Additional File 1: Supplementary Materials

Table S1. MOOSE Checklist for Meta-analyses of Observational Studies.

Table S2. International brand names for opioids collated using the UpToDate database.

Table S3. MEDLINE search strategy and results.

Table S4. Quality assessment of included studies, using the National Institute of Health, National Heart, Lung & Blood Institute Quality Assessment Tool for Observational Cohort & Cross-Sectional Studies with additional data.

Figure S1. Forest plot of the sensitivity analysis conducted for benzodiazepine co-prescriptions.

Figure S2. Forest plot of the sensitivity analysis conducted for gender.

Figure S3. Forest plots of factors not associated with the prescribing of high-dose opioids in primary care.

Table S5. Factors not associated with the prescribing of high-dose opioids reported by individual studies.

Table S6. All factors reported by included studies.
Table S1. MOOSE Checklist for Meta-analyses of Observational Studies.

| Item No | Recommendation                                      | Line numbers | Text                                                                                                                                 |
|---------|-----------------------------------------------------|--------------|-------------------------------------------------------------------------------------------------------------------------------------|
|         | Reporting of background should include              |              |                                                                                                                                       |
| 1       | Problem definition                                  | 105-107      | “understanding who is taking high doses and what may be driving high-dose prescribing would help reduce such uncertainties. However, evidence has not been synthesized to understand this uncertainty.” |
| 2       | Hypothesis statement                                | -            | -                                                                                                                                 |
| 3       | Description of study outcome(s)                     | 108          | “factors”                                                                                                                           |
| 4       | Type of exposure or intervention used               | 108          | “high-dose opioids”                                                                                                              |
| 5       | Type of study designs used                          | 108          | “observational evidence”                                                                                                          |
| 6       | Study population                                     | 109          | “primary care”                                                                                                                     |
|         | Reporting of search strategy should include         |              |                                                                                                                                       |
| 7       | Qualifications of searchers (eg, librarians and investigators) | Table S2 | “We developed the search strategy in consultation with an information specialist.”                                                 |
| 8       | Search strategy, including time period included in the synthesis and key words | 146 Table S2 | “The search terms and search strategy are available in S2 Table and S3 Table.” “Search terms included "opioid\*", "prescri\*", "factor\*", "primary healthcare" and variations of these, including specific drug and brand names of opioids (see Table S2). The search strategy was initially developed for Medline as presented in S3 Table, then adapted for Embase and Web of Science databases.” |
| 9       | Effort to include all available studies, including contact with authors | 128 153-154 | “We included all languages.” “we contacted authors of studies by electronic mail”                                                   |
| 10      | Databases and registries searched                   | 142          | “Medline (Ovid), Embase (Ovid), and Web of Science Core Collection”                                                               |
| 11      | Search software used, name and version, including special features used | 150 194-195 | “Endnote X8” “Stata software version 16.0”                                                                                         |
| 12      | Use of hand searching                               | 143-144      | “We hand searched forward citations and reference lists of eligible studies”                                                      |
| 13      | List of citations located and those excluded, including justification | 119-139 Figure 1 | “We included …” “We excluded studies if…”                                                                                         |
| 14      | Method of addressing articles published in languages other than English | 128          | “We included all languages.”                                                                                                        |
| 15      | Method of handling abstracts and unpublished studies | 144-147      | “Conference proceedings were also used to identify potentially eligible studies but were not included unless a complete manuscript was published.” |
| 16      | Description of any contact with authors             | 153-154      | “we contacted authors of studies by electronic mail for clarification of inclusion status.”                                       |
### Reporting of methods should include

|   | Description                                                                 | Lines | Notes                                                                 |
|---|-----------------------------------------------------------------------------|-------|----------------------------------------------------------------------|
| 17 | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 119-139 | “We included …” “We excluded studies if…” |
| 18 | Rationale for the selection and coding of data                               | 158-165 | “extracted data using a predeveloped data extraction spreadsheet…” |
| 19 | Documentation of how data were classified and coded                          | Not applicable | Not applicable |
| 20 | Assessment of confounding appropriate                                        | 175   | “adjustment for confounding” |
| 21 | Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results | 168-180 | “Quality and risk of bias assessment…” |
| 22 | Assessment of heterogeneity                                                  | 191-193 | “When considerable heterogeneity, defined as $I^2 \geq 75\%$…” |
| 23 | Description of statistical methods in sufficient detail to be replicated     | 182-195 | “Data synthesis and analysis…” |
| 24 | Provision of appropriate tables and graphics                                  | Table 1-2, Figures 1-2 | |

### Reporting of results should include

|   | Description                                                                 | Lines | Notes                                                                 |
|---|-----------------------------------------------------------------------------|-------|----------------------------------------------------------------------|
| 25 | Graphic summarizing individual study estimates and overall estimate          | Figure 2, Figures S1-S3 | - |
| 26 | Table giving descriptive information for each study included                 | Table 1 | - |
| 27 | Results of sensitivity testing (eg, subgroup analysis)                       | Figure S1 & S2 | - |
| 28 | Indication of statistical uncertainty of findings                            | 219-224 | Quality and risk of bias & the reporting of CIs |

### Reporting of discussion should include

|   | Description                                                                 | Lines | Notes                                                                 |
|---|-----------------------------------------------------------------------------|-------|----------------------------------------------------------------------|
| 29 | Quantitative assessment of bias (e.g. publication bias)                      | 363-406 | “…inherent limitations and complexities of using observational evidence impacts the quality and availability of data.” “…two large studies did not report data on the co-morbidities or the indication for high doses…” |
| 30 | Justification for exclusions                                                | 380-381 | “few studies were included in our review because most observational studies on the prescribing of high-dose opioids use population-level prescribing data” |
| 31 | Assessment of quality of included studies                                   | -     | In results, lines 219-224 |

### Reporting of conclusions should include

|   | Description                                                                 | Lines | Notes                                                                 |
|---|-----------------------------------------------------------------------------|-------|----------------------------------------------------------------------|
| 32 | Consideration of alternative explanations for observed results              | -     | - |
| 33 | Generalization of the conclusions                                           | 420   | “high-income primary care settings” |
| 34 | Guidelines for future research                                              | 424-426 | “Standardizing the reporting of all outcomes and promoting the sharing of data from observational studies” |
| 35 | Disclosure of funding source                                                | 532-537 | “Funding: …” |
Search strategy

We developed the search strategy in consultation with an information specialist. Search terms included “opioid*”, “prescri*”, “factor*”, “primary healthcare” and variations of these, including specific drug and brand names of opioids (see Table S2). The search strategy was initially developed for Medline as presented in Table S3, then adapted for Embase and Web of Science databases. The first search was run on 12 February 2018. We updated this search in all three databases on 5 April 2019.

