DOWNLOAD PDF SEXUAL DYSFUNCTION AND SCHIZOPHRENIA HEIDI J. WEHRING, DEANNA L. KELLY

Chapter 1 : Kelly, Deanna | University of Maryland School of Medicine

Deanna L Kelly1, Heidi J Wehring1, females and is also associated with sexual dysfunction and bone loss. These side effects increase risk of antipsychotic.*

Aripiprazole treatment has been associated with significant decreases in serum prolactin levels. In a recent double blind randomized trial by Kane and colleagues [36] mean prolactin levels decreased in the aripiprazole group from Aripiprazole has been shown to act as an agonist in pituitary cells at the molecular level and thus, lactotroph cells do not become blocked by aripiprazole treatment [38]. Consequences of elevated prolactin Methodological problems in the existing literature make it difficult to determine the prevalence of symptomatic hyperprolactinemia in persons treated with antipsychotics. Many previous studies have only examined prolactin levels and not assessed its symptomatic consequences. Due to inter-individual differences in responses to prolactin, elevated prolactin may at times be asymptomatic. Elevated prolactin levels with no apparent consequences are more common in males, as women tend to have menstrual period abnormalities and other effects with significantly elevated prolactin levels. Many studies in the past have done a poor job at assessing presence of symptomatic side effects in women. Additionally, cross sectional studies can only show an association between symptoms and raised prolactin; proving a causal relationship can be more complex. Ideally, it requires a follow up design to determine whether reversal of hyperprolactinemia is accompanied by symptom resolution. Few studies have taken these issues into account. Health professionals often fail to detect antipsychotic induced hyperprolactinemia symptoms [34]. There are several reasons for this, including the nature of the symptoms and the attitudes of both patients and health professionals. Some patients may be embarrassed to discuss endocrine and sexual symptoms, and do not normally volunteer symptoms to the clinical or research staff. Unlike some antipsychotic adverse effects e. Nonadherence to antipsychotic treatment is common with prolactin related side effects and may be due to many of symptoms discussed below. Galactorrhea Galactorrhea secondary to prolactin elevation is more common in women than in men. In this study, only 8 women reported the symptom on their own to the clinician, illustrating that symptomatic hyperprolactinemia is often unrecognized or under-reported. Lactation from the breast in the nonpregnant state is most likely distressing to women who suffer from a reality distortion illness and likely also to interfere with social and intimate relationships [41]. Gynecomastia also is common and can occur in both men and women. Menstrual abnormalities Menstrual abnormalities are a frequently occurring side effect that often goes unnoticed and under recognized in clinical trials. Typically, this information is not volunteered and clinical investigators do not evaluate this side effect. Seven cross sectional studies have investigated menstrual irregularities in women with schizophrenia receiving long-term treatment with conventional antipsychotics or risperidone. While these studies had small sample sizes and no clear definition of oligomenorrhea or amenorrhea, it is still evident that many women may experience these side effects. Women who experience amenorrhea or oligomenorrhea are likely infertile or subfertile. Long-term amenorrhea also increases the risk of bone mineral density loss and cardiovascular disease [47]. Sexual dysfunction Sexual dysfunction has been implicated as one of the major factors contributing to noncompliance with antipsychotic medications [48 - 51]. Quality of life may be improved with better hormonal and sexual functioning as well [53 , 54]. It can be hypothesized that a better focus on sexuality and preventing sexual dysfunction in schizophrenia would be a major benefit for improving treatment compliance and life quality. While sexual dysfunction and diminished sexual functioning during antipsychotic treatment also may be caused by sedation, weight gain, extrapyramidal side effects, tardive dyskinesia, cholinergic antagonism, alpha-adrenergic blockade and calcium channel blockade [55 - 58], the evidence that elevated prolactin contributes to sexual dysfunction is convincing. Hyperprolactinemia is known to cause hypogonadism and decrease testosterone levels [59]. Prolactin itself appears to have a direct effect on sexual activity as normalization of prolactin levels with bromocriptine has been shown to restore sexual functioning before testosterone levels increase [39

