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Antidepressant Effects on REM Sleep

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Abstract

Individuals who deal with depression are typically prescribed antidepressants in order to alleviate the depressive symptoms that they may be having. Polysomnographic sleep research has revealed that depression is associated with altered sleep architecture and distorted REM sleep quality.[2] Specifically, increased REM sleep duration and density have proved to be markers that predict recurrence and relapse for depressed individuals. REM sleep serves to stimulate regions of the brain that are important with learning and memory consolidation. However, an increased duration of REM sleep in depressed individuals proves to be unfavorable. Antidepressants drugs aim to weaken sleep quality, which is mainly due to increased noradrenergic or dopaminergic neurotransmission and the activation of serotonergic 5-HT_2 receptors.[4] Therefore, different classes of antidepressants have been developed to dampen REM sleep duration and density. Of course, this must be accomplished without determinantal effects for neuronal signaling within the brain. Selective serotonin reuptake inhibitors (SSRI), norepinephrine reuptake inhibitors (NRI), activating tricyclic antidepressants (TCA), serotonin and norepinephrine reuptake inhibitors (SNRI), and monoamine oxidase antidepressants (MAOI) are most commonly used in today's society. Current knowledge about antidepressants and their effects on REM sleep are explored in this review.

Sleep Cycle Overview

There are a few mechanisms that control sleeping periods in living organisms. First off, the molecule adenosine is produced by the degradation of adenosine triphosphate (ATP). The accumulation of adenosine during wakefulness is associated with the depletion of ATP reserve storages in the brain. This, along with your circadian rhythm, will trigger sleep.

A sleep cycle is the progression of someone to complete four different stages of sleep. Non-rapid eye movement (NREM) sleep is characterized by three different stages of sleep ranging from light to deep sleep. Light sleep is considered Stage 1 and Stage 2 of NREM sleep and deep sleep is defined to be Stage 3 of NREM sleep. Lastly, rapid-eye movement (REM) sleep is the final stage of the sleep cycle, which sleepers will display rapid eye movements and faster breathing and pulse. The first cycle typically will run 90 minutes in length, but will increase after as a normal sleep cycle lasts between 100-120 minutes. A typical person will complete four to five sleep cycles a night. Additionally, it is recommended that young adults get seven to nine hours of sleep.[10]

NREM sleep is the longest stage of the sleep cycle. Stage 1 is the lightest stage of the sleep cycle, and during this stage, it is often easy to be awakened by external sources. Brain activity slowly declines and many bodily processes begin to relax as the person is beginning to fall into heavier sleep.[30]

Stage 2 of NREM sleep is harder to be awakened than stage 1 of NREM sleep. Stage 2 of NREM sleep is the first defined cycle of NREM sleep as sleep spindles and K complexes begin to form in the brain. Slowly brain waves will decline as K complexes and sleep spindles begin to rapidly fire. Both of these brain activity waves serve as protection to awaken from sleep

in the middle of the night. In addition to this brain activity, heart rate starts to slow and body temperature decreases.

The final stage of NREM sleep, known as deep sleep, is unique as delta waves are present throughout the brain. It is very difficult to awaken a person who is in the third stage of NREM sleep. Human growth hormone is released and attempts to restore bodily processes during NREM sleep. The immune system will also replenish helper T cells and muscles throughout the body to be restored.[16]

Most of the dreams that individuals experience occurs during REM sleep, which is known as the fourth and final stage of the sleep cycle. Brain waves are the most active during this stage as well, along with movements of the eye that are rapid. REM sleep stimulates regions of the brain that are important with learning and also is important in memory consolidation.[25]

Antidepressant Effects on Sleep

Studies have shown that improvements in depression have been correlated with patients having reduced amounts of REM sleep. Antidepressants are often given to patients struggling with depression, as most antidepressants significantly reduce REM sleep. But, antidepressants, don't just reduce REM sleep. In addition, many of them also alter the sleep architecture of the patient and affect sleep consolidation.[9] The effects of these antidepressants is important for clinical response.

