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REVIEW ARTICLE

Why are Antidepressant Drugs Effective Smoking Cessation Aids?

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Abstract: ***Background*:** Before the advent of varenicline, antidepressant drugs were reported to exhibit better clinical efficacy than nicotine replacement therapy as smoking cessation aids. The most studied is bupropion, a clinically-effective antidepressant, the first to be marketed throughout Europe for smoking cessation. Since depression and tobacco smoking have a high incidence of co-occurrence, this would implicate an underlying link between these two conditions. If this correlation can be confirmed, then by treating one condition the related state would also be treated.

***Objectives*:** This review article will evaluate the various theories relating to the use of antidepressant drugs as smoking cessation aids and the underlying mechanisms link tobacco smoking and depression to explain the action of antidepressants in smoking cessation. One plausible theory of self-medication which proposes that people take nicotine to treat their own depressive symptoms and the affective withdrawal symptoms seen with abstinence from the drug. If the depression can instead be treated with antidepressants, then they may stop smoking altogether. Another theory is that the neurobiological pathways underlying smoking and depression may be similar. By targeting the pathways of depression in the brain, antidepressants would also treat the pathways affected by smoking and ease nicotine cravings and withdrawal. The role of genetic variation predisposing an individual to depression and initiation of tobacco smoking has also been discussed as a potential link between the two conditions. Such variation could either occur within the neurobiological pathways involved in both disorders or it could lead to an individual being depressed and self-medicating with nicotine.

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1. INTRODUCTION

1.1. Health Impact

Addiction to tobacco smoking is the most prevalent preventable cause of disease, morbidity and mortality across the world. The National Statistics Department reported that 25% of adults aged 16 and above in the UK were smokers in 2004. Smoking is the main cause of around 90% of lung cancer cases as well as a wide range of heart and respiratory diseases. It has been estimated that between 1998 and 2002, an average of 106,000 people a year died from smoking-related causes in the UK alone [1].

With up to 4000 chemical compounds in tobacco, nicotine is recognised as the addictive ingredient which leads to cigarette smoking becoming a habit [2]. Typically, nicotine-dependence is often characterised by smoking around 15 cigarettes a day. Heavy smokers can incur nicotine plasma concentrations of 23-35mg/ml [3]. Nicotine is a lipophilic alkaloid and can cross the blood-brain barrier where it appears to bind to nicotinic acetylcholine receptors (nAChR) in the brain. Of the multiple subtypes of nicotinic receptors found throughout the brain, specific subtypes of nAChRs have been shown to regulate the release of dopamine, noradrenaline and serotonin [4].

With so many negative aspects of tobacco smoking, particularly on health, it becomes clear why cessation is highly desirable. Ideally the mode of action would be the prevention of smoking initiation. Education and awareness schemes are already in place. For current smokers, a combination of behavioural interventions, like group counselling, and pharmacological treatments, such as nicotine-replacement and non-nicotine therapies, have been suggested to deliver the best abstinence results [5]. However, in order to make a greater impact on public health, health professionals need to develop more smoking cessation treatments that is more widely available at a lower cost to the smoker [6].

2. MECHANISM OF DISORDER: ACUTE EXPOSURE

It is well accepted that the DA-releasing properties of nicotine in the nucleus accumbens has been shown to underlie its primary reinforcing effects that are qualitatively similar to other strongly reinforcing drugs such as cocaine, am-

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phetamine and morphine [7, 8]. It is believed that nicotine's ability to activate the mesolimbic dopamine pathway in the brain *via* heteromeric nicotinic acetylcholine receptors (nAChRs) which are made up of different subunits (α2-α10 and β2-β4) is the primary determinant behind its dependence-producing effects in laboratory animals and humans [9]. Nicotinic receptor activation results in burst firing of the main dopamine (DA) pathway originating from the ventral tegmental area to the nucleus accumbens. Self-administration of nicotine by rodents has been shown to increase dopamine levels in the nucleus accumbens shell compared to that of the core [10]. This pathway has several other inputs notably from the limbic system which include projections from the amygdala, hippocampus, hypothalamus, striatum, orbitofrontal cortex and the prefrontal cortex. Naturally, an obvious method to suppress nicotine taking behaviour would be to supplement the nicotine in tobacco for less harmful alternatives, by way of nicotine replacement therapy (NRT) or utilising nicotinic receptor antagonists. After numerous studies, having been conducted to determine the efficacy of these methods, it has been revealed that nicotine replacement therapy has varied abilities to prevent nicotine taking behaviour in human clinical trials, apart from the currently used nicotinic acetylcholine partial antagonist, varenicline [10, 11].

