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Trends in long-term opioid prescriptions for musculoskeletal conditions in Australian general practice: a national longitudinal study using MedicineInsight, 2012-2018

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3 **1 Trends in long-term opioid prescriptions for musculoskeletal conditions in Australian**
4 **2 general practice: a national longitudinal study using MedicineInsight, 2012-2018**

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7 3 Short Title: Trends in long-term opioid prescribing in Australia
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1 ABSTRACT

2 **Objective:** Describe trends and patterns in long-term opioid prescriptions among adults with
3 musculoskeletal conditions (MSK).

4 **Design:** Interrupted time-series analysis based on an open cohort study

5 **Setting:** A representative sample of 402 Australian general practices contributing data to the
6 MedicineInsight database.

7 **Participants:** 811,174 patients aged 18+ years with a diagnosis of MSK and three or more
8 consultations in any two consecutive years between 2012 and 2018. Males represented 44.5%
9 of the sample, 28.4% had 65+ years and 1.9% were Aboriginal or Torres Strait Islanders.

10 **Primary and secondary outcome measures:** Annual prevalence and cumulative incidence
11 (%) of long-term opioid prescribing (3+ prescriptions in 90 days) among patients with a MSK.
12 Average duration of these episodes in each year between 2012 and 2018.

13 **Results:** The prevalence of long-term opioid prescribing increased from 5.5% in 2012 to 9.1%
14 in 2018 [annual change OR=1.09 IC95% 1.08-1.09], but a slightly lower incidence was
15 observed in 2018 [3.0% vs 3.6-3.8% in other years; annual change OR=0.99 IC95% 0.98-0.99].
16 The incidence was between 37%-52% higher among practices located in rural Australia or
17 lower socioeconomic areas. Individual risk factors included increasing age (3.4 times higher
18 among those aged 80+ years than the 18-34-year group in 2012, increasing to 4.8% in 2018),
19 identifying as Aboriginal or Torres Strait Islander (1.7-1.9 higher incidence than their peers),
20 or living in disadvantaged areas (36%-57% more likely than among those living in wealthiest
21 areas). Long-term opioid prescriptions lasted in average 287-301 days between 2012-2016,
22 reducing to 229 days in 2017 and 140 days in 2018. A longer duration was observed in practices
23 from more disadvantaged areas and females in all years, except in 2018.

24 **Conclusions:** The continued rise in the prevalence of long-term opioid prescribing is of
25 concern, despite a recent reduction in the incidence and duration of opioid management.

26 **Keywords:** Narcotic Analgesics, Electronic Health Records, Musculoskeletal Diseases,
27 Chronic Pain, Incidence

1 **ARTICLE SUMMARY**

2 **Strengths and limitations of this study**

- 3 • A national sample including 135,358 instances of long-term opioid prescriptions (3+ opioid
4 prescriptions in 90 days) and 811,174 adult patients with musculoskeletal conditions from
5 Australian general practice over seven years.
- 6 • Patients and practices from all Australian states, with different socioeconomic and
7 demographic profiles, and from urban and rural regions are included in the study.
- 8 • The study explores the incidence and duration of long-term opioid prescriptions over time
9 and their association with sociodemographic characteristics.
- 10 • Individuals attending multiple clinics for prescriptions are not tracked by MedicineInsight,
11 which may underestimate the real frequency. Moreover, the findings reflect prescribing
12 patterns rather than medication use, and the available data does not allow the investigation
13 of the place/professional that initiated these prescriptions.

1 INTRODUCTION

2 Musculoskeletal conditions (MSK) represent a public health problem worldwide due to their
3 increasing prevalence and contribution to the global burden of disability.^{1 2} In Australia, MSK
4 affect approximately 30% of adults (6.1 million individuals), but its prevalence is even higher
5 in lower socioeconomic groups and the elderly.³⁻⁵ In terms of health costs, MSK account for
6 9% of the total Australian health-care expenditure, representing the fourth most expensive
7 group of diseases in the country.⁶

8 MSK are among the ten most frequent problems managed by general practitioners (GPs).⁴ The
9 principal symptom associated with MSK and the main reason for visiting a GP is chronic pain.³⁻
10 ⁵ As a consequence, MSK represent the leading cause of disability due to the impact of chronic
11 pain on the quality of life.^{1 3 5-7}

12 Countries such as Australia, the United States, Canada, Belgium and the United Kingdom
13 recognise MSK and chronic pain management as a public health priority and have developed
14 national policies aiming to improve prevention and management.^{1 8} The strategies and actions
15 include models of care orientated toward high-value care options for MSK pain management,
16 as well as regular monitoring of their prevalence, patterns of medication use/prescription, and
17 side effects related to the use of these medications.^{1 2 8}

