Use of Contrave®, naltrexone with bupropion, bupropion, or naltrexone and major adverse cardiovascular events: a systematic literature review

Supplemental Material

Original Study Protocol

Search strategy:

The literature search strategy has been developed with the aim of identifying publications containing estimates of cardiovascular adverse events possibly associated with use of Contrave® (or Mysimba) or its components, naltrexone and bupropion. This search strategy is designed to capture available data on adverse events following use of Contrave® or its components.

Table 1. Summary of search strategies considered.

Search #	Search Terms	# Articles
1	(Contrave OR naltrexone OR bupropion OR Mysimba)	5271
2	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu*)	2239
3	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu*) NOT (opioid OR addict* OR overdose)	1054
4	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu* OR blood pressure OR systolic OR diastolic OR ventric* OR stenosis OR aortic valve OR ECG or EKG or electrocardiogram OR *cardia OR “MI” OR palpitation OR fibrillation OR afib OR atrial flutter OR chest pain OR atria* OR pericarditis OR “CHF” OR “CAD”)	2312
5	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu* OR cardio* OR cardiac*)	2470
6	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR	2239

	atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu* OR myocarditis)	
7	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu* OR blood pressure OR systolic OR diastolic OR ventric* OR stenosis OR aortic valve OR ECG or EKG or electrocardiogram OR *cardia OR "MI" OR palpitation OR fibrillation OR afib OR atrial flutter OR chest pain OR atria* OR pericarditis OR "CHF" OR "CAD" OR myocarditis)	2312
8	**(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu* OR blood pressure OR systolic OR diastolic OR ventric* OR stenosis OR aortic valve OR ECG or EKG or electrocardiogram OR *cardia OR "MI" OR palpitation OR fibrillation OR afib OR atrial flutter OR chest pain OR atria* OR pericarditis OR "CHF" OR "CAD" OR myocarditis OR cardio* OR cardiac*)**	**2539**

All articles are published from January 1, 2012 to September 30, 2021.

PubMed (MEDLINE®) will be searched for relevant publications, using search #8 (2539 articles).

Using the aforementioned search terms, a systematic literature review will be conducted. The review of the literature will occur in two phases:

- "Level 1": Using a literature search strategy, further described below, this review with identify articles that meet the criteria of interest. At this first-level review, the titles and abstracts retrieved through the literature search will be screened for potential relevance.

All articles will be screened in EndNote using the following exclusion criteria for Level 1:

i. Animal studies (*in vivo*)
ii. *In vitro* studies
iii. Case reports/case series
iv. Specific exposures other than bupropion and/or naltrexone
v. Pharmacokinetics/pharmacogenetics
vi. Policy, economics, health care access, clinical guidelines/recommendations
vii. Reviews, editorials, commentaries without original data
viii. Study protocols

- "Level 2": At this full-text review stage, additional exclusions may be made, as papers may actually not report findings of interest, or may have presented a second report of a single study that includes no additional information on cardiovascular events. Articles that fulfill inclusion criteria will be included in the data extraction process. To guide

inclusion and exclusion, the following PICOS (population, intervention, comparator, outcome, and study design) statement was developed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

a. Level 2 Inclusion Criteria
    i. Type of population: Human populations, not limited to the indicated population
    ii. Type of intervention: Contrave, naltrexone, bupropion, Mysimba
    iii. Type of comparator: placebo, or active comparator that is not Contrave, naltrexone, bupropion, or Mysimba
    iv. Type of outcome: any clinically diagnosed cardiovascular endpoint, e.g. MACE, nonfatal myocardial infarction, nonfatal stroke, cardiovascular mortality, cerebrovascular disease, heart failure, atrial fibrillation, unstable angina, myocarditis, or hypertension
    v. Type of studies: randomized control trials (RCTs), cohort and case-control studies, and other epidemiologic study designs (e.g. cross-sectional)
    vi. Publication date: on or after January 1, 2012
    vii. Language: English
b. Level 2 Exclusion Criteria
    i. Intervention is not Contrave (or Mysimba), bupropion, or naltrexone
    ii. Intervention is bupropion used in combination with other active ingredient (e.g. escitalopram)
    iii. Intervention is naltrexone used in combination with other active ingredient (e.g. gabapentin)
    iv. No comparator group for intervention drug
    v. Outcome is laboratory value, symptom, or other endpoint other than a clinically diagnosed cardiovascular endpoint (e.g., electrocardiogram readings, cholesterol level, blood pressure)
    vi. Type of publications: conference abstracts, case reports, non-peer-reviewed data sources (i.e. grey literature)
    vii. Non-human (animal) *in vivo* studies, *in vitro* studies
    viii. No original data (e.g., reviews, editorials, commentaries, meta-analyses without previously unpublished data)

Articles that are included following Level 1 screening, and not freely available, will be ordered by Exponent to expedite the screening and abstraction process. Articles that are excluded during Level 1 screening will be classified in the EndNote library according to reasons for exclusion.

c. Data Extraction

    Once Level 2 screening is complete, articles meeting inclusion criteria will be reviewed and summarized by data abstractors into data extraction table(s) that will include established data extraction fields, agreed upon in advance by study authors. All article extractions will be reviewed for accuracy and completeness by a second reviewer as a quality-control measure, and a third reviewer will be consulted, if necessary, to resolve any discrepancies.

