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Adjunctive Estrogens and SERMs in Schizophrenia

Despite positive results from clinical trials, use of estrogens and selective estrogen receptor modulators as adjunctive treatment in patients with schizophrenia is uncommon. According to a literature review, with age- and gender-appropriate physical health monitoring, adjunctive estrogen can be considered for women from post-puberty to post-menopause. Adjunctive SERMs appear to be promising but require further research.

For over 3 decades, acceptance has been growing that estrogens may partially explain gender differences in the onset of schizophrenia, psychotic symptoms, and treatment outcomes. Two interconnected hypotheses have been proposed: that estrogens provide protection against psychosis and that psychosis is associated with hypoestrogenism and dysfunction of the hypothalamic-pituitary-gonadal axis. Estradiol, a major form of estrogen, is a neuroactive steroid that enters the brain and interacts with the dopaminergic, serotonergic, and glutamatergic systems, with possible neuroleptic effects similar to second-generation antipsychotics.

Beginning in the 1990s, estrogens have been successfully tested in many clinical trials. Meta-analyses and reviews conclude that estrogens, particularly estradiol, could be an effective adjunct to antipsychotic medication in women. Broader acceptance of estrogens in psychiatry has been hampered by concerns raised by the Women's Health Initiative, which found associations between estrogen therapy and various adverse health outcomes. This study is now regarded as flawed, and the International Menopause Society regards the conclusions about estrogen's risks as excessively conservative.

Meanwhile, concern about estrogen safety has led to an increased focus on SERMs as a potentially safer alternative. Raloxifene (*Evista*), a second-generation SERM, is FDA-approved to treat osteoporosis but can also enter the brain, where it affects mood and cognition, possibly by modulating cholinergic, serotonergic, and dopaminergic neurotransmission. Several other SERMs are in development, but raloxifene has been the most widely investigated in postmenopausal women with schizophrenia. Study results are conflicting, possibly because of inconsistencies regarding the dosage and timing of administration. Two meta-analyses have reported improvement in schizophrenia symptoms with raloxifene in postmenopausal women.

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Although more research is needed, based on current evidence this review suggests that adjunctive estrogen therapy can be recommended for women with persistent schizophrenia if precautions are taken. Specifically, oral contraceptives may be considered for reproductive-age women, from post-puberty to age 45 years. Health monitoring, conducted at 6-month intervals, should include assessment of breast health, a cervical smear, clotting profile, and other appropriate tests. In perimenopausal women, aged 45–52 years, first-line estrogen treatment may consist of transdermal estradiol, with or without a progestin. If estrogen is contraindicated, raloxifene can be tried. In addition to the tests recommended in younger women, perimenopausal women should have evaluations of thyroid health; cardiac, liver, and renal function; and the cancer marker CA125. Existing estrogen therapy can be continued in postmenopausal women, up to age 65 years, although it should not be initiated in women over age 60 years. Postmenopausal women require the same monitoring as perimenopausal women. There is no consensus that estrogen must be stopped with advancing age.

Kulkarni J, Butler S, Riecher-Rössler: Estrogens and SERMS as adjunctive treatments for schizophrenia. *Frontiers in Neuroendocrinology* 2019; doi 10.1016/j.yfrne.2019.03.002. From Monash University, Melbourne, Australia; and the University of Basel Psychiatric Clinics, Switzerland. **This research was conducted without funding. The authors did not include disclosure of potential conflicts of interest.**

Antidepressants, Anxiolytics and Preeclampsia

According to the results of a large exploratory cohort study, women treated with antidepressants or anxiolytics in early pregnancy have a 3-fold increase in risk of preeclampsia. However, risk appears to be attenuated in women who discontinue the drugs before the 16th gestational week. It is unclear whether maternal disease is an underlying factor in the association.