Table S2. International brand names for opioids collated using the UpToDate database

| Drug name | Brand names | Countries | # of countries | Included or excluded |
|-----------|-------------|-----------|----------------|---------------------|
| Codeine   | N/A         | N/A       | N/A            | Included            |
| Morphine  | MS Contin   | AU, BE, CN, IT, LU, NL, VE, KR | 8 | Included |
| MST Contin | AE, AR, BF, BG, BH, BJ, CI, CY, CZ, EE, EG, ES, ET, GB, GH, GM, GN, HK, HR, ID, IE, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MT, MU, MW, MY, NE, NG, OM, PH, PK, PL, QA, RO, SA, SC, SD, SG, SK, SL, SN, SY, TH, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW | 61 | Included |
| Oramorph | BE, ES, FR, GB, IE, LU, PT, SE | 8 | Included |
| Sevredol | AU, CH, CZ, HR, IE, NZ, RO, SI, SK, TR | 10 | Included |
| Hydro- morphone | Himop | CR, DO, GT, HN, NI, PA, SV | 7 | Included |
| Jurnista | AT, AU, CR, CZ, DE, DK, DO, EE, ES, GT, HN, HU, ID, IT, MX, NI, NZ, PA, PH, PT, SA, SG, SI, SV, ZW | 25 | Included |
| Palladon* | CH, DK, FI, IS, NL, NO, SE, SI, SE, BE, CZ, EE, ES, GB, GR, HN, IE, IL, LU, PT | 20 | Included |
|                                | Liberaxim | CR, DO, GT, HN, MX, NI, PA, SV | 8     | Excluded |
|--------------------------------|-----------|--------------------------------|-------|----------|
| Nicomorphine                   | N/A       | N/A                            | N/A   | Included |
| Oxycodone                      | Oxycontin | AR, AT, BR, CH, CL, CN, CO, CR, CY, CZ, DK, DO, EC, EE, ES, FI, GB, GT, HK, HN, IE, IL, IT, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, SE, SG, SV, VE, HR, HU, IS, LU, RO, SI, SK, TR, VN | 45    | Included |
| Oxynorm                        | AT, AU, BE, CH, CY, DK, ES, FI, FR, GB, HK, IE, IS, MY, NO, NZ, PH, SE, SG, TR, JP, SG | 22    | Included |
| Dihydrocodeine                 | N/A       | N/A                            | N/A   | Included |
| Papaveretum                    | N/A       | N/A                            | N/A   | Included |
| Ketobemidone                   | N/A       | N/A                            | N/A   | Included |
| Pethidine                      | Meperidine| N/A                            | N/A   | Included |
| Dolosal                        | BR, CR, DO, GT, HN, NI, PA, SV | 8     | Included |
| Fentanyl                       | Abstral   | BM, ES, GB, HR, IE, PH, QA, TR | 8     | Included |
| Actiq                          | AU, CH, DE, DK, ES, FI, FR, GB, IE, IL, KR, PT, SE | 13    | Included |
| Durogesic                      | AE, AU, BH, CN, CO, CY, EG, ES, ID, IN, JO, KW, LB, LK, MX, NZ, PH, PK, PY, QA, SA, SG, TH, VN | 24    | Included |
| Instanyl                       | AT, BE, CZ, DE, DK, EE, ES, FR, HR, IS, LT, LU, MT, NL, PL, SE, SI, SK | 18    | Included |
| Ionsys                         | AT, BE, BG, CH, CZ, DE, DK, EE, FI, FR, GB, GR, HN, IE, IT, MT, NL, NO, PT, RU, SE, SK, TR | 23    | Included |
| Substance               | AR, AU, GB, IE, NZ, PH, ZA | 7 | Included |
|-------------------------|-----------------------------|---|----------|
| **Dextromoramide**      | N/A                         | N/A | Included |
| **Piritramide**         | N/A                         | N/A | Included |
| **Dextropropoxyphene**  | N/A                         | N/A | Included |
| **Bezitramide**         | N/A                         | N/A | Included |
| **Pentazocine**         | Fortral                      | AT, AU, BG, DE, DK, GB, HR, IE, NZ, PL | 10 | Included |
|                         | Fortwin                      | BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZM, ZW | 29 | Included |
|                         | Sosegon                      | AE, BF, BH, BJ, CI, CY, EC, EG, ET, GH, GM, GN, IL, IQ, IR, JO, JP, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PK, PT, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZM, ZW | 42 | Included |
| **Phenazocine**         | N/A                         | N/A | Included |
| **Buprenorphine**       | Norspan patch                | AU, DE, DK, EE, FI, HK, KR, NO, NZ, PH | 10 | Included |
|                         | Subutex                      | AE, AT, AU, BE, BG, CH, CZ, DE, DK, FR, GR, HR, ID, IE, IL, IS, LU, LV, MT, NO, PT, QA, SE, TW | 23 | Included |
|                         | Temgesic                     | AE, AT, BE, BF, BH, BJ, BR, CH, CI, CY, DE, DK, EE, EG, ET, FI, FR, GB, GH, GM, GN, GR, HK, IQ, IR, IT, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, NZ, OM, PK, QA, RU, SA, SC, SD, SE, SG, SK, SL, SN, SY, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW | 66 | Included |
| Drug       | Country Code | Included/Excluded |
|------------|--------------|-------------------|
| Transtec   | BE, CH, CL, CO, DE, DK, EC, ES, GB, HN, HR, HU, IE, IT, MX, NL, NO, PE, PL, PT, SK | 21 Included |
| Butorphanol| N/A          | N/A               | N/A Included |
| Nalbuphine | Bufigen      | CR, DO, GT, HN, MX, NI, PA, SV | 8 Excluded |
| Nalbuphine | Nalcopyne    | CR, DO, GT, HN, MX, NI, PA, SV | 8 Excluded |
| Nubain     | AE, AT, BF, BH, BJ, BR, CI, CY, CZ, DE, EE, EG, ET, GB, GH, GM, GN, GR, HU, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PH, PK, PL, QA, SA, SC, SD, SI, SL, SN, SY, TN, TZ, UG, VE, YE, ZA, ZM, ZW | 57 Included |
| Methadone  | Amidone      | CR, DO, GT, HN, NI, PA, SV | 7 Included |
| Methadone  | Rubidexol    | CR, DO, GT, HN, MX, NI, PA, SV | 8 Excluded |
| Tramadol   | Adamon       | AR, CR, DO, GT, HN, NI, PA, PY, SV | 9 Included |
| Tramadol   | Bongesic     | CR, DO, GT, HN, NI, PA, SV | 7 Excluded |
| Tramadol   | Mabron       | AE, BH, CY, EG, ET, IQ, IR, JO, KW, LB, LV, LY, MY, OM, QA, SA, SG, SY, YE | 20 Excluded |
| Tramadol   | Trabilin     | BB, BM, BS, BZ, CR, DO, GT, GY, HN, JM, NI, PA, SR, SV, TT | 15 Excluded |
| Tramadol   | Tradolan     | AE, BH, CY, EG, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SE, SY, YE | 16 Excluded |
| Drug       | Country Codes | Included |
|------------|---------------|----------|
| Tramal     | AE, AT, AU, BF, BH, BJ, CH, CI, CN, CO, CR, CU, CY, CZ, DE, DO, EC, EE, EG, ET, FI, GH, GM, GN, GR, GT, HN, HR, IO, IR, JO, JP, KE, KW, LB, LR, LU, LY, MA, ML, MR, MT, MU, MW, NE, NG, NI, NL, NZ, OM, PA, PE, PH, PK, PL, PT, QA, RU, SA, SC, SD, SK, SL, SN, SV, SY, TH, TN, TW, TZ, UG, VE, YE, ZA, ZM, ZW | 72       |
| Tramazac   | BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TH, TN, TZ, UG, ZM, ZW | 27       |
| Tilidine   | N/A           | N/A      | N/A  |
| Dezocine   | N/A           | N/A      | N/A  |
| Meptazinol | N/A           | N/A      | N/A  |
| Tapentadol | Palexia*      | AT, BG, CH, CR, CZ, DK, DO, EE, ES, FI, FR, GB, GT, HN, HR, IE, IL, LT, LU, LV, MT, NI, NL, NO, PA, PL, PT, SI, SK, SV, TR, AT, BG, CR, DE, DO, EE, ES, GT, HN, HR, LT, LV, MT, NI, NL, PA, PL, PT, RO, SK, SV | 52       |
**Table S3. MEDLINE strategy and results.**

