2009

Antipsychotics and sexual dysfunction: Sexual dysfunction: Part III

Anil Kumar Mysore Nagaraj
Mysore Medical College & Research Institute

nagesh Pai
University of Wollongong, nagesh@uow.edu.au

Satheesh Rao
K S Hegde Medical Academy

Antipsychotics and sexual dysfunction: Sexual dysfunction: Part III

Abstract

Satisfying sexual experience is an essential part of a healthy and enjoyable life for most people. Antipsychotic drugs are among the various factors that affect optimal sexual functioning. Both conventional and novel antipsychotics are associated with significant sexual side effects. This review has presented various studies comparing different antipsychotic drugs. Dopamine antagonism, increased serum prolactin, serotonergic, adrenergic and cholinergic mechanisms are all proposed to be the mechanisms for sexual dysfunction. Drug treatment for this has not given satisfactory long-term results. Knowledge of the receptor pharmacology of an individual antipsychotic will help to determine whether it is more or less likely to cause sexual side effects and its management.

Disciplines

Medicine and Health Sciences

Publication Details

Nagaraj, A., Pai, N. Brahmavar. & Rao, S. (2009). Antipsychotics and sexual dysfunction: Sexual dysfunction: Part III. Online Journal of Health and Allied Sciences, 8 (3), 1-6.

Online Journal of Health and Allied Sciences
Peer Reviewed, Open Access, Free Online Journal
Published Quarterly : Mangalore, South India : ISSN 0972-5997
Volume 8, Issue 3; Jul-Sep 2009

Review:

Antipsychotics and Sexual Dysfunction :: Sexual Dysfunction: Part III

Anil Kumar Mysore Nagaraj, Senior Resident, Dept of Psychiatry, Mysore Medical College & Research Institute, Mysore - 570001, India,
Nagesh Brahmavar Pai, Clinical Associate Professor, Graduate School of Medicine, University of Wollongong, Australia,
Satheesh Rao, Professor and Head, Dept of Psychiatry, K S Hegde Medical Academy, Mangalore, India

Address For Correspondence:
Anil Kumar Mysore Nagaraj,
Senior Resident, Dept of Psychiatry, Mysore Medical College & Research Institute, Mysore - 570001, India. **E-mail:** nagarajakm24@gmail.com

Citation: Anil Kumar MN, Pai NB, Rao S. Antipsychotics and Sexual Dysfunction. *Online J Health Allied Scs.* 2009;8(3):1
URL: http://www.ojhas.org/issue31/2009-3-1.htm
Open Access Archives: http://cogprints.org/view/subjects/OJHAS.html and http://openmed.nic.in/view/subjects/ojhas.html

Submitted: Sep 20, 2009; Accepted: Sep 30, 2009; Published: Nov 15, 2009

Abstract:
Satisfying sexual experience is an essential part of a healthy and enjoyable life for most people. Antipsychotic drugs are among the various factors that affect optimal sexual functioning. Both conventional and novel antipsychotics are associated with significant sexual side effects. This review has presented various studies comparing different antipsychotic drugs. Dopamine antagonism, increased serum prolactin, serotonergic, adrenergic and cholinergic mechanisms are all proposed to be the mechanisms for sexual dysfunction. Drug treatment for this has not given satisfactory long-term results. Knowledge of the receptor pharmacology of an individual antipsychotic will help to determine whether it is more or less likely to cause sexual side effects and its management.
Key Words: Sexual dysfunction, Desire, Erection, Orgasm, Ejaculation, Antipsychotics

