosis is a symptom of a number of underlying disorders, such as schizophrenia, bipolar disorder, severe depression, or substance misuse, rather than a disorder in and of itself. Antipsychotic drugs are classified into two types, like typical antipsychotic drug (older generation) and atypical antipsychotic drug (newer generation). Commonly used to treat mental illnesses such schizophrenia, bipolar disorder, and major depressive disorder are atypical antipsychotic medications (AAPs).Hyperprolactinemia is a serious side effect, despite the fact that these drugs are usually chosen because they are less likely to produce extrapyramidal side effects than conventional antipsychotics.When dopamine D2 receptors in the tuberoinfundibular pathway are blocked, the usual inhibitory control of prolactin release is disrupted, leading to elevated prolactin levels. Hyperprolactinemia can lead to a variety of adverse clinical consequences, particularly in vulnerable populations, such as pregnant women, individuals with hypothyroidism, and those at risk of osteoporosis.In patients with hypothyroidism, AAP-induced hyperprolactinemia is further compounded due to thyroid hormone deficiency, which can independently raise prolactin levels. Addressing both thyroid dysfunction and hyperprolactinemia is key to reducing symptoms and maintaining overall health. Increased prolactin levels can hasten the decrease of bone mineral density in osteoporosis patients, increasing their risk of fractures. For postmenopausal women, who are already at a higher risk of osteoporosis, this is especially important. In pregnancy, hyperprolactinemia poses challenges, including impaired fertility and potential negative outcomes for both mother and foetus. Monitoring prolactin levels in pregnant women is crucial, and strategies like dose adjustments or switching to antipsychotics with lower prolactin-elevating potential are recommended. The purpose of this systematic review is to determine the prevalence of hyperprolactinemia brought on by AAP and to analyse clinical care strategies for these unique diseases.

KEY WORDS:
Atypical antipsychotic drugs, dopamine blockers, hyperprolactinemia, pregnancy, osteoporosis, and hypothyroidism.

I. INTRODUCTION:

Since the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) was published in 1980, the term has been used to describe a significant impairment in reality testing, or a breakdown in the capacity to distinguish between the internal reality of the mind and the external reality of the surroundings [1]. The prevalence of psychotic disease varies between urban and rural populations [2]. Neurologic and psychiatric practice places a high priority on the evaluation and treatment of psychosis, as it is a common and disabling symptom of many medical, neurological, psychiatric, and neurodevelopmental disorders [3]. Our understanding of psychosis has been influenced by traditions in the study of mental illnesses during the last 170 years. The main clinical hallmarks are delusions, hallucinations, and thinking problems, among other symptoms [4].

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ANTI PSYCHOTIC DRUGS:

Earlier mental patients who would have been institutionalized are now able to function in the community thanks to antipsychotic medications, commonly referred to as neuroleptics [5]. Blockade of either the dopamine or serotonin receptor is how antipsychotic medications, a pharmacologically and structurally heterogeneous class of medications, produce their antipsychotic effects [6]. First- and second-generation antipsychotic medications are arbitrary classifications [7].

TYPICAL ANTIPSYCHOTIC DRUGS:

The first antipsychotic drug, chlorpromazine, was discovered in 1951.Chlorpromazine is an example of a first-generation antipsychotic, also referred to as a typical antipsychotic or neuroleptic [8]. They include thioxanthenes (thiothixene, chlorprothixene), dibenzoxazepines (loxapine), dihydroindoles (molindone), butyrophenones (haloperidol), and diphenylbutylpiperidines (pimozide). Trifluoperazine, perphenazine, prochlorperazine, acetophenazine, triflupromazine, and mesoridazine are a few examples of phenothiazines [9]. Dopaminergic neurotransmission is significantly disrupted by conventional antipsychotic medications, particularly those with strong potencies that have high avidity and affinity for D2 receptors (such as fluphenazine and haloperidol) [10]. Regretfully, a number of upsetting acute and delayed movement problems, commonly referred to as "extrapyramidal symptoms" (EPS), can be brought on by these medications [11]. Because extrapyramidal symptoms are severe, common, and cause complications, they are important adverse effects of antipsychotic medication [12]. Even at moderate dosages, it carries a comparatively high risk of extrapyramidal effects [10]. It was initially reported in 1952 following Parkinson disease-like symptoms brought on by chlorpromazine [13]. Treating extrapyramidal disorders is linked to the use of antipsychotic medications. These comprise akathisia, akinesia, dyskinesia, dystonic responses, and drug-induced parkinsonism [14].