3. MECHANISM OF DISORDER: CHRONIC EXPOSURE

Upon long exposure of nicotine to the brain, neuronal adaptations develop which is believed to be associated with learning of environmental cues linked with receiving the drug. Environmental smoking cues can be visual, olfactory or auditory stimuli which cause nicotine cravings in smokers. Behavioural cues can be seeing another person smoking or missing the physical action of smoking a cigarette. Findings from one paper concluded that environmental cues can be classically habituated to smoking [12]. These smoking related cues can elicit nicotine cravings, increase cardiac responses in smokers and based on the expectance of receiving the drug, the dopamine reward pathway is activated. Such reactivity to smoking cues could explain maintenance of the smoking habit and an increased likelihood of relapse when attempting to quit. Shahan *et al*. (1999) compared the effects of de-nicotinised and nicotine-containing cigarettes. The study was performed using a progressive ratio schedule of reinforcement amongst eight subjects. They found that the de-nicotinised cigarettes provided only the smoking-related stimuli and yet still produced similar reinforcing effects as normal cigarettes. However, when given the choice, many of the subjects preferred the nicotine-containing cigarettes. The sensory stimuli provided by the de-nicotinised cigarettes may function as a conditioned reinforcer and in addition to nicotine this augments the relative reinforcing effects of cigarettes [13]. A randomised controlled trial of nicotine cravings in 132 smokers concluded that smoking stimuli only increased cravings in smokers who knew they would soon be receiving nicotine [14]. These behavioural cues therefore highlight the difficulties confronted in treating nicotine dependence, as the adaptations take place in other neurological pathways and neurotransmitter systems.

4. BRAIN REGIONS ASSOCIATED WITH NICOTINE ADDICTION

With specific regards to nicotine addiction, the dopamine reward pathway is coupled with activity from numerous brain regions which are believed to contribute to nicotine dependence [15]. One such area is the anterior cingulate. This area of the brain is associated with emotional self-control and cognition *via* its role in the default mode network [16, 17]. Neuroimaging studies have identified that a clearly separate pathway correlates with the severity of nicotine addiction from the dorsal anterior cingulate cortex (dACC)-striatal circuits [18]. This may be involved in the risky decision-making tasks observed in nicotine addicts that allow them to be initially exposed to the drug to start down the path of becoming dependent, long-term [19].

In addition, ACC activity can be modulated by higher cortical processes and thus is involved in emotional processing [20, 21]. Emotional states are in direct control of the amygdala, which is involved in the process of memory consolidation for arousing events by assigning reward values to pleasurable stimuli and, in association with the bed nucleus of the stria terminalis, fear conditioning to novel stimuli [22, 23]. Smoking is strongly related with blunted amygdala responses to the harmful effects of tobacco smoking [24].

Other brain areas affected by nicotine administration are those involving cognition. nAChRs are heavily populated in all layers of the dorsal lateral prefrontal cortex (DLPFC) and α7 subtype receptors mainly being expressed in the hippocampus. These brain regions are therefore under continuous modulation by nicotine. Upon long-term exposure to nicotine *in vivo*, there is an upregulation of nAChR either by α4β2 activation or, as proposed by other groups, desensitisation of these receptors [25, 26]. This may be a possible mechanism of how cortical areas influence nicotine-induced excitation of the VTA dopaminergic neurones, and thus modulate the reward pathway [27]. However, studies indicate that cessation of nicotine intake after chronic smoking is associated with disturbances in working memory and attention as well as reduced PFC activation [28].

Another frontal region of the brain shown to be affected by nicotine includes the orbitofrontal cortex. The medial region of the OFC relates to the hippocampus and cingulate and is involved in assessing the familiarity of a situation and in the integration of outcome expectations. The lateral section, however, connects with the amygdala and insula, and is associated with the suppression of previously rewarded responses and is required to change behaviour in the form of "stop signals". Environmental stimuli associated with nicotine intake have been shown to enhance medial OFC activity, whereas, nicotine is also associated with reduced sensitivity of the lateral OFC [29, 30]. The consequence of which is an increase in tobacco craving [31].

Additionally, studies have indicated that, in the N. Acc. and caudate-putamen, there is an increased and prolonged expression of ΔfosB, which is associated with synaptic alterations and modulation [32]. The mRNA of this gene has been shown to be very stable and persists in these brain regions, especially upon chronic nicotine administration [33].

This therefore acts as a sustained "switch" that converts acute drug responses to stable adaptations that contribute to long-term neuronal and behavioural plasticity that underlies addiction [34].

