United we stand stronger:

Overcoming the discrepancy in depression research and treatment between the sexes; insight from interpersonal, pharmacological and neuro-endocrinological research

Eldering AA.

Abstract

Depression is considered to be the second leading cause in disability in the world (Ferrari et al, 2013), affecting 121 million people worldwide (Mechiel-Korte et al, 2015). Depression is a debilitating disease that incapacitates patients and is hard to treat, even the addition of antidepressants to treatment is effective as often as it is not (Nemeroff et al., 2007). Additionally, the occurrence of depression is twice as high in women as compared to men, a significant difference that is not well understood and underrepresented in research (Guttierrez-Lobos et al., 2002). For both men and women depression usually develops at the same developmental stage, adolescence (Kessler et al., 2005). But while the rate of depression increases for both sexes, the gender difference becomes apparent, more girls than boys display depressive symptoms (Angold et al., 1998). Not only is this the case, there are also a lot of intersexual differences in the treatment of depression with antidepressants. Although it is not clear where the differences come from, there are implications in research about;

1. Developmental and symptomatological intersexual differences;
2. Neuro-endocrinology, namely differences in the HPA-axis and the hippocampus and their response to stress;
3. Gender specific hormones, both estrogen and testosterone seem to play an integral part;
4. Pharmacokinetics, all parts of the ADME spectrum.

This article attempts to combine the research of these intersexual differences that can influence the efficacy of antidepressant treatment and the prevalence of depression and concludes that: firstly, antidepressive treatment and antidepressants leave a lot of room for improvement, the group that seems to suffer from this fact the most are women. They have been underrepresented in depression research for a long time, while they are overrepresented in cases of depression. Secondly, that the role of gonadal hormones, with in particular estrogen, is hugely important, nevertheless gonadal hormones do not explain the discrepancy on their own. A comprehensive study, which uses genomic, hormonal and cultural data is probably needed to unravel this problem. Finally, considering the importance of depression as a disease in our current day and age, all research is sorely needed. Researching pharmacokinetic, personal and physiological differences between men and women will benefit both groups. With the work that has already been done in these subjects, a lot of improvements in treatment already seem possible. It's important that current and future research is quickly translated into clinical research and eventually, treatment. Which hopefully can be personalized one day, so we can leave a lot of the adverse effects behind us.

Supervisor: Jocelien Olivier

CONTENTS

Contents 1
Introduction 2
Disparity in depression research 3
Differences between men and women in antidepressant treatment 3
Developmental and symptomatological intersexual differences 4
Neuro-endocrinology differences in relation to depression 5
Differences in the Hypothalamus - Pituitary - Adrenal - Axis (HPA-axis) 5
Differences in the hippocampus 6
Hormonal differences 7
The role of estrogen 7
The role of testosterone 8
Pharmacokinetic differences between the sexes 8
How sex hormones affect ADME 9
Discussion 11
Why personalized medicine? 11
In general 12
Conclusion 14
References 15

INTRODUCTION

Depression is considered to be the second leading cause in disability in the world (Ferrari et al, 2013), affecting 121 million people worldwide (Mechiel-Korte et al, 2015). Even worse, it's been speculated that depression will be the ultimate leading cause of disability by 2030. This speculation is strengthened by the WHO, who estimate that depression will be the second most common cause of disease and premature death worldwide (World Health Organization, 2011). Depression might be considered as one of the biggest problems of our time, yet treatment comes with a lot of difficulties and room for improvement. To effectively treat depression, long-term treatment is necessary. The addition of antidepressant medication to treatment is effective. However, with the large array of adverse effects discontinuation of treatment is common (Dunn et al, 1999). Most adverse effects of antidepressant medication occur early on in treatment (Bull et al, 2002), they can range from fatigue and drowsiness to nausea and anxiety. These adverse effects make it harder for patients to actually undergo the long-term treatment they need.

Due to the nature of depression, finding an exact pathophysiological mechanism is very hard, if not impossible. Depression is however associated with a deficiency in the monoamine neurotransmitters; serotonin (5-HT), noradrenaline and/or dopamine (DA) (Dimock et al., 2007). In most research, treatment and medication is focused on treating the possible deficiencies within the systems of these neurotransmitters. Therefore, most current antidepressants are based on these deficiencies within monoamine neurotransmitter systems. The most common antidepressant medications today are selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), with SSRIs being the most commonly prescribed antidepressant since their emergence in the 1980s (Vaswani et al, 2003). Even though these antidepressants are effective in the treatment of depression, a lot of patients do not respond to the treatment. This treatment resistance is probably due to the type of their depression (Prins et al, 2011). The two most common subtypes of depression, melancholic and atypical depression, may have completely different symptom profilesand it might not come as a surprise that SSRIs are not equally effective for both types of depression.

Additionally, the occurrence of depression is twice as high in women as compared to men, a significant difference that is not well understood (Gutierrez-Lobos et al., 2002). This sex difference is cross-cultural, emerges during adolescence and is most apparent during reproductive years (Gobinath et al., 2015). Not only are there more women affected by depression, symptom presentation is typically more severe in women. Adding on that depression is more likely to be chronic or recurrent in women with an earlier age of onset and poorer quality of life (Kornstein et al., 2000). It doesn't end there however. Women are more likely to present with comorbid anxiety disorders and atypical depression, which is associated with hypersomnia, hyperphagia or excessive fatigue (Keers and Aitchison, 2010). While the exact reason for these dramatic differences is unclear, the most prominent neurobiological hypothesis focuses on the role of gonadal hormones (Hammarstrom et al., 2009).Furthermore, men and women also seem to react differently to antidepressant therapy. This is a point of contention however, since some studies show differences between classes of drugs and differences in adverse effects (Keers and Aitchison, 2010), whereas other studies show no differences between the sexes (Dalla et al., 2010). The differences in treatment response that are found are most likely caused by variability in pharmacokinetic profiles.

This article highlights numerous differences between males and females that can influence the efficacy of antidepressant treatment, with a focus on pharmacokinetic differences between the sexes. Moreover it will show the importance of including both sexes in clinical and preclinical research to further improve and understand antidepressant treatment. An effect of gender on depression is also shown in this article, which is important when trying to understand the emergence of depression in humans.

DISPARITY IN DEPRESSION RESEARCH

As stated before, there is a higher prevalence of depression in women when compared to men. Moreover, there is strong evidence that symptomatology and pathophysiology are different between the sexes. However, this is not reflected by research into the disease, because most preclinical animal research is conducted on male animals instead of on both sexes. Females are harder to control by researchers due to fluctuations in female hormones, which makes it easier to exclusively use male subjects in animal research (Beery et al., 2011). The neglect of differences in sex hormones, pharmacokinetic profiles and overall neurological differences, creates a problem for the translation of preclinical research into clinical research and larger studies are needed (Belzung et al. 2014). This clinical research is however also having problems with including both sexes, there is a lack of sufficient male and female sample sizes per study (Gobinath et al,2015). It is necessary to include all aforementioned variables in the search for new antidepressant treatment, to develop treatment which is effective in treating both males and females.

DIFFERENCES BETWEEN MEN AND WOMEN IN ANTIDEPRESSANT TREATMENT

Antidepressants can be divided up into different categories, according to their mechanism of action; the non-selective inhibition of the presynaptic uptake of norepinephrine/dopamine/serotonin (Figure 1.) and inhibition of monoamine oxidases.

