ÚS DEL RALOXIFÈ EN L'ESQUIZOFRÈNIA

I Jornada del Grup de Treball en Psiconeuroendocrinologia (PNECAT): Actualització en esteroides sexuals i psicopatologia

JUDITH USALL I RODIÉ

PSICOFARMACOLOGIA SENSIBLE AL SEXE

- Incorpora coneixements de variables relacionades amb el sexe en les decisions clíniques, d' investigació i de docència en farmacoteràpia

TEORIA ESTROGÈNICA DE LA ESQUIZOFRÈNIA

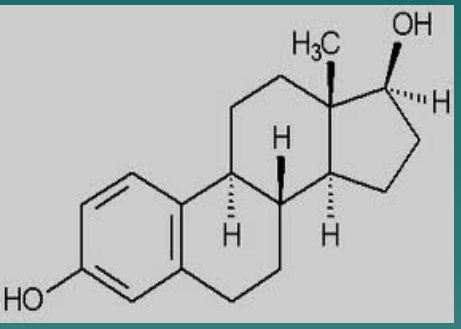
Efecte protector dels estròGens en les dones que presenten una vulnerabilitat a patir la malaltia

- EstròGens efecte modulador sistema dopaminèrgic, serotoninèrgic i glutamatèrgic *(Leung i Leung, 2000, Searles et al 2018)*
- Edat menarquia correlaciona amb edat inici malaltia i gravetat simptomatologia *(Cohen et al 1999, Hochman and Lewine 2004, Rubio et al, 2014)*

TEORIA ESTROGÈNICA DE L'ESQUIZOFRÈNIA

- Nivells d'estròGens en dones amb esquizofrènia significativament més baixos que en dones sanes *(Riecher-Rössler and Kulkarni. 2011)*
- Inici de la malaltia o recaigudes més freqüents coincidint amb les fases del cicle menstrual amb nivells baixos d'estròGens *(Riecher-Rössler et al. 1992; Huber et al. 2001)*
- Esquizofrènia d'inici tardà més freqüent en dones *(Castle et al. 1998, Seeman 2012)*

EFECTES PROTECTORS DELS ESTRÒGENS EN EL SNC



Possible Mechanisms of Estrogen/SERM Neuroprotection

ESTROGEN/SERMs

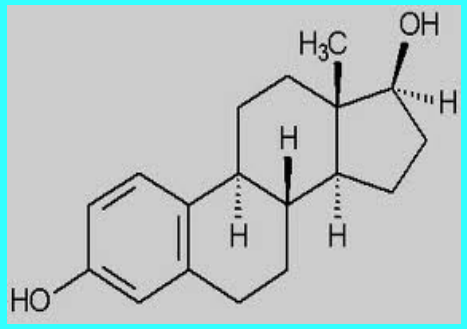
Neuroprotection

Genomic	Nongenomic	Antioxidant
• Requires pretreatment • Involves ER-mediation • Involves gene transcription	• Rapid effect • May or may not involve ER-mediation • May involve MAPK or AKT signaling	• Scavenges free radical oxidants • *Does not* involve ER-mediation • Usually only observed at very high *pharmaco-logical* concen-trations

ACCIONS PROTECTORES DELS ESTRÒGENS SOBRE EL SNC

- Efectes genòmics i no genòmics

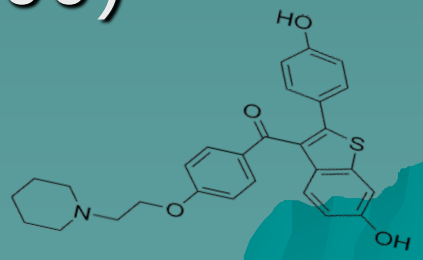
- Regulació síntesi de serotonina
- Increment receptors serotonina
- Modulació sistema dopaminèrgic
- Promoció regeneració neuronal
- Bloqueig mecanismes de mort neuronal



RALOXIFÈ. MODULADOR SELECTIU DELS RECEPTORS ESTROGÈNICS (SERM)

- Agonista en os i metabolisme lipídic, antagonista en úter i mama (Walf and Frye, 2010)

- Efecte agonista estrogènic en el SNC (Landry et al 2002, Cyr et al 2000)



Raloxifene as an Adjunctive Treatment for Postmenopausal Women With Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Trial

Judith Usall, MD, PhD; Elena Huerta-Ramos, MA; Raquel Iniesta, PhD; Jesús Cobo, MD, PhD; Susana Araya, MD; Mercedes Roca, MD; Antoni Serrano-Blanco, MD, PhD; Fernando Teba, MD; and Susana Ochoa, PhD

Table 1. Baseline Demographic and Clinical Characteristics for Women in the Raloxifene and Placebo Groups (N = 33)[a]

Characteristic	Raloxifene (n = 16)	Placebo (n = 17)	*P* Value[b]
Age, mean (SD), y	60.14 (6.41)	62.66 (4.54)	.20
Education, mean (SD), y	7.00 (3.40)	7.25 (3.69)	.66
Age at onset of disease, mean (SD), y	27.69 (6.97)	25.24 (11.12)	.41
Baseline PANSS score, mean (SD)			
Positive subscale	10.57 (3.56)	12.25 (5.04)	.27
Negative subscale	22.53 (4.73)	21.63 (5.34)	.69
General psychopathological subscale	30.80 (4.98)	31.63 (8.32)	.81
Total	62.64 (8.60)	65.50 (14.55)	.52
Participant medication, n (%)			
Antipsychotic			
First-generation antipsychotic	4 (12.12)	4 (12.12)	.61
Second-generation antipsychotic	9 (27.27)	7 (21.21)	
Combination	3 (9.09)	6 (18.18)	
Antidepressant, yes	5 (15.15)	4 (12.12)	.71
Antidepressant, no	11 (33.33)	13 (39.39)	
Biperiden, yes	4 (12.12)	3 (9.09)	.68
Biperiden, no	12 (36.36)	14 (42.42)	
Dosage of antipsychotic, median, mg/d[c]	4.25	6.00	.19
Patient status at baseline, n (%)			
Inpatient	4 (12.12)	4 (12.12)	1.00
Outpatient	12 (36.36)	13 (39.39)	

[a]Percentages are based on the total N of 33.
[b]*P* values are derived from 1-way analyses of variance.
[c]Antipsychotic drug doses are expressed as risperidone equivalence.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

