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Treatment of depressive symptoms in perimenopausal women: hormone replacement therapy, antidepressants or both?

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Date: 10-08-2016

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Abstract

Objectives: Research has found menopausal transition, the perimenopause, to be associated with an increased risk of depressive symptoms. Many studies focused on treatment options to improve psychological well-being of perimenopausal women. However, to date it is unknown which treatment, including hormone replacement therapy (HRT), antidepressants (AD) or a combination, is most effective. In this thesis we want to investigate and provide an answer as to which treatment is most effective in reducing depressive symptoms in perimenopausal women.

Methods: Computerised literature searches were performed with “major depression” and “menopause” as main search terms. Studies were considered if they included a measure of depressive symptoms and menopausal status was examined according STRAW-criteria. Comprehensive Meta-Analysis (CMA) was used for the analysis. Effect sizes were analyzed using the random effects model, in which the error term is composed of variation originating from both within-study variability and between-study differences.

Results: Six studies were included in the meta-analysis. No significant difference was found between the effects of HRT versus placebo on reducing depressive symptoms. AD compared with placebo showed that AD is more effective than placebo (effect size = -1.868, $z = -4.937$, $p < 0.001$). AD compared with HRT had an effect size of -1.460, $p = 0.033$.

Conclusion: The results of this meta-analysis should be interpreted with great caution, because of the small number of included studies. AD therapy was found to be more efficacious in treating depressive symptoms of perimenopausal women than placebo and HRT. The efficacy of HRT in reducing depressive symptoms in perimenopausal women cannot be established. However, further research is recommended.

1. Introduction

The menopausal transition is associated with an increased risk of depressive symptoms for women, independent of demographic, behavioral, psychosocial and health factors (Bromberger et al., 2007). Many studies focused on treatment options to improve psychological well-being of perimenopausal women. However, to date it is unknown which treatment, including Estrogen-Replacement Therapy (ERT), Hormone-Replacement Therapy (HRT), Antidepressants (AD) or a combination, is most effective in the treatment of perimenopausal women.

1.1. Characteristics of Depression

Depression is common and associated with functional impairment. According to the Central Statistics Office (2013) in 2012 one out of ten adults in the Netherlands felt depressed. The twelve-month prevalence of adults with a depressed mood or a depression in the Netherlands is 7.9% for men and 13.1% for women (Verweij & Houben-Van Herten, 2013). In the Diagnostic and Statistical Manual of mental disorders (DSM-5; American Psychiatric Association, 2014), the criteria for a major depressive disorder or a depressive episode are a depressed mood or a loss of interest/pleasure in daily activities for more than two weeks. At least 5 of the 9 specific symptoms have to be present nearly every day: depressed mood or irritability, decreased interest or pleasure in most activities, significant weight change, change in sleep, change in activity, fatigue or loss of energy, guilt or worthlessness, concentration problems and suicidality (DSM-5, 2014).

1.2. Menopausal transition

The STages of Reproductive Aging Workshop (STRAW) is the standard for characterizing reproductive aging through menopause. The staging recommendations are restricted to menstrual cycle bleeding and Follicle-Stimulating Hormone (FSH) levels. STRAW divides the adult female life into three phases: premenopause (reproductive years), perimenopause and postmenopause, see Figure 1 (Harlow et al., 2012). The early menopausal transition starts at stage -2 and is marked by an increased variability in menstrual cycle length and a difference of 7 days or more in the length of consecutive cycles. Most women enter this stage in their 40's, with a mean age of 47.5 years (Soares, Poitras & Prouty, 2003). The late menopausal transition starts at stage -1 and is defined as amenorrhea for 60 days or longer. This stage is characterized by an increased variability in cycle length, extreme fluctuations in

hormonal levels and FSH levels greater than 25 IU/L. The end of the 12-month period of amenorrhea starts at stage +1a and is defined as the postmenopause (Harlow et al., 2012).

Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	variable				variable	1-3 years	2 years (1+1)	3-6 years	Remaining lifespan	
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	Variable Length Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of ≥60 days				
SUPPORTIVE CRITERIA										
Endocrine			Low	Variable	↑ Variable	↑ >25 IU/L**	↑ Variable	Stabilizes		
FSH			Low	Low	Low	Low	Low	Very Low		
AMH				Low				Very Low		
Inhibin B										
Antral Follicle Count			Low	Low	Low	Low	Very Low	Very Low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms Likely	Vasomotor symptoms Most Likely			Increasing symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ = elevated
 **Approximate expected level based on assays using current international pituitary standard⁶⁷⁻⁶⁹

Figure 1. STRAW+10 staging system for reproductive aging in women (Harlow et al., 2012)

The transition from premenopause to perimenopause, the menopausal transition, is for some women a period of increased vulnerability for a depression or depressive symptoms (Bromberger et al., 2007; Schmidt, 2005). It has been found that depressive symptoms or the development of a first episode of depression significantly increase during menopausal transition, even after controlling for variables such as a history of depression or important life events (Cohen, Soares, Vitonis, Otto & Harlow, 2006; Freeman et al., 2004). Many studies concluded that women who entered the perimenopause or early postmenopause were 2 to 4 times more likely to experience a major depression or a major depressive episode compared to premenopausal women (Bromberger et al., 2011; Freeman, 2010; Cohen et al., 2006).

1.3. Gender differences, hormonal fluctuations and attitude toward menopause

Depression is more common among women than men. The World Mental Health Survey initiative reports for the Netherlands a 2:1 rate of depression for women compared to men, during a 12-month major depressive episode (Odds Ratio (OR)=2.3) (Bromet et al., 2011). An explanation for this gender difference can be found in the tendency to seek help, role differences, biological differences, exposure to stressful life events and coping factors (Hammen & Watkins, 2008). In this thesis, the biological differences between men and women are a topic of interest.

It is known that the brain responds to fluctuating hormone levels and will modify its function. In female brains a cyclic hormonal fluctuation occurs, because of the menstrual cycle. This requires a flexible and responsive mechanism to compensate for changes in neuroendocrine input (Deecher, Andree, Sloan & Schechter, 2008). During the menopausal transition these cycles become irregular and result in changeable hormone levels (Deecher et al., 2008; Harlow et al., 2012). During this period, hormone levels fluctuate. Estrogen levels increase during early perimenopause, before dropping and FSH levels will increase and stabilize at the postmenopausal state (Gibbs, Lee & Kulkarni, 2012). The female brain has to adapt to these changes in menstrual cycle and fluctuating hormone levels. According to Gibbs and colleagues (2012), the fluctuations in reproductive hormones could lead to a depression in vulnerable women, while Deecher and colleagues (2008) think that the inability to rapidly respond to these hormonal changes in the brain can lead to mood disorders.

Another explanation could be that neuroendocrine changes in the Hypothalamic-Pituitary-Gonadal (HPG) axis lead to lower levels of the neurotransmitter serotonin (5-Hydroxytryptamine receptors (5-HT)). The hormonal fluctuations during menopausal transition effects the HPG axis, which influences the function of 5-HT receptors. Lower levels of serotonin have been associated with depressive symptoms or a depression in combination with stressful life events (Deecher et al., 2008). This could be an alternate explanation for the increased risk on depressive symptoms or a depression in the perimenopause state (Deecher et al., 2008).

Also, the relation between attitudes towards the menopause and women's symptom experience has been investigated. It has been found that women with more negative attitudes prior to menopause experience higher frequencies of hot flushes during menopause (Ayers, Forshaw & Hunter, 2010). In another study with healthy women it was found that a negative

attitude toward aging was associated with later higher symptom intensity (Nosek et al., 2010). For these reasons, it is plausible that women experience and express more often depressive symptoms or a depression than men, especially during this period of their lives.

1.4. Treatment for women in perimenopause

There are many treatment possibilities for perimenopausal women with depressive symptoms or a depression, including for instance Estrogen-Replacement Therapy (ERT), Hormonal-Replacement Therapy (HRT) and antidepressants. The goal of most treatments is to improve psychological well-being.