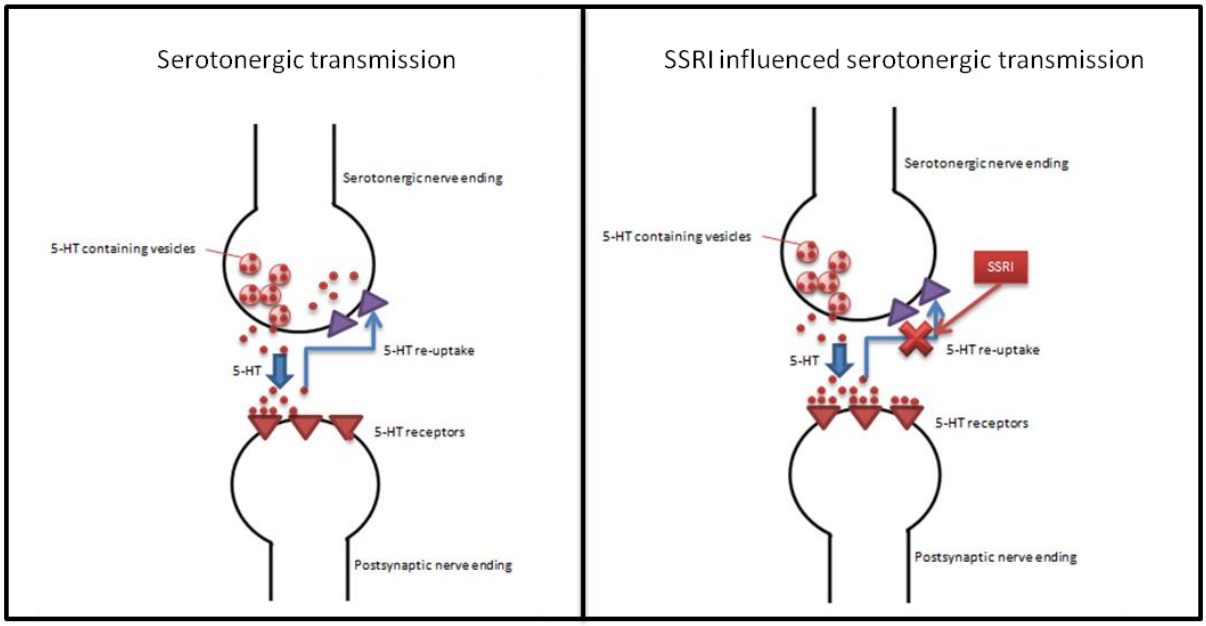

Figure 1. In normal serotonergic transmission, after an impulse reaches the serotonergic nerve ending, 5-HT is released (Left of the image). This 5-HT activates receptors on the postsynaptic nerve ending which consequently causes a stimulus in the postsynaptic nerve ending. The remaining 5-HT is removed from the synapse by denaturalisation or reabsorption into the axon, eventually stopping the stimulus. SSRIs block the reabsorption of 5-HT into the axon, which causes a higher concentration of 5-HT in the synapse and a stronger stimulus(Right side of the image). Noradrenaline is secreted, denaturalised and reuptaken in a similar fashion to 5-HT. TCAs have a similar effect to SSRIs, they block the reuptake of serotonin in addition to blocking the reuptake of Noradrenaline.

Despite the underrepresentation of women in depression research, a lot of studies have been performed to investigate sex differences in antidepressant treatment. The focus of this research tended to be on SSRIs and TCAs. Both drugs aim to increase the concentration of presynaptic monoamines in the brain, with a different mechanism of action. TCAs exert their effect by binding serotonin and noradrenaline transporters, inhibiting them and

increasing the concentration of both serotonin and noradrenalin in the synaptic cleft (Mechiel-Korte et al, 2015). SSRIs are more selective and mostly exert their effect on serotonin transporters, increasing extracellularserotonin levels across the brain (Keers et al., 2010). Because of the more selective effect of SSRIs, they have significantly fewer side effects (Anderson et al., 1998).

Differences in response to antidepressants exist between men and women. For example women treated with the TCA clomipramine have a lower clearance of the drug and consequently a higher plasma concentration compared to males (Gex-Fabry., 1990). Hildebrandt et al. (2003) ascribes this discrepancy to a difference in the metabolism rate of the drug between men and women. This might be one of the reasons why most studies that compare SSRI and TCA treatment, find that women tend to respond better to SSRIs compared to TCAs, with no difference between treatments for men. Another explanation might be that SSRIs mitigate the mood-destabilizing effects of changes in gonadal steroids, through the inhibition of serotonin uptake, increasing SSRI efficacy in women (Altemus et al., 2014).

Furthermore, higher plasma concentrations of TCAs in women can possibly lead to more adverse effects at similar doses of the drug, potentially leading to higher withdrawal rates amongst women (Kornstein et al., 2000). This effect might be due to the modulatory effects of estrogen, making it harder to reach the right therapeutic window with TCAs in women. Which would partly explain the higher response of women to SSRIs (Keers et al., 2010). This is in line with studies that focus on the use of SSRIs, which all report a better response of women to SSRIs compared to TCAs (Damoiseaux et al., 2015).

DEVELOPMENTAL AND SYMPTOMATOLOGICAL INTERSEXUAL DIFFERENCES

For both men and women depression usually develops at the same developmental stage, adolescence. This is a critical period for the development of depression and in about two-thirds to three quarters of lifetime cases, depression has its origin in adolescence (Kessler et al., 2005). Depression in women is linked to the start of the ovarian cycle, estrogen levels rise and with it an increased rate of major depression (Angold et al., 1998). But while the rate of depression increases for both sexes during the same developmental phase, a gender difference becomes apparent, more girls than boys display depressive symptoms (Angold et al., 1998). The increased risk of depression has only been found in girls with a family history in depression, suggesting that the start of puberty activates a genetic vulnerability (Hankin et al., 2007.)

Girls that have just reached puberty experience a greater number of objective and subjective stressors than boys of the same age, with the largest factor being interpersonal stress (Hankin et al. 2007). In a large cross gender study done by Hankin et al. (2015), N=665 (366 women and 299 men) across 3 different age groups of children from 3rd, 6th and 9th grade, it was shown that post-pubertal women, in comparison with their male counterparts, respond more strongly to heightened peer-stress with elevated depressive symptoms in combination with an increase of depressive episodes over time. The same studyalso looked at the interaction among development, genetics (In particular the 5-HTTLPR model of depression) and peer stress in the prediction of depression, and foundthese three factors are not likely to account for the gender difference in depression. However, the article is not sufficient to prove that gender has absolutely no influence on the development of depression and they conclude that a larger study is needed to prove a possible influence, or non-influence, of gender on the interaction between development, genetics and peer stress.

Pubertal timing seems to influence the effect of peer stress in adolescentsand ondepressive symptoms. Where low levels of peer stress can protect adolescents with early pubertal timing from depressive symptoms, it increases depressive symptoms in similar adolescents with high levels of peer stress (Conley et al., 2009). It's important to note that the results from Conley et al. (2009) are only significant for girls. However, a subsequent

study that looked at popularity (social reputation) as a potential moderator of the relationship between early pubertal timing and the development of depression in adolescents, postulated that the effect of popularity on the development of depression would show the same trend as peer stress and they expected that this effect would be revealed only for girls. The effect was however not limited to girls and social reputation seems to influence both genders significantly. A low social reputation in early pubertal timing increases depressive symptoms, where a high social reputation may have a protective effect from depressive symptoms in early pubertal timing (Teunissen et al., 2011).

