Prolonged-release oxycodone/naloxone reduces opioid-induced constipation and improves quality of life in laxative-refractory patients: results of an observational study

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Background: Opioids are an effective treatment for moderate-to-severe pain. However, they are associated with a number of gastrointestinal side effects, most commonly constipation. Laxatives do not target the underlying mechanism of opioid-induced constipation (OIC), so many patients do not have their symptoms resolved. Fixed-dose prolonged-release (PR) oxycodone/naloxone (OXN) tablets contain the opioid agonist oxycodone and the opioid antagonist naloxone. Naloxone blocks the action of oxycodone in the gut without compromising its analgesic effects.

Aim: To evaluate the effectiveness of PR OXN in patients with severe pain who had laxative-refractory OIC with their previous opioid.

Methods: The study was carried out in 13 centers across the UK and Ireland, using a bespoke online tool to capture patients’ data. Patients were reviewed according to normal clinical practice of each center and rated any changes in their constipation and quality of life (QoL) since starting PR OXN. Any change in patients’ laxative use was also recorded.

Results: One hundred and seven patients were entered into the database, and 81 went on to attend at least one review. Of these, 54 (66.7%) reported an improvement in constipation and 50 (61.7%) reported an improvement in QoL since starting PR OXN. Fifty-seven patients (70.4%) said they had reduced laxative intake; 48 (59.3%) only needed laxatives as required.

Conclusion: PR OXN reduced symptoms of constipation, improved QoL and reduced laxative intake in patients with OIC. It has a potential place early in any treatment strategy for severe pain in patients using opioids, particularly in patients who may be predisposed to constipation.

Keywords: laxatives, opioid, opioid-induced constipation, oxycodone/naloxone, PR OXN, real-world data, severe pain

Introduction

Opioids are a mainstay of pain management, offering an effective treatment for both acute and chronic pain conditions. The World Health Organization’s three-step analgesic ladder places non-opioids at Step 1, followed by opioids for mild-to-moderate pain (e.g. codeine, tramadol) at Step 2 and opioids for moderate-to-severe pain (e.g. oxycodone, morphine) at Step 3.1 This stepwise approach was originally developed for cancer pain, but is now also used in chronic non-cancer pain. Several modified versions of the ladder have been proposed, including one that incorporates a fourth step for treatment of chronic pain crises,2 and another that skips Step 2 in cancer pain.3

Alongside their analgesic action, opioids can cause a number of unwanted effects. Gastrointestinal (GI) side effects that are collectively termed “opioid-induced bowel
dysfunction” are often reported as particularly troublesome for patients, frequently overtaking pain as the primary complaint. The most common of these GI effects is opioid-induced constipation (OIC), which is likely caused by opioids binding to μ-opioid receptors in the submucosal and myenteric plexuses of the GI tract. This reduces GI secretions and peristaltic activity, and increases fluid reabsorption, resulting in dry, hard stools. Unlike other GI symptoms, patients rarely develop tolerance to OIC, so it does not resolve over time.

OIC negatively impacts patients’ quality of life (QoL), affecting their relationships, social life, dietary choices and ability to perform activities of daily living. To avoid OIC, some patients will reduce their opioid dose, or even stop taking opioids altogether, which can result in uncontrolled pain. Almost half of the 439 patients in a multinational survey reported that OIC moderately or completely interferes with pain control. However, the negative effects of OIC on pain management and QoL are often underappreciated by health care professionals, which can compromise patient care.

There is also a considerable economic burden associated with OIC: patients may need time off work or be less productive when at work, and may use additional health care resources. In Sweden and the US, it has been shown that total health care costs are significantly higher for patients with OIC than for those without. Traditionally, OIC is treated with laxatives, with stimulants and stool softeners typically recommended. However, laxatives do not affect opioid binding to receptors in the GI tract and therefore do not address the underlying mechanism of OIC. Consequently, many patients do not experience relief from constipation after treatment with traditional laxatives.

Fixed-dose prolonged-release (PR) oxycodone/naloxone (OXN) tablets (Targinact, Napp Pharmaceuticals, UK) contain the μ-opioid agonist oxycodone, combined with the μ-opioid antagonist naloxone. Naloxone counteracts OIC by blocking the action of oxycodone at opioid receptors in the GI tract. Given orally, naloxone has negligible bioavailability (<3%) as a result of extensive first-pass metabolism. Therefore, its effects on the central nervous system are minimal, and it does not interfere with the analgesic effects of oxycodone.