5. COMORBIDITY OF PSYCHIATRIC DISORDERS AND ADDICTION

Epidemiological studies have indicated that the occurrence of nicotine dependence is significantly higher in those with certain psychiatric illnesses [35]. This may be another reason why there has been much difficulty in relation to identification of successful treatments for nicotine dependence, given the comorbidity with other psychiatric conditions such as ADHD, depression, schizophrenia, anorexia nervosa and anxiety disorders. Studies regarding eating disorders have gathered substantial evidence suggesting that substance abuse can be found to occur in up to 49% of people with eating disorders and eating disorders occur in up to 32% of substance use cases [36-38] In addition, schizophrenic patients (60-90%) are chronic tobacco smokers [39-41]. With regards to depression specifically, studies have shown that the occurrence of depression is higher in those that exhibit chronic smoking behaviour compared to non-smokers. Moreover, during cessation of tobacco smoking, amongst the numerous withdrawal symptoms, are alterations to mood which mimic and, in some cases, even cause those seen in affective disorders [42, 43]. Interestingly, during early clinical trials, antidepressants have been used to investigate if there is any impact on tobacco smoking behaviour, effects on withdrawal or relapse rates.

6. BRAIN REGIONS CHANGED IN PSYCHIATRIC DISORDERS

Confluently, the brain regions that are related to substance abuse behaviour with nicotine are also implicated in numerous psychiatric disorders. Reduced activity in the anterior cingulate is seen in disorders that show high levels of impulsivity, such as ADHD and bipolar depression. Increased sensitivity and reduced volume of the amygdala is also seen in anxiety disorders and uni- and bi-polar depression [44, 45]. The hippocampus and OFC show the greatest level of variability in psychiatric disorders, however, specifically with depression, there is strongly evidence of an over activation in "stop signals" from the lateral OFC, under activation of medial OFC, as well as reduction in DLPFC activity [46].

With the correlation between diseases, and the lack of efficacious cessation aids for smoking, it has been suggested treating the affective symptoms of withdrawal may be a successful method for therapy. Pharmacological treatments have been introduced to reduce nicotine craving and withdrawal by altering neurotransmitter levels in the brain vis-à-vis modifying mood.

7. DRUG TRIALS WITH ANTIDEPRESSANTS FOR SMOKING CESSATION

The atypical antidepressant, bupropion hydrochloride, in 1997 by Hurt and colleagues, was reported to have successful efficacy by way of smoking cessation in a randomised, double-blinded, placebo-controlled trial. Subsequent to these findings, other studies have corroborated these results [47, 48]. These measures included smoking abstinence, body weight, symptoms of depression and withdrawal, including craving, anxiety, altered sleeping pattern, increased appetite and irritability.

Doses of 100mg, 150mg and 300mg of bupropion a day were taken for one week before the quit date and for seven weeks after it. After one year, the cessation rate for the 150mg group was 22.9% and the rate for the 300mg group was 23.1%. These were both significantly better than the cessation rate of 12.4% in the placebo group. The group concluded that cessation rates with bupropion appear to be dose-dependent and show continued benefit with the drug for up to a year. The trial identified the doses of 100mg and 300mg to have significantly higher number of abstinent smokers compared to placebo for the first 3 months. After longer periods, the 300mg dose group appeared to have greater success than the lower dose. Interestingly, the study did not find any significant reduction in withdrawal symptom scores in the first week of abstinence, although, in analysis following mean weekly withdrawal score, the treatment groups did show significant reductions. The 100mg treatment group had higher withdrawal scores than the placebo group. The authors proposed the possibility that this daily dose of bupropion could have induced side effects similar to withdrawal symptoms but was insufficient to reduce true withdrawal effects.

Another study by Jorenby *et al*. (1999) compared the cessation rates of bupropion with the efficacy of a nicotine patch. They found the abstinence rates at 12 months were 15.6% in the placebo group, 16.4% in the nicotine-patch group, 30.3% in the bupropion group and 35.5% in the group given bupropion and the nicotine patch. Treatment with sustained-release bupropion alone or in combination with a nicotine patch resulted in significantly higher long-term rates of smoking cessation than use of either the nicotine patch alone or placebo. Abstinence rates were higher with combination therapy than with bupropion alone, but the difference was not statistically significant [49].

Chengappa *et al*. (2001) studied 25 smokers with Major Depressive Disorder (MDD). Nine weeks after treatment with bupropion, 8 of the subjects remained abstinent. The group concluded that people attempting to quit smoking exhibited depressive symptoms and so the antidepressant effects of the drug were essential [50]. Studies have reported that bupropion users had less abstinence-associated depression and fewer depressive symptoms such as irritability and difficulty concentrating [51]. However, smokers who receive bupropion are also more likely to experience a rebound in depressive symptoms when bupropion is discontinued. A randomised controlled trial studied the effects of bupropion on nicotine cravings and withdrawal in 91 abstinent smokers [52]. After 14 days of treatment, those subjects given a higher dose of 300mg of bupropion per day showed significantly less depression, difficulty concentrating, irritability and appeared to have improved performance. The group concluded that although bupropion reduced some nicotine withdrawal symptoms, it did not alleviate cravings, anxiety, restlessness or hunger.