| Search # | Search terms | # of results |
|----------|--------------|--------------|
| 1        | exp Analgesics, Opioid/ | 109489 |
| 2        | exp Narcotics/ | 117473 |
| 3        | 1 or 2 | 117473 |
| 4        | opioid*.ti,ab. | 79690 |
| 5        | narcotic*.ti,ab. | 14579 |
| 6        | "opioid analgesic**".ti,ab. | 4475 |
| 7        | opiate*.ti,ab. | 24064 |
| 8        | opium.ti,ab. | 2439 |
| 9        | 4 or 5 or 6 or 7 or 8 | 112098 |
| 10       | codeine*.ti,ab. | 4774 |
| 11       | morphine*.ti,ab. | 48019 |
| 12       | ("MS Contin" or "MST Continus" or Oramorph or Sevredol).ti,ab. | 118 |
| 13       | Papaveretum.ti,ab. | 138 |
| 14       | Ketobemidone.ti,ab. | 134 |
| 15       | Dextromoramide.ti,ab. | 177 |
| 16       | Hydromorphone.ti,ab. | 1466 |
| 17       | (Himop or Jurnista or Palladon*).ti,ab. | 14 |
| 18       | Piritramide.ti,ab. | 353 |
| 19       | Dextropropoxyphene*.ti,ab. | 530 |
| 20       | Oxycodone.ti,ab. | 2989 |
| 21       | (Oxycontin or Oxynorm).ti,ab. | 240 |
| 22       | Dihydrocodeine.ti,ab. | 433 |
| 23       | (Meperidine or Pethidine*).ti,ab. | 4850 |
| 24       | Nicomorphine.ti,ab. | 43 |
| 25       | Dolosal.ti,ab. | 20 |
| 26       | Fentanyl.ti,ab. | 17437 |
|    | Drug Name                        |   |
|----|----------------------------------|---|
| 27 | Abstral.ti,ab.                   | 7 |
| 28 | Actiq.ti,ab.                     | 26|
| 29 | Durogesic.ti,ab.                 | 44|
| 30 | (Instanyl or Ionsys or Sublimaze).ti,ab. | 43|
| 31 | Methadone.ti,ab.                 | 12800|
| 32 | Amidone.ti,ab.                   | 44|
| 33 | Pentazocine.ti,ab.               | 2333|
| 34 | (Fortral or Fortwin or Sosegon).ti,ab. | 52|
| 35 | Bezitramide.ti,ab.               | 20|
| 36 | Phenazocine.ti,ab.               | 70|
| 37 | Buprenorphine.ti,ab.             | 6016|
| 38 | Norspan*.ti,ab.                  | 4 |
| 39 | Subutex.ti,ab.                   | 94|
| 40 | (Temgesic or Transtec).ti,ab.    | 70|
| 41 | Butorphanol.ti,ab.               | 1434|
| 42 | Nalbuphine.ti,ab.                | 885|
| 43 | Nubain.ti,ab.                    | 44|
| 44 | Tramadol.ti,ab.                  | 4608|
| 45 | Adamon.ti,ab.                    | 9 |
| 46 | (Tramal or Tramazac).ti,ab.      | 98|
| 47 | Tilidine.ti,ab.                  | 133|
| 48 | Tapentadol.ti,ab.                | 418|
| 49 | Palexia*.ti,ab.                  | 10|
| 50 | Dezocine.ti,ab.                  | 142|
| 51 | meptazinol.ti,ab.                | 219|
| 52 | 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 | 92514|
| 53 | 3 or 9 or 52                      | 196757|
|   | exp INAPPROPRIATE PRESCRIBING/ or exp Drug Prescriptions/ or exp Drug Utilization/ or exp Practice Patterns, Physicians'/ | 98731 |
|---|-------------------------------------------------------------------------------------------------|-------|
| 55 | exp Potentially Inappropriate Medication List/ | 279 |
| 56 | exp Prescription Drugs/ | 5235 |
| 57 | exp Prescription Drug Misuse/ | 11706 |
| 58 | exp Medical Overuse/ or exp Deprescriptions/ or exp Prescriptions/ | 39044 |
| 59 | exp Prescription Drug Overuse/ or exp Drug Misuse/ or exp Self Medication/ | 16227 |
| 60 | exp Behind-the-Counter Drugs/ or exp Nonprescription Drugs/ | 5885 |
| 61 | prescri*.ti,ab. | 195505 |
| 62 | Utiliz*.ti,ab. | 514119 |
| 63 | utilis*.ti,ab. | 44114 |
| 64 | dispens*.ti,ab. | 35225 |
| 65 | 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 | 852797 |
| 66 | 53 and 65 | 19678 |
| 67 | exp Primary Health Care/ | 145132 |
| 68 | exp Ambulatory Care Facilities/ | 52697 |
| 69 | exp Physicians, Primary Care/ | 2888 |
| 70 | exp Outpatient Clinics, Hospital/ | 16767 |
| 71 | exp Ambulatory Care/ | 51044 |
| 72 | exp Emergency Service, Hospital/ or exp Family Practice/ or exp General Practice/ | 142600 |
| 73 | exp General Practice, Dental/ | 4727 |
| 74 | exp Office Visits/ | 6681 |
| 75 | exp Physicians, Family/ or exp General Practitioners/ | 22706 |
| 76 | exp Emergency Medical Services/ | 128929 |
| 77 | exp Pharmacies/ or exp Community Pharmacy Services/ | 11288 |
| 78 | exp Community Health Services/ or exp Community Medicine/ or exp Community Health Nursing/ or exp Community Health Centers/ | 299456 |
|   | Description                                                                 | Count  |
|---|-----------------------------------------------------------------------------|--------|
| 79| exp Community Dentistry/                                                    | 1213   |
| 80| exp Home Nursing/ or exp Residential Facilities/                            | 58938  |
| 81| (ambulatory adj5 (department? or dept* or ward? or room? or unit? or service? or care or setting? or facilit*)).ti,ab. | 17870  |
| 82| ((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.        | 112376 |
| 83| ((primary* adj3 (care or health*)) or community or communities or population).ti,ab. | 1775651|
| 84| (clinic? or office or visit? or "health centre" or "health center" or "medical centre" or "medical center").ti,ab. | 560228 |
| 85| ("out of hours" or ooh or "after hours").ti,ab.                            | 4235   |
| 86| (emergency adj5 (department? or dept* or ward? or room? or unit? or service? or care or setting? or facilit*)).ti,ab. | 127109 |
| 87| exp Housing for the Elderly/ or exp Assisted Living Facilities/ or exp Home Care Services/ or exp Homes for the Aged/ | 60450  |
| 88| exp INSTITUTIONALIZATION/ or exp Long-Term Care/                           | 32735  |
| 89| ((nursing or residential or longterm or long-term or institutional) adj2 home).ti,ab. | 23609  |
| 90| (((residential or longterm or long-term) adj2 care) or facilit*).ti,ab.     | 624294 |
| 91| exp Home Care Services/                                                     | 45434  |
| 92| ((home or domiciliary) adj (visit* or call*)).ti,ab.                        | 8212   |
| 93| ((refill or repeat) adj prescri*).ti,ab.                                    | 461    |
| 94| 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 | 3285822|
| 95| 66 and 94                                                                   | 7761   |
| 96| predict*.ti,ab.                                                             | 1419106|
| 97| characteristic*.ti,ab.                                                     | 1259013|
| 98| varian*.ti,ab.                                                              | 480043 |
| 99| variat*.ti,ab.                                                              | 649635 |
|100| factor*.ti,ab.                                                              | 3073031|
|101| 96 or 97 or 99 or 100                                                       | 5779446|
|102| 95 and 101                                                                  | 2612   |
Table S4. Quality assessment of included studies, using the National Institute of Health, National Heart, Lung & Blood Institute Quality Assessment Tool for Observational Cohort & Cross-Sectional Studies with additional data to assess risk of bias.