Several studies have confirmed that treatment with PR OXN provides effective pain relief while reducing OIC. Patients treated with PR OXN (either for chronic nonmalignant pain or for chronic cancer pain) have reported an improvement in their QoL. Furthermore, a UK-based analysis has shown PR OXN to be a cost-effective option for treating patients with severe nonmalignant pain and OIC. Peripheral μ-opioid antagonists, such as naloxegol (Astra Zeneca, UK), are also available for the treatment of OIC that is refractory to laxatives.

A disadvantage of clinical trials is that they investigate medications under strictly controlled conditions in specific patient populations, and so may not reflect what happens in day-to-day clinical practice. Much of the available data for PR OXN focus on its clinical efficacy; although some data on QoL exist, more is needed, particularly in mixed pain populations. To address both these issues, we carried out an observational, cross-sectional study in patients prescribed PR OXN to evaluate the efficacy of medication and the impact on bowel function and QoL in patients with severe pain requiring an opioid, who were experiencing OIC despite taking laxatives, or who were unable to tolerate laxatives.

Methods

A bespoke online clinician audit tool was developed to support pain centers in collecting patient data and evaluating clinical outcomes of patients taking PR OXN. It was developed with input from a steering group of pain experts from the UK and Ireland with expertise in the management of chronic pain. Between November 2013 and January 2015, this audit tool was used in a study conducted in 13 centers in the UK and Ireland. Participating centers were located across the spectrum of patient care in primary care (Ireland) and secondary care (UK). Patients were prescribed PR OXN after continuing to experience OIC despite the use of laxatives with their previous opioid or if they were unable to tolerate laxatives due to their side effects. The decision to prescribe PR OXN was entirely at the investigator’s discretion, and was not based on any strict inclusion or exclusion criteria. The aim of the study was to assess the efficacy of PR OXN in terms of improvements in constipation and QoL.

At baseline, patients’ demographic data (age and gender), pain condition and previous pain medication (opioids and co-analgesics) were recorded. Any factors that may have contributed to the patient’s constipation (e.g. diet, reduced mobility, preexisting bowel conditions) were also documented. Patients’ current laxative regimen, whether the patient had failed laxatives, and the reason for laxative failure (i.e. intolerable adverse events [AEs] or lack of efficacy) were also captured. Finally, the starting dose of PR OXN was recorded, together with the objective for starting PR OXN treatment (improvement in constipation and/or other associated symptoms, improvement in QoL, or both). Patients were switched from their previous opioid to standard equianalgesic doses of PR OXN to ensure that analgesia was maintained. The starting dose of PR OXN was recorded.
Patients were then reviewed within normal clinical practice (i.e. during their usual consultations rather than at separate defined study visits); as a result, the number of reviews per patient and the time between reviews were not standardized between centers. Clinicians collated data from each patient review of any changes in constipation and QoL using the 7-point Patients’ Global Impression of Change scale,\(^\text{16}\) where 1 = very much improved and 7 = very much worse. Data relating to the type of laxatives used by patients and their frequency of use were collated as well as the objective for starting PR OXN which was reviewed at each consultation to understand if the objectives of PR OXN treatment had been met.

The decision to prescribe PR OXN had been made before the study period started, and data were collected within the course of normal clinical practice with patient consent. Therefore, the National Research Ethics Service (NRES) confirmed that formal ethics committee approval was not required. All data were anonymized.

### Data analysis

As an audit, this uncontrolled observational study was intended to give an overview of real-world clinical practice and outcome over a specified time period, and was not designed to provide applicable statistical power, so no formal sample size calculation was undertaken and no statistical model was applied.

Data were summarized descriptively using SAS\(^\text{®} \text{v9.3}\) (SAS Institute Inc., Cary, NC, USA); there was no imputation for missing data. Continuous data were presented as mean, standard deviation and range. Categorical data were presented as number and percentage. Presentation of data were developed in accordance with guidance from STROBE (strengthening the reporting of observational studies in epidemiology), details of which can be found at [www.strobe-statement.org](http://www.strobe-statement.org)