ERT and HRT are both hormonal-replacement therapies, which only differ in the addition of the hormone progesterin to HRT. The combination of estrogen with progesterin is needed for women with an uterus, to prevent irregular bleeding and to lower the risk of endometrial cancer (Studd, 2011). The route of administration in most studies is by transdermal skin patches (Soares, 2003). ERT and HRT lead to symptom relief of vasomotor symptoms, such as hot flushes and night sweats. Where a decrease in estrogens led to vaginal dryness and a loss of libido, an increase of estrogens can alleviate this symptoms (Studd, 2011). All treatments are associated with risk factors; ERT and HRT are no exception to this rule. There is an increased risk of breast cancer and cardiovascular events. To avoid increased risk, the use of this treatments should be limited to three to five years (Gordon & Girdler, 2014; Parry, 2010).

Widely used antidepressant treatments for women in perimenopause are Selective Serotonin Reuptake Inhibitors (SSRI) or Selective Serotonin and Noradrenalin Reuptake Inhibitors (SNRI) as paroxetine, fluoxetine, desvenlafaxine and escitalopram. SSRI's are believed to increase the level of serotonin by inhibiting the reuptake of this neurotransmitter. SNRI's work the same way, but act upon the neurotransmitters serotonin and noradrenalin. SSRI's and SNRI's improve mood and vasomotor symptoms (Soares et al., 2003). Most reported side effects of antidepressants are jitteriness, headache and nausea, but usually these side-effects will abate in the first weeks of the treatment. It can take six to eight weeks to achieve response and effectiveness (Santoro, Epperson, Mathews, 2015).

Different studies report different results for the treatments ERT, HRT and antidepressants for depression or depressive symptoms in perimenopausal women. In a study of Kornstein, Clayton, Bao and Guico-Pabia (2015) the antidepressant desvenlafaxine (SNRI) showed a significant effect in both perimenopausal and postmenopausal women with a major

depressive disorder, with a therapeutic dose of 50 mg/day. In this study depressive symptoms reduced significantly in perimenopausal women treated with desvenlafaxine compared to untreated perimenopausal women (Kornstein et al., 2015). In a previous study the effectiveness of the antidepressant escitalopram (SSRI) in perimenopausal women has been investigated. Remission was experienced by 12 out of 13 women who completed the entire trial. This study concluded that escitalopram is an effective and well tolerated treatment of depression in perimenopausal women (Freeman et al., 2006). Gartrell and colleagues (2001) reported that symptom relief was experienced by 57 percent of peri- and postmenopausal women when they were treated with antidepressants (SSRI's). For comparison, with HRT only 23 percent of the peri- and postmenopausal women experienced symptom relief (Gartrell et al., 2001).

According to Rubinow and colleagues (2015) there is little evidence to support the antidepressant efficacy of estradiol in perimenopausal women (Rubinow, Lanier Johnson, Schmidt, Girdler & Gaynes, 2015), and Parry (2010) concluded that estrogen treatment alone has not been shown as an efficacious monotherapy in major depressive disorders. The addition of estrogen to an antidepressant therapy with SSRI has been recommended to enhance the efficacy of this treatment (Parry, 2010). This is supported by another study, which reports that if you want to improve the efficacy of estrogens an addition of antidepressant is recommended (Studd, 2011).

1.5. Research questions

Many perimenopausal women experience depressive symptoms and may be treated with hormone replacement and/or antidepressant therapies. However, to date it is unknown what kind of treatment, including ERT, HRT or AD, is most effective for women in perimenopause who are experiencing depressive symptoms. In this thesis we want to investigate and provide an answer as to which treatment is most effective in reducing depressive symptoms in perimenopausal women, by performing a meta-analysis. It could be expected that both hormone-replacement therapies, such as ERT/HRT and antidepressant therapies are effective treatments. However, as the relation between circulating hormones and occurring menopausal symptoms during perimenopause is not very clear and controversial, we expect antidepressants as a monotherapy or a combination of hormone replacement therapies and antidepressants to be more effective in the treatment of depressive symptoms in perimenopause than hormone replacement therapy alone.