| Study ID     | 1 | 2 | 3 | 4 | 5a | 5b | 5c | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | Quality rating | Ethical approval | Enrolment incentives | Study sponsor | Pharmaceutical sponsorship | COI declared | Pharmaceutical COI |
|--------------|---|---|---|---|----|----|----|---|---|---|---|----|----|----|----|----|------------------|------------------|---------------------|---------------|----------------------|--------------|-------------------|
| Morasco, 2019 | ✔ | ✔ | ✔ | ✔ | ✗ | ✔ | ✔ | ✗ | ✔ | ✗ | ✔ | ✗ | ✔ | ✗ | ✗ | FAIR | NR | NR | ✔ | ✗ | ✔ | ✗ |
| Chang, 2018a  | ✔ | ✔ | NA | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✗ | ✗ | GOOD | NR | NA | NR | ✔ | ✗ | ✔ | ✗ |
| Chang, 2018b  | ✔ | ✔ | NA | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✗ | GOOD | Deemed not required | NA | NR | ✗ | ✔ | ✗ | ✔ |
| Campbell, 2015 | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✗ | ✔ | ✔ | ✔ | ✗ | ✗ | ✗ | FAIR | ✔ | $20 AUD to Pharmacists for referrals | ✔ | ✗ | ✔ | Reckitt Benckiser & Mundipharma |
| Chapman, 2013 | ✔ | ✔ | NA | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | GOOD | ✔ | NA | ✔ | ✗ | ✗ | None to report | ✗ |
| Kobus, 2012   | ✔ | ✔ | NA | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | GOOD | ✔ | NA | ✔ | ✗ | ✗ | None to report | ✗ |

✔: yes; ✗: no; COI: conflict of interest; NA: not applicable; NR: not reported; 5a refers to sample size justification, 5b power description and 5c a measure of variance and effect estimates.
**Figure S1.** Forest plot of the sensitivity analysis conducted for benzodiazepine co-prescriptions

| Study         | High-dose Yes | Low-dose Yes | Weight (%) |
|---------------|---------------|--------------|------------|
|               | 61,623        | 314,364      |            |
|               | 89,191        | 3,581,097    |            |
|               | 1,226         | 8,488        |            |
|               | 1,552         | 180,139      |            |
| Campbell 2015 | 172           | 169          | 17.80      |
|               | 253           | 491          |            |
| Kobus 2012    | 276           | 2,022        | 82.20      |
|               | 177           | 2,793        |            |
| Overall       |               |              | 1.47       |
|               |               |              | [1.37, 1.59]|

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$

Test of $\theta = 0$: $z = 10.36$, $p = 0.00$

Random-effects REML model
**Figure S2.** Forest plot of the sensitivity analysis conducted for gender

### Gender: Male

| Study         | High-dose Male | High-dose Female | Low-dose Male | Low-dose Female | Risk Ratio with 95% CI | Weight (%) |
|---------------|----------------|------------------|---------------|-----------------|-----------------------|------------|
| Morasco 2019 | 14             | 3                | 25            | 9               | 1.12 [ 0.83, 1.51]    | 1.14       |
|               | 72,692         | 78,122           | 1,464,693     | 2,430,768       |                       |            |
| Chang 2018b  | 1,468          | 1,310            | 83,150        | 102,699         | 1.18 [ 1.14, 1.22]    | 80.74      |
| Campbell 2015| 205            | 220              | 260           | 400             | 1.22 [ 1.07, 1.40]    | 5.46       |
| Chapman 2013 | 103            | 159              | 1,422         | 2,351           | 1.04 [ 0.89, 1.22]    | 4.19       |
| Kobus 2012   | 201            | 252              | 1,767         | 3,048           | 1.21 [ 1.08, 1.35]    | 8.48       |
| **Overall**  |                |                  |               |                 | 1.18 [ 1.14, 1.22]    |            |

**Heterogeneity:** $\tau^2 = 0.00$, $I^2 = 0.01\%$, $H^2 = 1.00$

**Test of $\theta = 0$:** $z = 10.11$, $p = 0.00$

Random-effects REML model
Figure S3. Forest plot of factors not associated with the prescribing of high-dose opioids in primary care

### Age

| Study       | High-dose | Low-dose | Weight (%) |
|-------------|-----------|----------|------------|
| Morasco 2019| 17        | 94       | 14.19      |
| Chang 2018a | 150,814   | 3,885,461| 30.14      |
| Campbell 2015| 425      | 660      | 27.63      |
| Kobus 2012  | 453       | 4,815    | 28.04      |

Random-effects REML model

### Caucasian

| Study       | High-dose | Low-dose | Risk Ratio with 95% CI | Weight (%) |
|-------------|-----------|----------|------------------------|------------|
| Morasco 2019| 15        | 24       | 1.25 [ 0.95, 1.65]     | 12.19      |
| Kobus 2012  | 362       | 1,201    | 1.09 [ 0.98, 1.20]     | 87.81      |

Overall

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 19.53\%$, $H^2 = 1.24$

Test of $\theta = 0$: $z = 1.57$, $p = 0.12$

Random-effects REML model

### Anxiety

| Study       | High-dose | Low-dose | Risk Ratio with 95% CI | Weight (%) |
|-------------|-----------|----------|------------------------|------------|
| Campbell 2015| 98        | 327      | 1.11 [ 0.88, 1.40]     | 49.46      |
| Kobus 2012  | 89        | 510      | 1.85 [ 1.51, 2.27]     | 50.54      |

Overall

Heterogeneity: $\tau^2 = 0.12$, $I^2 = 90.71\%$, $H^2 = 10.77$

Test of $\theta = 0$: $z = 1.42$, $p = 0.16$

Random-effects REML model
Table S5. Factors not associated with the prescribing of high-dose opioids reported by individual studies.

