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**MAYO CLINIC**

**Gender Differences in Antidepressant Pharmacotherapy**

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MPS-On Her Shoulders: The Impact of a Woman's Mental Health-10/1/2022

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Slide 2

**Learning Objectives**

- Understanding differences in clinical appearance of depression in women compared to men.
- To review the prescription patterns in men and women at the national and international level.
- To understand the role of age dependant hormonal changes in women as a contributor to antidepressant outcome.
- To understand the impact of age on antidepressant use in women versus men.

• Conclusions-Q&A

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**The National Health and Nutrition Examination Survey**

During 2013–2016, 8.1% of Americans aged 20 and over had depression in a given 2-week period.

Figure 1. Percentage of persons aged 20 and over with depression, by age and sex: United States, 2013–2016

Sex	All ages	20-39	40-69	60 and over
Both sexes	8.1	7.7	8.4	6.0
Men	8.1	7.7	8.4	6.0
Women	10.4	10.1	11.5	9.9

Women (10.4%) were almost twice as likely as were men (5.5%) to have had depression.

Brody et al., 2018. NCHS Data Brief 1–8.

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### The Experience of Symptoms of Depression in Men vs Women: National Comorbidity Survey Replication

Table 3. Male Symptoms Scale Results: Item Endorsement, Mean Score, and Prevalence of Male Depression

Item Description	Total	% (SE)	
		Men	Women
Stress	68.9 (1.6)	63.3 (1.3) <sup>a</sup>	75.2 (2.4) <sup>a</sup>
Irritability	90.3 (1.4)	86.6 (1.3)	94.7 (1.3) <sup>a</sup>
Anger attacks/aggression	92.05 (1.2)	94.85 (1.3) <sup>a</sup>	88.94 (1.4)
Sleep problems	37.7 (1.5)	29.2 (2.1)	47.1 (1.9) <sup>a</sup>
Alcohol/other drug abuse	51.6 (1.3)	61.4 (3.0) <sup>a</sup>	40.6 (1.3)
Loss of interest	88.7 (3.3)	87.6 (1.5)	91.6 (1.0) <sup>a</sup>
Risk-taking behavior	41.6 (1.5)	52.7 (2.0) <sup>a</sup>	29.1 (2.1)
Hyperactivity	57.9 (1.4)	57.6 (3.1)	58.4 (1.8)
Mean score	6.06	6.05	6.07
Prevalence, %	23.8	26.3 <sup>a</sup>	21.9

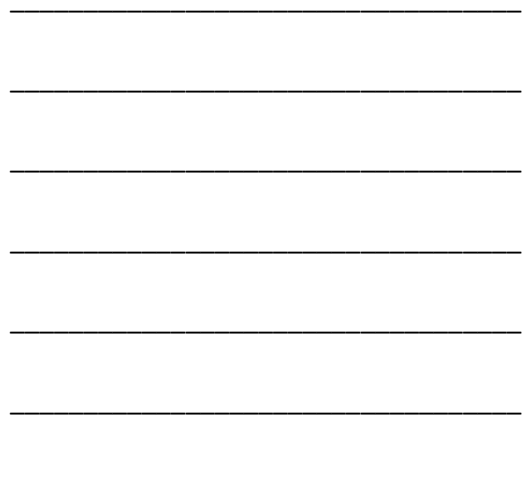
<sup>a</sup>P < .001  
<sup>b</sup>P < .05  
<sup>c</sup>P < .01