Introduction:
Sex is a motive force bringing two people into intimate contact. Satisfying sexual experience is an essential part of a healthy and enjoyable life for most people. Sexual dysfunction can result from a wide variety of psychological and physical causes like age, opportunity in the living condition, medical disorders, psychiatric disorders, medications. Among medications antihypertensives, diuretics, antihistamines, antidepressants, benzodiazepines and antipsychotics are the common agents associated with sexual dysfunction.(1) Antipsychotics, either typical or atypical are commonly used in the acute and maintenance phases of schizophrenia. Literature reveals significant rates of sexual dysfunction among both typical and atypical antipsychotics and this adverse effect is particularly important in many ways. It affects their self-esteem, causes trouble for their sexual partners, interferes with their quality of life and compromises treatment compliance.(2-6) Sexual dysfunction appears to be due to direct consequence of dopamine antagonism. However other mechanisms like elevated serum prolactin level, serotonergic, adrenergic and anticholinergic mechanisms are also important.(6-8) Bromocriptine, cabergoline, amantadine, shakuyaku-kanzo-to, and sildenafil are some of the drugs tried in antipsychotic induced sexual dysfunction. But there is no robust evidence that these agents have proper efficacy in treating the antipsychotic-induced sexual dysfunction.(9) Knowledge of the receptor pharmacology of an individual antipsychotic will help to determine whether it is more or less likely to cause sexual side effects.(10) This review presents various studies that have looked into different antipsychotics for sexual side effects and approved treatment options for antipsychotic associated sexual dysfunction.

Studies of sexual dysfunction due to antipsychotics in schizophrenia:
This aspect of antipsychotics was not extensively studies earlier, for two reasons. One is the low rate of spontaneous reporting by the patient and the other being embarrassment on the part of the clinician, especially when the patient is of opposite sex. Antipsychotics being the mainstay in the treatment of schizophrenia, sexual dysfunction due to antipsychotics have been currently studied extensively in this patient group.

The landmark study by Kotin and co-workers is one of the earliest studies in this area. They studied sexual dysfunction among 87 schizophrenic patients. Fiftyseven of them were on thioridazine and another 30 were on other antipsychotics like chlorpromazine, trifluperazine, fluphenazine, haloperidol and thiothixene. Sixty percent of those who were on thioridazine reported sexual dysfunction as against 25% of those on other antipsychotics. In this, 49% had ejaculatory problems including retrograde ejaculation and 44% had erectile problems in the thioridazine group, as against 0% and 19% respectively in the other group. The study was limited by direct interview technique, only male patients and low sample size.(11)

Ghadirian and colleagues studied sexual dysfunction and plasma prolactin levels in 55 neuroleptic treated schizophrenic patients of which 26 were males and 29 females. Most of them were on fluphenazine. A specially designed scale was used, though it was not validated. Fifty four percent of males and 30% of females reported impaired sexual functioning. Further, 91% of females reported menstrual problems. Plasma prolactin levels significantly correlated in male sexual dysfunction but not in females though here it was significantly correlated to their menstrual problems. There were no placebo controls.(12)

In the study of sexual function in men with schizophrenia, by Burke and his team, 50% reported erectile dysfunction. They were receiving either haloperidol or fluphenazine. Dysfunction was significantly associated with greater biological evidence of dopamine blockade, by way of severe

EPS and high serum prolactin levels. The sample size was too small (N = 20) and there was no control group. (13)

Another study compared sexual dysfunction among male schizophrenics with and without treatment. This was a unique study, first of its kind, in which there were 20 drug free patients, 51 patients on neuroleptics and 51 normal controls who were assessed on a questionnaire designed by Schiavi et al. (1990). It revealed that untreated schizophrenics had significantly reduced frequency of sexual thoughts, though erection and ejaculation was preserved. Impairment in arousal, erection and orgasm were reported significantly more by the treated patients than the untreated, though they also reported reduced desire. However it inferred that neuroleptic treatment has beneficial effect on sexual desire.(14)

Kockott and Pfeiffer studied sexual disorders in mixed population of non acute psychiatric outpatients which included 100 schizophrenics, 58 patients of affective psychosis and 30 patients receiving dermatological treatment, as control group. Rated on a sexuality questionnaire, 49% of schizophrenics, 36.2% of those with mood disorder and 13.3% of controls had a sexual dysfunction. The most frequent form of sexual dysfunction experienced in all groups was a low desire. 88 out of 100 patients with schizophrenia were on medication and depot preparations of haloperidol and flupenthixol were the medicines used by majority of patients. 60% of haloperidol group and 44% of flupenthixol group reported sexual dysfunction. Neither the nature of the pharmaceuticals nor the dose level had a specific influence on the frequency of sexual dysfunctions. (15)

