Naltrexone-bupropion (Mysimba®) in management of obesity: a systematic review and meta-analysis of unpublished clinical study reports

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ABSTRACT

Aims: To compare the benefits and harms of naltrexone-bupropion using evidence from clinical study reports (CSRs).

Methods: We searched FDA and EMA websites, PubMed, and Clinicaltrials.gov (May 2016) to identify pivotal trials; we then sent a freedom of information request to the EMA (July 2016). We included pivotal, phase III placebo-controlled trials. We assessed the risks of bias using the Cochrane criteria, and the quality of the evidence using GRADE. We used a random-effects model for meta-analyses.

Results: Over a 27-month period (July 2016 to August 2018), we received 31 batches of CSR documents containing over 65 000 pages of data from four pivotal trials (n=4536). Significantly more participants who took naltrexone-bupropion achieved ≥5% reduction in body weight: RR=2.1 (1.35 to 3.28, P=0.001, GRADE=low, NNT_B=5 (3 to 17); this represents a 2.53 kg (1.85 to 3.21) reduction in baseline body weight compared with placebo. Naltrexone-bupropion had significantly beneficial effects on other cardiovascular risk factors; however, the true effect sizes for these are uncertain because of incomplete outcome data. Naltrexone-bupropion significantly increased the risk of adverse events: RR=1.11 (1.05 to 1.18, P=0.0004, GRADE=low, NNT_H=12 (7 to 27); serious adverse events: RR=1.70 (1.38 to 2.1), P<0.00001, GRADE=moderate, NNT_H=21 (13 to 38); and discontinuation because of adverse events: RR=1.92 (1.65 to 2.24), P<0.00001, GRADE=moderate, NNT_D=9 (8 to 13).

Conclusions: Naltrexone-bupropion significantly reduces body weight by a small amount but significantly increases the risk of adverse events. A rigorous process of post-marketing surveillance is required.

INTRODUCTION

The prevalence of overweight and obesity continues to increase, and they have become major public health challenges [1]. In 2016, there were over 1.9 billion overweight adults globally, of whom 650 million were obese [2]. Cost-effective strategies to tackle this are urgently needed [3].

Several drugs have been licensed for the management of overweight and obesity over the last 70 years. Most of them have central mechanisms of action and many have been withdrawn from the market because of unfavourable benefit-harm profiles [4]. More recently, combination therapies that act via central pathways have been developed; these are now being licensed by drug regulatory authorities for clinical use.

Naltrexone-bupropion (N-B) is a combination formulation used as treatment option for long-term management of overweight and obesity, in addition to exercise and a reduced calorie diet. Naltrexone acts by autoinhibition of pro-opiomelanocortin (POMC) neurons in the hypothalamus, while bupropion is thought to increase the actions of dopamine at specific sites in the brain [5]. The combined effects of naltrexone and bupropion are thought to reduce food craving.

N-B was licensed for obesity management by the European Medicines Agency (EMA; Mysimba®) and the US Food and Drug Administration (FDA; Contrave®) in September and December 2014 respectively. However, in July 2017, the National Institute for Health and Care Excellence (NICE) did not recommend N-B for use in the UK, because of uncertainties over its clinical and cost effectiveness [6]; a reappraisal of the evidence for its effectiveness is expected to be conducted in 2020.

Clinical study reports (CSRs) are unabridged documents that provide detailed information on the methods and results of clinical trials [7]. They contain, among other things, core reports, study protocols (including amendments), statistical analysis plans, randomization codes, case report and patient consent forms, patients' listings, results listings, case narratives, and approval documents. CSRs are used by drug regulators to assess the benefits and harms of new medicines before they grant marketing licences, and they provide more comprehensive data on trial methods and results than journal publications [8,9].

There has been no previous assessment of the benefit-harm profile of N-B based on evidence from unpublished CSRs. Our objective was therefore to assess the benefits and harms of N-B in the management of overweight and obesity, using the evidence from unpublished CSRs of pivotal clinical trials.

METHODS

We searched the EMA and FDA websites (May 2016) to identify pivotal phase III trials used by the drug manufacturer to gain marketing authorization for N-B in both Europe and the USA (see Appendix 1). Using the approval documents from both regulatory websites, we searched for pivotal trials used to gain marketing approval. We mapped the IDs of pivotal trials in the regulatory documents to their corresponding journal publications by conducting searches on PubMed and clinicaltrials.gov (May 2016; see Appendix 2). We then contacted the EMA to request the CSRs of these trials. The review protocol was registered at PROSPERO (ID: CRD42018086618).

