Project TEACH
Cardiovascular and Psychiatric Adverse Events Associated with NRT and Bupropion

Sheila Kitaka MHP, PA-C

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Objectives

- Describe the current understanding of cardiovascular adverse events associated with NRT and Bupropion

- Describe the current understanding of psychiatric adverse events associated with NRT and Bupropion

Outline

1. - NRTs and Cardiovascular Events in 3 groups (general, smokers with no- known CVD, smokers with CVD)

2. - NRTs and Psychiatric Events

3. - Bupropion and Cardiovascular Events

4. - Bupropion and Psychiatric Events

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Background

- Smoking is a well known and an important risk for cardiovascular disease (CVD)

- Smoking cessation significantly reduces the CV risk by half or more within 1-2 years. At 5 years risk same as non-smokers

- Smoking is the main cause of premature death worldwide and the leading preventable cause of death in the USA

Background
(continued)

- 15% of adults in USA are current smokers and have a two - to fourfold increased risk of CVD
- Studies show suicide rate in smokers is about double that of non-smokers
- Stopping smoking (nicotine withdrawal) is associated with a short term increased risk of depression and suicide ideation/attempts

Background
(continued)

- Nicotine withdrawal is also associated with short-term worsening of psychiatric disorders independent of smoking cessation treatment.

- Smoking cessation results in improved quality of life with increase in life expectancy and reduction in healthcare costs.

Outline

1. - NRTs and Cardiovascular Events in 3 groups (general, smokers with no- known CVD, smokers with CVD)

2. - NRTs and Psychiatric Events

3. - Bupropion and Cardiovascular Events

4. - Bupropion and Psychiatric Events

NRT and CV Events (Smokers in General)

In recommended dosages studies show:

- NRT has less sympathetic autonomic stimulation compared to tobacco smoking

- NRT does not result in platelet aggregation and thrombotic CVD effects associated with smoking

NRT and CV Events (Smokers in general)
(continued)

- Nicotine patches do not result in platelet activation or elevation in fibrinogen levels

- Although Nicotine patches demonstrated greater autonomic effects than placebo patch, this was associated with minimal change in autonomic cardiac control

NRT and CV Events (Smokers in general)
(continued)

- No evidence of aggravation of myocardial ischemia or arrhythmias in smokers with coronary artery disease who received nicotine patch

- Similarly, nicotine gum and nasal sprays have shown that NRT does not cause coronary vasoconstriction in smokers

NRT and CV Events (Current Smokers)

How about using NRT while still smoking:

- Double-blinded placebo-controlled study- high dose nicotine patch along with cigarette smoking showed no additional adverse effects on HR, BP, fibrinogen levels or lipid profiles in long-term smokers

NRT and CV Events (Current Smokers)
(continued)

NRT along with cigarette smoking no additional harm:

- Possible explanation- the long-term smoker develops tolerance to nicotine and therefore has minimal cardiovascular changes with additional nicotine from NRTs.

NRT and CV Events (Smokers Without Known CVD)

- Extensively researched in this group: safe and effective
- Meta-analysis of 34 RCTs of smoking cessation with NRTs (excluded pts with CVD or risk factors) concluded: No difference in CVD events between smokers using nicotine patches and smokers using placebo.
- Similar results reported in a large population-based, case-control study

NRT and CV Events (Smokers With Known CVD)

- 2 major studies in smokers on NRT (patch) with CVD- found no significant increased risk of CVD compared to placebo
- No RCTs in patients in the first two weeks post acute coronary syndrome
- Therefore, Clinical Practice Guidelines recommends using NRT with caution in patients with CVD- especially within 2 weeks post MI, especially if they have serious arrhythmias or progressive angina

NRT and CV Events (Smokers With Known CVD)
(continued)

- The American College of Cardiology/American Heart Association recommends pharmacotherapy including NRT in combination with counseling for patients with heart attack at the time of hospital discharge if BP and HR are stable.

- NRT is preferable to cigarette smoking for patients who experience withdrawal symptoms from nicotine post hospital discharge.

NRT Cardiovascular Review

Summary:

- NRTs have a low risk of harm

- Benefits outweigh low risk of serious adverse CV events associated with use of tobacco treatment medications

- Many studies confirm that NRT even with concurrent smoking is safe in patients with CV disease

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Outline

1. - NRTs and Cardiovascular Events in 3 groups (general, smokers with no- known CVD, smokers with CVD)

2. - NRTs and Psychiatric Events

3. - Bupropion and Cardiovascular Events

4. - Bupropion and Psychiatric Events

NRT and Psychiatric Events

- NRTs are designed to partially replace nicotine obtained from tobacco use/smoking.

- The goal of NRTs to relieve withdrawal symptoms that are similar to psychiatric symptoms such as depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty concentration, restlessness.

NRT Psychiatric Review

Summary:

- NRT helpful and not harmful

Outline

1. - NRTs and Cardiovascular Events in 3 groups (general, smokers with no- known CVD, smokers with CVD)

2. - NRTs and Psychiatric Events

3. - Bupropion and Cardiovascular Events

4. - Bupropion and Psychiatric Events

Bupropion and CV Events

- First alternative to NRT (1997)

- Norepinephrine, dopamine reuptake inhibitor and nicotine receptor antagonist- which can result in dose-related risk of seizures and CVD side effects, especially hypertension.

Bupropion and CV Events

(continued)

- Major meta-analysis of 21 RCTs showed bupropion not harmful for Major Adverse Cardiac Events (MACEs) and appeared to have a cardioprotective effect.