2. Methods

2.1 Design

The design of this study is a meta-analysis.

2.2. Search of eligible studies for meta-analysis

In 2013 a psychiatrist of PsyQ Den Haag started with searching for relevant articles for the meta-analysis. Relevant articles were identified by the following search terms: *Major depression, major depressive disorder* in combination with the search terms *menopause, perimenopause, climacteric* and *female hormones, gonadal steroids, sex hormones*. Searches for articles on *perimenopausal, menopausal, climacteric* and *involutional depression* were also performed. The restrictions for these searches were humans, females and English language articles. This search led to 3,245 articles.

At first sight all articles were screened on title and abstract, which led to an elimination of 2,375 articles. Studies were considered if they included a measure of depressive symptoms and menopausal status was mentioned. With 870 articles left, the articles were further screened on in- and exclusion criteria.

The inclusion criteria were 1) a clear definition of menopause according STRAW, 2) subjects who were perimenopausal, 3) the use of a validated depressive scale, and 4) the presence of a diagnosis of depression according to a clinical interview. Studies were excluded if 1) it did not contain a treatment for perimenopausal women, 2) results were mixed for pre, peri- and postmenopausal women, 3) results of used depressive scales were not mentioned, because it was not significant or another reason, and 4) women were in a menopause clinic. This resulted in 105 relevant articles for the meta-analysis, which were further screened on data and usability. Many studies were not eligible for this meta-analysis, because of in- and exclusion criteria. Approximately 25 authors have been contacted by email and were requested for more detailed study results or results that were not mentioned because these were not significant. Only three authors responded. Studies of authors who did not respond were excluded. A total of 6 eligible articles were included in this meta-analysis into the most effective treatment for perimenopausal women. See Figure 2 for the flow chart of eligible studies.

2.3. Statistical Analysis

The statistical program Comprehensive Meta-Analysis version 2.0 (CMA) was used for the analysis (Borenstein, Hedges & Rothstein, 2007). Before entering data in CMA, the results from the studies were computed into effect size Cohen's *d*. The effect size Cohen's *d* has been calculated with an effect size calculator (<http://www.uccs.edu/~lbecker/>). Effect sizes were analyzed using the random effects model, in which the error term is composed of variation originating from both within-study variability and between-study differences (Borenstein, Hedges & Rothstein, 2007). The core analysis included the point estimate of the standard difference in the means, standard error, variance, 95% confidence interval (CI), Z-score and statistical significance. Heterogeneity was assessed by using the Q-statistic, its associated p-value and the I-squared. Significant heterogeneity indicates that differences across effect sizes are likely due to sources other than sampling error, such as different study characteristics. For all tests, significance was defined at $p < 0.05$.