### Results

#### Patients

In total, 107 patients were entered into the Targinact Treatment Evaluator (TTE) database. Table 1 shows the baseline characteristics of patients. Patients who did not undergo a subsequent review following enrollment were included in demographic and AE analysis only and were excluded from analyses of other parameters. Eighty-one of the 107 patients (75.7%) went on to attend at least one review and were included in the analysis. Patients were predominantly female and aged \(\leq 65\) years; nearly a third (29.9%) had two or more pain conditions. The majority of patients had at least one factor contributing to constipation at baseline (n=101; 94.4%). The incidence of predisposing factors was similar between older (aged \(\geq 65\) years) and younger (aged \(\leq 65\) years) patients, with the exception of reduced mobility: 27/42 patients (64.3%) aged \(\geq 65\) reported that reduced mobility contributed to their constipation, compared with 30/65 (46.2%) aged \(\leq 65\). For 63 patients (58.9%), the objective for starting PR OXN was to improve both their symptoms of constipation and their QoL.

#### Table 1 Age, gender, pain condition and factors contributing to constipation

| Parameter                                      | n=107 |
|------------------------------------------------|-------|
| Age (years)                                    |       |
| n (missing)                                    | 106 (1)|
| Mean (SD)                                      | 57.6 (19.65)|
| Min, max                                       | 21.0, 95.3|
| Age category, n (%) of patients                 |       |
| n (missing)                                    | 106 (1)|
| \(\leq 65\) years                              | 64 (59.8)|
| \(\geq 65\) years                              | 42 (39.3)|
| Gender, n (%) of patients                       |       |
| Male                                           | 41 (38.3)|
| Female                                         | 66 (61.7)|
| Pain condition, n (%) of patients               |       |
| Back pain                                      | 57 (53.3)|
| Neuropathic pain                               | 16 (15.0)|
| Musculoskeletal other                          | 15 (14.0)|
| Postoperative pain                             | 15 (14.0)|
| Osteoarthritis                                 | 9 (8.4)|
| Cancer                                         | 8 (7.5)|
| Visceral pain                                  | 8 (7.5)|
| Inflammatory arthropathy                       | 4 (3.7)|
| Rheumatoid arthritis                           | 1 (0.9)|
| Other                                          | 20 (18.7)|
| Factors contributing to constipation, n (%) of patients |       |
| Mobility                                       | 57 (53.3)|
| Diet                                           | 49 (45.8)|
| Hypothyroidism                                 | 2 (1.9)|
| Preexisting bowel condition                    | 15 (14.0)|
| Diverticular disease                           | 7 (6.5)|
| Crohn’s disease                                | 3 (2.8)|
| Ulcerative colitis                             | 1 (0.9)|
| Colorectal cancer                              | 6 (5.6)|
| Other neurological condition                   | 7 (6.5)|
| Other constipating medications                | 21 (19.6)|
| Number of factors contributing to constipation, n (%) of patients |       |
| 0                                              | 6 (5.6)|
| 1                                              | 59 (55.1)|
| 2                                              | 25 (23.4)|
| 3                                              | 12 (11.2)|
| 4                                              | 3 (2.8)|
| 5                                              | 1 (0.9)|
| 6                                              | 1 (0.9)|

Table 2 shows the patients’ previous opioid and co-analgesic medications, and laxative use at baseline. Laxative regimens that were used by patients included stool softeners such as PEG, stimulants including senna, biscodyl and docusate, osmotic laxatives such as lactulose and bulk-forming...
agents including methylcellulose. The most commonly used opioids were tramadol, morphine and oxycodone. Two-thirds of patients were using paracetamol as a co-analgesic. Most patients (102; 95.3%) were taking at least one laxative before they started using PR OXN. Sixty-five patients (60.7%) had failed their previous laxative regimen: 53 because of lack of efficacy and 12 because of intolerable AEs. The most common type of laxative taken by the 53 patients who failed because of lack of efficacy was stimulants (taken by 37 patients; 69.8%). In the 12 patients who failed because of AEs, the most common type of laxative taken was osmotics (taken by seven patients; 58.3%). The dose of PR OXN at the start of therapy and at last review is shown in Table 3.

Improvement in constipation and QoL
Of the 81 patients who underwent at least one review, 54 (66.7%) had an improvement in their constipation (Figure 1) on switching to PR OXN in an equianalgesic fashion from their previous opioid. In a small proportion of patients (n=5; 4.7%), PR OXN was considered to be ineffective and patients did not experience an improvement. For those patients experiencing improvement, there did not appear to be an association between age and improvement in constipation (Table 4). Additional sub-analyses indicated that there was likewise no association between improvements in constipation and gender, number of constipating factors, number of laxatives or reason for laxative failure (although the number of patients involved was low). There was some variation in the proportion of patients who had an improvement in constipation according to the number of constipating factors. The proportion of patients reporting improved constipation did not appear to vary among those who had been taking one or two laxatives before starting PR OXN, but was slightly higher in those who had been taking three laxatives.

