

REVIEW ARTICLE

VARENICLINE - A NEW PHARMACOTHERAPY FOR SMOKING CESSATION: IMPLICATION FOR SMOKERS WITH MENTAL HEALTH PROBLEMS

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Abstract

Objective: The smoking rate among patients with mental health problem is higher than in the general population. Effective pharmacotherapy to treat nicotine addiction is thus needed to reduce the morbidity and mortality associated with cigarette smoking among these patients. This article reviews the literature on the suitability of varenicline for smokers with mental health problems. **Methods:** A search of the literature was conducted using PubMed from year 2001 to July 2009 using key words varenicline alone and varenicline and mental health. Articles chosen were narrowed to those published in English. The type of articles chosen included clinical trials, meta-analyses, case reports, and review articles. **Results:** The search produced a total of 322 articles on varenicline and 14 articles on varenicline and mental health. Varenicline, a new drug for smoking cessation is an $\alpha 4\beta 2$ partial agonist and partial antagonist at nicotinic acetylcholine receptor. As a partial agonist, varenicline relieves craving and withdrawal symptoms that occur during smoking abstinence and also reduce the rewarding effects of smoking in patients who relapse. However, at present, there is concern regarding the neuropsychiatric side effects such as aggressive behaviour, suicidal ideation, mania and depression associated with varenicline use in patients with mental health problems, but these reports did not show a causal-link or lack of link between these symptoms and varenicline. **Conclusion:** Current available data support the effectiveness of varenicline to treat nicotine dependence. However its safety among smokers with mental health problems remains to be elucidated. At present, further safety assessment is needed in this patient population. Until new data is available regarding the safety of varenicline in these populations, psychiatrists and physicians

prescribing this medication should be extra cautious and monitor for possible psychiatric side effects when prescribing this medication to patients with pre-existing psychiatric disorders or have vulnerability to psychoses. ASEAN Journal of Psychiatry, Vol. 10(2): July- Dec 2009: XX XX

Keywords: Varenicline, $\alpha 4\beta 2$ partial agonist, mental health, smoking, cessation

Introduction

Cigarette smoking is the single most preventable cause of death in the world. Smoking is responsible for cardiovascular and respiratory diseases, cerebrovascular diseases and cancer. It is well known that the smoking prevalence among mental health patients is higher than the general population. For instance, smoking rate among schizophrenia patients is reported to be between two to four times higher than the general population. Smokers with schizophrenia also smoke more cigarettes per day and smoke stronger brands than other smokers [1].

Many smokers with schizophrenia report that smoking helps to reduce their symptoms [2]. This has been confirmed by studies showing that smoking is related to a reduction in the negative symptoms of schizophrenia, such as lack of motivation and social withdrawal. Smokers with schizophrenia also report that smoking increases their alertness, enhance concentration, thinking and learning. This is beneficial to schizophrenics whose illness or medication leads to cognitive problems. Patients with mental problems also report that smoking help them relax and reduce negative feelings such as anxiety, tension and anger, thus helping them deal with stressful situations [1]. It is

thought that these effects are caused by nicotine's ability to raise dopamine levels in areas of the brain involved in attention and engaging with one's surroundings [2]. Patients with mental health problems also report that smoking help to relieve boredom and improve social interaction, something which is of benefit in those with negative symptoms.

Given the negative effects of smoking on health, including greatly increased risk of heart disease and cancer, there is thus an urgent need for effective pharmacotherapy to treat smokers with mental health problems.

Why quit?

The benefits of stopping smoking had been well demonstrated. Smoking cessation provides both short-term and long-term health benefits and has been shown to reduce both morbidity and mortality related to nicotine addiction [3]. Stopping smoking improves health outcomes and could reverse disease progression. At 3 months of cessation, lung function may start to improve with decrease cough, sinus congestion, fatigue and shortness of breath [4]. At 1 year, risk of coronary heart disease is reduced by 50% among ex-smokers and by 5 years the risk of stroke returns to the level of people who have never smoked. By 10 years, the risk of lung

cancer reduces to 30-50% of those who continue to smoke and by 15 years cardiovascular heart disease becomes similar to never smokers [3-5].

