

Use of Contrave, Naltrexone with Bupropion, Bupropion, or Naltrexone and Major Adverse Cardiovascular Events: A Systematic Literature Review

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Abstract: Naltrexone/Bupropion extended release (ER; Contrave) is an extended-release, fixed-dose combination medication of naltrexone (8 mg) and bupropion (90 mg) for patients with obesity or overweight with at least one weight-related comorbidity. Obese and overweight patients with or without comorbidities are at increased cardiovascular (CV) risk. Due to the increased CV risk profile in this patient population, this systematic literature review was conducted to assess human studies reporting major adverse CV events (MACE) and other CV events. *A priori* eligibility criteria included clinical studies (randomized and observational) published from January 1, 2012, to September 30, 2021, with data comparing users of naltrexone/bupropion ER, naltrexone with bupropion, bupropion without naltrexone, or naltrexone without bupropion versus comparator groups (placebo or other treatments), and with sufficient information to determine the frequency of MACE or other CV adverse events by treatment group. Among 2539 English-language articles identified, 70 articles met the eligibility criteria: seven studies of naltrexone/bupropion ER or naltrexone with bupropion, 32 studies of bupropion, and 31 studies of naltrexone. No studies reported an increased risk of MACE among users of naltrexone/bupropion ER, naltrexone with bupropion, or bupropion or naltrexone individually compared with nonusers. One-half of the available studies ($n = 35$) reported no (zero) CV events and the other half ($n = 35$) reported that a non-zero frequency of CV events occurred. Four studies reported data on MACE, including three studies of bupropion and one study of naltrexone/bupropion ER. For composite MACE and its components, the difference in proportions between naltrexone/bupropion ER-, bupropion-, or naltrexone-treated patients compared with active comparators or placebo-treated patients did not exceed 2.5%. In conclusion, the available human evidence does not indicate an increased risk of CV events or MACE following use of naltrexone/bupropion ER, naltrexone with bupropion, or the individual components.

Keywords: MACE, obese, overweight, cardiovascular risk

Introduction

The prevalence of adults who are overweight or obese has increased steadily over recent decades; currently, nearly 40% of US adults are classified as overweight and an additional 40% are classified as obese, including 10% classified as severely obese (body mass index [BMI] ≥ 40 kg/m²).^{1–3} Globally, the World Health Organization estimates that approximately 39% of adults worldwide are overweight, including 13% who are obese. These figures represent a tripling of the global prevalence of obesity since the 1970s.⁴

Overweight and obese patients are at an increased risk of cardiovascular disease (CVD) and CV-related mortality.^{5–7} The importance of overweight/obesity as a determinant of CVD has been demonstrated in several large and well-established cohort studies, including the Framingham Heart Study and the Nurses' Health Study, in which overweight/obesity remained independently associated with increased CVD risk even after adjustment for other known CVD risk factors.^{8–11} Obesity has also been shown to directly increase the risk of developing CV risk factors, including hypertension, diabetes mellitus, and hypercholesterolemia. As overweight and obesity have a substantial impact on overall CV

health, effective weight loss interventions are critical for the prevention of CVD. Pharmacologic agents are an important treatment strategy for weight reduction. There is a desire to better understand the CV safety of currently prescribed medications intended to manage obesity.^{12,13}

Naltrexone/Bupropion extended release (ER; Contrave) is an extended-release, fixed-dose combination medication of naltrexone (8 mg) and bupropion (90 mg). Naltrexone/bupropion ER is indicated as an adjunct to increased physical activity and a reduced-calorie diet for chronic weight management in obese adults or overweight adults with at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia.¹⁴ Naltrexone and bupropion as stand-alone products are not approved for weight management but are approved for other indications. Naltrexone is an opioid antagonist used to treat alcohol and opioid addiction and bupropion is an aminoketone antidepressant used to treat major depressive disorder and seasonal affective disorder, and as an aid to smoking cessation treatment. Naltrexone/bupropion ER was first approved for use by the US Food and Drug Administration (FDA) in 2014 and is currently the only approved oral fixed-dose combination.

In this increased CV risk patient population, this systematic literature review was conducted to obtain information from clinical trials and observational studies of CV events in adult patients across all indications treated with naltrexone/bupropion ER or naltrexone with bupropion, or either of the components, bupropion and naltrexone. While the primary focus of this literature review was to evaluate incidence of MACE in naltrexone/bupropion ER, naltrexone with bupropion, bupropion, or naltrexone users versus comparator groups (placebo or other active treatments besides naltrexone and bupropion), other CV events were also assessed to more fully delineate and determine the CV risk profile by treatment group.

Material and Methods

Search Strategy and Selection Criteria

The review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the pre-specified protocol is provided in the [Supplemental Material Original Study Protocol](#) and [Table 1](#).¹⁵ While the New Drug Application (NDA) for naltrexone/bupropion ER was first submitted to the FDA in 2010, the CV safety profile of one ingredient of naltrexone/bupropion ER, bupropion, was established prior to the NDA submission. Hence, we queried PubMed for all publicly available, English-language primary literature published on or after January 1, 2012, until September 30, 2021. Briefly, the inclusion criteria specified that articles were required to be published, peer-reviewed, human observational studies or clinical trials presenting original data where the intervention was naltrexone/bupropion ER, naltrexone with bupropion, or the individual components bupropion or naltrexone, and results were also presented for a comparator group (placebo, other active comparator that was not naltrexone/bupropion ER, naltrexone with bupropion, bupropion, or naltrexone). The outcome of interest was any clinically diagnosed CV event, with a focus on three-point MACE (ie, CV death, myocardial infarction, and stroke) and its components. Other reported CV events were also extracted. Laboratory values (eg, electrocardiogram readings, cholesterol level, and blood pressure) and symptoms (eg, chest discomfort) were excluded, whereas clinical diagnoses such as hypercholesterolemia and hypertension were included. Review articles and meta-analyses were not eligible for inclusion, because they did not report original research results. However, cited articles in recently published review articles and meta-analyses were examined to identify any additional non-duplicate relevant studies. When multiple publications were based on the same at-risk population, the study reporting the largest patient population was used to inform total patient counts.

Data Extraction

All titles and abstracts were screened by one reviewer (EC). Subsequently, all articles eligible for full-text screening were reviewed by one of eight independent reviewers (AK, BD, CK, EC, MA, NO, RL, SD) trained on the inclusion and exclusion criteria. Data from each eligible article were extracted by one of the reviewers and checked for accuracy by a second reviewer. Any conflicts were resolved by another reviewer (ETC, SRW).