Antidepressants drugs weaken sleep quality, which is mainly due to increased noradrenergic or dopaminergic neurotransmission and the activation of serotonergic 5-HT_2 receptors.[13] The most common antidepressant drugs are known as selective serotonin reuptake

inhibitors (SSRI), activating tricyclic antidepressants (TCA), serotonin and norepinephrine reuptake inhibitors (SNRI), and monoamine oxidase antidepressants (MAOI).[22]

On the other hand, antidepressants that have a strong antagonistic action at serotonin 5-HT2 receptors (nefazodone and trazodone) rapidly improve sleep. Sedating TCA, mianserine, and mirtazapine are examples of antidepressants that have antihistaminergic action. Some patients have particularly described improvement of sleep quality within the first dose of the drug given.[3]

Studies look to outline parameters of sleep continuity, which has a framework that models sleep latency, total sleep time, sleep efficiency, wake after sleep onset, parameters of sleep depth, and parameters of REM sleep. Parameters of sleep depth monitors total and relative amounts of stage N3 sleep and delta sleep ratio. In addition, parameters of REM sleep examine REM latency, total and relative amounts of stage REM sleep, and REM density.[6] Hypnograms are typically used in studies to observe changes in sleep stages in depressed patients. Disturbances of sleep continuity, reduction of sleep, and disinhibition of REM sleep with shortening of REM latency and prolonged first REM period are characteristic of sleep in depression.[12]

The sleep architecture of a patient being tested is critical to determining the efficacy of the drug being tested. The first parameter of sleep continuity that is measured is sleep latency. This is known as the time from the start of recording to onset of sleep for the patient. Total sleep time (TST) reflects the total time the patient is sleeping. Additionally, sleep efficiency is noted as the percentage of time spent asleep during the recording period. Values are typically 85% in elderly patients, and 90% in younger children. Wake after sleep onset (WASO) should be scored as the time the patient is awake after sleep onset has occurred. For experimental purposes, this

time should not exceed 30 minutes. Another parameter looks at total and relative amounts of stage NREM3 (N3) sleep and it is the total amount of time and relative percentage of sleep occurring in NREM stage 3 sleep. Studies label delta sleep ratio as the amount of slow wave sleep that occurs during the first and second sleep cycles. The amount of time from the onset of sleep to the first cycle of REM sleep that occurs for the patient is defined as REM latency as well. Another parameter of REM sleep describes the total and relative amount of stage REM sleep and is expressed in as the duration in minutes and percentage relative to total sleep time in REM sleep. Lastly, REM density reflects the ratio of the intensity of rapid eye movements phasic activity to the amount of time in REM sleep. This value is typically expressed as the number of eye movements seen per minute of REM sleep.[32]

Drug class	Sleep continuity	SWS	REM latency	REM sleep	Mechanism of action related to effect on sleep
Sedative TCA (e.g., amitriptyline, doxepin, trimipramine)	↑	↑	↑	↓	antihistaminergic effect, inhibition of serotonin, and norepinephrine reuptake
Activating TCA (e.g., imipramine, desipramine)	↓	↓	↑	↓	inhibition of serotonin and norepinephrine reuptake
MAOI (e.g., tranylcypromine, moclobemide)	↓/0	?	↑	↓	inhibition of monoamine oxidase enzyme
SSRI (e.g., fluoxetine, escitalopram, paroxetine, sertraline)	↓/0	0/↑	↑	↓	selective inhibition of serotonin reuptake
SNRI and NRI (e.g., venlafaxine, duloxetine, reboxetine)	↓	0//↑	↑	↓	inhibition of serotonin and norepinephrine reuptake
Agomelatine	↑	↑	0	0	agonism at melatonin M1 and M2 receptors, antagonism at serotonergic 5-HT2C receptors
Bupropion	0/↓	0/↑	0/↓	0/↑	inhibition of norepinephrine and dopamine reuptake
Sedative antidepressants (e.g., mirtazapine, trazodone)	↑	↑	0	0	antihistaminergic effect, antagonism at serotonergic 5-HT2A receptors
Vortioxetine	0/↓	?	↑	↓	inhibition of serotonin reuptake and modulation of serotonergic receptors activity

Table 1. Effects of antidepressants on sleep are outlined by drug class, sleep continuity, SWS, REM latency, REM sleep, and mechanism of action.

