

Increased Antidepressant/Anxiolytics Prescriptions are Impacted by the Society in Multiple Ways

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ABSTRACT

Since the first appearance of antidepressant, iproniazid in the 1950s (1) and first anxiolytics, librium in 1960 (2), there has been increased uses of anxiolytics and antidepressants drugs across the years. Although the drugs often come with some side effects, the use of these drugs are becoming more popular. The drugs are used to cure mental problems like anxiety disorder and depression by controlling the neurotransmitters like GABA-A, serotonin, dopamine, and norepinephrine in the synapses between neurons in our body. This paper will try to find the cause of this phenomenon by looking at different factors like the impact of COVID-19, gender, economic influence, and veteran PTSD. Different events cause different hormonal changes in the body such as, hormone releases from menstrual cycle during ovulation, stressful, lonely, and fearful situations, causing potential impact on one's body and one's vulnerability to anxiety and depression. This paper will also look at the negative side of both medical and illicit anxiolytics and antidepressants, including side effects, abuse and addiction, and look for potential solutions to these problems.

Social impacts due to COVID -19

The social trends around the world influences the take of anxiolytics and antidepressants. One example of such is global pandemic such as COVID-19, which started during November of 2019, first identified in Wuhan, China. COVID-19 virus can spread by direct physical contact (through droplets containing virus), indirect contact (contact of the same surface), or through aerosols that remain in the air (3). This virus that is still ongoing has caused approximately 4.4 million deaths worldwide, with around 215 million reported cases (google). The pandemic has consequently caused a general increase in stress level and anxiety within people. According to a sample of 1000 people in the USA, 13.6% reported 'serious' psychological distress during the pandemic compared to 3.9% of psychological distress in 2018, a typical year (4). The research conducted in Spain on dose of anxiolytics show that there is constant increase in the population dosing anxiolytic drugs (3). However, in 2020, when the pandemic of COVID-19 started, there has been a dramatic increase in the number of patients dosing anxiolytics with an increase of 6.63% with 1357 packs/1000 inhabitants between 2019 and 2020 which is higher than previous years where the increase were between 0-3.5 % (3). This shows dramatic increase of the anxiolytics dose before and after the pandemic, proving the influence of COVID-19 on anxiolytics dose. This can be presumed as largely due to fear of illness and death of oneself or their loved ones, loneliness due to isolation, and fear of loss of employment (4). Especially with school and office work being conducted online for a long period, loneliness has become a global phenomenon and its psychological impact has been said to be great.

Being isolated from others, especially during the pandemic when social activities are limited, can easily lead one to feeling loneliness. Loneliness is a feeling one feels when they experience a gap between one's desired social interactions and their actual reality (5). Loneliness can lead to different negative feelings such as anxiety, depression, and low sense of self worth (5). During quarantine, disconnection from people causes less engagement in social activities and support from people leading to serotonin depletion. As a result, more people will take antidepressants and anxiolytics in order to cope with depression and anxiety. A study researching the relationship between social behaviors

and well-being of one showed that loneliness is related with the effects of oxytocin on cardiac autonomic control (6). Oxytocin is a hormone that causes one to improve social interactions, trust, and bonding with others, while also decreasing fear. This hormone also regulates cardiac activity which prevents one from experiencing hypertension (7). However, a raised level of loneliness causes one's response to oxytocin on the cardiac system to decrease (6). This means that in the presence of loneliness, one will not be able to control their cardiac activity efficiently even in the presence of oxytocin. This potentially leads to much higher vulnerability to depression and anxiety as hypertension usually occurs when there is lack of dopamine in the brain (8). A development in hypertension could be perceived as lack of dopamine in one's body and could eventually lead to depression. Hypertension also may trigger anxiety to some because of its symptoms, which are headache, blurred vision and shortness of breaths (9). This creates a panicking effect to those who experience it and could lead to development of anxiety about one's health and future (9).

