Clark A, Tate B, Urban B, et al. Bupropion Mediated Effects on Depression, Attention Deficit Hyperactivity Disorder, and Smoking Cessation. *Health Psychology Research*. 2023;11. doi:10.52965/001c.81043

General

Bupropion Mediated Effects on Depression, Attention Deficit Hyperactivity Disorder, and Smoking Cessation

Austin Clark, Brendan Tate, Bretton Urban, Ryan Schroeder, Sonja Gennuso, Shahab Ahmadzadeh, David McGregor, Brook Girma, Sahar Shekoohi[a], Alan D. Kaye

Keywords: Bupropion, antidepressant, ADHD, smoking-cessation, dopamine, norepinephrine

https://doi.org/10.52965/001c.81043

Health Psychology Research

Vol. 11, 2023

Bupropion had been in use since the late 1980s as an unconventional treatment for depression. Unlike other antidepressants, bupropion has no serotonergic activity and inhibits the reuptake of norepinephrine and dopamine. The drug has been used to treat depression, Attention Deficit Hyperactivity Disorder (ADHD), and smoking cessation. This investigation reviews the pharmacokinetic and pharmacodynamic effects of bupropion and its mechanisms of action and interactions with other drugs. We evaluated the efficacy of major on and off-label uses of bupropion, focusing on the indications, benefits, and adverse effects. Our review demonstrates that bupropion is superior to placebo and non-inferior to SSRIs such as escitalopram in treating major depressive disorder. More research is needed to determine positive patient-centered outcomes such as increases in quality of life. In the case of ADHD, the evidence for efficacy is mixed with poorly conducted randomized clinical trials, small sample sizes, and a lack of long-term assessments. The same is true in the case of bipolar disorder in which there is still limited and controversial data available on bupropion's safety and efficacy. In the case of smoking cessation, bupropion is found to be an effective anti-smoking drug with synergistic benefits when used as a combination therapy. We conclude that bupropion has the potential to provide benefit for a subset of patients who do not tolerate other typical antidepressants or anti-smoking therapies or for those whose treatment goals align with bupropion's unique side effect profile, such as smokers who wish to quit and lose weight. Additional research is needed to determine the drug's full clinical potential, particularly in the areas of adolescent depression and combination therapy with varenicline or dextromethorphan. Clinicians should use this review to understand the varied uses of the drug and identify the situations and patient populations in which bupropion can lend its greatest benefit.

INTRODUCTION

Bupropion was developed in the late 60's and 70's by Burroughs Wellcome (now GlaxoSmithKline) and approved by the U.S. Food and Drug Administration (FDA) in 1985 to treat major depressive disorder. Researchers sought to create a safer and more tolerable drug that was superior to tricyclic antidepressants (TCA's) and monoamine oxidase inhibitors (MAOI's). First introduced as a thrice-daily pill, bupropion as a therapy became safer and easier to adhere to with the introduction of a twice-daily sustained-release formulation in 1996 and once-daily extended-release pill in 2003.[1]

Early research showed it lacked antihistamine, anticholinergic, and serotonin reuptake inhibitory activity which were important causative mechanisms of many adverse effects of TCA's. At the time of FDA approval, the mechanism of action was unclear, although it was believed to have effects on levels of norepinephrine and possess dopaminergic activity. Today bupropion is understood to inhibit reuptake of norepinephrine and dopamine with complete lack of serotonergic activity.[2] With its unique chemical profile, bupropion provoked different side effects, provided unique neuropsychiatric benefits, and opened avenues to new clinical applications. It was set apart as unique from other antidepressants available whose main therapeutic effect was mediated by serotonergic reuptake inhibition.

By modulating levels of antihistamine, acetylcholine, and serotonin, earlier antidepressants commonly caused

a **Corresponding Author:** Sahar Shekoohi, Ph.D., Post-Doctoral Fellow, Department of Anesthesiology, Louisiana State University Health Sciences Center at Shreveport, 1501 Kings Highway, Shreveport LA 71103, sahar.shekoohi@lsuhs.edu

side effects such as sexual dysfunction, weight gain, and sedation.[1-3] As bupropion lacked activities on these neurotransmitters, it avoided these side effects. However, adverse effects included dose-dependent induction of seizures, especially before the creation of sustained and extended-release formulations. With its particular mechanism of action, bupropion was soon found to provide a unique benefit to patients, both on and off-label. Early clinical trials documented anti-smoking effects and weight loss as opposed to the typical antidepressant-induced weight gain. In addition, soon after the FDA approval for depression, clinical trials investigated the effects of bupropion on Attention Deficit Hyperactivity Disorder (ADHD).[4-6] Despite the evidence for these benefits, bupropion was originally only approved for the treatment of depression. However, this did not stop GlaxoSmithKline from promoting its off-label uses for weight loss, sexual dysfunction, substance addictions, and ADHD in the early 2000's (an act for which they were heftily fined $757,387,200 by the FDA).[7]

At present, bupropion has a role as an atypical antidepressant. The purpose of this review, therefore, is to characterize the effects of bupropion on brain and body chemistry and to examine its many clinical applications. We discuss pharmacokinetic and pharmacodynamic effects of bupropion, paying close attention to its mechanism of action and its interactions with other drugs. The present investigation studies indications and efficacy of its major on and off-label uses, e.g., depression, ADHD, and smoking cessation. We believe this review can be utilized by clinicians to understand the varied uses of the drug and to identify situations and patient populations in which bupropion can be of most beneficial. We also hope this review can be used to encourage additional studies into the advantages and disadvantages of bupropion in the treatment of depression, ADHD, smoking cessation, and obesity.

METHODS

Our literature review was conducted in the style of a narrative review. Our method of data collection included an electronic search of two databases, PubMed and Google Scholar. We placed no restrictions on country or date. We used several search terms: 'bupropion', 'history of bupropion', 'pharmacokinetics and pharmacodynamics of bupropion', 'bupropion and depression', 'bupropion and ADHD', 'bupropion and smoking cessation', 'bupropion and bipolar disorder', and 'bupropion and obesity'. We used the following inclusion criteria: articles of all types that were written in the English language, based on quantitative research, and focused on the current understanding of bupropion and its clinical applications. We used the following exclusion criteria: articles without the available full-text, articles of irrelevant content as laid out by our review focus, and articles made irrelevant by more recent studies of greater power with higher citation counts and impact factor. After the first article search round, additional articles were found through a cited references search round. Each article was independently reviewed by at least two authors for eligibility and relevant information. All significant results and conclusions drawn were discussed by at least two authors. Results from the literature review are reported in their respective sections. The authors discuss the information extracted from the studies, summarize the conclusions drawn, and demonstrate the paper's applicability to clinicians and future researchers in the discussion section.