Tricyclics

One of the most known classes of antidepressants is tricyclic antidepressants, which are known to be potent suppressors of REM sleep.[7] In addition, this class of antidepressants is important in decreasing the amount of time someone is in REM sleep and prolongs REM latency. Tricyclic antidepressants prolong REM latency, meaning the patient takes longer to transition into REM sleep.[15] The most potent of the REM-suppressing TCAs are desipramine and clomipramine. These TCAs increase stage 1 sleep, and overall, decrease the quality of sleep for the patient. A stronger serotonergic reuptake that has been shown to have inhibiting effects have the most effects on sleep. Desipramine accomplishes this by elevating noradrenaline at targets of the locus coeruleus and have a side effect profile that is limited. Cholinergic pontine neurons are inactivated via desipramine, ultimately leading to inhibition of REM sleep.[21]

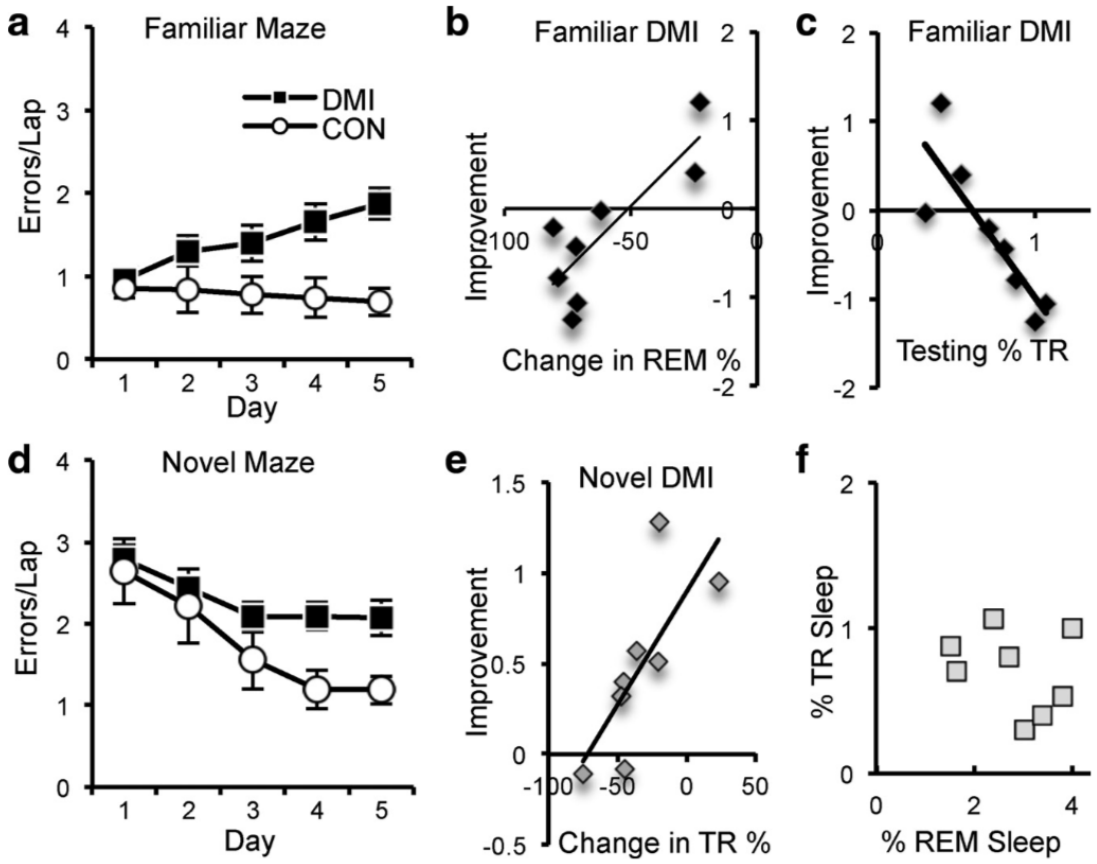

Figure 1. Consolidation and reconsolidation effects induced by desipramine. **A**. Effect of 10mg/kg desipramine on errors per lap in a spatial maze relative to control. **B**. Relationship between REM sleep and performance in maze reconsolidation task. **C**. Relationship between TR sleep during DMI treatment and performance on familiar maze. **D**. Effect of 10mg/kg of desipramine on errors per lap in novel maze. **E**. Change in percentage of TR and novel maze performance relationship. **F**. Correlation of REM and TR sleep states during DMI testing.