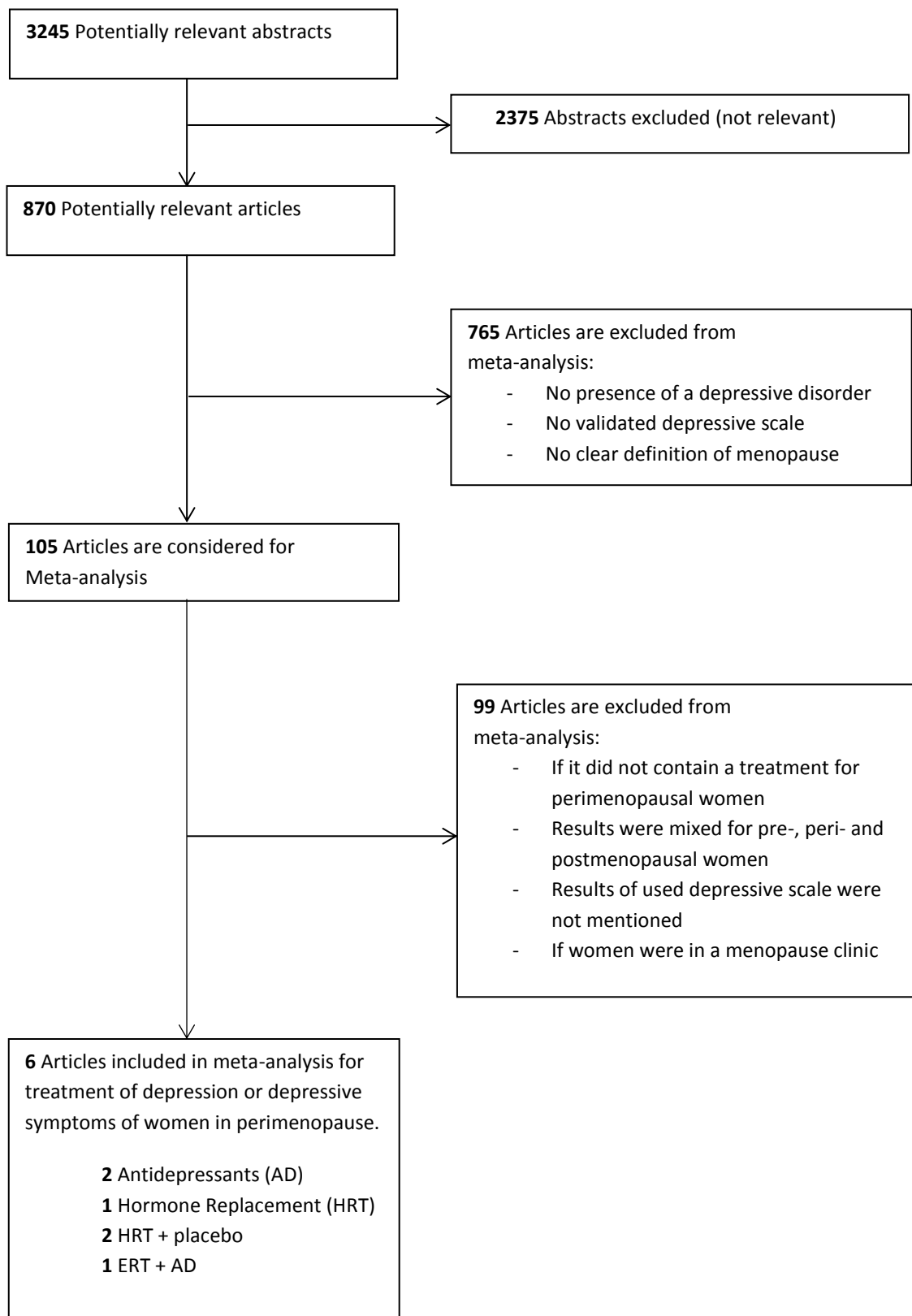


Figure 2. Search of eligible studies/flow-chart

3. Results

3.1. Characteristics of the studies

A total of six studies met all inclusion criteria and were used for the meta-analysis.

Table 1 displays the characteristics of these studies such as treatment, number of women, measurement instruments and the effect size. Table 2 displays the statistics for each study.

Table 1. *Characteristics of studies*

Study, year	Treatment	Perimenopausal Women (N)	Depression Measure ^a	Duration weeks ^b
Björn et al., (2003)	17 β -estradiol, 2 or 3 mg/d and addition of MPA ^c on day 17-28.	38	CD-scale	10
Cassano et al., (2005)	Fluoxetine, 20 mg/d (fixed dose)	28	HAM-D17	8
Ladd et al., (2005)	Venlafaxine, 75-225 mg/d	16	HAM-D17	8
Rasgon et al., (2002)	17 β -estradiol, 0.3 mg/d or as an adjunct to fluoxetine 30,0 \pm 4,8 mg	16	HAM-D28	8
Schmidt et al., (2005)	17 β -estradiol, 0.05 mg/d, additional 1 wk of combined estradiol and MPA (10 mg/d)	34	CES-D	4
Soares et al., (2001)	100 μ g 17 β -estradiol or placebo skin patches.	50	MADRS	12

Note.

a. CD-scale: CyclityDiagnoser, HAM-D: Hamilton Rating Scale for Depression, CES-D: Center for Epidemiologic Studies Depression, MADRS: Montgomery-Asberg Depression Scale.

b. Duration in weeks: The shortest or most effective period in weeks

c. MPA: Medroxyprogesterone acetate

The six studies included four studies on ERT/HRT; two of these studies used a control group (placebo). In two studies AD were examined in the treatment of depression in perimenopausal women. As only one study compared the effects of ERT and AD combined, it was not possible to examine the efficacy of combined treatment.