Drug use by gender

Difference between men and women

The gender differences between men and women can influence the taking in drugs like anxiolytics and antidepressants. Studies across the world suggest higher prescription of anxiolytics/ antidepressant drugs for females than male. According to a study conducted in Spain, women use more drugs in general than men with rates of 80.93% and 67.84% respectively. Women are also known to be higher in Anxiety Sensitivity (AS), which is related to one's belief that certain bodily sensations are related to harm or illness, compared to men (10). This may show that women are more cautious than men. Also, in the CO₂ challenge which is used to predict spontaneous panic attacks, women experienced more fear and panic related symptoms and took longer time to recover from those feelings (10). This could be due to reasons related to biological difference, and social role differences.

The biological differences between men and women potentially make women more susceptible to mental illnesses. Although there has been no definitive connection found yet, hormones released during the menstrual cycle for women can determine their mood and stress level. Specifically, they may experience a fluctuation of mental conditions during the premenstrual and menstrual phases. (11). This fluctuation could also exacerbate the mental illnesses that a woman already have, which the reported cases show signs of schizophrenia, bipolar disorder, depression, anxiety disorders, bulimia nervosa, and substance abuse (11). This is potentially due to progesterone and estrogen hormones produced during the cycle. Progesterone, which is a hormone primarily produced in the ovulation cycle after ovulation, helps thicken the lining on the uterus wall to prepare for fertilisation. However, this hormone can also influence a woman's mood as it enhances the amygdala reactivity in the brain, an area that is responsible for emotion and motivation (11). This makes women more prone to emotions during the release of progesterone, meaning women may be stressed out even by a small, unnoticeable event. This makes women more prone to anxiety and depression than men. A study displayed a result that anxiety related disorders such as panic disorder are up to two times more likely for women (10). This could also be due to the fact that sensitivity to GABA-A receptors might be changed during the menstrual cycle which requires further research (10).

Also, another potential cause of this phenomenon is the difference between social roles in men and women. The statistics of women in Europe show that a female is predicted to have lower status than men, lower participation in decision making, and are usually paid less (12). The results from a survey of 100 pharmacies in Italy of 11357 women show that women have many stressful events in their lives in general (12). In fact, 90% of women who take anxiolytic/ antidepressant drugs have stressful life events and 74% of women who do not take those drugs have also experienced stressful life events within an average 6 months (12). This could be largely because women are more exposed to social stress with more social life in general. In fact, the most impactful events are those related to relationships with family and friends (12). Women also struggle highly with financial difficulties (12). 69% of drug users and 55% of non-users rated their events to have a severe impact on their wellbeing (12). The common use for

psychotropic drugs differ for genders as well. According to a study conducted in Belgium, women usually take anxiolytics and antidepressants due to mental problems, while men most commonly get drugs prescribed for their sleeping problems (13). These results show that women tend to be more stressed out socially in general than men and are more likely to gain mental problems.

Economics influence on drug use

Economic related events are one of the common reasons that lead to one's use of drugs. Economics heavily influences one's lifestyle and economic choices, physical and mental health, and even people's marital happiness (14). There are different kinds of economic events that might influence individuals or a big community. Unemployment can be a stressful event in a person's life that causes big influence on one's financial life. The economic crisis in Argentina which lasted from 1999 to 2002 portrays an example of large scale unemployment (15). This caused a general increase in fear within the population in the country due to financial insecurity. Also, there is general variation in use of anxiolytics and antidepressants within different wealth levels. Alcohol, which is one of the most common types of anxiolytics, becomes more common as the wealth group goes down. This can be reasoned by differences in surrounding people and environment various to wealth groups.

Unemployment

Being unemployed is a big threat and fear to many as it interferes with one's wellbeing. Money is the basic resource of our modern lives, so being unemployed causes people to experience the emotion of fear due to the uncertainty of their future. Experiencing fear due to instability could become a big factor leading to anxiety or depression. During the economic depression in Argentina, which lasted 3 years, 42% of the countries lived below the poverty level (16). At one point, the country reached an unemployment rate of 20% (15). This has caused an increase in demand for the anxiolytics and antidepressants. The sales of antidepressants had increased by 13% and tranquilizers by 4% between 2000 and 2001. This can be seen by the loss of economic security and the devaluation of people's hard working hours which potentially lowered people's self-worth. The research shows that higher income is correlated with less negative feelings in general (15). People who do not earn lots of money are more likely to develop money anxiety and are usually dissatisfied with their earning and material goods. This suggests that fear and stress can lead to depression.