For studies that reported at least one CV event, data abstraction of study descriptors, patient descriptors, treatment descriptors, adverse event descriptors, and adverse event results was conducted. A full listing of the data abstraction

fields can be found in the [Supplementary Material](#). For studies that reported “no adverse events”, “no serious adverse events”, or “no deaths”, or where it could otherwise be clearly inferred that no CV events occurred, data extraction was limited to the study population assessed for safety.

Statistical Analysis

Where studies did not report effect measures (eg, relative risks or risk differences) comparing the proportion of CV adverse events between treatment groups, we calculated Fisher’s exact p-values to compare crude proportions.

Results

A total of 2552 unique articles were screened for inclusion and 70 studies met the inclusion criteria. [Figure 1, PRISMA diagram]

Of the 70 included studies, 35 studies enrolling a total of 6393 patients reported zero CV events (Table 1).^{16–50} (This total includes studies that reported zero occurrences of certain specified CV events, for example, serious CV adverse

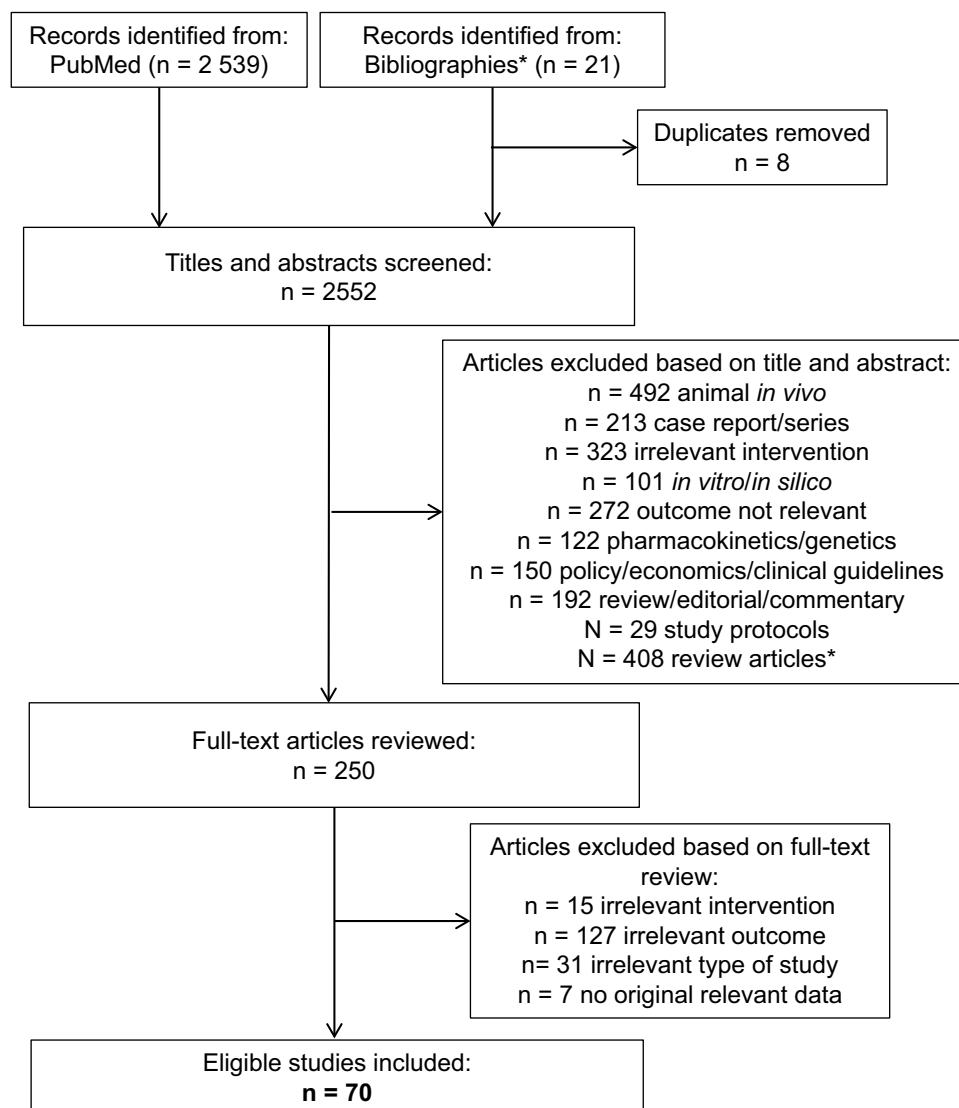


Figure 1 PRISMA flow diagram detailing study selection, inclusion and exclusion. *Bibliographies of all review articles published in 2021 and a subset of earlier reviews selected based on titles and abstracts were screened for additional relevant articles.

Note: Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.¹⁵

Table 1 Breakdown of Publications Identified by Treatment of Interest

	Treatment	Contrave [®] /N-B	Bupropion	Naltrexone	Total
Total	n	7	32	31	70
Reported CV adverse events	n	7	19	9	35
	%	100	59.4	29	-
	# patients	11,536	3,112,198	9422	3,133,156
Reported zero CV adverse events	n	0	13	22	35
	%	0	40.6	71	-
	# patients	0	3,627	2,766	6,393

Abbreviations: CV, cardiovascular; N, number (of); N-B, naltrexone-bupropion.

events or CV deaths, without reporting whether or not other CV events occurred.) The remaining 35 studies, enrolling a combined total of 3,133,156 patients, each reported at least one CV event (not restricted to MACE).^{51–85} Four studies reported data on MACE, enrolling a combined total of 26,195 patients.

Seven studies, all of which were randomized controlled trials (RCTs), evaluated naltrexone/bupropion ER or naltrexone with bupropion as the intervention (Table 2).^{53,65,66,76,78,84,85} Naltrexone-bupropion studies are considered naltrexone/bupropion ER studies if the treatment is naltrexone (32 mg/day) + bupropion (360mg/day). Only one reported on MACE (Nissen et al 2016) (Table 3).⁷⁸

Nissen et al was an RCT (NCT01601704) evaluating CVD risk in overweight or obese patients treated with naltrexone/bupropion ER or placebo across 266 US centers.

