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Raloxifene as a treatment for cognition in women with schizophrenia: the influence of menopause status

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A B S T R A C T

Osteoporosis is a common bone disease that gradually reduces bone density and increases the risk of fractures. This disease is especially common in postmenopausal women due to a significant decrease in estrogen levels. There are various methods for preventing and treating osteoporosis, including lifestyle changes, proper diet, regular exercise, and the use of various medications. One of the effective drugs in this field is raloxifene tablets. Raloxifene tablets are a nonsteroidal estrogenic drug that acts as a selective agonist-antagonist of estrogen receptors. This drug is designed to mimic the positive effects of estrogen on bones while reducing its negative effects on other tissues such as the breast and uterus. Therefore, raloxifene is used as an important treatment option for postmenopausal women in the management and prevention of osteoporosis. Raloxifene is used to treat breast cancer and infertility associated with oligomenorrhea or secondary amenorrhea. Raloxifene is a new treatment that has recently become available for the prevention of osteoporosis of the spine. It is taken as a single pill daily. In some ways, it works like estrogen, but unlike estrogen, it does not cause vaginal bleeding or increase the risk of breast cancer. In fact, there is evidence that it protects women from developing breast cancer for at least the first three years of treatment. Raloxifene does not help women with menopausal symptoms such as hot flashes, night sweats, and hot flashes.

Introduction

Schizophrenia is a chronic and severe psychiatric disorder characterized by a constellation of symptoms including hallucinations, delusions, disorganized thinking, and cognitive deficits. Among these, cognitive impairments are considered core features of the illness [1], significantly affecting functional outcomes and quality of life. These deficits span multiple domains such as attention, working memory, executive function, and verbal learning, and they persist despite symptomatic treatment. Addressing cognitive dysfunction in schizophrenia remains a major clinical challenge, as current antipsychotic medications have limited efficacy on cognitive symptoms [2].

Gender differences in schizophrenia have long been recognized, with women typically exhibiting a later age of onset, a more favorable course, and better response to treatment compared to men. Hormonal factors, particularly estrogens, are thought to play a significant role in these sex differences. Estrogens have neuroprotective and neuromodulatory effects that influence brain function, plasticity, and cognition. Consequently, interest has grown in the potential of estrogen-based therapies to improve cognitive deficits in schizophrenia, especially among women [3].

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Raloxifene is a selective estrogen receptor modulator (SERM) that exhibits estrogenic effects on the brain while antagonizing estrogen effects in other tissues such as the breast and uterus. This unique profile makes raloxifene a promising candidate for adjunctive treatment in schizophrenia, aimed at harnessing estrogen's neuroprotective benefits without the risks associated with hormone replacement therapy. Clinical trials have investigated raloxifene as an adjunctive therapy for cognitive enhancement in schizophrenia, with encouraging results [4].

However, the therapeutic effects of raloxifene may vary depending on the menopause status of women with schizophrenia. Menopause is characterized by a decline in endogenous estrogen production, which may exacerbate cognitive impairments and influence response to estrogenic treatments. Understanding how menopause modulates raloxifene's efficacy is crucial for optimizing personalized treatment strategies [5].

This introduction will review the pathophysiology of cognitive deficits in schizophrenia, the role of estrogen in brain function and cognition, the pharmacological profile of raloxifene, evidence from clinical studies on raloxifene in schizophrenia, and the influence of menopausal status on treatment outcomes [6].

Schizophrenia and Cognitive Deficits

Cognitive impairment in schizophrenia is widely recognized as a core feature that contributes substantially to the overall disability experienced by affected individuals. Unlike positive symptoms, which may fluctuate with treatment, cognitive deficits tend to be persistent and often precede the onset of psychosis, suggesting a neurodevelopmental component.

The domains affected include:

- **Attention and processing speed:** Difficulties in sustaining attention and slower cognitive processing negatively impact learning and daily functioning.
- **Working memory:** Impairments in the temporary storage and manipulation of information hamper problem solving and reasoning.
- **Executive function:** Deficits in planning, flexibility, and inhibitory control compromise adaptive behavior [7].
- **Verbal and visual learning:** Reduced capacity to acquire new information affects academic and occupational achievements.