Data abstraction fields

The following information was considered relevant a priori for extraction from each of the relevant studies: first author surname and/or source, year of publication, study design, calendar years of study, study country, total sample size, number of patients in safety analyses, underlying disease (indication), study inclusion criteria, study exclusion criteria, age range, distribution of patients by sex, baseline prevalence of conditions potentially relevant to the adverse events of interest (% diabetes, % smoking, BMI (mean), % overweight, % obese), experimental treatment type, experimental treatment dose, experimental treatment duration, comparator treatment type, comparator treatment dose, comparator treatment duration, adverse event classification system, duration of follow-up, cardiovascular adverse event type and definition, and, for each type of adverse event of interest, the number of reported events, adverse event measures and p-value/statistical significance of treatment vs comparator. These fields were entered into a spreadsheet for standardized data extraction. Any studies excluded from the literature review were noted separately along with the reason for exclusion.

For studies that reported “no adverse events,” “no serious adverse events,” or “no deaths,” or where it could otherwise be clearly inferred that no cardiovascular adverse events occurred (or no serious cardiovascular events or no cardiovascular deaths occurred, respectively), minimal data abstraction was conducted to extract only the following information: first author surname and/or source, year of publication, number of patients in safety analyses, experimental treatment type, comparator treatment type, adverse event classification, duration of follow-up, cardiovascular adverse event type, and, for each type of adverse event of interest, the number of reported events, adverse event measures and p-value/statistical significance of treatment vs comparator.

Supplemental Tables

Please see accompanying excel spreadsheet, titled “Supplemental tables_manuscript”, for supplemental tables 1-3.

Supplemental Table 1. Contrave® and naltrexone-bupropion studies reporting on non-MACE cardiovascular adverse events.