What more clearly shows the differences between the sexes are the actual differences in symptomatology, men and women show clear differences when it comes to the expression of depression. One clear difference is that significantly more women than men are diagnosed with a life-time anxiety disorder (de Graaf et al., 2002). Women are also more likely to show atypical depressive symptoms compared to males, suggesting that depressed women are more susceptible to developing metabolic syndrome (Seppala et al., 2012). An even more clear difference between the sexesis the excess of comorbid alcohol abuse and dependence in depressed men compared to the other sex (Schuch et al., 2014). This effectcould be explained by a higher number of substance abuse and/or dependency prior to the onset of depression (de Graaf et al., 2003) in men when compared to women, which is a risk factor for the development of depression (Falk et al., 2008).

NEURO-ENDOCRINOLOGY DIFFERENCES IN RELATION TO DEPRESSION

Due to the scope of this article, a lot of neurological differences, mostly those pertaining to different stages of development, will not be described here. The review by Gobinath et al. from 2015 will provide a broader view on all these differences

DIFFERENCES IN THE HYPOTHALAMUS - PITUITARY - ADRENAL - AXIS (HPA-AXIS)

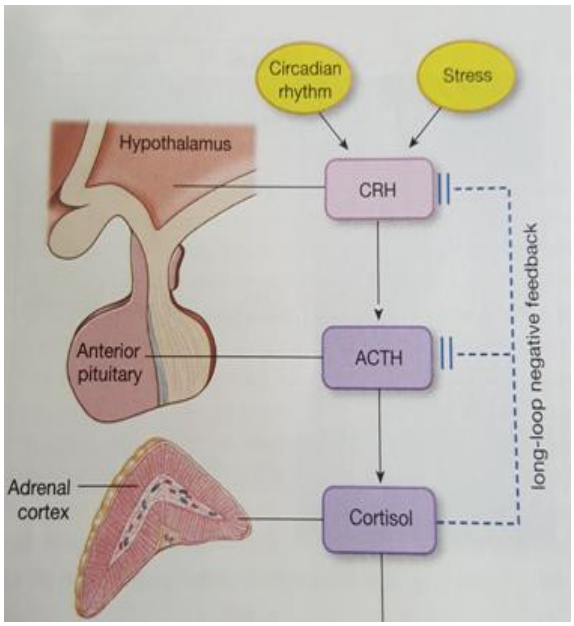

Figure 2. The HPA-axis regulates the stress response of the body. When the body endures stress, the hypothalamus releases corticotrophin releasing hormone (CRH) into the hypothalamic-hypophyseal portal system. The CRH is then transported to the anterior pituitary and stimulates it to release adrenocorticotrophic hormone (ACTH). ACTH in turn affects the adrenal cortex, which will release cortisol. Cortisol acts as a negative feedback signal on ACTH and CRH secretion.

Chronic stress is an important factor in the development of depression (Tennant, 2002), in a subpopulation of depressed patients the neuroendocrine system known as the HPA-axis is altered by chronic stress. The changes to the HPA-axis include HPA negative feedback regulation, elevated basal cortisol levels and disrupted diurnal cortisol secretion patterns (Stetler and miller, 2011). Negative feedback function of the HPA-axis can be restored by chronic treatment with antidepressants, something that coincides or slightly

precedes the alleviation of depressive symptoms (Ising et al., 2007). Antidepressants that influence the HPA negative feedback dysregulation to normalize it, are more tied to remission in women than in men (Binder et al., 2009).

In rats, more profound HPA-axis dysregulation as a result of chronic stress is seen in females as compared to males. Female rats had larger elevations in corticosterone, which is the main glucocorticoid in rats (Dalla et al., 2005). This indicated similarities between the stress system of rodents and humans. Considering this, attention has been focused on finding a causal role for sex differences in the HPA-axis generating sex differences in vulnerability to depression. The sex differences in the HPA-axis however, are not as profound in humans as they are in rodents. Results show that differences are smaller and less consistent (Panagiotakopoulos and Neigh, 2014). Concluding, even though there are differences between men and women in the regulation of the HPA-axis, the role of HPA-axis dysregulation in humans is yet to be determined.

As stated before, females have naturally higher levels of corticosterone than males. This difference is something that may contribute to the higher incidence of depression in females (Vieau et al., 2002). Furthermore, the stress response is more severe in women, with a more rapid and intense release of glucocorticoids and a slower de-escalation of the HPA-axis drive (Galea et al., 1997). This difference is partly caused by estrogen, which increases adrenocorticotropin releasing hormone (ACTH) and corticosterone secretion, whereas androgens decrease the secretion of these hormones(Lund et al., 2004).

Moreover, Viau et al (2005) looked at differences between male and female rats in their pre-pubertal stage (30 day old) and post pubertal stage (60 day old), to determine the effects of gonadal hormones on the HPA-axis. They compared basal conditions of these rats to 30 minutes of restraint. 60-d old male rats seem less reactive to restraint stress compared to their younger counterparts, with lower levels of arginine vasopressin heteronuclear RNA and Fos protein in the paraventricular nucleus, in which females did not show a similar change. Females showed an increase of basal CRH mRNA expression levels in the paraventricular nucleus with age, whereas males only showed an age-related increase of basal CRH mRNA in the central amygdala. Suggesting that these parts of the HPA-axis develop differently across sex, and is heavily influenced by gonadal hormones.

Even though the HPA-axis is not as directly related to depression in humans as it is in rodents and sex differences in this mechanism are less outspoken in humans, it's still an important part of the road tounderstanding the mechanisms underlying sex differences in HPA-axis activity. Which can further increase our understanding of the etiology of depression (Goel et al., 2014).

DIFFERENCES IN THE HIPPOCAMPUS

The hippocampus is a structure of the brain that is highly plastic and continues to be so in adulthood (Leuner and Gould, 2010). The hippocampus is however, very sensitive to the effects of chronic stress and is influenced by sex hormones. Stress influences the volume of the hippocampus by changing neurogenesis (the growth of new neurons and connections), neuropil (the amount of areas high in unmyelinated axons) and apoptosis(the controlled cell death of neurons). Chronic stress usually leads to a decrease in hippocampal volume (Gobinath et al. 2015). The decrease in hippocampal volume and neurogenesis can be restored with current antidepressants, when administered chronically. For instance, young adults who are treated for depression with TCAs show increased cell proliferation in the hippocampus (Boldrini et al, 2012), an effect that can also be reached by treatment with other antidepressants like SSRIs and MAOIs in rodents (Malberg et al, 2000).

Depressed patients usually suffer from decreased cell proliferation in the dentate gyrus of the hippocampus (Boldrini et al, 2012). Furthermore, every animal model used to model human depression reports decreased hippocampal neurogenesis (Brummelte and Galea, 2010). In addition, a large meta-analysis performed by McKinnon et al., found that untreated depressed patients, for at least 2 years, have a decreased hippocampal volume.

This decrease of volume comes with a disparity between men and women. The reduced volume is usually more profound in men when compared with women (Frodl et al, 2002).

Depressed women do not only have a smaller decrease in hippocampal volume, their hippocampus reacts differently to treatment as well. In 2000 Valiki et al. found that even though both sexes have an increase in hippocampal volume after successful treatment with antidepressants, this increase is more outspoken in women. Later on, in the year 2013, Epp at all found that this was probably due to differences in neurogenesis. Women show a larger ratio of immature to mature neurons in the hippocampus after antidepressive treatment when compared to controls. The ratio of immature to mature neurons in males that were treated with similar drugs were unaffected however.