ATYPICAL ANTIPSYCHOTIC DRUG:

Since the mid-1990s, atypical antipsychotics have been marketed [15]. Since their introduction in the 1990s, second-generation atypical antipsychotics have been the accepted treatment for schizophrenia. It is thought that atypical antipsychotics are less likely to produce extrapyramidal symptoms (EPS) than their first-generation rivals [16].Compared to conventional dopamine antagonists, atypical antipsychotics are less likely to result in aberrant movement. In addition to being dopamine (D) receptor antagonists, they are also rather potent serotonin (5-HT) receptor antagonists [17]. Atypical antipsychotics cause fewer movement abnormalities than traditional dopamine antagonists [18]. The newest class of antipsychotics, referred to as third-generation antipsychotics, are categorized based on the way human bodies' dopamine receptors work. The third generation of antagonists, as opposed to the first and second generations, act as a partial agonist at the D2 receptors [19].

SEVERAL ATYPICAL DRUGS:

1) RISPERIDONE
2) OLANZAPINE
3) QUETIAPINE
4) ZIPRASIDONE
5) ARIPIPRAZOLE
6) PALIPERIDONE
7) ASENAPINE
8) LURASIDONE
9) ILOPERIDONE
10) CARIPRAZINE
11) BREXPIPRAZOLE
12) CLOZAPINE

RISPERIDONE:

Following its introduction as the first novel second-generation antipsychotic in the 1990s, risperidone gained widespread acceptance [20]. Risperidone, a new antipsychotic medication derived from benzisoxazole, has a high affinity for histamine H1 receptors, α1- and α2-adrenergic receptors, and a significant binding affinity for serotonin 5-HT2 receptors [21]. Risperidone has been a generally successful treatment for psychoses, leading to a widespread recommendation for the medication as a first-line option [22]. Risperidone has an absolute oral bioavailability of around 70%. It is quickly absorbed after oral treatment, reaching its peak plasma level around an hour later [23]. During its prolonged metabolism, namely hydroxylation and oxidative N-de-alkylation, risperidone exhibits comparable pharmacological action to its primary metabolite, 9-hydroxy-risperidone [24]. More extrapyramidal side effects and a definite rise in prolactin production are observed with risperidone compared to most other SGAs [25]. When given risperidone, a much lower percentage of patients used antiparkinsonian medications [26].

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OLANZAPINE:

In September 1996, the US Food and Drug Administration (FDA) first approved the atypical antipsychotic olanzapine for the treatment of schizophrenia [27]. In vitro, the receptor affinity profile of olanzapine, a thienobenzodiazepine derivative, is similar to that of clozapine [28]. In vivo, olanzapine is a potent antagonist at DA and 5-HT receptors but weaker at α-adrenergic and muscarinic receptors [29]. The clinical pharmacokinetic profile of olanzapine, which has a dosage range of 5–10 mg, a target dose of 10 mg/day, and a maximum dose of 20 mg/day, supported oral dosing once day [27].Olanzapine's main disadvantage, aside from clozapine, was that it increased weight gain and associated metabolic problems more than any other second-generation antipsychotic drug[30]. Serum prolactin levels were found to drop over the first two months of olanzapine treatment and to slightly rise towards the end of the third month [31].