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Table 2. Baseline PANSS and Last Evaluation to week 12 for Raloxifene and Placebo Groups

	mean (sd)				
	Raloxifene Group		Placebo Group		
PANSS Dimensions	Baseline	Last eval	Baseline	Last eval	p value
Positive	10.57(3.56)	9.14(2.35)	12.25(5.04)	13.06(6.31)	0.008
Negative	22.53(4.73)	18.93(4.57)	21.63(5.34)	19.81(5.44)	0.048
General	30.8(4.98)	28.27(4.66)	31.63(8.32)	33.25(9.54)	0.040
Total	62.64(8.60)	55.79(9.07)	65.5(14.55)	66.13(18.24)	0.009

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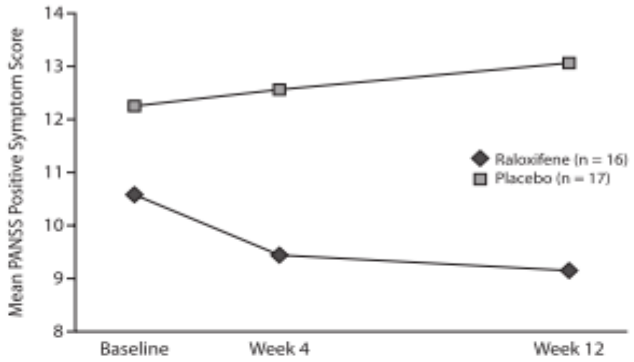
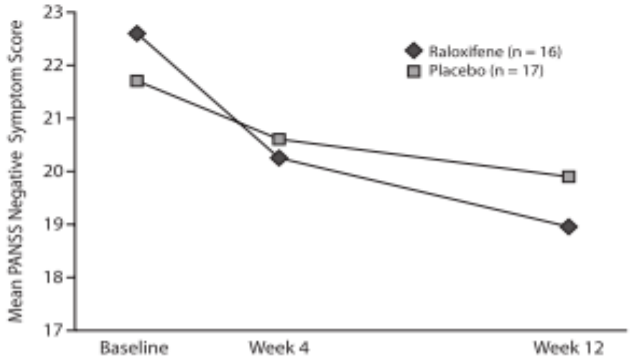
Figure 1. Mean Positive and Negative Syndrome Scale (PANSS) Positive Symptoms at Baseline (day 0) and at Weeks 4 and 12 for Raloxifene and Placebo Groups[a]



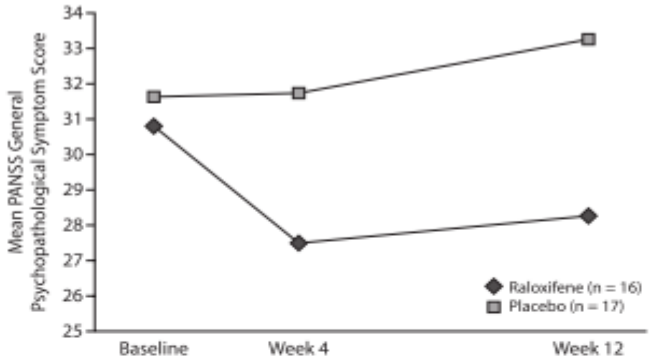
[a]Analysis-of-variance time × group interaction *P* value = .031.

Figure 2. Mean Positive and Negative Syndrome Scale (PANSS) Negative Symptoms at Baseline (day 0) and at Weeks 4 and 12 for Raloxifene and Placebo Groups[a]



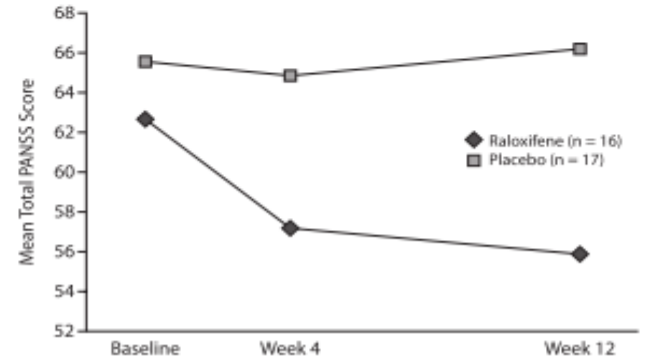
[a]Analysis-of-variance time × group interaction *P* value = .044.

Figure 3. Mean Positive and Negative Syndrome Scale (PANSS) General Psychopathological Symptoms at Baseline (day 0) and at Weeks 4 and 12 for Raloxifene and Placebo Groups[a]



[a]Analysis-of-variance time × group interaction *P* value = .045.

Figure 4. Mean Positive and Negative Syndrome Scale (PANSS) Total Scores at Baseline (day 0) and at Weeks 4 and 12 for Raloxifene and Placebo Groups[a]



[a]Analysis-of-variance time × group interaction *P* value = .014.

Raloxifene as an Adjunctive Treatment for Postmenopausal Women With Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Trial

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table 3. Baseline and Last evaluation for Uku and Simpson scales regarding treatment groups

	mean (sd)				
	Raloxifene Group		Placebo Group		
	Baseline	Last Eval	Baseline	Last Eval	p.value
Uku	7.15 (3.99)	4.77 (2.86)	9.50 (8.68)	6.57 (4.29)	0.827
Simpson	3.08 (2.1)	2.69 (1.93)	4.27 (3.47)	3.87 (3.35)	0.97

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Effects of raloxifene on cognition in postmenopausal women with schizophrenia: A double-blind, randomized, placebo-controlled trial ☆

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Table 2 Baseline cognitive and last evaluation to week 12 for raloxifene and placebo groups.