Despite some clinical trials showing no efficacy of bupropion [53, 54], it summarily became the one of the first drugs approved as a smoking cessation agent and currently still holds the position of first-line therapy. It is regarded as the prototypic smoking cessation antidepressant and has set the standard to which other antidepressants are now compared. There have been many clinical efficacy trials involving bupropion and several review articles have been written discussing whether it is effective than conventional cessation aids like nicotine replacement therapies (NRT). A group led by Hughes produced an important review of antidepressants as cessation aids. This paper meta-analysed the results from 19 long-term clinical studies of bupropion alone and concluded a pooled Odds Ratio of 2.06 with a 95% Confidence Interval of 1.77-2.40 [55, 56].

Pre-clinical data supported the clinical observations in which rats treated with bupropion showed a 40-50% reduction in nicotine self-administration and, although this was not statistically significant, they concluded that relatively high doses of bupropion could decrease the reinforcing effects of nicotine on a fixed ratio schedule [57]. The same paper also deduced that a progressive ratio represented the reinforcing properties of smoking and the motivation to obtain nicotine and surprisingly was not affected by bupropion pre-treatment.

Using a discrete-trial intracranial self-stimulation (ICSS) method in rats, Cryan *et al*. (2003a) could measure the current intensity changes during treatment with bupropion. These measurements illustrated a dose-dependent decrease in reward thresholds with bupropion, making it easier for the rats to obtain feelings of reward and reverse nicotine withdrawal symptoms [58]. The study concluded that bupropion was acting on multiple levels to elicit these unique anti-smoking properties.

Derived from *in vitro* and *in vivo* studies, bupropion is thought to act by inhibiting the reuptake of dopamine through the dopamine reuptake transporter (DAT) and thus increasing the extracellular levels of dopamine, thus alleviating the affective symptoms of depression [59-62]. With regards to nicotine dependence, this effect is believed to produce a nicotine-like effect which is capable of attenuating certain withdrawal states, as shown in rats [63, 64]. However, studies have shown that bupropion does not increase extracellular dopamine in the human striatum and produces less than 22% striatal DAT occupancy, *via* positron emission tomography (PET) [65-67]. This suggests that the mode of action underlying the therapeutic efficacy, in both depression and nicotine dependence, may involve other systems other than dopamine reuptake transporters.

Growing evidence has shown that bupropion can act as a nAChR antagonist which would counter the effects of nicotine [68, 64]. There are several theories for the mechanism of action underlying the clinical success of bupropion. One pre-clinical study showed no effect of the drug on mesolimbic dopamine pathways in rats and suggested that bupropion only increased noradrenaline release and extracellular levels which indirectly increased serotonin firing rates [69]. Another pre-clinical report concluded that bupropion blocks nAChRs non-competitively, α4β2 and α3β4 subtypes, and this in turn reduces the psychoactive and addictive effects of nicotine and thus facilitating people to quit smoking [68].

A study by Wilkinson *et al*. (2010), investigated if bupropion acted as an interceptive substitute for the effects of nicotine. Their findings showed that pre-treatment did not have any effect on nicotine-conditioned responding at low doses, however, as 20mg/kg bupropion successfully attenuated this response. Further to this, the group also stated that the, 2S,3S-hydroxybupropion isomer, a major metabolite of bupropion in humans, showed no ability to substitute nicotine conditioned stimuli [70]. There is evidence to suggest, however, that pharmacokinetics of bupropion and its metabolites vary between species, with mice being more akin to humans [71, 72]. Counter to what was found in the rat studies, analysis by Damaj and colleagues (2010) showed that bupropion and, more so, 2S,3S-hydroxybupropion reversed affective and somatic withdrawal signs in nicotine-dependent mice. Further data suggests that this metabolite may be a better drug candidate for smoking cessation than bupropion itself because of its higher potency at the relevant nAChR targets [68, 73, 74] and was shown to attenuate nicotine self-administration in rats [75]. Pharmacokinetic species variations are important to consider upon future preclinical analysis. Greater recognition of these variations may increase translatability of potential pharmacotherapies into human studies.

Overall, the complex pharmacology of bupropion and its metabolites on DAT and nAChRs may hold the key with regards to its success as a smoking cessation agent. This has encouraged researchers to investigate further and develop new analogues of bupropion that may be effective as aids to smoking cessation [76].