Fifty (61.7%) of the 81 patients who underwent at least one review had an improvement in their QoL (Figure 1). There did not appear to be an association between age and improvement in QoL (Table 5), and similarly, there was no association between improvements in QoL and number of laxatives or reason for laxative failure. The proportion of patients reporting improved QoL did not appear to vary among those who had been taking one or two laxatives before starting PR OXN, but was slightly lower in those who had been taking three laxatives. While there was no recognizable association between improvements in QoL and gender, it was noted that fewer females than males reported an improvement (56.3% vs. 69.7%, respectively).

Laxative use
Of the 81 patients who underwent at least one review, 57 (70.4%) reduced their laxative intake after starting PR OXN; 48 patients (59.3%) said they were now only using laxatives as required (Figure 2). Three-quarters of patients aged ≥65 (25/33; 75.8%) said they were only using laxatives as required, compared with approximately half of those aged ≤65 (23/48; 47.9%). Two-thirds of patients who had previously failed laxatives because of lack of efficacy (28/42; 66.7%) said they were only using laxatives as required,
Figure 1 Improvements in constipation (A) and QoL (B) at last review (n=81).

Note: Patients were asked to rate any changes in constipation and QoL using the 7-point Patients’ Global Impression of Change scale, where 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse and 7 = Very much worse.

Abbreviations: QoL, quality of life; PGIC, Patients’ Global Impression of Change.

Table 4 Improvement in constipation at last review by age

| PGIC score | Age, years | Total, N (%) |
|------------|------------|--------------|
|            | ≤65 (n=48), | ≥65 (n=33),  |
| 1 (Very much improved) | 5 (10.4) | 10 (12.3) |
| 2 (Much improved) | 13 (27.1) | 23 (28.4) |
| 3 (Minimally improved) | 14 (29.2) | 21 (25.9) |
| 4 (No change) | 11 (22.9) | 21 (25.9) |
| 5 (Minimally worse) | 2 (4.2) | 3 (3.7) |
| 6 (Much worse) | 1 (2.1) | 1 (1.2) |
| 7 (Very much worse) | 2 (4.2) | 2 (2.5) |

Abbreviation: PGIC, Patients’ Global Impression of Change.

Table 5 Improvement in quality of life at last review by age

| PGIC score | Age, years | Total, N (%) |
|------------|------------|--------------|
|            | ≤65 (n=48), | ≥65 (n=33),  |
| 1 (Very much improved) | 2 (4.2) | 4 (4.9) |
| 2 (Much improved) | 14 (29.2) | 24 (29.6) |
| 3 (Minimally improved) | 14 (29.2) | 22 (27.2) |
| 4 (No change) | 11 (22.9) | 20 (24.7) |
| 5 (Minimally worse) | 3 (6.3) | 6 (7.4) |
| 6 (Much worse) | 3 (6.3) | 4 (4.9) |
| 7 (Very much worse) | 1 (2.1) | 1 (1.2) |

Abbreviation: PGIC, Patients’ Global Impression of Change.
compared with less than half who had failed laxatives because of intolerable AEs (5/11; 45.5%).

Subsequent treatment
Twenty-four (29.6%) of the 81 patients who underwent at least one review fully achieved their objective for starting PR OXN; 35 patients (43.2%) partially achieved it.

Information about subsequent treatment was recorded for 34 of the 107 patients in the database. No further treatment was needed in 21 patients, nine were put on a regimen where the opioid was rotated and laxative titrated as required, three were advised to manually evacuate as required and one returned to their previous treatment regimen.

Safety
All 107 patients in the database were included in the safety analysis; 28 (26.2%) had at least one AE during PR OXN treatment. The most common AE was nausea (n=3; 2.8%; Table 6). Crohn’s disease, death, increased heart rate, lung neoplasm, sensory loss and elective surgery were also recorded as AEs in one patient each; however, these are not thought to be related to PR OXN. Lack of efficacy was also recorded in 4.7% (n=5) of patients.