Smith and co-workers studied sexual dysfunction among 101 schizophrenic patients on typical antipsychotics (flupenthixol, fluphenazine, haloperidol, zuclopenthixol, thioridazine, trifluoperazine, pimozide), 57 normal controls and 55 controls attending a sexual dysfunction clinic. Assessed on a sexual functioning questionnaire designed by the authors, 45% of schizophrenic patients, 17% normal controls and 61% of controls attending the sexual dysfunction clinic reported sexual dysfunction. This study has also compared different typical antipsychotics for sexual dysfunction among both males and females. Impaired libido was most common with aliphatic phenothiazines in males where as in females, with substituted benzamides. Arousal difficulties were most common with substituted benzamides and orgasmic/ejaculatory problems with thioxanthines in both sexes. Absence of unmedicated psychiatric patients and smaller sample to ascertain the effect of specific medications limited the study.(2)

Raja and Azzoni studied various aspects of sexual behavior including awareness of high risk behavior, sexually transmitted diseases and sexual problems due to psychotropics among mixed population of psychotic patients. They assessed 117 symptomatic patients of both sexes, 39 each of schizophrenia, schizoaffective disorder and bipolar disorder, by the modified version of the sexual interest and sexual performance questionnaire developed by Azzoni and his team. The patients were on different antipsychotics, benzodiazepines and anticholinergic drugs, but the names of drugs are not mentioned in the study. Overall, 38.5% of patients reported detrimental effects of psychoactive drugs on their sexuality. Impaired desire was the most commonly reported sexual dysfunction. Patients with schizophrenia scored low on all aspects of sexuality compared to other groups.(16)

The above studies infer that all the classes of typical antipsychotics (Dopamine receptor antagonists) are associated with significant sexual side effects. Atypical antipsychotics (Serotonin Dopamine antagonists) became popular by the end of last century and were thought to have a better side effect profile. It became essential to study their sexual side effects as that was a significant factor for medication compliance.

Studies comparing sexual dysfunction due to typical & atypical antipsychotics:

A study by Hummer and his colleagues compared sexual dysfunction among schizophrenics on clozapine, an atypical antipsychotic with those on haloperidol, a typical antipsychotic. One hundred patients on clozapine and 53 patients on haloperidol (including males and females) were rated on UKU side effect rating scale. Fifty eight percent had reduced desire, 27% impaired arousal and 22% orgasmic difficulties in the haloperidol group, as compared to 50% reduced desire, 24% arousal difficulties and 21% orgasmic difficulties in the clozapine group. Thus interestingly there was no statistically significant difference between haloperidol and clozapine with regard to their propensity to induce sexual dysfunction.(17)

Another study compared sexual dysfunction in male schizophrenics on clozapine (N = 30) with those on other typical antipsychotics (N = 30) including depot preparation of haloperidol and fluphenazine and oral perphenazine. Rated on a sexual function questionnaire, significant difference was found in frequency of desire for sex, masturbatory erections and number of orgasms per month, inferring that maintenance therapy with clozapine may be associated with a lesser degree of sexual dysfunction than the typical antipsychotics. The study was limited by only male patient population and small sample size, especially in the typical antipsychotic group.(18)

Wirshing and associates also compared typical and atypical antipsychotics for sexual dysfunction in 25 male schizophrenic patients. There were three groups, clozapine (N = 5), risperidone (N = 14) and haloperidol / fluphenazine combination (N = 6). Assessed on a sexual functioning questionnaire developed by Burke et al.(1994), the majority of risperidone (71%) and haloperidol / fluphenazine (61%) treated subjects but less of clozapine (40%) treated subjects reported overall worsening of sexual functioning including desire, erection and orgasm. But the small and unbalanced number of subjects makes type II errors clearly possible and hampers any conclusions about legitimate drug- drug differences.(3)

In the Nithsdale Schizophrenia Survey 24, assessing sexual dysfunction among schizophrenic patients in comparison to healthy control group, at least one sexual dysfunction was reported by 82% of men and 96% of women with schizophrenia on a gender specific questionnaire. Among men, 52% each had desire and arousal difficulties and 35% had orgasmic difficulties. Seventy three percent of females reported reduced desire and 46% orgasmic difficulties. Patients taking typical and atypical antipsychotics were evenly matched. Patients on both groups of antipsychotics showed similar frequency of sexual dysfunction. There was no association between sexual dysfunction and type of antipsychotic drug.(19)