This study showed that in depressed individuals, DMI that was taken orally reduced REM sleep for 5 to 8 hours. The 10 mg/kg desipramine dose in the eight subjects resulted from an average time in 12 h light phase sleep that went from 8.35 ± 1.24% to 3.51 ± 1.22%. REM sleep, in addition, was consistent across all testing days when t tests were paired on first and last days.

This would suggest that no REM sleep adaptation was present with administration of desipramine.

Monamine Oxidase Inhibitors

One of the first class of antidepressants that were developed were monoamine oxidase inhibitors. Monoamine oxidase breaks down dopamine, serotonin, and norepinephrine. REM sleep can also be outright eliminated in some patients if they are prescribed a monoamine oxidase inhibitor. However, this means that the patient will encounter a significant REM rebound when weaned off the antidepressant. Moclobemide, a known MAOI, is thought to enhance REM sleep and decreases REM latency. Not all monoamine oxidase inhibitors have the same effects for example. When 450mg was given to the patient every day for four weeks, moclobemide was shown to increase wakefulness, increase sleep latency, and decrease total sleep time for the patient. Moclobemide has been shown in many studies to enhance REM sleep, but other studies have concluded that the MAOI has suppressed REM sleep.

A study conducted in 2018 in adult male rats look at the effect of tranylcypromine, a known monoamine oxidase inhibitor. A decrease in REM sleep and dizziness was shown in the rats, along with leading to severe hypotension. The total amount of time in REM sleep was decreased and a longer time of REM sleep latency was found. Tranylcypromine acts as an irreversible inhibitor and is nonselective.[7]

Selective Serotonin Reuptake Inhibitors

The first known selective serotonin reuptake inhibitor (SSRI), fluoxetine, was developed and brought to the United States in 1988. Since then, studies have been conducted to determine

its efficacy. At the time, fluoxetine was the most available antidepressant and its selectivity for specific serotonin receptors made it the ideal SSRI of choice.[9] Fluoxetine side effects can include skin reactions, but this side effect can't be eliminated due to the fact that reducing the dose of the SSRI will have no effect. More of the neurotransmitter that it is available to interact with is accomplished by the increase of inhibition of serotonin reuptake. 5-HT_3 receptors are stimulated when SSRI therapy is initiated on a patient, but this side effect can be combated by reducing the dose of the SSRI.

The most common symptom that is developed when a patient is taking an SSRI is nausea. Other frequent side effects via SSRI therapy includes gastrointestinal disturbances. Fluvoxamine is another common SSRI whose most frequent side effect includes gastrointestinal disturbances, while other SSRIs like fluoxetine and sertraline side effects commonly include insomnia, agitation, and anxiety. Also, the most adverse effects of being on SSRI therapy can have implications on weight gain, sexual dysfunction, and sleep disturbance.

Many studies have proved to show that weight gain can be a possible side effect with the long term use of SSRIs. During initial therapy, some SSRIs were associated with weight loss. But, after long term use, weight is often regained or six months after use. On average, patients on fluoxetine gained 21 pounds, those on sertraline gained 15 pounds, and those on paroxetine gained 24 pounds. Subtle differences may not show direct causation, but the data behind the long term use of these SSRIs points that these values are significant. Citalopram has been shown to least likely cause a weight gain from long term use, but, a great deal of patients report having mood and anxiety disorders within five weeks of SSRI therapy.

The mechanisms behind to why SSRIs can directly affect sexual dysfunction are not completely known. However, researchers believe that it can be possibly affecting patients due to

nitric oxide. This is due to the stimulation of the postsynaptic 5-HT_2 receptors located on the spinal cord. Sexual dysfunction can vary greatly across genders due to the obvious biological differences.[27] Roughly 2 to 7 percent of patients report sexual side effects when on SSRI therapy, so the side effects appear to be minimal. However, when patients are given a sexual dysfunction questionnaire, these numbers change significantly. 55 percent of patients report sexual dysfunction through the use of SSRI therapy. This enormous difference speaks to the fact that most patients are not always comfortable speaking about these topics with their physicians. Because of this discrepancy, it is suggested the physicians obtain a sexual function history of their patients before starting their patient on SSRI therapy.