8. TRICYCLIC ANTIDEPRESSANTS

8.1. Nortriptyline

After the success of bupropion, further investigations have been carried out on other types of antidepressants. The second generation tricyclic antidepressant, nortriptyline, is regarded as the most promising alternative to bupropion, with noradrenaline and serotonin transporters (NET and SERT) being their main inhibitory targets [56]. So far it has been seen in comparative trials with the nicotine patch and has been tested in patients with and without a history of depression. In a human study, the efficacy of nortriptyline at 75mg a day was tested against placebo. From the 68 smokers randomised to nortriptyline treatment, 20.6% remained abstinent after 6 months compared to only 5.3% of the 76 subjects in the placebo group. Nortriptyline was therefore shown to significantly increase the rates of cessation from smoking without any significant side effects [77].

Another randomised controlled trial of 214 patients studied the efficacy of nortriptyline compared to a placebo for smoking cessation [78]. The cessation rate at 6 months was 14% in the nortriptyline group and 3% in the placebo control group (P=0.003). The group concluded that nortriptyline led to an increased short-term cessation rate compared with pla-

cebo. In addition, there were significant, but relatively small, reductions in withdrawal symptoms including anxiety, tension, anger, irritability, difficulty concentrating, restlessness and impatience by day 8 after quit day. The same group performed another trial and observed six month cessation rates of 23% with nortriptyline and nicotine patch compared to only 10% with the nicotine patch [79]. In this trial, nortriptyline did not have any significant effect on nicotine withdrawal symptoms and caused frequent side effects such as dry mouth and sedation. However, it was highly criticised by the scientists themselves as results for the patch were inconsistent with other studies and most of the subjects tested were already trying to quit. They concluded that such therapy would offer an alternative option for smokers who had failed to quit using other techniques.

Hall *et al*. (2004) compared nortriptyline and cognitive-behaviour therapy as treatments for smoking cessation in individuals with and without a history of depression. They recommended nortriptyline as "a promising adjunct for smoking cessation" and concluded that whilst nortriptyline gave better abstinence rates than the placebo and alleviated withdrawal symptoms, depressed patients needed more intense therapy to prevent a relapse [81, 82]. In a later trial, the same group found that extended treatments and a combination of nortriptyline and psychological interventions produced consistent abstinence rates in the long term (Fig. **2**). At one year follow-up the group reported 50% cessation with extended nortriptyline and 42% cessation with extended placebo, this was compared to brief treatment cessation rates of 18% and 30% respectively [81]. Reduced anticholinergic side effects were seen upon administration of 10-OH-nortriptyline, a main active metabolite of nortriptyline, which has stronger NET inhibition as well [83].

Nortriptyline is thought to produce its effects *via* noradrenergic and dopaminergic mechanisms independently of its antidepressant actions. An evaluation of the cost-effectiveness of nortriptyline compared to bupropion and psychological intervention revealed that although the differences were not significant, the psychotherapy was the cheapest overall, with nortriptyline as the cheaper drug option [84]. A review of five nortriptyline trials [85], deduced that nortriptyline was "well-tolerated, safe and cheaper than bupropion and should be prescribed as first-line therapy" for smoking cessation. Other researchers would like to see more direct comparisons between bupropion and nortriptyline before deciding [86]. That said, a meta-analysis performed by Hughes *et al*. (2004) concluded that nortriptyline almost doubled cessation rates, with efficacy levels similar to those of bupropion and NRT [55]. From a pharmacological perspective, *in vivo* studies in rats measuring somatic signs of nicotine withdrawal, nortriptyline and bupropion have demonstrated comparable effects with regards to alleviation of the physical withdrawal states. However, nortriptyline did not suppress locomotor activity when withdrawal was precipitated by mecamylamine [87]. On nicotine reinforcement, acute nortriptyline treatment suppressed intravenous nicotine self-administration behaviour in rats but was also found to attenuate aversive stimulus effects of nicotine, suggesting that some of the effects may arise from non-specific effects of the antidepressant [88].

8.2. Doxepin

This serotonergic tricyclic antidepressant has only briefly been described as a smoking cessation aid. A double-blind study analysed the effects of 150mg/day of doxepin on withdrawal symptoms in smoking cessation and identified that on day 28, subjects expressed significantly less craving [89]. Further evidence corroborated these findings when after two months there was 78% abstinence with doxepin and 10% with placebo. This provided further evidence that doxepin significantly decreased nicotine withdrawal symptoms and affected nicotine cravings during abstinence [90]. However, further studies with a larger sample size and extended follow-up is warranted to determine full reliability.