	Median (range)						
	Raloxife group			Placebo group			
	Baseline	Last eval	n	Baseline	Last eval	n	*P* value*
TMT-A	102.0 (60-250)	85.0 (50-210)	12	120.0 (25-315)	137.0 (41-350)	12	.078
TMT-B	329.0 (146-595)	400.0 (125-570)	7	375.0 (90-755)	369.0 (105-660)	9	.470
TAVEC							
Learning curve	34.5 (12-54)	41.5 (24-57)	14	32.0 (21-45)	32.5 (20-53)	12	.041
Semantic memory strategies	3.0 (0-15)	6.0 (4-17)	14	5.5 (0-9)	3.0 (0-13)	12	.076
Short-term memory	6.0 (1-13)	8.5 (1-12)	14	7.0 (4-10)	7.5 (1-12)	12	.403
Long-term memory	7.5 (0-12)	10.0 (0-13)	14	6.0 (3-10)	8.5 (3-13)	12	.462
Recognition	14.0 (2-16)	15.0 (11-16)	14	13.5 (4-16)	15 (10-16)	12	.705
CPT							
Omisions	33.0 (9-71)	19.5 (5-40)	7	60.0 (5-108)	38.0 (3-123)	7	.902
Comisions	24.0 (4-30)	11.5 (2-21)	7	15.0 (8-22)	19.0 (7-29)	7	.128
Hit	606.4 (369.2-617)	517.8 (423-713.2)	7	639.2 (432.4-1096)	515.8 (305.9-1092.5)	7	.902
Perseverations	7.0 (2-50)	7.0 (1-45)	7	7.0 (0-62)	4.0 (0-39)	7	.902
STROOP							
Words	68.0 (48-92)	68.5 (40-92)	10	76.0 (44-93)	64.50 (29-89)	11	.387
Words and colors	27.0 (16-39)	28.0 (5-45)	10	36.0 (17-42)	33.0 (20-46)	11	.503
WAIS III							
Digits	10.0 (5-15)	9.5 (6-15)	14	8.5 (4-14)	9.0 (4-13)	12	.865
Arithmetic	6.0 (4-10)	6.0 (5-11)	13	7.0 (6-10)	7.0 (5-9)	10	.343
Letters and numbers	7.5 (1-12)	4.5 (3-8)	10	9.0 (4-11)	4.0 (3-9)	7	.601
Phonemic fluency task	16.0(2-33)	20.5 (11-30)	14	13.0 (3-43)	12.0 (3-38)	12	.011
Animals fluency task	12.0 (2-22)	11.5 (4-23)	14	10.0(6-24)	10.0 (4-23)	12	.560

Abbreviation: TMT=Trail Making test, TAVEC=Spanish complutense verbal learning test, CPT=Continuous Performance Test, WAIS=Wechsler Adult Intelligence Scale.

*P values are derived from Mann-Whitney U test.

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Raloxifene as an Adjunctive Treatment for Postmenopausal Women With Schizophrenia: A 24-Week Double-Blind, Randomized, Parallel, Placebo-Controlled Trial

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†See Acknowledgments for list of collaborators.

Raloxifene as an Adjunctive Treatment for Postmenopausal Women With Schizophrenia: A 24-Week Double-Blind, Randomized, Parallel, Placebo-Controlled Trial

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- Mostra: 70 pacients
- Diagnòstic d' esquizofrènia. Posmenopausa. Simptomes negatius significatius.
- Tractament: Raloxifè 60 mg/dia
- Seguiment: 6 mesos

Raloxifene as an Adjunctive Treatment for Postmenopausal Women With Schizophrenia: A 24-Week Double-Blind, Randomized, Parallel, Placebo-Controlled Trial

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Table 1. Demographic Data and Baseline for the Women in the Raloxifene and Placebo Groups ($N = 70$)[a]

Characteristic	Raloxifene ($n = 38$)	Placebo ($n = 32$)	P Value[b]
Age, mean (SD), y	62.03 (9.39)	61.34 (10.41)	.77
Education y, mean (SD), y	8.13 (3.10)	7.73 (3.26)	.64
Age at onset of disease, mean (SD), y	26.29 (8.64)	27.04 (11.37)	.78
Baseline PANSS score, mean (SD)			
Positive	17.05 (4.53)	17.22 (5.66)	.89
Negative	24.39 (5.32)	22.81 (4.05)	.17
General	39.03 (8.14)	34.63 (7.18)	.020
Total	80.47 (14.30)	74.66 (13.26)	.084
Participant medication type, *n* (%)			
Antipsychotic			
First-generation antipsychotic	2 (3.1%)	4 (6.2%)	.53
Second-generation antipsychotic	28 (43.1%)	21 (32.3%)	
Combination	5 (7.7%)	5 (7.7%)	
Antidepressant, yes	12 (17.6%)	5 (7.4%)	.16
Antidepressant, no	25 (36.8%)	26 (38.2%)	
Biperiden, yes	9 (43.2%)	9 (3.2%)	.78
Biperiden, no	28 (41.2%)	22 (32.4%)	
Dosage of antipsychotic, median, mg/d[c]	750	600	.42
Patient status at baseline, *n* (%)			
Inpatient	27 (38.6%)	29 (41.4%)	.070
Outpatient	11 (15.7%)	3 (4.3%)	

Note: PANSS: Positive and Negative Syndrome Scale
[a]Percentages based on the total N of 70.
[b]P-values derived from Student t Test, Mann-Whitney U test, $\chi 2$ test, or Fisher's Exact Test.
[c]Antipsychotic drug doses are expressed as chlorpromazine equivalence.

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	mean (sd)				
	Raloxifene Group		Placebo Group		
PANSS Dimensions	**Baseline**	**Last eval**	**Baseline**	**Last eval**	**p-value**
Positive	17.05 (4.53)	15.42 (4.85)	17.22 (5.66)	16.81 (5.28)	**0.250**
Negative	24.39 (5.32)	20.87 (5.77)	22.81 (4.05)	21.94 (6.45)	**0.010**
General	39.03 (8.14)	33.95 (7.40)	34.62 (7.18)	35.84 (10.25)	**0.001**
Total	80.47 (14.30)	70.24 (14.82)	74.66 (13.26)	74.59 (19.54)	**0.001**

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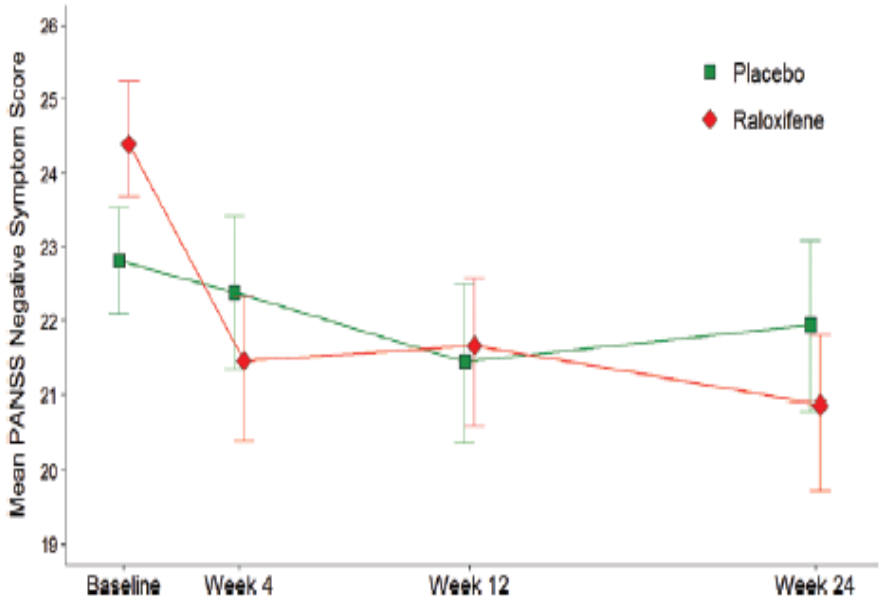