]. Similar results were reported by Burke et al. Other studies have had variable results for correlational type analyses but most generally report higher rates of sexual dysfunction and menstrual disturbances with higher prolactin levels [62 - 65]. The psychiatric literature contains several reports describing sexual disturbances in schizophrenia, but very few well-designed studies address this issue. Few reports describe sexual function or dysfunction in women. The definition and measurement of sexual dysfunction has been inconsistent, but a few general classifications appear in the existing literature [66]. Difficulty achieving and maintaining erection is a common complaint as is delayed or inhibited ejaculation, retrograde and spontaneous ejaculation. Diminished libido and decreased orgasm quality are also commonly reported in men. Priapism, a sustained painful erection that can result in permanent impotence, has also been reported [68 , 69]. Women report decreased libido and orgasmic dysfunction, including difficulty achieving orgasm, changes in the quality of orgasm and anorgasmia [40 , 59]. Women may also experience dysparenuria secondary to vaginal atrophy and dryness. Sexual dysfunction appears to be a particularly salient issue in women treated with antipsychotic medications: Other adverse effects Bone mineral density Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. People with schizophrenia represent a high-risk group for developing osteoporosis because of the disease itself, long-term antipsychotic drug treatment, lack of exercise, poor nutrition and high rates of smoking [72 , 73]. Hyperprolactinemia is known to increase the risk of bone mineral density BMD loss in patients with schizophrenia with long term antipsychotic drug treatment, either through secondary hypogonadism [74] or hyperprolactinemia itself [75]. Bone fractures occur more frequently in people with schizophrenia taking antipsychotics than in the nonpsychiatric population [77 , 78]. Other recent evidence suggests that having amenorrhea or using prolactin elevating antipsychotic drugs are associated with a higher risk for osteoporosis and fracture [79 - 82]. Very recently, Graham and others [83] published a literature review showing that first generation antipsychotics and certain second generation agents such as risperidone show high prolactin elevations and are associated with an increased risk of osteoporosis and fracture. Knocking out the Dc receptor in mice results in a striking progressive increase in lactotroph cells in the pituitary gland and the rate of pituitary tumors [84]. In these same mice, prolactin levels are 6 times higher in females as compared to males and females develop tumors much earlier than males. Long term treatment with antipsychotics in mice have led to the development of pituitary adenomas and adenocarcinomas [85]. Another prospective study found that pituitary volume significantly increases over one year in people treated with prolactin elevating antipsychotics [87]. The true risk of pituitary tumor with prolactin elevating medications remains unclear. Among the few studies that have addressed whether dopamine receptor antagonists increase risk of breast cancer, results have been conflicting [88]. However, until more data is available, it remains of concern with long term use. This was the first study to examine prolactin related effects as a risk factor of suicide. The authors report that prolactin related effects were profoundly associated with increased suicide risk: The exact mechanism for the suicide risk increase is unclear. Potential causes include nonadherence to treatment, low quality of life associated with sexual dysfunction or increased rates of depression and anxiety associated with prolactin elevation effects [89 - 91]. Nonetheless, our increasing knowledge of significant prolactin related side effects and this new data on very large relative increases in risks of suicidality associated with these side effects mandate increased attention to prolactin-mediated adverse effects of antipsychotic treatments and a search for effective treatments for antipsychotic-induced hyperprolactinemia, particularly in women. Outcome measures include resolution of menstrual abnormalities or galactorrhea, improvement in sexual functioning, prolactin level improvement, changes in bone resorption measures, psychiatric symptoms, quality of life and related metabolic effects. We are pleased to bring attention to our ongoing study and to publish protocol details as ongoing attention to clinical trials will help improve recognition and reporting of side effects related to antipsychotic-induced prolactin elevations as well as impact on study recruitment NCT Below is the rationale for why we use low dose aripiprazole and a summary of the study methodology. Treatment rationale Few evidence-based treatment options are available