18 The management of chronic pain among patients with MSK can be challenging.⁸⁻¹⁴ Current
19 guidelines recommend non-pharmacological interventions as the primary initial approach for
20 managing MSK pain. At the same time, non-steroidal anti-inflammatory drugs (NSAIDs)
21 represent the first-line pharmacological therapy.^{8 12 15} The use of opioids for pain management
22 is discouraged due to the increased risk of severe side effects, especially in elderly patients or
23 among long-term users.⁸⁻¹⁵ Harmful effects associated with opioid use include sedation, falls,
24 respiratory depression, and death, as well as an increased risk of dependence and diversion.
25 Moreover, long-term use of opioids can potentiate chronic pain mechanisms, reducing the
26 effect of these drugs at standard doses.^{8 13 15}

27 Despite their recognised harmful effects, opioid use has increased in the last decades, especially
28 among high-income countries such as the United States, Canada, the United Kingdom,
29 Germany, Norway, Australia and New Zealand.¹⁶⁻²⁰ However, some of these countries have
30 reported an apparent plateau of opioid use among patients with MSK in recent years.^{14 21-26} In
31 Australia, a systematic review showed a significant rise in opioid use up to 2017, mainly driven

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5 1 by oxycodone.²⁷ Nonetheless, most data regarding opioid use in Australia analysed data from
6 2 the Pharmaceutical Benefits Scheme (PBS) database.²⁷ PBS data represent an efficient and
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8 3 cost-effective way to monitor dispensed medicines and trends over time²⁸. However, studies
9
10 4 based on dispensed medications tend to underestimate opioid use²⁹, the investigation of patterns
11
12 5 is usually restricted to age and sex distribution, and the use of aggregated data cannot
13
14 6 distinguish between incident users, prevalent users or long-term users.²⁷ Understanding the
15
16 7 determinants and patterns of long-term opioid prescription/use is fundamental to inform
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18 8 stakeholders and propose targeted interventions aiming to reduce their use for MSK
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20 9 management.^{9-11 18 27} In Australia, only a few studies have examined opioid prescribing and its
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22 10 association with sociodemographic characteristics at the local level but not across states or
23
24 11 including urban and rural areas.^{30 31}

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26 12 In this sense, MedicineInsight is a national longitudinal database established in 2011 by NPS
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28 13 MedicineWise to collect comprehensive, de-identified patient data from GP electronic medical
29
30 14 records (EMR) across Australia.³² Data from MedicineInsight has previously used to assess
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32 15 trends and patterns of preventive activities, medication prescriptions and laboratory requests
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34 16 for acute and chronic conditions managed in Australian general practice.^{5 32-37} This study aims
35
36 17 to utilise MedicineInsight data to estimate the prevalence and cumulative incidence of long-
37
38 18 term opioid prescription among adult patients with MSK. Furthermore, it describes trends in
39
40 19 opioid prescriptions between 2012-2018 and investigates associations with patient and practice
41
42 20 characteristics.

43 22 **METHODS**

44 23 *Study design*

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47 24 This is an interrupted time-series study analysing data from MedicineInsight, a large general
48
49 25 practice database including patients from 662 general practices (8.2% of all general practices
50
51 26 in Australia) and over 2,700 GPs across Australia.³² Although practices participating in
52
53 27 MedicineInsight were recruited using a non-random process, all Australian states and regions
54
55 28 are represented, and the database includes practices vary in size and type of services offered.
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57 29 Patients in the database have been found to be comparable with the general population as
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59 30 measured by sociodemographic variables and clinical conditions.^{5 32} The information extracted
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4 1 from MedicineInsight for the present study include EMR dating between 1 January 2011 and
5 2 31 December 2018.

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8 3 Patients within a practice have a unique identifying number which allows all the EMR held in
9 4 the database for an individual to be linked and tracked over time. Patients' EMR are collected
10 5 monthly, de-identified and securely transferred to NPS MedicineWise's data warehouse.
11 6 Routinely collected information includes: demographics (gender, aboriginality, year of birth,
12 7 patient postcode and area of residence), clinical information (diagnoses, reasons for
13 8 consultation, immunisations), prescribed medications (generic and brand names, doses, active
14 9 ingredient and number of repeats reasons for prescription, known allergies, drug reactions),
15 10 pathology test results, clinical measurements (temperature, blood pressure, weight, height,
16 11 waist circumference), and smoking status.³²

12 *Participants*

13 To improve data quality, only practices established for at least two years before the end of the
14 14 analysis period, with recorded data (i.e., diagnosis, reason for encounter, or reason for
15 15 prescription) in at least 10% of clinical encounters, an average of 30 or more prescriptions per
16 16 week and a consistent number of consultations over time (i.e. ratio between the highest and
17 17 lowest number of annual total consultations lower than five, no gaps of more than six weeks in
18 18 the previous two years in practice data) were included.