HORMONAL DIFFERENCES

THE ROLE OF ESTROGEN

Estrogens are a group of endogenous steroids comprised of several hormones, including estradiol, estriol and estrone (Rannevik et al., 2008). Estradiol is the most potent of the estrogens and the predominant estrogen during the reproductive years of women (Gruber et al., 2002). Additionally estradiol is usually the hormone used for hormone replacement theraphy following a ovariectomy (Borrow et al., 2014). There is a strong relation between estradiol and depression, as shown in figure 3 taken from an article from Borrow et al (2014). Studies that use exogenous hormonal manipulation have shown that they can decrease depressive symptoms in clinical populations of women (Keyes et al., 2013). Additionally the cohort of reproductive aged women that use oral contraceptives (OCs) is correlated with lower levels of depression, moreover women with depression that use OCs have decreased depressive symptoms (Young et al., 2007).

The effect of estrogens on antidepressants has already been shown in this article. Summarily; SSRI's might mitigate the destabilizing behavioral effects of gonadal hormones, including estrogens, through the inhibition of serotonin uptake. Which increases SSRI efficacy in women (Altemus et al., 2014). Estrogen also seem to have a modulatory effect on TCAs, making it harder to use TCAs in women (Keers et al., 2010).

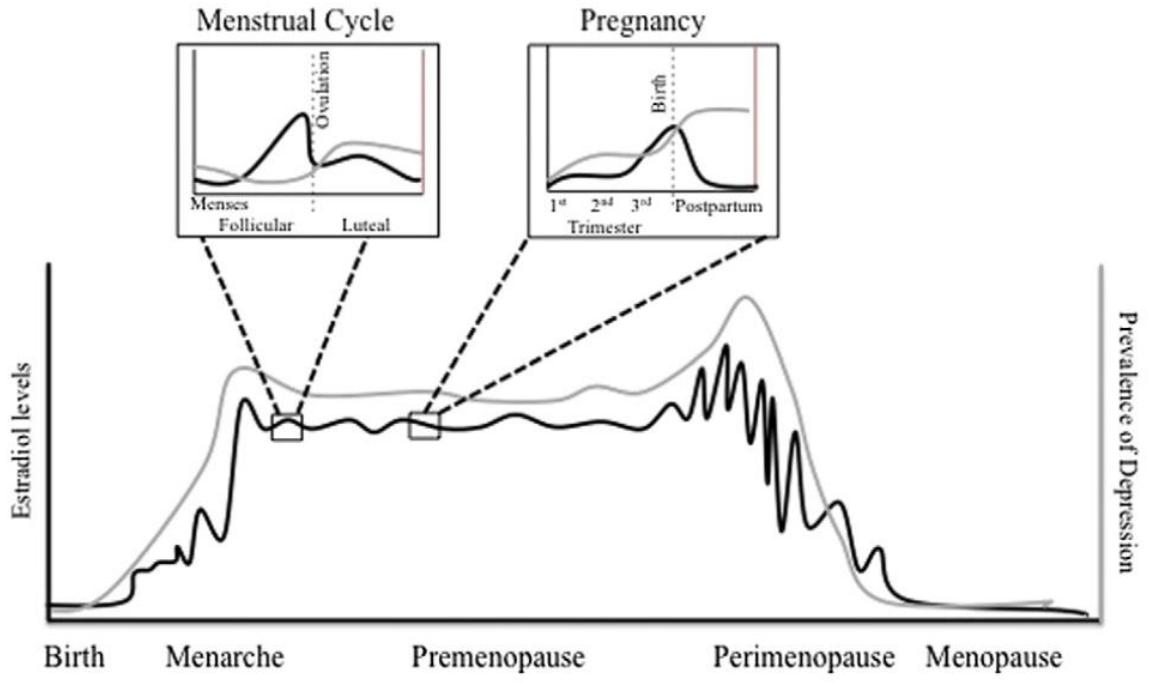

Figure 3. A simple representation of the natural fluctuations in peripheral estrogen levels across the human female lifespan. Combined with the prevalence of depression (Borrow et al., 2014).

Pharmacokinetics is the study of how the body reacts to medication, there is a strong differentiation between the sexes in this field in regards to antidepressants (Bigos et al., 2009). Research has been done into the subject of the effects of sex on the pharmacokinetics of antidepressants, and estrogen is responsible for some of the inter-sexual differences in the pharmacokinetics of the metabolism of drugs (Higashi et al.,2007. Dickmann et al., 2013). The menstrual cycle also seems to alter some parts of the distribution of antidepressants through the body (Schmidt et al., 2010). This subject is large and can be found in its entirety in the next chapter on pharmacokinetics.

THE ROLE OF TESTOSTERONE

There is a relationship between testosterone levels and depression in humans, which is evident in males with hypogonadism (Shores et al., 2004). The gonads of these males have decreased functional activity which results in decreased levels of testosterone. Males with this condition exhibit a significantly higher prevalence of anxiety and depression, compared to males with normal levels of androgens (Zarrouf et al., 2009). The same prevalence is found in males who are treated with androgen depleting drugs for prostate cancer (DiBlasio et al., 2008). Moreover, if males with hypogonadism are treated with testosterone replacement therapy the symptoms of their depression are mitigated (Zarrouf et al., 2009). There are however some reports that have found contradictory results to the positive effects of testosterone on mood in men. According to the review of Mchenry et al. (2014) these results are largely based on the less effective administration of testosterone. Transdermal application is most effective when using testosterone to improve mood (Zarrouf et al., 2009). Overall, most studies acknowledge the positive effects of testosterone on mood in men, especially of those with lower levels of this hormone (Mchenry et al., 2014).

While this field is, understandably so, less studied in women. There are some positive results which might warrant further research. For instance, research has shown that when low doses of testosterone are administered to women with treatment resistant major depressive disorder, they show significantly improved ratings of depression (Miller et al., 2009). Additionally, women who had their ovaries surgically removed usually suffer from increased depressive symptoms, which most likely stem from a decreased sexual desire and pleasure and a decreased general sense of well-being. These negative symptoms are reversed by treatment with transdermal testosterone (Shifren et al., 2000). Even though these effects are great, caution is also required when using testosterone in women. Apart from the masculinizing effects,large doses of testosterone can negatively impact mood in women and they can contribute to the onset of major depressive disorder (Rohr et al., 2002).

PHARMACOKINETIC DIFFERENCES BETWEEN THE SEXES

A large difference between men and women is the way their bodies react to antidepressants. Any difference in this reaction can lead to differences in therapeutic effects and the occurrence of negative side-effects of the therapeutic drugs. When men and women are given the same dose of medication, either sex can be over- or underdosed when the dose is based on only one of the sexes. However, not surprisingly, the US FDA found that women experience more adverse effects with drug use than men and are more often overdosed than men (Soldin et al,2009).

Pharmacokinetics and pharmacodynamics are supposedly influenced by fluctuations in hormones during a person’s life and during the menstrual cycle (Kashuba et al,1998). Important mechanisms that are involved in pharmacokinetics are the absorption, distribution, metabolism and excretion (ADME) of drugs (Kokras et al, 2011).

HOW SEX HORMONES AFFECT ADME

Absorption

The absorption of drugs is largely done by the stomach and the intestine and is influenced by the degree of ionization of drug molecules (Damoiseaux et al., 2014). An influential part of absorption is the gut transit time, which is different between men and women. Overall, women seem to have a longer gut transit time than men, this is probably because of a higher stomach pH (Grossman et al.,1963). The difference in pH levels is an important factor in the treatment of depression, since the majority of antidepressants are weak bases. The high stomach pH increases the absorption of weak bases, which is further enhanced by slow gut transit times and the slower gastric emptying (Bigos et al., 2009). On the other hand, a delayed intestinal transit suspends absorption of antidepressants and would decrease antidepressant peak levels. The combination of these effects has however not yet been studied in antidepressant research (Kokras et al., 2011).