Table 2. *Statistics for each study*

Study, year	Treatment	Effect size ^a	95% CI		z-value	p-value
			Lower limit	Upper limit		
Björn et al., (2003)	HRT	1.317	0.739	1.895	4.467	0.000
Cassano et al., (2005)	AD	-2.432	-3.122	-1.741	-6.899	0.000
Ladd et al., (2005)	AD	-2.057	-2.972	-1.141	-4.401	0.000
Rasgon et al., (2002)	ERT	-1.855	-2.903	-0.807	-3.468	0.001
Schmidt et al., (2005)	HRT	-1.697	-2.505	-0.889	-4.116	0.000
	Placebo	-2.246	-3.081	-1.412	-5.277	0.000
Soares et al., (2001)	HRT	-2.123	-2.816	-1.429	-6.002	0.000
	Placebo	-0.876	-1.457	-0.296	-2.959	0.003

Note.

a. Effect size: Standardized difference in means

3.2. *Testing the research questions*

3.2.1. *What is more effective: AD or Placebo?*

The mean effect size of the two studies on AD was -2.259 (95% CI, -3.309 to -1.210, $p < 0.001$). The mean effect size of the placebo group (based on two studies) was -1.502, $p < 0.001$. Four studies comparing AD with placebo showed that AD is more effective than placebo (effect size = -1.868, $z = -4.937$, $p < 0.001$). Heterogeneity was significant, $Q(3) = 14.233$ ($p = 0.003$) and $I^2 = 78.921$, indicating that 78.92% of the observed variance reflects real differences in effect sizes.

3.2.2. *What is more effective: HRT or Placebo?*

The mean effect size of the HRT group was -1.068 (95% CI, -2.738 to 0.601, $p = 0.210$). The effect size of the placebo group was -1.550 (95% CI, -3.898 to 0.798, $p = 0.196$). The random effects analysis showed an effect size of -1.230, $z = -1.772$, $p = 0.076$. Thus, no significant difference was found between the effects of HRT versus placebo on reducing depressive symptoms. Heterogeneity was significant, $Q(5) = 85.431$, $p < 0.001$ and $I^2 = 94.147$.

Table 3. *Random effects analysis*

Treatment	Number of studies	Effect size	Lower limit	Upper limit	z-value	p-value
AD	2	-2.247	-4.576	0.082	-1.891	0.059
HRT	4	-1.068	-2.713	0.577	-1.272	0.203
Overall	6	-1.868	-2.804	-0.117	-2.130	0.033

3.2.3. Which treatment is more effective: AD or HRT?

The AD group compared with HRT group had an effect size of -1.460, $p = 0.033$, see Table 3. AD was found to be more efficacious in treating depression than HRT. Heterogeneity was significant, $Q(5) = 98.065$, $p < 0.001$ and $I^2 = 94.901$.

4. Discussion

4.1. Answers to the research questions

The aim of this meta-analysis was to understand more about the treatment of depressive symptoms in the perimenopause, a period of hormonal imbalances with an increased risk of developing depressive symptoms. We were interested in the most effective treatment for women in perimenopause who are experiencing depressive symptoms.

AD therapy was found to be more efficacious in treating depressive symptoms of perimenopausal women than placebo and HRT. This meta-analysis provides supportive evidence for the efficacy of the antidepressants fluoxetine (SSRI) and venlafaxine (SNRI) in improving psychological well-being of perimenopausal women (Cassano et al., (2005); Ladd et al., 2005). Other studies support these findings. In the study of Kornstein, Clayton, Bao and Guico-Pabia (2015) depressive symptoms reduced significantly in perimenopausal women treated with desvenlafaxine. Other antidepressants, for example, escitalopram (SSRI) has been concluded efficacious in the treatment of depression in perimenopausal women (Freeman et al.,2006).