The Hamilton Depression Rating Scale provides a way to determine a patient's level of depression before, during, and after treatment of a certain antidepressant. An interview is conducted via the researcher and is scored on a 5-point scale, ranging from 0 (not present in the individual) to 4 (severe). The SDS Zung Self-Rating Depression Scale attempts to cover physiological, affective, and somatic symptoms associated with depression. It is based on a 20-item self-report questionnaire and is framed in positive/negative statements. Each item is scored on a 1 to 4 Likert scale with a score of 50-60 indicating depression and 70+ outlining severe depression. The AIS Athens Insomnia Scale assess insomnia symptoms in individuals with sleep disorders. The scale is based on eight factors which cover problems with nocturnal sleep and daytime dysfunction. Score are then rated on a 0-3 scale indicating no problem present or very delayed/not sleeping at all. Lastly, CGI-S Clinical Global Impression - Severity Scale assesses a severity aspect of a patient's illness. The Severity Scale is based on a 7-point scale with 1 being normal to 7 displaying the most extremely ill patients. The clinician is asked to rate the severity of the patient's illness with past experience of patients who have underwent the same diagnosis.

Variables	Baseline	Week 1	Week 2	Week 6	Week 12	Week 24
	Estimated marginal means (SE)					
HDRS						
Mirtazapine	23.0 (1.2)	19.0 (1.3)	15.5 (1.3)	9.6 (1.4)	9.3 (1.5)	5.9 (1.6)
SSRIs	23.1 (0.9)	19.2 (0.9)	16.9 (0.9)	12.9 (1.0)	9.5 (1.0)	5.4 (1.1)
Sertraline	23.2 (1.1)	19.1 (1.2)	16.3 (1.1)	12.1 (1.2)	8.7 (1.3)	5.3 (1.4)
Paroxetine	22.9 (1.5)	19.4 (1.5)	17.8 (1.5)	14.6 (1.7)	11.2 (1.8)	5.8 (2.0)
SDS						
Mirtazapine	56.0 (1.7)	52.4 (1.8)	46.6 (1.8)	44.0 (1.9)	43.7 (2.1)	38.0 (2.2)
SSRIs	57.6 (1.3)	54.8 (1.3)	52.8 (1.3)	48.7 (1.4)	44.9 (1.5)	41.8 (1.6)
Sertraline	57.4 (1.6)	54.1 (1.7)	51.2 (1.6)	47.2 (1.7)	42.4 (1.8)	40.3 (1.9)
Paroxetine	57.9 (2.1)	56.1 (2.1)	55.0 (2.1)	51.4 (2.3)	49.8 (2.5)	44.5 (2.8)
AIS						
Mirtazapine	11.5 (0.9)	8.4 (0.9)	6.6 (0.9)	5.8 (1.0)	6.8 (1.1)	5.0 (1.1)
SSRIs	12.9 (0.6)	10.2 (0.6)	9.3 (0.6)	7.5 (0.7)	6.6 (0.7)	5.5 (0.8)
Sertraline	12.8 (0.8)	10.0 (0.8)	8.1 (0.8)	6.9 (0.8)	5.3 (0.9)	4.6 (1.0)
Paroxetine	13.1 (1.0)	10.5 (1.0)	11.3 (1.0)	8.8 (1.2)	9.2 (1.2)	7.2 (1.4)
CGI-S						
Mirtazapine	4.4 (0.2)	3.8 (0.2)	3.2 (0.2)	2.8 (0.2)	2.6 (0.2)	1.8 (0.2)
SSRIs	4.3 (0.1)	4.0 (0.1)	3.6 (0.1)	3.1 (0.1)	2.7 (0.1)	2.1 (0.2)
Sertraline	4.4 (0.2)	4.0 (0.2)	3.6 (0.2)	3.0 (0.2)	2.6 (0.2)	2.1 (0.2)
Paroxetine	4.2 (0.2)	4.1 (0.2)	3.6 (0.2)	3.5 (0.2)	3.0 (0.3)	2.0 (0.3)

Table 2. Clinical efficacy outcomes for all patients. HDRS 17-Item Hamilton Depression Rating Scale, SDS Zung Self-Rating Depression Scale, AIS Athens Insomnia Scale, CGI-S Clinical Global Impression- Severity Scale. Mirtazapine is a noradrenergic and specific serotonergic antidepressant while sertraline and paroxetine and selective serotonin reuptake inhibitors.