- It is possible that antidepressant effects of bupropion reduces vascular stress.

Bupropion and CV Events

(continued)

- French Pharmacovigilance Database from 2001-2004 on serious adverse effects – Did not show an increase in CVD risk with the use of bupropion for smoking cessation

- Caution: Bupropion can cause increase in HR and BP at higher doses due to sympathomimetic activity.

Bupropion Cardiovascular Review

Summary:

- Bupropion not harmful for Major CV events but may have a cardioprotective effect.

- At higher doses, use with caution in patients with hypertension or increase heart rates

Outline

1. - NRTs and Cardiovascular Events in 3 groups (general, smokers with no- known CVD, smokers with CVD)

2. - NRTs and Psychiatric Events

3. - Bupropion and Cardiovascular Events

4. - Bupropion and Psychiatric Events

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Bupropion and Psychiatric Events

- French Pharmacovigilance Database 2001-2004: 700,000 patients

- 1700 adverse reactions were reported. Among those 17% were serious neuropsychiatric. A cause of concern were suicide attempts/suicides- although risk factors (history of depression, suicide attempts, etc) were described for 66% of patients experiencing these events.

Bupropion and Psychiatric Events
(continued)

- In 2009, FDA issued a black-box warning for Bupropion regarding the risk of psychiatric events such as depressed mood, suicidal tendency and hostility
- Decision based on post-marketing reports on all antidepressants
- May have been confounded by underlying nicotine dependence, tobacco-withdrawal or other psychiatric illnesses

Bupropion and Psychiatric Events
(continued)

- A Cochrane review (2014) found little evidence of increased risk of psychiatric adverse events associated with bupropion use except 1 study using FDA's adverse Effects Reporting System database which found elevated risk associated with both Varenicline and bupropion use.
- After that review FDA updated the warning that there is no solid evidence

Bupropion and Psychiatric Events
(continued)

Use with caution

- Bipolar patient due to possibility of manic activity
- Heavy alcohol use
- Some psychotropic medication such as tricyclic antidepressants
- Current or previous history of anorexia
- Current or previous history of a seizure disorder

Newest Published Study

A large multinational trial (EAGLES) **published LANCET** April 22, 2016

Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders: double-blind, randomized, placebo-controlled clinical trial

1- Patients **without** a current or past history of a psychiatric disorder- No difference in neuropsychiatric adverse-effects for Chantix, Bupropion, patch compared to placebo

2- Patients **with** current (stable) or past history of psychiatric disorder- No difference in neuropsychiatric AEs across treatment verse placebo

3- However a 4% increase in rate of neuropsychiatric AE in the psychiatric cohort compared to the non- psychiatric cohort across treatments and placebo

Newest Published Study

Limitations of study:

-Study included only smokers with stable and treated psychiatric disorders.

-It did not include patients with substance use disorder in past 12 months

Findings cannot be generalized to those with active substance use disorders

Conclusion: Smoking cessation medication (Chantix, bupropion and patch) have similar neuropsychiatric AEs to placebo among patients with or without a psychiatric diagnosis or history.

Patients with psychiatric diagnosis or history have a 4 % increase in neuropsychiatric AEs when they try to quit smoking regardless of medication or placebo.

NRT Safety - Conclusion

- NRT- does not have a significant risk factor for CV disease and is used to relieve withdrawal symptoms which includes psychiatric symptoms

- NRT does not appear to provoke acute CV events, even in people with pre-existing CV disease

- The use of NRT is much safer than smoking

Bupropion Safety - Conclusion

- No excess of CVD events for bupropion users
- There is little evidence of increased risk of psychiatric adverse events associated with bupropion
- Avoid use in patient's at risk for seizures.

References

- The health risk profile of medicinal nicotine was the subject of extensive review in the recent Royal College of Physician's report, "Harm Reduction In Nicotine Addiction", published in October, 2007.20
- Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. Arch Intern Med. 2000;160:939–44.5
- Lucini D, Bertocchi F,Malliani A, PaganiM. Autonomic effects of nicotine patch administration in habitual cigarette smokers: a double-blind, placebo-controlled study using spectral analysis of RR interval and systolic arterial pressure variabilities. J Cardiovasc Pharmacol. 1998;31:714–20
- Zevin S, Jacob 3rd P, Benowitz NL. Dose-related cardiovascular and endocrine effects of transdermal nicotine. Clin Pharmacol Ther. 1998;64:87–95.
- Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, Steele BG, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N Engl J Med. 1996;335:1792–8.
- Haustein KO, Krause J, Haustein H, Rasmussen T, Cort N. Comparison of the effects of combined nicotine replacement therapy vs. cigarette smoking in males. Nicotine Tob Res. 2003;5:195–203.37.
- Greenland S, Satterfield MH, Lanes SF. A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. Drug Saf. 1998;18:297–308.
- Circulation. 2014 Jan 7;129(1):28-41. doi: 10.1161/CIRCULATIONAHA.113.003961. Epub 2013 Dec 9. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. Mills EJ1, Thorlund K, Eapen S, Wu P, Prochaska JJ.
- Am J Psychiatry. 2001 Apr;158(4):635-7. Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. Weiner E1, Ball MP, Summerfelt A, Gold J, Buchanan RW.)
- Mills EJ, Thorlund K, Eapen S,Wu P, Prochaska JJ. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. Circulation. 2014;129:28–41.
- 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;31:1017–26
- J.R. Hughes, L.F. Stead, J. Hartmann-Boyce, K. Cahill, T. Lancaster Antidepressants for smoking cessation. Cochrane Database Syst. Rev. (1) (2014), p. CD000031