PHARMACOKINETICS AND PHARMACODYNAMICS

ABSORPTION, DISTRIBUTION, AND ELIMINATION

Bupropion is administered orally and is subsequently absorbed by the gastrointestinal tract. The rate of absorption of intermediate release (IR) bupropion is rapid (T_{max} 1.3-1.9 hours).[8] Although bupropion has been shown to have a nearly 100% absorption rate, first-pass metabolism decreases its bioavailability.[9] Studies in animal models estimate the absolute bioavailability of bupropion to be 5-20%.[10] As intended, sustained-release (SR) and extended-release (ER) bupropion have higher T_{max} values.[11, 12] The bioavailability of SR bupropion is similar to IR bupropion, with ER bupropion being slightly less.[11] The active metabolites of bupropion include hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Hydroxybupropion and threohydrobupropion have higher maximum concentration (C_{max}) values compared to bupropion while the C_{max} of erythrohydrobupropion is similar to or lower than bupropion.[11,12]

The mean volume of distribution (Vd) of bupropion is around 19L/Kg.[8] This relatively high Vd can be attributed to the drug's lipophilic structure. Bupropion and its three main metabolites have been shown to cross the blood-brain barrier and subsequently bind to dopamine transporters.[13] The drug has also been found in placental tissue and umbilical blood.[14] Studies have shown that CYP2B6 is the primary enzyme by which bupropion is metabolized into hydroxybupropion with CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP 3A4 having a minor role.[15-19] Carbonyl reductases are responsible for threohydrobupropion and erythrohydrobupropion production.[20] The mean elimination half-life ($t_{1/2}$) of bupropion is 21 hours, with hydroxybupropion having a comparative $t_{1/2}$ of 20 hours.[12] Erythrohydrobupropion and threohydrobupropion have longer $t_{1/2}$ values (33 and 37 hours respectively). Bupropion is primarily excreted in the urine, but it is also found to a lesser extent in feces.[8]

METABOLIC INTERACTIONS

The major mechanism by which bupropion is metabolized to hydroxybupropion is through the CYP2B6 enzyme.[15] Other drugs metabolized by this enzyme have the potential to competitively inhibit bupropion metabolism. Several drugs that act as substrates of CYP2B6 have been described including efavirenz, nevirapine, methadone, and cyclophosphamide.[14-18] It has also been shown that CYP2D6 is inhibited by both bupropion and hydroxybupropion.[21] Many drugs are known to be CYP2D6 substrates, including several classes of antidepressants.[22] Drug interactions may

occur in patients taking multiple drugs that utilize this enzyme. For example, a study revealed increased adverse effects in patients taking CYP2D6-inhibiting antidepressants, such as SSRI's and bupropion, when co-administered with beta-blockers.[23] Increased risk of falls has been shown in patients taking multiple drugs that either inhibit or act as substrates for CYP2D6.[24] Caution should be used in patients who are prescribed multiple antidepressants, especially elderly patients due to decreased rates of drug breakdown observed in this population. There have been a few cases reports revealing successful treatment of depression with combined monoamine oxidase inhibitor/bupropion therapy with no serious adverse effects.[25,26] However, due to the lack of research regarding the concomitant use of these drugs, patients undergoing this specific drug regiment should be closely monitored for potential induction of hypertension.[27] Tamoxifen, an estrogen receptor modulator used for breast cancer treatment, is another substrate of CYP2D6, causing concern for a potential interaction between tamoxifen and other CYP2D6 inhibitors, such as bupropion.[28] However, a recent systematic review found that there was no net negative effect in administering these drugs simultaneously.[29]

MOLECULAR AND PHYSIOLOGIC EFFECTS OF BUPROPION

Bupropion's mechanism of action is not completely understood, but it has been shown to act as an inhibitor of dopamine and norepinephrine transporters, DAT and NET respectively.[30] Inhibition of DAT and NET leads to decreased reuptake of dopamine and norepinephrine in the synaptic cleft. Bupropion's low affinity for DAT and NET transporters, when compared to other antidepressants, is further evidence that bupropion likely has other modes of action.[10] Studies in rats have shown that bupropion decreases the activity of noradrenergic neurons in the locus coeruleus, which affect sleep and arousal.[31] Bupropion increases dopamine levels in the nucleus accumbens, thereby modulating reward and dependence stimulation.[32] Bupropion does not seem to directly affect either transport or release of serotonin.[30] It has also been shown that bupropion acts as an inhibitor of neuronal nicotinic acetylcholine receptors.[33]

ADVERSE EFFECTS

At recommended dosages, bupropion is well tolerated by most patients.[34] Some adverse effects that have been reported include insomnia, headache, nausea, dry mouth, anxiety, and rhinitis. Seizures are of the more serious possible adverse effects of bupropion usage.[12,35] Patients who have a lower seizure threshold, either due to the presence of comorbid conditions or usage of other drugs that lower seizure threshold, should be cautioned about this possible interaction. The incidence of seizures in patients taking therapeutic dosages of 450mg/day or less is between 0.35-0.44%.[35] Other serious adverse effects include skin hypersensitivity reactions, cardiovascular ischemia, hypertension, myalgia, hallucinations, agitation, and tachycardia.[34,36,37]

Although bupropion does not seem to directly influence serotonin at normal dosages, there have been several reports of serotonin syndrome in patients taking bupropion with other drugs that increase serotonin levels.[38,39] Serotonin toxicity has also been shown to occur in single drug bupropion overdoses.[40] Serious cardiac deficits such as QT prolongation and QRS widening have been shown to occur in patients who take an excess dosage of bupropion.[41] From 2000-2013, there were 975 cases of intentional single-substance bupropion overdoses reported to national poison control centers.[42] 45.4% of these cases occurred in individuals between the ages of 13-19. This raises a concern for adolescents prescribed bupropion for the treatment of depression or other conditions.

DEPRESSION

THE THERAPEUTIC MECHANISM OF ACTION OF BUPROPION IN MAJOR DEPRESSION DISORDER

Bupropion is a nicotinic acetylcholine antagonist and inhibits the reuptake of norepinephrine and dopamine, with a weaker effect on dopamine. In the body, it is converted to three major active metabolites hydroxybupropion, threohydrobupropion, and erythrohydrobupropion.[43] Bupropion's mechanism of action in treating major depressive disorder has not been exactly defined, a common theme amongst antidepressants.[44] However, it likely involves bupropion's unique ability to inhibit norepinephrine and dopamine reuptake without affecting other neurotransmitters or their receptors.[43]

THERAPEUTIC EFFICACY OF BUPROPION IN TREATING DEPRESSION

Most randomized controlled trials report bupropion to be superior to placebo in treating depression. However, several systematic reviews and meta-analysis have cautioned interpreting their results secondary to study quality and bias concerns. A 2016 meta-analysis reported that bupropion was able to reduce depression scores in 24 of 27 trials testing monotherapy. They caution interpreting these findings secondary to study design concerns and age of studies.[45] A more recent 2023 meta-analysis of 34 double-blind, randomized, placebo-controlled trials (n=9384) focused on antidepressant treatment parameters during the maintenance phase. Bupropion was comparable to placebo in efficacy, acceptability, and tolerability. These parameters were measured by 6-month depression relapse rate, all-cause discontinuation, and the discontinuation rate due to adverse events respectively. Though their findings suggest bupropion doesn't outperform placebo, they did only include one study specifically focused on bupropion.[46,47]