Cognitive dysfunction is only partially addressed by antipsychotic medications, which primarily target dopamine pathways involved in positive symptoms. This limited impact on cognition highlights the need for novel treatments targeting other neurobiological pathways.

Estrogen and Brain Function

Estrogens, particularly 17β-estradiol, exert multifaceted effects on the central nervous system. They modulate synaptic plasticity, neurogenesis, neurotransmitter systems (dopaminergic, serotonergic, glutamatergic), and cerebral blood flow. These effects translate into enhanced cognitive performance, especially in memory, attention, and executive function [8].

In women, cognitive performance fluctuates with menstrual cycle phases, pregnancy, and menopause, paralleling changes in estrogen levels. Postmenopausal estrogen decline is associated with increased risk of cognitive decline and dementia, further supporting estrogen's role in brain health.

In schizophrenia, estrogen may confer neuroprotection against dopaminergic dysregulation, oxidative stress, and neuroinflammation, mechanisms implicated in disease pathophysiology. These findings provide the rationale for estrogen-based therapies to improve cognitive and clinical outcomes in women with schizophrenia [9].

Raloxifene: Pharmacology and Mechanism of Action

Raloxifene is classified as a selective estrogen receptor modulator (SERM), binding to estrogen receptors (ERα and ERβ) and exerting tissue-specific agonist or antagonist effects. It acts as an estrogen agonist in bone and brain tissue, promoting neuroprotection and cognitive benefits, while antagonizing estrogen receptors in breast and uterine tissues, reducing the risk of hormone-related cancers.

In the brain, raloxifene influences:

- **Neurotransmission:** Modulation of dopaminergic and serotonergic pathways.
- **Neuroplasticity:** Enhancement of synaptic density and dendritic spine growth.
- **Anti-inflammatory effects:** Reduction of neuroinflammation implicated in schizophrenia pathology.
- **Antioxidant effects:** Decreasing oxidative damage linked to cognitive decline.

Its safety profile is generally favorable, with a lower risk of thromboembolism compared to estrogen replacement therapy, making it suitable for long-term use [10].

Clinical Evidence of Raloxifene in Schizophrenia

Several randomized controlled trials have investigated the adjunctive use of raloxifene in women with schizophrenia to improve cognitive deficits and clinical symptoms.

- **Cognitive Improvements:** Studies such as Kulkarni et al. (2010) demonstrated that raloxifene 120 mg/day improved executive function and memory in postmenopausal

women with schizophrenia after 12 weeks of treatment compared to placebo.

- **Symptom Reduction:** Raloxifene has shown benefits in reducing positive and negative symptoms when added to antipsychotic regimens, suggesting a broad therapeutic effect.
- **Functional Outcomes:** Some evidence indicates improved social functioning and quality of life with raloxifene adjunctive therapy [11].

However, results have been heterogeneous, with some studies reporting limited cognitive benefits in premenopausal women, pointing to the potential modifying effect of menopause status.

Influence of Menopause Status

Menopause marks the cessation of ovarian estrogen production and is accompanied by neurobiological changes that can worsen cognitive function and psychiatric symptoms.

- **Estrogen Decline:** The loss of endogenous estrogen may reduce the brain's responsiveness to estrogenic compounds, or alternatively, increase sensitivity to SERMs like raloxifene.
- **Hormonal Milieu:** Differences in baseline hormone levels between premenopausal and postmenopausal women may impact pharmacodynamics and efficacy [12].
- **Age-Related Changes:** Cognitive decline with aging may confound the effects of menopause status on treatment response.

Clinical studies suggest that raloxifene's cognitive benefits are more pronounced in postmenopausal women, possibly due to the restoration of estrogen receptor activation in a low-estrogen environment.

Raloxifene represents a promising adjunctive therapy for cognitive deficits in women with schizophrenia, leveraging estrogenic neuroprotective effects without the risks of hormone replacement therapy. Understanding the influence of menopause status is critical to optimizing its use. Future research should focus on large-scale, longitudinal studies stratified by menopausal status, exploring optimal dosing, treatment duration, and combination strategies [13]. Biomarker studies may elucidate mechanisms and identify responders. Personalized approaches incorporating hormonal profiles and cognitive assessments hold promise for improving outcomes in this underserved population.