Martin et al., 2013 JAMA Psychiatry 70, 1100

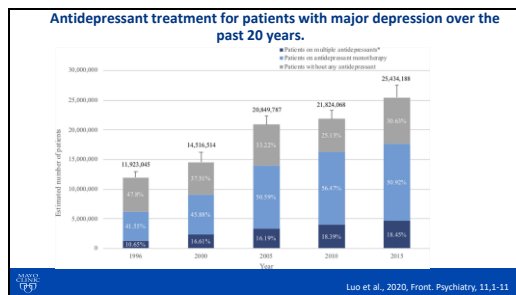


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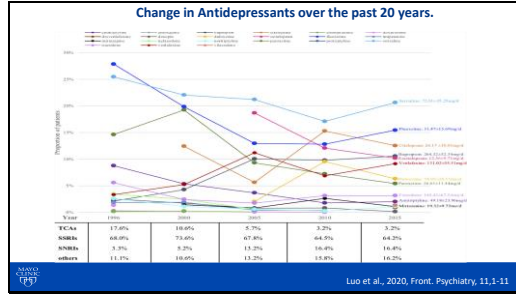
- ### Depression in women
- Appear to present a greater number of symptoms than men (1)
  - More likely to present:
    - reverse vegetative or atypical symptoms, (increased appetite and weight gain),
    - anxiety and somatic symptoms (2).
  - Tends to be more severe (3,4)
  - Associated with increased functional impairment (4).
  - Women are more likely to attempt suicide, but the rate of "successfully carried out" suicide is higher in men (5,6,7,8).
1. Angst and Dobler-Matelo, 1984; 2. Korstein, 1997; Silverstein, 1999; 3. Thase et al., 1994; 4. Korstein et al., 1996; 5. Kessler et al., 1981; 6. Iso Metsa et al., 1994; 7. Canetto and Siskindsky, 1998; 8. Murphy, 1998



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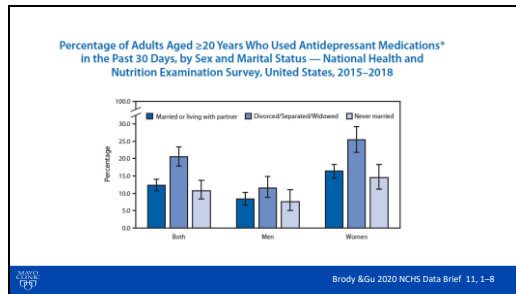


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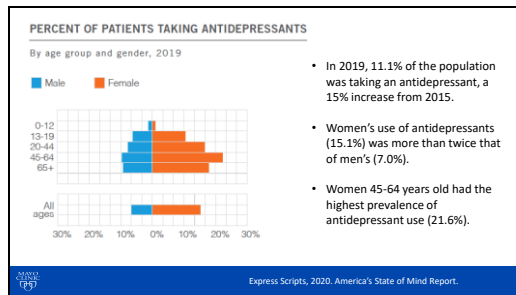


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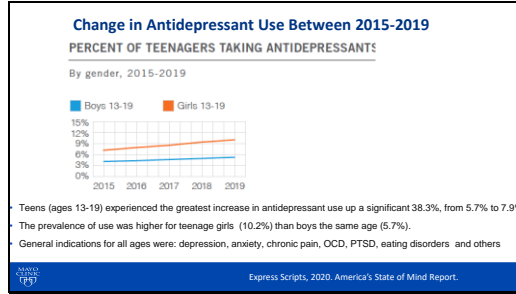


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#### Table 1 Characteristics of patients from each of the four study databases

Characteristic	IBM MarketScan® Commercial Database (CAE)	IBM MarketScan® Multi-State Medicaid Database (MDCD)	IBM MarketScan® Medicare Supplemental Database (MDCR)	Optum® De-identified Clinformatics® Data Mart Database
Number of patients	28,114,000	20,100,000	20,100,000	20,100,000
Gender	50.5%	50.5%	50.5%	50.5%
Age (mean)	46.0	46.0	46.0	46.0
Diagnoses				
Major depressive disorder	12.1%	12.1%	12.1%	12.1%
Minor depressive disorder	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with bipolar disorder	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with anxiety disorder	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with personality disorder	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with substance use disorder	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with dementia	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with intellectual disability	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with autism spectrum disorder	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with schizophrenia	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with bipolar disorder	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with anxiety disorder	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with personality disorder	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with substance use disorder	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with dementia	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with intellectual disability	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with autism spectrum disorder	12.1%	12.1%	12.1%	12.1%
Major depressive disorder with schizophrenia	12.1%	12.1%	12.1%	12.1%

Kern et al. BMC Psychiatry (2020) 20:4

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Journal of Affective Disorders

Research paper

#### Antidepressant use in Denmark, Germany, Spain, and Sweden between 2009 and 2014: incidence and comorbidities of antidepressant initiators