The incidence of AEs was lower in patients aged ≥65 (9/42; 21%) than in patients aged ≤65 (19/65; 29%). Whereas the incidence of GI events was similar, fewer elderly patients reported non-GI events such as nervous system and psychiatric disorders (Table 6).

More females than males reported GI events (6/66; 9.1% vs. 2/41; 4.9%). The incidence of non-GI events was similar between genders.

Discussion
OIC is common, and laxatives are often not an effective treatment. For example, in the multinational PROBE1 survey of 322 patients receiving opioids for chronic pain, 81% of patients reported OIC, despite taking laxatives. Another multinational survey of 489 patients with chronic non-cancer
patients taking one laxative for OIC and 38% taking two had an inadequate response to treatment. A small Dutch pilot study in patients receiving oxycodone for chronic pain showed that 43% were nonresponders to laxatives; among those patients with severe OIC, this rose to 71%.22

Clearly, there is a need for alternative treatment options for OIC. Our study in a heterogeneous population that is representative of patients seen in routine clinical practice showed that PR OXN is an effective option: it reduces constipation, improves QoL and reduces laxative use in patients with OIC. Overall, the improvements in constipation and QoL are consistent with other recently published small observational studies in patients with chronic pain and laxative-refractory OIC.29,32,33 However, it appears that a number of patients did not experience an improvement in QoL, despite their constipation being reduced. This may have been influenced by the underlying medical condition, with some patients having several factors that would need improvement before they feel their overall QoL is improved.

Importantly, improvements observed in this study in levels of constipation were independent of opioid dose, as all patients were switched from their previous opioid to equianalgesic doses of PR OXN. These data support a recently published patient survey that indicated taking laxatives did not improve symptoms of OIC for patients, irrespective of opioid strength, or dose or number of laxatives taken.37 The use of laxatives is often associated with side effects such as bloating, gas, fecal soiling and alterations in electrolyte haemostasis;37 medication that can reduce or perhaps eliminate the use of laxatives has the potential to improve patients’ lives.

Many of the patients in the study population had previously failed laxatives, either because of lack of efficacy or because of intolerable side effects. Owing to prescribing restrictions on opioids in the UK, PR OXN is often used after laxatives have failed, but only in specific groups of patients. We would argue that patient selection is important and that PR OXN should be available early in the treatment pathway to any patient who would be likely to benefit, for example, those who have previously had bowel surgery and must avoid constipation. However, to allow identification of these patients, algorithms need to be developed.

Most patients in the study also had several additional factors that contributed to their constipation; the most common were reduced mobility and diet. These non-pharmacological factors are important and should ideally be corrected before pharmacological treatment is initiated. However, improving a patient’s mobility without sufficient pain relief is difficult; these patients would likely benefit from an analgesic with a reduced potential to cause OIC. Thirty-two patients (29.9%) had preexisting abdominal conditions that may also have had an impact on both their pain and bowel function. Although abdominal pain was not a specific pain type recorded in this study, it is likely that it would have had an impact on a number of patients.

The patient population in this study was predominantly female. This is to be expected given the higher prevalence of chronic pain in females compared with males,38 and is consistent with a previous longitudinal survey in OIC.21 A subgroup analysis showed that gender made no difference to the overall study results.

PR OXN was well tolerated, particularly in older patients (≥65 years); in fact, the incidence of AEs was lower in this group than in younger patients. This is interesting, given that older patients are generally considered to be more susceptible to AEs than younger patients.39 One explanation may be that the older patients had a lower daily intake of opioid, resulting in fewer non-GI side effects: 66.7% of patients aged ≥65 started on the lowest dose of PR OXN (5/2.5 mg), compared with 20% of those aged ≤65 years.

Limitations

Using the TTE to collect data means that we have obtained a “real-world” perspective on the effectiveness of PR OXN in patients with OIC. Real-world data are becoming increasingly important, particularly to decision-making bodies: large-scale clinical trials have been criticized because they do not truly reflect what happens in day-to-day clinical practice. However, there were some limitations to the study. One key limitation is the introduction of potential bias due to the lack of a controlled study design. Additionally, as the time interval between reviews was not specified, there could have been a degree of variability in the data obtained. Another limitation of this study is the low patient numbers which means that the data must be interpreted with caution.40 Carrying out the patient reviews as part of normal clinical practice meant that limited data were collected for some patients who may only have had one or two reviews scheduled during the predefined timeframe of the study (15 months). A final potential confounder of the data in this study are missing follow-up review data from 26 patients; whether this is due to late study entry or the lack of scheduling before study end cannot be determined. The nature of the study may have given rise to inclusion bias: it is possible that centers tended to include patients with particularly challenging constipation. However, each of the 13 centers included similar numbers of patients,
so the results can be assumed to be representative of a broad population of patients with OIC. A further limitation is that there are likely to have been differences between centers in protocols for using PR OXN. Despite the limitations of an audit rather than a controlled clinical study, the data observed here do indicate that real-world patient outcomes observed are substantively comparable to those data observed in true controlled clinical studies.\textsuperscript{30–33}