The therapeutic efficacy of Bupropion may differ amongst different age groups. A nationwide population-based cohort study in Taiwan (n=16,981) of youth (less than 20 years old) from 1997 to 2013 found data suggesting bupropion may be better than current first-line treatment

in preventing significant outcomes like psychiatric hospitalization and medication discontinuation.[48] However, a similar large-scale national cohort study in Taiwan (n=207,946) involving elderly patients (above the age of 60 years old) did not replicate the findings found in the youth population. Bupropion, compared with the other antidepressants, did not statistically improve or reduce psychiatric hospitalization risk in elderly patients with depression.[49]

BUPROPION AS MONOTHERAPY VERSUS COMBINATION THERAPY

A 2022 meta-analysis of 39 randomized clinical trials, 7 of which specifically focused on bupropion combination therapy, compared the acute treatment of depression with combination therapy versus monotherapy. They found data suggesting bupropion combination therapy was not associated with significant improvement in treatment outcomes compared with monotherapy.[50] Interestingly, a new combination of bupropion and dextromethorphan (AXS-05) developed by Axsome Therapeutics has recently gained U.S. FDA approval in August 2022 for the treatment of MDD in adults. A 6-week randomized double-blind trial (n=97) of AXS-05 versus a bupropion monotherapy control was performed. They report findings that suggest AXS-05 significantly improved symptoms of depression when compared to bupropion monotherapy. Of course, it is important to note that this study was funded by Axsome Therapeutics.[51]

THE USE OF BUPROPION VERSUS OTHER ANTIDEPRESSANTS IN REDUCING BIPOLAR DISORDER (BPD) ASSOCIATED MANIA

There is limited and controversial data available on the safety and efficacy of antidepressant therapy for bipolar disorder. A 2013 report released by The International Society for Bipolar Disorders (ISBD) Task Force concluded data was too limited and of poor quality to make recommendations for or against using antidepressants in BPD. Therefore, a comparison amongst the antidepressants including bupropion, was limited to a higher risk of worsening mood with tetracyclines and venlafaxine.[52]

ATTENTION DEFICIT HYPERACTIVITY DISORDER

THE THERAPEUTIC MECHANISM OF ACTION OF BUPROPION IN ADHD

Bupropion has been used as an off-label treatment for ADHD in both adult and pediatric populations.[57,58] The exact cause of ADHD hasn't been fully defined but a problem in dopaminergic transmission may be involved.[59] Bupropion is a nicotinic acetylcholine receptor antagonist and inhibits the reuptake of norepinephrine and dopamine. The reuptake inhibition of norepinephrine and dopamine keeps these catecholamines in the neuronal synaptic cleft longer, increasing neurotransmission. Stimulants used for ADHD work through a different mechanism but have a similar outcome.[60,61]

THERAPEUTIC EFFICACY OF BUPROPION IN TREATING ADHD

Even though it is being used as an alternative to stimulants in treating ADHD, the quality of evidence to support its efficacy has been the subject of debate. A 2011 systematic review of randomized clinical trials (RCT's) suggested bupropion was safe and effective for ADHD in adults.[62] However, a 2017 systematic review found similar evidence that bupropion decreases the severity of ADHD symptoms in adults but cautioned that the quality of this evidence remains low as the RCT's were poorly conducted, subject to bias, and had small sample sizes. There were also no long-term assessments even though ADHD is a chronic condition.[57] A 2017 systematic review focused on RCT's in the pediatric population similarly cautioned the interpretation of current findings secondary to low data.[58] A comparative analysis of bupropion to other treatments for ADHD recommended against its use.[63] A 2018 meta-analysis of treatments for ADHD found bupropion was more effective than placebo in the clinician-rated treatment of adult ADHD symptoms. However, bupropion was not superior to placebo in parent or adult self-ratings in the treatment of core ADHD symptoms. Again, they cite that these findings should be interpreted with caution as they had a large confidence interval.[64]

OTHER TREATMENTS OF ADHD AND THEIR COMPARISON TO BUPROPION

Treatment of ADHD can be divided into pharmacological and non-pharmacological categories. Pharmacologic treatment of ADHD can further be subdivided into stimulant and non-stimulant categories.[57,65] Behavioral therapy may be the only non-pharmacological treatment that can significantly impact ADHD.[66] Stimulant medications such as methylphenidate and dexamphetamine are the first line of treatment in ADHD as evidence from multiple meta-analysis have suggested they are the most effective at treating ADHD.[66,67] The norepinephrine reuptake inhibitor atomoxetine has been established as second line treatment based on evidence along with other non-stimulant medications like guanfacine and clonidine.[66,68] A 2015 meta-analysis comparing the efficacy of bupropion with atomoxetine, lisdexamfetamine, and methylphenidate found evidence it was inferior in reducing ADHD symptoms.[69] A 2017 meta-analysis recommended against using bupropion for the treatment of ADHD as it found that lisdexamfetamine was superior in efficacy while bupropion had the highest rate of withdrawals.[63] While non-stimulant medications including bupropion have been shown to be less effective, there are situations where they may be considered an option. This includes when first and second-line stimulants do not work or if there is a contraindicated concurrent medication use, comorbidity, or risk of substance abuse.[57,65] However, reports of bupropion misuse serve to counter

Table 1. Comparison of Bupropion and Other Antidepressants in Major Depressive Disorder