Joan Ferrer<sup>1,2</sup>, Anna Purgatoriu<sup>3</sup>, Tamara Rodríguez<sup>4</sup>, Beatriz Pardo-López<sup>5</sup>, Rosa Miras<sup>6,7</sup>, Leon Børsting<sup>8</sup>, Miguel Carmen Abadía<sup>9</sup>, María Rodríguez<sup>10</sup>, Tania Sánchez<sup>11</sup>, Alexandra Pardo-López<sup>12</sup>, María Clara Rodríguez<sup>13</sup>, David Hogg<sup>14</sup>, Roger Hogg<sup>15</sup>, José Carlos<sup>16,17</sup>, Emanuele Jacquot<sup>18</sup>, Nicolas Durrant<sup>19</sup>, Brian Patten Gifford<sup>20</sup>, Muel Pluijms<sup>21</sup>, Johan Kouvonen<sup>22</sup>

**Background:** We aimed to describe patterns of use and characteristics of 10 commonly used antidepressants for the period 2009–2014 in Denmark, Germany, Spain, and Sweden.

**Methods:** Adult initiators from 2009 to 2014 of each study antidepressant were identified in four countries using five data sources: the Danish National registers, GePaRD (Germany), EpiChron (Aragon, Spain), SIDAP (Catalonia, Spain), and the Swedish National Registers. The study included 10 study antidepressants: citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, mirtazapine, and agomelatine.

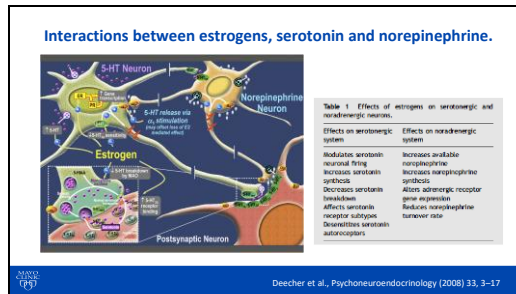
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Number of study participants (millions) with age and sex distribution

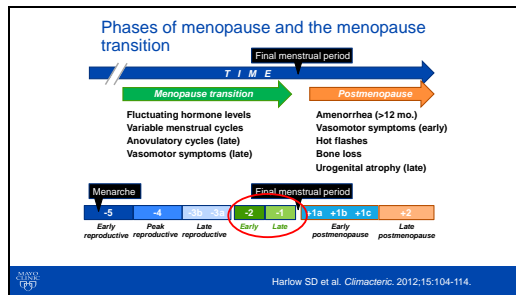
Research	USA, Germany	UK, China, Japan, Spain	BRM, Canada, Italy	Sweden
<b>Study period</b>				
Number of study participants (millions) n (%)				
Colspan	203,033 (20%)	483,794 (47%)	61,023 (5%)	52,076 (5%)
Healthspan	57,388 (27%)	77,762 (16%)	32,204 (52%)	28,429 (51%)
Flourish	13,468 (7%)	40,702 (8%)	17,493 (28%)	23,784 (45%)
Rejuvenate	13,968 (7%)	50,141 (10%)	20,213 (33%)	24,688 (47%)
Rebalance	127,663 (62%)	162,889 (32%)	12,000 (20%)	28,510 (54%)
Rejuvenate	37,338 (18%)	79,466 (16%)	33,794 (55%)	13,389 (26%)
Rebalance	67,366 (33%)	147,300 (30%)	11,061 (18%)	13,077 (25%)
Rejuvenate	34,468 (17%)	56,277 (11%)	22,213 (36%)	28,419 (54%)
Rejuvenate	167,200 (82%)	276,741 (57%)	23,473 (38%)	28,524 (54%)
Rejuvenate	22,462 (11%)	63,009 (13%)	10,071 (16%)	19,068 (37%)
<b>Age</b>				
18-24	879,024	1,733,443	111,384	201,722
<b>Gender (%)</b>				
Colspan	62%	67%	69%	76%
Healthspan	62%	67%	69%	76%
Flourish	62%	67%	69%	76%
Rejuvenate	62%	67%	69%	76%
Rebalance	62%	67%	69%	76%
Rejuvenate	62%	67%	69%	76%
Rejuvenate	62%	67%	69%	76%
Rejuvenate	62%	67%	69%	76%
Rejuvenate	62%	67%	69%	76%
Rejuvenate	62%	67%	69%	76%
<b>Age, Healthspan, Spain</b>				
Colspan	53 (26-76)	54 (14-79)	43 (16-79)	53 (14-75)
Healthspan	52 (27-69)	52 (28-63)	56 (12-73)	44 (28-61)
Flourish	41 (28-64)	47 (28-67)	50 (28-68)	47 (27-63)
Rejuvenate	44 (28-61)	46 (27-63)	40 (18-68)	41 (28-61)
Rebalance	44 (28-61)	52 (14-63)	43 (14-78)	41 (14-61)
Rejuvenate	44 (27-61)	51 (14-61)	40 (14-75)	41 (14-61)
Rejuvenate	40 (13-67)	51 (14-61)	53 (13-70)	41 (13-61)
Rejuvenate	53 (14-63)	53 (14-67)	53 (14-67)	53 (14-61)
Rejuvenate	54 (14-72)	53 (14-71)	47 (14-61)	53 (14-71)
Rejuvenate	54 (14-67)	53 (14-61)	54 (14-67)	53 (14-61)