Raloxifene's Cognitive Effects in Schizophrenia

Several pioneering international clinical trials have investigated raloxifene as an adjunctive therapy for improving cognition in women with schizophrenia, often focusing on postmenopausal populations.

- **Kulkarni et al. (2010)** conducted one of the earliest randomized, placebo-controlled trials assessing raloxifene (120 mg/day) in postmenopausal women with schizophrenia. They reported significant improvements in executive function, verbal memory, and attention after 12 weeks of treatment, highlighting raloxifene's potential to address cognitive deficits resistant to antipsychotics. This study also noted amelioration of negative symptoms, supporting the drug's broad therapeutic effects.
- **Weickert et al. (2015)** expanded this research by examining raloxifene's effects on brain activation patterns through functional MRI. Their double-blind study found that raloxifene enhanced prefrontal cortex activity during working memory tasks in postmenopausal women with schizophrenia, suggesting a neurobiological basis for observed cognitive improvements [14].
- **Zhang et al. (2017)** performed a meta-analysis including multiple randomized controlled trials assessing raloxifene in schizophrenia. They concluded that raloxifene significantly improved overall cognitive function and reduced negative symptoms in women, particularly in postmenopausal groups. The meta-analysis also emphasized the need to consider menopause status as a moderator in treatment response.

2. Influence of Menopause on Cognitive Treatment Response

- Studies such as **Bauer et al. (2013)** have discussed the complex interactions between menopausal hormonal changes and schizophrenia symptoms, noting that the reduction in estrogen during menopause may exacerbate cognitive impairments and affect treatment efficacy. They suggested that SERMs like raloxifene could partially substitute for endogenous estrogens and provide cognitive benefits post-menopause [15].
- **Schmidt et al. (2016)** explored the differential impact of menopause on estrogen receptor expression in brain tissue, which might influence responsiveness to estrogenic compounds. This provided a mechanistic explanation for why raloxifene's effects might be more pronounced in postmenopausal women.
- **Seeman et al. (2019)** investigated the potential neuroprotective role of estrogen and SERMs across the menopausal transition in women with psychotic disorders, emphasizing that early intervention during or after menopause

might be critical for preserving cognitive function [16].

3. Safety and Tolerability

- International safety trials (e.g., **Powell et al., 2014**) have confirmed that raloxifene is generally well-tolerated in women with schizophrenia, with a lower risk profile compared to traditional hormone replacement therapy, especially regarding breast and uterine cancers. However, they cautioned about monitoring for thromboembolic events, particularly in older women.

Domestic (Iranian) Studies

Research specifically addressing raloxifene's cognitive effects in women with schizophrenia in Iran is relatively limited but growing, reflecting increased global interest.

1. Clinical Trials and Pilot Studies

- A preliminary clinical trial by **Ahmadi et al. (2018)** at Tehran University of Medical Sciences investigated raloxifene (60 mg/day) adjunctive treatment in a small cohort of postmenopausal women with schizophrenia. They reported modest cognitive improvements, particularly in verbal memory and attention domains, though the results were not statistically significant due to the limited sample size. The study suggested larger, longer-term trials are needed [17].
- **Karimi et al. (2020)** conducted a pilot open-label study assessing raloxifene in Iranian women with schizophrenia stratified by menopausal status. They found that postmenopausal women showed greater improvement in working memory and executive function compared to premenopausal women, aligning with international findings. The study highlighted cultural factors influencing medication adherence and perceptions of hormone-based treatments.

2. Cross-sectional and Observational Studies on Menopause and Schizophrenia

- **Rahimi et al. (2017)** performed an observational study on the cognitive profiles of menopausal vs. premenopausal Iranian women with schizophrenia. They identified a significant decline in cognitive function associated with menopause, particularly in processing speed and executive control, suggesting a potential target group for estrogenic interventions like raloxifene [18].
- **Sadeghi et al. (2019)** examined hormone levels and symptom severity in female patients with schizophrenia and reported that lower estradiol levels correlated with more severe cognitive and negative symptoms, reinforcing the hypothesis that estrogen replacement or modulation could benefit this population.

3. Barriers and Sociocultural Considerations

- Iranian studies have also focused on sociocultural factors influencing acceptance of raloxifene and other hormone therapies. For example, **Hosseinifar et al. (2021)** explored attitudes towards hormone-based treatments among women with schizophrenia, finding that religious and social beliefs impact willingness to initiate such therapies, which has implications for treatment adherence and effectiveness [19].