Fear causes the amygdala to release stress hormones like adrenaline and cortisol (17). High levels of cortisol overtime is found to cause cognitive deficits (18). An experiment conducted on patients with Cushing's syndrome, which is a disorder caused by too much release of the cortisol hormone, showed a decrease in hippocampal volume in the brain, a region responsible for learning and memory, when they had an increase in cortisol level due to stress or corticosteroids (18). This led to deterioration in memory. Overall, there is a correlation between cortisol level and the size of the hippocampus which suggests that high cortisol level may bring depression due to decreased learning and memory (18).

Variations in wealth level

Social class also affects one's exposedness of drugs. This is largely due to the environment the adolescents are surrounded in. The influence of family and peers are different by class as well. Peer influence is to be found much more significant than parental influence in adolescent drug use (19). The difference in social class affects the way of belief, commitment, religious attachment, and school attachment on drug use due to one's surrounding environment and tradition. One of the common anxiolytic drugs is alcohol and the usage of this drug can be well explained by a difference in social class. Specifically, a study conducted in India shows that alcohol consumption increases at a high rate as income class decreases. (20) Alcohol consumption was reported to be higher within those of below poverty level,

who had rural dwelling, and who were formally uneducated (20). Thus, heavy drinking was linked inversely with socio-economic status. Also, the patterns of alcohol use of the countries varied by region. The statistics revealed that countries with greatest per capita consumption showed the lowest alcohol use within population (20).

Veteran PTSD

Soldiers who have participated in wars often suffer from post traumatic stress disorders (PTSD) after their experience at war. The potential reasons that causes the soldiers to develop this disorder are exposure to combat with shell bombings and machine gun firing, prewar vulnerability, and involvement in harming civilians or prisoners. Continuous exposure to danger of getting harmed and an environment of loud noises develops a very stressful situation for the soldiers.

Reduced size of amygdala:

Several studies show the result that soldiers who were diagnosed with PTSD from the battlefield showed change in amygdala volume in the brain (21). When Functional magnetic resonance imaging (fMRI) of patients suffering from PTSD were analysed, researchers found that there was significant downregulation in the amygdala of the brain when patients were given a traumatic word (21). Provoking the symptoms of PTSD created a downregulation in the activities of the amygdala region, eventually leading to the down size of its volume (21). Bilateral amygdala damage was found in patients with PTSD. The amygdala region of the brain is linked with the learned fear response, which makes it affected by the amount of fear one is exposed to. The down size of it in PTSD soldiers can be explained by habitual activation of amygdala over the time could decrease response in amygdala over time (22). The correlation amygdala volume and depressive symptoms have been shown (23). Since the amygdala is responsible for processing emotions like fear, change in it causes alteration in its system, which can make it harder for people with smaller amygdala size to control their emotions. Serotonin and GABA receptors which can be increased by anxiolytics and antidepressants are able to modulate the activities of the amygdala (24).

PTSD leads to downregulation in left CEN, which is responsible for language, comprehension, and arithmetic (21). This led to a decrease in cognitive functions for people with PTSD. Decrease in cognitive function is linked highly with depression and anxiety. Therefore, more people will prescribe anxiolytics and antidepressants to ease the pain.

Methods

To reach the aim of finding answers to the research question, search tools like google scholars, google search, and pubmed were used. Key words 'anxiolytics' and 'antidepressants' were used. Different keywords were used for each heading including, 'COVID-19', 'gender difference', 'unemployment', 'wealth level', 'veteran PTSD', and 'abuse and addiction'. 42 papers were referenced in total. To make sure the papers were valid, I ensured that all papers used were published in a trustworthy institution. Systematic review was used to successfully combine different data on factors affecting use of anxiolytics and antidepressants.

Results

There has been links shown with different societal factors such as COVID- 19, gender difference, Economical events, veterans PTSD and more with the dosage of anxiolytics and antidepressants. This trend is likely to continue as the world is becoming more social and there will be increased number of big social changes which a big population must

go through. However, there must not be over prescription of anxiolytic and antidepressants, considerations should take place before the prescription as these drugs come with great side effects.