Fig. 3. Mean Positive and Negative Syndrome Scale (PANSS) Negative Symptoms at baseline (d 0) and at 4, 12, and 24 weeks for raloxifene and placebo groups[a].Error bars indicate standard error of the mean.[a]ANOVA time × group interaction *P*-value = .010

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ORIGINAL PAPER

Effects of raloxifene on cognition in postmenopausal women with schizophrenia: a 24-week double-blind, randomized, parallel, placebo-controlled trial

Elena Huerta-Ramos[1,2,3,4] · Javier Labad[5] · Jesus Cobo[5] · Christian Núñez[1,2,4] · Marta Creus[6] · Gemma García-Parés[7] · Daniel Cuadras[1,2,4] · José Franco[6] · Eva Miquel[1] · Julio-César Reyes[6] · Silvia Marcó-García[1,2,4] · RALOPSYCAT Group · Judith Usall[1,2,3,4]

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Table 2 Baseline cognitive assessment and last evaluation to week 24 for raloxifene and placebo groups

	Median (range)						*p* value*
	Raloxifene group			Placebo group			
	Baseline	Last evaluation	*n*	Baseline	Last evaluation	*n*	
	Mean (range)	Mean (range)		Mean (range)	Mean (range)		
TMT-A	63.0 (29–193)	121.5 (25–496)	28	54.5 (25–62)	109.5 (25–782)	28	0.972
TMT-B	240.0 (77–743)	227.5 (63–790)	10	128.0 (84–318)	114.5 (100–328)	6	0.643
TAVEC							
Learning curve	30.0 (7–59)	33.0 (16–64)	31	24.5 (10–55)	31.0 (9–64)	27	0.639
Semantic memory strategies	4.0 (0–22)	6.0 (4–40)	31	2.0 (0–12)	5.0 (0–20)	27	0.678
Short-term memory	5.0 (0–12)	5.0 (0–15)	31	4.5 (0–12)	6.0 (0–14)	27	0.304
Long-term memory	6.0 (0–14)	6.0 (0–15)	31	4.0 (0–12)	5.5 (0–14)	27	0.499
Recognition	13.0 (4–16)	14.0 (3–16)	31	12.0 (3–16)	13 (9–16)	27	0.263
CPT							
Omissions	24.0 (1–118)	23.0 (2–74)	18	32.5 (7–106)	26.0 (8–168)	15	0.782
Commissions	18.0 (3–29)	15.0 (5–32)	18	18.5 (3–32)	13.0 (1–33)	15	0.692
Hit	554 (400–1203)	560 (385–793)	18	545 (432–1231)	579 (432–1127)	15	0.968
Perseverations	7.0 (0–106)	9.5 (0–79)	18	7.0 (0–57)	9.0 (0–90)	15	0.830
STROOP							
Words	75.0 (44–114)	66.0 (24–120)	26	75.0 (52–103)	68.0 (39–124)	26	0.127
Words and colors	33.0 (15–53)	26.5 (15–81)	26	33.5 (29–43)	26.5 (12–48)	26	0.453
WAIS III							
Digits	10.0 (4–16)	8.0 (3–15)	31	9.0 (4–17)	9.0 (4–18)	29	0.175
Arithmetic	6.0 (4–11)	6.0 (4–9)	30	6.0 (2–10)	6.0 (3–11)	28	0.339
Letter-number sequencing	4.0 (1–9)	5.0 (1–11)	15	5.0 (0–10)	6.0 (0–10)	11	0.908
Vocabulary	21.5 (5–49)	20.0 (8–50)	30	20 (5–46)	18.0 (4–47)	29	0.864
Phonemic fluency task	13.0 (0–61)	13.0 (0–44)	31	13.0 (0–43)	13.0 (0–53)	29	0.580
Animals fluency task	12.0 (4–33)	10.0 (4–24)	31	11.0 (1–24)	11.0 (5–28)	29	0.736

TMT Trail Making Test, *TAVEC* Spanish complutense verbal learning test, *CPT* Continuous Performance Test, *WAIS* Wechsler Adult Intelligence Scale

*p values are derived from Mann–Whitney U test

Arch Womens Ment Health (2018) 21:31–41
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REVIEW ARTICLE

Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a meta-analysis of randomized controlled trials

Qi Wang[1] · Xiaomei Dong[1] · Yan Wang[1] · Xiaobai Li[1]

Table 1 Main characteristics extracted from the six articles used in the meta-analysis

Study	Number	Diagnosis	Diagnostic criteria	Setting	Study duration (wks)	Mean age (years) / duration of illness (Mean ± SD)	Control group	Intervention group		Jadad score	Risk of bias[e]
							Aps (mg/day) (Mean ± SD) /median	Aps (mg/day) (Mean ± SD) /median	Raloxifene (mg/day)		
Kulkarni et al. (2010)[a]	R: 9 P: 13	SCZ, SCA, SCD	DSM-IV	Inpatients	12	54.6 ± 4.6 / 11.6 ± 6.5 50.9 ± 4.2 / 24.9 ± 11.5	6.5 ± 7.7[c]	11.0 ± 9.8[c]	60	5	4
Kulkarni et al. (2010)[b]	R: 13 P: 13	SCZ, SCA, SCD	DSM-IV	Inpatients	12	53.3 ± 8.0 / 25.7 ± 10.1 50.9 ± 4.2 / 24.9 ± 11.5	6.5 ± 7.7[c]	6.6 ± 3.0[c]	120	5	4
Usall et al. (2011)	R: 16 P: 17	SCZ	DSM-IV	In- and Outpatients	12	60.14 ± 6.41 / NR 62.66 ± 4.54 / NR	6.00[c]	4.25[c]	60	6	6
Gilda Kianimehr et al. (2014)	R: 23 P: 23	SCZ	DSM-IV-TR	Inpatients	8	61.9 ± 4.49 / 17.24 ± 12.03 60.44 ± 5.28 / 13.64 ± 12.41	6.0[c]	6.0[c]	120	5	5
Usall et al. (2016)	R: 38 P: 32	SCZ	DSM-IV-TR	In- and Outpatients	24	62.03 ± 9.39 / NR 61.34 ± 10.41 / NR	600[d]	750[d]	60	6	6
Kulkarni et al. (2016)	R: 26 P: 30	SCZ, SCD	DSM-IV	In- and Outpatients	12	52.92 ± 8.07 / NR 53.07 ± 7.43 / NR	8.23 ± 6.71[c]	6.63 ± 4.77[c]	120	6	6
Weiser et al. (2017)	R: 100 P: 100	SCZ, SCA	DSM-IV-TR	In- and Outpatients	16	56.60 ± 4.60 / NR 55.80 ± 4.70 / NR	NR	NR	120	5	5

Aps antipsychotics, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders 4th edition, *NR* not reported, *SCA* schizoaffective disorder, *SCD* schizophreniform disorder, *SCZ* schizophrenia, *wks* week, *p* placebo group, *R* raloxifene group

[a,b] The same article but describe two different doses of raloxifene

[c] Risperidone mg equiv.