Methods: The study cohort was derived from the population of women who received prenatal care at a Canadian university hospital clinic between 2005 and 2010. Women with singleton pregnancies were invited to participate in the study at the first prenatal visit, at an average of 15 weeks gestation. Those with chronic hepatic or renal disease or who were receiving treatment with antipsychotics, anticonvulsants, or stimulants were excluded. Use of antidepressants and anxiolytics was assessed throughout the pregnancy and extracted from patient records after delivery. Gestational hypertension was defined as new-onset systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after the 20th gestational week. Preeclampsia was defined as either gestational hypertension with proteinuria or preexisting hypertension with new or worsening proteinuria. Incidence of these outcomes was compared between women who did and did not receive an antidepressant and/or anxiolytic.

Results: A total of 6761 pregnant women were included in the analysis. Of these, 218 were exposed to antidepressants or anxiolytics before the 16th gestational week, an additional 41 women had depression or anxiety but did not receive pharmacotherapy, and 6502 had neither depression nor anxiety. SSRIs were the most widely used category (48.5% of women), followed by SNRIs (27%) and benzodiazepines (17.8%).

In the full cohort, gestational hypertension developed in 202 women and preeclampsia in 127. Risk of gestational hypertension was elevated but did not reach statistical significance in treated women. Because the frequency of preeclampsia was low, users of all the medications were grouped to estimate relative risks. Women who started using antidepressants or anxiolytics before the 16th week of gestation had a significantly increased risk of preeclampsia which remained after adjustment for other potential confounders (adjusted odds ratio,* 3.09; p=0.001). Among drug categories, TCAs were associated with the highest risk for preeclampsia (odds ratio, 7.36), but these drugs were used by few women and the increase did not reach significance. Odds ratios were significant for SNRIs and SSRIs (6.46 and 3.09, respectively). Women who continued their medication after the 16th week (n=167) continued to have increased risk of

preeclampsia (odds ratio, 3.41; p=0.001), but in those who stopped the medication before the 16th week risk was not significantly greater than in unexposed women. Women with unmedicated depression or anxiety were also at increased risk of preeclampsia (odds ratio, 2.92), but the risk was not significantly greater than women without depression or anxiety.

Discussion: There are plausible biological mechanisms for an association between exposure to antidepressants and/or anxiolytics and gestational hypertensive disorders (e.g., antidepressant-mediated vasoconstriction, noradrenergic effects, increased levels of vasoactive amines). However, it is noteworthy that women with unmedicated depression or anxiety also had an elevated odds ratio for preeclampsia. While this did not reach significance, the statistical power was low because there were few women in this group.

Bernard N, Forest J, Tarabulsy G, Bujold E, et al: Use of antidepressants and anxiolytics in early pregnancy and the risk of preeclampsia and gestational hypertension: a prospective study. *BMC Pregnancy and Childbirth* 2019; doi 10.1186/s12884-019-2285-8. From Université Laval, Quebec City, Canada. **Funded by the Canadian Institutes of Health Research. The authors declared no competing interests.**

***See Reference Guide.**

Switching Antidepressants for Sexual Dysfunction

In a manufacturer-sponsored study in patients with well controlled depression who were experiencing SSRI-associated sexual dysfunction, switching to vortioxetine improved sexual function while maintaining antidepressant efficacy.[1]

Background: Treatment-emergent sexual dysfunction is a common adverse effect of serotonergic antidepressants, affecting 4% to 73% of treated patients, depending on the antidepressant administered. Patients experiencing sexual dysfunction whose depression is not adequately responding to treatment are frequently switched to an alternate antidepressant. However, there is little evidence regarding antidepressant changes in patients whose depressive symptoms are well controlled with their existing regimen.

Methods: Study subjects were adults, aged 18–55 years, with a Clinical Global Impression–Severity* score of ≤3 after ≥8 weeks of treatment with either citalopram, paroxetine, or sertraline, who were experiencing treatment-emergent sexual dysfunction. Patients were switched from their initial antidepressant to double-blind, flexibly-dosed vortioxetine or escitalopram and treated for 8 weeks. Sexual function was assessed using the 14-item Changes in Sexual Functioning Questionnaire (CSFQ-14). The primary outcome (previously reported) was change in CSFQ-14 score. The present post-hoc analysis evaluated the influence of baseline factors (e.g., age, duration of treatment, number of prior episodes) on sexual function outcomes, as well as effects on antidepressant response.