8.3. Imipramine

Despite having apparent limited success in very early clinical studies [91], recent preclinical studies indicate that it may be more efficacious with regards to the modulating the affective aspects of nicotine intake. A study in rodents identified a decrease in conditioned responding to the nicotine CS and thus reducing incentive value of drug administered [92]. An analogue of imipramine, has also shown recent success preclinically [93]. This analogue was utilised due to the shared norepinephrine reuptake inhibition properties of bupropion and nortriptyline, but not their dopaminergic (bupropion) or serotonergic (nortriptyline) effects [94-96]. Previous studies assessed the effects of noradrenergic manipulations on alternative measures of nicotine dependence-related behaviours [97], with focus on nicotine self-administration, but not on the affective aspects of nicotine withdrawal. This study by Paterson *et al*. (2009) suggests that chronic exposure to noradrenaline reuptake inhibitors may be effective anti-smoking treatments that reduce anhedonic depression-like and somatic components of nicotine withdrawal.

9. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI)

9.1. Fluoxetine

Due to the previous success of antidepressants in smoking cessation, and the common prescription of fluoxetine as main drug used to treat depression, it has been the focus of several trials for smoking cessation aids. One multi-centre clinical trial tested fluoxetine hydrochloride, in addition to cognitive behaviour therapy sessions, in 989 patients. Their study revealed enhanced quit rates associated with both 60mg and 30mg doses of fluoxetine. These results suggest a modest, short-term effect of fluoxetine on smoking cessation but abstinence rates were not sustained in the long-term [98]. This may, however, not be due to lack of efficacy, but in the structure of the trial, and how the drug is administered and a real-world alternative for providing smoking cessation. A recent randomised, open-label clinical trial investigated the efficacy of sequential use of fluoxetine for smokers with increased depressive symptoms. The findings reveal that the best outcome for smoking cessation is when fluoxetine is prescribed before the target quit date [99].

In addition, a double-blind placebo-controlled trial, that investigated fluoxetine alongside nicotine patches and cogni-

tive-behavioural group therapy, suggests that fluoxetine may also moderate withdrawal symptoms, despite not being manifested in improved smoking cessation rates. Additionally, it also showed that fluoxetine may also be considered if weight gain hinders smoking cessation and has been shown to improve both positive and negative mood states after quitting smoking [100, 101].

9.2. Paroxetine

A double-blind randomised experiment of 224 smokers looked at the effects of the nicotine patch with or without paroxetine [102]. Patients taking the drug reported a greater reduction in cravings and depressive symptoms. The four-week abstinence rates with the patch and paroxetine were high at 64-74%, however by 26 weeks these had fallen to just 33-38% and showed no statistical difference compared to the placebo.

Evidence from rodent studies suggests that nicotine can exert anxiolytic effects *via* a serotonergic mechanism and this ability to diminish stress is a leading factor correlated with high relapse rates upon abstinence [103]. Therefore, another study looked at the effects of paroxetine on physiological response to stress and smoking. The findings show that the drug reduced stress-induced increases in systolic and diastolic blood pressure in smokers. However, the study stated that further examination is needed to determine the long term cardiovascular impact of taking such a drug [103].

9.3. Sertraline

Sertraline is another SSRI antidepressant that has been investigated for smoking cessation characteristics. One trial tested sertraline in 134 smokers with a history of depression [104]. Sertraline reportedly lowered withdrawal symptoms like irritability, anxiety, cravings and restlessness. However, abstinence rates after treatment were not statistically significant at 6-month follow-up. Another study verifies these findings by indicating that there was a significant effect of sertraline on post-quit Hamilton Depression Rating Scale scores but not on abstinence [105]. This shows sertraline when given alone was ineffective as a cessation aid and would suggest that the drug only has antidepressant properties. The combination of sertraline, buspirone and cognitive behavioural therapy has, however, shown optimal promotion of smoking cessation [106].

It has been hypothesised that nicotine stimulates the release of neuronal serotonin. Unusual reports of nausea with smoking suggested that nicotine may also increase serotonin release in the small intestinal nerve plexus. Enhanced levels of 5-HT by sertraline may cause nausea. An investigation of two case studies reporting a link between nausea and smoking showed that sertraline produced nausea in 26.1% of patients [107]. Sertraline may not actually stop people smoking but studies such as this implicate it as a negative reinforcement therapy in smoking cessation programs, much like disulfiram for alcohol dependence.

9.4. Venlafaxine

At low doses venlafaxine acts as a selective serotonin reuptake inhibitor (SSRI), at medium doses the drug acts as a noradrenaline reuptake inhibitor (NRI) and at very high doses it has been seen to inhibit dopamine reuptake.