Bobes and colleagues studied cross-sectionally sexual dysfunction with risperidone, olanzapine, quetiapine and haloperidol among 636 patients of schizophrenia; assessing them on UKU side effect rating scale. Patients were on a single antipsychotic. Frequency of sexual dysfunction was 38% with haloperidol, 35.3% with olanzepine, 43.2% with risperidone and 18.2% with quetiapine. None of the atypical antipsychotics studied significantly improved sexual dysfunction due to typical antipsychotics. Lesser sexual dysfunction due to quetiapine was presumed to be due to short-term treatment.(20)

A recent randomized, double-blind, 12 week trial has studied 27 patients of schizophrenia who were on fluphenazine(n=9), risperidone(n=12) and quetiapine(n=6) for sexual dysfunction. The patients were rated on 'Changes in Sexual Function Questionnaire'. Seventy-eight percent of patients on fluphenazine reported sexual dysfunction as compared to 42% on risperidone and 50% on quetiapine. However orgasmic quality/ability improved significantly for quetiapine as compared to other study drugs. Forty percent of quetiapine treated patients reported that they felt better about their sexuality as compared to previous treatment, as did 55% on risperidone and only 13% on fluphenazine. Prolactin elevation and consequent hormonal problems were highest with risperidone.(21)

There have been several studies as sited above that have compared either typical and atypical antipsychotics or several atypical antipsychotics with a typical antipsychotic. Many studies have shown that there is no statistical significance in the occurrence of sexual side effects among typical and atypical antipsychotics. However in general, atypical antipsychotics have better short term side effect profile. Thus by the beginning of this century, usage of typical antipsychotics was much reduced. Though most of the atypical antipsychotics are associated with sexual dysfunction, it is important to know which is relatively safer among them, with respect to sexual side effects.

Studies comparing different atypical antipsychotics for sexual dysfunction:

Knegtering and associates studied 49 patients of schizophrenia and other psychotic disorders for sexual dysfunction due to quetiapine (200-1200 mg/day) (n=25) and risperidone (1-6 mg/day) (n=24) in a randomized open label study. Assessed on a sexual functioning questionnaire, 16% of those on quetiapine reported sexual dysfunction as compared to 50% on risperidone thus concluding that sexual dysfunction is significantly less common in quetiapine than risperidone. (22) This finding is supported by another study in which the author switched schizophrenic patients on risperidone (n=7) and haloperidol (n=1) who had developed sexual dysfunction due to these agents, to quetiapine for six weeks and found significant improvement both in sexual dysfunction, as assessed by Arizona Sexual Experience Scale as well as in psychotic symptoms as assessed on PANSS.(23)

Melkersson studied cross-sectionally the degree and frequency of prolactin elevation and related symptoms of menstrual disturbances, galactorrhea, impotence and decreased libido in patients with schizophrenia, schizophreniform and schizoaffective disorders who are on clozapine (n=28), olanzapine (n=29) and risperidone (n=18). Elevated prolactin was found in 89% of those on risperidone, 24% of those on olanzapine and none among those on clozapine. Further, impotence and reduced libido were reported in 44% of risperidone treated patients as compared to 3% of olanzapine and none of clozapine treated patients. However whether the severity of these adverse effects is related to the extent of hyperprolactinemia was not studied here. Overall, clozapine was found to be the more favourable agent when compared to risperidone and olanzapine, with respect to sexual functioning.(24)

Montejo and colleagues studied sexual side effects of quetiapine alone, in an open-label, prospective, naturalistic study having five assessments over six months. They rated 82 patients with a diagnosis of schizophrenia or schizophreniform disorder, on quetiapine in a real practice setting, on 'Psychotropic-Related Sexual Dysfunction Questionnaire'. Total scores on this questionnaire decreased progressively and significantly from baseline to the study end point. The authors infer that quetiapine shows a low frequency of sexual dysfunction during long-term treatment. (25)

In contrast to the above mentioned study, Atmaca and co-workers studied quetiapine alone for sexual dysfunction. They evaluated 36 schizophrenic patients on quetiapine for 4 weeks using Arizona Sexual Experience Scale and found that 31.6% of males and 28.6% of females had impaired libido which was not there at baseline. Thus they concluded that even quetiapine causes significant sexual dysfunction.(26)

