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Smoking Cessation Treatments Varenicline (Chantix®), NRTs, and Nicotine Dependence

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Introduction

According to the 2017 Morbidity and Mortality Weekly Report (MMWR), 47.4 million people in the United States where reported to have been using tobacco products (Wang 2018). It is well known that heart diseases, respiratory diseases, and cancer can result from tobacco product use and addiction. Even though we have seen a 6.9% decrease in substance use from 2005 to 2017, it is still a leading cause of death and disease (CDC 2019). Varenicline (Chantix®) is a medication that was approved in 2006 by the FDA for use in smoking cessation (Fagerström et al. 2008). Varenicline was designed to bind with α4β2 nicotinic acetylcholine receptors (nAChR) to work as both an agonist and antagonist. When the receptors are bound, dopamine is released, and nicotine is not able to bind to its receptors. While varenicline has been shown to decrease relapse events, it had also been labeled with a black box warning of side effects affecting mental stability and causing suicidal ideation that was later removed. In this paper, the mechanism of varenicline will be reviewed, which allows it to assist the patient in quitting tobacco smoking and preventing nicotine withdrawals. Even after someone quits smoking tobacco products with carcinogenic additives, they may still be dependent on nicotine through nicotine replacement therapy drugs (NRTs) like nicotine gum or patches. There is also a rise in the use of electronic cigarettes and vaporizers. The long-term effects of these devices and how they may contribute to the use of smoking cessation and nicotine dependence are now a current topic of study (Selya et al. 2018). The question that drives this review on nicotine dependence as new forms of nicotine devices and NRTs are still providing the stimuli for dopamine release is as

follows: Is nicotine dependence harmful to patients, if the smoke is not causing respiratory issues and lung cancer?

Varenicline (Chantix®) molecular mechanism

Varenicline is used for smoking cessation because it inhibits nicotine-induced dopamine release by competitively binding to α4β2 nAChRs. The structure and function of the α4β2 receptors are not well understood. However, the beta subunit has been found to be essential to the receptor protein and induced dopamine release is not carried out if it is absent (Arias et al. 1960**)**. This drug is a partial agonist and minimally activates the receptor to release a lesser amount of dopamine in the brain compared to when nicotine binds. The proposed mechanism is the conformational change of loop C in the protein that disrupts nAChr gating (Arias et al. 1960).

Nicotinic acetylcholine receptors are ligand-gated ion channels with three protein domains. There is an extracellular (EC), transmembrane (TM), and an intracellular (MA) domain (Liu et al. 2008). These domains are labeled and shown in figure 1. These domains consist of five subunits that make nAChR pentamers. The nicotinic acetylcholine receptor is a type of acetylcholine receptor named for nicotine acting as an agonist. Normally, two acetylcholine molecules are needed to bind to the two alpha subunits of the receptor. Once this happens, a conformational change is induced and the pore in the neuronal membrane opens allowing for positively charged ions to flow into the cell. This quickly depolarizes the membrane potential and allows for an action potential to occur and release neurotransmitters to other neurons (Goodsell 2005). The channels do not stay open for extended amounts of time because acetylcholine is naturally degraded by acetylcholinesterase (Goodsell 2005). Nicotine can increase the number of receptors being activated because it allosterically binds to the nAChRs.

While the mechanism for nAChR agonists is still unconfirmed, it is widely hypothesized that the C-loop of the receptor undergoes a conformational change when acetylcholine, nicotine, or an agonist binds. This movement is transferred down to M2 subunits in the middle of the transmembrane domain, which then allows the channel pore to open. When an agonist binds in the amino acid residue pocket that creates the ligand binding site, it causes a change in the C-loop that results in the binding site to be in a capped, closed position. This is the proposed mechanism for how nAChR agonists affect smoking cessation by continuing to release dopamine through the conformational change and allowing the channel to open, but it also blocks other ligands like nicotine from binding (Gay et al. 2007).