We included pivotal, placebo-controlled, phase III trials on which marketing authorizations were based. If the pivotal trials contained other active comparator arms, such arms were excluded from the review.

Our primary outcomes were body weight (dichotomous outcome; proportion of participants who lost at least 5% body weight from baseline), adverse events, and discontinuations due to adverse events. Secondary outcomes were body weight (continuous outcome), proportion of participants who lost at least 10% body weight from baseline, serious adverse events, waist circumference, systolic and diastolic blood pressures, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, blood glucose, and impact of weight on quality of life. We checked the retrieved CSRs using the following two criteria: (i) completeness; and (ii) internal consistency (see protocol for full description of terms). We extracted data on study ID, study design and setting, participant characteristics, description of interventions and placebos, study duration, lifestyle adjustments, and primary and secondary outcomes. We also extracted data on adverse events reported by trial investigators as possibly related or related to the intervention. Data were extracted by one reviewer (IJO) and were independently cross-checked by a second reviewer (JJL). We assessed the risk of bias using the Cochrane criteria [10]. Two reviewers (IJO and JJL) independently assessed the risk of bias in the included CSRs. Disagreements were resolved through discussion.

We used an intention-to-treat (ITT) analysis (all randomized participants) to compare outcomes between N-B and placebo. When there were two or more active treatment arms, they were combined to create single pair-wise comparisons [11]. Using the random-effects model of RevMan 5.3 software [12], we computed risk ratios (RR) and 95% confidence intervals (CI) for dichotomous outcomes, and mean differences (MD) with 95% CIs for

continuous outcomes. One reviewer (IJO) entered the data for meta-analysis, and these were independently cross-checked by the second reviewer (JJL). Disagreements were resolved through discussion. Using the control group event rates, we computed the number needed to treat to benefit (NNT_B), the number needed to treat to harm (NNT_H), and the number needed to treat to discontinue treatment (NNT_D), with their respective 95% CIs. We analysed the data on adverse events for all participants, and for participants whose adverse events were reported by the investigators as possibly related or related to the intervention. We assessed the quality of the evidence for each outcome using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria [13], which examine the following domains: (i) study design; (ii) risk of bias; (iii) inconsistency; (iv) indirectness; and (v) imprecision. Using the GRADEpro software (version 3.6) [14], we rated evidence from "high" to "very low". Because there were fewer than 10 pivotal trials, the publication bias domain was not used in rating the quality of the evidence. The quality of the evidence is upgraded when the overall effect estimate is dramatic: i.e. large (RR >2 or <0.5) or very large (RR >5 or <0.2) for dichotomous outcomes; or large (MD>0.8) for continuous outcomes. We used GRADE evidence profiles (EP) to present the results.

RESULTS

Over a 27-month period (between July 2016 and August 2018), we received 31 batches of CSR documents from the EMA, containing over 65 000 pages of relevant data for four pivotal trials (Figure S1) (see Appendix 3 for a list of the component items in the CSRs). The four pivotal trials and their corresponding journal publications were NB-301 [15], NB-302 [16], NB-303 [17], and NB-304 [18] (see Appendix Table 1 for regulatory, clinicaltrials.gov, and PubMed matching IDs); all were conducted in the USA, comprised 4536 participants in total, and lasted 6–12 months (see Appendix Table 2). The baseline body weight was 99.6–

104.5 kg across the four studies. Active interventions were naltrexone sustained-release (SR) 16 or 32 mg plus bupropion SR 360 mg. The composition of the placebo was not reported.

The risk of bias in five domains was low (Figure 1). We judged the "incomplete outcome reporting" domain as "unclear", because full datasets were only reported for weight loss outcomes. We judged the "other bias" domain as "high", because (i) most of the investigators had financial ties to the drug sponsor – industry affiliation is associated with poor adherence to clinical trial practices [19]; and (ii) there were high discontinuation rates across the trials. Overall, we rated the risk of bias as moderate.

Effect on body weight and other cardiovascular risk profiles

Significantly more participants in the N-B group achieved at least a 5% reduction in body weight compared with placebo: RR = 2.1 (1.35 to 3.28); P=0.001; I^2=92%; GRADE = low; NNT_B = 5 (3 to 17) (Table 1; Figure 2). We observed similar findings when we compared participants who achieved at least a 10% reduction in body weight: RR = 2.58 (1.84 to 3.61); P<0.00001; I^2=68%; GRADE=moderate (Appendix Figure 2). Participants in the N-B group lost significantly more body weight from baseline: MD = –2.53 kg (–3.21 to –1.85); P<0.00001; I^2=92%; GRADE = low (Table 1; Appendix Figure 3).