Gut transit time is still something that is not fully understood in women, since it might be influenced by the menstrual cycle (Kashuba et al., 1998). Further studies into the hormonal effects on gut transit time however, haven't yielded satisfactory results and the exact effects remain unclear. It is a matter of importance, considering that fluctuations in gut transit times could lead to overdoses and adverse effects in women (Damoiseaux et al., 2014). Further research is needed to fully understand the hormonal effects of the menstrual cycle on the absorption of drugs. Further understanding could not only lead to an increase in the treatment quality for women, but it can also help studies that use female test-subjects.

Distribution

The distribution of a drug amongst the body is dependent on two things. Firstly, it is dependent on the physicochemical properties of a drug, the affinity for binding proteins and the water and lipid properties (Yonkers et al., 1992). Secondly, it is dependent on the body to which it is administered, namely the distribution of water and lipids in the body and plasma protein levels (Sramek et al., 2011).

Due to the area of effectiveness of antidepressants, the brain, antidepressants are made to cross the blood-brain barrier. For this end, most antidepressants are highly lipophilic (Kokras et al., 2011). Women have a higher percentage of body fat and adipose tissue. The combination of the lipophilic antidepressants and the high adipose tissue in women can result in a higher volume of distribution when compared to men. There is also speculation that apart from the volume of distribution in women, they also might have a more rapid and extensive distribution, a lower rate of redistribution and a consequently lower clearance (Nicolas et al., 2009).

Apart from the differences in body fat and adipose tissue, there are other differences that influence the distribution of antidepressants. Women have a lower intravascular volume, lower organ blood flow, lower body weight and less muscle compared with men. All these differences may interfere with the volume of distribution of antidepressants (Kokras et al., 2011).

The other factor in distribution, the protein binding of the antidepressants, seems to be only partly influenced by sex. Albumin for instance seems not to be influenced by sex, whereas lipoproteins and transport protein concentrations may vary between sexes. How these proteins influence the pharmacokinetics in both sexes has not been established (Meibohm et al., 2002). There are however two different glycoproteins, which are both involved in the distribution of antidepressants and are influenced by sex. Namely the alpha1-Glycoprotein (AAG) and the drug-efflux pump P-glycoprotein.

The menstrual cycle influences available levels of binding proteins. There is some evidence that alpha1-Glycoprotein (AAG) concentrations fluctuate across the menstrual cycle, with a peak concentration at menses (Cederblad et al., 1977). The AAG binding protein is important for the binding of antidepressants, the peak of concentration that is seen at menses could influence the unbound fraction of antidepressant drugs. Whether this

change in unbound fraction could result in in clinically relevant changes in unbound fraction and therapeutic effects, is however unlikely (Schmidt et al., 2010).

The drug-efflux pump P-glycoprotein has some distinct effects on antidepressants. Firstly, it serves as a barrier for the brain and the gastrointestinal tract and secondly it helps to eliminate antidepressants in the liver and kidneys (Kokras et al., 2011). The P-glycoprotein is lower in women than in men, which might also be true for other drug transporters (Meibohm et al., 2002). Additionally, gonadal hormones downregulate the expression of P-glycoprotein via the MDR1 gene. The same gene that also increases the absorption of drugs via the inhibition of P-glycoproteins' function in the gastrointestinal tract (Nicolson et al., 2010). The exact contribution of P-glycoprotein effect on the sex-differentiated pharmacokinetics of antidepressants, is not fully understood.

Metabolism

In a review by Pitychoutis et al.(2010) sex, apart from other inter individual differences, is a significant factor that contributes to the observed variability in the metabolism of antidepressants. With the influence of hormones as one of the crucial factors. Take Gonadotrophin hormone (GH) for instance, which has a different secretion profile between males and females. This different pattern of secretion is mainly pre-programmed during the development of the brain by estrogens, creating differences between the sexes. GH is secreted in discrete pulses in males, where in females it is secreted continuously. The different secretion profiles between the sexes directly control the expression and activity of the cytochrome P450 (CYP) enzyme, creating sex-differentiated responses to antidepressants (Veldhuis et al., 2003).

According to current knowledge, the largest intersexual difference in pharmacokinetic parameters may well be the metabolism of antidepressants (Kokras et al., 2011). Apart from what was mentioned before, the metabolism of antidepressants is also largely influenced by phase 1 metabolic pathways, which can differ for each antidepressant considering the different affinity for the various CYP enzymes. Even similar antidepressants, of the same class, may be affected differentially by sex, due to the affinity of each chemical molecule for CYP isozymes (Martin et al., 2000).

Since estrogen is a substrate for several CYP isozymes, and estrogen levels vary throughout the menstrual cycle, estrogen can impact the metabolic capacity of these enzymes throughout the different phases of the menstrual cycle (Bigos et al., 2009). A CYP enzyme which is influenced by estrogen is CYP2A6, this CYP isozyme was found to be induced by estrogen via the estrogen receptor (Higashi et al.,2007). Furthermore, the metabolic activity of CYP2B6 seems to have a positive correlation with the increase of estradiol during pregnancy. These enzymes seem to indicate that estrogens are capable of inducing CYP isozymes (Dickmann et al., 2013), further differentiating female from male antidepressant metabolism. Additionally, estrogen might also influence the hepatic metabolism by changing the blood flow to the liver and thereby decreasing the hepatic metabolism (Frackiewicz et al., 2000).

Some of the differences in the metabolism of antidepressants are caused by innate differences between the sexes, as shown before. Another big factor that separates the two sexes by influencing the pharmacokinetic metabolism, is the use of OCs by women (Damoiseaux et al., 2014). This is not entirely unexpected, since most OCs contain a combination of estrogen and progesterone and as stated before, estrogen can influence metabolism. Not surprisingly, the pathways that are affected by OCs are the Phase 1 metabolic pathways, CYP1A2 is one of the isozymes that is influenced. CYP1A2 is inhibited by gonadal steroids, which is reinforced by the use of OCs. Furthermore the clearance of CYP1A2 substrates is lower in women. This lower clearance in combination with OCs causes drugs that are metabolized by CYP1A2 to accumulate (Schwartz et al., 2007). Also, CYP2C19 shows overall less activity in women, which is more pronounced in women taking OCs (Tamminga et al., 1999).

A well-studied cytochrome is CYP2B6, as mentioned before in relation to estradiolincrease during pregnancy. There Dickmann et al. (2013) showed a positive

correlation between the metabolic activity of CYP2B6 and an increase of estradiol. When hormone replacement therapy with estradiol (2mg) and levonorgestrel (250µg) is given to women however, their metabolism of CYP2B6 is inhibited (assessed with buproprion). This effect was also shown, but to a lesser extent, in women taking an OC that contains ethinylestradiol 30µg and desogestrel 150µg (Palovaara et al., 2003). This shows not only the effects of estrogen on CYP2B6, but also a possible effect of progesterone. Thus the female hormone system and OCs can affect antidepressant metabolism and should be considered when prescribing antidepressants. However, these results also show the difficulty of studying the effects of hormones in vivo, as in vivo there is always more than one hormone affecting metabolism (Damoiseax et al., 2014).

There are a lot of ways sex hormones can affect the metabolism of antidepressants, interestingly this might also work the other way around. Some antidepressants are able to inhibit certain CYP enzymes. Fluvoxamine and fluoxetine are such antidepressants, they are known to be capable of inhibiting CYP3A4, which is involved in the metabolism of numerous drugs. This inhibition of CYP3A4 by antidepressants might shift the metabolism of estrogen from CYP3A4 to CYP1A2. This shift between isozymes reduces the production of 16-α-hydroxyestrone, an enzyme that may have an anticarcinogenic effect on breast cancer (Thompson et al., 2003).

