



Antipsychotic drug induced sexual dysfunction

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ABSTRACT

Sexual dysfunction is defined as any discomfort experienced by an individual or a couple during any stage of a normal sexual activity. According to ICD-10 sexual dysfunction is a condition in which an individual or couple is unable to perform sexual intercourse as both would wish. Atherosclerosis of the arteries supplying genital tissue which elevate sexual function. Typical antipsychotic induce relatively high chances of developing sexual dysfunction in comparison to atypical antipsychotics.

Keywords : Sexual dysfunction, Antipsychotics, Sexual intercourse, ICD-10.

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INTRODUCTION

Sexual dysfunction is defined as any discomfort experienced by an individual or a couple during any stage of a normal sexual activity. Even sexual dysfunction occur both men and women. Sexual relationship is an important issue and sexual dysfunction has a great impact on population and their quality of life ⁽¹⁾. According to ICD-10 sexual dysfunction is a condition in which an individual or couple is unable to perform sexual intercourse as both would wish. The main cause of this may lack of interest, lack of enjoyment and other physiological response failure or inability to control orgasm ⁽²⁾. Atherosclerosis of the arteries supplying genital tissue which elevate sexual function. These are the conditions which increase sexual problems are Hyperprolactinaemia, hypertension, obesity ^(1,2).

Healthy physical relationship between a couple plays an important role in marital life. if both are not satisfied with each other then life became unromantic or incomplete. Sexual intercourse is vital link between husband and wife. During sexual activity sometime individual privation of a required sexual intercourse ⁽³⁾. Antipsychotic drug induced sexual dysfunction is a major problem associated with the treatment of mental disease like hypertension, depression, schizophrenia, and diabetes. Major depressive patient may also develop psychotic feature like hallucination or delusion and the symptoms of major depression include (concentration difficulty, irritability, social isolation, loss of appetite, threats of suicide) these symptoms affect daily life of patient. it is important for the patient to report all the adverse effect or unwanted effect of the prescribed medication which may affect quality of life like decreased libido (in both man and women), erectile dysfunction (in men) .prescriber should be aware for the drug therapy because sexual problem are sometimes difficult for the patient to share about actual problem for example delayed orgasm or decreased libido ⁽⁴⁾. Arizona sexual experience scale (ASEX) is data collection tools were demographic data questionnaire including age gender, level of education, type of drug received, type of mental and physical disease and hospitalization word ⁽³⁾.

Types of sexual dysfunction: -

- Sexual desire disorder – decreased libido (absence of sexual desire in both male and female.
- Sexual arousal disorder –arbitrate by CNS and parasympathetic system.
- Sexual pain disorder –lack of insufficient lubrication of vagina during sex.
- Orgasm disorder- failure to achieve climax. Delayed ejaculation.

Sexual desire

Desire is believed to be a combination of cognitive, physiologic, and developmental factors. Androgens may play a part in sexual desire in men and women; however, the mechanism is unclear. Variations in testosterone concentrations have been correlated with the extent of sexual desire, and administration of exogenous testosterone in men has been found to increase sexual thoughts and desire. Other hormones, such as estrogen and prolactin, may also contribute to dysfunction. Elevated prolactin secondary to reduced central dopaminergic activity can decrease sexual interest. Hormonal changes during the menstrual cycle has been considered as a primary component of desire in women; however, inconsistent results in the importance^(6, 8, 9)

Typical antipsychotics such as Fluphenazine, Haloperidol, Chlorpromazine, Thioridazine, and Thiothixene can all decrease sexual desire. The antidopaminergic action of the antipsychotics increase prolactin concentrations thereby decreasing libido. The atypical agent Risperidone also effects prolactin levels and is believed to affect sexual functioning in a similar manner. Olanzapine, Clozapine, and Quetiapine are all associated with minimal effects on prolactin and should be considered as alternatives. Antidepressants can also decrease desire, possibly due to their anticholinergic and sedative properties. Problems have been reported with several tricyclic antidepressants (TCAs), including Amitriptyline, Imipramine, Desipramine and Nortriptyline, the Monoamine oxidase inhibitors (MAOIs) Phenelzine, Isoearboxazid and tranylcypromine, Amoxapine, and Trazodone^(9,10).