In this meta-analysis no significant differences were found between HRT and placebo. Thus, the efficacy of HRT in reducing depressive symptoms in perimenopausal women cannot be established. This is supported by the study of Gartrell and colleagues (2001). They reported that symptom relief was experienced by 57 percent of peri- and postmenopausal women when they were treated with antidepressants (SSRI's). For comparison, with HRT only 23 percent of the peri- and postmenopausal women experienced symptom relief (Gartrell et al., 2001). Other studies reported little evidence for the antidepressant efficacy of estradiol in perimenopausal women and recommended an addition of antidepressants to hormonal therapies to improve the efficacy (Rubinow, Lanier Johnson, Schmidt, Girdler & Gaynes, 2015; Studd, 2011).

However, the small number of included studies, the included studies Schmidt et al., (2005) and Soares et al., (2001) have shown contrasting results. The study of Schmidt and colleagues (2005) has shown a higher effect size for the placebo group than the treatment group, while Soares and colleagues (2001) has shown a higher effect size for the treatment group than the placebo group. This could be due the fact that in the study of Schmidt et al., (2005) included only women that were placebo-nonresponders. This could have affected the

study results. Therefore, based on the results of this meta-analysis, it is not possible to conclude HRT to be a not efficacious treatment.

4.2. Limitations

A critical point of this study is the small number of studies that were eligible for this meta-analysis. The reasons for this can be found in strict in- and exclusion criteria and studies of authors who did not respond, after they had been contacted by email, were excluded. The results of this meta-analysis should be interpreted with great caution and cannot be generalized to the population. This meta-analysis is limited by potential publication bias and is biased because of including only English-language publications. Studies are reporting not standardized outcomes, unclear in- and exclusion criteria and there is a lack of consistency between studies. A lack of consistency between studies is most evident in extremely varying dose of the medication and/or hormone preparation. Another limitation was that in many studies the results were given for perimenopausal and postmenopausal women in one outcome. Mixing these results should not be done, because these women are not in the same physiologic state (Rubinow et al., 2015).

This meta-analysis had strict in- and exclusion criteria. One of the important inclusion criteria was the definition of menopausal status according to STRAW criteria. But, one exception was made for the study of Ladd (2005); this study was included despite the fact that only 7 out of 14 women were recruited according STRAW criteria. If all women would not be recruited according STRAW, this would lead to exclusion of this study. However, this exception is a limitation, because it could have effected the results.

As only one previous study examined the combined treatment effects of ERT and AD in perimenopausal women, this meta-analysis did not examine the effectiveness of combined treatment. However, many studies support the idea of the effectiveness of a combination of estradiol/estrogen and antidepressants. They concluded that estrogen treatments and antidepressants therapy are not efficacious monotherapies, a combination is recommended (Rubinow, Lanier Johnson, Schmidt, Girdler & Gaynes, 2015; Studd, 2011; Parry, 2010).

4.3. Recommendations

This meta-analysis has shown that it is too soon to conclude that the AD treatment is the most effective treatment for perimenopausal women who experience depressive symptoms, because of some limitations. These limitations, summed up earlier, lead to recommendations for future and further research. Studies vary greatly in design and have contrasting results. Differences at recruitment of women, STRAW-criteria, route of administration and dosage of medication or hormone preparation causes a lack of consistency between studies. Consistency between studies is recommended. Also, larger, standardized, long-term follow-up treatments are needed for reliable outcomes. This is needed to accurately determine relative benefits and adverse effects of treatments. The challenge for most studies are the recruitment of women, which explains the small number of women in the perimenopause state.

It is recommended for future research to take these limitations into account and create more consistency between studies. The effectiveness of the combined treatment of AD and HRT should be the focus of further research, because many studies support the idea of the effectiveness of a combination of estradiol/estrogen and antidepressants.

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