Study	Drug Comparison with Mechanism of Action	Study Design	MADRS Change from Baseline to Study Endpoint	Conclusions
Koshino (2022) The efficacy and safety of bupropion sustained-release formulation for the treatment of major depressive disorder: a multi-center, randomized, double-blind, placebo-controlled study in Asian patients[53]	**Bupropion** **vs** **Placebo**	Double-blind, randomized placebo-controlled trial 569 Asian patients with a diagnosis of Major Depressive Disorder were treated with 125mg or 300 mg of Bupropion vs placebo over a period of 8 weeks.	**Bupropion (150mg):** -14.4 **Bupropion (300mg):** -12.9 **Placebo:** -13.9 **Mean Difference (BU150):** -0.5 **95% CI:** -2.7, 1.7 **P-Value:** .853 **Mean Difference (BU300):** N/A **95% CI:** N/A	Bupropion did not exhibit significant improvement in MDD symptoms compared to placebo.
Tabuteau (2022) Effect of AXS-05 (Dextromethorphan-Bupropion) in Major Depressive Disorder: A Randomized Double-Blind Controlled Trial[54]	**AXS-05** Bupropion 105mg + Dextromethorphan 45mg Non-competitive NMDA Antagonist	Double bind, randomized controlled trial 80 patients with the diagnosis of Major Depressive Disorder were randomized into groups receiving AXS-05 and bupropion (105 mg) over a period of 6 weeks.	**AXS-05:** -13.7 **Bupropion:** -8.8 **Least-squares mean difference:** -4.9 **95% CI:** -3.1, -6.8 **P-Value:** <.0001	Both AXS-05 and Bupropion were effective at reducing MDD symptoms with AXS-05 having a slightly greater effect.
Iosifescu (2022) Efficacy and Safety of AXS-05 (Dextromethorphan-Bupropion) in Patients With Major Depressive Disorder: A Phase 3 Randomized Clinical Trial (GEMINI)[55]	**AXS-05** **vs** **Placebo**	Double bind, randomized placebo-controlled trial 327 patients with DSM-5 diagnosis of MDD were randomized to receive placebo or AXS-05 for 6 weeks.	**AXS-05:** -15.9 **Placebo:** -12.0 **Least-squares mean difference:** -3.9 **95% CI:** -1.4, -6.4 **P-Value:** .002	AXOS-05 exhibited significantly greater improvements in all outcomes measured at all time points including MADRS score when compared to placebo.
Shen (2019) Efficacy and safety of bupropion hydrochloride extended-release versus escitalopram oxalate in Chinese patients with major depressive disorder: Results from a randomized, double-blind, non-inferiority trial[56]	**Bupropion** **vs** **Escitalopram** Selective Serotonin Reuptake Inhibitor (SSRI)	Double bind, randomized controlled trial 534 patients in China with the diagnosis of MDD were randomized to receive 150-300mg of Bupropion extended release or 10-20mg of Escitalopram for 8 weeks.	**Escitalopram:** -19.5 **Bupropion:** -18.6 **Least-squares mean difference:** 0.9 **95% CI:** -.69, 2.4 **P-Value:** .278	Bupropion was non-inferior to escitalopram when treating major depressive symptoms in an outpatient setting after eight weeks.

AXOS-05: 45mg Dextromethorphan + 105mg Bupropion
HAMD-17: Hamilton Depression Rating Scale-17
MADRS: Montgomery-Asberg Depression Rating Scale
MDD: Major Depressive Disorder

the argument for its application in managing ADHD patients that are at risk for abusing stimulants.[70]

SMOKING CESSATION

THE THERAPEUTIC MECHANISM OF ACTION OF BUPROPION IN SMOKING CESSATION

Nicotine acts on a variety of cholinergic receptors throughout the brain and body. Those of the central nervous system subsequently release acetylcholine, dopamine, norepinephrine, serotonin, and a variety of other neurotransmitters and neuroactive compounds.[71,72] Nicotine's addictiveness is attributed to a variety of these effects, predominately those of dopamine from the ventral tegmental area, nucleus accumbens, and the mesolimbic and mesocortical pathways. These pathways mediate the motivation, satisfaction, reward, and behaviors associated with nicotine use and addiction.[71,73] Bupropion is effective for providing both anti-craving and anti-withdrawal acting on these circuits within the central nervous system.[74-76] Bupropion's known mechanism of action involves inhibition of the reuptake of monoamines such as dopamine and norepinephrine. The effects on dopamine are thought to be the primary mechanism that bupropion acts to inhibit the reward pathways in nicotine addiction.[75-78] Bupropion may also exert antagonism of nicotinic cholinergic receptors, contributing to its smoking cessation enhancing effects.[74,76,78]

THERAPEUTIC EFFICACY OF BUPROPION IN SMOKING CESSATION

A 2013 meta-analysis observed bupropion demonstrated similar smoking cessation efficacy as nicotine replacement therapy compared to placebo.[79] Weight gain is another common manifestation of nicotine withdrawal. Bupropion has also been studied as an agent for overweight and obese individuals due to its appetite suppressant effects. These effects are mediated through the activation of proopiomelanocortin and dopamine agonism within the reward circuits mentioned previously and have been hypothesized to increase bupropion benefit in smoking cessation therapy.[71,72,80,81] Different groups of individuals also struggle with quitting at varying rates, including those with lower education, mental health issue, and lower socioeconomic status.[82,83] Bupropion and other interventions have been studied within these various subgroups. In adolescents and pregnant individuals, long-term cessation was lower than reported in other studies including older, non-pregnant adults.[82,84,85] Nicotine withdrawal can be complicated by pre-existing depressive symptoms. This is specifically relevant in relation to major depressive disorder, where smoking is reported at 1.5 times the rate of those without.[86,87]

OTHER TREATMENTS FOR SMOKING CESSATION AND THEIR COMPARISON TO BUPROPION

Bupropion, varenicline, and nicotine replacement therapies are effective abstinence tools in these individuals as well.[87] Varenicline is a partial agonist of the receptors that nicotine binds to within the central nervous system. As a partial agonist, varenicline acts as an antagonist in the presence of nicotine while attenuating withdrawal effects that are seen with full antagonism of the receptor.[88,89] In patients with major depressive disorder, varenicline was shown to be more effective than bupropion and nicotine replacement therapy when coupled with counseling the patient on smoking cessation.[87] Both bupropion and varenicline are effective smoking cessation monotherapies, but a number of meta-analyses have shown that combination therapy with varenicline and bupropion shows higher rates of smoking cessation compared to either drug as a monotherapy.[90-93] Adherence to pharmacologic therapy is pivotal in the success of smoking cessation.[94] One factor that may contribute to medication non-adherence is adverse effects. Although both bupropion and varenicline are approved by the FDA for smoking cessation in adults and are generally deemed safe, they are associated with adverse effects.[79,83] Bupropion has been associated with insomnia, headache, dry mouth, and agitation. Bupropion also carries a mild risk of seizure, however, a previous review found less incidence of seizure than expected following bupropion therapy.[79] Varenicline is associated with primarily nausea, followed by insomnia, vivid dreams, and headache with other more serious side effects being rare and their causal link to varenicline unclear.[83,95] Neither of the drugs has been clearly associated with any increase neuropsychiatric, cardiovascular, or other serious adverse effects in both pregnant and non-pregnant individuals.[82,83,85,92,93,95] Bupropion and varenicline are effective smoking cessation treatments in non-pregnant adults of all demographics and can be used as monotherapy or combination therapy. Treatment strategies should be primarily determined based on patient preferences, adverse effects experienced, and willingness to adhere to the pharmacologic intervention to maximize smoking cessation success.

DISCUSSION

Our review has examined the diverse pharmacological effects and clinical applications of bupropion. With its unique drug profile, bupropion has the potential to provide benefits for a subset of patients with depression who do not tolerate other typical antidepressants or who have certain comorbid conditions such as ADHD, obesity, or nicotine dependence. Our investigation utilized a review of the current literature to determine the current understanding of its efficacy in such cases to guide its clinical use.