Smoking cessation at any age also increases life expectancy [4]. It has been reported that stopping smoking at 50 years old reduces the risk of death from smoking related causes by half. The effect is better if quitting at an early age, where stopping smoking at age 30 had been shown to avoid smoking related mortality. It was also shown that the benefits of stopping smoking was observed regardless of age when stopping smoking, but stopping sooner appeared to be the most beneficial. In general in those who continue to smoke, smoking reduces survival an average of 10 years [6].

Methods

A search of the literature was conducted using PubMed from year 2001 to July 2009 using key words varenicline alone and varenicline and mental health.

Results

The search produced a total of 322 articles on varenicline and 14 articles on varenicline and mental health. Articles chosen were narrowed to those published in English and limited to studies done on human subjects. Case reports, meta-analyses, review articles and clinical trials evaluating the safety, efficacy and adverse effects of varenicline were included [7-25].

Discussion

Varenicline

It is difficult to stop smoking and this is due to the highly addictive nature of nicotine. Nicotine is responsible for the physical and psychological rewards of smoking reinforcement. After inhalation, nicotine from cigarettes reach the brain in less than 10 seconds and binds predominantly to the $\alpha 4\beta 2$ subtype of the nicotinic receptor in the brain. Recent evidence supports the role of $\alpha 4\beta 2$ nicotinic acetylcholine receptor in the reinforcing effects of nicotine use [18]. Varenicline is a $\alpha 4\beta 2$ partial agonist, a compound with dual agonist and antagonist activities. This is believed to result in lesser amount of dopamine release from the ventral tegmental area at the nucleus accumbens (32-45%) as well as the prevention of nicotine binding at the $\alpha 4\beta 2$ receptors, thus preventing a pharmacologic reward during relapse. When used as part of a programme that includes advice from a healthcare professional, varenicline has been shown to relieve nicotine craving and withdrawal symptoms while reducing the reinforcing effects of nicotine [8]. Varenicline is indicated as an option for smokers who have expressed a desire to stop smoking, and should be prescribed only as part of a programme of behavioural support. It is also emphasized that smoking cessation treatments were more successful in patients who were provided with additional advice and support.

The efficacy of varenicline in treating tobacco dependence is believed to result from partial agonist activity at the $\alpha 4\beta 2$ nicotinic receptor. By preventing binding of nicotine, varenicline reduces craving and withdrawal symptoms (agonist activity) and produces a reduction of the rewarding and reinforcing effects of smoking (antagonist activity) by preventing nicotine binding to $\alpha 4\beta 2$ receptors. A study on both male and female smokers in an outpatient setting reported that 44% of smokers treated with varenicline were abstinent at 12 weeks compared to placebo (17.7%) [19].

The most common adverse event associated with varenicline treatment was nausea but this was described as mild or moderate and was generally at the start of therapy and decreased over time. Other reported adverse events were abnormal dreams, insomnia and headache. Rare side effects reported were change in taste, vomiting, abdominal pain, flatulence and constipation. However, the reported discontinuation of treatment from varenicline was 7-14% [19].

Suitability for use in patients with mental health problems

The efficacy and safety of varenicline in Asian smokers has been established in randomised double-blind, placebo controlled trials among smokers in Taiwan, Japan, Korea, China, Thailand and Singapore [14-16]. However, the literature has reported contradictory reports regarding the safety and efficacy of varenicline in psychiatric patients [8, 20-25]. Some reports regarding varenicline have been favourable. A recent study found varenicline to be safe