PSY - average age range.

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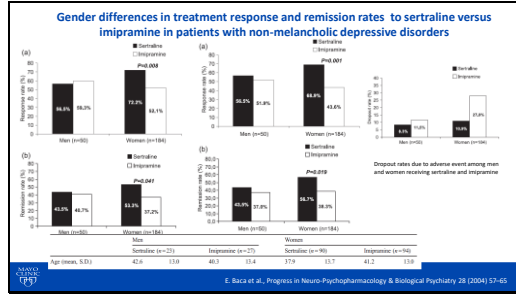


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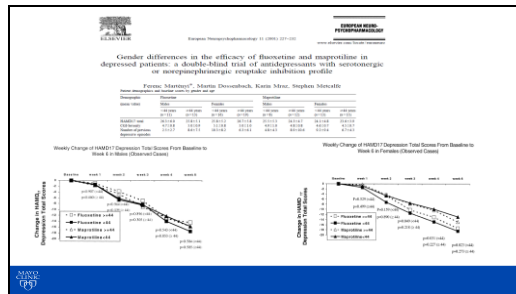




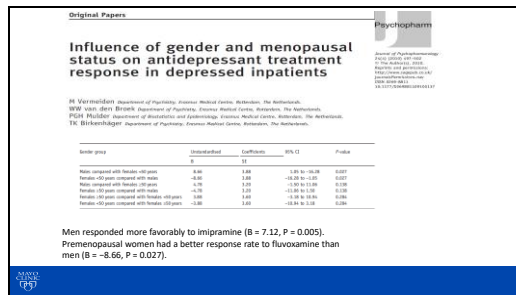
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### Gender Differences in Treatment Response to Sertraline Versus Imipramine in Chronic Depression

- Premenopausal women responded significantly better to sertraline than to imipramine, whereas response rates to the two drugs in postmenopausal women were similar. Among those taking imipramine, premenopausal women were significantly more likely to discontinue treatment than postmenopausal women. These findings suggest that the gender differences in imipramine response found in our study were due primarily to poor response and tolerability in premenopausal women.

FIGURE 1. Rates of Response to Sertraline and Imipramine at Endpoint Among Men and Women With Chronic Depression in a 12-Week Double-Blind Treatment Study\*

Gender	Imipramine (%)	Sertraline (%)
Women (N=400)	~45	~60
Men (N=235)	~55	~45

Kornstein et al., Am J Psychiatry 157:9, September 2000

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### Age, gender, and HRT moderate response to antidepressant medications

TABLE 2. RELATIVE EFFICACY OF VENLAFAXINE AND SSRI: REMISSION RATES AMONG AGE AND SEX SUBGROUPS

Subgroup	Women			Men		
	PBO <sup>a</sup>	SSRI	VEN	PBO	SSRI	VEN
<50 years	26% (54/211)	36% (127/350)	44% (172/394)	28% (35/123)	36% (72/200)	47% (106/233)
≥50 years	17% (11/65)	28% (37/131)	48% (78/161)	21% (10/47)	35% (24/68)	41% (26/63)
HRT -	16% (7/45)	27% (28/105)	50% (63/127)	NA <sup>b</sup>	NA	NA
HRT +	20% (4/20)	35% (9/26)	44% (15/34)	NA	NA	NA

\*PBO, placebo; SSRI, selective serotonin reuptake inhibitor; VEN, venlafaxine; HRT, hormone replacement therapy.  
<sup>a</sup>NA, nonapplicable.