DEPRESSION

Within the context of MDD, our investigation found that most evidence demonstrates bupropion is superior to placebo and non-inferior to SSRI's such as escitalopram. The studies showing increased efficacy of bupropion in preventing hospitalization and medication discontinuation in Taiwanese youth demonstrate that age may play a role the drugs success. However, more clinical research needs to be done comparing positive patient-centered outcomes such as increases in quality of life. Also, if bupropion is a potential drug of choice for youth, further research needs to be done on the risk of abuse in this age group. The

initial clinical trial success of the new combination drug AXS-05 should be taken into consideration when prescribing bupropion in cases where patients can afford it. Further clinical trials with larger sample sizes should be done comparing AXS-05 to other first-line treatments of MDD. In the case of bipolar disorder, there is still limited and controversial data available on the safety and efficacy of the use of bupropion.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

As a treatment for ADHD, our study found the evidence for efficacy to be mixed with poorly conducted randomized clinical trials, small sample sizes, and a lack of long-term assessments. Our review also found it to be inferior to other stimulant and non-stimulant treatments. Moreover, reports of bupropion misuse further counters the argument for its application in managing ADHD patients at risk of substance abuse. Altogether, the use of bupropion in the treatment of ADHD should be limited to situations of first and second-line treatment failure, contraindicated concurrent medication use, or comorbidity.

SMOKING CESSATION

Our investigation found bupropion to be an effective anti-smoking drug. Reviews of its efficacy show it to be as effective as nicotine replacement though less effective than treatment with varenicline and counseling. However, the literature supports its efficacy as a combination therapy with varenicline, showing higher rates of smoking cessation compared to either drug as a monotherapy. In addition, due to its appetite suppressing effects, bupropion may have an added benefit for obese patients or those quitting nicotine who do not wish to gain weight. Treatment strategies should be primarily determined based on patient preferences, adverse effects experienced, and willingness to adhere to the pharmacologic intervention to maximize smoking cessation success.

CONCLUSION

Our findings emphasize the known benefit of the application of bupropion in depression. We find it may be of special use in the cases of people who are young, resistant to other treatments, or obese. This is of special importance because these are populations that may be difficult to treat due to comorbidities or lack of adherence to other medications. The evidence for bupropion's benefit in smoking cessation is important, as bupropion has a unique side effect profile. It may be of special use in patients who cannot tolerate varenicline or those who do not wish to gain weight from quitting nicotine. Our review highlights the lack of quality evidence in the treatment of people with ADHD with bupropion. Further research should investigate the long-term efficacy and safety of using bupropion as a treatment for ADHD with comparisons to first and second-line treatments. Additionally, future studies should aim to conduct well-designed randomized controlled trials with large sample sizes to better assess the effectiveness of bupropion across different age ranges. Furthermore, the research could explore the potential benefits and drawbacks of combining bupropion with other treatments for depression, such as the new combination drug AXS-05. Finally, studies could investigate the reasons for the high rate of withdrawals associated with bupropion use in some studies and explore the rates of bupropion misuse.

FUNDING

No funding or sponsorship was received for this study or publication of this article.

COMPETING INTERESTS

None.

AUTHOR CONTRIBUTIONS

All authors listed have made a direct and intellectual contribution to the work and approved for publication.

COMPLIANCE WITH ETHICAL GUIDELINES

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Fava M, Rush AJ, Thase ME, et al. 15 Years of Clinical Experience With Bupropion HCl: From Bupropion to Bupropion SR to Bupropion XL. *Prim Care Companion CNS Disord*. 2005;7(3). doi:10.4088/pcc.v07n0305

2. Stahl SM, Pradko J, Haight BR, Modell JG, Rockett CB, Learned-Coughlin S. A Review of the Neuropharmacology of Bupropion, a Dual Norepinephrine and Dopamine Reuptake Inhibitor. *Prim Care Companion CNS Disord*. 2004;6(4):159-166. doi:10.4088/pcc.v06n0403

3. Soroko FE, Maxwell RA. The pharmacologic basis for therapeutic interest in bupropion. *J Clin Psychiatry*. 1983;44(5 Pt 2):67-73.

4. Ferry L, Johnston JA. Efficacy and safety of bupropion SR for smoking cessation: data from clinical trials and five years of postmarketing experience. *Int J Clin Pract*. 2003;57(3):224-230. doi:10.1111/j.1742-1241.2003.tb10468.x

5. Gardner EA. Effects of bupropion on weight in patients intolerant to previous antidepressants. *Eff Bupropion Weight Patients Intoler Previous Antidepressants*. 1984;35(2):188-199.

6. Wender PH, Reimherr FW. Bupropion treatment of attention-deficit hyperactivity disorder in adults. *Am J Psychiatry*. 1990;147(8):1018-1020. doi:10.1176/ajp.147.8.1018

7. GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data. Published July 2, 2012. Accessed March 22, 2023. https://www.justice.gov/opa/pr/glaxosmithkline-plead-guilty-and-pay-3-billion-resolve-fraud-allegations-and-failure-report

8. Findlay JWA, Van Wyck Fleet J, Smith PG, et al. Pharmacokinetics of bupropion, a novel antidepressant agent, following oral administration to healthy subjects. *Eur J Clin Pharmacol*. 1981;21(2):127-135. doi:10.1007/bf00637513

9. Schroeder DH. Metabolism and kinetics of bupropion. *J Clin Psychiatry*. 1983;44(5 Pt 2):79-81.

10. Foley KF, DeSanty KP, Kast RE. Bupropion: pharmacology and therapeutic applications. *Expert Rev Neurother*. 2006;6(9):1249-1265. doi:10.1586/14737175.6.9.1249

11. Connarn JN, Flowers S, Kelly M, et al. Pharmacokinetics and Pharmacogenomics of Bupropion in Three Different Formulations with Different Release Kinetics in Healthy Human Volunteers. *AAPS J*. 2017;19(5):1513-1522. doi:10.1208/s12248-017-0102-8

12. Jefferson JW, Pradko JF, Muir KT. Bupropion for major depressive disorder: Pharmacokinetic and formulation considerations. *Clin Ther*. 2005;27(11):1685-1695. doi:10.1016/j.clinthera.2005.11.011

13. Learned-Coughlin SM, Bergström M, Savitcheva I, Ascher J, Schmith VD, Långstrom B. In vivo activity of bupropion at the human dopamine transporter as measured by positron emission tomography. *Biol Psychiatry*. 2003;54(8):800-805. doi:10.1016/s0006-3223(02)01834-6

14. Wang X, Vernikovskaya DI, Abdelrahman DR, Hankins GDV, Ahmed MS, Nanovskaya TN. Simultaneous quantitative determination of bupropion and its three major metabolites in human umbilical cord plasma and placental tissue using high-performance liquid chromatography–tandem mass spectrometry. *J Pharm Biomed Anal*. 2012;70:320-329. doi:10.1016/j.jpba.2012.05.008

15. Hesse LM, Venkatakrishnan K, Court MH, et al. CYP2B6 Mediates the In Vitro Hydroxylation of Bupropion: Potential Drug Interactions with Other Antidepressants. *Drug Metab Dispos*. 2000;28(10):1176.