QUETIAPINE:

In 1985, researchers at AstraZeneca (then Zeneca) Pharmaceuticals created quetiapine [32]. The dibenzothiazepine derivative quetiapine is structurally similar to clozapine and olanzapine [33]. It has a moderate affinity for α1- and α2-adrenergic receptors, a poor affinity for muscarinergic M1 receptors, and a considerable attraction to brain serotonergic (5HT2A), histaminergic (H1), and dopaminergic D1 and D2 receptors [1]. Quetiapine was rapidly absorbed when given orally in human pharmacokinetic studies, and it took an average of one to two hours to reach the maximum plasma concentration that was measured [34]. With a mean terminal half-life of seven hours, quetiapine displays linear pharmacokinetics in humans [35]. Because of its adverse effect profile, quetiapine is a helpful drug for patient populations that are more susceptible to the side effects of drugs [36]. As a result, physicians can raise the dosage of quetiapine with confidence without running the risk of hyperprolactinemia, or EPS [37]. possible advantages of quetiapine for the management of substance dependency disorder [38].

ZIPRASIDONE:

In the US, Europe, and, more recently, Canada, the atypical antipsychotic ziprasidone has been authorized for the treatment of psychotic illnesses [39]. The benzisothiazolylpiperazine molecule ziprasidone was created by combining tiospirone, an antipsychotic that shares chemical similarities with others. Ziprasidone binds to serotonin (5-HT2A) receptors more strongly than dopamine (D2) receptors, just like other atypical antipsychotics [40]. Comparing ziprasidone to amisulpride, olanzapine, and risperidone, it may be a little less effective antipsychotic medication [41]. When treating positive, negative, and affective symptoms in schizoaffective disorder and schizophrenia, ziprasidone is useful. Due to its safety profile, ziprasidone has several advantages. It is not linked to any anticholinergic adverse effects, little to no influence on prolactin levels, or metabolic side effects that are clinically relevant [42]. There is little chance that ziprasidone will make you gain weight. A novel therapy option with a constrained adverse effect profile is ziprasidone [43].

ARIPIPRAZOLE:

Aripiprazole is a novel therapy tool for serious psychiatric illnesses. APD, or third-generation antipsychotic drugs, are categorized due to their unique pharmacological characteristics [44]. A derivative of quinolinone, aripiprazole is the first medication in a novel class of atypical antipsychotics [45]. Aripiprazole is a unique atypical antipsychotic that combines strong antagonism at 5HT2A receptors with moderate agonist action at D2 and 5HT1A receptors. It has a distinct receptor binding profile [46]. The highest plasma concentrations of Aripiprazole occur three to five hours after dosing, indicating good absorption. Aripiprazole's mean elimination half-life is around 75 hours,however, the half-life of its active metabolite is 94 hours [47].Although akathisia was the most common extrapyramidal symptom, the incidence was low [48]. Aripiprazole may also increase prolactin levels at lower dosages by functioning as a functional antagonist [49].

PALIPERIDONE:

Paliperidone, a 9-hydroxy metabolite of risperidone, has a somewhat altered receptor profile but a pharmacokinetic profile that is very distinct from risperidone[50]. The recently developed depot formulation of paliperidone is called paliperidone palmitate [51]. Paliperidone received approval in the United States in 2006 to treat schizophrenia and in 2009 to treat schizoaffective disorder. Paliperidone interacts with dopamine D2 and serotonin 5-HT2A receptors, just like other second-generation antipsychotics[52]. These comprise dyslipidaemia, hyperprolactemia, hyperglycemia, orthostatic hypotension, leucopenia, seizures, weight gain, cerebrovascular illness (in older individuals), QT prolongation, extrapyramal symptoms, neuroleptic malignant syndrome, and dyskinesia[53].

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Paliperidone palmitate is a long-acting injectable antipsychotic drug[54]. It performed as well as, if not better than, other long-acting drugs like risperidone or olanzapine in patients with schizophrenia[50].