At the final end of the study analysis, with a median follow-up of 121 weeks in both groups, the proportion of MACE events in the naltrexone/bupropion ER-treated population was slightly less than in the placebo-treated population at 2.7% and 2.8%, respectively, yielding an adjusted hazard ratio of 0.95 (99.7% confidence interval [CI]: 0.65–1.38) for naltrexone/bupropion ER vs placebo. For MACE plus hospitalization for unstable angina (“MACE+”), the proportion remained slightly lower for naltrexone/bupropion ER than placebo at 3.7% vs 3.8% (hazard ratio = 0.95, 99.7% CI: 0.69–1.31). After

Table 2 Breakdown of Studies Reporting CV Events According to Study Design

Treatment		Contrave [®] /N-B	Bupropion	Naltrexone
Total Studies		7	19	9
Randomized controlled trial	N	7	8	7
	%	100	42.1	77.8
	Patients*	11,536	17,835	1,118
Observational cohort	N	0	10	1
	%	0	52.6	11.1
	Patients	0	2,768,655	8,226
Other observational study design	N	0	1	1
	%	0	5.3	11.1
	Patients	0	325,708	78

Notes: Patients is the sum of study participants from each distinct study population. For studies that conducted analyses on the same patient population, only the study reporting the full patient population is counted here to avoid duplication of patients.

Abbreviations: N, number (of); N-B, naltrexone-bupropion.

Table 3 Studies Reporting on MACE and MACE+

Treatment	Contrave®/Naltrexone-Bupropion ER	Bupropion				
		Author	Year	Study design	Study indication	Reported length of follow-up
	Nissen ⁷⁸	Benowitz ⁵⁴	Eberg ⁶¹	Eisenberg ⁶²	Kittle ⁶⁹	
	2016	2018	2019	2013	2017	
	RCT	RCT	Observational cohort	RCT	RCT	
	Weight loss	Smoking cessation	Smoking cessation	Smoking cessation	Smoking cessation	
	Median 121 weeks, interquartile range 114–128 weeks	52 weeks	1 year	12 months	>6 weeks	
	8,905	8,058	233,738	392	7224	1616
Adverse event frequency, treatment group	Naltrexone-bupropion: MACE 119/4455 (2.7%) at end of study 90/4455 (2.0%) at 50% interim 35/4455 (0.8%) at 25% interim MACE30* 47/4455 (1.1%) at end of study 43/4455 (1.0%) at 50% interim 23/4455 (0.5%) at 25% interim MACE+† 164/4455 (3.7%) at end of study 133/4455 (3.0%) at 50% interim 63/4455 (1.4%) at 25% interim MACE30+‡ 226/4455 (5.1%) at end of study 188/4455 (4.2%) at 50% interim 91/4455 (2.0%) at 25% interim	Bupropion: MACE 9/2006 (0.4%) MACE+§ 15/2006 (0.7%)	MACE+¹ 13/9931 (0.1%)	MACE Bupropion: 25/192 (13.0%)	Bupropion vs placebo (primary comparison) MACE 3/4,297 (0.070%; 95% CI: 0.014–0.204%) MACE+[¶] 6/4297 (0.140%; 95% CI: 0.051–0.304%)	Bupropion vs active control group (secondary comparison): MACE 1/598 (0.2%) MACE+^{¶¶} NR

(Continued)

Table 3 (Continued).

Treatment	Contraceptive/Naltrexone-Bupropion ER	Bupropion				
Adverse event frequency, comparator group	Placebo: MACE 124/4450 (2.8%) at end of study 102/4450 (2.3%) at 50% interim 59/4450 (1.3%) at 25% interim MACE30* 39/4450 (0.9%) at end of study 37/4450 (0.8%) at 50% interim 30/4450 (0.7%) at 25% interim MACE+† 171/4450 (3.8%) at end of study 142/4450 (3.2%) at 50% interim 79/4450 (1.8%) at 25% interim MACE30+‡ 244/4450 (5.5%) at end of study 205/4450 (4.6%) at 50% interim 105/4450 (2.4%) at 25% interim	MACE Varenicline: 3/2016 (0.1%) NRT: 6/2022 (0.3%) Placebo: 8/2014 (0.4%) MACE+§ Varenicline: 10/2016 (0.5%) NRT: 10/2022 (0.5%) Placebo: 12/2014 (0.6%)	MACE+¶ Varenicline: 90/68,468 (0.1%) NRT: 513/155,339 (0.3%)	MACE Placebo: 22/200 (11.0%)	Placebo: MACE 4/2927 (0.137%; 95% CI: 0.037–0.349%) MACE+¶¶ 7/2927 (0.239%; 95% CI: 0.096–0.492%)	Active comparator: MACE 0/1018 (0%) MACE+¶¶ NR
Effect measure	HR (99.7% CI): MACE 0.95 (0.65–1.38) at end of study 0.88 (0.57–1.34) at 50% interim 0.59 (0.39–0.90) at 25% interim MACE30* 0.99 (0.52–1.87) at end of study 0.97 (0.50–1.88) at 50% interim 0.71 (0.41–1.22) at 25% interim MACE+† 0.95 (0.69–1.31) at end of study 0.93 (0.66–1.33) at 50% interim 0.80 (0.57–1.11) at 25% interim MACE30+‡ 0.92 (0.70–1.20) at end of study 0.91 (0.68–1.23) at 50% interim 0.87 (0.65–1.15) at 25% interim	MACE Varenicline: RD (95% CI) = -0.91 (-4.78 to 2.96) HR (95% CI) = 0.37 (0.12–1.13) NRT: RD (95% CI) = 0.22 (-2.48 to 2.93) HR (95% CI) = 1.46 (0.53–4.02) Placebo: RD (95% CI) = -0.08 (-2.63 to 2.48) HR (95% CI) = 1.09 (0.42–2.83) MACE+§ Varenicline: RD (95% CI) = -0.59 (-2.84 to 1.67) HR (95% CI) = 0.67 (0.30–1.46) NRT: RD (95% CI) = 0.27 (-1.95 to 2.49) HR (95% CI) = 1.46 (0.67–3.21) Placebo: RD (95% CI) = 0.11 (-2.04 to 2.25) HR (95% CI) = 1.21 (0.57–2.58)	MACE+¶ Adjusted HR (95% CI): Varenicline/Bupropion: 1.08 (0.57–2.04)/1.00 (ref) Bupropion/NRT: 0.76 (0.43–1.33)/1.00 (ref)	MACE Fisher's exact p = 0.64 (calculated)	Difference in proportions: MACE p = 0.4517 MACE+¶¶ p = 0.3998	MACE Fisher's exact p = 0.37 (calculated)

