Review

Women and Psychopharmacology

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ABSTRACT AND INTRODUCTION

Abstract

Despite the fact that women are the primary consumers of psychotropic medication, little attention has been paid to sex differences in psychopharmacology. Sex differences have been found in the absorption, metabolism, and excretion of many medications. Women tend to respond more favorably to SSRIs than to tricyclics, have more side effects with psychotropic medication, and are more likely to develop tardive dyskinesia. They may also be more concerned about certain side effects such as weight gain from neuroleptic medication. In treating women patients, the clinician must be aware of the possible effect of the menstrual cycle on serum levels of medications. It is also essential to understand the effects of such medication during pregnancy and the postpartum period. Tricyclic and SSRI antidepressants have not been found to cause organic or behavioral teratogenesis when given in pregnancy. Lithium has been associated with Ebstein's anomaly and carbamazepine and valproic acid with the occurrence of neural tube defects. Although small quantities of all psychotropic drugs pass through breast milk, they do not appear to have an immediate effect on the infant. Women also take exogenous hormones. Oral contraceptives differentially affect the blood levels of various benzodiazepines, increasing levels of diazepam, and decreasing levels of temazepam. Drugs such as carbamazepine can interfere with the action of oral contraceptives. Postmenopausal women may require lower doses of antipsychotics. Although hormone replacement therapy in itself does not seem to be a treatment for depression, it may have some benefit in augmenting the effects of antidepressant medication.

Introduction

Women take more psychotropic medications than men. About two thirds of antidepressants and tranquilizers dispensed in the United States are prescribed to women.[1] Also, more women than men take multiple medications.[1,2] In general, women tend to have more side effects and adverse effects with psychotropic medication than do men.[2] Women's exposure to monthly variations in gonadal hormones may alter the metabolism, distribution, elimination, and, therefore, response to medication. In addition, women become pregnant, breastfeed, go through menopause, and may take hormone replacement therapy (HRT). All of these conditions may have an impact on the psychotropic medication used, dosage required for efficacy, and response. Thus, it is important for the clinician to understand how physiology at various times in the female lifecycle may affect a woman's response to psychotropic treatment.

Psychopharmacology: Physiologic Differences Between Women and Men

The effectiveness of medication depends on how it is absorbed, metabolized, distributed, and excreted in the body. There are numerous ways in which these processes differ between men and women.[3] Research is still being carried out to determine how these processes work together or counteract each other in the case of specific psychotropic medications.

Absorption and Bioavailability

The majority of studies show that premenopausal women have slower gastric emptying times than men.[4,5] This results in delayed passage of the drug into the small intestine, which has the greater absorptive capacity. In turn, this can lead to slower absorption, delayed peak levels, and lower peak serum concentrations of the drug. Women have also been found to have lower basal gastric acid secretion as compared with men,[6] which may increase the absorption of bases, such as tricyclic antidepressants, benzodiazepines, and phenothiazines, and decrease gastric absorption of acids such as phenytoin and barbiturates.

Distribution

Women on average weigh less than men and have lower body surface areas. They tend to have lower total blood volumes than men.[7] Adult women age 25-35, on average, have an absolute percentage of body fat that is 11% higher than men in the same age range.[8] For a given dosage of drug, this may result in women initially having a lower serum concentration compared with men. Over time, however, the gradual release of lipophilic medications stored in fat tissue may lead to higher serum levels in women.[9] The rate of cerebral blood flow, which may be higher in women, may affect the distribution of psychotropic drugs to the brain.[10] Distribution may also be affected by the degree of protein binding, although there is no convincing evidence that this differs between men and women.[11]

Metabolism and Elimination

The liver is the most important site of metabolism. There seem to be sex differences in the activity of various drug-metabolizing systems involved in the biotransformation of drugs.[3] As well, sex differences in renal clearance may mean that for drugs eliminated via the kidney, women could have higher serum levels of drug than men for a given dosage.[12]

Overall, women tend to have greater bioavailability and slower clearance of drugs compared with men, the consequence being that optimal doses for men may be relatively high in women. This may be the reason that women generally experience side effects of psychotropic drugs about twice as often as men.[13] Reports vary about the incidence of extrapyramidal side effects, with some finding more dystonias in women[14] and others finding fewer.[15] Women have also been found to have a higher rate than men of tardive dyskinesia.[16]

PSYCHOPHARMACOLOGY IN WOMEN: CHANGES THROUGHOUT THE LIFE CYCLE

Menstrual Cycle Effects

Physiologic changes. Women's physiology changes throughout the menstrual cycle. The majority of studies have found that there is a 28% to 36% decrease in the rate of gastric emptying premenstrually.[17,18] The possible decreases in serum level of drug as a result are likely offset by the slower, small intestinal transit time,[19] thereby tending to result in higher serum levels of drugs premenstrually. As well, a decrease in gastric acid secretion that probably also occurs premenstrually[20] would increase blood levels of base drugs such as tricyclic antidepressants.