[d] Chlorpromazine mg equiv.

[e] Number of low risk judgment

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REVIEW ARTICLE

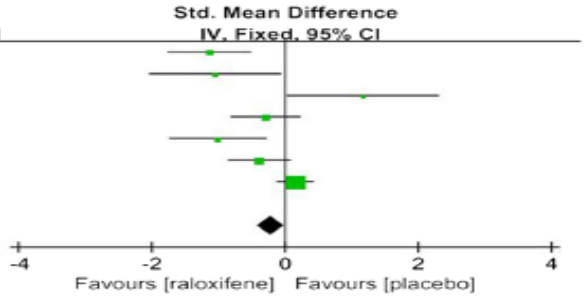
Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a meta-analysis of randomized controlled trials

Qi Wang[1] · Xiaomei Dong[1] · Yan Wang[1] · Xiaobai Li[1]

a

Study or Subgroup	raloxifene Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Kianimehr 2014	14.32	4.33	23	21.12	7.07	23	9.3%	-1.14 [-1.77, -0.51]
Kulkarni 2010 (120mg)	-4.12	2.32	13	-1.57	2.32	7	3.8%	-1.05 [-2.04, -0.06]
Kulkarni 2010 (60mg)	-0.17	1.13	9	-1.57	1.13	6	2.8%	1.17 [0.02, 2.31]
Kulkarni 2016	-2.63	3.75	26	-1.51	3.75	30	13.2%	-0.29 [-0.82, 0.23]
Usall 2011	-1.42	2.31	16	0.81	2	17	6.9%	-1.01 [-1.74, -0.28]
Usall 2016	-1.63	3.08	38	-0.41	3.08	32	16.3%	-0.39 [-0.87, 0.08]
Weiser 2017	18.7	4.9	100	18	4.6	100	47.7%	0.15 [-0.13, 0.42]
Total (95% CI)			**225**			**215**	**100.0%**	**-0.22 [-0.41, -0.02]**

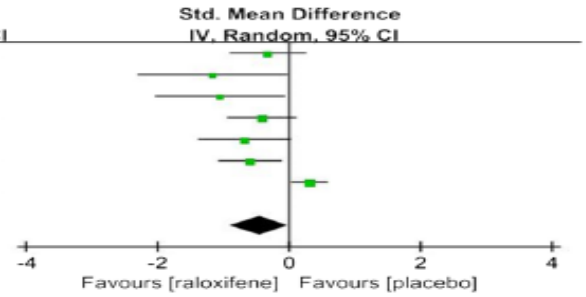
Heterogeneity: Chi² = 28.43, df = 6 (P < 0.0001); I² = 79%
Test for overall effect: Z = 2.20 (P = 0.03)



b

Study or Subgroup	raloxifene Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kianimehr 2014	19.6	8.66	23	23.08	12.08	23	15.3%	-0.33 [-0.91, 0.26]
Kulkarni 2010 (60mg)	-1.33	1.28	9	0.25	1.28	6	8.5%	-1.16 [-2.30, -0.02]
Kulkarni 2010 (120mg)	-2.26	2.29	13	0.25	2.29	7	10.0%	-1.05 [-2.04, -0.06]
Kulkarni 2016	-2.04	3.37	26	-0.61	3.37	30	16.1%	-0.42 [-0.95, 0.11]
Usall 2011	-3.5	2.13	16	-1.81	2.66	17	13.6%	-0.68 [-1.39, 0.02]
Usall 2016	-3.52	4.38	38	-0.88	4.38	32	16.8%	-0.60 [-1.08, -0.11]
Weiser 2017	23.4	6	100	21.7	5.1	100	19.6%	0.30 [0.03, 0.58]
Total (95% CI)			**225**			**215**	**100.0%**	**-0.46 [-0.89, -0.02]**

Heterogeneity: Tau² = 0.23; Chi² = 23.20, df = 6 (P = 0.0007); I² = 74%
Test for overall effect: Z = 2.07 (P = 0.04)



c

Study or Subgroup	raloxifene Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kianimehr 2014	34.56	10.78	23	37.84	11.89	23	15.4%	-0.28 [-0.87, 0.30]
Kulkarni 2010 (120mg)	-7.42	5.68	13	-1.19	5.68	7	10.2%	-1.05 [-2.04, -0.06]
Kulkarni 2010 (60mg)	-1.31	0.1	9	-1.19	0.1	6	8.8%	-1.13 [-2.26, 0.01]
Kulkarni 2016	-5.42	5.77	26	-1.71	5.77	30	16.0%	-0.63 [-1.17, -0.09]
Usall 2011	-2.53	5.71	16	1.62	5.07	17	13.6%	-0.75 [-1.46, -0.04]
Usall 2016	-5.08	7.65	38	1.22	7.65	32	16.7%	-0.81 [-1.30, -0.32]
Weiser 2017	4.1	1	100	3.9	0.9	100	19.3%	0.21 [-0.07, 0.49]
Total (95% CI)			**225**			**215**	**100.0%**	**-0.55 [-0.99, -0.11]**

Heterogeneity: Tau² = 0.24; Chi² = 24.28, df = 6 (P = 0.0005); I² = 75%
Test for overall effect: Z = 2.43 (P = 0.01)

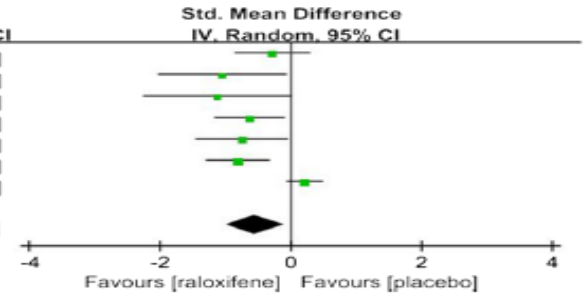


Fig. 3 a Forest plot for positive symptom scores as assessed by the PNSS scale. b Forest plot for negative symptom scores as assessed by the PNSS scale. c Forest plot for general symptom scores as assessed by the PNSS scale