This study conducted by Tasuku Hashimoto and his team aimed to evaluate if mirtazapine could be used as a first choice for depressive episodes instead of SSRIs on benzodiazepine use in patients diagnosed with major depressive disorder. HDRS scores between mirtazapine and SSRI groups were not statistically significant, as well as changes within the AIS and CGI-S scores. SDS scores of paroxetine and mirtazapine reflects that SDS scores of the mirtazapine group showed significant improvement than those of the paroxetine group in the week-to-week trials.[8]

In a study completed McCarthy and his colleagues, the researchers looked at well-known SSRIs and how they compare to a known TCA. 51 rats were observed as the changes in REM sleep observed in major depressive disorder are similar to the effects of REM sleep restricted sleep in humans and animals. The two SSRIs, known as citalopram and paroxetine showed that REM sleep inhibition by these antidepressants was unaltered by the presence of REM sleep pressure. NREM sleep time was also fully compensated in the citalopram and paroxetine treated group. On the other hand, the TCA imipramine showed a complete recovery adding to the response to prior REM sleep restriction. Imipramine REM restriction showed that NREM sleep time was reduced and not fully compensated up to 36 hours post treatment. SSRIs also may inhibit REM sleep by reducing NREM to REM transitions. This is accomplished without altering the lengths of time of NREM sleep. Imipramine extends NREM sleep time, which induces greater sensitization and a byproduct of a reduced opportunity for REM sleep. During the recovery period, however, this leads to an increase in REM sleep.[17]

Serotonergic Antidepressants

The classification of other serotonergic antidepressants differs from SSRIs due to their effect on sleep and specifically their neurotransmission. SSRIs prevent the reuptake of serotonin whereas serotonergic antidepressants (SNRIs) prevent the reuptake of norepinephrine and serotonin. Trazodone has been shown in patients to enhance slow-wave sleep, prolong REM latency, and increase total sleep time. The dose dependent effects of these antidepressants differs from study to study. A study done by van Bemmel and his colleagues reported no change in slow-wave sleep. They concluded that 5% to 9% of their patients underwent REM sleep suppression. Earlier studies used double the amount of trazodone that was done in this particular

study. In 20 of 21 patients that had MAOI-associated insomnia, they reported that the administration of trazodone improved their sleep. Clinically, trazodone is viewed as a sedating antidepressant and can have effects in alertness during the day.[21] At higher doses, this becomes more of a problem as the sedative effects can affect the individual's performance in daily activities.

Another serotonergic antidepressant that is widely used includes nefazodone. Particularly, this antidepressant is given in 400 mg to 600 mg doses. Armitage and others report that the administration of nefazodone increases stage 2 sleep but has shown to have little to no effect on REM sleep.[28] In addition, nefazodone decreases awake and movement time during sleep, and it also proves to keep individuals in a more relaxed state. Short duration arousals are common for individuals taking this antidepressant. Nefazodone is different from SSRIs and trazodone since it inhibits synaptic uptake of 5-HT and possess 5-HT2 antagonism. In patients that have depression, a reduction in REM sleep is often essential to start seeing anti-depressive like behavior.

Alternatives to Antidepressants

Numerous other treatments may be used instead of antidepressants for treated individuals with depression or other mental health conditions. One of the most popular therapies is known as cognitive behavioral therapy. Cognitive behavioral therapy is a division of psychotherapy that relates to changing the thought patterns and behaviors of a certain individual.[17] Ultimately, it is an interventional that will teach patients how to overcome negative thoughts. Interpersonal therapy, exercise, and self-help groups are also helpful options to explore.[23] Interpersonal therapy is similar to cognitive behavioral therapy, but it will focus on problems one might have

having with friends and family members. Therefore, they might be able to understand the difficulties they are having in their relationships and can learn how to better communicate with other individuals. Regular exercise boosts levels of serotonin and dopamine, which will elevate your mood. In addition, self-esteem and confidence can be boosted over time with normalized exercise. Self-help groups are provide individuals another option for depressed individuals. Individuals can find ways to support others, keep up with social activities, and reach out to others who make them feel safe and secure.