Evidence remains inconclusive that total body water changes over the course of the menstrual cycle. However, in those women who retain water premenstrually, a decrease in serum levels of water-soluble drugs may occur because of a dilution effect. Although studies of renal elimination have also produced mixed results, Hamilton and Yonkers[3] found that the bulk of the evidence suggests there may be a significant decline in renal clearance between the luteal and early follicular phase. As well, for some women, changes in metabolism or effects on central neurotransmitters or CNS receptor numbers or sensitivity may vary throughout the menstrual cycle.

Practical application. Women may suffer from premenstrual dysphoric disorder (PMDD) or have an exacerbation of symptoms of another ongoing psychiatric illness during the premenstrual phase. Selective serotonin reuptake inhibitors (SSRIs)[21,22] and venlafaxine[23] have been found to be effective in treating PMDD. One should begin by giving the drug for the duration of a menstrual cycle. It may take several cycles to assess the benefit of a particular dosage of medication. Once an effective dosage is found, the individual may try taking the drug only in the second part of the cycle beginning approximately around ovulation time and continuing until a few days after the onset of menses.[24]

In women with premenstrual exacerbation of a major psychiatric illness, one should first try increasing the dosage of the medication throughout the entire cycle. For women who continue to be more symptomatic in the premenstrual phase, one may have the option of further increasing the constant daily dose of the medication for the whole cycle or increasing the dose for only 3-5 days before the predicted onset of the increased symptoms, decreasing again 2-3 days after the start of the menses.

Pregnancy Effects

Physiologic changes. The increase in total body water that occurs during pregnancy may lower serum concentrations of drug. Total protein is also reduced, however, thereby decreasing drug binding and thus increasing its serum concentration. Drug absorption is altered by a decrease in the emptying rate of the gastrointestinal tract as well as by a decrease in gastric acid secretion. Glomerular filtration rates increase during pregnancy, resulting in a faster excretion of some drugs, such as lithium, so higher doses are required. In the second trimester of pregnancy, there is often a physiologic drop in blood pressure, which may add to the orthostatic hypotension effects of some antipsychotic and tricyclic antidepressant drugs. Constipation, which is common in pregnancy, may be worsened by medications with anticholinergic side effects.[25] In general, higher doses of medication are often required in pregnancy to achieve therapeutic serum levels. Postdelivery, the dosage must be reviewed and usually decreased to prevent toxicity.

Practical application. Although, ideally, women who are trying to become pregnant should not be taking any psychotropic medication, practically this is not always possible. For women who are still being treated for past episodes of psychiatric illness, it may be more harmful to them to cease taking medication and thereby increase the risk of their developing a reoccurrence of illness before or in the early stages of pregnancy. Neuroleptics and antidepressant medications, such as imipramine, amitriptyline, and sertraline, can lead to hyperprolactinemia, which may interfere with fertility. This, therefore, should be considered if a woman is having difficulty becoming pregnant; dosages may have to be lowered or drugs changed.

Detailed reviews of the use of psychotropic drugs during pregnancy and lactation are found elsewhere.[25-28] In general, because of the poor quality of much of the research, it is impossible to guarantee that any psychotropic drug is entirely safe during pregnancy. However, for a majority of drugs, there is little evidence of either physical malformations or behavioral teratogenicity.

Generally speaking, women who require psychotropic medication during pregnancy should receive the lowest effective doses, and the medication should be given in divided doses so that they have less effect on the fetus. During the first trimester, high-potency agents tend to be preferred because they cause fewer autonomic anticholinergic and cardiovascular effects as well as less hypotension and sedation. The atypical antipsychotics have not been well studied. Although monoamine oxidase inhibitors (MAOIs) can be teratogenic,[29] there is no clear evidence for such harm caused by tricyclics or SSRIs.[30]

Recent studies of lithium have suggested that it may be less teratogenic than previously thought,[31] although the risk of Ebstein's anomaly still seems to be 10-20 times as common after first-trimester exposure than in the general population.[32] Unstable bipolar patients may be maintained on lithium with close monitoring and targeted ultrasound and fetal echocardiograms at week 18 of gestation to rule out cardiovascular malformation.[33] Sodium-depleting diuretics and low-salt diets should be avoided, and lithium levels should be monitored monthly. Lithium should be given in divided doses to a maximum of 300 mg each. Carbamazepine has been associated with craniofacial defects[34] and neural tube defects,[35] as has valproic acid[36] when taken during the first trimester of pregnancy. If carbamazepine or valproic acid is required to stabilize the pregnant patient, she should also take 5 mg daily of folic acid to decrease the risk of neural tube defects. Ultrasound should be performed at weeks 10-19 of gestation to detect possible abnormalities.