Results: A total of 447 patients (mean age, 40 years; 59% women) were randomized and 80% completed the study, with similar withdrawal rates in the vortioxetine and escitalopram groups. The previous antidepressant was citalopram in 235 patients, sertraline in 146, and paroxetine in 66. At baseline, depressive symptoms had remitted in nearly 80% of study subjects (Montgomery-Asberg Depression Rating Scale score ≤10), but scores on the CSFQ-14, which did not differ across groups, indicated significant sexual dysfunction.

Participants switched to vortioxetine had significantly greater improvement in CSFQ-14 total score than those switched to escitalopram; between-group differences were statistically significant by week 4. While patients in both groups improved, changes with vortioxetine were significantly greater for most of the individual items of the CSFQ-14.[2]

Regardless of prior SSRI, patients in both groups maintained antidepressant response after the switch, with remission rates remaining in the range of 66–83%. In terms of overall CSFQ-14

scores, patients who switched from sertraline to vortioxetine showed greater improvement than those who switched to escitalopram, while results of the switch did not differ statistically in patients initially taking paroxetine or citalopram. Improvement in sexual functioning were significantly greater with vortioxetine than escitalopram in women aged ≤45 years (p=0.04), in patients with ≥1 year of prior SSRI treatment (p=0.001), in those with a history of 1–3 prior major depressive episodes (p=0.001), and those with a history of SSRI treatment in a previous episode (p=0.04).

Tolerability and incidence of adverse effects following the switch were similar across the treatment groups, regardless of which agent patients received previously. Nausea was the only adverse effect that occurred significantly more often with vortioxetine than with escitalopram (25% vs 5%), but it typically resolved within 2 weeks.

Discussion: These results suggest that a direct switch to vortioxetine is both safe and effective for adults with well-treated major depression experiencing SSRI-associated sexual dysfunction. The strategy may be particularly effective in patients whose dysfunction is associated with sertraline.

[1]Jacobsen P, Nomikos G, Zhong W, Cutler A, et al: Clinical implications of directly switching antidepressants in well-treated depressed patients with treatment-emergent sexual dysfunction: a comparison between vortioxetine and escitalopram. *CNS Spectrums* 2019; doi 10.1017/S1092852919000750. From Takeda Development Center Americas, Inc., Deerfield, IL; and other institutions. **Funded by Takeda Pharmaceutical Company, Ltd.; and H. Lundbeck A/S. All 6 study authors disclosed potentially relevant financial relationships with commercial sources including Takeda Pharmaceutical Company, Ltd.**

[2]Jacobsen P, et al: Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction. *Journal of Sexual Medicine* 2015;12 (10):2036–2048.

C*ommon Drug Trade Names*: citalopram—*Celexa*; escitalopram—*Lexapro*; paroxetine—*Paxil*; sertraline—*Zoloft*; vortioxetine—*Trintellix*

***See Reference Guide.**

Cortical Excitability, Plasticity with Psychotropics

Psychotropic medications can affect neuronal excitability and plasticity, and according to a comprehensive review, these actions can influence outcomes of brain stimulation in patients with psychiatric disorders.

Background: The use of brain stimulation as a treatment for psychiatric disorders is increasing, and experimental transcranial magnetic stimulation (TMS) protocols have been used to test the effects of psychotropic drugs on cortical excitability (i.e., the threshold for generating neuronal action potential) and plasticity (i.e., changes over time in the structure and function of neurons). This review aims to further the understanding of these effects because they could have important implications for optimizing multimodal treatment of psychiatric disorders.

Methods: A comprehensive literature search identified studies of psychotropic drug effects on cortical excitability and plasticity (measured using TMS protocols) in human subjects. Studies were generally limited to healthy research subjects rather than patients with psychiatric disorders, and they involved single or short-term drug exposures, often at subtherapeutic dosages.