Another alternative to investigate is the consumption of omega-3 fatty acids. Intake of omega-6 fatty acids has dramatically increased in the Western diet in the 21st century. Omega-6 fatty acids are elongated in the body to form arachidonic acid while omega-3 fatty acids are elongated to form eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The eicosanoids formed when more omega-6 fatty acids are consumed result in more proinflammatory eicosanoids. Blood clotting and inflammation are encouraged because of this. On the other hand, an ingestion of more omega-3 fatty acids will result in less proinflammatory eicosanoids limiting inflammation and blood clotting. Ingestion of omega-3 fatty acids is believed to reduce cardiovascular risks as well.

EPA, a known omega-3 fatty acid, inhibits the synthesis of prostaglandin E2. This will inhibit the synthesis of p-glycoprotein, which is generally considered a useful maker for antidepressant resistance. A study conducted by Peet and Horrobin looked at using ethyl-eicosapentaenoate for 70 adults who had persistent depression despite already being treated with an antidepressant. They observed a higher response rate in subjects that received 1g/d EPA for 12 weeks than the other patients who received a placebo. These results proved to be statistically significant as the rate was 53% of the subjects who received EPA to 29% with the other

individuals who received a placebo. There was also remarkable enhancements in depressed moods, suicidality, and sleep disturbance. This study also showed that adults that received more than 1 g/d of EPA showed little improvement for a drug to placebo difference. This might point to there being an optimal dose of omega-3 fatty acid intake within humans before a plateau occurs.[20]

A study conducted by Frangou and his researchers followed a similar pattern to Peet and Horrobin's study. They treated 75 depressed individuals with ethyl-eicosapentaenoate at 1 g/d, 2 g/d, and placebo for 12 weeks. The EPA group showed to be beneficial based on HAM-D scores in comparison to the placebo groups from the experiment. This study also suggested that the higher dose of 2 g/d created no additional benefit when looking back at the 1 g/d group.[5]

Limitations of Studies

Circadian factors can alter the effects of antidepressants as pharmacological treatments target circadian gene products.[11,17] Studies that attempted to inhibit REM sleep are distorted to some degree by the timing of the light-dark cycle. Our circadian rhythm, along with adenosine signaling, trigger our body to sleep. Circadian factors need to be more thoroughly looked at to determine if certain genes are altered as well.

Most omega-3 fatty acid studies are limited to the sample size taken. Depressive evaluation tests performed by patients will offer some variability patient to patient based on the rating they give themselves. Depressive vs manic symptoms also need to be implored in research to point which is specifically downregulated in regards to a decrease in REM sleep. Some studies grouped depressed patients in one group instead of dividing them out based on the condition they were diagnosed with. Many of the studies showed a small sample size and were

not necessarily representative of the whole population of patients who tolerate depressive symptoms.

Conclusion

In regards to alleviating depressive symptoms, a decrease in the overall time in REM sleep is clear in many patients. Longer REM sleep latency and shorter REM duration lead to more favorable outcomes. Many of the antidepressants used today provide an overall improvement in alleviating depressive symptoms. Antidepressants typically have half lives of 24 hours and are eliminated out of your body within 4-5 days. Based on preliminary studies, tricyclic antidepressants serve to decrease REM sleep time, increase REM sleep latency, and show REM sleep rebound over a 72 hour period. This may serve more favorable outcomes when REM sleep time is initially decreased but REM sleep lost can be rebounded. However, this is not the only best-for-all approach solution to fixing all problems. Prescribing the right antidepressant for each patient is also key to the patient's outcome. This may be based on particular symptoms, interactions with other essential medications, and possible side effects.

Many side effects due to long term use are seen and cost vs benefit approach needs to be explored. Treatment will not be the exact same for each patient, and many patients will need multiple treatment options to experience relief. A combined treatment approach may improve the patient's quality of life since it is not always one simple fix to improve each patient's overall quality of life. Patients typically still have to take antidepressants up to one year after depressive symptoms seem to be eliminated. Focusing on lifestyle changes for the individual during that time as well may improve quality of life faster them as they transition their outlook. More personalization and medical advances in the future will provide individuals with better outcomes.

Future Work

Further work should be done to examine how the circadian rhythm and REM sleep homeostasis interact to help provide a mechanism of REM sleep regulation. Many of the studies conducted will need to have a certain depressive symptom common in all individuals and need to evaluate how much alleviation occurs. Universal wide depressive scales based on the disorder need to be developed in order to get more accurate and precise results.

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