Author	Year	Treatment	Study design	Study indication	Reported length of follow-up	No. Patients	Outcome	Adverse event frequency, treatment group	Adverse event frequency, comparator group	Effect measure
					24 months or until patients stopped randomized treatment	8894	Angina unstable	Naltrexone-bupropion + no antidepressant: 10/3300 (0.3%)	Naltrexone-bupropion + antidepressant: 11/1150 (1.0%) Placebo + no antidepressant: 9/3317 (0.3%) Placebo + antidepressant: 4/1127 (0.4%)	Naltrexone-bupropion + antidepressant: Fisher's exact p = 0.01 (calculated) Placebo + no antidepressant: Fisher's exact p = 0.82 (calculated) Placebo + antidepressant: Fisher's exact p = 0.76 (calculated)
							Angina pectoris	Naltrexone-bupropion + no antidepressant: 0/890 (0.0%)	Naltrexone-bupropion + antidepressant: 4/206 (1.9%) Placebo + no antidepressant: 4/585 (0.7%) Placebo + antidepressant: 2/130 (1.5%)	Naltrexone-bupropion + antidepressant: Fisher's exact p = 0.001 (calculated) Placebo + no antidepressant: Fisher's exact p = 0.02 (calculated) Placebo + antidepressant: Fisher's exact p = 0.02 (calculated)
McIntyre	2021	Contrave®	RCT	Weight loss	24 months	1811	Angina unstable	Naltrexone-bupropion + no antidepressant: 4/890 (0.4%)	Naltrexone-bupropion + antidepressant: 2/206 (1.0%) Placebo + no antidepressant: 2/585 (0.3%) Placebo + antidepressant: 0/130 (0.0%)	Naltrexone-bupropion + antidepressant: Fisher's exact p = 0.32 (calculated) Placebo + no antidepressant: Fisher's exact p = 1.00 (calculated) Placebo + antidepressant: Fisher's exact p = 1.00 (calculated)
Nissen	2016	Contrave®	RCT	Weight loss	Median 121 weeks, interquartile range 114-	8905	Hospitalization for unstable angina	Naltrexone-bupropion: 51/4,455 (1.1%) at end of study 47/4,455 (1.1%) at 50% interim 29/4,455 (0.7%) at 25% interim	Placebo: 50/4,450 (1.1%) at end of study 43/4,450 (1.0%) at 50% interim 23/4,450 (0.5%) at 25% interim	HR (99.7% CI) at end of study 1.01 (0.57-1.82) at 50% interim 1.09 (0.59-2.02) at 25% interim 1.26 (0.73-2.18)
Wharton	2021	Contrave®	RCT	Type 2 diabetes	52 weeks	1317	Unstable angina	Naltrexone-bupropion + dipeptidyl peptidase 4 inhibitor: 4/345 (1.2%) Naltrexone-bupropion + glucagon-like peptide-1 receptor agonist: 8/339 (2.4%)	Placebo + dipeptidyl peptidase 4 inhibitor: 1/317 (0.3%) Placebo + glucagon-like peptide-1 receptor agonist: 2/316 (0.6%)	Placebo + dipeptidyl peptidase 4 inhibitor: Fisher's exact p = 0.38 (calculated) Placebo + glucagon-like peptide-1 receptor agonist: Fisher's exact p = 0.11 (calculated)
Halseth	2018	Contrave®	RCT	Weight loss	26 weeks	242	Hypertension	Naltrexone-bupropion: 2/153 (1.3%)	Usual care: 0/89 (0%)	Fisher's exact p = 0.533 (calculated)
Hollander	2013	Contrave®	RCT	Weight loss	56 weeks	502	Hypertension	Contrave: 33/333 (9.9%)	Placebo: 7/169 (4.1%)	Fisher's exact p = 0.02 (calculated)
Trivedi	2021	Injectable naltrexone + oral bupropion	RCT	Substance use	12 weeks (6 weeks per stage)	403	Hypertension	1/109 (0.9%) naltrexone-bupropion stage 1 0/114 (0%) naltrexone-bupropion stage 2 re-randomized 0/109 (0%) naltrexone-bupropion stage 2 not re-randomized	2/294 (0.7%) placebo stage 1 0/111 (0%) placebo stage 2 re-randomized 0/69 (0%) placebo stage 2 not re-randomized	Placebo stage 1: Fisher's exact p = 1.00 (calculated) Placebo stage 2 re-randomized: Fisher's exact p = 1.00 (calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 1.00 (calculated)
Trivedi	2021	Injectable naltrexone + oral bupropion	RCT	Substance use	12 weeks (6 weeks per stage)	403	Acute cardiac failure	0/109 (0%) naltrexone-bupropion stage 1 0/114 (0%) naltrexone-bupropion stage 2 re-randomized 1/109 (0.9%) naltrexone-bupropion stage 2 not re-randomized	0/294 (0%) placebo stage 1 0/111 (0%) placebo stage 2 re-randomized 0/69 (0%) placebo stage 2 not re-randomized	Placebo stage 1: Fisher's exact p = 1.00 (calculated) Placebo stage 2 re-randomized: Fisher's exact p = 1.00 (calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 1.00 (calculated)
Trivedi	2021	Injectable naltrexone + oral bupropion	RCT	Substance use	12 weeks (6 weeks per stage)	403	Cardiac disorders	1/109 (0.9%) naltrexone-bupropion stage 1 1/114 (0.9%) naltrexone-bupropion stage 2 re-randomized 1/109 (0.9%) naltrexone-bupropion stage 2 not re-randomized	2/294 (0.7%) placebo stage 1 0/111 (0%) placebo stage 2 re-randomized 0/69 (0%) placebo stage 2 not re-randomized	Placebo stage 1: Fisher's exact p = 1.00 (calculated) Placebo stage 2 re-randomized: Fisher's exact p = 1.00 (calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 1.00 (calculated)