Nonpharmacologic treatments of anxiety such as relaxation techniques, cognitive therapy, and psychotherapy should be used when possible. If anxiolytics are needed, they should be given in the lowest effective dose for the briefest possible period of time. Generally, anxiety is better treated with antidepressant medication.

In the second and third trimester, most psychotropic drugs seem to be safe. Although the central nervous system continues to develop throughout pregnancy, no clear association has been noted between the use of psychotropic drugs and the occurrence of microcephaly or mental retardation. Pregnancy-related physiologic changes may require an increased dosage of medication during the third trimester. Lithium use during this time may infrequently cause a large goiter in the fetus, ultimately necessitating a cesarean section.[37] Although some physicians have recommended lowering or discontinuing antidepressant medications 2 weeks before the expected date of delivery to reduce the possibility of side effects, toxicity, and withdrawal in the newborn, others are concerned that discontinuing drugs at this time may increase the risk of postpartum psychiatric disorders.[25]

Small doses of major and minor tranquilizers have long been used by obstetricians during labor. It is best to avoid long-acting benzodiazepines because they may adversely affect the neonate. Lithium should be lowered or discontinued a couple of weeks before delivery to avoid toxicity in the mother or in the baby postdelivery. It is wise to have the patient restart the lithium very soon after delivery, being careful to monitor blood levels, as there is some evidence that prompt resumption of treatment can reduce the chances of postpartum mania from 10% to 50% in vulnerable women.[38]

Postpartum Effects

Physiologic changes. Dramatic changes in hormone and electrolyte balance and fluid volume level occur during labor and postpartum.[39] Progesterone and estradiol levels rapidly fall to prepregnancy levels by the third day postpartum. Prolactin is no longer blocked and lactation begins. Plasma corticosteroid levels decrease significantly within 4 hours postpartum. Thyroid functions return to prepregnancy levels by approximately 4 weeks after delivery. Plasma renin levels fall. Sodium excretion increases while calcium secretion decreases. Rapid weight loss occurs.

The major concern about drugs used in the postpartum period has to do with the effects on the breastfeeding infant. Drugs pass into the milk in a nonionized form. As milk is rich in fat and slightly acidic, drugs that are acidic, ionized, protein-bound, or lipid insoluble will have high plasma to milk ratios. Antipsychotic drugs, being highly protein-bound, will therefore have low milk concentrations. As infants have little body fat, reduced protein binding, and lower excretion rates, the effects of the drugs absorbed through breastfeeding will tend to be increased.[28]

Practical applications. Ten to fifteen percent of women suffer from a major depressive episode during the postpartum period and .01% to .02% develop a psychotic illness postpartum. Many of these mothers have chosen to breastfeed and may be worried about the consequences of taking psychotropic medication during this time.

It is always useful to first ascertain whether the mother wishes to continue breastfeeding. For some women, breastfeeding is the one positive thing they feel they can give to their baby when, generally, they feel like very bad mothers as a result of their depressed mood. For other women, breastfeeding may become an agony when they are having difficulty coping with even simple day-to-day tasks. If the mother wishes to continue breastfeeding, it is important to be knowledgeable about the effects of various medications on the infant.

The majority of psychotropic medications pass from the maternal plasma to the breast milk in very small quantities. A critical review of the literature[40] found that amitriptyline, nortriptyline, desipramine, clomipramine, and sertraline were not found in quantifiable amounts in nursing infants, and no adverse effects were reported. Infants older than 10 weeks showed no accumulation of doxepine or fluoxetine and were at low risk for adverse effects. Stowe and colleagues[41] found no adverse short-term effects with maternal ingestion of paroxetine. The effects of MAOIs are unknown. Overall, the American Academy of Pediatrics[42] does not preclude the use of non-MAOI antidepressants in breastfeeding women but labels them as "drugs whose effects on nursing infants are unknown but may be of concern." No data are available on the long-term effects of breastfeeding while taking antidepressants; however, infants exposed to fluoxetine or tricyclics during the first trimester of pregnancy have now been followed up to school age with no evidence of malformation or behavioral teratogenicity.[30] This may suggest that the small amounts taken in breastfeeding may be safe in the long term.