Thase et al., J Womens Health (Larchmt) 2005 Sep 14(7):609-16

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### Sex Differences in Antidepressant Response in Recent Antidepressant Clinical Trials

Study	Drug	N	Mean Age	% Male	Mean BDI-II	Mean Change	% Responders
Study 1	Escitalopram	11	42.4	48.7	21.46	-10.97	73.2
	Placebo	11	42.0	50.1	22.75	-8.63	51.8
Study 2	Venlafaxine	12	40.8	50.7	22.32	-10.58	61.5
	Placebo	12	41.1	51.1	22.32	-10.58	50.0
Study 3	Escitalopram	10	42.4	48.7	21.46	-10.97	73.2
	Placebo	10	42.0	50.1	22.75	-8.63	51.8
Study 4	Venlafaxine	10	41.2	49.2	22.10	-10.20	61.0
	Placebo	10	41.5	49.5	22.10	-10.20	51.0
Study 5	Escitalopram	10	42.4	48.7	21.46	-10.97	73.2
	Placebo	10	42.0	50.1	22.75	-8.63	51.8
Study 6	Venlafaxine	10	41.2	49.2	22.10	-10.20	61.0
	Placebo	10	41.5	49.5	22.10	-10.20	51.0
Study 7	Escitalopram	10	42.4	48.7	21.46	-10.97	73.2
	Placebo	10	42.0	50.1	22.75	-8.63	51.8
Study 8	Venlafaxine	10	41.2	49.2	22.10	-10.20	61.0
	Placebo	10	41.5	49.5	22.10	-10.20	51.0
Study 9	Escitalopram	10	42.4	48.7	21.46	-10.97	73.2
	Placebo	10	42.0	50.1	22.75	-8.63	51.8
Study 10	Venlafaxine	10	41.2	49.2	22.10	-10.20	61.0
	Placebo	10	41.5	49.5	22.10	-10.20	51.0
Study 11	Escitalopram	10	42.4	48.7	21.46	-10.97	73.2
	Placebo	10	42.0	50.1	22.75	-8.63	51.8
Study 12	Venlafaxine	10	41.2	49.2	22.10	-10.20	61.0
	Placebo	10	41.5	49.5	22.10	-10.20	51.0
Study 13	Escitalopram	10	42.4	48.7	21.46	-10.97	73.2
	Placebo	10	42.0	50.1	22.75	-8.63	51.8
Study 14	Venlafaxine	10	41.2	49.2	22.10	-10.20	61.0
	Placebo	10	41.5	49.5	22.10	-10.20	51.0
Study 15	Escitalopram	10	42.4	48.7	21.46	-10.97	73.2
	Placebo	10	42.0	50.1	22.75	-8.63	51.8

Kahn et al., J Clin Psychopharmacol 2005;25:318-324



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**Sex Differences in Antidepressant Response in Recent Antidepressant Clinical Trials**

	Men			Women		
	Placebo	SNRIs	SNRI	Placebo	SSRIs	SNRI
No. of subjects	65	59	22	80	71	26
Mean age ± SD in years	40.7 ± 13.4	45.1 ± 18.3	41.0 ± 15.6	41.2 ± 12.9	43.5 ± 15.2	44.7 ± 13.9
Percentage of completers	84.6	81.4	77.3	77.2	84.5	80.8
Mean baseline total HAM-D-17 score ± SD	24.8 ± 3.3	24.1 ± 3.4	23.2 ± 3.3	25.4 ± 3.2	25.1 ± 3.2	25.0 ± 3.7
Mean change in total HAM-D-17 at LOCF ± SD	-7.4 ± 7.3	-10.6 ± 8.1	-12.1 ± 7.6	-8.8 ± 7.4	-14.9 ± 7.0	-14.4 ± 6.5
Mean baseline total MADRS score ± SD	31.8 ± 4.2	30.9 ± 4.7	30.9 ± 5.9	31.7 ± 3.4	31.7 ± 4.8	31.2 ± 5.6
Mean change in total MADRS score at LOCF ± SD	-9.7 ± 9.4	-12.8 ± 10.2	-16.7 ± 11.5	-11.3 ± 11.1	-19.6 ± 9.9	-19.2 ± 10.9
% of responders - ≥ 50% reduction from baseline to final visit on HAM-D-17	24.6	47.5	59.1	40.0	64.8	69.2
% of subjects achieving remission - final HAM-D-17 score ≤ 7	15.4	35.6	45.5	13.8	45.1	46.2