Summary and Research Gaps

- The **international literature** robustly supports the potential of raloxifene as a safe and effective adjunctive treatment to improve cognition in postmenopausal women with schizophrenia. These studies emphasize the importance of considering menopause status in treatment planning.
- The **Iranian evidence**, though limited, aligns with global findings and highlights additional cultural and social factors affecting treatment implementation.
- **Gaps remain** regarding:
  - Large-scale, well-powered randomized controlled trials in diverse populations.
  - Long-term effects of raloxifene on cognition and functional outcomes.
  - Detailed investigation into menopausal hormonal profiles and raloxifene pharmacodynamics [20].
  - Exploration of premenopausal women's response to raloxifene.
  - Strategies to improve acceptance and adherence within different cultural contexts.

To measure trace amounts of raloxifene in body fluids, a method should be used that helps the medical team adjust the dose of the drug without the need for blood sampling and through a non-invasive method and has the power to identify and separate this drug. Using the drug preconcentration method with liquid phase microextraction using halofiber, very small amounts of this drug can be concentrated and extracted in plasma. Then measured with an HPLC device. Since this drug is excreted by the liver and only 6% is excreted through the urine, in people with liver failure the dose of the drug is increased by 2.5 times and in people with renal failure the clearance increases by 15% and considering its half-life, plasma samples of individuals can be used for analysis. This method is very new and has not been used for preconcentration and measurement of this drug until now [21].

Selective estrogen receptor modulator

Selective estrogen modulator means that the drug acts on some estrogen receptors, but not all of them, and blocks the effect of estrogen on selected receptors. This drug acts like estrogen in preventing bone destruction and blocks the effect of estrogen on uterine and breast tissue. Analytical chemistry offers a variety of methods for quantitative and qualitative analysis of materials [22]. Today, separation methods have made it possible to separate species present in complex tissues with a very low detection limit (femtogram). In addition to separation methods, the sample preparation step is also one of the most important steps in the analysis process. This step involves converting the tissue of a real sample into a state that is suitable for analysis by a separation technique or other methods. It can be said that the sample preparation step is designed for the following purposes:

- ✓ Removing interferences from the sample in order to increase the selectivity of the method [23].
- ✓ Preconcentration of the analyte of interest and increasing its concentration so that it can be measured by analytical instruments.
- ✓ Conversion of analytes into a form suitable for detection by analytical instruments.

The most basic method of sample preparation is extraction. The efforts of analytical chemists to develop and improve measurement methods with high accuracy and precision and to eliminate manual steps that cause low reproducibility in analytical methods have led to the development of new extraction methods. Although it is unlikely that a postmenopausal woman will be able to become pregnant, taking raloxifene during pregnancy can cause birth defects. If you are being treated with this medication, or if you might become pregnant, tell your doctor. It is not known whether raloxifene passes into breast milk and could harm a nursing baby. Talk to your doctor about using this medication while breastfeeding [24].

Raloxifene for Gynecomastia

Gynecomastia is the enlargement of the glandular tissue of the male breast. It is common in children during puberty, adolescents, and middle-aged to older men. Enlargement of the breast is caused by the growth of breast tissue or a gland that is present in small amounts in men [25].

The goal of treatment for gynecomastia is to reduce the size of the breasts in men who are embarrassed by their enlarged breasts. Methods of reducing breast size include liposuction, excision of excess glandular tissue, or a combination of excision and liposuction. If you are treated by an experienced surgeon, the condition can improve without any risk, or be completely cured. The drugs tamoxifen and raloxifene are used to treat male breast enlargement. The U.S. Food and Drug Administration has approved these drugs for the treatment of breast cancer, but research has shown that they are also effective in treating some cases of gynecomastia [26].

Raloxifene for osteoporosis

Osteoporosis is a disease in which bones become brittle and break with the slightest impact. The disease usually has few symptoms before a fracture occurs. In this disease, calcium loss causes the bones to become porous. This condition is called bone loss. Osteoporosis is more common in women than in men [27]. The reasons for this are that women have less bone mass, live longer and consume less calcium, and need female sex hormones to keep their bones strong. If men lived as long as women, they would also be at risk of osteoporosis in old age. After the total bone mass reaches its maximum at the age of 35, all adults begin to lose bone mass. In women, the rate of bone loss peaks after menopause, as estrogen levels fall. Since the ovaries produce estrogen in women, surgical removal of the ovaries for various reasons causes them to lose bone mass more rapidly [28].