Notes: *MACE within 30 days of last treatment. †MACE + hospitalization for unstable angina. ‡MACE + hospitalization for unstable angina within 30 days of last treatment. §Any MACE or a new-onset or worsening peripheral vascular disease requiring intervention, a need for coronary revascularization, or hospitalization for unstable angina. ¶Composite of myocardial infarction, coronary revascularization, stroke, and all-cause mortality. ¶¶MACE + new diagnosis of peripheral vascular disease + hospitalization for unstable angina or coronary revascularization.

accruing one quarter of the expected MACE events (25% interim), the frequency of MACE among patients in the naltrexone/bupropion ER arm was significantly lower than in the placebo arm. After accruing half of the expected events (50% interim) and at the final end of the study analysis, there was not a statistically significant difference in MACE between the naltrexone/bupropion ER and placebo groups.⁷⁸ No elevated risk of MACE – including MACE, MACE+, and the individual components of MACE – was observed in the naltrexone/bupropion ER-treated group compared with placebo at the 25% interim analysis, the 50% interim analysis, or the end of the study (Table 3).

Literature on the constituent active ingredients (bupropion and naltrexone) was used to further inform the CV safety profile of naltrexone/bupropion ER. Among the 28 eligible studies that reported at least one CV event, 19 studies evaluated bupropion and 9 evaluated naltrexone (Table 2). Most of the bupropion studies were observational in design (N = 11 of 19), whereas most of the naltrexone studies were RCTs (N = 7 of 9). The studies reporting on MACE are described further below.

Mace

Three bupropion studies, summarized alongside Nissen et al in Table 3, reported on the occurrence of MACE. No studies of naltrexone provided data on MACE. Across the three bupropion studies, the proportion of patients with MACE was similar between bupropion comparator (active comparators or placebo) groups. In particular, the observed proportion of MACE was <0.5% in all treatment groups after at least 6 weeks of follow-up in a pooled analysis of RCTs (Kittle et al 2017) and after 52 weeks of follow-up in a single RCT of bupropion for smoking cessation (Benowitz et al 2018, NCT01574703). MACE occurred in 11–13% of patients after 12 months of follow-up in a third RCT that evaluated bupropion in a high-risk population of smokers who were enrolled at the time of hospitalization for acute myocardial infarction, which is a component of three-point MACE (Eisenberg et al 2013, NCT00689611).^{54,62,69}

Mace+

As shown in Table 3, three bupropion studies evaluated MACE+, defined in various ways as composite MACE plus at least one other CV endpoint. No studies of naltrexone reported on the frequency of MACE+. Two of the bupropion publications with data on MACE+ had also reporting on MACE (Kittle et al 2017; Benowitz et al 2018), and the third was an observational cohort study of bupropion compared with varenicline or nicotine replacement therapy for smoking cessation after 1 year of follow-up (Eberg et al 2019).^{54,61,69} All three of these studies reported proportions of MACE+ <1% across all treatment groups. The proportion of MACE+ differed by <0.4% between those treated with bupropion and those treated with active comparators or placebo in all studies.

Components of MACE

Cardiovascular Death

Ten studies, including one study of naltrexone/bupropion ER, five studies of bupropion (n = 5 RCTs), and four studies of naltrexone (n = 3 RCTs), reported data on CV death (Table 4). The length of follow-up across the 10 studies varied from 6 weeks to 4.9 years. The frequency of CV death was <1% and the incidence rate, where reported, was <1 per 1000 person-years, except in an RCT of bupropion for high-risk patients initially hospitalized with acute myocardial infarction (Eisenberg et al 2013). In that high-risk study population, CV death occurred in 4.7% (9/192) of those with bupropion and 3.0% (6/200) of those with placebo (Fisher's exact p = 0.44).⁶² None of the ten studies reported a difference of 2.0% or more in CV death between treatment groups.

Myocardial Infarction

Nine studies reported on the incidence of myocardial infarction, including two naltrexone/bupropion ER studies (n = 2 RCTs), six bupropion studies (n = 3 RCTs), and one naltrexone study (n = 1 RCT) (Table 5). The length of follow-up among these nine studies ranged from 6 weeks to 14 years. Acute myocardial infarction occurred in <3% of all treatment groups across studies that reported this information (excluding two bupropion studies that did not report the proportion of acute myocardial infarction), and the proportion was comparable between the treatment of interest (ie, naltrexone/bupropion ER, naltrexone with bupropion, bupropion, or naltrexone) and comparator groups. None of the nine studies

Table 4 Studies Reporting on Cardiovascular Death

	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	
Contrave®	Nissen ⁷⁸	2016	RCT	Weight loss	Median 121 weeks, interquartile range 114–128 weeks	8,905	Cardiovascular death	Naltrexone-bupropion:	Placebo:	HR (99.7% CI)	
								26/4455 (0.6%) at end of study	42/4450 (0.9%) at end of study	0.61 (0.30–1.27) at end of study	
								17/4455 (0.4%) at 50% interim	34/4450 (0.8%) at 50% interim	0.50 (0.21, 1.19) at 50% interim	
								5/4455 (0.1%) at 25% interim	19/4450 (0.4%) at 25% interim	0.26 (0.10–0.70) at 25% interim	
								Cardiovascular death within 30 days of last treatment	Naltrexone-bupropion:	Placebo:	HR (99.7% CI)
									9/4455 (0.2%) at end of study	11/4450 (0.2%) at end of study	0.67 (0.18–2.54) at end of study
									8/4455 (0.2%) at 50% interim	10/4450 (0.2%) at 50% interim	0.67 (0.17–2.72) at 50% interim
									4/4455 (0.1%) at 25% interim	7/4450 (0.2%) at 25% interim	0.57 (0.16–1.94) at 25% interim
Bupropion	Anthenelli ⁵²	2016	RCT	Smoking cessation	24 weeks	8,058	CV death within 30 days of last dose	Non-psychiatric bupropion: 0/989 (0.0%) (0 cardiovascular deaths > 30 days after last dose)	Non-psychiatric nicotine patch: 0/1006 (0.0%) (0 cardiovascular deaths > 30 days after last dose)	Fisher's exact p = 1.00 (calculated)	
									Non-psychiatric placebo: 0/999 (0.0%) (1 death (0.1%) from myocardial infarction > 30 days after last dose)	Fisher's exact p = 1.00 (calculated)	
								Psychiatric bupropion: 1/1017 (0.1%) death from cardiovascular event (0 cardiovascular deaths > 30 days after last dose)	Psychiatric varenicline: 0/1026 (0.0%) (0 cardiovascular deaths > 30 days after last dose)	Fisher's exact p = 1.00 (calculated)	
									Psychiatric nicotine patch: 0/1016 (0.0%) (0 cardiovascular deaths > 30 days after last dose)	Fisher's exact p = 0.50 (calculated)	
									Psychiatric placebo: 1/1015 (0.1%) death from pulmonary embolism (0 cardiovascular deaths > 30 days after last dose)	Fisher's exact p = 1.00 (calculated)	