16. Faucette SR, Hawke RL, Shord SS, Lecluyse EL, Lindley CM. Evaluation of the Contribution of Cytochrome P450 3A4 to Human Liver Microsomal Bupropion Hydroxylation. *Drug Metab Dispos*. 2001;29(8):1123.

17. Faucette SR, Hawke RL, Lecluyse EL, et al. Validation of Bupropion Hydroxylation as a Selective Marker of Human Cytochrome P450 2B6 Catalytic Activity. *Drug Metab Dispos*. 2000;28(10):1222.

18. Sager JE, Choiniere JR, Chang J, Stephenson-Famy A, Nelson WL, Isoherranen N. Identification and Structural Characterization of Three New Metabolites of Bupropion in Humans. *ACS Med Chem Lett*. 2016;7(8):791-796. doi:10.1021/acsmedchemlett.6b00189

19. Kirchheiner J, Klein C, Meineke I, et al. Bupropion and 4-OH-bupropion pharmacokinetics in relation to genetic polymorphisms in CYP2B6. *Pharmacogenetics*. 2003;13(10):619-626. doi:10.1097/00008571-200310000-00005

20. Costa R, Oliveira NG, Dinis-Oliveira RJ. Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspects. *Drug Metab Rev*. 2019;51(3):293-313. doi:10.1080/03602532.2019.1620763

21. Sager JE, Tripathy S, Price LSL, et al. In vitro to in vivo extrapolation of the complex drug-drug interaction of bupropion and its metabolites with CYP2D6; simultaneous reversible inhibition and CYP2D6 downregulation. *Biochem Pharmacol*. 2017;123:85-96. doi:10.1016/j.bcp.2016.11.007

22. Taylor C, Crosby I, Yip V, Maguire P, Pirmohamed M, Turner RM. A Review of the Important Role of CYP2D6 in Pharmacogenomics. *Genes*. 2020;11(11):1295. doi:10.3390/genes11111295

23. Shin J, Hills NK, Finley PR. Combining Antidepressants with β-Blockers: Evidence of a Clinically Significant CYP2D6 Drug Interaction. *Pharmacotherapy*. 2020;40(6):507-516. doi:10.1002/phar.2406

24. Dahl ML, Leander K, Vikström M, et al. CYP2D6-inhibiting drugs and risk of fall injuries after newly initiated antidepressant and antipsychotic therapy in a Swedish, register-based case-crossover study. *Sci Rep*. 2021;11(1):5796. doi:10.1038/s41598-021-85022-x

25. Pierre JM, Gitlin MJ. Bupropion-Tranylcypromine Combination for Treatment-Refractory Depression. *J Clin Psychiatry*. 2000;61(6):450-451. doi:10.4088/jcp.v61n0610h

26. Quante A, Zeugmann S. Tranylcypromine and Bupropion Combination Therapy in Treatment-Resistant Major Depression: A Report of 2 Cases. *J Clin Psychopharmacol*. 2012;32(4):572-574. doi:10.1097/jcp.0b013e31825de0a7

27. Calvi A, Fischetti I, Verzicco I, et al. Antidepressant Drugs Effects on Blood Pressure. *Front Cardiovasc Med*. 2021;8:704281. doi:10.3389/fcvm.2021.704281

28. Andrade C. Breast Cancer and Antidepressant Use. *J Clin Psychiatry*. 2012;73(09):e1156-e1157. doi:10.4088/jcp.12f08054

29. Bradbury M, Hutton B, Beltran-Bless AA, et al. Time to Update Evidence-Based Guideline Recommendations About Concurrent Tamoxifen and Antidepressant Use? A Systematic Review. *Clin Breast Cancer*. 2022;22(3):e362-e373. doi:10.1016/j.clbc.2021.10.003

30. Shalabi AR, Walther D, Baumann MH, Glennon RA. Deconstructed Analogues of Bupropion Reveal Structural Requirements for Transporter Inhibition versus Substrate-Induced Neurotransmitter Release. *ACS Chem Neurosci*. 2017;8(6):1397-1403. doi:10.1021/acschemneuro.7b00055

31. Pakdel FG, Amirabadi S, Naderi S, et al. Effects of Acute Intracerebroventricular Microinfusions of Bupropion on Background Spike Activity of Locus Coeruleus Neurons in Rats. *Neurophysiology*. 2014;46(4):316-322. doi:10.1007/s11062-014-9450-5

32. Sidhpura N, Redfern P, Rowley H, Heal D, Wonnacott S. Comparison of the effects of bupropion and nicotine on locomotor activation and dopamine release in vivo. *Biochem Pharmacol*. 2007;74(8):1292-1298. doi:10.1016/j.bcp.2007.06.025

33. Slemmer JE, Martin BR, Damaj MI. Bupropion Is a Nicotinic Antagonist. *J Pharmacol Exp Ther*. 2000;295(1):321.

34. Aubin HJ. Tolerability and Safety of Sustained-Release Bupropion in the Management of Smoking Cessation. *Drugs*. 2002;62(Supplement 2):45-52. doi:10.2165/00003495-200262002-00005

35. Pesola GR, Avasarala J. Bupropion seizure proportion among new-onset generalized seizures and drug related seizures presenting to an emergency department. *J Emerg Med*. 2002;22(3):235-239. doi:10.1016/s0736-4679(01)00474-7

36. Beyens MN, Guy C, Mounier G, Laporte S, Ollagnier M. Serious Adverse Reactions of Bupropion for Smoking Cessation: Analysis of the French Pharmacovigilance Database from 2001 to 2004. *Drug Saf*. 2008;31(11):1017-1026. doi:10.2165/00002018-200831110-00006

37. Shepherd G, Velez LI, Keyes DC. Intentional bupropion overdoses. *J Emerg Med*. 2004;27(2):147-151. doi:10.1016/j.jemermed.2004.02.017

38. Munhoz RP. Serotonin Syndrome Induced by a Combination of Bupropion and SSRIs. *Clin Neuropharmacol*. 2004;27(5):219-222. doi:10.1097/01.wnf.0000142754.46045.8c

39. Thorpe EL, Pizon AF, Lynch MJ, Boyer J. Bupropion Induced Serotonin Syndrome: A Case Report. *J Med Toxicol*. 2010;6(2):168-171. doi:10.1007/s13181-010-0021-x

40. Sidlak AM, Koivisto KO, Marino RT, Abesamis MG. Serotonin toxicity from isolated bupropion overdoses. *Clin Toxicol*. 2020;58(12):1347-1349. doi:10.1080/15563650.2020.1742920