ASENAPINE:

The tertiary amine asenapine is a member of the dibenzo-oxepinopyrroles class [55]. Second-generation (atypical) antipsychotics like asenapine are not sold as swallowable pills; instead, they are sold as sublingual and transdermal formulations[56]. Asenapine is an atypical antipsychotic that is approved for the treatment of schizophrenia in the United States, Japan, and other nations, but not in the European Union. It is also referred to as Saphris® or Sycrest®.It is taken sublingually twice daily [57]. Asenapine really exhibits, like other SGAs, a low affinity for the type 2 (D2) dopamine receptor and a high affinity for the serotonin (5HT) receptor of type 2A (5HT2A)[58]. In the therapeutic dosage range, asenapine exhibits no muscarinic receptor activation. As a result, asenapine does not result in the metabolic syndrome or other undesirable effects related to anticholinergic drugs, such as olanzapine and clozapine [59]. Asenapine was found to result in more extrapyramidal symptoms compared to olanzapine, but it also caused less weight gain or elevations in triglycerides that were clinically relevant [60]. Likewise, asenapine had negligible effects on metabolic indices and prolactin levels[61]. Asenapine side effects that are most commonly reported include somnolence, akathisia, and oral hypoesthesia [57]. When applied sublingually, bioavailability is 35%; however, if consumed, it is less than 2% [62]. In Japan and the US, asenapine is the antipsychotic for schizophrenia, while blonanserin is the antipsychotic accessible in transdermal formulation globally [63].

LURASIDONE;

Japan's Dainippon Sumitomo Pharma Corporation created the innovative benzisothiazole medication lurasidone, a second-generation antipsychotic [64]. Lurasidone, like other atypical antipsychotics, is antagonistic to dopamine D2 and serotonin 5-HT2A. Its affinity for cholinergic M1 receptors, α1-adrenergic receptors, and histamine H1 receptors is modest, nevertheless. Additionally, it is a potent 5-HT7 antagonist, which may have an impact on mood and memory[65]. Lurasidone does not bind to muscarinic M1 receptors or histamine H1[66]. The incidence of adverse effects related to metabolism is lower with lurasidone than with other atypical antipsychotics [65]. The most often reported side effect associated with lurasidone was akathisia [67].Metabolic abnormalities,low risk of weight gain, QT interval prolongation, and hyperprolactinemia was linked to lurasidone [68]. It is only available in oral form, works best when taken once a day (40–160 mg), and food has an impact on how well it is absorbed [69]. Lurasidone, a second-generation antipsychotic, is licensed for the treatment of schizophrenia at a starting dose of 40 mg per day, given once daily with food (≥ 350 calories). The recommended maximum dosage is 80 milligrams per day[70].

ILOPERIDONE;

In early 2010, iloperidone was introduced to the market andwas just authorized in the United States to treat schizophrenia. Currently, it is being considered for approval in Europe [71]. Risperidone and iloperidone share structural similarities [72]. Iloperidone, a benzisoxazole phenylethanone, binds to serotonin-2a receptors more strongly than dopamine-2 receptors[73]. Iloperidone's most frequent side effects included weight gain, tachycardia, dizziness, dry mouth, exhaustion, nasal congestion, and orthostatic hypotension [74]. Gaining weight is feasible at any dosage [73]. Little prolactin rise and no changes in cholesterol or glucose levels that are medically significant [75]. During the first week of treatment, orthostatic hypotension was frequently observed as a side effect. For individuals whose adherence is limited by these adverse consequences,it is a desirable option due to its favorable EPS and akathisia profile [76]. Iloperidone has a 96% bioavailability and is well absorbed when taken orally, according to pharmacokinetic research [74].

CARIPRAZINE;

The Food and Drug Administration approved the novel antipsychotic cariprazine (Vraylar®), which is produced by Forest Laboratories in New York, NY, in September 2015 [77]. A new kind of antipsychotic medication called capriprazine (RGH-188) partially antagonizes 5HT2B receptors, partially agonizes 5HT1A receptors, and partially agonizes D3 receptor-preferential binding of dopamine D2/D3 receptors[78].A slightly higher mean body weight and a statistically significant higher risk of EPS-related adverse events were linked to cariprazine. On the prolactin level or cardiovascular measures, there were no statistically significant impacts [79]. Medication hypersensitivity reactions are the only circumstances in which capiprazine should not be

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used. As a monotherapy alone, capriprazine is recommended for the management of acute manic or mixed episodes associated with bipolar 1 disease and schizophrenia[80].