| Study ID   | Variable                              | High-dose  | Low-dose  | RR (95% CI) |
|------------|---------------------------------------|------------|-----------|-------------|
|            |                                       | Count (%)  | Count (%) |             |
|            |                                       |            |           |             |
| **Sociodemographic characteristics** |                                       |            |           |             |
| Kobus, 2012| Ethnicity                             |            |           |             |
|            | Black                                 | 7 (2%)     | 134 (3%)  | 0.56 (0.26, 1.18) |
|            | Native American/Alaskan               | 9 (2%)     | 49 (1%)   | 1.95 (0.97, 3.95) |
|            | Asian Pacific Islander                | 4 (1%)     | 40 (1%)   | 1.06 (0.38, 2.96) |
|            | Hispanic                              | 5 (2%)     | 93 (3%)   | 0.57 (0.23, 1.40) |
|            | Other                                 | 7 (2%)     | 99 (2%)   | 0.75 (0.35, 1.61) |
| Morasco, 2019| Employment status                    |            |           |             |
|            | Employed                              | 1 (6%)     | 3 (9%)    | 0.67 (0.07, 5.94) |
|            | Receiving disability                  | 12 (71%)   | 20 (60%)  | 1.20 (0.79, 1.82) |
|            | Other                                 | 1 (6%)     | 4 (12%)   | 0.50 (0.06, 4.13) |
|            | Marriage status                       |            |           |             |
|            | Married                               | 7 (41%)    | 11 (32%)  | 1.27 (0.60, 2.69) |
|            | Separated/divorced                    | 8 (41%)    | 16 (47%)  | 1.00 (0.54, 1.85) |
|            | Single                                | 2 (12%)    | 5 (15%)   | 0.80 (0.17, 3.71) |
|            | Widowed                               | 0 (0%)     | 2 (6%)    | 0.39 (0.02, 7.68) |
| Kobus, 2012| Insurance coverage                    |            |           |             |
|            | Medicaid                              | 1 (0.2%)   | 3 (0.06%) | 3.54 (0.37, 33.99) |
| **Treatment-related characteristics** |                                       |            |           |             |
| Campbell, 2015| Australian Schedule 4 drug           | 146 (34%)  | 197 (30%) | 1.15 (0.97, 1.37) |
|            | Over-the-counter analgesic use        | 259 (61%)  | 424 (64%) | 0.95 (0.86, 1.04) |
|            | Past week oxycodone                   | 251 (59%)  | 400 (61%) | 0.91 (0.82, 1.01) |
|            | Past week buprenorphine               | 36 (8%)    | 209 (32%) | 0.25 (0.18, 0.35) |
|            | Past 3-month doctor shopping          | 6 (1%)     | 5 (1%)    | 1.86 (0.57, 6.07) |
|            | Used other person’s opioid medication past 3-months | 12 (3%) | 12 (2%) | 1.55 (0.70, 3.42) |
| **Substance use** |                                       |            |           |             |
| Campbell, 2015| Lifetime overdose on any substance     | 79 (19%)   | 103 (16%) | 1.19 (0.91, 1.55) |
|            | Past 12 months risky drinking (>5 standard drinks) | 96 (23%) | 165 (25%) | 0.90 (0.73, 1.13) |
| **Physical health and patient behaviours** |                                       |            |           |             |
|            |                                       | Median (IQR) | Median (IQR) | Mean difference |
| clinical factors                                                                 | Type of pain                                      | Count (%) | Count (%) | RR (95% CI)          |
|---------------------------------------------------------------------------------|--------------------------------------------------|-----------|-----------|----------------------|
| Tobacco use                                                                     | Smoking                                          | 256 (57%) | 2,489 (52%) | 1.09 (1.00, 1.19)    |
|                                                                                | BMI ≥ 30                                          | 235 (52%) | 2,388 (50%) | 1.05 (0.95, 1.15)    |
| Kobus, 2012                                                                     | Comorbidity (RxRisk) score                       | 895.9 (653–2,115) | 895.9 (653–1,432) | 0                   |
| Kobus, 2012                                                                     | ED visit with back pain diagnosis                | 131 (29%) | 1,348 (28%) | 1.03 (0.89, 1.20)    |
Table S6. All factors reported by included studies

1. Sociodemographic characteristics

1.1 Age

| Study ID       | Mean age (years) | SD  | Mean age (years) | SD  | Mean difference, years (95% CI) |
|----------------|------------------|-----|------------------|-----|----------------------------------|
| Morasco, 2019  | 54.2             | 9.7 | 53.0             | 10.0| 1.20 (-4.6, 6.9)                |
| Chang, 2018a   | 53.8             | 12.7| 55.4             | 15.8| -1.6 (-1.7, -1.5)               |
| Chang, 2018b   | 47.22            | 10.6| -                | -   | -                                |
| Campbell, 2015 | 55.4             | 13.2| 61.3             | 13.6| -5.9 (-7.5, -4.3)               |
| Kobus, 2012    | 54.7             | 15.0| 54.7             | 15.5| 0 (-1.5, 1.5)                   |

Chapman, 2013 Age was reported for all participants on opioids, split by women and men. Women had a mean age of 67 years (SD: 17, range: 24 to 104 years) and men were 62 years (SD: 16, range: 19 to 97 years).

1.2 Gender (male)

| Study ID       | High-dose       | Low-dose       | RR (95% CI)  |
|----------------|-----------------|----------------|--------------|
|                | Count (%)       | Count (%)      |              |
| Morasco, 2019  | 14 (82%)        | 25 (74%)       | 1.12 (0.83, 1.51) |
| Chang, 2018a   | 72,692 (48%)    | 1,464,693 (38%)| 1.28 (1.28, 1.29) |
| Chang, 2018b   | 1,468 (53%)     | 83,150 (44%)   | 1.18 (1.14, 1.22) |
| Campbell, 2015 | 205 (48%)       | 260 (39%)      | 1.22 (1.07, 1.40) |
| Chapman, 2013  | 103 (39%)       | 1,422 (38%)    | 1.04 (0.89, 1.22) |
| Kobus, 2012    | 201 (44%)       | 1,767 (37%)    | 1.21 (1.08, 1.35) |

1.3 Ethnicity

| Variable       | High-dose       | Low-dose       | RR (95% CI)  |
|----------------|-----------------|----------------|--------------|
|                | Count (%)       | Count (%)      |              |
| Morasco, 2019  | Caucasian       |                | 1.25 (0.95, 1.65) |
| Kobus, 2012    | Caucasian       |                | 1.06 (1.01, 1.12) |
| Kobus, 2012    | Black           | 7 (2%)         | 0.56 (0.26, 1.18) |
|                | Native American/Alaskan | 9 (2%)    | 1.95 (0.97, 3.95) |
|                          | Asian Pacific Islander | Other | Unknown/declined to answer | Hispanic |          |
|--------------------------|------------------------|-------|---------------------------|----------|----------|
|                          | 4 (1%)                 | 7 (2%)| 64 (14%)                  | 5 (2%)   | 1.06 (0.38, 2.96) |
|                          | 40 (1%)                | 99 (2%)| 879 (18%)                 | 93 (3%)  |          |
|                          |                        |       |                           |          |          |
| Employment status        |                        |       |                           |          |          |
| Morasco, 2019            | Unemployed             | 3 (18%)| 7 (21%)                  | 0.86 (0.25, 2.91) |
| Campbell, 2015           | Unemployed             | 245 (58%)| 263 (40%)                | 1.45 (1.28, 1.64) |
| Morasco, 2019            | Employed               | 1 (6%) | 3 (9%)                   | 0.67 (0.07, 5.94) |
|                          | Other                  | 1 (6%) | 4 (12%)                  | 0.50 (0.06, 4.13) |
|                          | Receiving disability   | 12 (71%)| 20 (60%)                 | 1.20 (0.79, 1.82) |
| Education                |                        |       |                           |          |          |
| Morasco, 2019            | Years of education     | 15.2 (2.6) | 13.5 (2.0)              | 1.7      |
| Marriage status          |                        |       |                           |          |          |
| Morasco, 2019            | Married                | 7 (41%)| 11 (32%)                 | 1.27 (0.60, 2.69) |
|                          | Separated/divorced     | 8 (41%)| 16 (47%)                 | 1.00 (0.54, 1.85) |
|                          | Single                 | 2 (12%)| 5 (15%)                  | 0.80 (0.17, 3.71) |
|                          | Widowed                | 0 (0%) | 2 (6%)                   | 0.39 (0.02, 7.68) |
| State of residence       |                        |       |                           |          |          |
| Chang, 2018a             | California             | 47,446 (31%)| 1,416,000 (36%)       | 0.87 (0.86, 0.87) |
|                          | Florida                | 54,338 (36%)| 1,207,982 (31%)     | 1.16 (1.15, 1.17) |
|                          | Georgia                | 20,692 (14%)| 689,886 (18%)        | 0.77 (0.76, 0.78) |
## 1.8 Insurance coverage

| Study ID | Variable                      | Medicare       | Medicaid      | RR (95% CI)       |
|----------|-------------------------------|----------------|--------------|-------------------|
| Kobus, 2012 |                               | 154 (34%)      | 1 (0.2%)     | 1.21 (1.06, 1.39) |
|           |                               | 1,352 (28%)    | 3 (0.06%)    | 3.54 (0.37, 33.99) |