Excretion

The excretion of antidepressants is dependent on the blood flow to the liver and kidneys, women are known to have a smaller liver and organ blood flow than men (Kokras et al., 2011). Renal glomerular filtration rate is lower in women than in men, which is proportional to body weight (Martin et al., 2000). Additionally, women undergo some changes to the physiology of the renal system during the different phases of the menstrual cycle (Damoiseaux et al., 2014).

Research on the subject of excretion is limited, compared to the other three parts of the ADME cycle of antidepressants. Data for the excretion of antidepressants are lacking and possible effects of sexual differences are therefore not well understood. From the research on the renal excretion of other drugs however, there are suggestions that sex differences in excretion may very well exist (Schwartz et al.,2007). Research on this subject is needed as to create a complete picture of the influences of sexual differences and sex hormones on ADME.

DISCUSSION

WHY PERSONALIZED MEDICINE?

Depression is a disease that has to be treated to get it under control, though only 50% of patients respond to treatment after one treatment trial. Of these patients only 30% achieve full remission. The patients who do not achieve remission after one trial are less likely to even achieve it at all, remission rates drop significantly with multiple trials. The remission rate after four trials is only 60% (Rush et al., 2006). Treatment is long and arduous, it can take as long as 8 to 12 weeks to conclude if a trial is a success or a failure. This time can frustrate patients and families, increasing suicide risk in patients. Even when full remission can be achieved, the time between partial response and full remission is enough to act out suicidal thoughts (Sadock et al, 2007).

There is a lot of disparity in treatments of depression between men and women, with the most notable and researched difference the one between SSRIs and TCAs. SSRIs being superior for women with a smaller variation between the two for men (Keers et al., 2010). Estrogen seems to be a regulatory mechanism for the distinction between these drugs, making women more receptive for SSRIs. Both because of the effects of SSRIs on estrogen and the effects of estrogen on the metabolism of TCAs. The fluctuating hormones of the

menstrual cycle make it hard to achieve the narrow therapeutic window of TCAs (Hildebrandt et al., 2003) , however this doesn't necessarily mean that we shouldn't strive for the use of TCAs in women. A larger understanding of when and how to use TCAs to treat depression in women could have benefits we do not yet know of. Just because a certain type of medicine seems to work better statistically, doesn't mean it should work better personally.

The ADME spectrum is essential to our understanding of antidepressant effects and our knowledge of the entirety of the spectrum is lacking, however it is very clear that treatment and dosage of antidepressants should be based on knowledge about ADME. Some parts however, seem more interesting than others, the metabolism, through the CYP enzymes, is greatly influenced by estrogens for instance. Estrogens fluctuate during the menstrual cycle influencing metabolic capacity of enzymes, influencing drug levels and effects (Bigos et al., 2009) and consequently these drugs also influence hormone levels. Hypothetically women could be under dosed during three weeks of the menstrual cycle, whilst the same dose could be considered an overdose during the last week of the menstrual cycle. An antidepressant can be the right fit for a female patient, but our lack of knowledge on how to effectively administer the drug increases the overall risks that the drug brings.

The Absorption and Distribution parts of ADME both have implications for antidepressant use that are influenced by the menstrual cycle. Gut transit time for absorption and the distribution by the drug-efflux pump P-glycoprotein are influenced by the menstrual cycle (Kokras et al., 2011, Kashuba et al., 1998). But how they are affected and to what extent this influences the treatment with antidepressants is not clear. Research should be done to show the extent to which these mechanisms are influenced and how large their effect is on the body.

Even though it was only a short part in this article, since they influence the metabolism of antidepressants, OCs can influence antidepressive treatment. This effect is probably related to the effect of hormones on antidepressant drugs and vice versa. Understanding the full range of effects of OCs, or at least in parts, can improve treatment for women. This is something that should not be overlooked in future research, considering that in a country like the United States, 28 percent of women use oral contraceptives (Jones et al., 2012).

IN GENERAL

As shown in this article, there is a large disparity between the way depression has been researched in the past and what is needed. Ironically, even though there are twice as many women that suffer from depression, research was predominantly done on male subjects. There has been a lot of research into sexual differences to make up for this fact, what we know however, is not yet enough. This article highlighted a lot of the differences and focusses on the female side of the condition, to show what has been missing in anti-depressive treatment for a long time and to show what knowledge can and should be used to improve treatment. Continually, it can benefit both sexes to understand what differences there are.

A broader understanding of the effects of the menstrual cycle on all the parts of the ADME spectrum is needed, this is not only needed for better dosage and selection of the different kinds of antidepressants. It's also needed to increase the quality of research into the subject. As stated before, a lot of researchers excluded, or exclude, females from clinical and preclinical trials because of the difficulty to control for hormone fluctuations during the menstrual cycle (Beery et al., 2011).Furthermore it shouldn't be an argument to exclude females from trials, but a sign that we should increase our knowledge of the menstrual cycle so we can control for it and keep it in consideration during treatment.

Male and female bodies react differently to stress, from a neurological standpoint women seem to suffer more from prolonged exposure to stress. They have a stronger reaction to stress and a slower de-escalation of the HPA-axis drive, combined with estrogen that increases ACTH and corticotrophin release. Men seem to get some sort of protection from anxiety and stress from due to higher concentrations of testosterone. Whether the

disparity between the two sexes in regards to depression is explained by this, remains unclear. It can however be an important component in the explanation of the disparity, which, in combination with other factors like genomics and interpersonal differences can lead to a broader understanding of the condition in general.

CONCLUSION

Antidepressive treatment and antidepressants leave a lot of room for improvement, the group that seems to suffer from this fact the most are women. They have been underrepresented in depression research for a long time, while they are overrepresented in cases of depression. Research needs to catch up and although a lot of work has already been done into the subject, a comprehensive explanation of why more women suffer from depression has not been found yet. The role of gonadal hormones, with in particular estrogen, is hugely important, nevertheless gonadal hormones do not explain the discrepancy on their own. A comprehensive study, which uses genomic, hormonal and cultural data is probably needed to unravel this problem.

Considering the importance of depression as a disease in our current day and age, all research is sorely needed. Researching pharmacokinetic, personal and physiological differences between men and women will benefit both groups.With the work that has already been done in these subjects, a lot of improvements in treatment already seem possible. It's important that current and future research is quickly translated into clinical research and eventually, treatment.Which hopefully can be personalized one day, so we can leave a lot of the adverse effects behind us.

REFERENCES

Abernethy DR, Greenblatt DJ, Shader RI. Imipramine disposition in users of oral contraceptive steroids. ClinPharmacolTher. 1984;35:792–7

Altemus M, Sarvaiya N, Epperson CN. Sex differences in anxiety and depression clinical perspectives. Frontiers in Neuroendocrinology 2014;35:320–330

Anderson IM. SSRIs versus tricyclic antidepressants in depressed patients: a meta-analysis of efficacy and tolerability. Depress Anxiety. 1998;7(suppl 1):11–17.

Angold A, Costello E, Erkanli A. Comorbidity. J. Child Psychol. Psychiatry 1999;40, 57–87.

Beery AK, and Zucker I. Sex bias in neuroscience and biomedical research. Neurosci. Biobehav. Rev. 2011;35, 565–572.