BREXPIPRAZOLE;

Brexpiprazole, also referred to Lu-AF41156, also known as OPC-34712, is a recently created molecular molecule that shares structural and chemical similarities with aripiprazole [81]. The drug brexpiprazole was approved in 2015 [82]. The oral atypical antipsychotic drug brexpiprazole (Rxulti®, Rexulti®) is authorized for the management of adult patients with schizophrenia in the USA, the EU, and a few other countries,such as Japan [83]. The neuroscience-based nomenclature classifies brexpiprazole as a receptor partial agonist (D2, D3, 5-HT1A) and a receptor antagonist (5-HT2A/B, α1B/α2C)[84].In particular, this new medication may be more appropriate for long-term usage because of its lower risk of weight gain, hyperprolactinemia, psychosis, sleeplessness, akathisia,restlessness and nausea/vomiting. These benefits may also help patients reintegrate into society [85].

CLOZAPINE;

Clozapine was the first atypical antipsychotic created[86]. The antipsychotic drug 8-chloro-11-(4-methyl-1-piperazinyl)-3H-dibenzo (b,e)(1,4) diazepinel is a member of the dibenazepine class[87]. Clozapine is an antagonist of D2-5HT2[88]. Orally, the medication has a quick absorption rate (bioavailability = 0.27) [4]. Hepatic microsomal enzymes break down the drug substantially to produce N-desmethyl and N-oxide metabolites [89]. Clozapine is a very effective medication, but it also has a number of potentially fatal side effects. When the total number of neutrophils is less than 500/µl, it is known as severe neutropenia or agranulocytosis. For both neutropenia and severe neutropenia, the estimated chances are 3% and 0.8%, respectively [90]. A 50% death rate can result from myocarditis, which affects 1 in 500 to 1 in 10,000 people [91]. In a 10-year cohort, a mean weight increase was seen of 30 pounds; the majority ofthe first six to twelve months were when the weight gain occurred. Finally, clozapine and a higher incidence of diabetes mellitus are strongly correlated[92]. Clozapine treatment results in hyperprolactinemia [93].

RELATIONSHIP BETWEEN THE DOPAMINE AND PROLACTIN:

One of the main dopamine routes in the brain, the tuberoinfundibular pathway starts in the hypothalamus.Dopamine is transported to the pituitary gland via the tuberoinfundibular pathway from the hypothalamic arcuate nucleus. Antipsychotic medications cause hyperprolactinemia by blocking dopamine receptors in this route. Dopamine acts as a hormone in this pathway instead of a neurotransmitter, and it prevents the anterior lobe of the pituitary gland from releasing prolactin[94].

II. METHODOLOGY:

This is a systematic review,and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement was followed in the reporting of this study. Inclusion criteria based on the condition, such as osteoporosis, pregnancy, hypothyroidism, and others, are excluded.The following databases were used to conduct the review: Pubmed, the Cochrane Library, Scopus, and Google Scholar. These studies meet the inclusion criteria. Dopamine, hyperprolactinemia, and antipsychotic were the research words employed.Examined the abstracts and titles of the papers that were obtained from the databases. Full-text papers were evaluated for eligibility using the inclusion and exclusion criteria after duplicates were eliminated. Key findings were summarized according to the impact of adverse reactions and prolactin levels.