Another recent study compared risperidone, olanzapine and quetiapine for sexual dysfunction using the same questionnaire, Arizona Sexual Experience Scale (ASEX). It was a cross-sectional study with a sample size of 238 (quetiapine-57, olanzapine-94, risperidone-87). The mean scores on ASEX were relatively low in quetiapine group compared to the other two drugs. However patients in all the treatment groups experienced a moderately high degree of sexual dysfunction. Though quetiapine group experienced slightly lesser degree of sexual dysfunction, it differed significantly with olanzapine only. Because the patients were not randomized, the authors opine that conclusions must be interpreted within the context of the quasi-experimental design.(27)

In a unique, six week study, Knegtring and colleagues compared prolactin rising and prolactin sparing antipsychotics for sexual dysfunction. The objective was to study whether the sexual side effects of prolactin rising antipsychotics are reducible to serum prolactin. Around 40% of emerging sexual side effects in schizophrenia were attributable to the prolactin rising properties of antipsychotics. Of this attributable fraction, around one-thirds to two-thirds was directly reducible to the effect of serum prolactin.(28)

Antipsychotic induced hyperprolactinemia and sexual dysfunction:

The prolactin is secreted from the anterior pituitary in a pulsatile manner and is regulated by inhibitory and stimulatory influences from the hypothalamus. There are 13-14 peaks per day with an interpulse interval of about 95 min. The primary influence is tonic inhibitory, and dopamine has a major role in mediating this inhibition. Dopamine released into the hypophysial portal blood from tuberoinfundibular neurons activates D2 receptors on lactotrophs in the anterior pituitary.(4) All antipsychotics are dopamine blockers, while some antipsychotics are also serotonin blockers. Blockade of dopamine receptors by antipsychotics in the tuberoinfundibular tract releases the inhibition of prolactin

storage cells, resulting in elevation of prolactin levels. In contrast to dopamine, serotonin acts to stimulate prolactin release, thus having an inhibiting effect on the dopaminergic influence on the tuberoinfundibular tract. A consequence of this mechanism is that serotonergic influences can modulate prolactin release, but serotonin can only show this effect as long as the dopaminergic influence is present. Atypical antipsychotics are antagonists of both serotonin and dopamine, exerting opposing effects on prolactin release. The net effect would depend on the relative strength of the two actions. Thus risperidone causes greater degree of prolactin elevation, olanzapine has only marginal effect and quetiapine has no effect on prolactin elevation.(29)

Elevation of the prolactin level can have different consequences for male and female antipsychotic users. Leutinising hormone (LH) stimulates testosterone production in men. If prolactin levels are rising, gonadotropin-releasing hormone (GnRH) levels and consequently LH levels will fall. This might result in a decrease of testosterone levels, which might contribute to sexual function disorders. These include loss of libido, erectile dysfunction, and difficulty in ejaculating or an ejaculation without orgasm, though the effects of prolactin on arousal and orgasm remain equivocal. In women, elevated prolactin levels can result in changes of pulse released GnRH and lack of estrogen, which can induce inhibition of menstrual cycle (amenorrhoea). It also causes galactorrhoea, gynaecomastia and various types of sexual dysfunction, especially loss of libido.(4,29)

A number of studies on antipsychotic induced sexual dysfunction have incorporated the procedure of measurement of prolactin level. Almost all of them have found a positive correlation between hyperprolactinemia and sexual dysfunction. (2,8,10,12,21,24,28,30) When it comes to the proportion of cases where hyperprolactinemia was associated with sexual dysfunction, studies infer it to be 25-40%. (28, 31) Thus it is not just hyperprolactinemia, and there are other mechanisms that are involved in sexual dysfunction. Studies have revealed significant contribution of dopaminergic, adrenergic, serotonergic and cholinergic actions of antipsychotics for sexual dysfunction. (7,8,32) In fact a recent study has reported that the mostly responsible mechanism of sexual dysfunction is the direct consequence of dopamine antagonism.(8)