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REVIEW ARTICLE

Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a meta-analysis of randomized controlled trials

Qi Wang[1] · Xiaomei Dong[1] · Yan Wang[1] · Xiaobai Li[1]

Conclusions

This study showed that adjunctive raloxifene appears to be efficacious and safe for postmenopausal women with schizophrenia. Adjunctive raloxifene treatment did not have greater discontinuation or adverse drug reactions compared to the placebo. Moreover, raloxifene may be efficacious for patients with less severe symptoms. However, given the low to moderate quality of the evidence of the included studies, these results must be considered suggestive and not definitive. Better designed studies that include more detailed descriptions of the methods employed are needed to confirm (or disprove) these results. In addition, future studies with a large sample size are needed to confirm these findings, and the long-term effects of raloxifene on psychopathology should be examined.

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Targeting hypothalamic-pituitary-adrenal axis hormones and sex steroids for improving cognition in major mood disorders and schizophrenia: a systematic review and narrative synthesis

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Table 3

Randomized, double-blind, placebo-controlled trials of adjunctive raloxifene for improving cognition in patients with schizophrenia.

Reference	Raloxifene dose	Design	Duration	Sample size	Reproductive status (women)	Results
Huerta-Ramos et al., 2014	60 mg/day	Randomized, double-blind, placebo-controlled trial	12 weeks	33 women	Postmenopausal	Improvements in verbal memory and executive functioning
Weickert et al., 2015	120 mg/day	Randomized, double-blind, placebo-controlled, crossover trial	17 weeks	79 (49 men, 30 women)	Premenopausal	Improvements in verbal memory, attention and processing speed
Kulkarni et al., 2016	120 mg/day	Randomized, double-blind, placebo-controlled trial	12 weeks	56 women	Peri/postmenopausal	No cognitive improvement
Weiser et al., 2017	120 mg/day	Randomized, double-blind, placebo-controlled trial	16 weeks	200 women	Postmenopausal	No cognitive improvement

Table 1 SNP information.

SNP reference number	Gene	Alleles	Characteristics	Minor Allele frequency Source:1000 Genomes European population	Other information
rs9340799	*ESR1*	A/G	Non-coding intronic	G: 0.3082	Also known as *Xba* I
rs2234693	*ESR1*	C/T	Non-coding intronic	C: 0.4225	Also known as *Pvu* II
rs1801132	*ESR1*	C/G	Coding non-synonymous	G: 0.2107	Residue position Pro325
rs1042597	*UGT1A8*	C/G	Missense	G: 0.2495	Residue position Ala173Gly, also known as UGT1A8*2

Table 3 Changes in PANSS general psychopathology subscale by rs2234693 genotype in the *ESR1* gene.

	Raloxifene			Placebo		
	TT $N=14$	TC $N=14$	CC $N=8$	TT $N=9$	TC $N=13$	CC $N=7$
PANSS - General (Baseline)[a]	38.8 (9.3)	40.6 (7.9)	37.6 (7.3)	35.2 (8.4)	35.3 (8.4)	34.0 (6.5)
PANSS - General (Month 1)[a]	35.4 (7.6)	36.4 (10.4)	36.5 (6.3)	32.3 (8.7)	35.5 (8.2)	40.4 (14.6)
PANSS - General (Month 3)[a]	32.8 (7.2)	36.7 (9.9)	36.8 (4.8)	33.1 (8.5)	36.1 (7.7)	39.3 (14.9)
PANSS - General (Month 6)[a]	32.3 (7.3)	34.9 (9.0)	35.8 (5.4)	35.2 (10.5)	36.3 (7.8)	38.9 (15.2)

Data are mean (SD).
Abbreviation: PANSS=Positive and Negative Syndrome Scale.
[a]A significant group × time × genotype interaction ($F=3.238$, $p=0.040$) was obtained when conducting an ANOVA for repeated measures comparing PANSS general psychopathology subscores between groups.

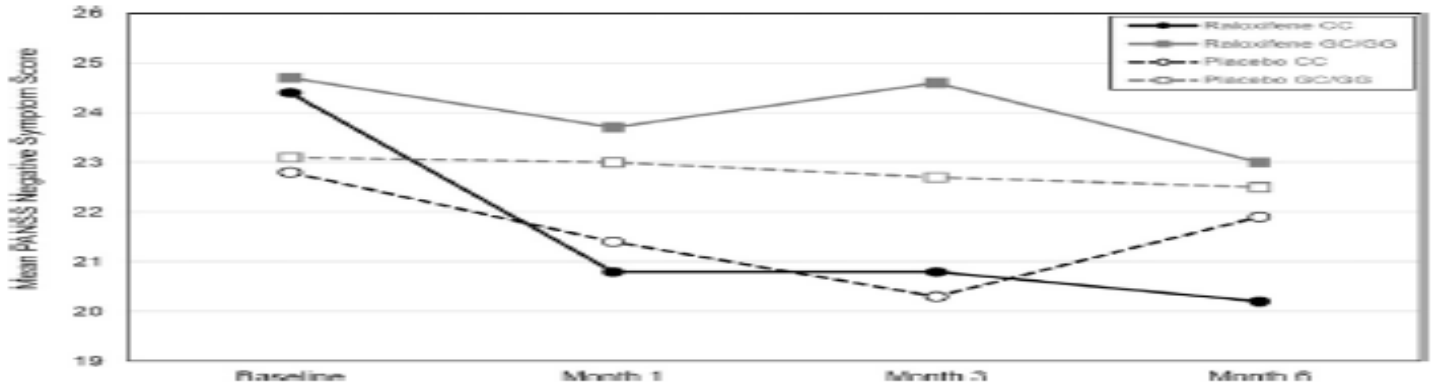

Figure 1 Changes in negative symptoms by rs1042597 in the *UGT1A8* gene and treatment subgroups during the study period. Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Labad et al. European Neuropsychopharmacology 2016

European Archives of Psychiatry and Clinical Neuroscience
https://doi.org/10.1007/s00406-018-0938-7

ORIGINAL PAPER

Specificity proteins 1 and 4 in peripheral blood mononuclear cells in postmenopausal women with schizophrenia: a 24-week double-blind, randomized, parallel, placebo-controlled trial