	Benowitz ⁵⁴	2018	RCT	Smoking cessation	52 weeks	8,058	CV death	Bupropion: 2/2006 (0.1%)	Varenicline: 1/2016 (<0.1%) NRT: 0/2022 (0.0%) Placebo: 2/2014 (0.1%)	Varenicline: Fisher's exact p = 0.62 (calculated) NRT: Fisher's exact p = 0.25 (calculated) Placebo: Fisher's exact p = 1.00 (calculated)
	Eisenberg ⁶²	2013	RCT	Smoking cessation	12 months; 9 weeks for primary analysis	392	Cardiac death	Bupropion: 9/192 (4.7%) 4 cardiac deaths occurred during the 9-week treatment period: - 2 days post-randomization due to coronary dissection - 5 days post-randomization due to cardiac arrest - 9 days post-randomization due to multisystem organ failure post-coronary artery bypass graft - 4 weeks post-randomization due to myocardial infarction leading to cardiac arrest	Placebo: 6/200 (3.0%) 2 cardiac deaths occurred during the 9-week treatment period: - 9 weeks post-randomization due to complications related to duodenal perforation and recurrent septic shock - 9 weeks post-randomization due to ischemic event in bowel or spinal cord, possible embolic event could not be ruled out	Fisher's exact p = 0.44 (calculated)
	Kittle ⁶⁹	2017	RCT	Smoking cessation	≥ 6 weeks	7,224	CV death	Bupropion vs placebo: 0/4297 (0%)	Placebo comparator: 0/2927 (0%)	Fisher's exact p = 1.00 (calculated)
	Svanström ⁸²	2012	Observational cohort	Smoking cessation	6 months (primary analyses)	35,852	CV death	Bupropion: 6 events per 8425 person-years. Incidence rate per 1000 person-years: 0.7	Varenicline: 3 per 8281 person-years. Incidence rate per 1000 person-years: 0.4	HR (95% CI) 1.96 (0.50–7.69)
Naltrexone	Bisaga ⁵⁵	2018	RCT	Substance use	NR	378	CV death	Naltrexone/placebo/buprenorphine: 0/126 (0.0%)	Naltrexone/placebo: 0/126 (0.0%) Placebo: 0/126 (0.0%)	Fisher's exact p = 1.00 (calculated)
	Kelty ⁶⁸	2019	Observational cohort	Substance use	Mean ± SD from start of treatment to start of new treatment, death, or end of follow-up (31 December 2012): Naltrexone implant: 4.9 ± 3.3 years Methadone: 5.5 ± 3.3 years Buprenorphine: 4.5 ± 3.4 years	8,226	CV death	Naltrexone implant (1461 users): 0.6 per 1000 patient-years (95% confidence interval: 0.2–1.5)	Methadone (3515 users): 0.9 per 1000 patient-years (95% confidence interval: 0.5–1.4)	NR
									Buprenorphine (3250 users): 0.8 per 1000 patient-years (95% confidence interval: 0.4–1.4)	
	Krupitsky ⁷²	2013	RCT	Substance use	18 months from baseline	114	CV death	Continued on naltrexone: 0/67 (0%)	Switched from placebo to naltrexone: 0/47 (0%)	Fisher's exact p = 1.00 (calculated)
Krupitsky ⁷³	2019	RCT	Substance use	48 weeks	200	Death from heart disease	Oral naltrexone: 0/100 (0%) Naltrexone implant: 2/100 (2.0%)	NA	Fisher's exact p = 0.50 (calculated)	

Table 5 Studies Reporting on Myocardial Infarction

	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
Contrave®	Apovian ⁵³	2013	RCT	Weight loss	56 weeks; 28 weeks for primary efficacy analyses	1,484	Myocardial infarction	Naltrexone-bupropion: 1/992 (0.1%) Naltrexone-bupropion treated participant had active coronary artery disease, angina pectoris, hyperlipidemia, and hypertension.	Placebo: 0/492 (0.0%)	Fisher's exact p = 1.00 (calculated)
	Nissen ⁷⁸	2016	RCT	Weight loss	Median 121 weeks, interquartile range 114–128 weeks	8,905	Nonfatal myocardial infarction	Naltrexone-bupropion: 68/4455 (1.5%) at end of study 54/4455 (1.2%) at 50% interim 23/4455 (0.5%) at 25% interim	Placebo: 67/4450 (1.5%) at end of study 54/4450 (1.2%) at 50% interim 33/4450 (0.7%) at 25% interim	HR (99.7% CI) 1.01 (0.61–1.66) at end of study 1.00 (0.57–1.75) at 50% interim 0.70 (0.41–1.18) at 25% interim
							Fatal or nonfatal myocardial infarction	Naltrexone-bupropion: 69/4455 (1.5%) at end of study 55/4455 (1.2%) at 50% interim 24/4455 (0.5%) at 25% interim	Placebo: 71/4450 (1.6%) at end of study 57/4450 (1.3%) at 50% interim 34/4450 (0.8%) at 25% interim	HR (99.7% CI) 0.96 (0.59–1.58) at end of study 0.96 (0.55–1.67) at 50% interim 0.70 (0.42–1.19) at 25% interim
							Nonfatal myocardial infarction within 30 days of last treatment	Naltrexone-bupropion: 26/4455 (0.6%) at end of study 24/4455 (0.5%) at 50% interim 13/4455 (0.3%) at 25% interim	Placebo: 22/4450 (0.5%) at end of study 21/4450 (0.5%) at 50% interim 16/4450 (0.4%) at 25% interim	HR (99.7% CI) 0.98 (0.42–2.30) at end of study 0.96 (0.40–2.3) at 50% interim 0.77 (0.37–1.60) at 25% interim