for hyperprolactinemia and associated side effects in patients who are treated with a potent D2 blocking drug. A reduction in dose in the offending antipsychotic is the simplest treatment strategy, but its effectiveness is questionable and it carries the risk or precipitating an exacerbation or relapse of psychotic symptoms. Switching to a prolactin sparing antipsychotic may be effective for decreasing prolactin [16 , 95 -]. However, these studies provide insufficient evidence to examine the effects of switching on symptom changes and relapse rates or on symptomatic improvement of prolactin related side effects and the risk of relapse is present [95 ,]. Clinicians do not appear to have as much confidence in the efficacy of monotherapy with aripiprazole compared to risperidone, as evidenced by the smaller market share of aripiprazole relative to other first line antipsychotics. No data are available from large-scale non-industry sponsored clinical trials comparing the efficacy of aripiprazole to the efficacy with risperidone or other second generation antipsychotics. Observational studies have reported greater effectiveness for symptom improvement with olanzapine and risperidone than with aripiprazole [,]. Other pharmacologic treatments for prolactin elevation have been tried but have side effects of their own. Bromocriptine, a dopamine agonist has been investigated in several studies for its potential to decrease prolactin levels. However, dopamine agonists such as bromocriptine have also been associated with worsening of psychosis [ ]. However, cardiopulmonary complications are a concern with ergot derived dopamine agonists [ ]. Metformin was recently studied as an adjunct to antipsychotic treatment in a randomized double blind placebo controlled trial. In other studies, selegiline and cyproheptadine were not effective for sexual dysfunction and one small double blind trial has found benefits with sildenafil for sexual dysfunction but this was not focused on prolactin as a culprit [,]. As mentioned, our preliminary work has shown that aripiprazole can significantly improve hyperprolactinemia and related side effects as an adjunct to haloperidol in people with schizophrenia [94]. We have also found that aripiprazole added to dopamine raising antipsychotics can decrease prolactin levels and lead to women regaining their menstrual periods. This strategy is highly effective at decreasing prolactin levels and improving related side effects. There are a few case reports with aripiprazole improving hyperprolactinemia in patients as compared to their previous treatments [-]. Aripiprazole monotherapy [-] in double blind trials has shown improvement in prolactin levels compared to baseline. While there were no statistically significant decreases in clinical psychiatric symptoms, aripiprazole was found to improve prolactin elevations in both men and women , with the authors suggesting this deserves further study as a treatment. In a published study by our group in both men and women we found that adjunct aripiprazole therapy with haloperidol significantly decreased prolactin in the majority of patients relative to placebo [94].

Chapter 2 : - NLM Catalog Result

Participants had elevated prolactin (>24 ng/mL) and were experiencing galactorrhea, amenorrhea, oligomenorrhea, or sexual dysfunction on a prolactin-elevating antipsychotic. Participants were evaluated biweekly for prolactin elevation and galactorrhea and completed a menstrual diary review.