41. Caillier B, Pilote S, Castonguay A, et al. QRS widening and QT prolongation under bupropion: a unique cardiac electrophysiological profile. *Fundam Clin Pharmacol*. 2011;26(5):599-608. doi:10.1111/j.1472-8206.2011.00953.x

42. Stassinos GL, Klein-Schwartz W. Bupropion "Abuse" Reported to US Poison Centers. *J Addict Med*. 2016;10(5):357-362. doi:10.1097/adm.0000000000000249

43. Stahl SM, Pradko J, Haight BR, Modell JG, Rockett CB, Learned-Coughlin S. A Review of the Neuropharmacology of Bupropion, a Dual Norepinephrine and Dopamine Reuptake Inhibitor. *Prim Care Companion CNS Disord*. 2004;6(4):159-166. doi:10.4088/pcc.v06n0403

44. Dhillon S, Yang LPH, Curran MP. Bupropion. *Drugs*. 2008;68(5):653-689. doi:10.2165/00003495-200868050-00011

45. Patel K, Allen S, Haque MN, Angelescu I, Baumeister D, Tracy DK. Bupropion: a systematic review and meta-analysis of effectiveness as an antidepressant. *Ther Adv Psychopharmacol*. 2016;6(2):99-144. doi:10.1177/2045125316629071

46. Kishi T, Ikuta T, Sakuma K, et al. Antidepressants for the treatment of adults with major depressive disorder in the maintenance phase: a systematic review and network meta-analysis. *Mol Psychiatry*. 2023;28(1):402-409. doi:10.1038/s41380-022-01824-z

47. Weihs KL, Houser TL, Batey SR, et al. Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. *Biol Psychiatry*. 2002;51(9):753-761. doi:10.1016/s0006-3223(01)01317-8

48. Lee SY, Wang LJ, Yang YH, Hsu CW. The comparative effectiveness of antidepressants for youths with major depressive disorder: a nationwide population-based study in Taiwan. *Ther Adv Chronic Dis*. 2022;13:20406223221098110. doi:10.1177/20406223221098114

49. Hsu CW, Tseng WT, Wang LJ, Yang YH, Kao HY, Lin PY. Comparative effectiveness of antidepressants on geriatric depression: Real-world evidence from a population-based study. *J Affect Disord*. 2022;296:609-615. doi:10.1016/j.jad.2021.10.009

50. Henssler J, Alexander D, Schwarzer G, Bschor T, Baethge C. Combining Antidepressants vs Antidepressant Monotherapy for Treatment of Patients With Acute Depression: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2022;79(4):300-312. doi:10.1001/jamapsychiatry.2021.4313

51. Tabuteau H, Jones A, Anderson A, Jacobson M, Iosifescu DV. Effect of AXS-05 (Dextromethorphan-Bupropion) in Major Depressive Disorder: A Randomized Double-Blind Controlled Trial. *Am J Psychiatry*. 2022;179(7):490-499. doi:10.1176/appi.ajp.21080800

52. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. The International Society for Bipolar Disorders (ISBD) Task Force Report on Antidepressant Use in Bipolar Disorders. *Am J Psychiatry*. 2013;170(11):1249-1262. doi:10.1176/appi.ajp.2013.13020185

53. Koshino Y, Bahk WM, Sakai H, Kobayashi T. The efficacy and safety of bupropion sustained-release formulation for the treatment of major depressive disorder: a multi-center, randomized, double-blind, placebo-controlled study in Asian patients. *Neuropsychiatr Dis Treat*. 2013;9:1273-1280. doi:10.2147/ndt.s48158

54. Tabuteau H, Jones A, Anderson A, Jacobson M, Iosifescu DV. Effect of AXS-05 (Dextromethorphan-Bupropion) in Major Depressive Disorder: A Randomized Double-Blind Controlled Trial. *Am J Psychiatry*. 2022;179(7):490-499. doi:10.1176/appi.ajp.21080800

55. Iosifescu DV, Jones A, O'Gorman C, et al. Efficacy and Safety of AXS-05 (Dextromethorphan-Bupropion) in Patients With Major Depressive Disorder: A Phase 3 Randomized Clinical Trial (GEMINI). *J Clin Psychiatry*. 2022;83(4):21-14345. doi:10.4088/jcp.21m14345

56. Shen Y, Zhao Q, Yu Y, et al. Efficacy and safety of bupropion hydrochloride extended-release versus escitalopram oxalate in Chinese patients with major depressive disorder: Results from a randomized, double-blind, non-inferiority trial. *J Affect Disord*. 2019;257:143-149. doi:10.1016/j.jad.2019.07.023

57. Verbeeck W, Bekkering GE, Van den Noortgate W, Kramers C. Bupropion for attention deficit hyperactivity disorder (ADHD) in adults. *Cochrane Database Syst Rev*. 2017;2017(10):CD009504. doi:10.1002/14651858.cd009504.pub2

58. Ng QX. A Systematic Review of the Use of Bupropion for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *J Child Adolesc Psychopharmacol*. 2017;27(2):112-116. doi:10.1089/cap.2016.0124

59. Tripp G, Wickens JR. Neurobiology of ADHD. *Neuropharmacology*. 2009;57(7-8):579-589. doi:10.1016/j.neuropharm.2009.07.026

60. Costa R, Oliveira NG, Dinis-Oliveira RJ. Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspects. *Drug Metab Rev*. 2019;51(3):293-313. doi:10.1080/03602532.2019.1620763

61. Learned-Coughlin SM, Bergström M, Savitcheva I, Ascher J, Schmith VD, Långstrom B. In vivo activity of bupropion at the human dopamine transporter as measured by positron emission tomography. *Biol Psychiatry*. 2003;54(8):800-805. doi:10.1016/s0006-3223(02)01834-6

62. Maneeton N, Maneeton B, Srisurapanont M, Martin SD. Bupropion for adults with attention-deficit hyperactivity disorder: meta-analysis of randomized, placebo-controlled trials. *Psychiatry Clin Neurosci*. 2011;65(7):611-617. doi:10.1111/j.1440-1819.2011.02264.x

63. Li Y, Gao J, He S, Zhang Y, Wang Q. An Evaluation on the Efficacy and Safety of Treatments for Attention Deficit Hyperactivity Disorder in Children and Adolescents: a Comparison of Multiple Treatments. *Mol Neurobiol*. 2017;54(9):6655-6669. doi:10.1007/s12035-016-0179-6

64. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2018;5(9):727-738. doi:10.1016/s2215-0366(18)30269-4

65. Nazarova VA, Sokolov AV, Chubarev VN, Tarasov VV, Schiöth HB. Treatment of ADHD: Drugs, psychological therapies, devices, complementary and alternative methods as well as the trends in clinical trials. *Front Pharmacol*. 2022;13:1066988. doi:10.3389/fphar.2022.1066988