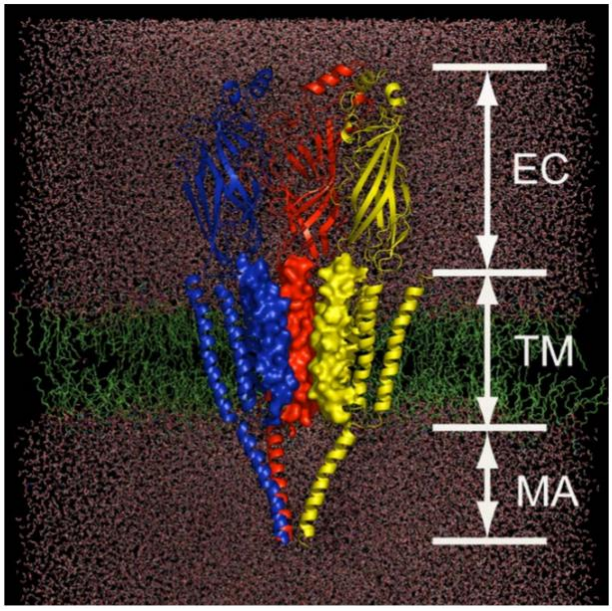

Figure 1. 3D protein model from Lie et al. 2008. This figure displays the three protein domains that make up the nicotinic acetylcholine receptor. These are an extracellular (EC), transmembrane (TM), and intracellular (MA) domain (Lui et al. 2008).

Varenicline mode of action and how it reduces smoking addiction

When an individual uses nicotine products, the neuronal membrane pores open, an action potential is generated, and dopamine is released in the brain. Dopamine is a neurotransmitter that has an important impact on the reward system of addiction behavior. Normally, there is a basal level of dopamine that is released to the nucleus accumbens and other nuclei in the striatum (Solinas et al. 2019). When the receptors are induced through the use of drugs like nicotine, cocaine, heroin, and alcohol, the dopamine level increase past the normal range. With constant use of these substances, the body must maintain homeostasis and the basal level is increased. Then, when these drugs are stopped, one gains withdrawal symptoms because the brain is now more hypersensitive to stress (Solinas et al. 2019). This may cause the user to begin the substance again because of negative reinforcement. They continue the addiction because they don't want to feel the bad side effects and the pain of the hypersensitivity.

Varenicline was approved in 2006 by the FDA, following other smoking cessation treatments since nicotine gum in 1984 (Fagerström et al. 2008). The morbidities that are associated with smoking products like cigarettes have motivated pharmaceutical companies to focus efforts on producing new treatments for smoking addiction. Smoking tobacco products can lead to respiratory, cardiovascular diseases and lung cancer. Depending on the patient's lifestyle and willingness, varenicline can be administered at a 12-week or 24-week treatment regime. Regardless, they are given a one-month starting pack that begins with 0.5 mg daily for three days, 0.5 mg twice daily for 4 days, and 1 mg twice daily for the rest of the month. The 12-week cessation then continues for 2 more months, and the 24-week cessation gets refills for 5 more months (Pfizer 2018). Figure 2 displays this information for the "fixed quit", "flexible quit", and "gradual quit" treatment plans.