Elia Vila[1] · Elena Huerta-Ramos[2,3,4,5] · Christian Núñez[2,3,5] · Judith Usall[2,3,4,5] · Belén Ramos[1,3,4,6]

Received: 9 May 2018 / Accepted: 9 August 2018

A

	Raloxifene (n=7)		Placebo (n=7)	
dfPANSS scale	SP1 r	SP4 r	SP1 r	SP4 r
Negative	-0.468[a]	-0.681[a]	0.167[a]	-0.151[a]
General	-0.351[a]	**-0.868[a]***	0.006[a]	-0.369[a]
Total	-0.422[a]	**-0.839[b]***	0.121[a]	-0.153[a]

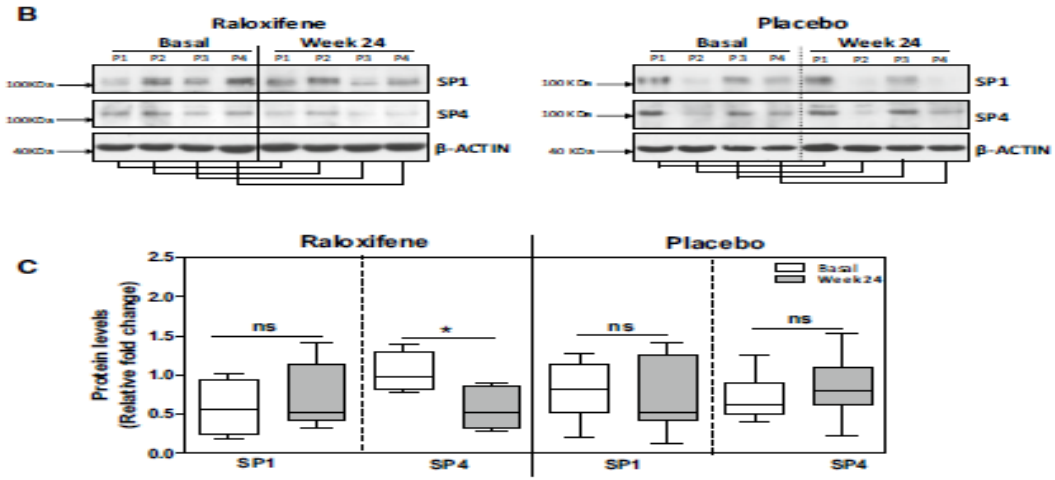

Fig. 2 Analysis of SP transcription factors in peripheral blood mononuclear cells of postmenopausal women with schizophrenia treated with adjunctive raloxifene or placebo. SP proteins from peripheral blood mononuclear cells of postmenopausal women with schizophrenia in raloxifene intervention and placebo groups were analysed at baseline and 24 weeks by immunoblot. Participants were evaluated by the Positive and Negative Syndrome Scale (PANSS) also at baseline and week 24. **a** Correlation between SP1 and SP4 protein levels after treatment (24 weeks) with the mean change from the baseline and final ratings of PANSS subscales (dfPANSS) in the raloxifene and placebo groups. *r* is shown for each comparison; [a]Pearson's *r* for parametric variables; [b]Spearman's *r* for non-parametric variables (*$p<0.05$). Significant associations were maintained after correction for multiple comparisons (SP4-dfPANSS-General: uncorrected $p=0.011$, *q* value = 0.054; dfPANSS-Total: uncorrected $p=0.018$, *q* value = 0.054, *p* value threshold = 0.033) with a false discovery rate (FDR) acceptance set at 0.1. **b** Images show representative SP1, SP4, and β-ACTIN immunoblots of four raloxifene and four placebo participants at baseline and week 24. Molecular marker weights are labelled and shown in KDa. The lines at the bottom of the panel indicate protein bands for the same individual (before and after treatment). **c** Comparison of SP protein levels between baseline and after treatment with raloxifene (baseline $n=4$; 24-week $n=7$) or placebo ($n=7$/group). Each box represents the median and interquartile range of protein levels at baseline and after 24 weeks of treatment. Protein levels were normalized to actin values. Statistical analysis was performed using unpaired *t* test (*$p<0.05$; ns, not significant). SP1 significant association was maintained after correction for multiple comparisons (SP4: uncorrected $p=0.014$; *q* value = 0.029, *p* value threshold = 0.050) with a false discovery rate (FDR) acceptance set at 0.1

Implicacions pràctiques

CNS Drugs
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REVIEW ARTICLE

Neurocognitive, Neuroprotective, and Cardiometabolic Effects of Raloxifene: Potential for Improving Therapeutic Outcomes in Schizophrenia

Mohammad M. Khan[1]

Abstract Raloxifene is a selective estrogen receptor modulator that has been approved for treating osteoporosis and breast cancer in high-risk postmenopausal women. However, recent evidence suggests that raloxifene adjunct therapy improves cognition and reduces symptom severity in men and women with schizophrenia. In animal models, raloxifene increases forebrain neurogenesis and enhances working memory and synaptic plasticity. It may consequently repair the neuronal and synaptic connectivity that is disrupted in schizophrenia. It also reduces oxidative stress and neuroinflammation, which are potent etiological factors in the neuropathology of schizophrenia. Furthermore, in postmenopausal women, raloxifene reduces the risks for atherosclerosis, diabetes mellitus, and weight gain, which are serious adverse effects associated with long-term antipsychotic treatment in schizophrenia; therefore, it may improve the safety and efficacy of antipsychotic drugs. In this review, recent insights into the neurocognitive, neuroprotective, and cardiometabolic effects of raloxifene in relation to therapeutic outcomes in schizophrenia are discussed.

Key Points

Raloxifene improves cognition and reduces symptom severity in men and women with schizophrenia.

Raloxifene improves neurological outcome in animal models by enhancing neurogenesis, synaptic plasticity, and reducing oxidative stress and neuroinflammation.

Raloxifene reduces the risk of atherosclerosis, diabetes mellitus, and weight gain in postmenopausal women; it may improve the safety and efficacy of antipsychotic drugs.