She completed residency training in psychiatric pharmacy practice at the University of Maryland in and became board certified in psychiatric pharmacy practice in Kelly has led and been involved in numerous clinical trials in schizophrenia and has been active in psychopharmacology research for the past 21 years. Kelly has coauthored and authored 18 books and book chapters, published peer-reviewed articles, presented over posters and has given over invited lectures. Adjunctive Minocycline in clozapine treated schizophrenia patients with persistent symptoms. Evaluation of the safety of clozapine use in patients with benign neutropenia. J Clin Psych ;77 Gliadin-related antibodies in schizophrenia. Addressing barriers to clozapine underutilization: Brain Behav Immun ; Increased circulating regulatory T cells in medicated people with schizophrenia. Pharmacologic treatment of schizophrenia. First Edition, Caddo, OK Second Edition, Caddo, OK Third Edition, Caddo, OK, The long-term efficacy, effectiveness and safety of second-generation antipsychotic drugs. Csernansky JG, Lauriello J. Rakel R and Bope E. Saunders, Philadelphia , pp. Saunders, Philadelphia , Antipsychotic Therapeutics Efficacy and Side Effects. Thaker G, Carpenter WT. Kelly DL, Weiner E. Reaching for wellness in schizophrenia: Boggs D, Kelly DL. Sexual Dysfunction in Schizophrenia. Medical Illness in Schizophrenia, second edition American Psychiatric Publishing, Inc. Schizophrenia, in Pharmacotherapy Principles and Practice, second edition. Therapeutic Strategies in Schizophrenia. Matthias, and Marie A. Rehospitalization rates of depot antipsychotics and pharmacoeconomic implications: American Journal of Health-Systems Pharmacy. Substitution of immediate release valproic acid for divalproex sodium for adult psychiatric inpatients. Olanzapine response in therapy-refractory schizophrenia with substance abuse. Weight gain in adolescents treated with risperidone and conventional antipsychotics. The Journal of the Child and Adolescent Psychopharmacology. Differential olanzapine plasma concentrations by sex in a fixed dose study. Rehospitalization rates of patients recently discharged on a regimen of risperidone or clozapine. American Journal of Psychiatry. Treatment-resistant schizophrenic patients respond to clozapine after olanzapine non-response. A dose-outcome analysis of risperidone. Ziprasidone and the QTc: Biperiden for excessive sweating associated with clozapine use. Management of treatment-resistant schizophrenia. Comparison of discharge rates and drug costs for patients with schizophrenia treated with risperidone or olanzapine. Current status of antipsychotic treatment. Circumstances of suicide among patients with schizophrenia. Novel factor-based symptom scores in treatment-resistant schizophrenia: Clozapine in Treatment-Resistant Schizophrenia. Annals of Clin Psychiatry. Six-month review of weight and metabolic parameters in patients on clozapine, risperidone, olanzapine and quetiapine. Journal of Clinical Psychiatry. Clozapine treatment in patients with prior substance abuse. Canadian Journal of Psychiatry. Evaluating sexual function in patients with treatment-resistant schizophrenia. Deaths from diabetic ketoacidosis after long-term clozapine treatment. Measurement of antipsychotic-induced side effects: Adjunctive quetiapine decreases symptoms of tardive dyskinesia in a patient taking risperidone: Rehospitalization risk with second-generation and depot antipsychotics. Annals of Clinical Psychiatry. The Efficacy of High Dose Olanzapine vs. Clozapine in Treatment-Resistant Schizophrenia: A Double-Blind Crossover Study. Perception of depot antipsychotics by mental health professionals. Fluoxetine augmentation of haloperidol in chronic schizophrenia. Psychotropic prescribing for acute inpatient admissions in patients with severe psychosis. J of Psychiatric Research. The effects of clozapine and high dose olanzapine on brain function in treatment-resistant schizophrenia: Cardiovascular disease in Relation to Weight in deceased persons with schizophrenia. Medicinal Chemistry Reviews- Online. The prevalence of hyperprolactinemia after long-term haloperidol use in patients with chronic schizophrenia. J Clin Psychopharmacol ; Second-generation antipsychotics for schizophrenia: Israel

Journal of Psychiatr and Related Sciences. Risperidone and quetiapine vs. A comparison of clozapine use in Maryland and in Victoria, Australia. Thyroid function in treatment-resistant schizophrenia patients treated with quetiapine, risperidone or fluphenazine. Tardive dyskinesia predicts prolactin response to buspirone challenge in people with schizophrenia. Journal of Neuropsychiatry and Clinical Neurosciences. Treatment Considerations in Women with Schizophrenia. A randomized double-blind week study of quetiapine, risperidone or fluphenazine on sexual functioning in people with schizophrenia. Considerations for Clinicians and Patients. Quetipine at High doses for Treatment Refractory Schizophrenia. A randomized double blind trial of atomoxetine for cognitive impairments in 32 people with schizophrenia. Cardiac-Related findings at autopsy in people with severe mental illness treated with clozapine or risperidone. Cardiovascular disease mortality in patients with chronic schizophrenia treated with clozapine: Nonresponse to clozapine and premorbid functioning in treatment of refractory schizophrenia. The relationship of brain weight to body mass index BMI upon autopsy in young people with severe mental illness. Adjunctive risperidone for partially responsive people with schizophrenia treated with clozapine Neuropsychopharmacology. Drug and Alcohol Dependence. The impact of substance abuse on osteoporosis screening and risk of osteoporosis in women with psychotic disorders. Cannabinoids and metabolites in expectorated oral fluid after eight days of controlled around-the-clock oral THC administration. Analytical and Bioanalytical Chemistry, ; Placebo-controlled trial of atomoxetine for weight reduction in people with schizophrenia treated with clozapine or olanzapine. Clin Schizophr Relat Psychoses. Cigarette smoking and mortality risk in people with schizophrenia. Varenicline for smoking cessation in people with schizophrenia: Exercise program adherence using a 5-kilometer event and an achievable goal in people with schizophrenia. Biol Res Nurs ;