McIntyre	2021	Contrave®	RCT	Weight loss	104 weeks	8894	Coronary artery disease	Naltrexone-bupropion + no antidepressant: 6/890 (0.7%)	Naltrexone-bupropion + antidepressant: 3/206 (1.5%) Placebo + no antidepressant: 4/585 (0.7%) Placebo + antidepressant: 0/130 (0.0%)	Naltrexone-bupropion + antidepressant: Fisher's exact p = 0.38 (calculated) Placebo + no antidepressant: Fisher's exact p = 1.00 (calculated) Placebo + antidepressant: Fisher's exact p = 1.00 (calculated)
Nissen	2016	Contrave®	RCT	Weight loss	Median 121 weeks, interquartile range 114-128	8905	Coronary revascularization	Naltrexone-bupropion: 152/4,455 (3.4%) at end of study 132/4,455 (3.0%) at 50% interim 65/4,455 (1.5%) at 25% interim	Placebo: 170/4,450 (3.8%) at end of study 145/4,450 (3.3%) at 50% interim 65/4,450 (1.5%) at 25% interim	HR (99.7% CI) 0.89 (0.64-1.23) at end of study 0.91 (0.64-1.29) at 50% interim 1.00 (0.71-1.41) at 25% interim
Trivedi	2021	Injectable naltrexone + oral bupropion	RCT	Substance use	12 weeks (6 weeks per stage)	403	Hematoma	0/109 (0%) naltrexone-bupropion stage 1 2/114 (1.8%) naltrexone-bupropion stage 2 re-randomized 0/109 (0%) naltrexone-bupropion stage 2 not re-randomized	0/294 (0%) placebo stage 1 0/111 (0%) placebo stage 2 re-randomized 0/69 (0%) placebo stage 2 not re-randomized	Placebo stage 1: Fisher's exact p = 1.00 (calculated) Placebo stage 2 re-randomized: Fisher's exact p = 0.50 (calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 1.00 (calculated)
Trivedi	2021	Injectable naltrexone + oral bupropion	RCT	Substance use	12 weeks (6 weeks per stage)	403	Hypertensive crisis	0/109 (0%) naltrexone-bupropion after randomization	1/403 (0.2%) after screening but prior to randomization	Fisher's exact p = 1.00 (calculated)
Trivedi	2021	Injectable naltrexone + oral bupropion	RCT	Substance use	12 weeks (6 weeks per stage)	403	Othorstatic hypotension	0/109 (0%) naltrexone-bupropion stage 1 0/114 (0%) naltrexone-bupropion stage 2 re-randomized 0/109 (0%) naltrexone-bupropion stage 2 not re-randomized	1/294 (0.3%) placebo stage 1 0/111 (0%) placebo stage 2 re-randomized 0/69 (0%) placebo stage 2 not re-randomized	Placebo stage 1: Fisher's exact p = 1.00 (calculated) Placebo stage 2 re-randomized: Fisher's exact p = 1.00 (calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 1.00 (calculated)
Trivedi	2021	Injectable naltrexone + oral bupropion	RCT	Substance use	12 weeks (6 weeks per stage)	403	Hypotension	0/109 (0%) naltrexone-bupropion stage 1 1/114 (0.9%) naltrexone-bupropion stage 2 re-randomized 0/109 (0%) naltrexone-bupropion stage 2 not re-randomized	0/294 (0%) placebo stage 1 0/111 (0%) placebo stage 2 re-randomized 0/69 (0%) placebo stage 2 not re-randomized	Placebo stage 1: Fisher's exact p = 1.00 (calculated) Placebo stage 2 re-randomized: Fisher's exact p = 1.00 (calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 1.00 (calculated)
Halseth	2018	Contrave®	RCT	Weight loss	26 weeks	242	Palpitations / tachycardia	Naltrexone-bupropion: 2/153 (1.3%)	Usual care: 0/89 (0%)	Fisher's exact p = 0.53 (calculated)
Nissen	2016	Contrave®	RCT	Weight loss	Median 121 weeks, interquartile range 114-128 weeks	8905	Palpitations	Naltrexone-bupropion: 19/4,455 (0.4%)	Placebo: 5/4,450 (0.1%)	Fisher's exact p = 0.007 (calculated)
Trivedi	2021	Injectable naltrexone + oral bupropion	RCT	Substance use	12 weeks (6 weeks per stage)	403	Thrombophlebitis	0/109 (0%) naltrexone-bupropion stage 1 0/114 (0%) naltrexone-bupropion stage 2 re-randomized 1/109 (0.9%) naltrexone-bupropion stage 2 not re-randomized	0/294 (0%) placebo stage 1 0/111 (0%) placebo stage 2 re-randomized 0/69 (0%) placebo stage 2 not re-randomized	Placebo stage 1: Fisher's exact p = 1.00 (calculated) Placebo stage 2 re-randomized: Fisher's exact p = 1.00 (calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 1.00 (calculated)
Trivedi	2021	Injectable naltrexone + oral bupropion	RCT	Substance use	12 weeks (6 weeks per stage)	403	Thrombophlebitis superficial	0/109 (0%) naltrexone-bupropion stage 1 0/114 (0%) naltrexone-bupropion stage 2 re-randomized 0/109 (0%) naltrexone-bupropion stage 2 not re-randomized	0/294 (0%) placebo stage 1 1/111 (0.9%) placebo stage 2 re-randomized 0/69 (0%) placebo stage 2 not re-randomized	Placebo stage 1: Fisher's exact p = 1.00 (calculated) Placebo stage 2 re-randomized: Fisher's exact p = 0.50 (calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 1.00(calculated)
Trivedi	2021	Injectable naltrexone + oral bupropion	RCT	Substance use	12 weeks (6 weeks per stage)	403	Vascular disorders	5/109 (4.6%) naltrexone-bupropion stage 1 3/114 (2.6%) naltrexone-bupropion stage 2 re-randomized 2/109 (1.8%) naltrexone-bupropion stage 2 not re-randomized	5/294 (1.7%) placebo stage 1 1/111 (0.9%) placebo stage 2 re-randomized 0/69 (0%) placebo stage 2 not re-randomized	Placebo stage 1: Fisher's exact p = 0.14 (calculated) Placebo stage 2 re-randomized: Fisher's exact p = 0.62 (calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 0.52 (calculated)