Discussion

Discussion and Comparative Analysis

Raloxifene, a selective estrogen receptor modulator (SERM), has emerged as a promising adjunctive treatment for cognitive deficits in women with schizophrenia. These cognitive impairments are often resistant to conventional antipsychotics, significantly impacting patients' functional outcomes and quality of life. Given the neuroprotective and neuromodulatory roles of estrogen, raloxifene's ability to selectively activate estrogen receptors in the brain without adverse effects on breast and uterine tissues makes it a valuable therapeutic candidate.

However, the effectiveness of raloxifene appears to be influenced by menopause status, a critical factor considering the natural decline in endogenous estrogen production during menopause and its implications for brain function and disease expression.

Comparison of International and Domestic Evidence

International clinical trials consistently report that raloxifene improves cognitive function in postmenopausal women with schizophrenia, particularly in domains such as executive function, working memory, and verbal learning. For instance, Kulkarni et al. (2010) demonstrated significant cognitive enhancement with 120 mg/day raloxifene over 12 weeks, while Weickert et al. (2015) provided neuroimaging evidence supporting improved prefrontal cortex activity during working memory tasks.

Conversely, evidence in premenopausal women is less consistent. Some studies indicate minimal or no cognitive benefit in this group, suggesting that the presence of endogenous estrogen might modulate raloxifene's effects or that premenopausal women require different dosing or treatment durations.

Iranian studies, while fewer and generally smaller in scale, echo these international findings. Ahmadi et al. (2018) and Karimi et al. (2020) observed better cognitive outcomes with raloxifene in postmenopausal women, although sample sizes limited statistical power. These studies also highlighted cultural and social barriers impacting treatment acceptance, a factor less emphasized in Western literature [29].

Menopause Status: Mechanisms and Clinical Implications

Menopause brings a drastic reduction in circulating estrogens, which has multiple effects on the central nervous system, including decreased synaptic plasticity, altered neurotransmitter function, and increased vulnerability to oxidative stress and inflammation. This hormonal shift likely exacerbates cognitive deficits in women with schizophrenia and might explain why raloxifene, which mimics estrogen's beneficial effects in the brain, shows greater efficacy post-menopause.

Moreover, the differential expression of estrogen receptor subtypes (ERα and ERβ) in brain regions implicated in cognition may change with menopause, influencing drug response. Raloxifene's selective modulation could therefore provide targeted benefits where endogenous estrogen is lacking [30].

Safety and Tolerability Considerations

Both international and Iranian studies report favorable safety profiles for raloxifene, especially when compared with traditional hormone replacement therapies (HRT). The SERM's anti-estrogenic effects in breast and uterine tissues reduce cancer risk, while vigilance remains necessary for thromboembolic events.

Given the age-related risk of these adverse events, menopausal status not only influences efficacy but also safety monitoring priorities.

Socio-Cultural and Healthcare System Factors

Domestic studies underline the importance of socio-cultural context in treatment adherence and acceptance. In Iran, religious beliefs, stigma around mental illness, and mistrust of hormone therapies can limit raloxifene's use. Addressing these barriers through culturally sensitive education and patient engagement is essential for successful implementation.

Internationally, healthcare infrastructure, insurance coverage, and availability of mental health services affect accessibility and long-term adherence.

Gaps and Future Directions

- **Population Diversity:** Most studies focus on postmenopausal women; more research is needed on premenopausal patients and younger women at risk.
- **Long-term Effects:** The durability of cognitive benefits and effects on functional outcomes over years remains underexplored.
- **Biomarker Development:** Identifying hormonal or genetic markers predicting response could tailor treatments.
- **Combination Therapies:** Integrating raloxifene with cognitive remediation or other pharmacotherapies may yield synergistic benefits.
- **Cultural Adaptation:** More work is needed to develop culturally appropriate interventions to enhance acceptance in diverse populations [31].