Chapter 3 : Adjunct Aripiprazole for Symptomatic Hyperprolactinemia in Female Schizophrenia - Deanna K

Sexual dysfunction and schizophrenia / Heidi J. Wehring, Deanna L. Kelly. Managing the health outcomes of schizophrenia treatment in children and adolescents / Christoph U. Correll. Medical health in aging persons with schizophrenia / Samantha Brenner, Carl I. Cohen.

This article has been cited by other articles in PMC. Abstract Prolactin elevations occur in people treated with antipsychotic medications and are often much higher in women than in men. Hyperprolactinemia is known to cause amenorrhea, oligomenorrhea, galactorrhea and gynecomastia in females and is also associated with sexual dysfunction and bone loss. These side effects increase risk of antipsychotic nonadherence and suicide and pose significant problems in the long term management of women with schizophrenia. In this manuscript, we review the literature on prolactin; its physiology, plasma levels, side effects and strategies for treatment. We also present the rationale and protocol for an ongoing clinical trial to treat symptomatic hyperprolactinemia in premenopausal women with schizophrenia. More attention and focus are needed to address these significant side effects and help the field better personalize the treatment of women with schizophrenia. Women, Prolactin, Amenorrhea, Galactorrhea, Clinical trial, Sexual dysfunction, Osteoporosis, Aripiprazole Background Hyperprolactinemia and related consequences are known side effects of several first and second generation antipsychotics. Elevation of serum prolactin by antipsychotic drug and clinical manifestations associated with this condition has been recognized for more than three decades [1]. Nevertheless, the syndrome of antipsychotic-induced hyperprolactinemia has been relatively neglected. A review article in reported that from â€" a search of the Medline database returned journal articles on antipsychotics and extrapyramidal side effects, yet only articles on antipsychotics and hyperprolactinemia [2]. Hallewell and colleagues [3] performed a survey and reported that both psychiatrists and psychiatric nurses underestimate the prevalence of key symptoms associated with hyperprolactinemia. In recent years this issue has begun to gain more attention. The last iteration of the Patient Outcomes Research Team PORT guidelines specifically addresses the issue of hyperprolactinemia associated with antipsychotic use however, too few randomized double blind trials were available to make and evidence based recommendation [5]. Also very recently, suicide risk has been found to be significantly increased with symptomatic hyperprolactinemia [6]. Our group has been addressing hyperprolactinemia for over a decade and are currently running an adjunct treatment trial to improve outcomes in women with this distressing side effect. In this manuscript, we review the physiology and treatment of elevated prolactin secondary to antipsychotic medications and present the rationale and protocol for an ongoing clinical trial that addresses this issue in women. Prolactin physiology The main physiologic function of prolactin is to cause breast enlargement during pregnancy and milk production during lactation. Prolactin is an amino acid polypeptide hormone secreted by the lactotroph cells of the anterior pituitary. Transient and mild increases in prolactin levels occur in response to sexual activity, stress and eating [8]. In women, prolactin levels are typically higher during mid cycle and the second half of the menstrual cycle. During pregnancy, serum prolactin levels increase to reach levels 10â€"20 times the normal value. The reductions in sexual functioning and fertility associated with nursing may have evolutionary advantages. In animals, prolactin is known to have an important function in promoting maternal behavior; however, this has not been proven in humans. Because women have a physiologic purpose for prolactin elevations, the female prolactin system may be more likely to respond to stimuli, which may underlie significantly higher prolactin levels in women versus men after dopamine antagonist treatment. Men are more likely to have a buffer system in place to guard against significant prolactin elevations. Normal prolactin levels Despite these variations in serum prolactin levels, both within and between individuals, there is a reasonable consensus regarding the upper limit of the normal range. Prolactin control Inhibition and stimulation Prolactin secretion is under the control of various peptide and steroid hormones and neurotransmitters [19]. Dopamine, however, is the predominant prolactin-inhibiting factor in humans and