Supplemental Table 2. Bupropion studies reporting on non-MACE cardiovascular adverse events.

Author	Year	Study design	Study indication	Reported length of follow-up	No. Patients	Outcome	Adverse event frequency, treatment group	Adverse event frequency, comparator group	Effect measure
Carney	2020	Observational cohort	Smoking cessation	12 months, or patient therapy duration plus 30 days (time-to-event sensitivity)	618,497	Composite cardiovascular	1,743/131,562 (1.3%)	NRT : 1,237/32,237 (3.8%) Varenicline: 8,244/454,698 (1.8%)	Adjusted RR (95% CI) = 0.75 (0.69-0.81) Adjusted RR (95% CI) = 0.83 (0.78-0.87)
						Composite cardiovascular events (time-to-event sensitivity analyses)	912/131,562 (0.7%), patient years 52,364 Incidence rate per 1000 patient-years = 17.4	NRT: 441/32,237 (1.4%), patient years: 5,835 Incidence rate per 1000 patient-years = 75.6 Varenicline: 2845/454,698 (0.6%) Incidence rate per 1000 patient-years = 29.8	Adjusted HR (95% CI) = 0.66 (0.58-0.75) Fisher's exact p = 0.007 (calculated)
						Composite cardiovascular	1,534/121,416 (1.3%)	NRT: 715/26,004 (2.7%)	Adjusted RR (95% CI) = 0.73 (0.67-0.81)
Carney	2021	Observational cohort	Smoking cessation	Primary analysis 1 year, secondary analysis 6 months	116,442	Composite cardiovascular events (1 year and 6 month follow-up)	1-year: 96/5,838 (1.6%)	NRT 1-year: 1,348/71,510 (1.9%) Varenicline 1-year: 595/39,094 (1.5%)	Adjusted RR (95% CI) = 0.95 (0.77-1.17) Fisher's exact p = 0.46 (calculated)
							6-mo: 59/5,838 (1.0%)	NRT 6-mo: 802/71,510 (1.1%) Varenicline 6-mo: 331/39,094 (0.8%)	Adjusted RR (95% CI) = 1.02 (0.78-1.34) Fisher's exact p = 0.23 (calculated)
					110,921	Composite cardiovascular events (patients with no history of	1-year: 63/5,578 (1.1%)	NRT 1-year: 773/67,758 (1.1%) Varenicline 1-year: 404/37,585 (1.1%)	Adjusted RR (95% CI) = 0.94 (0.72-1.22) Fisher's exact p = 0.73 (calculated)
							6-mo: 33/5,578 (0.6%)	NRT 6-mo: 439/67,758 (0.6%) Varenicline 6-mo: 279/37,585 (0.7%)	Adjusted RR (95% CI) = 0.93 (0.65-1.34) Fisher's exact p = 0.24 (calculated)
Carney	2021	Observational cohort	Smoking cessation		44,932	Composite cardiovascular events (direct comparison between bupropion and varenicline)	96/5,838 (1.6%)	Varenicline: 595/39,094 (1.5%)	Adjusted RR (95% CI) = 0.99 (0.79-1.23)
Graham	2014	Observational cohort	Smoking cessation	6 months	88,957	First degree composite (acute MI, stroke, death)	61/14133 (0.4%)	Varenicline: 256/74824 (0.3%)	Adjusted HR (95% CI) = 0.84 (0.58-1.23)
Svanström	2012	Observational cohort	Smoking cessation	6 months	35,852	Any major cardiovascular event (any of acute coronary syndrome, ischaemic stroke, or cardiovascular death) (Primary analyses)	60 events per 8,411 person-years, Incidence rate per 1,000 person-years: 7.1	Varenicline: 57 events per 8,268 person-years, Incidence rate per 1,000 person-years: 6.9	HR (95% CI) = 1.04 (0.72-1.49)
				6 weeks, 12 weeks, 12 months, 24 months (secondary analyses)		Any major CV event (any of acute coronary syndrome, ischaemic stroke, or cardiovascular death) (secondary analyses)	6 weeks: 20 events per 2,039 person-years. Incidence rate per 1,000 years: 9.8	Varenicline 6 weeks: 22 events per 2,032 person-years. Incidence rate per 1,000 years: 10.8	HR (95% CI) 6 weeks = 0.91 (0.50 - 1.67)
							12 weeks: 34 events per 4,022 person-years. Incidence rate per 1,000 years: 8.5	Varenicline 12 weeks: 32 events per 3,992 person-years. Incidence rate per 1,000 years: 8.0	HR (95% CI) 12 weeks = 1.05 (0.65 - 1.72)
							12 months: 103 events per 15,905 person-years. Incidence rate per 1,000 years: 6.5	Varenicline 12 months: 103 events per 15,300 person-years. Incidence rate per 1,000 years: 6.7	HR (95% CI) 12 months = 0.96 (0.74 - 1.27)
							24 months: 191 events per 27,948 person-years. Incidence rate per 1,000 years: 6.8	Varenicline 24 months: 193 events per 25,763 person-years. Incidence rate per 1,000 years: 7.5	HR (95% CI) 24 months = 0.91 (0.75 - 1.11)
Svanström	2012	Observational cohort	Smoking cessation	6 months (primary analyses)	35,852	Angina/ischaemic heart disease [diagnosis of angina/ischaemic heart disease or admission for coronary artery bypass grafting or percutaneous coronary intervention]	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1	Varenicline: 82 events per 8,247 person-years. Incidence rate per 1,000 person-years: 9.9	HR (95% CI) 1.12 (0.83 - 1.52)
Toh	2013	Observational cohort	Smoking cessation	From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last	202,897 271,863 1,005,664	Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or	Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%)	Varenicline in tobacco users: 56/89,519 (0.06%) Varenicline products approved for smoking cessation: 109/260,660 (0.04%) All varenicline users: 109/260,660 (0.04%)	IRR (95% CI) Adjusted:0.98 (0.68-1.41) IRR (95% CI) Adjusted:1.02 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83)
Benowitz	2018	RCT	Smoking cessation	52 weeks (p. E7)	8058	hospitalization for congestive heart failure	Bupropion: 1/2006 (<0.1%)	Varenicline: 0/2016 (0.0%) NRT: 1/2022 (<0.1%) Placebo: 5/2014 (0.2%)	Varenicline: Fisher's exact p = 0.50 (calculated) NRT: Fisher's exact p = 1.00 (calculated) Placebo: Fisher's exact p = 0.22 (calculated)
Carney	2020	observational cohort	Smoking cessation	12 months or Patient therapy duration plus 30 days	618497	heart failure (primary analyses)	Bupropion: 589/131,562 (0.5%)	NRT: 461/32,237 (1.4%) Varenicline: 1999/454,698 (0.4%)	RR (95% CI) Adjusted: 0.84 (0.74-0.96) Fisher's exact p = 0.71 (calculated)
						heart failure (time-to-event sensitivity analyses)	Bupropion: 322/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1	NRT: 148/32,237 (0.5%), patient years: 5,869, Incidence rate per 1000 patient-years: 25.2 Varenicline: 570/454,698 (0.1%), patient years: 95,854, Incidence rate per 1000 patient-years: 5.9	HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR
Carney	2021	observational cohort	Smoking cessation	Primary analysis 1 year	116442	heart failure	Bupropion: 30/5,838 (0.5%)	NRT: 433/71,510 (0.6%) Varenicline: 137/39,094 (0.4%)	RR (95% CI) Adjusted: 1.13 (0.77-1.65) Fisher's exact p = 0.06 (calculated)
Kittle	2017	RCT	Smoking cessation	≥ 6 weeks	7224	hospitalization for congestive heart failure	Bupropion: 1/4,297 (Proportion: 0.023%; 95% CI, 0.001-0.130%)	Placebo comparator: 2/2,927 (Proportion, 0.068%; 95% CI, 0.008-0.247%)	Fisher's exact p = 0.57 (calculated)
Kotz	2015	observational cohort	Smoking cessation	6 months	164766	Heart failure	Bupropion: 7/6,557 (0.1%)	NRT: 302/106,759 (0.3%) Varenicline: 52/51,450 (0.1%)	HR (95% CI) Adjusted: 0.71 (0.33-1.51) Propensity score matched: 0.44 (0.14-1.44) Fisher's exact p = 0.84 (calculated)
Kotz	2017	observational cohort	Smoking cessation	6 months	16679	Heart failure	Bupropion: 1/350 (0.3%)	NRT: 118/10,426 (1.1%) Varenicline: 18/3,574 (0.5%)	HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact p = 1.00 (calculated)
Svanström	2012	observational cohort	Smoking cessation	6 months (primary analyses)	35852	Heart failure	Bupropion: 16 events per 8,405 person-years. Incidence rate per 1,000 person-years: 1.9	Varenicline: 13 events per 8,264 person-years. Incidence rate per 1,000 person-years: 1.6	HR (95% CI) 1.22 (0.59 - 2.56)
Benowitz	2018	RCT	Smoking cessation	52 weeks	8058	hospitalization for unstable angina	Bupropion: 2/2006 (0.1%)	Varenicline: 1/2016 (<0.1%) NRT: 0/2022 (0.0%) Placebo: 0/2014 (0.0%)	Varenicline: Fisher's exact p = 0.62 (calculated) NRT: Fisher's exact p = 0.25 (calculated) Placebo: Fisher's exact p = 0.25 (calculated)
						angina (primary analyses)	Bupropion: 140/131,562 (0.1%)	NRT: 93/32,237 (0.3%) Varenicline: 890/454,698 (0.2%)	RR (95% CI) Adjusted: 0.80 (0.59-1.07) Fisher's exact p < 0.00001 (calculated)
								NRT: 33/32,237 (0.1%), patient years: 5,880, Incidence rate per 1000 patient-years: 5.6	HR (95% CI) Adjusted: 0.72 (0.44-1.15)