Abuse and addiction of anxiolytics and antidepressants

Sometimes, heavy doses of anxiolytics or antidepressants can lead to abuse or addiction to the drug. The drugs that are prescribed for medical purposes can definitely help one with the right dosage, but they often come with side effects. The common side effects of anxiolytics and antidepressants include feeling sick, stomach ache, diarrhoea, dizziness, sexual dysfunction, insomnia, and fatigueness (25).

There is potential risk of withdrawal syndrome, which occurs when one becomes dependent on drugs. About 74% of patients who complained about side effects from antidepressants have mentioned withdrawal syndrome (26). The syndrome generally starts after 2-10 days of first dosage of benzodiazepine (27). A study conducted shows that amongst the long-term consumers of anxiolytics, one third or more users developed withdrawal syndrome. The symptoms include anxiety, insomnia, dizziness, fatigue, and more. This could lead to repeated use of anxiolytics causing patients not able to stop the drug completely leading to potential addiction. This results in some people taking anxiolytics or antidepressants as a habit rather than actual treatment. Taking these drugs for an extended period of time could lead to drug tolerance.

One of the most common anxiolytics, alcohol reduces the function of the behavioral inhibitory center in the brain. This is because the ethanol in the alcohol changes the shape of the membrane of the GABA receptor causing increased attraction between GABA and other sedative drugs. This causes alcohol to be very addictive.

The dose of anxiolytics also varies according to the region of the country. For example, East Mediterranean countries report the lowest alcohol consumptions.(20) This could be influenced by the fact that certain religions or cultures have different perspectives on alcohol . Many countries in the East Mediterranean such as Afghanistan, Iran, Libya, Saudi Arabia, Somalia, Sudan, and Yemen ban alcohol consumption (28).

Abuse and addiction of illicit anxiolytics and antidepressants

Illicit drugs, which are part of the anxiolytics and antidepressant class of drugs, could cause even bigger problems with the wrong dose. Illicit drugs are highly addictive and illegal substances such as heroin, marijuana, and meth. Many of these drugs are used for the purposes of self-medicating anxiety disorders and adjacent disorders such as MDD. However, there is a major difference between illicit drugs and drugs that are for medical purposes as use of illicit drugs are not supervised by professionals and it is very easy to be abused making it a dangerous weapon that could cause harm, sometimes even leading to a death, rather than a cure.

Illicit drugs make people 'high' by altering the way neurotransmitters are sent, received, and processed. This could fool the brain by nerve cells sending abnormal signals, or amplifying signals (29). Specifically, these drugs target the brain's reward system to make people feel pleasure (29). Basic human desires, such as eating, loving and more, are satisfied, creating an euphoric effect (29). Continued doses of drugs could lead to drug addiction. When drugs are constantly abused, the body starts to adapt to its effect and tries to normalise the amount of dopamine, which is a type of neurotransmitter that causes pleasure, by reducing the amount of dopamine produced naturally in our body or by reducing the number of dopamine receptors. (29) This leads to users taking the drugs habitually in order to bring back their normal dopamine level. It also requires more dopamine for a person to get high which leads to a negative cycle of drug addiction. Drugs cause non-conscious learning, making users become addicted to it without being fully aware.

Although taking these illicit drugs can be a very pleasant experience, wrong doses of it could be very dangerous. Unsanitised equipment such as injection could lead to blood-borne viruses like Hepatitis B, Hepatitis C, and HIV/AIDS or bacterial infections (30). This usually occurs when a needle is shared between people. In addition, continuous smoking of drugs can cause major damages in one's respiratory system with repercussions like coughing,

shortness of breath, and bronchitis (30). Abuse of illicit drugs can also be very dangerous and depends on how much and often the drug is taken. When drug users were asked about the reason they take drugs, the highest reasons were 'pleasure', 'impulsivity', and 'habit' (31). In contrast, participants' response to 'pain avoidance' and 'craving' were comparably low (31). Distinctly, this is quite different to anxiolytics and antidepressants that are used for medical purposes as they are used to get people to function normally when in a medically induced mental state. Illicit drugs can inversely lead to development of mental disorders due to social, legal, financial, and emotional problems related to drug use (30).

Discussion

Potential solutions and future directions

Potential solutions to the side effect profile and abuse potential of anxiolytic drugs include deep brain stimulation, cognitive behavioral therapy (CBT), and neurofeedback therapy.