Kahn et al., J Clin Psychopharmacol 2005;25:318-324

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**Sex Differences in Antidepressant Response: Other Studies**

Sample	Design	Intervention	Control	Measure	Result
Kornstein et al., 2014	Mean Age 42-43 Recurrent MDD W(Pw&Postmenop) vs. M	Multiplace, double blind Venlafaxine XR 75-300 mg (65% W)	Fluoxetine 20-60 mg (65% W)	HAM-D17	Treatment outcomes did not differ on the basis of sex and menopausal status.
Kornstein et al., 2006	Age 18 years or > MDD	Pooled data, 7 double blind RCT Duloxetine 40-120 mg M (N = 318)	Placebo M (N = 242) CGI-S PGI-4 W (N = 494)	HAM-D17 CGI-S PGI-4	Efficacy of duloxetine did not differ significantly in male and female patients.
Young et al., 2009	Age 18-75 years Mean age: 40.8 ± 13.0 MDD	STAR*D Level-1 12-14 week open label Citalopram (N=2876; 63.7% female)	NA	HAM-D17	Women were more likely to reach remission and response with citalopram than men
Grigoriadis et al., 2003	Age 40-60 years 201 (115 W, 86 M) <44 years; n = 91 >50 years; n = 24	8 week open label flexible dose SSRI (parox, citalop, fluox, sertr) Nefazodone Venlafaxine	NA	HAM-D17	Response and remission: Younger/older women Response to SSRI: Younger/older women
Dewan-Tanha et al., 2016	Postmenopausal women	RC DR 12 wks Venlafaxine 75 mg Citalopram 20 mg	Placebo	PSQI	Hot flashes&PSQI reduced sig. with citalopram/sertraline

Kornstein et al., 2014, J Clin Psychiatry 75(11):16-86; Kornstein et al., 2006, J Clin Psychopharmacol 26(6):763-770; Young et al., J Psych Res 43(10):1009-1013; Grigoriadis et al., 2003, J Clin Psychopharmacol 23(4):405-407; Dewan-Tanha et al., 2016, Arch Gynecol Obstet 293(1):1007-1013

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**Age-dependent sex differences in the prevalence of selective serotonin reuptake inhibitor treatment: a retrospective cohort analysis (1)**


- Primary aim:** to assess the cross-sectional prevalence of antidepressant use and potential sex-related differences
- Secondary aim:** to investigate age-dependent differences in antidepressant prescriptions by sex.
- Method:** Retrospective data analysis;  
Right Drug, Right Dose, Right Time: Using Genomic Data to Individualize Treatment (RIGHT 10K) participants,
- RIGHT 10K: collaboration Mayo Clinic and Baylor College of Medicine n= 11,098 individuals with previously stored DNA samples at the Mayo Clinic Biobank (2),
- Electronic health records (EHRs) within the REP, a medical records-linkage system of different regional health care providers from southern Minnesota and western Wisconsin (3).

1. Sanchez-Ruiz et al. under review; 2. Olson et al., 2019; 3. St Sauver et al., 2012



**Conclusions**

- Antidepressant treatment outcome shows age-sex interaction.
- Females are better responders to SSRI's at premenopausal years vs. postmenopausal years.
- Males are more stable in response and side effects to antidepressants.
- Further studies are needed to understand the effect of age- and sex-dependent patterns of antidepressant use in the context of reproductive health and specific indication for prescription.



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