A study concluded that there was no difference between abstinence rates for venlafaxine and a placebo after 8 weeks and that the drug induced more side-effects than the placebo [108]. Another clinical trial tested venlafaxine against a placebo in 136 smokers [109]. At a twelve-month follow-up, there was reportedly no significant increase in abstinence amongst the venlafaxine group. These findings of not being able to aid long term abstinence of tobacco smoking has been verified by other trials, however, this drug has shown potential in reducing the total number of cigarette packs consumed in conjunction with nicotine replacement and behavioural counselling [109].

Furthermore, two groups of animals, one exposed to tobacco smoke and the other not exposed to tobacco smoke, were subjected to Porsolt's test for testing antidepressant activity and Morris Water Maze Test for spatial memory function. In the group exposed to tobacco smoke, joint administration of venlafaxine and nicotine induced a significant reduction of immobility as compared to the control and nicotine groups. In the Morris Water Maze Test, single and chronic administration of venlafaxine, alone and with nicotine, showed reduced of escape latencies and lower numbers of crossed quadrants in both exposed and non-exposed rats, which indicates improved performance. This indicates an alternative approach to smoking cessation by antidepressant use that targets cognitive dysfunction associated with nicotine withdrawal as well as mood alteration [110].

In terms of interpersonal variation on treatment response, a genetic mutation in the dopamine D2 receptor gene has been correlated with altered efficacy of venlafaxine. It was found that individuals with an A2/A2 genotype for this receptor responded better to the cessation drug and suffered from fewer adverse effects than with an A1/A1 genotype [111]. Results like these suggest a role of genetic variation in determining how individuals will react to certain drug therapies.

10. NORADRENALINE REUPTAKE INHIBITORS

10.1. Reboxetine

Although no clinical trials have been performed with reboxetine, a noradrenaline reuptake inhibitor, one preclinical study investigated whether reboxetine could modify noradrenaline, dopamine, serotonin or acetylcholine transporters in rat brain. They concluded that reboxetine potently and selectively inhibits noradrenaline uptake in the hippocampus of rats, four times more than dopamine and serotonin uptake transporters are inhibited. The drug did not appear to alter the function of the three neurotransmitters but it may modify the neurotransmitter transporters and this could explain the delay of its effects. It was also suggested that the drug inhibits the nAChRs, $\alpha4\beta2$ and $\alpha3\beta4$, which could explain the varying efficacies of antidepressants as smoking cessation aids. Furthermore, the results indicated that noradrenaline may be more important in nicotine reward than first thought, as previously seen with imipramine. The study concluded that considering the concordance of smoking behaviour and mood disorders, reboxetine could potentially be an alternative cessation aid [74]. Subsequently, it

has been shown that reboxetine blocked responses induced by nicotine conditional stimuli and nicotine-induced hyperactivity [92].

11. MONOAMINE OXIDASE INHIBITORS

11.1. Moclobemide

Since the discovery of monoamine oxidase (MAO) inhibition and nAChR both increase synaptic monoamines and that tobacco smoke contains non-nicotinic compounds that inhibit MAO, it has been suggested that MAO inhibitors may be another drug class used for treatment of tobacco smoking [112, 113].

As a proof-of-concept, moclobemide (MAO A inhibitor) was investigated in a long-term placebo-controlled trial as a smoking cessation aid [114]. Subjects were given 400mg of the drug every day for one week prior to quit and for two months after. This was then decreased to 200mg per day for another month. They reported a significant decrease in smoking with the drug at 6 months but not at 12 months. This study did not show the drug to have any effect on withdrawal from nicotine either.

11.2. Selegiline

With regards to MAO-B inhibitors, selegiline was investigated against placebo in a randomised controlled trial, of 109 smokers, for effects on smoking cessation [115]. Patients were given 2.5mg daily doses of either selegiline or a placebo for one week prior to quit and then 5mg a day for 26 weeks after. At the 12-month follow-up, 25% of the selegiline group remained abstinent from smoking compared to only 11% in the placebo group. Selegiline also appeared to reduce nicotine cravings at 4 weeks. These findings have been verified by other studies, showing that inhibition of MAO-B successfully increases abstinence and that this enzyme places a significant role in smoking behaviour and cessation. A preliminary placebo-controlled trial of selegiline hydrochloride in 40 smokers also showed some positive results in smoking cessation [116]. After 8 weeks of treatment this study reported 45% abstinence in the selegiline group and 15% in the placebo group. However, these results fell to 20% for selegiline and 5% for the placebo group at the 6-month follow-up and were no longer significant.

Overall, trials of selegiline as a smoking cessation agent have produced some promising results. Selegiline appears to reduce cravings and decrease the number of cigarettes smoked by reducing threshold levels of smoking satisfaction [117]. From these findings, it may be suggested that by pharmacologically reducing MAO-B activity during early stages of abstinence, it may help long-term cessation rates.