Results: In general, antidepressants with potent 5HT transporter inhibition (e.g., citalopram, clomipramine) reduce cortical excitability, while antidepressants with either less potent 5HT activity or with other mechanisms of action (e.g., paroxetine, mirtazapine, selegiline) generally lack this effect. There has been little study of the effects of antidepressants on cortical plasticity, but patterns appear to be similar to those for excitability. Benzodiazepines appear to have negligible effects on excitability and moderate and variable effects on plasticity. Although results have varied, antiepileptic drugs generally show an opposite pattern of reduced excitability without affecting plasticity.

Glutamate antagonists (e.g., ketamine, memantine) have demonstrated inconsistent effects on cortical excitability, but robustly reduce cortical plasticity. Catecholaminergic drugs used in the treatment of ADHD (e.g., stimulants, atomoxetine, guanfacine), antipsychotics with dopamine, serotonin, or adrenergic activity (e.g., haloperidol, quetiapine), and lithium appear to have minimal effects on excitability but exhibit robust and complex, nonlinear effects on plasticity.

Discussion: Changes in both excitability and plasticity have implications for the clinical use of rTMS. Clinicians routinely reevaluate and adjust stimulation intensity when changes are made to a patient's pharmacotherapy. Additional research is warranted, as a more complete understanding of the effects of specific drug therapies on cortical excitability and plasticity could potentially lead to use of pharmacotherapy to promote plasticity in a way that could augment the clinical response to rTMS.

Minzenberg M, Leuchter A: The effect of psychotropic drugs on cortical excitability and plasticity measured with transcranial magnetic stimulation: implications for psychiatric treatment. *Journal of Affective Disorders* 2019;253:126-140. doi 10.1016/j.jad.2019.04.067. From the University of California, Los Angeles. **Funded by UCLA. The authors declared no competing interests.**

Common Drug Trade Names*: atomoxetine—*Strattera*; citalopram—*Celexa*; clomipramine—*Anafranil*; guanfacine—*Intuniv*; haloperidol—*Haldol*; ketamine—*Ketalar*; memantine—*Namenda*; mirtazapine—*Remeron*; paroxetine—*Paxil*; quetiapine—*Seroquel*; selegiline—*Zelapar

Zolpidem and Suicide Risk

A population-wide case-control study found an increased risk of suicide in patients receiving zolpidem (*Ambien*) with both an antidepressant and a benzodiazepine, compared with those receiving zolpidem alone. However, a case-crossover analysis conducted in the same population found no differences in risk.

Background: An FDA postmarketing safety review raised concern about potential suicide following an initial prescription for zolpidem. Benzodiazepines, antidepressants, and opioids are also suspected to increase suicide risk. The increased risk of suicide related to zolpidem in previous studies was suspected to be the result of concurrent use with these other types of drugs, but no epidemiologic study has yet addressed the issue.

Methods: The investigators analyzed claims data from a research cohort of >1 million patients from the Korean national health insurance program. Case patients were adults, aged ≥19 years, who attempted suicide between 2002 and 2013. Each subject was matched with 10 controls according to age, sex, and several other factors. Drug exposure was assessed during the 60 days preceding the suicidal behavior or the same dates in controls. Suicide risk was compared between those exposed to zolpidem alone and 7 different combinations of zolpidem with benzodiazepines, antidepressants, and/or opioid analgesics. In the subsequent case-crossover study, each individual with suicidality served as his or her own control. Drug exposure was compared between the 60 days before the suicide attempt and 5 previous 60-day control periods. Results of both analyses were adjusted for psychiatric and medical comorbidity.

Results: The case-control study included 1928 patients with a suicide attempt (64% men) and >18,000 controls. Use of all medications of interest was increased in the 60 days before a suicide attempt, but only the combination of zolpidem with benzodiazepines and antidepressants was associated with greater risk than zolpidem alone (4.8% vs 1.2%; adjusted odds ratio,* 2.80).

For the case-crossover analysis, 1803 patients were compared during the exposure period and >9,000 control periods. No increased risk for suicide was observed with any drug combination, relative to zolpidem alone. Results of both analyses were robust to different sensitivity analyses.