## 2. Treatment-related characteristics

### 2.1 Coprescription

| Study ID       | Variable                              | High-dose Count (%) | Low-dose Count (%) | RR (95% CI)     |
|----------------|---------------------------------------|---------------------|--------------------|-----------------|
| Chang, 2018a   | Benzodiazepines                       | 61,623 (41%)        | 314,364 (8%)       | 5.06 (5.03, 5.10) |
| Chang, 2018b   | Benzodiazepines                       | 1,226 (44%)         | 8,488 (5%)         | 9.36 (9.96, 10.28) |
| Campbell, 2015 | Benzodiazepines                       | 172 (40%)           | 169 (26%)          | 1.58 (1.33, 1.88) |
| Kobus, 2012    | Sedative-hypnotic prescription 6-months before/after index visit | 276 (61%)          | 2,022 (42%)        | 1.45 (1.34, 1.57) |
| Campbell, 2015 | Antidepressants                       | 246 (58%)           | 323 (49%)          | 1.18 (1.06, 1.32) |

### 2.2 Opioid schedule

| Study ID       | Schedule                        | Count (%) | Count (%) | RR (95% CI)     |
|----------------|---------------------------------|-----------|-----------|-----------------|
| Campbell, 2015 | Australian Schedule 4           | 146 (34%) | 197 (30%) | 1.15 (0.97, 1.37) |
|                 | OTC analgesic use               | 259 (61%) | 424 (64%) | 0.95 (0.86, 1.04) |
| Kobus, 2012    | Long-acting                     | 400 (88%) | 1,637 (34%) | 2.60 (2.47, 2.74) |

### 2.3 Type of opioid drug

| Study ID       | Drug                            | Count (%) | Count (%) | RR (95% CI)     |
|----------------|---------------------------------|-----------|-----------|-----------------|
| Campbell, 2015 | Past week oxycodone             | 251 (59%) | 400 (61%) | 0.91 (0.82, 1.01) |
|                 | Past week morphine              | 86 (20%)  | 75 (11%)  | 1.78 (1.34, 2.37) |
|                 | Past week buprenorphine         | 36 (8%)   | 209 (32%) | 0.25 (0.18, 0.35) |

### 2.4 Adverse events and adverse drug reactions

| Study ID       | High-dose Median (IQR) | Low-dose Median (IQR) | Statistical analysis |
|----------------|------------------------|-----------------------|----------------------|
| Campbell, 2015 | Number of adverse      | 91-199: 5             | 21-90: 4 (1-)        | Not possible      |
|                          | Events | Count (%) | RR (95% CI) | Count (%) | RR (95% CI) |
|--------------------------|--------|-----------|-------------|-----------|-------------|
| **Campbell, 2015**      |        |           |             |           |             |
| ICD-10 lifetime pharmaceutical opioid dependence | 49 (12%) | 28 (4%) | 2.72 (1.7, 4.25) | 26 (6%) | 13 (2%) | 3.11 (1.61, 5.98) |
| ICD-10 12-month pharmaceutical opioid dependence | | | | |

### 2.5 Duration of opioid use

|                          | High-dose | Low-dose | Statistical analysis |
|--------------------------|-----------|----------|----------------------|
| **Campbell, 2015**      |           |          |                      |
| Years prescribed opioids | 91-199: 6 | 21-90: 3 | Not possible |
|                         | (2-13)    | (1.1-8)  |                      |
|                         | ≥200: 7.8 | 1-20: 2.5|                      |
|                         | (3-15)    | (0.6-5)  |                      |

### 2.6 Opioid treatment problems and risks

|                          | High-dose | Low-dose | Mean difference |
|--------------------------|-----------|----------|-----------------|
| **Morasco, 2019**       |           |          |                 |
| Risk for prescription opioid misuse from the Pain Medication Questionnaire | 26.6 (6.4) | 25.3 (9.2) | 1.3 |

|                          | Count (%) | Count (%) | RR (95% CI) |
|--------------------------|-----------|-----------|-------------|
| **Campbell, 2015**      |           |           |             |
| Prescribed opioid difficulty scale (PODS) intermediate- high (≥8) | 297 (70%) | 367 (56%) | 1.26 (1.15, 1.38) |

### 2.7 Treatment-related behaviours

|                          | High-dose | Low-dose | RR (95% CI) |
|--------------------------|-----------|----------|-------------|
| **Campbell, 2015**      |           |          |             |
| Past 3-month tampering  | 38 (9%)   | 29 (4%)  | 2.03 (1.27, 3.25) |
| Past 3-month doctor shopping | 6 (1%)  | 5 (1%)  | 1.86 (0.57, 6.07) |
| Past 3-month different drug route | 7 (2%)  | 1 (0.2%) | 10.87 (1.34, 88.04) |
| Used other person’s     | 12 (3%)   | 12 (2%)  | 1.55 (0.70, 3.42) |
### 2.8 Number of opioid drugs

| Study ID     | Variable                          | High-dose (Median IQR) | Low-dose (Median IQR) | Statistical analysis |
|--------------|-----------------------------------|------------------------|-----------------------|----------------------|
| Campbell, 2015 | Number of opioid drugs           | 91-199: 1 (1-1)        | 21-90: 1 (1-1)        | Not possible         |
|              |                                   | 200: 1 (1-2)           |                       |                      |

#### Clinical Characteristics

#### 3. Substance use

##### 3.1 Illicit drug use

| Study ID     | Variable                               | High-dose (Count %) | Low-dose (Count %) | RR (95% CI)          |
|--------------|----------------------------------------|---------------------|--------------------|----------------------|
| Campbell, 2015 | Illicit drug use past 12 months       | 71 (17%)            | 67 (10%)           | 11.03 (5.75, 21.14)  |

##### 3.2 Non-illicit substance use

| Study ID     | Variable                               | Mean (SD) | Mean (SD) | Mean difference |
|--------------|----------------------------------------|-----------|-----------|-----------------|
| Morasco, 2019 | Days of alcohol use in past 30 days   | 0.6 (1.3) | 2.1 (5.1) | -1.5            |

##### 3.3 Substance use problems/disorders

| Study ID     | Variable                               | Count (%) | Count (%) | RR (95% CI)          |
|--------------|----------------------------------------|-----------|-----------|----------------------|
| Chang, 2018b | Opioid disorders                       | 530 (19%) | 1,243 (1%)| 28.95 (26.34, 31.82)|
| Campbell, 2015 | Lifetime overdose on any substance  | 79 (19%)  | 103 (16%) | 1.19 (0.91, 1.55)   |
| Kobus, 2012  | Substance use disorder                 | 141 (31%) | 1,151 (24%)| 1.30 (1.13, 1.51)   |

| Study ID     | Variable                               | Mean (days) | Mean (days) |
|--------------|----------------------------------------|-------------|-------------|
| Chang, 2018b | Magnitude of high-risk use in 2012     | 115.7       | -           |

##### 3.4 Potential substance use problems

| Study ID     | Variable                               | Count (%) | Count (%) | RR (95% CI)          |
|--------------|----------------------------------------|-----------|-----------|----------------------|
| Campbell, 2015 | Past 12 months risky drinking (>5 standard drinks) | 96 (23%)  | 165 (25%) | 0.90 (0.73, 1.13)   |
## 4. Physical health and patient behaviours