66. Catalá-López F, Hutton B, Núñez-Beltrán A, et al. The pharmacological and non-pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: A systematic review with network meta-analyses of randomised trials. *PloS One*. 2017;12(7):e0180355. doi:10.1371/journal.pone.0180355

67. Moriyama TS, Polanczyk GV, Terzi FS, Faria KM, Rohde LA. Psychopharmacology and psychotherapy for the treatment of adults with ADHD—a systematic review of available meta-analyses. *CNS Spectr*. 2013;18(6):296-306. doi:10.1017/s109285291300031x

68. Asherson P, Bushe C, Saylor K, Tanaka Y, Deberdt W, Upadhyaya H. Efficacy of atomoxetine in adults with attention deficit hyperactivity disorder: an integrated analysis of the complete database of multicenter placebo-controlled trials. *J Psychopharmacol*. 2014;28(9):837-846. doi:10.1177/0269881114542453

69. Stuhec M, Munda B, Svab V, Locatelli I. Comparative efficacy and acceptability of atomoxetine, lisdexamfetamine, bupropion and methylphenidate in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis with focus on bupropion. *J Affect Disord*. 2015;178:149-159. doi:10.1016/j.jad.2015.03.006

70. McCabe DJ, McGillis E, Willenbring BA. The Timing of Clinical Effects of Bupropion Misuse Via Insufflation Reported to a Regional Poison Center. *J Emerg Med*. 2022;62(2):175-181. doi:10.1016/j.jemermed.2021.07.052

71. Tiwari RK, Sharma V, Pandey RK, Shukla SS. Nicotine Addiction: Neurobiology and Mechanism. *J Pharmacopuncture*. 2020;23(1):1-7. doi:10.3831/kpi.2020.23.001

72. Picciotto MR, Kenny PJ. Mechanisms of Nicotine Addiction. *Cold Spring Harb Perspect Med*. 2021;11(5):a039610. doi:10.1101/cshperspect.a039610

73. Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature*. 1996;382(6588):255-257. doi:10.1038/382255a0

74. Hays JT, Hurt RD, Rigotti NA, et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. a randomized, controlled trial. *Ann Intern Med*. 2001;135(6):423-433. doi:10.7326/0003-4819-135-6-200109180-00011

75. Hughes J. Depression during tobacco abstinence. *Nicotine Tob Res*. 2007;9(4):443-446. doi:10.1080/14622200701243185

76. Giulietti F, Filipponi A, Rosettani G, et al. Pharmacological Approach to Smoking Cessation: An Updated Review for Daily Clinical Practice. *High Blood Press Cardiovasc Prev*. 2020;27(5):349-362. doi:10.1007/s40292-020-00396-9

77. Huecker MR, Smiley A, Saadabadi A. Bupropion. In: *StatPearls*. StatPearls Publishing; 2022. Accessed January 30, 2023. http://www.ncbi.nlm.nih.gov/books/NBK470212/

78. Warner C, Shoaib M. How does bupropion work as a smoking cessation aid? *Addict Biol*. 2005;10(3):219-231. doi:10.1080/13556210500222670

79. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*. 2013;2013(5):CD009329. doi:10.1002/14651858.cd009329.pub2

80. Son JW, Kim S. Comprehensive Review of Current and Upcoming Anti-Obesity Drugs. *Diabetes Metab J*. 2020;44(6):802-818. doi:10.4093/dmj.2020.0258

81. Wang GJ, Volkow ND, Logan J, et al. Brain dopamine and obesity. *Lancet*. 2001;357(9253):354-357. doi:10.1016/s0140-6736(00)03643-6

82. Patnode CD, Henderson JT, Coppola EL, Melnikow J, Durbin S, Thomas RG. Interventions for Tobacco Cessation in Adults, Including Pregnant Persons: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2021;325(3):280-298. doi:10.1001/jama.2020.23541

83. Rigotti NA, Kruse GR, Livingstone-Banks J, Hartmann-Boyce J. Treatment of Tobacco Smoking: A Review. *JAMA*. 2022;327(6):566-577. doi:10.1001/jama.2022.0395

84. Yan T, Goldman RD. Bupropion for smoking cessation in adolescents. *Can Fam Physician*. 2021;67(10):743-745. doi:10.46747/cfp.6710743

85. Kranzler HR, Washio Y, Zindel LR, et al. Placebo-controlled trial of bupropion for smoking cessation in pregnant women. *Am J Obstet Gynecol MFM*. 2021;3(6):100315. doi:10.1016/j.ajogmf.2021.100315

86. Weinberger AH, Bandiera FC, Leventhal AM, et al. Socioeconomic Disparities in Smoking Among U.S. Adults With Depression, 2005–2014. *Am J Prev Med*. 2018;54(6):765-775. doi:10.1016/j.amepre.2018.02.008

87. Cinciripini PM, Kypriotakis G, Green C, et al. The effects of varenicline, bupropion, nicotine patch, and placebo on smoking cessation among smokers with major depression: A randomized clinical trial. *Depress Anxiety*. 2022;39(5):429-440. doi:10.1002/da.23259

88. Jordan CJ, Xi ZX. Discovery and development of varenicline for smoking cessation. *Expert Opin Drug Discov*. 2018;13(7):671-683. doi:10.1080/17460441.2018.1458090

89. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *J Med Chem*. 2005;48(10):3474-3477. doi:10.1021/jm050069n

90. Guo K, Wang S, Shang X, et al. The effect of Varenicline and Bupropion on smoking cessation: A network meta-analysis of 20 randomized controlled trials. *Addict Behav*. 2022;131:107329. doi:10.1016/j.addbeh.2022.107329

91. Vogeler T, McClain C, Evoy KE. Combination bupropion SR and varenicline for smoking cessation: a systematic review. *Am J Drug Alcohol Abuse*. 2016;42(2):129-139. doi:10.3109/00952990.2015.1117480

92. Zaso MJ, Hendershot CS. Effects of varenicline and bupropion on laboratory smoking outcomes: Meta-analysis of randomized, placebo-controlled human laboratory studies. *Addict Biol*. 2022;27(5):e13218. doi:10.1111/adb.13218

93. Zhong Z, Zhao S, Zhao Y, Xia S. Combination therapy of varenicline and bupropion in smoking cessation: A meta-analysis of the randomized controlled trials. *Compr Psychiatry*. 2019;95:152125. doi:10.1016/j.comppsych.2019.152125

94. Karadoğan D, Önal Ö, Şahin DS, Kanbay Y, Alp S, Şahin Ü. Treatment adherence and short-term outcomes of smoking cessation outpatient clinic patients. *Tob Induc Dis*. 2018;16:38. doi:10.18332/tid/94212

95. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2016;2016(5):CD006103. doi:10.1002/14651858.cd006103.pub7