**Conclusion**

PR OXN provides an additional treatment choice in OIC, particularly for patients who are running out of options. The results give a fresh perspective on the epidemiology of constipation, revealing that many patients with OIC have other predisposing factors. We suggest that there is a place for PR OXN early in a treatment strategy for severe pain: predisposing factors (e.g. diet and reduced mobility) should be corrected first, followed by prescription of an analgesic that has a reduced potential to cause constipation, particularly in patients for whom constipation is already, or is anticipated to become, an issue.

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**Author contributions**

Carsten Bantel, Shiva S Tripathi, David Molony, Tony Heffernan, Susmita Oommen and Vivek Mehta helped to collect data and critically revised the manuscript. Sara Dickerson is the guarantor of the article, and helped design the audit study and analyze the data, and critically revised the manuscript. All authors approved the final version of the manuscript.

**Disclosure**

Carsten Bantel has served as a speaker, consultant and advisory board member for Mundipharma International Limited and Napp Pharmaceuticals Limited, and has received research funding from the Higher Education Funding Council for England (HEFC-E). Shiva S Tripathi was a board member to design the Targinact Treatment Evaluator (TTE) database, and has served as a speaker for Napp Pharmaceuticals Limited. Vivek Mehta has served as a speaker for Grünenthal Ltd. Sara Dickerson is an employee of Mundipharma International Limited. David Molony, Tony Heffernan and Susmita Oommen report no conflicts of interest in this work.

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## Supplementary material

| Item No | Recommendation |
|--------|----------------|
| **Title and abstract** | (a) Indicate the study's design with a commonly used term in the title or the abstract  
(b) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | Explain the scientific background and rationale for the investigation being reported |
| **Objectives** | State specific objectives, including any prespecified hypotheses |
| **Methods** | Present key elements of study design early in the paper |
| **Setting** | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| **Participants** | (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  
Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants  
(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed  
Case-control study—For matched studies, give matching criteria and the number of controls per case |
| **Variables** | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| **Data sources/measurement** | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| **Bias** | Describe any efforts to address potential sources of bias |
| **Study size** | Explain how the study size was arrived at |
| **Quantitative variables** | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| **Statistical methods** | (a) Describe all statistical methods, including those used to control for confounding  
(b) Describe any methods used to examine subgroups and interactions  
(c) Explain how missing data were addressed  
(d) Cohort study—if applicable, explain how loss to follow-up was addressed  
Case-control study—if applicable, explain how matching of cases and controls was addressed  
Cross-sectional study—if applicable, describe analytical methods taking account of sampling strategy  
(e) Describe any sensitivity analyses |
| **Results** | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
(b) Give reasons for non-participation at each stage  
(c) Consider use of a flow diagram |
| **Descriptive data** | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  
(b) Indicate number of participants with missing data for each variable of interest  
(c) Cohort study—Summarise follow-up time (eg, average and total amount) |
| **Outcome data** | Cohort study—Report numbers of outcome events or summary measures over time  
Case-control study—Report numbers in each exposure category, or summary measures of exposure  
Cross-sectional study—Report numbers of outcome events or summary measures |

*Continued*
Table S1 (Continued)

| Item No | Recommendation |
|---------|----------------|
| 16      | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| 17      | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |

Discussion

Key results 18

Summarise key results with reference to study objectives

Limitations 19

Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

Interpretation 20

Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

Generalisability 21

Discuss the generalisability (external validity) of the study results

Other information

Funding 22

Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Notes: Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies. An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org and Strengthening the reporting of observational studies in epidemiology (STROBE) statement. Guidelines for reporting observational studies, von Elm E, Altman DG, Egger M et al, volume 335, pages 806-808, copyright 2007 with permission from BMJ Publishing Group Ltd.

Reference

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