animals. In the tuberoinfundibular neurons of the hypothalamus, dopamine is produced and released from nerve endings. It is transported by the portal hypophyseal circulation to the pituitary, where it binds to dopamine D2 receptors on the membrane of the lactotroph cells [20]. The presence of dopamine suppresses the release of prolactin to a minimum. Dopamine D2 antagonists, such as most antipsychotics, bind to the D2 receptors and lead to the release of prolactin in the lactotroph cells. Animal and human studies demonstrate that serotonin may stimulate prolactin secretion [21] as well as several peptide neurotransmitters, including thyrotropin releasing hormone and cholecystokinin [19]. These effects are not as well characterized or robust as that of dopamine on prolactin control. Antipsychotic medications and prolactin Virtually all antipsychotic drugs have the capacity to block D2 receptors in the mesolimbic and mesocortical areas, which is believed to be integral for efficacy of these agents. In other areas of the brain, however, areas of D2 blockade can cause significant adverse effects. Extrapyramidal side effects such as Parkinsonism result from D2 antagonism in the striatum, while blockade of D2 receptors on lactotroph cells causes hyperprolactinemia, since the main inhibitory influence i. Conventional antipsychotics in people with schizophrenia as well as healthy individuals cause prolactin elevations within hours of taking these agents [22 , 23]. The propensity to elevate prolactin levels varies among second-generation antipsychotics SGAs. Clozapine has a low propensity to block dopamine in the tuberinfundibular pathway and has a negligible effect on plasma prolactin levels [25]. Olanzapine causes transient elevations in plasma prolactin levels. As with FGAs, elevation of prolactin with olanzapine appears to be a dose related phenomenon [27]. Quetiapine has negligible effects on the elevation of prolactin. In all of the large trials of quetiapine, prolactin levels were reported to decrease from baseline to endpoint during quetiapine treatment and no differences were noted between quetiapine and placebo [29 - 32]. It appears as though elevations may occur with ziprasidone. Of all the SGAs, risperidone and paliperidone [34] have the highest propensity to elevate plasma prolactin levels, and do so in a dose-related fashion. It is also well established that, while high potency FGAs have prolactin raising capabilities, risperidone and paliperidone elevate prolactin significantly more than FGAs. Aripiprazole treatment has been associated with significant decreases in serum prolactin levels. In a recent double blind randomized trial by Kane and colleagues [36] mean prolactin levels decreased in the aripiprazole group from Aripiprazole has been shown to act as an agonist in pituitary cells at the molecular level and thus, lactotroph cells do not become blocked by aripiprazole treatment [38]. Consequences of elevated prolactin Methodological problems in the existing literature make it difficult to determine the prevalence of symptomatic hyperprolactinemia in persons treated with antipsychotics. Many previous studies have only examined prolactin levels and not assessed its symptomatic consequences. Due to inter-individual differences in responses to prolactin, elevated prolactin may at times be asymptomatic. Elevated prolactin levels with no apparent consequences are more common in males, as women tend to have menstrual period abnormalities and other effects with significantly elevated prolactin levels. Many studies in the past have done a poor job at assessing presence of symptomatic side effects in women. Additionally, cross sectional studies can only show an association between symptoms and raised prolactin; proving a causal relationship can be more complex. Ideally, it requires a follow up design to determine whether reversal of hyperprolactinemia is accompanied by symptom resolution. Few studies have taken these issues into account. Health professionals often fail to detect antipsychotic induced hyperprolactinemia symptoms [34]. There are several reasons for this, including the nature of the symptoms and the attitudes of both patients and health professionals. Some patients may be embarrassed to discuss endocrine and sexual symptoms, and do not normally volunteer symptoms to the clinical or research staff. Unlike some antipsychotic adverse effects e. Nonadherence to antipsychotic treatment is common with prolactin related side effects and may be due to many of symptoms discussed below. Galactorrhea Galactorrhea secondary to prolactin elevation is more common in women than in men. In this study, only 8 women reported the symptom on their own to the clinician, illustrating that symptomatic hyperprolactinemia is often unrecognized or under-reported. Lactation from the breast in the nonpregnant state is most likely distressing to women who suffer from a reality distortion illness and likely also to interfere with social and