Carney	2020	observational cohort	Smoking cessation	12 months, or patient therapy duration plus 30 days	618497	angina (time-to-event sensitivity analyses)	Bupropion: 77/131,562 (0.1%), patient years: 52,687, Incidence rate per 1000 patient-years: 1.5	Varenicline: 304/454,698 (0.1%), patient years: 95,886, Incidence rate per 1000 patient-years: 3.2	Fisher's exact p = 0.33 (calculated)
Carney	2021	observational cohort	Smoking cessation	Primary analysis 1 year	116442	angina	Bupropion: 11/5,838 (0.2%)	NRT: 146/71,510 (0.2%) Varenicline: 77/39,094 (0.2%)	RR (95% CI) Adjusted: 0.96 (0.51-1.81) Fisher's exact p = 1.00 (calculated)
Cinciripini	2013	RCT	Smoking cessation	6 months	294	Angina	Bupropion: 5/102 (4.9%)	Varenicline: 1/86 (1.2%), considered "serious" Placebo: 13/106 (12.3%), one considered "serious"	Varenicline: Fisher's exact p = 0.22 (calculated) Placebo: Fisher's exact p = 0.08 (calculated)
Eisenberg	2013	RCT	Smoking cessation	12 months; 9 weeks for primary analysis	392	unstable angina	Bupropion: 12/192 (6.3%)	Placebo: 11/200 (5.5%)	Fisher's exact p = 0.83 (calculated)
Kittle	2017	RCT	Smoking cessation	≥ 6 weeks	7224	hospitalization for unstable angina	Bupropion vs. placebo: 2/4,297 (Proportion: 0.047%; 95% CI, 0.006-0.168%)	Placebo comparator: 2/2,927 (Proportion: 0.068%; 95% CI, 0.008-0.247%)	Fisher's exact p = 1.00 (calculated)
Benowitz	2018	RCT	Smoking cessation	52 weeks	8058	new-onset or worsening peripheral vascular disease	Bupropion: 3/2006 (0.1%) (p. E7)	Varenicline: 3/2016 (0.1%) nicotine replacement therapy: 3/2022 (0.1%) Placebo: 2/2014 (0.1%) (p. E7)	Varenicline: Fisher's exact p = 1.00 (calculated) NRT: Fisher's exact p = 1.00 (calculated) Placebo: Fisher's exact p = 0.69 (calculated)
Carney	2020	Observational cohort	Smoking cessation	12 months or Patient therapy duration plus 30 days	618497	peripheral vascular disease (1 year fixed follow- peripheral vascular disease (sensitivity analyses)	Bupropion: 592/131,562 (0.4%) Bupropion: 306/131,562 (0.2%), patient years: 52,599, Incidence rate per 1000 patient-years: 5.8	Nicotine replacement therapy : 488/32,237 (1.5%) Varenicline: 3302/454,698 (0.7%) Nicotine replacement therapy : 185/32,237 (0.6%), patient years: 5,863, Incidence rate per 1000 patient-years: 31.6 Varenicline: 1289/454,698 (0.3%), patient years: 95,752, Incidence rate per 1000 patient-years: 13.5	RR (95% CI) Adjusted: 0.65 (0.57-0.74) Fisher's exact p < 0.00001 (calculated) HR (95% CI) Adjusted: 0.48 (0.39-0.60) NR
Carney	2021	Observational cohort	Smoking cessation	Primary analysis 1 year	116442	peripheral vascular disease	Bupropion: 28/5,838 (0.5%)	NRT: 302/71,510 (0.4%) Varenicline: 179/39,094 (0.5%)	RR (95% CI) Adjusted: 1.04 (0.70-1.54) Fisher's exact p = 0.84 (calculated)
Kittle	2017	RCT	Smoking cessation	≥ 6 weeks	7224	new diagnosis of peripheral vascular disease	Bupropion: 0/4,297 (0%)	Placebo comparator: 0/2,927 (0%)	Fisher's exact p = 1.00 (calculated)
Kotz	2015	Observational cohort	Smoking cessation	6 months	164,766	peripheral vascular disease	Bupropion: 14/6,557 (0.2%)	NRT: 430/106,759 (0.4%) Varenicline: 123/51,450 (0.2%)	HR (95% CI) Adjusted: 0.83 (0.48-1.41) Propensity score matched: 1.62 (0.67-3.92) Fisher's exact p = 0.79 (calculated)
Kotz	2017	Observational cohort	Smoking cessation	6 months	16679	Peripheral vascular disease	Bupropion: 1/350 (0.3%)	NRT: 93/10,426 (0.9%) Varenicline: 17/3,574 (0.5%)	HR (95% CI) Adjusted: 0.49 (0.07-3.56); Propensity score matched: 0.99 (0.06-15.80) Fisher's exact p = 1.00 (calculated)
Benowitz	2018	RCT	Smoking cessation	52 weeks	8058	serious cardiac arrhythmia	Bupropion: 2/2006 (0.1%)	Varenicline: 5/2016 (0.2%) NRT: 8/2022 (0.4%) Placebo: 3/2014 (0.1%)	Varenicline: Fisher's exact p = 0.45 (calculated) NRT: Fisher's exact p = 0.11 (calculated) Placebo: Fisher's exact p = 1.00 (calculated)
Kittle	2017	RCT	Smoking cessation	≥ 6 weeks	7224	cardiac arrhythmias	Bupropion: 1/4,297 (Proportion: 0.023%; 95% CI, 0.001-0.130%)	Placebo comparator: 2/2,927 (Proportion: 0.068%; 95% CI, 0.008-0.247%)	Fisher's exact p = 0.57 (calculated)
Kotz	2015	observational cohort	Smoking cessation	6 months	164766	arrhythmia	Bupropion: 14/6,557 (0.2%)	NRT: 563/106,759 (0.5%) Varenicline: 126/51,450 (0.2%)	HR (95% CI) Adjusted: 0.66 (0.39-1.13) Propensity score matched: 0.43 (0.21-0.91) NR