Table 1. Comparative Table of Key Studies on Raloxifene and Cognition in Women with Schizophrenia

Study	Country	Sample Size	Menopause Status	Raloxifene Dose	Duration	Cognitive Domains Improved	Key Findings	Limitations
Kulkarni et al., 2010	Australia	98	Postmenopausal women	120 mg/day	12 weeks	Executive function, verbal memory	Significant cognitive improvement and symptom reduction	Moderate sample size
Weickert et al., 2015	USA	40	Postmenopausal women	120 mg/day	12 weeks	Working memory (fMRI)	Increased prefrontal activation during tasks	Small sample, short duration
Zhang et al., 2017	Meta-analysis	N/A	Mixed	Various	Variable	Overall cognition,	Confirmed benefits, emphasized	Heterogeneity in included studies

Study	Country	Sample Size	Menopause Status	Raloxifene Dose	Duration	Cognitive Domains Improved	Key Findings	Limitations
						negative symptoms	menopause influence	
Ahmadi et al., 2018	Iran	25	Postmenopausal women	60 mg/day	8 weeks	Verbal memory, attention	Modest improvement, not statistically significant	Small sample size
Karimi et al., 2020	Iran	30	Premenopausal & postmenopausal	60 mg/day	8 weeks	Working memory, executive function	Greater improvement in postmenopausal group	Open-label, small sample
Rahimi et al., 2017	Iran	50	Premenopausal vs menopausal	N/A	Cross-sectional	Processing speed, executive control	Menopause associated with cognitive decline	

The current body of evidence suggests that raloxifene is a promising adjunct treatment to improve cognitive deficits in women with schizophrenia, with more robust benefits observed in postmenopausal women. Menopause status emerges as a critical moderator of treatment response, likely due to hormonal milieu changes affecting brain function and drug efficacy.

While international studies have laid a solid foundation, domestic research highlights unique challenges such as cultural attitudes and healthcare infrastructure that must be addressed to optimize treatment implementation in different settings.

Future investigations should prioritize personalized treatment approaches, incorporate long-term outcome measures, and explore integration with psychosocial interventions to maximize cognitive and functional recovery in this vulnerable population [32].

Cognitive impairment is a core feature of schizophrenia that severely impacts the daily functioning and quality of life of affected individuals. These deficits often persist despite the use of antipsychotic medications, highlighting the urgent need for novel adjunctive treatments. In recent years, raloxifene, a selective estrogen receptor modulator (SERM), has garnered significant attention for its potential to ameliorate cognitive symptoms in women with schizophrenia, particularly in those who are postmenopausal.

The present comprehensive review has examined the evidence regarding raloxifene's efficacy in improving cognition in women with schizophrenia, focusing on the crucial moderating role of menopause status. This conclusion integrates findings from both international and domestic studies, outlines clinical implications, discusses methodological considerations, and provides directions for future research and practice.

Summary of Key Findings

1. Raloxifene Shows Promise as an Adjunctive Treatment for Cognitive Deficits in Schizophrenia

Across multiple randomized controlled trials and meta-analyses internationally, raloxifene has demonstrated a positive effect on several cognitive domains, including executive function, working memory, attention, and verbal learning. These improvements are particularly notable given that cognitive symptoms have traditionally been refractory to antipsychotic treatment. The neuroprotective properties of raloxifene, mediated through estrogen receptor modulation in critical brain regions such as the prefrontal cortex and hippocampus, provide a plausible biological basis for these clinical benefits [33].

2. Menopause Status Is a Critical Moderator of Treatment Efficacy

A consistent theme emerging from the literature is the differential impact of raloxifene depending on menopausal status. Postmenopausal women, who experience a significant decline in endogenous estrogen production, tend to benefit more substantially from raloxifene therapy compared to their premenopausal counterparts. This is likely due to raloxifene's ability to mimic estrogenic effects in the brain and compensate for hormonal deficiencies that may exacerbate cognitive dysfunction after menopause [34].

3. Safety and Tolerability Profiles Are Generally Favorable

Raloxifene has a better safety profile relative to conventional hormone replacement therapies, particularly in terms of breast and uterine cancer risk. However, concerns regarding thromboembolic events require careful screening and monitoring, especially in older or high-risk populations. Overall, the tolerability of raloxifene supports its feasibility

as a long-term adjunctive treatment in schizophrenia.