for patients with mental health problems and was superior in maintaining smoking abstinence. The study was a non-randomised study of 412 smokers in a community clinic which included 111 patients with mental health problems [the primary diagnosis were depression (64), bipolar disorder (14), psychosis (7), psychosis and depression (24) and bipolar disorder (2)]. However the small sample size and varying psychiatric diagnosis precluded any firm conclusion [8]. A preliminary investigation also demonstrated that varenicline significantly reduced alcohol self-administration and was well tolerated, either varenicline alone and in combination with alcohol in heavy-drinking smokers and suggested that varenicline should be investigated as a potential treatment for alcohol use disorders [23]. However the literature has also reported several cases including suicidal ideation and occasional suicidal behaviour, erratic behaviour and drowsiness [24]. There was also a single case of an activated psychotic relapse in a schizophrenic patient receiving varenicline [20]. Another report described a hypomania with agitation episode associated with varenicline use in bipolar II disorder and another case report described an induction of a manic episode in a bipolar patient [25]. Another published case was regarding a person who shot his neighbour after being a state of delirium caused by taking varenicline with a high dose of alcohol. It was also unclear whether the episode was related to the drug or a state of alcohol intoxication. Other post-marketing reports included agitation and depression [26]. As for inpatient setting, a recent article reported worsening of psychosis and agitation in a patient who was treated for nicotine cravings, but

returned of mental status to baseline upon discontinuation of varenicline [24]. Most recently, acute hepatic injury with raised liver enzymes were reported in an alcoholic patient. The enzyme alkaline phosphatase level was reported to reduce to normal within one month of discontinuation of varenicline and the enzyme aminotransferase level was shown to reduce to normal after four months of discontinuation of the drug. In all the cases reported above, a causal connection or lack of connection between varenicline and these symptoms were not established [24]. However, varenicline is reported to cause dysregulation of the dopaminergic system, and this may lead to exacerbation of psychotic symptoms in patients with psychotic disease. Varenicline has also been linked to neuronal $\alpha 7$ nAChR1, which is linked to major psychiatric disorders [20, 25].

At present, whether the neuropsychiatric symptoms reported is causal, coincidental or a result of varenicline remains to be elucidated [17]. In all the examples stated in the paragraph above, it was not clear whether the psychiatric symptoms were related to the drug or nicotine withdrawal symptoms. As a result of these reports, the US FDA has now issued an order for the manufacturer of this drug to highlight these effects on the product box [25].

On the other hand, the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition- Text Revision* acknowledged that some of the psychological symptoms from nicotine withdrawal include dysphoric and depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty concentrating and restlessness. Thus, when prescribing

varenicline to mental health patients, it is prudent to consider the beneficial effect of varenicline in achieving and maintaining abstinence in millions of smokers compared to the reported adverse events.

Prior to starting varenicline, it is thus important to enquire regarding mental illness in smokers. Until new data pertaining to the safety of varenicline in mental health patients become available, based on current information and knowledge from the literature, it is recommended that: (1) Patients with mental problems should be given advice and alerted to the risk of varenicline on their existing illness. Extra caution is needed in patients with psychiatric illness such as schizophrenia, bipolar disorder and major depressive illness who may experience worsening of their pre-existing illness when prescribed varenicline. For smokers with mental health problems who have been prescribed varenicline, advice should be given to their families and carers to be alert to changes in mood and behaviour. If such changes do occur, it is important to seek immediate medical assistance. (2) Alternative pharmacotherapy should be considered for smokers with mental health problems who wish to stop smoking as thus far there is insufficient data to certify the safety of varenicline for smokers with mental health problems. However, psychiatrists and health personnel who do decide to prescribe varenicline should monitor their patients for serious neuropsychiatric symptoms such as changes in behaviour, agitation, depressed mood, suicidal ideas and suicidal behaviour. If in doubt, another smoking cessation pharmacotherapy should be considered. (5) Patients with serious mental health problems should

be offered other type of pharmacological treatment, e.g. nicotine replacement therapy.

Conclusion

The prevalence of smoking among mental health patients is higher than the general population. Cigarette smoking on the other hand is an important cause of morbidity and mortality. Thus, effective smoking cessation treatment is needed to curb these health problems among mental health patients. Varenicline is a new class of drug for smoking cessation. It is a selective partial nicotinic receptor agonist which reduce craving and blocks the reward from smoking and offers a new pharmacotherapy option for smoking cessation. Thus far, more information is needed regarding the safety of varenicline in smokers with mental health problems. Hence caution is needed when prescribing varenicline to patients known to have mental health problems. Further research is needed to establish the safety profile of varenicline in these patients.

Declaration of interest:

The authors have taken part in seminars and conferences pertaining to pharmacotherapy for smoking cessation, and have received funding to attend conference from Pfizer (M) Sdn Bhd.

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