Conversely, there is evidence from a double-blind, placebo-controlled, randomised clinical trial that selegiline doesn't improve smoking abstinence rates compared to placebo, despite being safe and well-tolerated by adult smokers [118].

11.3. Tryptophan

Tryptophan is a precursor for the neurotransmitter serotonin. It is regarded as to having antidepressant properties and is thought to elicit its effects due to its ability to increase brain serotonin levels [119]. This is also inferred when reducing levels of serotonin by inducing acute tryptophan depletion (ATD) in nicotine-dependent schizophrenic patients and controls. This showed that ATD increased the desire to smoke in both groups by intensifying psychopathological symptoms [120]. This suggests an important role of serotonin in both smoking and mood. It also implicates the tryptophan supplementation as a potential smoking cessation method.

However, there has been contradicting evidence from a randomised double-blind placebo-controlled trial on tryptophan depletion and the modulation of smoking withdrawal and nicotine action [121]. This study shows that although tryptophan depletion resulted in reduced levels of serotonin in the brain, it did not appear to affect nicotine withdrawal symptoms such as mood or electroencephalographic (EEG) readings.

A short-term study using tryptophan as a cessation aid revealed that the serotonin enhancing actions of tryptophan and a high carbohydrate diet could relieve nicotine withdrawal symptoms [122]. After 2 weeks, subjects treated with tryptophan smoked less cigarettes per day as well as reports of reduced reports of anxiety and withdrawal symptoms. In addition to this, a preclinical study showed tryptophan rich food supplementation had reduced nicotine withdrawal-induced depression and anxiety in rats, using the Elevated Plus Maze, Open Field Test and Forced Swim Test [123]. This further underlines the potential of tryptophan or tryptophan based substances as a possible adjunct therapy for nicotine cessation.

12. DISCUSSION

There is an intricate and diverse link between depression and smoking dependence. It includes neurobiological, genetic and environmental aspects which overlap one another to produce a complex condition which is difficult to treat. The variations in individuals potentially determine how effective different antidepressant agents are for smoking cessation. An extensive range of antidepressant drugs have been evaluated in smoking cessation trials, compounds that exhibit diverse pharmacological targets. These trials were largely compared against nicotine replacement therapy for reference purposes.

Despite the clinical success of antidepressants such as bupropion and nortriptyline, the development and subsequent success of varenicline has diminished interest in further developing antidepressants as potential smoking cessation aids. Consequently, varenicline is stated to be the most efficacious smoking cessation aid available clinically, with the mechanism of action not fully understood. However, it has been postulated that the drug works by attenuating the reinforcing properties of nicotine and thus, reduces tobacco intake.

Counter to this theory, varenicline has been shown to have antidepressant-like activity *in vivo* in the forced swim test, as well as being able to augment sertraline's effect, *via* its action on the α4β2 receptor [124]. Some of these effects

may also be mediated *via* the α7 nicotinic receptor as this subtype has also been shown to enhance the antidepressant effects of serotonin uptake blockers [125]. In addition, withdrawal from nicotine administered *via* osmotic minipumps has shown to impair attentional processes measured within the 5-choice serial reaction time task that was time-dependent which are similar in nature to the disturbances in attention reported by smokers during withdrawal [125, 126]. Furthermore, nicotine and other subtype nAChR agonists have been demonstrated to improve sustained and divided aspects of attention using the five-choice serial reaction time task [128]. Nicotine administered both acutely and subchronically in normal non-compromised rats improves performance in the attentional set shifting test [129]. Corroboratively, there is clinical and preclinical evidence that shows that varenicline also can have a positive effect on cognitive performance upon nicotine withdrawal 130, 131]. These neurocognitive models propose that targeting the impaired upper cortical functions by pharmacological means may be more effective than simply attenuating the reinforcing properties of nicotine in the VTA and N. Acc. Thus, several researchers are repositioning the use of commonly available cognitive enhancers as potential treatment for tobacco withdrawal.

Due to the antidepressant and cognitive restorative properties of varenicline, there may be a requirement for a new generation of antidepressants that can provide multiple actions; manage the underlying depression and facilitate smoking cessation. Effective strategies for smoking cessation include targeting the impaired cognitive function and emotional states during the process of withdrawal with nicotinic compounds along with antidepressants as adjuncts. These forms of treatment will require optimisation as smokers with depression are more nicotine dependent and are more likely to have lower quit rates, and thus an ever-increasing strain on health services globally.

CONCLUSION

There is strong need for systematic approaches to smoking cessation, and psychiatric treatment. Researchers have found, these conditions are more complex than targeting one pathway and expecting substantial drug efficacy. The suggested approach of targeting multiple pathways to address specific symptoms may allow for higher efficacy and, if successful, better translation to numerous other psychiatric and neurological conditions.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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