Bupropion	Benowitz ⁵⁴	2018	RCT	Smoking cessation	52 weeks	8,058	Nonfatal MI	Bupropion: 4/2006 (0.2%)	Varenicline: 2/2016 (0.1%) NRT: 3/2022 (0.1%) Placebo: 5/2014 (0.2%)	Varenicline: Fisher's exact p = 0.45 (calculated) NRT: Fisher's exact p = 0.73 (calculated) Placebo: Fisher's exact p = 1.00 (calculated)
	Chen ⁵⁸	2021	Observational cohort	Psychiatric	Maximum 1999–2013	500,990	Myocardial infarction	NR	NR	HR (95% CI) Bupropion ≥ 180 days vs 0 or < 180 days: adjusted 1.25 (0.78–2.03) Bupropion < 180 cumulative defined daily doses vs 0: adjusted 1.024 (0.664–1.580) Bupropion ≥ 180 cumulative defined daily doses vs 0: adjusted: 0.528 (0.075–3.733)
	Eisenberg ⁶²	2013	RCT	Smoking cessation	12 months; 9 weeks for primary analysis	392	Myocardial infarction	Bupropion: 5/192 (2.6%)	Placebo: 5/200 (2.5%)	Fisher's exact p = 1.00 (calculated)
	Graham ⁶⁴	2014	Observational cohort	Smoking cessation	6 months	88,957	Acute myocardial infarction	Bupropion: 31/14,133 (0.2%)	Varenicline: 133/74,824 (0.2%)	Adjusted HR (95% CI) 0.79 (0.5–1.24)
	Kittle ⁶⁹	2017	RCT	Smoking cessation	≥ 6 weeks	7,224	Nonfatal myocardial infarction	Bupropion vs placebo: 2/4297 (Proportion: 0.047%; 95% CI, 0.006–0.168%)	Placebo comparator: 3/2927 (Proportion: 0.102%; 95% CI, 0.021–0.299%)	Fisher's exact p = 0.40 (calculated)
	Monárrez-Espino ⁷⁷	2018	Other observational	Smoking cessation	12 weeks	325,708	Myocardial infarction	Bupropion: 1–14 days before event: 16 discordant pairs during case period, 14 during control period 15–28 days before event: 14 discordant pairs during case period, 19 during control period 29–84 days before event: 47 discordant pairs during case period, 60 during control period 1–84 days before event: 73 discordant pairs during case period, 86 during control period	Varenicline: 1–14 days before event: 46 discordant pairs during case period, 43 during control period 15–28 days before event: 40 discordant pairs during case period, 43 during control period 29–84 days before event: 107 discordant pairs during case period, 140 during control period 1–84 days before event: 171 discordant pairs during case period, 173 during control period	OR (95% CI) Bupropion vs none: 1–14 days before event: 1.14 (0.55–2.34) 15–28 days before event: 0.73 (0.36–1.46) 29–84 days before event: 0.78 (0.53–1.14) 1–84 days before event: 0.84 (0.62–1.15)
Naltrexone	Garbutt ⁶³	2016	RCT	Substance use	12 weeks	80	Myocardial infarction	Naltrexone: 1/40 (2.5%) "One serious adverse event, a myocardial infarction, was not attributed to naltrexone treatment"	Placebo: 0/40 (0.0%)	Fisher's exact p = 1.00 (calculated)

found a difference of more than 2.5% in the occurrence of myocardial infarction between treatment groups, and relative risks were close to the null in the four studies that reported effect measures.

Stroke

Ten studies, including one of naltrexone/bupropion ER (n = 1 RCT) and nine of bupropion (n = 2 RCTs), reported on the incidence of stroke or cerebral infarction (Table 6). No studies of naltrexone reported data for stroke. The length of follow-up, across these 10 studies, ranged from 6 weeks to 128 weeks. The proportion of stroke was $\leq 1\%$ in all treatment groups (two studies did not report proportions), and incidence rates were < 5 per 1000 person-years (reported in two studies), except in the nicotine replacement therapy group in two studies (Carney et al 2020, Kotz et al 2015). In both of the latter studies, the incidence rate of cerebral infarction was significantly lower in the bupropion group than the nicotine replacement therapy group [Carney et al 2020 rate ratio (95% CI) = 0.78, 95% CI: 0.64–0.96; Kotz et al 2015 adjusted hazard ratio (95% CI) = 0.55 (0.35–0.89)].^{56,70} Across the remaining eight studies, the proportion of stroke differed by $< 0.6\%$ between patients treated with naltrexone/bupropion ER or bupropion vs those treated with active comparators or placebo.

Except for a statistically significantly lower proportion of cerebral infarction in the bupropion group than the nicotine replacement group in one study (Carney et al 2020), no statistically significant Fisher's exact p-values were found when comparing the proportion of MACE or its components between naltrexone/bupropion ER or its components vs comparators (Tables 3–6).

Other Non-MACE Cardiovascular Adverse Events

Besides MACE and its components, 23 other types of CV events were described in the 35 studies of naltrexone/bupropion ER, naltrexone with bupropion, bupropion, or naltrexone with non-zero data. These results are summarized in Supplemental Tables 1–3. Several of these CV event types were reported in a single study each; for instance, only Trivedi et al reported acute cardiac failure, hematoma, hypertensive crisis, hypotension, thrombophlebitis, and vascular disorders.⁸⁴ The frequencies of the non-MACE CV events were generally similar between treatment and comparator groups, with values ranging from 0% to 15%, depending on the type of CV event and the characteristics of the study population. Where reported (n = 7 studies), relative risks comparing the frequency of non-MACE CV events between treatment groups were close to the null value of 1.0. With the exception of one study, none reported statistically significant differences. In that one study, Carney et al 2020 reported significantly lower incidence rates of the following CV events in the bupropion-treated group than the nicotine replacement therapy group: peripheral vascular disease [adjusted incidence rate ratio (IRR) (95% CI): 0.65 (0.57–0.74)], heart failure [adjusted IRR (95% CI): 0.84 (0.74–0.96)], and ischemic heart disease [adjusted IRR (95% CI): 0.79 (0.69–0.91)].⁵⁶ No statistically significant Fisher's exact p-values were found for the following non-MACE CV events when comparing the proportion of non-MACE CV events between naltrexone/bupropion ER or its components vs comparators (Supplemental Tables 1–3): acute cardiac failure, cardiac disorders, coronary artery disease, hematoma, hypertensive crisis, hypotension, orthostatic hypotension, thrombophlebitis, thrombophlebitis superficial, vascular disorders, heart failure, hospitalization for congestive heart failure, serious cardiac arrhythmia, arrhythmia, hospitalization for atrial fibrillation, serious hypertensive adverse event, death from cardiopulmonary arrest, deep vein thrombosis and serious cardiomyopathy.