Impotence or Erectile Dysfunction

Impotence is defined as the inability to achieve or to maintain erection sufficient to allow satisfactory sexual intercourse. Disease states such as diabetes, high blood pressure, and cardiac dysfunction are associated with impotence and should be considered as contributing factors. The etiology of impotence may be hormonal, neurologic, vascular, and/or psychogenic^(5,6,7). With vascular disease being the single most common cause. Arousal has the physical characteristics of penile tumescence in the male and pelvic vasocongestion and vagina lubrication in the female. The mechanism of the penile tumescence is thought to be controlled by two pathways: the parasympathetic pathway controlling the reflexogenic erections and the sympathetic pathway that mediates the psychological sexual stimulation^(5, 6, and 7). Sexual motivation in women is still under research. Female arousal is thought to be mediated by a peptidergic innervation involving a vasoactive intestinal peptide. Adrenergic and cholinergic nerves have been suggested to play a part in erectile dysfunction. The physiology of erection begins with a parasympathetic neural impulse, which is transmitted to the arterioles within the corpus cavernosum via the pelvic plexus. The nonadrenergic neurotransmitter nitric oxide induces relaxation of the cavernosal

tissue allowing blood flow to the penis⁽⁸⁾. As pressure within the corporeal bodies increases, the small emissary veins become occluded, decreasing venous outflow and trapping blood within the corpus cavernosum. Erection is maintained until a sympathetic neural impulse from the hypogastric plexus results in ejaculation, and parasympathetic tone is reduced, causing detumescence^(9, 10). Antidepressants that contribute to erectile dysfunction include the TCAs, especially the tertiary amines, and the MAOIs Amoxapine and Trazodone. The mechanism by which antidepressants interfere with erection is unclear. Antipsychotics associated with erectile dysfunction include Fluphenazine, Chlorpromazine, Haloperidol, Pimozide, and Thioridazine⁽⁶⁾. Central and peripheral action of these drugs on dopaminergic blockade has been implicated as the causative factor in erectile dysfunction⁽¹¹⁾.

Antihypertensive agents are also associated with erectile dysfunction also other drug like Hydrochlorothiazide, Chlorthalidone, and high-dose Spironolactone have all been implicated⁽¹²⁾. Sympatholytic agents such as Methyldopa, Guanethidine, and Reserpine not only affect libido but also erectile function. Lipophilic beta blockers (e.g., Propranolol) are more likely to cause dysfunction than the hydrophilic beta blockers. Reports of dysfunction with pindolol, metoprolol, and nadolol are less common. Angiotensin-converting enzyme inhibitors such as Captopril and Enalapril have minimal sexual side effects and should be considered as alternative therapy. Other medications that may cause erectile dysfunction include lithium, digoxin, Alprazolam and Clonidine are medications that effecting erectile dysfunction.

Premature Ejaculation

Premature or rapid ejaculation is defined as a persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the individual wishes it. The pathophysiology of rapid ejaculation is unknown; however, many believe it to be psychologically based. Conflicts with the sexual partner, hostility toward women, performance anxiety, and organic factors such as prostatitis, nrethritis, and pelvic fracture have all induced premature ejaculation⁽¹¹⁾. Drug withdrawal from drugs such as Trifluoperazine and narcotic agents has also caused this problem.

Orgasm

The mechanism by which the orgasmic stage of sexual intercourse is produced in men includes two phases: an emission phase and an ejaculatory phase. The emission phase, under sympathetic control, is mediated by norepinephrine, which acts on alpha-adrenergic receptors, the vas deferens, the prostate, and the seminal vessels, which help to promote the flow of the seminal fluid into the urethra^(6, 7). The ejaculatory phase is mediated by a sacral spinal reflex, which

involves the striated muscles around the bulbar urethra, that contract and causes the projection of semen. Little information exists regarding the physiology of female orgasm. Oxytoein has been the subject of study, but before a definite relationship can be established, further study is needed. Central increases in serotonergic receptor activation have been associated with orgasmic inhibition or anorgasmia. Antipsychotics are believed to contribute to orgasmic dysfunction by their alpha-adrenergic blocking effects. Those that have been associated with orgasmic or ejaculatory disturbances include Trifluoperazine, Perphenazine, Mesoridazine, Chlorprothixene, Chlorpromazine, and Thioridazine, with Thioridazine causing the most problems. Fluphenazine and haloperidol have also been shown to cause these disturbances. Antidepressants affecting orgasm and ejaculation include SSRIs such as Fluoxetine, Paroxetine, and Sertraline; MAOIs such as Phenelzine and Tranylcypromine; TCAs such as Desipramine, Imipramine, Nortriptyline, Amitriptyline, Elomipramine, and Doxepin; and Amoxapine and Trazodone. Benzodiazepines such as Alprazolam and lorazepam have been shown to cause an ejaculatory delay ⁽⁶⁾. The mechanism of this is unclear but may be related to the sedative properties of the benzodiazepines. Other agents that may cause problems with orgasm and ejaculation include Guanethidine, Labetalol, Methyldopa, Reserpine, and Nifedipine.