Discussion: Case-crossover studies are designed to assess acute trigger effects in association with short-term exposure, as opposed to chronic effects. The conflicting results of the present analyses may indicate that short-term use could be less relevant as a suicide trigger than longer-term exposure to multiple medications.

Sung H, Li J, Nam J, Won D, et al: Concurrent use of benzodiazepines, antidepressants, and opioid analgesics with zolpidem and risk for suicide: a case-control and case-crossover study. *Social Psychiatry and Psychiatric Epidemiology* 2019; doi 10.1007/s00127-019-0713-x. From Sungkyunkwan University, Suwon, South Korea; and the University of California, Irvine. **Funded by Sungkyunkwan University. The authors declared no competing interests.**

***See Reference Guide.**

Flibanserin and Alcohol Use

At the time of its initial approval for treatment of generalized hypoactive sexual desire disorder in premenopausal women, the serotonergic drug flibanserin (*Addyi*) was required to carry a boxed warning contraindicating its use with alcohol because of the possibility for severe hypotension and syncope. Following a review of postmarketing studies, the FDA has determined that, although concern still exists about alcohol consumption in close temporal association with flibanserin dosing, alcohol need not be avoided completely by women taking the drug. While the boxed warning will remain, the label will be updated to reflect that women should discontinue drinking alcohol ≥2 hours before taking flibanserin at bedtime or to skip the dose that evening. Women should not consume alcohol until at least the following day after taking flibanserin at bedtime.

FDA News Release: FDA orders important safety labeling changes for Addyi. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635847.htm.

Genotype and Antipsychotic Effects

Results of a retrospective study in patients receiving aripiprazole or risperidone suggest preemptive CYP2D6 genotyping might be useful for predicting the best starting dose and for optimizing these drugs.

Methods: Patient data for this retrospective analysis were obtained from a routine therapeutic drug monitoring database at a Norwegian hospital over a 13-year period. More than 90% of patients were of Scandinavian ancestry. The CYP2D6 metabolizer genotype was defined as poor, intermediate, normal, or ultrarapid. The study aims were to assess how CYP2D6 status predicted the metabolic ratio (conversion of each antipsychotic to its primary metabolite), exposure (serum concentrations) of each drug, and treatment failure, defined as the rate of switching from aripiprazole or risperidone to a different antipsychotic within 1 year of the drug assay. For patients with >1 serum concentration measurement, only the latest value that was not preceded by recent a dose adjustment was included.

Results: The study included 890 patients treated with aripiprazole and 725 treated with risperidone who underwent routine pharmacokinetic analyses to determine drug exposure. Compared with normal metabolizers, the metabolic ratio for risperidone was significantly increased in ultrarapid metabolizers and decreased in poor and intermediate metabolizers ($p<0.0001$ for all comparisons). The metabolic ratio for aripiprazole did not differ between normal and ultrarapid metabolizers but was significantly decreased in poor and intermediate metabolizers ($p<0.0001$). The active moiety of each drug—the sum of the parent drug and its active metabolite—also varied as a function of metabolizer status. For each drug, active moiety was increased in patients who were poor or intermediate metabolizers. In the poor metabolizers, daily dosages were lower by an average of 19% for risperidone and 15% for aripiprazole.

The incidence of switching to another antipsychotic was also compared among the CYP2D6-genotype subgroups. Switching from risperidone was nearly twice as common in poor metabolizers and 3 times as common in ultrarapid metabolizers, compared with normal metabolizers. The frequency of switching from aripiprazole was not related to CYP2D6 metabolizer status.

Discussion: While poor and intermediate metabolizers received lower daily doses, they were not low enough to compensate for higher drug exposure. The study authors suggest intermediate and poor metabolizers should receive 30% lower starting doses than normal metabolizers. Appropriate dosing decisions, which could be aided by pretreatment genotyping, could minimize dose titration times, reduce the incidence of adverse effects, and prevent inefficacy due to underdosing. A cost–benefit analysis was not undertaken in this study. However, the impact of CYP2D6 genotyping before initiating aripiprazole or risperidone could be substantial given that the combined frequency of poor, intermediate, and ultrarapid metabolizers may be as high as 50% in some ethnic populations.