The quantity of major tranquilizers found in breast milk is usually less than 30% of that found in maternal plasma.[43] Some minor short-term side effects have been noted, such as drowsiness with chlorpromazine and galactorrhea with chlorpromazine and thioridazine. One study showed that the breast milk of a mother on haloperidol had 2/3 the maternal serum levels of the drug, although the infant was developing normally at 6 and 12 months.[44] Data on atypical antipsychotics are limited to case studies. Breastfeeding mothers should be on only 1 antipsychotic, at the lowest possible total dose, and should take it in divided doses right after breastfeeding. Women who require very high doses or more than 1 antipsychotic should avoid breastfeeding.

Benzodiazepines can lead to lethargy, jaundice, and poor temperature regulation in the infant, especially when taken during the first 6 weeks while the infant still has difficulty metabolizing these

agents. Sustained use of benzodiazepines and those with a long half-life are contraindicated during breastfeeding.

Levels of lithium in breast milk are 40% to 50% of those in maternal serum.[45] It has been shown to cause such toxic effects in the infant as cyanotic episodes, lethargy, hypothermia, and hypotonia[46]; breastfeeding mothers should not take lithium.[42] Both carbamazepine and valproic acid are found in the serum of infants breastfed by mothers on these drugs, but levels are lower than therapeutic levels for childhood epilepsy. Extensive reviews have not found any long-term cognitive or behavioral adverse effects,[27] and these drugs are deemed compatible with breastfeeding by the American Academy of Pediatrics.[42] Newer anticonvulsants used to treat bipolar illness (topiramate, lamotrigine, and gabapentin) all pass into breast milk. Although information is still limited, there do not appear to be any reports of immediate adverse effects or problems with long-term cognition in infants breastfed by mothers on gabapentin or lamotrigine. Bar-Oz and associates[27] recommend allowing breastfeeding while monitoring the infant for drug levels and side effects. The use of topiramate is not recommended because of possible psychomotor slowing and somnolence.[27]

Menopause and Age-Related Changes

Physiologic changes. The majority of studies have poorly discriminated between effects resulting from the menopausal transition and those of aging. Aging tends to be associated with the following: decreased levels of serum albumen, which increases the concentration of unbound active drug; decreased lean body mass, which increases concentration of water-soluble drugs; lower hepatic blood flow; decreased activity of hydroxylation or conjugation; and decreased renal excretion and elimination.[3] In women, all of these processes may result in an increase in serum levels and half-lives of many psychotropic drugs. Generally, however, age effects are less marked in women than in men.[47] The decreased ability in older men to clear drugs produces psychopharmacokinetics more like those of younger women.

Practical applications. As women age, they may require even lower doses of psychotropic medication. There is a greater prevalence of tardive dyskinesia with age[48]; in addition, women may present with more severe forms of this disorder. Hamilton[16] has proposed that this is due to diminishing levels of estrogen with age. Women older than 50 years of age are also more likely than men to show neuroleptic-induced agranulocytosis.[49]

EFFECTS OF EXOGENOUS HORMONES

Oral Contraceptives (OCs)

Nearly 27% of women of childbearing age in the United States use OCs.[50] These contain synthetic estrogen, progesterone, or a combination of the two. Synthetic estrogen stimulates protein synthesis, which may affect protein-binding of various drugs; inhibits various cytochrome P450 isoenzymes; and affects conjugation with glucuronic and sulfuric acid.[51] OCs increase the metabolism of some benzodiazepines, such as temazepam; decrease that of chlordiazepoxide, diazepam, and nitrazepam; and have no effect on alprazolam or lorazepam.[52] Therefore, except for these latter 2 drugs, one must be aware that differences in effects of benzodiazepines may occur in the weeks on or off OCs. OCs decrease serum tricyclic levels and may potentiate the prolactin response of antipsychotics. Carbamazepine and phenobarbital may reduce OC efficacy. Patients need to be cautioned about this possibility; they may require an increased dose of estradiol or a switch to a different mood stabilizer such as valproic acid, which does not tend to affect the efficacy of OCs.

Hormone Replacement Therapy

More than 31 million prescriptions for HRT were dispensed in the United States in 1992.[53] As opposed to OCs, which use synthetic estrogens that affect the cytochrome P450 oxidase system, some formulations of HRT contain conjugated estrogens that do not affect that system. The levels of hormones in HRT preparations are much lower than those in OCs. Progesterone on its own has been thought to be associated with dysphoric moods[54]; continuous combined therapy with estrogen and progesterone may counteract this effect of progesterone.