### 4.1 Morbidity measures

| Study ID       | Variable                                                                 | High-dose | Low-dose | Mean difference |
|----------------|--------------------------------------------------------------------------|-----------|----------|-----------------|
| Chang, 2018a   | Chronic disease score                                                   | 27.3      | 13.3     | 14              |
| Chang, 2018b   | Aggregated diagnostic cluster morbidity group (ADG) 2012                | 8.4       | -        | -               |
|                | Aggregated diagnostic cluster morbidity group (ADG) 2013                | 8.3       | -        | -               |
|                | Rx-defined morbidity groups (Rx-MGs) 2012                               | 8.9       | -        | -               |
|                | Rx-defined morbidity groups (Rx-MGs) 2013                               | 8.8       | -        | -               |
|                | Count of chronic conditions 2012                                        | 4.0       | -        | -               |
|                | Count of chronic conditions 2013                                        | 4.0       | -        | -               |
|                | Active ingredients 2012                                                 | 13.1      | -        | -               |
|                | Active ingredients 2013                                                 | 12.8      | -        | -               |
|                | Concurrent risk score 2012                                              | 4.7       | -        | -               |
|                | Concurrent                                                              | 4.8       | -        | -               |
| Study ID         | Risk score (RxRisk) score | Median | IQR      | Median | IQR      | Mean difference |
|------------------|----------------------------|--------|----------|--------|----------|-----------------|
| Kobus, 2012     |                            | 895.9  | 653–2,115| 895.9  | 653–1,432 | 0               |

### 4.2 Smoking

| Study ID    | High-dose | Low-dose | RR (95% CI) |
|-------------|-----------|----------|-------------|
| Morasco, 2019 | 30.7% of the sample endorsed smoking cigarettes | Not possible |
| Kobus, 2012 | 256 (57%) | 2,489 (52%) | 1.09 (1.00, 1.19) |

### 4.3 Body Mass Index (BMI)

| Study ID | BMI ≥ 30 | RR (95% CI) |
|----------|----------|-------------|
| Kobus, 2012 | 235 (52%) | 2,388 (50%) | 1.05 (0.95, 1.15) |

### 4.4 Physical health score

| Study ID     | Variable          | High-dose | Low-dose | Statistical analysis |
|--------------|-------------------|-----------|----------|----------------------|
| Campbell, 2015 | SF-12             |           |          |                      |

### 5. Pain measures

#### 5.1 Duration of pain

| Study ID     | Variable                        | High-dose | Low-dose | RR (95% CI) |
|--------------|---------------------------------|-----------|----------|-------------|
| Campbell, 2015 | Years living with pain | 91-199: 11 (5-22) | 21-90: 10 (2-21) | Not possible |
|              |                                 | ≥200: 15 (5-12) | 1-20: 11 (3-23) |             |
|              | 12 month chronic pain conditions | 91-199: 2 (2-3) | 21-90: 2 (1-3) | Not possible |
|              |                                 | ≥200: 2 (2-3) | 1-20: 2 (1-3) |             |

#### 5.2 Pain measures

| Study ID     | Variable       | High-dose | Low-dose | Linear regression model |
|--------------|----------------|-----------|----------|-------------------------|
| Morasco, 2019 | Delay discounting | -5.8 (2.3) | -4.8 (2.0) | DD was significantly associated with |
### Pain severity from the Multi-dimensional Pain Inventory

|           | Mean (SD)       | Mean (SD)       | Mean difference |
|-----------|-----------------|-----------------|-----------------|
| Morasco, 2019 |                 |                 |                 |
| Pain severity | 4.5 (1.0)       | 4.1 (0.9)       | 0.40            |
| Pain interference | 4.7 (1.0)       | 4.6 (1.0)       | 0.10            |

### Pain interference from the Multi-dimensional Pain Inventory

|           | Mean (SD)       | Mean (SD)       | RR (95% CI)     |
|-----------|-----------------|-----------------|-----------------|
| Campbell, 2015 |                 |                 |                 |
| Pain severity | 91-199: 5.4 (1.6) | 21-90: 4.8 (1.8) | 1.21 (1.11, 1.31) |
|              | ≥200: 5.4 (1.8)  | 1-20: 4.4 (1.8)  | 1.21 (1.1, 1.35) |
| Pain interference | 91-199: 6.1 (2.1) | 21-90: 5.3 (2.3) | 1.18 (1.09, 1.26) |
|              | ≥200: 6.2 (2)    | 1-20: 4.7 (2.3)  | 1.23 (1.13, 1.34) |
| Pain self-efficacy (PSEQ) | 91-199: 27.4 (12.7) | 21-90: 31.8 (12.3) | 0.97 (0.96, 0.99) |
|              | ≥200: 24.7 (12.5) | 1-20: 35.8 (13.8) | 0.96 (0.94, 0.97) |

### Type of pain conditions

|                   | High-dose       | Low-dose       | RR (95% CI)     |
|-------------------|-----------------|----------------|-----------------|
|                   | Count, %        | Count, %       |                 |
| Campbell, 2015    |                 |                |                 |
| Arthritis or     | 256 (60%)       | 424 (64%)      | 0.94 (0.85, 1.03)|
| rheumatism        |                 |                |                 |
| Back or neck      | 344 (81%)       | 484 (73%)      | 1.10 (1.03, 1.18)|
| problems          |                 |                |                 |
| Frequent/severe   | 134 (32%)       | 170 (26%)      | 1.22 (1.01, 1.48)|
| headaches         |                 |                |                 |
| Visceral pain     | 96 (23%)        | 141 (21%)      | 1.06 (0.84, 1.33)|

### 6. Healthcare utilisation

#### 6.1 Clinic visits
| Study ID        | Variable                                                                 | High-dose | Low-dose | Median difference |
|-----------------|---------------------------------------------------------------------------|-----------|----------|-------------------|
| Kobus, 2012     | Clinic visits of any type 6 months before/after index date                | 22        | 17       | 5                 |
|                 | **Count (%)** **RR (95% CI)**                                            | **Count (%)** **RR (95% CI)**                  |
| Kobus, 2012     | Any pain clinic visit 6 months before/after index date                    | 104 (23%) | 530 (11%) | 2.09 (1.73, 2.51) |

### 6.2 Secondary & tertiary care use

| Study ID        | Variable                                                                 | High-dose | Low-dose | RR (95%) |
|-----------------|---------------------------------------------------------------------------|-----------|----------|----------|
| Chang, 2018b    | >1 emergency visit in 2012                                               | 829 (30%) | 51,534 (27%) | 1.09 (1.03, 1.16) |
|                 | >1 emergency visit in 2013                                               | 765 (28%) | 34,338 (18%) | 1.51 (1.42, 1.61) |
| Kobus, 2012     | ER visit 6 months before/after index visit                                | 277 (50%) | 1,878 (39%) | 1.57 (1.45, 1.70) |
| Chang, 2018b    | >1 hospitalisation in 2012                                              | 443 (16%) | 17,061 (9%)  | 1.76 (1.62, 1.92) |
|                 | >1 hospitalisation in 2013                                              | 396 (14%) | 11,110 (6%)  | 2.42 (2.21, 2.66) |

| Study ID        | Variable                                                                 | Mean (SD) | Mean (SD) | Mean difference |
|-----------------|---------------------------------------------------------------------------|-----------|-----------|-----------------|
| Kobus, 2012     | Hospitalisation 6 months before/after index date                        | 1.9 (1.3) | 1.5 (1.1) | 0.4             |