Bigos KL, Pollock BG, Stankevich BA, Bies RR. Sex differences in the pharmacokinetics and pharmacodynamics of antidepressants: an updated review. Gender Medicine. 2009;6(4):522–543.

Binder EB, Kunzel HE, Nickel T, Kern N, Pfennig A, Majer M, et al. HPA-axis regulation at in-patient admission is associated with antidepressant therapy outcome in male but not in female depressed patients. Psychoneuroendocrinology 2009;34: 99–109.

Boldrini M, Hen R, Underwood MD, Rosoklija GB, DworkAJ, Mann JJ. Hippocampal angiogenesis and progenitorcell proliferation are increased with antidepressant use in majordepression.Biol Psychiatry 2012;72: 562–571.

Borrow AP, Cameron NM. Estrogenic mediation of serotonergic and neurotrophic systems:
Implications for female mood disorders. 22Progress in Neuro-Psychopharmacology & Biological Psychiatry 54 2014; 13–25.

Bull SA, Hunkeler EM, Lee JY, Rowland CR, Williamson TE, Schwab JR, Hurt SW. Discontinuing or switching selective serotonin reuptake inhibitors. Ann Pharmacother 2002;36:578–584.

Cederblad G, Hahn L, Korsan-Bengtsen K, Pehrsson NG, Rybo G. Variations in blood coagulation, fibrinolysis, platelet function and various plasma proteins during the menstrual cycle. Haemostasis. 1977;6:294–302

Conley CS, Rudolph KD. The emerging sexdifference in adolescent depression: interacting contributionsof puberty and peer stress.Development and Psychopathology 2009; 21: 593–620.

Dalla C, Antoniou K, Drossopoulou G, Xagoraris M, Kokras N, Sfikakis A, et al. Chronic mild stress impact: are females more vulnerable? Neuroscience 2005;135: 703–714.

Dalla C, Pitychoutis PM, Kokras N, and Papadopoulou-Daifoti Z. Sex differences in animal models of depression and antidepressant response. Basic Clin. Pharmacol. Toxicol. 2010;106: 226–233.

Damoiseaux VA, Proost JH, Jiawan VCR, Melgert BN. Sex differences in the pharmacokinetics of Antidepressants: Influence of female sex hormones and oral contraceptives. ClinPharmacokinet. 2014;53:509-519.

DiBlasio CJ, Hammett J, Malcolm JB, Judge BA, Womack JH, Kincade MC, Ogles ML, Mancini JG, Patterson AL, Wake RW, Derweesh IH. Prevalence and predictive factors for the development of de novo psychiatric illness in patients receiving androgen deprivation therapy for prostate cancer. Can. J. Urol. 2008;15: 4249–4256, discussion 4256.

Dickmann LJ, Isoherranen N. Quantitative prediction of CYP2B6 induction by estradiol during pregnancy: potential explanation for increased methadone clearance during pregnancy. Drug MetabDispos. 2013;41:270–4.

Dimock K, McGrath S, Cook L. The nervous system: antidepressant drugs. In: Rang HP, Dale MM, Ritter JM, Flower RJ, editors. Rang and Dale's pharmacology. 6th ed. Oxford: Elsevier, Ltd; 2007. pp. 557–73.

Dunn RL, Donoghue JM, Ozminkowski RJ, Stephenson D, Hylan TR. Longitudinal patterns of antidepressant prescribing in primary care in the UK: comparison with treatment guidelines. J Psychopharmacol 1999;13:136–143.

Epp JR, Beasley CL, and Galea LA. Increased hippocampal neurogenesis and p21 expression in depression: dependent on antidepressants, sex, age and antipsychotic exposure. Neuropsychopharmacology 2013;38: 2297–2306.

Falk DE, Yi HY, Hilton ME. Age of onset and temporal sequencing of lifetime DSM-IV alcohol use disorders relative to comorbid mood and anxiety disorders. Drug Alcohol Depend. 2008;94: 234–245.

Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: Findings from the Global Burden of Disease Study 2010. PLoS Med 2013;10: e1001547.

Grossman MI, Kirsner JB, Gillespie IE. Basal and histalog stimulated gastric secretion in control subjects and in patients with peptic ulcer or gastric cancer. Gastroenterology. 1963;45:14–26.

Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. N Engl J Med 2002;346:340–52.

Frackiewicz EJ, Sramek JJ, Cutler NR. Gender differences in depression and antidepressant pharmacokinetics and adverse events. Ann Pharmacother. 2000;34:80–8.

Galea LA, McEwen BS, Tanapat P, Deak T, Spencer RL, Dhabhar FS. Sex differences in dendritic atrophy of CA3 pyramidal neurons in response to chronic restraint stress. Neuroscience 1997;81: 689-697.

Gex-Fabry M, Balant-Gorgia AE, Balant LP, Garrone G. Clo-mipramine metabolism. Model-based analysis of variabilityfactors from drug monitoring data. Clin Pharmacokinet.1990;19:241–55.

Goel N, Innala L, Viau V. Sex differences in serotonin (5-HT) 1A receptor regulation of HPA axis and dorsal raphe responses to acute restraint. Psychoneuroendocrinology 2014;40, 232—241.

de Graaf R, Bijl RV, Spijker J, Beekman AT, Vollebergh WA. Temporal sequencing of lifetime mood disorders in relation to comorbid anxiety and substance use disorders findings from the Netherlands Mental Health Survey and Incidence Study. Soc. PsychiatryPsychiatr. Epidemiol. 2003;38: 1–11.

de Graaf R, Bijl RV, Smit F, Vollebergh WA, Spijker J. Risk factors for 12-
month comorbidity of mood, anxiety, and substance use disorders:findings from the Netherlands Mental Health Survey and Incidence Study. Am. J. Psychiatry 2002;159: 620 – 629.

Gutierrez-Lobos K, Scherer M, Anderer P, Katschnig H. The influence of age on the female/male ratio of treated incidence rates in depression. BMC Psychiatry 2002;2:3.

Hammarstrom A, Lehti A, Danielsson U, Bengs C, Johansson EE. Gender-related explanatory models of depression: a critical evaluation of medical articles. Public Health 2009;123: 689–693.

Hankin B, Mermelstein R, Roesch L, Sex differences in adolescent depression: Stress exposure and reactivity models. Child Dev. 2007; 78: 279–295.

Higashi E, Fukami T, Itoh M, Kyo S, Inoue M, Yokoi T, et al. Human CYP2A6 is induced by estrogen via estrogen receptor. Drug MetabDispos. 2007;35:1935–41.

Hildebrandt MG, Steyerberg EW, Stage KB, Passchier J, Kragh-Soerensen P. Danish University Antidepressant Group. are gender differences important for the clinical effects of antidepressants? Am J Psychiatry.2003;160:1643–50.

Ising M, Horstmann S, Kloiber S, Lucae S, Binder EB, Kern N, et al. Combined dexamethasone/corticotropin releasing hormone test predicts treatment response in major depression – a potential biomarker? Biol. Psychiatry 2007;62:47–54.

Jones J, Mosher WD, Daniels K. Current contraceptive use in the United States, 2006–2010, and changes in patterns of use since 1995, *National Health Statistics Reports*, 2012, No. 60

Kashuba AD, Nafziger AN. Physiological changes during the menstrual cycle and their effects on the pharmacokinetics and pharmacodynamics of drugs. ClinPharmacokinet. 1998;34:203–18.

Keers R, Aitchison KJ. Gender differences in antidepressant drug response. Int Rev Psychiatry. 2010;22:485–500.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry. 2005; 62:593–602.