The effects of N-B on other cardiovascular risk profiles are shown in Appendix Figures 4-12. Compared with placebo, participants in the N-B group had significant reductions in waist circumference (MD = –3.14 cm (–3.69 to –2.59), P<0.0001, I^2=0%); fasting triglycerides (MD = –0.05 mg/dL (–0.09 to –0.01), P=0.03, I^2=80%); fasting LDL cholesterol (MD = –2.92 mg/dL (–5.16 to –0.69), P=0.01, I^2=22%); and fasting blood glucose (MD = -1.19 mg/dL (–2.15 to –0.23), P=0.02, I^2=1%); with significant increases in HDL cholesterol (MD

= 3.04 mg/dL (2.40 to 3.68), P<0.00001, I^2=0%); systolic blood pressure (MD = 1.47 mmHg (0.48 to 2.47), P=0.004, I^2=51%); and diastolic blood pressure (MD = 0.98 mmHg (0.50 to 1.45), P<0.0001, I^2=0%). There were no significant differences in total cholesterol concentrations or quality-of-life scores. These results were not based on all randomized participants; we were unable to impute data to account for missing values, because of incomplete outcome data [20,21] (see Appendix Table 3 for the proportions of participants for whom outcome data were reported for cardiovascular risk profiles).

Adverse events

The data on adverse events are summarized in Table 2, Figure 3, and Appendix Figures 13-41. Overall, there was a significantly increased risk of adverse events with N-B: RR = 1.11 (1.05 to 1.18); I^2=72%; P<0.00001 GRADE = low; NNT_H = 12 (7 to 27). The risk of adverse events reported by investigators as related or possibly related to the intervention was also significantly greater with N-B: RR = 1.75 (1.48 to 2.06); I^2=80% P<0.00001; GRADE = very low; NNT_H = 4 (3 to 6). Nervous system, psychiatric, vascular, gastrointestinal, and ear and labyrinth adverse events were significantly more common with N-B.

The data on serious adverse events are summarized in Table 3 and Figure 4. Serious adverse events were significantly more common with N-B than placebo: RR = 1.70 (1.38 to 2.10); P<0.00001; I^2=0%; GRADE = moderate; NNT_H = 21 (13 to 38). The risk of serious adverse events reported by investigators as related or possibly related to intervention was significantly greater with N-B: RR = 5.72 (3.09 to 10.58); P<0.00001; I^2=36%; GRADE = high; NNT_H = 16 (8 to 37).

Discontinuations

Discontinuation rates were 42–47% across the four studies (Appendix Table 2). Overall, there were no significant differences in discontinuation rates between the N-B and placebo groups. The data on discontinuations due to adverse events are summarized in Table 4, Figure 5, and Appendix Figures 42-47. The risk of discontinuation because of adverse events was significantly higher with N-B: RR = 1.92 (1.65 to 2.24); P<0.00001; GRADE = moderate; NNT_D = 9 (8 to 13). Discontinuations due to gastrointestinal adverse events, including nausea, vomiting, and constipation, were significantly more common with N-B, as were discontinuations due to nervous system events, including headaches and dizziness.

Among participants in whom adverse events were reported as related or possibly related to the intervention (n = 1979), the frequency of investigator-initiated drug withdrawals was significantly higher with N-B: RR = 1.79 (1.53 to 2.11, I^2 = 0%, P<0.00001), number needed to treat for drug withdrawal (NNT_W) = 5 (4 to 8) (Appendix Figure 48).