Hyperprolactinaemia and its role in sexual dysfunction

Hyperprolactinaemia is main cause of sexual dysfunction high level of prolactin hormone secreted from lactotroph cells in the anterior pituitary gland due to the dopamine which may inhibit the effect on prolactin secretion. ^(5,6). Reduction in dopamine can occur via the administration of antipsychotics which act on D2 receptor in the tuberoinfundibular pathway of the brain reduced amount of dopaminergic input to the lactotroph cells results in a sudden increase in prolactin secretion. high serum prolactin level have effect on sexual dysfunction, decrease libido, reproductive health, hypogonadism, infertility in women and low sperm count in men and amenorrhea^(5,6).

Pathophysiology of antipsychotics

Antipsychotic drug mechanisms which can cause sexual dysfunction are histamine receptor antagonism, dopamine receptor antagonism, cholinergic receptor antagonism alpha-adrenergic alpha receptor antagonism and dopamine D2 receptor antagonism. With combine to histaminergic receptors may spoil arousal by increasing sedation activity. Dopaminergic receptor antagonism may decrease the libido by interfere drive .Blockage of dopamine D2 receptor in the tuberoinfundibular pathway by antipsychotics decrease libido, erectile dysfunction and irregular orgasm. Cholinergic receptor antagonism may increase erectile dysfunction by decreasing

peripheral vasodilatation, alpha adrenergic alpha receptor antagonism can decrease peripheral vasodilatation causing erectile dysfunction in men and decrease lubrication in women. Irregular ejaculation is associated with the anti-adrenergic effect of treatment^(4, 5, and 6).

The main cause of sexual dysfunction is Hyperprolactinaemia in male and female using antipsychotics by anterior mechanism. Due to the blockage of dopamine D₂ receptor Risperidone, Haloperidol, are prolactin elevating antipsychotics. (4)

Sexual dysfunction due to typical and atypical antipsychotic drug.

According to study by Hummer and his colleagues correlate sexual dysfunction among schizophrenics on Clozapine an atypical antipsychotic with those on haloperidol a typical antipsychotic. 100 cases on Clozapine and 53 cases on haloperidol including both genders were rated in UKU side effect rating scale. 58 percent had decrease libido, 27 percent impaired arousal and 22 percent orgasm disorder in the haloperidol group and on other hand 50 percent decrease sexual desire, 24 percent arousal problems and 21 percent orgasm disorder (delayed ejaculation) in the Clozapine group. Thus Clozapine and haloperidol with regard to in their tendency to induce sexual dysfunction.

Drug induced sexual dysfunction

Haloperidol

Haloperidol is a butyrophenone-derivative which inhibit the ascending reticular system via the caudate nucleus it blocks postsynaptic dopamine receptor in the mesolimbic dopaminergic system so increase turnover of brain dopamine. It acts on D₂-receptor and show effect on 5HT₂ and α₁ receptors. Haloperidol widely used to treat delirium because it shows decrease hypotension, sedation and also has anticholinergic effect in comparison of other antipsychotic⁽¹⁵⁾. It is high potency first generation neuroleptic agent⁽¹⁶⁾. It raises serum prolactin levels to 20-40 ng/ml in therapeutic doses and it may cause libido, amenorrhea, gynecomastia, erectile dysfunction/ sexual dysfunction, and galactorrhea.

Risperidone

Risperidone is a second generation antipsychotic agent used for acute treatment of schizophrenia and psychotic disorder like bipolar disorder and mania. It is a potent inhibitor of serotonin 5-HT₂ and dopamine D₂ receptor it undergoes α-hydroxylation in the liver predominantly catalyzed by the cytochrome P₄₅₀ enzyme, CYP2D6 TO produce α-hydroxy-Risperidone metabolic route for Risperidone include oxidative N-dealkylation and hydroxylation to 7-hydroxy-risperdone⁽¹⁷⁾.