intimate relationships [41]. Gynecomastia also is common and can occur in both men and women. Menstrual abnormalities Menstrual abnormalities are a frequently occurring side effect that often goes unnoticed and under recognized in clinical trials. Typically, this information is not volunteered and clinical investigators do not evaluate this side effect. Seven cross sectional studies have investigated menstrual irregularities in women with schizophrenia receiving long-term treatment with conventional antipsychotics or risperidone. While these studies had small sample sizes and no clear definition of oligomenorrhea or amenorrhea, it is still evident that many women may experience these side effects. Women who experience amenorrhea or oligomenorrhea are likely infertile or subfertile. Long-term amenorrhea also increases the risk of bone mineral density loss and cardiovascular disease [47]. Sexual dysfunction Sexual dysfunction has been implicated as one of the major factors contributing to noncompliance with antipsychotic medications [48 - 51]. Quality of life may be improved with better hormonal and sexual functioning as well [53 , 54]. It can be hypothesized that a better focus on sexuality and preventing sexual dysfunction in schizophrenia would be a major benefit for improving treatment compliance and life quality. While sexual dysfunction and diminished sexual functioning during antipsychotic treatment also may be caused by sedation, weight gain, extrapyramidal side effects, tardive dyskinesia, cholinergic antagonism, alpha-adrenergic blockade and calcium channel blockade [55 - 58], the evidence that elevated prolactin contributes to sexual dysfunction is convincing. Hyperprolactinemia is known to cause hypogonadism and decrease testosterone levels [59]. Prolactin itself appears to have a direct effect on sexual activity as normalization of prolactin levels with bromocriptine has been shown to restore sexual functioning before testosterone levels increase [39]. Similar results were reported by Burke et al. Other studies have had variable results for correlational type analyses but most generally report higher rates of sexual dysfunction and menstrual disturbances with higher prolactin levels [62 - 65]. The psychiatric literature contains several reports describing sexual disturbances in schizophrenia, but very few well-designed studies address this issue. Few reports describe sexual function or dysfunction in women. The definition and measurement of sexual dysfunction has been inconsistent, but a few general classifications appear in the existing literature [66]. Difficulty achieving and maintaining erection is a common complaint as is delayed or inhibited ejaculation, retrograde and spontaneous ejaculation. Diminished libido and decreased orgasm quality are also commonly reported in men. Priapism, a sustained painful erection that can result in permanent impotence, has also been reported [68 , 69]. Women report decreased libido and orgasmic dysfunction, including difficulty achieving orgasm, changes in the quality of orgasm and anorgasmia [40 , 59]. Women may also experience dysparenuria secondary to vaginal atrophy and dryness. Sexual dysfunction appears to be a particularly salient issue in women treated with antipsychotic medications: Other adverse effects Bone mineral density Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. People with schizophrenia represent a high-risk group for developing osteoporosis because of the disease itself, long-term antipsychotic drug treatment, lack of exercise, poor nutrition and high rates of smoking [72 , 73]. Hyperprolactinemia is known to increase the risk of bone mineral density BMD loss in patients with schizophrenia with long term antipsychotic drug treatment, either through secondary hypogonadism [74] or hyperprolactinemia itself [75]. Bone fractures occur more frequently in people with schizophrenia taking antipsychotics than in the nonpsychiatric population [77 , 78]. Other recent evidence suggests that having amenorrhea or using prolactin elevating antipsychotic drugs are associated with a higher risk for osteoporosis and fracture [79 - 82]. Very recently, Graham and others [83] published a literature review showing that first generation antipsychotics and certain second generation agents such as risperidone show high prolactin elevations and are associated with an increased risk of osteoporosis and fracture. Knocking out the Dc receptor in mice results in a striking progressive increase in lactotroph cells in the pituitary gland and the rate of pituitary tumors [84]. In these same mice, prolactin levels are 6 times higher in females as compared to males and females develop tumors much earlier than males.