DISCUSSION

Summary of main findings

N-B caused a significantly greater reduction in weight than placebo when estimated by the number of participants who lost at least 5% of their body weight. Overall, this translates to 2.5 kg more weight loss than with placebo over a 12-month period. A significantly greater proportion of participants who took N-B also achieved at least 10% weight loss in body weight from baseline compared with placebo. N-B had significantly beneficial effects on other markers of cardiovascular risk; however, the true extent of the effects is unclear because of incomplete outcomes data. N-B significantly increased the risk of adverse events, including abdominal pain, vomiting, constipation, dry mouth, headaches, tinnitus, vertigo,

dysgeusia, insomnia, tremors, palpitations, and hot flushes. N-B significantly increased the risk of serious adverse events and discontinuation due to adverse events. N-B also significantly increased the risk of investigator-initiated drug withdrawals because of adverse events. That the overall discontinuations rates were similar between N-B and placebo despite significantly greater withdrawals with N-B could be due to more withdrawals in placebo group because of failure to lose weight. The meta-analysis results (along with the associated NNTs) should be interpreted with caution because of heterogeneity in some of the analyses. The substantial heterogeneity observed with body weight outcomes is probably due to variation in baseline demographics across the four trials.

To our knowledge, this is the first systematic review of the benefits and harms of N-B using evidence from CSRs. For the first time we have also reported data on harms adjudged by trial investigators to be related or possibly related to the intervention.

Comparison with existing literature

Our results are partly consistent with those of three previous reviews that assessed the benefits and harms of N-B using data from journal publications of clinical trials [22,23,24]; all three reviews concluded that N-B has significant beneficial effects on body weight but also significantly increases the risk of harms.

However, the availability of CSRs enabled us to access and analyse data that were not accounted for in those reviews and makes our review the most comprehensive to date. We assessed the protocol and trials for internal consistency in the trial regimen by evaluating data on protocol amendments and changes to statistical analysis plans. We computed the data on weight loss outcomes using the ITT analysis comprising the most complete sets of

257 randomized subjects, i.e. including all randomized participants. For example, the effect size
258 for the proportion of participants who lost >5% in body weight in our review was smaller
259 than those reported in the three previous reviews.
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261 Although the aggregated data on other cardiovascular risk outcomes were incomplete, we
262 were able to report the data based on the proportion of randomized participants for whom
263 outcomes were reported across the trials. We reported data on adverse events by system and
264 reported data on individual adverse events. We also extracted and analysed data on harms
265 outcomes classified by trial investigators as related or possibly related to interventions.
266 Furthermore, we evaluated data on investigator-initiated drug withdrawals because of adverse
267 events.
268
269 **Strengths and limitations**
270 We obtained data on full unabridged CSRs from the EMA. We assessed the consistency of
271 reporting between the protocols and the core reports. We rated the quality of the evidence of
272 each outcome. We reported body weight outcome in both binary and continuous data. We
273 also reported outcomes on other cardiovascular parameters. For the first time, we have
274 reported data and rated the quality of the evidence for harms outcomes reported by
275 investigators as related or possibly related to the interventions; this included investigator-
276 initiated drug withdrawals because of adverse events.
277
278 However, we recognize some limitations. The high degree of heterogeneity observed for
279 body weight outcomes limits the accuracy of our effect estimates. We were unable to conduct
280 sensitivity or subgroup analyses because of the small number of included studies; however,
281 the studies had large sample sizes and heterogeneity was low in most of the harms outcomes.

Despite obtaining unabridged CSRs, we are limited by incomplete data, especially for cardiovascular outcomes. We did not have access to patient-level data, including individual case report forms, which would have allowed better evaluation of harms. The extent to which the protocol amendments influenced the reported effect sizes is unclear [25]; in all cases, the trial protocols were amended – these involved changes in inclusion/exclusion criteria in three trials (see Appendix 4). The extensive exclusion criteria used in all four studies limit the applicability of review findings (see Appendix 5) – many patients in clinical practice would not be eligible for treatment given the extensive categories of exclusions. Our definitions for ITT analysis differed from the definitions used in the CSRs; however, we used data from the CSRs that corresponded to our *a priori* definitions: i.e. ITT corresponding to baseline-observation-carried-forward populations in the CSRs.

Implications for research

Sustained weight losses of 5–10% can produce cardiovascular benefits [26]; however, the evidence from the included CSRs was insufficient to demonstrate such benefits. Although we found significant beneficial effects for some cardiovascular profiles, these were based on incomplete outcomes data. In the protocols, the investigators specified that they would measure these outcomes at baseline and at endpoint. While body weight outcomes were fully reported, the data on other cardiovascular measures were incomplete. Future trials could incorporate targeted study designs aimed at identifying what groups of overweight or obese subjects will benefit the most from N-B; for example, those with low risks of cardiovascular or psychiatric adverse events who are struggling to lose weight through dietary or lifestyle modifications.