In total, we found eight studies with statistically significant Fisher's exact p-values when comparing the proportion of non-MACE CV events between naltrexone/bupropion ER, naltrexone with bupropion or the components vs comparators. The use of naltrexone/bupropion ER, naltrexone-bupropion, or the components were associated with a significantly lower incidence of angina, composite cardiovascular events, peripheral vascular disease, and ischemic heart disease. For the remaining non-MACE CV events which were hypertension and tachycardia or palpitations, the use of naltrexone/bupropion ER, naltrexone with bupropion, or the components were associated with a significantly higher incidence compared to active comparators or placebo. For the outcome hypertension, one naltrexone/bupropion ER study (Hollander et al, 2013) evaluated naltrexone (32 mg/day)/bupropion (360mg/day) treated individuals against placebo treated individuals. In both groups, the proportion of individuals experiencing hypertension was under 10%. There was one naltrexone/bupropion ER (Nissen et al, 2016), one bupropion (Sheridan et al, 2018), and one naltrexone study

Table 6 Studies Reporting on Stroke

	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
Contrave®	Nissen ⁷⁸	2016	RCT	Weight loss	Median 121 weeks, interquartile range 114–128 weeks	8,905	Nonfatal stroke	Naltrexone-bupropion: 28/4455 (0.6%) at end of study 21/4455 (0.5%) at 50% interim 7/4455 (0.2%) at 25% interim	Placebo: 21/4450 (0.5%) at end of study 19/4450 (0.4%) at 50% interim 10/4450 (0.2%) at 25% interim	HR (99.7% CI) 1.32 (0.57–3.08) at end of study 1.10 (0.44, 2.78) at 50% interim 0.70 (0.27–1.83) at 25% interim
							Fatal or nonfatal stroke	Naltrexone-bupropion: 31/4455 (0.7%) at end of study 22/4455 (0.5%) at 50% interim 7/4455 (0.2%) at 25% interim	Placebo: 23/4450 (0.5%) at end of study 21/4450 (0.5%) at 50% interim 11/4450 (0.2%) at 25% interim	HR (99.7% CI) 1.34 (0.60–2.99) at end of study 1.04 (0.43–2.55) at 50% interim 0.63 (0.25–1.64) at 25% interim
							Nonfatal stroke within 30 days of last treatment	Naltrexone-bupropion: 12/4455 (0.3%) at end of study 11/4455 (0.2%) at 50% interim 6/4455 (0.1%) at 25% interim	Placebo: 7/4450 (0.2%) at end of study 7/4450 (0.2%) at 50% interim 7/4450 (0.2%) at 25% interim	HR (99.7% CI) 1.35 (0.33–5.47) at end of study 1.25 (0.30–5.18) at 50% interim 0.72 (0.24–2.16) at 25% interim
Bupropion	Benowitz ⁵⁴	2018	RCT	Smoking cessation	52 weeks	8,058	Nonfatal stroke	Bupropion: 4/2006 (0.2%)	Varenicline: 0/2016 (0.0%) Nicotine replacement therapy: 3/2022 (0.1%) Placebo: 1/2014 (<0.1%)	Varenicline: Fisher's exact p = 0.06 (calculated) NRT: Fisher's exact p = 0.73 (calculated) Placebo: Fisher's exact p = 0.22 (calculated)
	Carney ⁵⁶	2020	Observational cohort	Smoking cessation	12 months or patient therapy duration plus 30 days	618,497	Cerebral infarction (primary analyses)	Bupropion: 290/131,562 (0.2%)	Nicotine replacement therapy: 192/32,237 (0.6%) Varenicline: 1052/454,698 (0.2%)	RR (95% CI) Adjusted: 0.78 (0.64–0.96) Fisher's exact p = 0.49 (calculated)
							Cerebral infarction (time-to-event sensitivity analyses)	Bupropion: 138/131,562 (0.1%), patient years: 52,680, Incidence rate per 1000 patient-years: 2.6	NRT: 57/32,237 (0.2%), patient years: 5878, Incidence rate per 1000 patient-years: 9.7 Varenicline: 288/454,698 (0.1%), patient years: 95,893, Incidence rate per 1000 patient-years: 3.0	HR (95% CI) Adjusted: 0.77 (0.54–1.10) Fisher's exact p = <0.00001 (calculated)
	Carney ⁵⁷	2021	Observational cohort	Smoking cessation	Primary analysis 1 year	116,442	Cerebral infarction	Bupropion: 9/5838 (0.2%)	NRT: 186/71,510 (0.3%) Varenicline: 83/39,094 (0.2%)	RR (95% CI) Adjusted: 0.73 (0.37–1.45) Fisher's exact p = 0.44 (calculated)
	Graham ⁶⁴	2014	Observational cohort	Smoking cessation	6 months	88,957	Stroke	Bupropion: 13/14,133 (0.1%)	Varenicline: 83/74,824 (0.1%)	HR (95% CI) Adjusted: 1.27 (0.63–2.55)
	Kittle ⁶⁹	2017	RCT	Smoking cessation	≥ 6 weeks	7,224	Nonfatal stroke	Bupropion vs placebo: 1/4297 (0.023%; 0.001–0.130%)	Placebo comparator: 1/2927 (0.034%; 0.001–0.190%)	Fisher's exact p = 1.00 (calculated)
	Kotz ⁷⁰	2015	Observational cohort	Smoking cessation	6 months	164,766	Cerebral infarction	Bupropion: 18/6557 (0.3%)	Nicotine replacement therapy: 871/106,759 (0.8%) Varenicline: 164/51,450 (0.3%)	HR (95% CI) Adjusted: 0.55 (0.35–0.89) Propensity score matched: 0.46 (0.24–0.89) Fisher's exact p = 0.64 (calculated)

(Continued)

Table 6 (Continued).