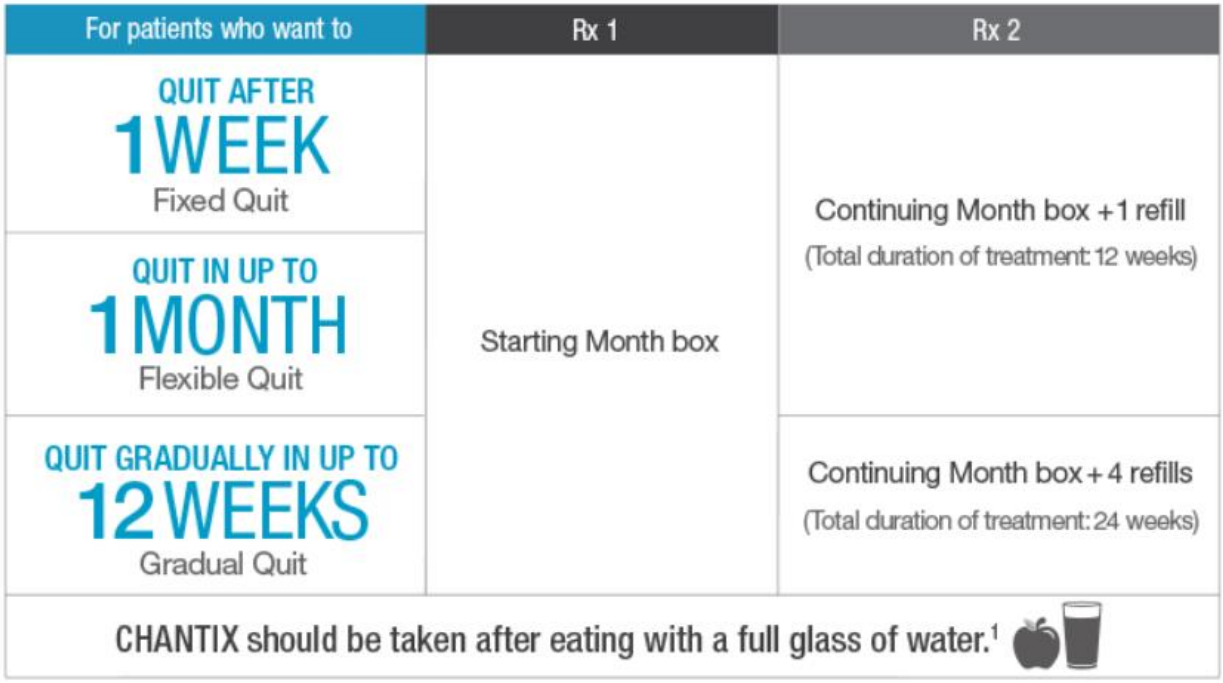

Figure 2. Pfizer treatment plan for 12-week and 24-week cessation regimes. Rx 1 refers to the starting pack that titrates from 0.5 mg daily for three days to twice daily for four days and then increased to 1 mg twice daily (Pfizer 2018).

With varenicline and NRTs as an option for smoking cessation, the rates have decreased, but there is still a high number that participate in this carcinogenic activity. The medication works to decrease nicotine craving and withdrawal by a dual action mechanism that releases dopamine in smaller amounts than with nicotine itself. The capping protein conformation that varenicline induces inhibits nicotine from binding to the receptors. This contributes towards smoking cessation because a patient who decides to smoke during the treatment process will not get the additional high from the consumed nicotine. This also alleviates withdrawal symptoms because the brain is not fully being cut off from the excess dopamine levels. This alleviates nicotine-induced dopamine release, but varenicline and NRTs still continue substance dependence (Fagerström et al. 2008). The agonist binds to the receptor and allows for a minimal

amount of the neurotransmitter dopamine to be released to the nucleus accumbens in the brain. The nucleus accumbens has been shown to be an important part of the reward circuit by acting as the "limbic-motor interface" when dopamine is released in this region (Nicola et al. 2005).

Varenicline (Chantix®) black box warning

In the first few years of varenicline being on the market and available for use, there were enough reports on it causing neurological side effects, and this resulted in the medication gaining a black box warning label. From a patient's perspective, these side effects may come out of nowhere and cause them severe harm. Derek de Koff, a writer for *New York Magazine*, narrates his experience using varenicline for smoking cessation. He states that on the patient information sheet, the most common symptoms of nausea, constipation, gas, and dream changes were clearly displayed in a bolded font (de Koff 2008). He gives a detailed explanation of his nightmares and mental processing weeks into treatment. We read his story knowing that he was well aware of the possible neurological changes he might have, but many patients may not know about the warning and aren't able to control or stop fatal outcomes. The suicidal thoughts that are warnings from varenicline use are displayed with his case (de Koff 2008). However, recent studies have contradicted these earlier symptoms of varenicline. More studies have been conducted to test for the neurological changes in patients with a placebo drug, bupropion, and varenicline showing that nausea may be the only real side effect (Gibbons et al. 2013).

Varenicline research had begun to test the symptoms that had given it its black box warning. Many showed that drugs like varenicline and bupropion did not increase psychiatric events (Gibbons et al. 2013). The side effects that were found to be present for varenicline was nausea and insomnia for bupropion (Brown University 2016). In 2016, a study was conducted to test the mental effects that had been proposed to be caused by varenicline use. This was the first

large-scale study done, and they tested subjects with and without a history of previous psychiatric events. They also compared this with bupropion, another smoking cessation drug, and found that it did not increase suicidal ideation in stable patients. The psychiatric patients were primarily diagnosed with mood disorders and 34% had previous suicidal ideation (Brown University 2016). They concluded that negative psychological effects were not substantial in the non-psychiatric group and that the black label warning should be reevaluated (Brown University 2016). This same year (2016) the FDA removed the black box warning for both varenicline and bupropion based on a wide review of these clinical trial studies (FDA 2016).

Nicotine replacement therapy (NRTs) as a treatment for cessation

NRTs have proven to be successful in smoking cessation and decreased numbers of relapse events. However, they still contain small amounts of nicotine and dopamine is still being released. This results in a continued dependence of substance use for preventing withdrawal symptoms. In 2015, a Danish data analysis was conducted with 112 participants answering a questionnaire on NRT use. The majority were former smokers using the therapy, and they had reported that they wished they could stop the NRTs. The reasons behind this were the cost of the medication and possible health outcomes from it. According to GoodRx, the price of Nicorette, nicotine gum, at the common retail pharmacies vary around 50 dollars, and Nicoderm, nicotine patch, can be priced around 100 dollars (GoodRx). The authors concluded that there is a need for more long-term studies and that nicotine dependence is still an issue with the nicotine replacement therapy drugs (Borup et al. 2015).