Jukic M, Smith R, Haslemo T, Molden E, et al: Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. *Lancet Psychiatry* 2019;6 (May):418–426. doi 10.1016/S2215-0366(19)30088-4. From the Karolinska Institute, Stockholm, Sweden; and other institutions. **Funded by the Swedish Research Council; and other sources. The authors declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; risperidone—*Risperdal

Pharmacotherapy for Agitation in Pregnancy

Acute agitation in pregnant women should be considered an obstetric emergency. If untreated, agitation in pregnancy can lead to adverse outcomes such as premature delivery, low birth weight, growth retardation, postnatal death, and spontaneous abortion. After ruling out physical causes for the agitation, de-escalation in a safe, nonstimulating environment should be considered. However, pharmacotherapy may be necessary.

Antihistamines. Studies of antihistamines in pregnancy have not reported major malformations with first-trimester exposure. Dose-dependent anticholinergic adverse effects are possible, but these typically affect elderly, nonpregnant patients. Given the low risk of adverse effects, diphenhydramine is considered safe for use in pregnancy.

Antipsychotics. There is no evidence of significant teratogenic effects of first-generation antipsychotics, and mid- to high-potency agents (e.g., haloperidol) are less likely than low-potency agents (e.g., chlorpromazine) to have sedative or hypotensive effects. However, case reports and small observational studies do suggest a theoretical risk of neonatal extrapyramidal symptoms with exposure to first-generation antipsychotics in the third trimester. Second-generation antipsychotics appear to be safe, with no specific pattern of adverse outcomes.

Benzodiazepines. Large population-based cohort studies and meta-analyses have found no evidence of increased risk of major malformations in neonates born to mothers receiving benzodiazepines during the first trimester. Third-trimester exposure has been associated with neonatal withdrawal syndrome and "floppy-baby" syndrome. While these are more likely to occur with long-term use, risk of these outcomes with a single acute exposure has not been studied.

Agitated patients with a history of good response to one of these medications or who are currently receiving one as needed, should be treated with that agent. For patients with no history of treatment for agitation, presenting symptoms, differential diagnosis, and the route of administration and speed of onset should be considered. In all pregnant women, response should be monitored closely, as pregnancy-related changes in drug distribution, metabolism, and clearance may require dosing modifications.

Recommendations for Pharmacotherapy of Acute Agitation in Pregnancy		
Drug	**Initial Dosing**	**Possible Adverse Effects**
Antihistamines		
Diphenhydramine	25–50 mg oral, IV, or IM; maximum, 300 mg/day	Sedation, anticholinergic effects
First-generation antipsychotics		
Haloperidol	5–10 mg oral, IV, or IM; maximum 20 mg/day	Extrapyramidal symptoms, dystonia, sedation, neuroleptic malignant syndrome, anticholinergic effects
Second-generation antipsychotics		
Olanzapine	5–10 mg oral or IM; maximum 20–30 mg/day	Sedation, orthostatic hypotension, extrapyramidal symptoms
Ziprasidone	20 mg IM; maximum 40 mg/day	Sedation, headache, nausea, extrapyramidal symptoms
Benzodiazepines		
Lorazepam	0.5–2 mg oral, IV, or IM	Sedation, respiratory depression

Niforatos J, Wanta J, Shapiro A, Yax J, et al: How should I treat acute agitation in pregnancy [One minute consult]. *Cleveland Clinic Journal of Medicine* 2019; 86 (April):243–247. From Case Western Reserve University, Cleveland, OH; and other institutions. **No information regarding funding or potential conflicts of interest was included.**

Common Drug Trade Names*: diphenhydramine—*Benadryl, Dicopanol FusePaq*; haloperidol—*Haldol*; lorazepam—*Ativan*; olanzapine—*Zyprexa*; ziprasidone—*Geodon

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Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.