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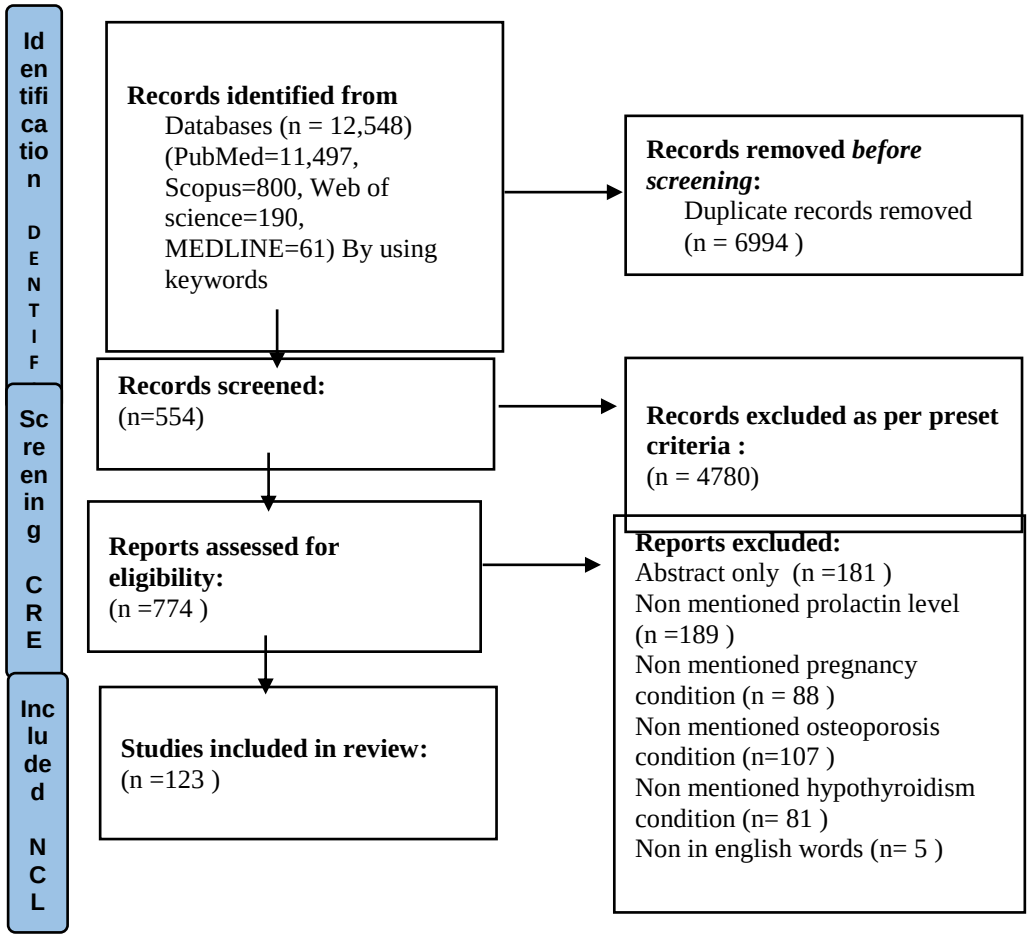

III. RESULT AND DISCUSSION:

We talked about the conditions in this topic, how atypical antipsychotic medications treat them, which medications are appropriate for treating them, and the precautions that should be taken.

HYPOTHYROIDISM:

A deficiency in the production of thyroid hormone as a result of insufficient stimulation by thyroid stimulating hormone (TSH) in an otherwise healthy thyroid gland is known as hypothyroidism [95]. Thyrotropin-releasing hormone (TRH) and thyroid hormone's negative feedback loops work together to primarily regulate TSH output. Other variables, such as the detrimental effects of glucocorticoids, dopamine, and hypothalamic somatostatin, directly affect TSH secretion.Peripheral tissue signals that may indirectly affect thyrotrope secretion include gonadal hormones, leptin, and other signals linked to eating habits or sleep patterns. Hypothyrodism pathogenesis is associated with disruptions in several regulatory systems [96]. At an incidence of 1 in 16,000 to 1 in 100,000, hypothyrodism is still regarded as quite unusual [97].Additionally, the drugs may alter the way iodine is absorbed by thyroid cells or complex iodine, making it unavailable for thyroid hormone synthesis and lowering thyroid hormone levels in the blood, or they may decrease thyroid peroxidase activity and, as a result, T3 and T4 synthesis. They can also improve T4 to T3 deiodination by stimulating deiodinase activity [98]. Reduced levels of thyroid hormone are the primary side effect of antidepressant medications. Mostly acting as iodine capture modifiers, phenothiazines are antipsychotics that also reduce hormone that stimulates the thyroid (TSH) sensitivity to the hormone that releases thyroid hormone (TRH)and complex and deactivate an iodine receptor. Standard antipsychotics, nonphenothiazines, have the ability to increase TSH levels and cause the development of thyroid autoantibodies. The amount of TRH-stimulated TSH may be reduced by atypical antipsychotics [99]. The pharmacological effects of inhibiting Dopaminergic D2 receptors in the tuberoinfundibular pathway of