Improved precision in harms reporting could be achieved if researchers compared the rates of harms for both the overall data and data reported as related or possibly related to the new medicine, as we have done in this review. Such methods could increase the certainty with which we predict the risks of harms from new medicines, especially when integrated with data from real-life practice. Although the current package insert for N-B recommends discontinuation of therapy after 12 weeks of maintenance [27] if there is no reduction of at least 5% in body weight, discontinuation also ought to be considered in the context of any harms experienced.

Post-marketing studies of N-B have not provided robust evidence about its benefit-harm profile, because of premature termination [28, 29] and a failure of scheduled trials to start owing to disputes between drug sponsors [30,31]. More recently (April 2018), the original sponsor announced that they have entered into an agreement to sell the company, and they have also reached an agreement with the FDA to conduct a new cardiovascular outcomes trial [32]. That there are no completed post-marketing trials four years after initial granting of marketing licences for N-B indicates failure on the part of drug regulators to robustly enforce guidelines on post-marketing drug assessment, a lack of commitment by the drug sponsors to conduct (and transparently report) post-authorization studies, or a combination of the two. Positive collaborations across stakeholders aimed at removing the uncertainties around the clinical effectiveness of N-B should be encouraged.

Implications for practice and policy

Physicians should weigh the potential benefits and harms when prescribing N-B, especially in patients with a history of (or risk factors for) nervous or psychiatric disorders. Caution should also be exercised when considering prescriptions in patients with a history of insomnia,

hypertension, or hot flushes. The intensity of the adverse events associated with the use of N-B could result in premature discontinuation of the drug. The long-term benefits and harms of N-B are unknown; it is unclear whether any weight reductions generated through use of N-B is sustained over longer periods. Because of the low proportion of participants with BMI <30 kg/m^2 across the trials (<3%), N-B should not be prescribed as first-line weight loss agent to overweight individuals. Regulators should be aware that they did not have access to full intention-to-treat analyses when considering N-B for licensing. In addition, it is unclear whether N-B will be cost-effective compared with alternatives. According to NICE [6], the economic model presented by the drug manufacturer did not take into account episodes of retreatment, which are likely with use of the drug. A more recent evaluation in 2018 by the Irish National Centre for Pharmacoeconomics (NCPE) did not recommend N-B for reimbursement, because of uncertainties around its cardiovascular safety and cost-effectiveness [33]. Until there is sufficient evidence of the clinical and cost-effectiveness of N-B (including cardiovascular benefits), regulators should be circumspect about approving its use in the general population.

CONCLUSIONS

The evidence from CSRs of pivotal trials shows that N-B causes significant but small reductions in body weight compared with placebo. N-B also appears to have small beneficial effects on other markers of cardiovascular risk; however, the extent is unclear because of incomplete outcome data. N-B significantly increases the risk of adverse events, serious adverse events, and discontinuations due to adverse events. Post-marketing studies assessing its benefits and harms are urgently required.

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Authors' contributions:

IJO was involved in protocol development, electronic searches, requesting and obtaining of clinical study reports, quality assessment, data extraction, data analysis and interpretation, and co-drafting of the review.

JJL was involved in quality assessment, data extraction, data analysis and interpretation, and co-drafting of the review.

KRM was involved in protocol development, data interpretation, and co-drafting of the review.

JKA was involved in protocol development, data analysis and interpretation, and co-drafting of the review.

CJH was involved in protocol development, data analysis and interpretation, and co-drafting of the review.

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Declarations of interest:

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391 with some international partners which are based on a non-profit making model. . JKA has
392 written and edited articles and textbooks on adverse drug reactions, including *Meyler's Side*
393 *Effects of Drugs* (16th edition, 2016), its companion volumes the *Side Effects of Drugs*
394 *Annuals*, and *Stephens' Detection and Evaluation of Adverse Drug Reactions* (6th edition,
395 2011). He is an Associate Editor of BMJ Evidence-Based Medicine and a member of the
396 CEBM (see above). JJL has no interests to disclose.
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Legends to Figures:

Figure 1: Risk of bias in pivotal clinical trials of naltrexone-bupropion (Mysimba®)

Figure 2: Effect of naltrexone-bupropion (N-B) on the proportion of participants who achieved ≥5% weight loss

Figure 3: Effect of naltrexone-bupropion (N-B) on the frequency of adverse events

Figure 4: Effect of naltrexone-bupropion (N-B) on the frequency of serious adverse events

Figure 5: Effect of naltrexone-bupropion (N-B) on the frequency of discontinuation due to adverse events