Increased use of electronic smoking devices and nicotine-dependence

Today, there has been an increase in the use of electronic smoking devices and vaporizers. Many people are making the switch to e-cigarettes that promote the absence of

smoke and harmful additives. Products like the e-cigarette JUUL® and other popular devices have even become a recent trend for the younger population. Most of these products are nicotine-based. While nAChR agonists are providing a type of non-nicotine dependence, these devices bring the population back to nicotine-dependence without the additive carcinogenic chemicals. In a recent longitudinal study conducted on young adults for conventional smoking vs. e-cigarettes, it was concluded that e-cigarette smoking did not lead to conventional smoking later on, but conventional smokers often went to e-cigarettes for smoking reduction. However, many adults had also stated that they were smoking through both methods. It was shown that conventional smoking and nicotine dependence had led the participants to e-cigarettes to try and reduce the harmful effect, while still maintaining the nicotine addiction (Selya et al. 2018).

That use of nicotine has commonly been seen as not harmful to the dependent individual. It is well known that there are carcinogenic additives in tobacco products along with nicotine that contribute to the onset of diseases and lung cancer. These additives include tobacco-specific N-nitrosamines (TSNA) (Sanner and Grimsrud 2015). However, there are two studies that reveal the concern for nicotine on its own. NNK is one of the carcinogens that is formed with the use of tobacco, and NNAL is a metabolite from this molecule. These substances are mainly metabolized in the liver before they are excreted through the renal system. NNAL has been found in a small amount within the urine of electronic smoking device users (Sanner and Grimsrud 2015). These electronic devices are advertised to be better for health because they do not contain the additives that would form NNK, but NNAL is still being seen in excretion. This poses the question of how patients are being affected by only nicotine. In Sanner and Grimsrud's study, they show that nicotine induces cell proliferation and tumor growth, as well as DNA strand breaks through oxidative stress in rodents *in vitro* (Sanner and Grimsrud 2015). It will be

useful to continue this type of research, and eventually testing if nicotine results in proliferation and strand breaks in humans using NRTs and electronic devices.

Along with the possible cancer risk, the cardiovascular system is still changed by the binding of nicotine to nAChRs. The stimulation results in an increase in pulse, blood pressure, and inspiration. Blood flow in the coronary arteries is decreased as the skeletal muscle flow increases. This can cause the onset of coronary artery disease due to damage caused by lack of blood flow and oxygen on the heart (Mishra et al. 2015). The authors in this study also review the risk of cell proliferation and cancer in various organ systems with the use of nicotine. An interesting point that they discuss is the use of nicotine as a cheap pesticide beginning in the 17th century. As a natural product of tobacco plants, nicotine is toxic and useful in defending against pests, but humans decided to also use it in smoking. The use of this molecule as a pesticide has been banned, which lead these authors to look further into the effects of nicotine (Mishra et al. 2015).

Conclusion

Varenicline is a commonly advertised smoking cessation drug that can be used with tobacco products for the first several weeks (Pfizer 2018). It has shown to be effective, along with many other cessation drugs like NRTs. Electronic devices that ideally help with the addictive behavior to help quit tobacco products like JUUL® have been up and coming in today's population as a trend (Selya et al. 2018). While some drugs and devices are seen as safe to the public for only containing nicotine and not the carcinogenic additives, they still feed nicotine to the receptors for an above average increase in dopamine levels in the brain and contribute to the continuation of nicotine dependence (Solinas et al. 2019). Nicotine is still extremely addictive, and it alters the basal dopamine level in the brain to increase

hypersensitivity to stress regardless of the other additive carcinogens in tobacco products (Solinas et al. 2019). Dependence on a substance that causes unfavorable symptoms during withdrawal that interrupts the daily lives of the individual should be considered harmful to the population. Separate from the painful withdrawals, there is also the concern that nicotine can lead to cancers by inducing cell proliferation in rodents (Sanner and Grimsrud 2015). It has been suggested that nicotine use be highly supervised by a medical professional due to the list of harmful effects it can have on many organ systems including the cardiovascular system (Mishra et al. 2015). Further investigation into the effects of nicotine on humans and may help bring these issues to the minds of the public and push pharmaceutical companies to invest research on alternative cessation methods.

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