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the pituitary cause hyperprolactinemia, which is the reason for the strong correlation between the prevalence of sexual dysfunction and antipsychotic drugs [100]. Sexual dysfunction and hyperprolactinemia are potential adverse effects of widely prescribed antipsychotics, including risperidone, amisulpride, and paliperidone.The effects of quetiapine and aripiprazole on prolactin are minimal, but minor effects are seen with chlorpromazine, ziprasidone, clozapine, sertindole, olanzapine, and lurasidone [101]. Age-related increases in the incidence of hypothyroidism are seen in women with psychosis illness more frequently than in men.There is disagreement regarding hypothyroidism's independent role as a risk factor for the development of sexual dysfunction. Therefore, more research is required to determine how hypothyroidism affects sexual function in those who suffer from psychotic illnesses [102]. Tricyclic antidepressants interact with thyroid peroxidase and iodine to deactivate them;By decreasing the thyroid stimulating hormone (TSH) response to thyroid stimulating hormone (TRH), they also induce deiodinase activity and interfere with the hypothalamo-pituitary-thyroid (HPT) axis. Depending on the kind of adverse effect, dose- dependence could be present or absent, and its degree could change. There seemed to be a dose-related relationship between Parkinsonism, hyperprolactinemia, weight increase, and cognition impairment [103]. It has been demonstrated that phenothiazines can cause autoimmune hypothyroidism by upregulating the major histocompatibility complex antigen's expression and producing antibodies against either antithyroglobulin or antithyroperoxidase [98]. Thyroid problems, primarily hypothyroidism, have been linked to quetiapine. The pathogenesis of these anomalies may involve both immunological and nonimmunological pathways, and it is not always evident whether drugs are to blame for the abnormalities. Before beginning quetiapine, it is prudent to ask patients for TFTs, particularly if they have a family history of hypothyroidism or are elderly [104]. TSH and prolactin (PRL) secretion levels were downregulated by aripiprazole and olanzapine; however, when these medications were stopped, TSH and PRL secretions recovered more smoothly, and the patient's symptoms became less severe [105]. A benzisoxazole derivative, risperidone inhibits serotonin's effects through the serotonin 5-ht2 receptors and competes with dopamine at the d2 receptors to a lesser degree.It has a low to moderate effective affinity for serotonin (5ht1a, 5-ht1c, and 5-ht1d) and histaminic h1 receptors, while having a negligible affinity for the dopamine d1 receptor. To expedite the restoration of the symptoms, levothyroxine and risperidone may be the recommended antipsychotic combination [106].

OSTEOPOROSIS:

It is well acknowledged that osteoporosis is a serious public health concern that can result in bone fractures, discomfort, and incapacity. People with schizophrenia are becoming more aware that they have a higher risk of osteoporosis [107]. Osteoporosis is a degenerative condition that weakens the skeletal structure by causing a noticeable reduction in bone mass and alteration in the bone tissue's microstructure [108]. The fragility fractures that are commonly brought on by this condition are associated with a rise in morbidity and mortality as well as a reduction in general quality of life[109]. Women are occasionally high prone than men to develop certain physical and mental conditions as they age and go through menopause, such as osteoporosis and late-onset schizophrenia [110]. Antipsychotic-induced increases in prolactin levels, which have been connected to hypogonadism in both male and female schizophrenia patients and are caused by inhibiting D2 receptors in the hypothalamic-pituitary axis.Chronically high prolactin levels in women limit the release of luteinizing hormone-releasing hormone from the hypothalamus [111]. The onset of osteoporosis can be attributed to increased osteoclast activity or duration, decreased osteoblast activity or duration, or a combination of the two [112]. The hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which regulate the synthesis and release of gonadal steroids, are subsequently reduced as a result of this [113]. In vivo human investigations have demonstrated that standard antipsychotics, along with the atypical antipsychotics amisulpride and risperidone, elevate serum prolactin levels. In vitro and in vivo studies on humans and animals have demonstrated that elevated prolactin levels adversely affect bone cell metabolism and accelerate the pace of bone mineral density loss, raising the risk of fracture[114]. Risperidone does not appear to be associated with an increased risk of fractures attributable to osteoporosis, in contrast to other atypical antipsychotic drugs[115]. When necessary, preventive measures should also include a balanced diet with adequate calcium and vitamin D, regular weight-bearing activity, stopping smoking, obtaining enough sunlight, and appropriate medication monitoring (including measuring

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prolactin blood levels)[116]. Low bone density in schizophrenia patients is linked to alcoholism and cigarette smoking [117]. Psychosis and drug misuse could be risk factors [118].

HYPERPROLACTINEMIA AND OSTEOPOROSIS;
While some atypical antipsychotic medications do not produce hyperprolactinemia, all conventional antipsychotics do [119].

↓

A reduction in bone mass density is caused by hyperprolactinemia (BMD) [120].

↓

It raises the possibility of osteopenia or osteoporosis [120].

PREGNANCY:
LEVELS OF PROLACTIN AND PREGNANCY:
Generally speaking, normal prolactin levels include:

- For males at birth -20 ng/mL
- For females at birth - 25 ng/mL
- For pregnant or breastfeeding women- 400 ng/mL [121].

ATYPICAL ANTIPSYCHOTICS FOR PREGNANT OR BREASTFEEDING WOMEN:
Due to risperidone's inadequate blood-brain barrier penetration, prolactin levels rise more than those of other atypical antipsychotics [25].
Patients with psychosis appear to have higher prolactin levels when taking the other atypical antipsychotics, especially paliperidone and lurasidone [53,68].
Prolactin levels are slightly elevated by another atypical antipsychotic called iloperidone [75].
Therefore, in order to reduce the risk of hyperprolactinemia, additional medications such as ziprasidone ,carbamazine, asenapine, aripiprazole, quetiapine, and brexpiprazole can be used to treat psychosis in pregnant and lactating women [122].
ATYPICAL ANTIPSYCHOTICS AND GESTATIONAL DIABETES:
Pregnant women should not use olanzapine or clozapine because of the higher risk of gestational diabetes and big birth weight associated with their usage during pregnancy.Therefore, the best and safest atypical antipsychotic for use during pregnancy is quetiapine [123].

IV. CONCLUSION:

In thisreview,compared to atypical antipsychotics, typical antipsychotics have higher side effects, particularly hyperprolactinemia.Therefore, these articles provide a general overview of the atypical antipsychotic medication for use in treating various medical disorders, including pregnancy, osteoporosis, and hypothyroidism.

In pregnancy condition:
The safest and most effective atypical antipsychotic to take while pregnant is quetiapine. Since quetiapine reduces the risk of hyperprolactinemia and has no significant side effects, it is superior to all other atypical antipsychotic drugs.
In osteoporosis condition:
Among other atypical antipsychotic medications, risperidone does not seem to be linked to an increased risk of fractures caused by osteoporosis. Its effectiveness is enhanced when combined with other supplements, such as calcium or vitamin D.
In hypothyroidism condition:
Currently, risperidone is used to treat hypothyroidism. It indicates that levothyroxine with risperidone works well together as opposed to risperidone used alone.

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