Role of Estrogen in Treatment of Mood Disorders

There is growing interest in the use of estrogen to treat depression, although the results have been mixed. Klaiber and colleagues[55] showed statistical but not clinical improvement in a group of women treated with supraphysiologic doses of estrogen. This group included both premenopausal and postmenopausal women. Saletu and associates[56] examined women with laboratory-confirmed menopausal status and found that there was no benefit of the estrogen compared with placebo. Zweifel and O'Brien[57] carried out a meta-analysis of 26 studies and concluded that estrogen may be of some benefit for women with depressed mood or mild depressive symptoms but not for women with a major depression. Yonkers and coworkers[58] have proposed that studies look more closely at the type of estrogen used, as this might be an important variable.

Gregoire and colleagues[59] studied 61 women with postpartum depression who were treated with estradiol for 3 months followed by 3 months with added cyclical dydrogesterone; statistically and clinically significant reductions occurred in depressive symptoms. Because at least half of these women were on concurrent antidepressant medication, the beneficial effects of estrogen may have been an augmentation of the antidepressant effects. There is some suggestion that estrogen can increase tricyclic blood levels.[60]

Postmenopausal women not taking HRT have been found to have an apparent desensitization of serotonin receptors or a blunted serotonergic responsivity. Unfortunately, the effect of estrogen on serotonergic responsivity in postmenopausal women has not been well studied. Schneider and associates[61] found that women being treated with fluoxetine who were also taking concurrent HRT had an improved response. The value of estrogen as an augmentor remains unclear because many studies suffer from failure to determine menopause status, lack of a double-blind, placebo-controlled trial design, and failure to note the different types of estrogen used or to distinguish between adding estrogen alone or estrogen and progesterone. , However, in the face of treatment-resistant depression in a postmenopausal woman, the addition of HRT (barring any contraindications) should be tried.

OTHER ISSUES

Choice of Antidepressants

There has been some limited research indicating that men and women respond differently to different types of antidepressant. A meta-analysis of 35 studies demonstrated that men respond more favorably to imipramine than do women.[62] In patients with atypical depression with panic attacks, women responded better to MAOIs and men to tricyclic antidepressants.[63] In patients with chronic depression, Kornstein and colleagues[64] showed that premenopausal women were significantly more likely to respond to sertraline than to imipramine. Women also responded more slowly to imipramine. Postmenopausal women showed similar rates of response to the two medications. Therefore, the clinician should be aware that men and women may respond differently to a given antidepressant, and in women menopausal status should be taken into account when choosing an antidepressant.

Compliance

Women's compliance with recommended medications may be affected by a number of sociocultural factors -- for example, male partners who do not agree with the use of psychotropic medication and interfere with the woman's using it. Many women are cautious about taking medication, having heard for many years that women tend to be overmedicated and perhaps having experienced overmedication personally. It is very important to differentiate between the nature of antidepressant or antipsychotic medication and minor tranquilizers. Many women are very afraid of becoming addicted to medication and need careful explanations of the different qualities of these medications.

Side Effects

Proper attention to dosage in women is very important to prevent excessive side effects. Women may need lower doses of antidepressant than men as their physiology tends to result in higher serum levels of drug. On the other hand, there may be times during the menstrual cycle, such as premenstrually, when women require more medication.

Certain side effects may be particularly worrisome for women. The atypical antipsychotics, although very effective, are associated with a great deal of weight gain. This can be horrifying and

demoralizing for many women who may stop taking the medication because of this side effect. As well, women may be troubled by the sexual side effects that are associated with a number of antidepressant medications. Often women are not informed that there is potential for sexual side effects and experience their decreased interest or inability to have an orgasm as another shortcoming on their part. It is important to inform women about these effects and monitor their reactions to the medication. Sildenafil, 50-100 mg, 1 hour before intercourse may be helpful. Alternatively, a switch to an antidepressant such as bupropion or nefazedone that is less likely to cause sexual problems may be indicated.

Hyperprolactinemia caused by antipsychotic medication can cause infertility, irregular menses, and osteoporosis. The key clinical indicator of hyperprolactinemia is amenorrhea. If this occurs, possibilities for management include decreasing the antipsychotic dosage, switching to an antipsychotic with less effect on prolactin (such as clozapine or quetiapine), treating with bromocriptine, or adding OC medication to replenish estrogen.

SUMMARY

The study of specific gender responses to medications is a relatively new one. Women were habitually excluded from drug trials to avoid the complications of their physiologic cycling and the risk of pregnancy. However, women do have cycles, become pregnant, take exogenous hormones, and still require psychotropic medication. Many of these issues remain poorly researched. In the meantime, it is important for the physician prescribing psychotropic medications to be aware of general physiologic differences between women and men in relation to psychopharmacology, the effects of menstrual cycles and reproductive events, and the possible interactions with OCs and HRT.

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