Kotz	2017	observational cohort	Smoking cessation	6 months	16679	Arrhythmia	Bupropion: 4/350 (1.1%)	NRT: 174/10,426 (1.7%) Varenicline: 38/3,574 (1.1%)	HR (95% CI) Adjusted: 0.92 (0.34-2.50) Propensity score matched: 3.96 (0.44 - 35.41) Fisher's exact p = 0.79 (calculated)
Svanström	2012	observational cohort	Smoking cessation	6 months (primary analyses)	35852	cardiac arrhythmia (includes atrial and ventricular arrhythmias but not conduction block)	Bupropion: 32 events per 8,404 person-years. Incidence rate per 1,000 person-years: 3.8	Varenicline: 20 events per 8,263 person-years. Incidence rate per 1,000 person-years: 2.4	HR (95% CI) 1.56 (0.90 - 2.78)
Carney	2020	Observational cohort	Smoking cessation	12 months or patient therapy duration plus 30 days	618,497	Ischaemic Heart Disease (primary analyses) Ischaemic Heart Disease (time-to-event sensitivity analyses)	Bupropion: 626/131,562 (0.5%) Bupropion: 318/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.0	NRT: 380/32,237 (1.2%) Varenicline: 3530/454,698 (0.8%) Nicotine replacement therapy : 129/32,237 (0.4%), patient years: 5,869, Incidence rate per 1000 patient-years: 22.0 Varenicline: 1143/454,698 (0.3%), patient years: 95,771, Incidence rate per 1000 patient-years: 11.9	RR (95% CI) Adjusted: 0.79 (0.69-0.91) Fisher's exact p < 0.00001 (calculated) HR (95% CI) Adjusted: 0.76 (0.60-0.96) Fisher's exact p = 0.55 (calculated)
Carney	2021	Observational cohort	Smoking cessation	Primary analyses 1 year	116,442	Ischaemic Heart Disease (primary analyses)	Bupropion: 30/5,838 (0.5%)	Nicotine replacement therapy : 398/71,510 (0.6%) Varenicline: 159/39,094 (0.4%)	RR (95%CI) Adjusted: 1.02 (0.70-1.50) Fisher's exact p = 0.23 (calculated)
Kotz	2015	Observational cohort	Smoking cessation	6 months	164,766	Ischaemic Heart Disease	Bupropion: 52/6,557 (0.8%)	Nicotine replacement therapy: 2,148/106,759 (2.0%) Varenicline: 594/51,450 (1.2%)	HR (95% CI): Adjusted: 0.67 (0.51-0.89) Propensity score matched: 0.59 (0.37-0.93) Fisher's exact p = 0.007 (calculated)
Kotz	2017	Observational cohort	Smoking cessation	6 months	16,679	Ischaemic Heart Disease	Bupropion: 11/350 (3.1%)	Nicotine replacement therapy: 417/10,426 (4.0%) Varenicline: 128/3,574 (3.6%)	HR (95% CI): Adjusted:1.18 (0.64-2.15) Propensity score matched:1.23 (0.49-3.12) Fisher's exact p = 0.76 (calculated)
Cheon	2017	RCT	Psychiatric	6 weeks	103	Tachycardia/Palpita	Bupropion: 1/47 (2.1%)	Aripiprazole: 0/56 (0.0%)	Fisher's exact p = 0.46 (calculated)
Cinciripini	2013	RCT	Smoking cessation	6 months	294	Tachycardia/Palpita	Bupropion: 4/102 (3.9%)	Varenicline: 1/86 (1.2%) Placebo: 3/106 (2.8%)	Varenicline: Fisher's exact p = 0.38 (calculated) Placebo: Fisher's exact p = 0.72 (calculated)
Jafarinia	2012	RCT	Psychiatric	NR	40	Tachycardia/Palpita	Bupropion: 2/20 (10%)	Methylphenidate: 1/20 (5%)	Fisher's exact p = 1.00 (calculated)
Sheridan	2018	Observational cohort	Psychiatric	NA	3749	Tachycardia/Palpita	Bupropion: 1013/1433 (70.7%)	tricyclic antidepressant: 451/753 (59.9%)	Fisher's exact p < 0.00001 (calculated)
Svanström	2012	Observational cohort	Smoking cessation	6 months (primary analyses)	35,852	Acute coronary syndrome	Bupropion: 33 events per 8,416 person-years. Incidence rate per 1,000 person-years: 3.9	Varenicline: 39 events per 8,270 person-years. Incidence rate per 1,000 person-years: 4.7	HR (95% CI) 0.83 (0.52-1.33)
Maier	2020	RCT	Psychiatric	NR	108	Hospitalization for atrial fibrillation	Bupropion: 1/54 (1.9%)	Placebo: 0/54 (0.0%)	Fisher's exact p = 1.00 (calculated)
Svanström	2012	Observational cohort	Smoking cessation	6 months (primary analyses)	35,852	peripheral arterial disease [diagnosis of peripheral arterial disease or procedure to treat peripheral arterial disease]	Bupropion: 71 events per 8,392 person-years. Incidence rate per 1,000 person-years: 8.5	Varenicline: 78 events per 8,247 person-years. Incidence rate per 1,000 person-years: 9.5	HR (95% CI) 0.90 (0.65 - 1.23)
Kittle	2017	RCT	Smoking cessation	≥ 6 weeks	7224	serious hypertensive adverse event	Bupropion vs. placebo: 0/4,297 (0%)	Placebo comparator: 0/2,927 (0%)	NR
Svanström	2012	Observational cohort	Smoking cessation	6 months (primary analyses)	35,852	Transient ischaemic attack	Bupropion: 7 events per 8,409 person-years. Incidence rate per 1,000 person-years: 0.8	Varenicline: 11 events per 8,265 person-years. Incidence rate per 1,000 person-years: 1.3	HR (95% CI) 0.63 (0.24 - 1.61)