Treatment options:
The robust evidence that we have today as a mechanism of sexual dysfunction is hyperprolactinema. Thus the principle behind treating antipsychotic induced sexual dysfunction is reducing prolactin levels. The reverting back of the prolactin levels to normal range has been found to set right the sexual dysfunction. The treatment protocol may involve a morning random measurement of the non-fasting serum prolactin level. Following are the various treatment options.(5, 9)

- Discontinuation of the antipsychotic if clinically indicated
- Dose reduction of conventional antipsychotic or risperidone
- Switching to clozapine, olanzapine or quetiapine
- Hormone replacement therapy
- Addition of drugs like dopaminergic agonists

The last of the above options is used where dose reduction has failed and switching is contra-indicated. The following are some of the drugs used to reduce prolactin levels.

Bromocriptine: It is an ergot alkaloid derivative, having dopamine agonist properties. It is the choice of treatment of hyperprolactinemia, irrespective of the etiology. It is given in daily divided doses of 5-10 mg. It can be safely used in modest doses in patients taking conventional antipsychotics. It is found to improve the libido, normalize the menstrual cycle and increase the serum testosterone levels.(33,34)

Amantadine: It also acts as dopamine agonist and is beneficial in the treatment of antipsychotic induced hyperprolactinemia. When used in the dose of 100 mg/day, it reverses the sexual dysfunction.(35)

Cabergoline: It is a synthetic ergoline, a selective and long-lasting D2 receptor agonist that inhibits prolactin secretion. It is found to be effective at a dose of 0.5 mg twice a week. However it is not as effective as the other two dopamine agonists.(36)

Sildenafil: Only three case reports and one open-label trial mentioned the use of sildenafil in antipsychotic induced sexual dysfunction. (37-40) However, the limitation with its use is that it cannot be used on a regular basis for a long time due to cardiovascular adversities.

Shakuyaku-Kanzo-To (TJ-68): It is a Japanese medicine that is composed of two herbs (Radix paeoniae & Radix glycyrrhizae) that are used to treat menstrual pains. Although the mechanism is unknown, TJ-68 may have a direct inhibitory effect on prolactin release from pituitary. It also may have an indirect effect by reducing estradiol.(41,42)

These pharmacological strategies described above, once initiated, should not be discontinued until a minimum of two weeks of therapy have been administered. One can also combine certain non-pharmacological therapies along with the medication. The most important among them is a thorough psychoeducation about the course and prognosis of psychotropic associated sexual dysfunction, as many patients are of the opinion that this sexual dysfunction is everlasting. Drug holiday (43) and watchful waiting for sexual side effects to disappear (44) are other useful methods.

Conclusion:
Sexual dysfunction is an important antipsychotic associated side effect. All patients on follow up need an evaluation for sexual dysfunction. Hyperprolactinemia is a neuroendocrine side effect of conventional antipsychotics and risperidone, and is a likely cause of sexual disturbances in patients taking antipsychotics. Successful management of sexual side effects is very crucial for treatment adherence to antipsychotics. The existing studies have rarely used procedures like nocturnal penile tumescence or penile plethysmography, which can rule out any organic sexual disorder. Such methodological shortcomings should be overcome in future studies. Further, much research is required in the area of treatment of antipsychotic induced sexual dysfunction

References:

1. Schiavi RC, Segraves RT. The biology of sexual function. *Psychiatr Clin North Am* 1995;18(1):7-23.
2. Smith SM, O' Keane V, Murray R. Sexual dysfunction in patients taking conventional antipsychotic medication. *Br J Psychiatry* 2002;181:49-55.
3. Wirshing DA, Joseph MP, Marder SR, Saunders CS, Wirshing WC. Sexual side effects of novel antipsychotic medications. *Schizophr Res* 2002;56:25-30.
4. Compton MT, Miller AH. Sexual side effects associated with conventional and atypical antipsychotic. *Psychopharmacol Bull* 2001;54(3):89-108.
5. Compton MT, Miller AH. Antipsychotic induced hyperprolactinemia and sexual dysfunction. *Psychopharmacol Bull* 2002;36:143-164.
6. Culter AJ. Sexual dysfunction and antipsychotic treatment. *Psychonendoendocrinology* 2002;28 (suppl 1):69-82.
7. Segraves RT. Effects of psychotropic drugs on human erection and ejaculation. *Arch Gen Psychiatry* 1989;46:275-84.
8. Konarzewska B, Szulc A, Poptawska R, Galinska B, Juchnowicz D. Impact of neuroleptic-induced hyperprolactinemia on sexual dysfunction in male schizophrenic patients. *Psychiatr Pol.* 2008;42(1):87-95.
9. Costa AM, de Lima MS, Faria M, Filho SR, de Olivera JR et al. A naturalistic 9 month follow up comparing olanzapine and conventional antipsychotics on sexual dysfunction and hormonal profile for males with schizophrenia. *J Psychopharmacol* 2007 Mar;1(2):165-70.
10. Smith SM. The impact of hyperprolactinemia on sexual function in patients with psychosis. *J Psychopharmacol.* 2008 Mar;22(2 suppl):63-9.
11. Kotin J, Wilbert DE, Verburg D, Soldinger SM. Thioridazine and sexual dysfunction. *Am J Psychiatry* 1976;133:82-85.
12. Ghadirian AM, Chouinard G, Annable L . Sexual dysfunction and prolactin levels in neuroleptic treated Schizophrenic outpatients. *J Nerv Ment Dis* 1982;170:463-467.
13. Burke MA, McEvoy JP, Ritchie JC. A pilot study of a structured interview addressing sexual function in men with Schizophrenia. *Biol Psychiatry* 1994;35:32-35.
14. Aizenberg D, Zemishlany Z, Dolfman-Etrog P, Weizman A. Sexual dysfunction in male Schizophrenic patients. *J Clin Psychiatry* 1995;56:137-141.
15. Kockott G, Pfeiffer W. Sexual disorders in non acute psychiatric outpatients. *Comprehensive psychiatry* 1996;37(1):56-61.
16. Raja M, Azzoni A. Sexual behaviour and sexual problems among patients with severe chronic psychosis. *Eur Psychiatry* 2003;18:70-76.
17. Hummer M, Kemmler G, Kurz M, Kurzthaler I, Oberbaner H, Fleishhacker WW. Sexual disturbances during clozapine and haloperidol treatment for schizophrenia. *Am J Psychiatry* 1999;156:631-633.
18. Aizenberg D, Modai I, Landa A, Gil-Ad I, Weizman A. Comparison of sexual dysfunction in male Schizophrenic patients maintained on treatment with classical antipshchotics versus Clozapine. *J Clin Psychiatry* 2001; 62: 541-544.
19. MacDonald S, Halliday J, MacEwan T, Sharkey V, Farrignton S, Wall S, McCreadic RG. Nithsdale Schizophrenia surveys 24: sexual dysfunction. *Br J Psychiatry* 2003;182:50-56.
20. Bobes J, Gare A, Portilla MP, Rejas J et al. Frequency of sexual dysfunction and other reproductive side-effects in patients with Schizophrenia treated with risperidone, olanzepine, quetiapine, or haloperidol: the results of the EIRE study. *J Sex Marital Ther* 2003;29(2):125-47.
21. Kelly DL, Conley RR. A randomized double-blind 12 week study of quetiapine, risperidone or fluphenazine on sexual functioning in people with schizophrenia. *Psychoneuroendocrinology* 2006;31(3):340-6.
22. Knegtering R, Casrelein A, Bous H, Van Der Linsle I. A randomized open label study of impact of quetiapine versus risperidone on sexual functioning. *J Clin Psychopharmacol* 2004;24(1):56-61.
23. Byerly MJ, Lescouflair E, Weber MT, Bugno RM, Fisher R et al. An open label treatment of quetiapine for antipsychotic-induced sexual dysfunction. *J Sex Marital Ther* 2004;30(5):325-32.
24. Melkersson K. Differences in prolactin elevation and related symptoms of atypical antipsychotics in schizophrenic patients. *J Clin Psychiatry* 2005;66(6):761-7.
25. Montejo Gonzalez AL, Rico-Villademoros F, Tafalla M, Majadas S; Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. A 6-month prospective observational study on the effects of quetiapine on sexual functioning. *J Clin Psychopharmacol.* 2005 Dec;25(6):533-8.
26. Atmaca M, Kuloglu M, Tezcan E. A new atypical antipsychotic: quetiapine-induced sexual dysfunctions. *Int J Impot Res* 2005;17(2):201-3.
27. Byerly MJ, Nakonezny PA, Bettcher BM, Carmody T, Fisher R et al. Sexual dysfunction associated with second-generation antipsychotics in outpatients with schizophrenia or schizoaffective disorder: An empirical evaluation of olanzapine, risperidone, and quetiapine. *Schizophrenia Research.* 2006;81(2-3):311-16.
28. Knegtring H, Van den Bosch R, Castelein S, Bruggeman R, Sytema S et al. Are sexual side effects of prolactin-rising antipsychotics reducible to serum prolactin? *Psychoneuroendocrinology.* 2008 Jul;33(6):111-7.
29. Dickson RA, Glazer WM. Neuroleptic induced hyperprolactinemia. *Schizophr Res.* 1999;35:75-86.
30. Dickson RA, Seeman MV, Corenblum B. Hormonal side effects in women: typical versus atypical antipsychotic treatment. *J Clin Psychiatry.* 2000;61(suppl 3):10-15.
31. Rajiv Tandon. Safety and tolerability: how do newer generation 'atypical' antipsychotics compare? *Psychiatric Quarterly.* 2002;73(4);297-311.
32. Zajecka J, Fawcett J, Schaff M, Jeffriess H, Guy C. The role of serotonin in sexual dysfunction: fluoxetine associated orgasm dysfunction. *J Clin Psychiatry* 1991;52(2):66-8.