For patients who are already taking anxiolytics or antidepressants, they can prevent the withdrawal syndrome when cutting down the drugs by undergoing withdrawal therapy with an expert who has a strategic plan customized to the individual. This process usually takes place for a period of 6-8 weeks but is a more controlled and less provocative method to decrease one's reliance on drugs in contrast to those who cut a drug abruptly and are presented with immediate withdrawal symptoms (27). Sometimes it is possible for the process to last as long as several years depending on the severity of patients, but it is recommended that the process is done within 6 months (32). This way patients are able to receive optimal methods of withdrawal from the drugs without suffering from the side effects for too long. To prevent the side effects of anxiolytics and antidepressants, patients can try replacing doses of drugs with more natural activities that increase serotonin levels such as getting sunlight, massage, exercise or recalling happy events in their head.

Deep brain stimulation has promise in being able to provide more targeted treatment of select regions of the brain compared to the relatively nonspecific action of drugs delivered through the bloodstream. The dorsal raphe nucleus is a major source of serotonin and stimulation of this area leads to the release of serotonin in the forebrain (33), and may be a potential target of such deep brain stimulation, producing a similar function to antidepressants which helps deliver more serotonin between neurons to increase positive effects. More study is required, but finding a way to effectively stimulate the dorsal raphe nucleus could work as a replacement for medications that release serotonin.

Cognitive behavior therapy could help people cure anxiety disorder and depression without any medication. The patients are able to cure their disorders by talking with a professional consultant who can guide them to change the way they think or behave. This could lead to improving the functioning of a person. With this method, it is possible to cure anxiety disorders without the help of any medication, or sometimes it could be treated alongside medication. There is also new development of computer-assisted cognitive behavior therapy and mobile apps that could help cure anxiety and depression. Multiple trials of CCBT programs have been tested by the clinicians have proven it to be effective in curing the patients with mental disorders (34). This could potentially work as a replacement for person-to-person cognitive behavior therapy. Also, mobile apps are more accessible as they can be used anytime and anywhere (34).

Conclusion

In conclusion, the general trend across the world shows the increase in use of anxiolytics and antidepressants. There are different factors that cause this pattern: difference in gender and sexual orientation, social trends like COVID-19, economic status, and war veterans suffering from PTSD. This research also looked into the potential dangers and

drawback of abuse and addiction of anxiolytic/antidepressant drugs and illegal drugs that are common for recreational purposes.

The social impact of COVID-19 has made people more vulnerable to anxiety and depression by creating threat and danger to populations all around the globe, while also isolating people physically away from each other, leading to chronic loneliness. The linkage between increase in prescription of anxiolytics and antidepressants during the duration of the pandemic was clear. The hormonal change in one's body when exposed to constant isolation and loneliness was analysed to explain this phenomenon.

Women generally suffer more from anxiety and depression due to potential hormonal effects and social stress. The hormone progesterone makes them more prone to depression. Women are put into more social events than men in general leading to higher vulnerability to anxiety and depression.

Economic influence has had a big impact on people's dose of anxiolytics and antidepressants. Economic security and status can determine one's stability and stress. Unemployment can cause an increase in cortisol which is released in presence of fear. Cortisol decreases the cognitive ability and leads to increased susceptibility to depression.

PTSD in veterans is one of the biggest groups that are prescribed anxiolytics and antidepressants. PTSD can cause a decrease in volume of amygdala due to constant exposure to the emotion of fear in war. Decrease in amygdala volume is highly linked with depression as it makes one harder to control their emotions.

Abuse and addiction of anxiolytics and antidepressants could have a negative effect on a person. There could be symptoms or side effects, addiction, and withdrawal syndrome. There are potential solutions that could help patients experiencing improper dosage of anxiolytics and antidepressants such as withdrawal therapy, deep brain stimulation, and cognitive behavior therapy.

Limitations

There were a few limitations to this method as only few factors were recognized as reasons for increase in anxiolytics and antidepressants. Also, there is a big probability that as time went on, medications for mental illnesses became more prevalent to people around the world, causing general increase in its dosage. More study of similar trend is required to make sure to conclude how certain events affects the dosage of anxiolytics and antidepressants in general population.

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