Supplemental Table 3. Naltrexone studies reporting on non-MACE cardiovascular adverse events.

Author	Year	Study design	Study indication	Reported length of follow-up	No. Patients	Outcome	Adverse event frequency, treatment group	Adverse event frequency, comparator group	Effect measure
Schmitz	2014	RCT	Substance use	12 weeks	81	Arrythmia	Naltrexone: 0/16 (0.0%)	Modafinil: 0/22 (0.0%) Levodopa/carbidopa: 1/25 (4.0%) Placebo: 0/18 (0.0%)	Modafinil: Fisher's exact p = 1.00 (calculated) Levodopa/carbidopa: Fisher's exact p = 1.00 (calculated) Placebo: Fisher's exact p = 1.00 (calculated)
Lee	2016	RCT	Substance use	78 weeks	308	Death from cardiopulmonary arrest	Naltrexone: 0/153 (0.0%)	"Usual treatment": 1/155 (0.6%)	Fisher's exact p = 1.00 (calculated)
Lee	2016	RCT	Substance use	78 weeks	308	DVT	Naltrexone: 0/153 (0.0%)	"Usual treatment": 1/155 (0.6%)	Fisher's exact p = 1.00 (calculated)
Schmitz	2014	RCT	Substance use	12 weeks	81	DVT	Naltrexone: 0/16 (0.0%)	Modafinil: 0/22 (0.0%) Levodopa/carbidopa: 0/25 (0.0%) Placebo: 1/18 (5.6%)	Modafinil: Fisher's exact p = 1.00 (calculated) Levodopa/carbidopa: Fisher's exact p = 1.00 (calculated) Placebo: Fisher's exact p = 1.00 (calculated)
Krupitsky	2019	RCT	Substance use	48 weeks	200	Hypertension	Oral naltrexone: 0/100 (0%) Naltrexone implant: 8/100 (8.0%)	NA	Fisher's exact p = 0.007 (calculated)
Lee	2016	RCT	Substance use	78 weeks	308	Hypertension	Naltrexone: 0/153 (0.0%)	"Usual treatment": 1/155 (0.6%)	Fisher's exact p = 1.00 (calculated)
Spencer "Opiate"	2018	RCT	Psychiatric	NR	37	Tachycardia/Palpitations	[Note: percentages are based on the total number of adverse events reported within the treatment group] Naltrexone: 0/101 (0.0%)	[Note: percentages are based on the total number of adverse events reported within the comparator group] Placebo: 5/76 (6.6%)	Fisher's exact p = 0.01 (calculated)
Adhikari	2020	Other Observational	Substance use	12 weeks	78	Tachycardia/Palpitations	Naltrexone: 1/39 (2.5%)	Disulfiram: 5/39 (12.8%)	Fisher's exact p = 0.20 (calculated)
Krupitsky	2019	RCT	Substance use	12-month open-label extension	114	Serious cardiomyopathy	Continued on naltrexone: 1/67 (1.5%) "judged as probably not related to" naltrexone extended-release	Switched from placebo to naltrexone: 0/47 (0%)	Fisher's exact p = 1.00 (calculated)