Keyes KM, Cheslack-Postava K, Westhoff C, Heim CM, Haloossim M, Walsh K. Association of hormonal contraceptive use with reduced levels of depressive symptoms: anational study of sexually active women in the United States. Am J Epidemiol 2013;178:1378–88.

Kokras N, Dalla C, Papadopoulou-Daifoti Z. Sex differences in pharmacokinetics of antidepressants, Expert Opinion on Drug Metabolism & Toxicology. 2011;7:2, 213-226.

Kornstein SG, Schatzberg AF, Thase ME, Yonkers KA, McCullough JP, Keitner GI, Gelenberg AJ, Ryan CE, Hess AL, Harrison W, Davis SM, Keller MB. Gender differences in chronic major and double depression. J Affect Disord. 2000;60:1–11.

Lund TD, Munson DJ, Haldy ME, Handa RJ. Androgen inhibits, while oestrogen enhances, restraint-induced activation of neuropeptide neurones in the paraventricular nucleus of the hypothalamus. J. Neuroendocrinol. 2004;16: 272—278.

Malberg JE, Eisch AJ, Nstler EJ, Duman RS. Chronicantidepressant treatment increases neurogenesis in adult rathippocampus.J Neurosci20: 2000; 9104–9110.

Martin G, Gan TJ. Gender difference: hype or fact? SeminAnesthPerioperat Med Pain 2000;19(2):76-82.

McHenry J, Carrier N, Hull E, Kabbaj M. 2014. Sex differences in anxiety and depression: role of testosterone. Front Neuroendocrinol. 2014 Jan;35(1):42-57.

Meibohm B, Beierle I, Derendorf H. How important are gender differences in pharmacokinetics? ClinPharmacokinet. 2002;41(5):329-42.

Mechiel-Korte, S, Prins, J, Krajnc, A.M, Hendriksen, H, Oosting R.S, Westphal K.G, Korte-Bouws GAH, Olivier, B. The many different faces of major depression: It is time for personalized medicine. European Journal of Pharmacology 753 2015;88–104.

Miller KK, Perlis RH, Papakostas GI, Mischoulon D, Losifescu DV, Brick DJ, Fava M. Low-dose transdermal testosterone augmentation therapy improves depression severity in women. CNS Spectr. 2009;14: 688–694.

Nemeroff CB. Prevalence and management of treatment-resistant depression. J Clin Psy-chiatry 2007;68:17–25.

Nicolas JM, Espie P, Molimard M. Gender and interindividual variability in pharmacokinetics. Drug Metab Rev. 2009;41:408–21.

Nicolson TJ, Mellor HR, Roberts RR. Gender differences in drug toxicity. Trends Pharmacol Sci. 2010;31(3):108-14.

Panagiotakopoulos L, Neigh G. Development of the HPA axis: where and when do sex differences manifest? Front Neuroendocrinol. 2014;35: 285–302.

Pitychoutis PM, Zisaki A, Dalla C, et al. Pharmacogenetic insights into depression and antidepressant response: does sex matter?. Curr Pharm Des. 2010;16(20):2214-23.

Prins J, Olivier B, Korte SM. Triple reuptake inhibitors for treating subtypes of major depressive disorder: the monoamine hypothesis revisited. Expert OpinInvestig Drugs. 2011 Aug;20(8):1107-30.

Rannevik G, Jeppsson S, Johnell O, Bjerre B, Laurell-Borulf Y, Svanberg L.A longitudinalstudy of the perimenopausal transition: altered profiles of steroid and pituitary hor-mones, SHBG and bone mineral density. Maturitas 2008;61:67–77.

Rohr UD. The impact of testosterone imbalance on depression and women's health. Maturitas 2002;41 (Suppl. 1): S25–46.

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BDM, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry, 2006;163:1905-1917.

Sadock BJ, Kaplan HI, Sadock VA. Kaplan &Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry. Lippincott Williams & Wilkins, Philadelphia, 2007.

Schmidt S, Gonzalez D, Derendorf H. Significance of protein binding in pharmacokinetics and pharmacodynamics. J Pharm Sci. 2010;99:1107–22.

Schuch JJ, Roest AM, Nolen WA, Penninx BW, de Jonge P. Gender differences in major depressive disorder: results from the Netherlands studyof depression and anxiety. Journal of Affective Disorders. 2014;156:156-63.

Schwartz JB. The current state of knowledge on age, sex, and their interactions on clinical pharmacology. ClinPharmacolTher. 2007;82(1):87-96.

Seppala J, Vanhala M, Kautiainen H, Eriksson J, Kampman O, Mantyselka P, Oksa H, Ovaskainen Y, Viikki M, Koponen H. Prevalence of metabolic syndrome in subjects with melancholic and non-melancholic depressive symptoms: a Finnish population-based study. J. Affect. Disord. 2012;136: 543–549.

Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR, Caramelli KE, Mazer NA. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N. Engl. J. Med. 2000;343: 682–688.

Shores M.M, Sloan KL, Matsumoto AM, Moceri VM, Felker B, Kivlahan DR. Increased incidence of diagnosed depressive illness in hypogonadaloldermen. Arch. Gen. Psychiatry 2004;61: 162–167.

Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. ClinPharmacokinet. 2009;48:143–57.

Tamminga WJ, Wemer J, Oosterhuis B, et al. CYP2D6 and CYP2C19 activity in a large population of Dutch healthy volunteers: indications for oral contraceptive-related gender differences. Eur J ClinPharmacol. 1999;55(3):177-84.

Teunissen HA, Adelman CB, Prinstein MJ, Spijkerman R, Poelen EA, Engels RC, Scholte RH. The Interaction Between Pubertal Timing and Peer Popularity for Boys and Girls: AnIntegration of Biological and Interpersonal Perspectives on Adolescent Depression. J Abnorm Child Psychol. 2011 Apr;39(3):413-23.

Thompson DS, Kirshner MA, Klug TL, Kastango KB, Pollock BG. A preliminary study of the effect of fluoxetine treatment on the 2:16-alpha-hydroxyestrone ratio in young women. Ther Drug Monit. 2003;25:125–8.

Vakili K, Pillay SS, Lafer B, Fava M, Renshaw PF, Bonello-Cintron CM, et al. Hippocampal volume in primary unipolar major depression: a Magnetic Resonance Imaging study. Biol. Psychiatry 1999;47: 1087–1090.

Vaswani M, Linda FK, Ramesh S. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. ProgNeuropsychopharmacolBiolPsychiatry. 2003 Feb;27(1):85-102.

Veldhuis JD, Bowers CY. Human GH pulsatility: an ensemble property regulated by age and gender. J Endocrinol Invest. 2003;26(9):799-813.

Viau V. Functional cross-talk between the hypothalamic-pituitary-gonadal and -adrenal axes. J. Neuroendocrinol. 2002;14: 506–513.

Viau V, Bingham B, Davis J, Lee P, Wong M. Gender and puberty interact on the stress-induced activation of parvocellular neurosecretory neurons and corticotropin-releasing hormone messenger ribonucleic acid expression in the rat. Endocrinology 2005;146: 137—146.

Yonkers KA, Kando JC, Cole JO, Blumenthal S. Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. Am J Psychiatry. 1992;149:587–95.

Young EA, Kornstein SG, Harvey AT, Wisniewski SR, Barkin J, Fava M, et al. Influences of hormone-based contraception on depressive symptoms in premenopausal women with major depression. Psychoneuroendocrinology 2007;32:843–53.

Zarrouf FA, Artz S, Griffith J, Sirbu C, Kommor M. Testosterone and depression: systematic review and meta-analysis. J. Psychiatr. Pract. 2009;15: 289–305.

.
.