Risperidone is a representative atypical antipsychotic drug with a high probability of prolactin elevation. Risperidone elevates the serum prolactin in a dose dependent manner and up to a level

of 30~60 ng/ml when used at therapeutic doses. A small scale study reported gynecomastia, galactorrhea, and priapism in male patients. Further, female patients were reported to experience amenorrhea and galactorrhea.⁽⁴⁾

Clozapine

Clozapine is an atypical antipsychotic which is benzodiazepine and have central anti-dopaminergic activity peak blood level occur in body is 2.1 hours and mean half life of 12 hour and also 95% bound to plasma and completely metabolized prior to excretion⁽¹⁸⁾. Clozapine is a prototypical atypical antipsychotic whose metabolism covariant with CYP_{1A2} activity⁽¹⁹⁾. Clozapine also induce a risk of agranulocytosis an increased reduction in the number of white blood cell in the body. The inability of Clozapine to elevate serum prolactin level may be related to the activate the effect of Clozapine on tuberoinfundibular dopamine neurons and to achieve effective blockade of dopamine D₂ receptor of pituitary. It also exerts antagonism of D₁ receptor and show interaction of Clozapine among D₂, D₁, D₄ and 5HT₂ receptors produced in a characteristic conversion in function of pre and post synaptic dopamine elements⁽²⁰⁾.

Clozapine was associated with low prolactin serum level as compared to classical antipsychotics Clozapine 27ng/ml. Clozapine produces a low incidence of Hyperprolactinaemia related adverse Sexual events including decreased libido and impaired arousal relative to classical antipsychotics⁽³⁾.

Olanzapine

Olanzapine elevates prolactin level increase level of prolactin may abolish hypothalamic GnRH and this promote in reduced pituitary gonadotropin secretion and it may inhibit reproduction function by damaged gonadal steroidogenesis in both gender patients gynecomastia(men boobs), galactorrhea, amenorrhea and erectile dysfunction have been reported in patient taking Olanzapine⁽²¹⁾.

Olanzapine temporarily increases the prolactin level. Moreover, in most cases, the elevated prolactin level returns to a normal level. In a double blind clinical trial, prolactin elevation Olanzapine produces a low incidence of adverse sexual events in men as compared to Risperidone-treated men^(2, 5, and 7).

Olanzapine is second generation antipsychotic agent and bind with serotonin 5HT_{2A/2C}, dopamine D₁₋₄, histamine H₁ and adrenergic receptor. It is an antagonist with balanced attraction binding for serotonin in 5HT₃ and muscarinic M₁₋₅ and weakly bind with GABA A, B-adrenergic and B₂D receptor⁽²¹⁾.

Aripiprazole

Aripiprazole used for the treatment of schizophrenia and bipolar disorder it is a dopamine partial agonist and also has binding attraction for the serotonin 5HT_{2A} receptor. Aripiprazole reduce dopaminergic neurotransmission through D₂ partial agonism it bind with CNS receptor mainly partial D₂ agonist, 5HT_{2A} antagonist, and partial 5HT_{1A} agonist. It has lower intrinsic efficacy that's why it triggers lower than dopamine and higher than an antagonist it modulates neurotransmission mainly mesolimbic and mesocortical pathway via partial D₂ agonist (22).

According to double-blind clinical trial studies, Aripiprazole did not increase the prolactin level or normalize prolactin levels in patients with elevated baseline levels caused by typical antipsychotics. Aripiprazole was associated with a significant improvement in sexual desire, erectile dysfunction, and ejaculatory disorder^(3, 5).

MANAGEMENT OF ANTIPSYCHOTICINDUCED SEXUAL DYSFUNCTION

Dopamine agonist (Bromocriptine, Cabergoline) and dopamine releasing agent (Amantadine) were tried in a patient suffering from sexual dysfunction secondary to antipsychotics, The patients reported significant improvement while taking Sildenafil in the number of adequate erections⁽³⁾.

CONCLUSION

After reviewing several articles on antipsychotic drug induced sexual dysfunction it is identified that atypical antipsychotic drug induced sexual dysfunction especially erectile dysfunction in man and decreased libido in both men & women. So it is responsibility for a psychiatrist the choice of antipsychotic is appropriate for minimum the risk of sexual dysfunctions.

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