| Study ID        | Variable                                                                 | Count (%) | Count (%) | RR (95%) |
|-----------------|---------------------------------------------------------------------------|-----------|-----------|----------|
|                 | ED visit with back pain diagnosis                                         | 131 (29%) | 1,348 (28%) | 1.03 (0.89, 1.20) |
|                 | Filled opioid prescription 5 days after ED visit                         | 285 (63%) | 2,696 (56%) | 1.12 (1.04, 1.21) |
6.3 Multiple prescribers

| Chang, 2018a | Obtain opioids from ≥ 4 unique prescribers & pharmacies over a 90 day period | 1,176 (0.78%) | 1,948 (0.05%) | 15.6 (14.51, 16.76) |
|--------------|--------------------------------------------------------------------------------|----------------|----------------|---------------------|

| Kobus, 2012 | Median opioid prescribers | 4 | 3 | 1 (p=<0.001) |

6.4 Healthcare costs

| Chang, 2018b | $ (USD) | $ (USD) |
|--------------|---------|---------|
| Total concurrent cost (2012) | 30,486 | - |
| Total prospective cost (2013) | 31,045 | - |
| Medical cost 2012 | 19,275 | - |
| Medical cost 2013 | 19,663 | - |
| Pharmacy cost 2012 | 11,211 | - |
| Pharmacy cost 2013 | 11,382 | - |
| Opioid medication cost 2012 | 6,169 | - |
| Opioid medication cost 2012 | 6,079 | - |

7. Mental health

7.1 Depression

| High-dose | Low-dose |
| Study ID       | Variable & measure/metric                      | Count (%) | Count (%) | RR (95%)     |
|---------------|-----------------------------------------------|-----------|-----------|--------------|
| Campbell, 2015| Moderate-severe depression [score of 10 on the PHQ-9] | 221 (52%) | 256 (39%) | 1.34 (1.17, 1.53) |
| Kobus, 2012   | ICD-9 diagnostic codes for depression: 296.2, 296.3, 300.4, 309.0, 309.1, 311 | 190 (42%) | 1,425 (30%) | 1.42 (1.26, 1.59) |

| Mean (SD) | Mean (SD) | Mean difference |
|-----------|-----------|-----------------|
| Morasco, 2019 | Severity of depressive symptoms using the Beck Depression Inventory-2 | 21.5 (12.1) | 20.0 (13.7) | 1.5 |

### 7.2 Anxiety

| Study ID | Variable & measure/metric | High-dose | Low-dose | Mean difference |
|----------|----------------------------|-----------|----------|-----------------|
| Morasco, 2019 | Severity of anxiety symptoms using the Generalized Anxiety Disorder-7 | 9.9 (5.6) | 9.9 (6.0) | 0 |

| Count (%) | Count (%) | RR (95%)     |
|-----------|-----------|--------------|
| Campbell, 2015 | Moderate-severe anxiety | 98 (23%) | 137 (21%) | 1.14 (0.85, 1.53) |
| Kobus, 2012 | ICD-9 diagnostic codes for anxiety: 300.0 – 300.09 | 89 (20%) | 510 (11%) | 2.06 (1.61, 2.65) |

### 7.3 Post-traumatic stress disorder (PTSD)

| Study ID | Variable & measure/metric | High-dose | Low-dose | RR (95%)     |
|----------|----------------------------|-----------|----------|--------------|
| Kobus, 2012 | Posttraumatic stress disorder diagnostic code 309.81 | 20 (4%) | 96 (2%) | 2.21 (1.38, 3.55) |
### 7.4 Any of depression, anxiety, PTSD or substance use

| Study ID   | Description                                          | Count (%) | Count (%) | RR (95% CI) |
|------------|------------------------------------------------------|-----------|-----------|-------------|
| Kobus, 2012| Report of depression, anxiety, PTSD and/or substance use disorder | 280 (62%) | 2,263 (47%) | 1.32 (1.22, 1.42) |

### 8. Patient beliefs

#### 8.1 Relief from current medicines

| Study ID  | Variable                                                                 | Median (IQR) | Median (IQR) | Statistical analysis |
|-----------|--------------------------------------------------------------------------|--------------|--------------|----------------------|
| Campbell, 2015 | 91-199: 6 (5-8)  
≥200: 6 (5-8)                          | 121-199: 7 (5-8)  
≥200: 7 (5-8) | Not possible |

### 9. Prescriber behaviours

#### 9.1 High-risk prescribers

| Study ID | Variable                                         | High-dose | Low-dose | RR (95% CI) |
|----------|--------------------------------------------------|-----------|----------|-------------|
| Chang, 2018a | Proportion of prescriptions from high-risk prescribers | 122,159 (81%) | 973,865 (25%) | 3.24 (3.23, 3.25) |

#### Percentile group

| Study ID   | Count (%) | Count (%) | RR (95% CI) |
|------------|-----------|-----------|-------------|
| Chang, 2018a | 100% (all opioid prescriptions from high-risk prescribers) | 77,217 (51%) | 572,633 (15%) | 3.48 (3.46, 3.50) |
|            | 50-99% of prescriptions from high-risk prescribers | 51,277 (34%) | 471,351 (12%) | 2.81 (2.79, 2.83) |
|            | 1-49% of prescriptions from high-risk prescribers | 8,747 (6%) | 222,041 (6%) | 0.10 (0.10, 0.10) |
|            | 0% (no prescriptions from high-risk prescribers) | 13,573 (9%) | 2,629,436 (68%) | 0.13 (0.13, 0.15) |

#### 9.2 High-volume prescribers

| Study ID | Variable                          | Mean | SD  | Mean | SD  | Mean difference |
|----------|-----------------------------------|------|-----|------|-----|-----------------|
| Chang, 2018a | Daily opioid dose per transaction | 120  | 70.8| 48   | 42.7| 72              |
|            | Days supplied per transaction      | 27   | 6.8 | 25   | 8.3 | 2               |
|            | Opioid volume per person           | 56   | 36.4| 3    | 7.0 | 53              |
|                                | Count (%) | Count (%) | RR (95% CI) |
|--------------------------------|-----------|-----------|-------------|
| **Chang, 2018a**               |           |           |             |
| Proportion of total opioid volume | 50,975 (34%) | 1,488,066 (38%) | 0.88 (0.88, 0.89) |
| Proportion of total opioid prescriptions | 16,590 (11%) | 1,406,261 (36%) | 0.31 (0.30, 0.31) |

### 9.3 Low-volume prescribers

|                                |          |          | Mean difference |
|--------------------------------|----------|----------|-----------------|
|                                |          |          | Mean | SD | Mean | SD |       |
| **Chang, 2018a**               |          |          |      |    |      |    |       |
| Daily opioid dose per transaction | 102 | 70.2 | 35 | 27.9 | 67 |
| Days supplied per transaction | 23 | 10.2 | 15 | 11.2 | 8 |
| Opioid volume per person | 10 | 21.4 | 1 | 3.6 | 9 |
| Opioid prescription per person | 4 | 7.5 | 3 | 4.0 | 1 |

|                                | Count (%) | Count (%) | RR (95% CI) |
|--------------------------------|-----------|-----------|-------------|
| **Chang, 2018a**               |           |           |             |
| Proportion of total opioid volume | 8,747 (6%) | 864,792 (22%) | 0.26 (0.26, 0.27) |
| Proportion of total opioid prescriptions | 3,620 (2%) | 1,967,208 (51%) | 0.05 (0.05, 0.05) |