33. Thorner MO, Besser GM. Bromocriptine treatment of hyperprolactinemic hypogonadism. *Acta Endocrinol (Copenh)*. 1978;88:131-146.
34. Matsuoka I, Nakai T, Miyake M, Hirai M, Ikawa G. Effects of bromocriptine on neuroleptic-induced amenorrhea, galactorrhea and impotence. *Jpn J Psychiatry Neurol.* 1986;40(4):639-46.
35. Valevski A, Modai I, Zbarski E, Zemishlany Z, Weizman A. Effect of amantadine on sexual dysfunction in neuroleptic-treated male schizophrenic patients. *Clin Neuropharmacol.* 1998;21(6):355-7.
36. Tollin SR. Use of the dopamine agonists bromocriptine and cabergoline in the management of risperidone-induced hyperprolactinemia in patients with psychotic disorders. *J Endocrinol Invest.* 2000;23(11):765-70.
37. Benatov R, Reznik I, Zemishlany Z. Sildenafil citrate (Viagra) treatment of sexual dysfunction in a schizophrenic patient. *Eur Psychiatry.* 1999;14(6):353-5.
38. Lare SB, Labbate LA. Sildenafil and erectile dysfunction. *Am J Psychiatry.* 2000;157(12):2055-6.
39. Atmaca M, Kuloglu M, Tezcan E. Sildenafil use in patients with olanzapine-induced erectile dysfunction. *Int J Impot Res.* 2002;14(6):547-9.
40. Aviv A, Shelef A, Weizman A. An open-label trial of sildenafil addition in risperidone-treated male schizophrenia patients with erectile dysfunction. *J Clin Psychiatry.* 2004;65(1):97-103.
41. Yamada K, Kanba S, Yagi G, Asai M. Effectiveness of herbal medicine (shakuyaku-kanzo-to) for neuroleptic-induced hyperprolactinemia. *J Clin Psychopharmacol.* 1997;17(3):234-5.
42. Yamada K, Kanba S, Yagi G, Asai M. Herbal medicine (Shakuyaku-kanzo-to) in the treatment of risperidone-induced amenorrhea. *J Clin Psychopharmacol.* 1999;19(4):380-1.
43. Nemeth A, Arato M, Trener T. Treatment of fluvoxamine induced anorgasmia with a partial drug holiday. *American J Psychiatry.* 1996;153(10):13-15.
44. Montejo AL, Llorca G, Izquierdo JA et al. Incidence of sexual dysfunction associated with antidepressant agents: A prospective multicentre study of 1022 patients. *J Clinical Psychiatry.* 2001;62(Suppl 3):10-20.