1 Introduction

Apart from displaying positive and negative symptoms

Hindawi
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Review Article

Translational Significance of Selective Estrogen Receptor Modulators in Psychiatric Disorders

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Accumulating data from various clinical trial studies suggests that adjuvant therapy with ovarian hormones (estrogens) could be effective in reducing cognitive deficit and psychopathological symptoms in women with psychiatric disorders. However, estrogen therapy poses serious limitations and health issues including feminization in men and increased risks of thromboembolism, hot flashes, breast hyperplasia, and endometrium hyperplasia when used for longer duration in older women (aged ≥ 60 years) or in women who have genetic predispositions. On the other hand, selective estrogen receptor modulators (SERMs), which may (or may not) carry some risks of hot flashes, thromboembolism, breast hyperplasia, and endometrial hyperplasia, are generally devoid of feminization effect. In clinical trial studies, adjuvant therapy with tamoxifen, a *triphenylethylene* class of SERM, has been found to reduce the frequency of manic episodes in patients with bipolar disorder, whereas addition of raloxifene, a *benzothiophene* class of SERM, to regular doses of antipsychotic drugs has been found to reduce cognitive deficit and psychological symptoms in men and women with schizophrenia, including women with treatment refractory psychosis. These outcomes together with potent neurocognitive, neuroprotective, and cardiometabolic properties suggest that SERMs could be the potential targets for designing effective and safer therapies for psychiatric disorders.

npj | Schizophrenia

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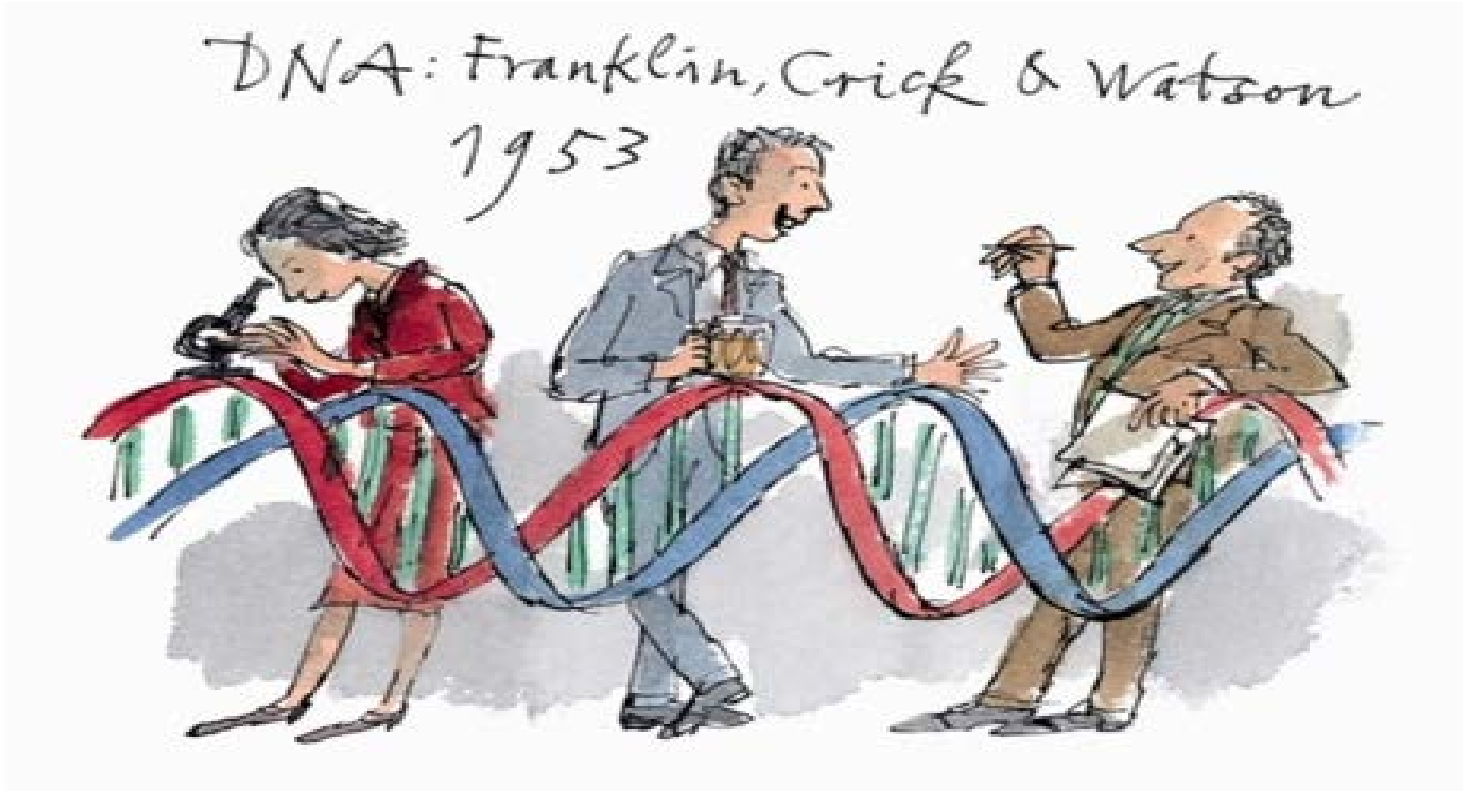
REVIEW ARTICLE OPEN

The effect of raloxifene augmentation in men and women with a schizophrenia spectrum disorder: a systematic review and meta-analysis

anna de Boer[1], Merel Prikken[1], Wan U. Lei[1], Marieke Begemann[1] and Iris Sommer[2,3]

Recognizing the robust sex differences in schizophrenia prevalence, the selective estrogen receptor modulator (SERM) raloxifene is a likely candidate for augmentation therapy in this disorder. Therefore, a systematic search was performed using PubMed (Medline), Embase, PsychInfo, and Cochrane Database of Systematic Reviews. Randomized controlled trials investigating the effect of raloxifene in schizophrenia spectrum disorders were included in the quantitative analyses. Outcome measures were psychotic symptom severity, depression, and cognition. Meta-analyses were performed using Comprehensive Meta-Analysis software. A random-effects model was used to compute overall weighted effect sizes in Hedges' *g*. Nine studies were included, investigating 561 patients with a schizophrenia spectrum disorder. Raloxifene was superior to placebo in improving total symptom severity ($N = 482$; Hedge's $g = .57$, $p = 0.009$), as well as positive ($N = 561$; Hedge's $g = 0.32$, $p = 0.02$), negative ($N = 561$; Hedge's $g = 0.40$, $p = 0.02$), and general ($N = 526$; Hedge's $g = 0.46$, $p = 0.01$) subscales, as measured by the Positive and Negative Syndrome Scale. No significant effects were found for comorbid depression and cognitive functioning. Altogether, these results confirm the potential of raloxifene augmentation in the treatment of schizophrenia.

npj Schizophrenia (2018)4:1 ; doi:10.1038/s41537-017-0043-3


DNA: Franklin, Crick & Watson
1953

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