	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
	Kotz ⁷¹	2017	Observational cohort	Smoking cessation	6 months	16,679	Stroke	Bupropion: 3/350 (0.9%)	Nicotine replacement therapy: 155/10,426 (1.5%) Varenicline: 34/3574 (1.0%)	HR (95% CI) Adjusted: 0.62 (0.20–1.96) Propensity score matched: 0.49 (0.12–1.95) Fisher's exact p = 1.00 (calculated)
	Monárrez-Espino ⁷⁷	2018	Other observational	Smoking cessation	12 weeks	249,430	Ischemic stroke	Bupropion: 1–14 days before event: 7 discordant pairs during case period, 6 during control period 15–28 days before event: 7 discordant pairs during case period, 5 during control period 29–84 days before event: 29 discordant pairs during case period, 31 during control period 1–84 days before event: 41 discordant pairs during case period, 38 during control period	Varenicline: 1–14 days before event: 29 discordant pairs during case period, 23 during control period 15–28 days before event: 25 discordant pairs during case period, 28 during control period 29–84 days before event: 62 discordant pairs during case period, 73 during control period 1–84 days before event: 99 discordant pairs during case period, 93 during control period (p. 611)	OR (95% CI): Bupropion vs none: 1–14 days before event: 1.16 (0.39–3.47) 15–28 days before event: 1.40 (0.44–4.41) 29–84 days before event: 0.93 (0.56–1.55) 1–84 days before event: 1.07 (0.69–1.67) Varenicline vs none: 1–14 days before event: 1.26 (0.72–2.17) 15–28 days before event: 0.89 (0.52–1.53) 29–84 days before event: 0.84 (0.60–1.19) 1–84 days before event: 1.06 (0.80–1.41)
	Svanström ⁸²	2012	Observational cohort	Smoking cessation	6 months (primary analyses)	35,852	Ischaemic stroke	Bupropion: 21 events per 8419 person-years. Incidence rate per 1000 person-years: 2.5	Varenicline: 16 events per 8278 person-years. Incidence rate per 1000 person-years: 1.9	HR (95% CI): 1.30 (0.68–2.50)

(Spencer et al 2018a) which had a significantly higher incidence of tachycardia or palpitations in the treatment group compared to active comparators or placebo.

Discussion

Overweight and obese patients are at an increased risk of CVD and CV-related mortality.⁵⁻⁷ Due to the increased cardiovascular risk profile in this patient population, this systematic literature review was conducted to assess human studies reporting major adverse cardiovascular events (MACE) and other CV events. In particular, we sought to determine whether the types and proportions of CV events, especially MACE, differed between naltrexone/bupropion ER, naltrexone with bupropion, bupropion, or naltrexone and placebo or active comparators. The overall body of literature and individual studies therein do not demonstrate an increased risk of MACE or other CV events with the use of naltrexone/bupropion ER or its individual components, bupropion and naltrexone. We identified one study of naltrexone/bupropion ER that reported specifically on MACE (Nissen et al 2016). In this RCT, there was no statistically significant increase in the incidence of MACE, MACE+, or the components of MACE between overweight/obese patients treated with naltrexone/bupropion ER and those treated with placebo.¹² Overall, the published literature provided no consistent or statistically significant evidence of increased risk of CV events with use of naltrexone/bupropion ER, naltrexone with bupropion, or the components. One half of the 70 studies included in this review reported no CV events in patients treated with naltrexone/bupropion ER, naltrexone-bupropion, or the components, or a comparison treatment, while the remainder reported no increase in the incidence of MACE or MACE+ events in patients treated with naltrexone/bupropion ER, naltrexone with bupropion, bupropion, or naltrexone.

The risk of CV events in each study was dependent on the study population, especially comorbidities and indication for treatment. Observation of CV events also depended on duration of follow-up, sample size (such that rare events were unlikely to be observed in smaller studies), and, potentially, comparator treatment type (placebo or active comparator). The underlying patient populations in studies of naltrexone/bupropion ER, naltrexone with bupropion, bupropion, and/or naltrexone are at increased CV risk compared with the general population due to patient comorbidities, which include obesity, type 2 diabetes mellitus, and smoking.⁵⁻⁷ These conditions are known risk factors for MACE and other CVD. Despite the increased risk of CV events in these study populations, half of studies herein reported an absence of CV events, and none reported an elevated risk for CV events in patients treated with naltrexone/bupropion ER or its components.⁸⁶

The limitations to the studies evaluated in this review are considered in our overall conclusion. The diversity of study designs, lengths of follow-up, indications, and methods of defining, ascertaining, and reporting CV events, as well as overlapping study populations across some articles, a summary incidence of MACE or other CV events among all combined studies preclude a numeric calculation.

The included observational studies incorporated techniques that did not adjust for confounding by indication – that is, biased comparisons from differences in CVD risk due to the underlying indication for treatment, such as overweight/obesity, type 2 diabetes, or smoking. Selection bias in observational studies may contribute to observed differences (or lack thereof) in CVD risk if participation rates and reasons for non-participation vary between treatment groups. It is understood that this patient population is at increased CV risk.⁵⁻⁷

Few of the eligible studies included herein specifically evaluated naltrexone/bupropion ER or naltrexone with bupropion as the intervention of interest, and only one study reported on MACE with naltrexone/bupropion ER, and after accruing half of the expected events (50% interim) and at the final end of the study analysis, there was not a statistically significant difference in MACE between the naltrexone/bupropion ER and placebo groups.⁷⁸ There was no elevated risk of MACE – including MACE, MACE+, and the individual components of MACE – observed in the naltrexone/bupropion ER-treated group compared with placebo. Studies of bupropion or naltrexone generally had shorter durations of follow-up than studies of naltrexone/bupropion ER or naltrexone with bupropion, impacting their contribution to the body of evidence on the long-term CV safety of naltrexone/bupropion ER. Our findings are consistent with existing systematic reviews regarding the same interventions and outcome. Sposito et al conducted a systematic literature review and meta-analysis of Phase 3 RCTs evaluating bupropion, naltrexone, or naltrexone with bupropion, and found no significant difference in the incidence of MACE between treatment groups.⁸⁷

Finally, only published articles identified in accordance with the literature search protocol were included in this review. Despite extensive efforts to identify all relevant sources available through a pre-defined search strategy, with input from experts in both the product literature and systematic literature reviews, some sources with relevant information may have been overlooked or not identified for inclusion.

Conclusion

Based on 22 RCTs supplemented by 13 observational studies with relevant data, the overall body of literature and individual studies herein do not demonstrate an increased risk of MACE or other CV events with the use of naltrexone/bupropion ER or its individual components, bupropion and naltrexone.

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SD, ETC, SRW, PD are employees and ETC and SRW are stockholders of Exponent, a multidisciplinary science and engineering consultancy. MER is a consultant and EG is an employee of Currax Pharmaceuticals, LLC, a specialty pharmaceutical business focused on acquiring and commercializing prescription drugs within the US market. Currax Pharmaceuticals owns the world-wide rights to Contrave. The authors report no other conflicts of interest in this work.

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