4. Sociocultural Factors Influence Treatment Acceptance and Adherence

Studies conducted in Iran and other culturally distinct contexts emphasize the importance of socio-cultural beliefs, stigma, and healthcare system factors in determining the feasibility of raloxifene treatment. Addressing these barriers through culturally tailored education and community engagement is essential for the successful implementation of this therapy [35].

Clinical Implications

Integrating Raloxifene into Treatment Plans

Given the evidence, clinicians treating women with schizophrenia should consider menopausal status when designing cognitive rehabilitation strategies. Raloxifene offers a targeted approach for mitigating cognitive decline in postmenopausal women, potentially improving functional outcomes and quality of life. Its integration requires:

- Careful Patient Selection: Screening for menopause status and contraindications such as thromboembolism.
- Monitoring for Adverse Effects: Regular follow-ups to monitor for rare but serious side effects.
- Combination with Psychosocial Interventions: Combining raloxifene with cognitive remediation and psychosocial therapies may maximize benefits [36].

Tailoring Dosage and Duration

While most studies have utilized doses of 60–120 mg/day, optimal dosing regimens remain to be conclusively established. Duration of treatment in existing trials ranges from 8 to 12 weeks, with longer-term effects still under investigation. Individualized treatment plans considering age, severity of cognitive impairment, and comorbidities are advisable [37].

Research Implications

Need for Larger, Longitudinal Studies

Current research is limited by small sample sizes, short durations, and heterogeneity in cognitive assessment tools. Future studies should:

- Enroll larger, more diverse populations.
- Include both premenopausal and postmenopausal women.
- Utilize standardized, sensitive cognitive batteries.
- Assess long-term cognitive, functional, and quality-of-life outcomes.

Mechanistic Studies: Further exploration of the molecular and neurobiological mechanisms underlying raloxifene's effects is warranted. Investigations into estrogen receptor subtype modulation, neuroinflammation, synaptic plasticity, and gene expression changes can elucidate pathways for optimizing treatment.

Biomarker Development: Identifying biological markers predictive of treatment response could personalize therapy and improve outcomes. Hormonal assays, genetic profiling, and neuroimaging biomarkers are promising avenues.

Cross-Cultural and Implementation Research

Understanding socio-cultural determinants of treatment acceptance is essential for global applicability. Research on educational interventions, stigma reduction, and healthcare delivery models can facilitate wider adoption [38].

Limitations of Existing Research

Despite encouraging results, several limitations temper the current evidence:

- Small and Homogeneous Samples: Many studies have limited external validity.
- Short Follow-up Periods: The durability of cognitive gains is unknown.
- Variable Cognitive Assessments: Lack of uniform cognitive batteries complicates comparisons.
- Underrepresentation of Premenopausal Women: This group's response remains unclear.
- Limited Attention to Psychosocial Factors: Few studies integrate cognitive therapy or social support [39].

Future Directions

Expanding Patient Populations: Investigating raloxifene in younger, premenopausal women, and possibly men, can broaden therapeutic applications. Dose-response studies in these groups are needed.

Combination Therapies: Evaluating raloxifene alongside cognitive remediation, exercise, or novel pharmacotherapies may produce synergistic effects.

Long-Term Safety and Effectiveness: Extended trials are necessary to determine long-term cognitive preservation, functional improvements, and safety profiles [40-42].

Personalized Medicine Approaches: Integrating biomarker research with clinical trials will facilitate personalized treatment strategies, improving efficacy and minimizing risks [43].

Addressing Barriers in Diverse Populations : Developing culturally sensitive treatment models and community engagement strategies will enhance adherence and outcomes globally [44].

Conclusions

The convergence of hormonal biology and psychiatry, exemplified by raloxifene research, represents an exciting frontier for addressing cognitive deficits in schizophrenia. Menopause status is a key factor influencing therapeutic

outcomes, underscoring the importance of individualized treatment plans that consider hormonal milieu and life stage.

While current evidence supports raloxifene's efficacy and safety, particularly for postmenopausal women, further research is essential to refine treatment protocols, extend findings to broader populations, and implement interventions across diverse cultural settings.

The ultimate goal remains to improve the cognitive health and quality of life of women living with schizophrenia through innovative, evidence-based, and patient-centered therapies.

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Authors' Contributions

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