19 The sample included all regular patients (i.e. individuals with three or more consultations in
20 20 any two consecutive years) aged 18 years or older (Figure 1). The sample was further restricted
21 21 to patients with at least one recorded visit in the 12 months preceding the initial opioid
22 22 prescription and follow-up time ended six months after the last medical encounter, in order to
23 23 differentiate between past and current patients on opioids.²¹ Therefore, despite data in
24 24 MedicineInsight was available since 2011, the analyses were restricted to the period 2012-
25 25 2018. Patients were also excluded if they had a record of cancer or neuropathic pain up to 12
26 26 months before or six months after the start date of the initial long-term opioid prescription
27 27 episode. Therefore, we used data from 811,174 regular adult patients with MSK attending 402
28 28 general practices across Australia.

29 *[FIGURE 1 HERE]*

30 *Musculoskeletal conditions*

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5 1 Data regarding MSK conditions were extracted from the database using previously published
6
7 2 algorithms.⁵ The diagnosis, reason for encounter and reason for prescription fields were used
8
9 3 to identify patients with a potentially painful MSK condition, as these are typical fields used
10
11 4 by GPs to record morbidity in Australian general practice.³² Most general practices use coding
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13 5 systems (i.e. 'Docle', 'Pyefinch' or the International Classification of Primary Care 2), and
14
15 6 these were mapped to the Systematized Nomenclature of Medicine - Clinical Terms
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17 7 (SNOMED-CT).^{5 32 38} The list of MSK conditions included i) osteoarthritis, ii) osteoarthrosis,
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19 8 iii) spondylarthritis, iv) fibromyalgia, v) polymyalgia rheumatica, vi) rheumatoid arthritis, vii)
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21 9 psoriatic arthritis, viii) myofascial pain, ix) chronic fatigue syndrome, x) gout, xi) Paget
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23 10 disease, xii) osteoporosis, xiii) tenosynovitis, xiv) chronic back pain and xv) other conditions
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25 11 recorded as 'chronic musculoskeletal pain'. Synonyms and misspellings of these terms were
26
27 12 also used, considering that GPs can also use free-text in the completion of the diagnosis. The
28
29 13 data extraction algorithms used in this study are available from the authors by request.

14 *Prescription data*

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16 Data regarding opioid prescriptions (i.e. codeine, tramadol, tapentadol, oxycodone, morphine,
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18 fentanyl, buprenorphine, hydromorphone) were extracted from the prescription dataset using
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20 generic and brand names.³⁹ Using recommendations from the literature,^{21 40} a new 'episode of
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22 opioid prescription' was defined as a prescription provided to the patient where no opioid was
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24 prescribed within six months from the 'end of the last episode'. The 'end date' of an 'episode
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26 of opioid prescription' was considered as being 28 days after the last prescription was provided
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28 (i.e. in Australia, opioids can be prescribed for up to 28 days without repeats).^{8 39} An episode
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30 of 'long-term opioid prescription' was defined as patients receiving i) three or more scripts
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32 (including the initiating script) within 90 days of the initial script or ii) a total of 10 or more
consecutive scripts with an interval lower than 180 between 'episodes of opioid prescription',
even though the first three were not provided within 90 days. An episode of 'long-term opioid
prescription' ended when the patient had not received a prescription for opioids for six or more
months.^{8 39} A total of 135,358 instances of long-term opioid prescriptions were identified over
the period (Figure 1), with 88% of them matching a consultation when the GP recorded a MSK
as the reason for diagnosis, reason for encounter and/or reason for prescription (i.e. excluding
cancer or neuropathic pain) within a period lasting from 30 days before the initial opioid
prescription, or up to 120 days after it.^{8 39}

32 *Data analysis*

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5 1 The prevalence of long-term opioid prescriptions was estimated as the percentage of regular
6 2 patients with MSK attending the practice that year that were on opioids (i.e. long-term opioid
7 3 prescription), either because these prescriptions started in that year or previous years. The
8 4 cumulative incidence of long-term opioid prescription was estimated as the percentage of
9 5 regular patients with MSK in any year between 2012 and 2018 starting opioids that year (i.e.
10 6 patients “at risk” not on opioids). The average annual change in the prevalence or incidence of
11 7 long term opioid prescription was investigated using logistic regression, and the results
12 8 expressed as odds ratios (OR) with their respective 95% confidence intervals (95% CI).

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19 9 The association between sociodemographic characteristics and the incidence of long-term
20 10 opioid prescription was also explored using logistic regression, and the variables were included
21 11 in the models considering two hierarchical levels. The first level included practice
22 12 characteristics: state, rurality (i.e. major cities, inner regional, or outer regional/remote
23 13 Australia) and the practice’s Index of Relative Socioeconomic Advantage and Disadvantage
24 14 [IRSAD, as provided by MedicineInsight (based on the postcode of the practice) and divided
25 15 in quintiles]. IRSAD is a relative indicator of economic and social advantage/disadvantage of
26 16 people and households within an area generated by the Australian Bureau of Statistics and
27 17 based on a range of census variables.⁴¹ Higher IRSAD scores indicate that the practice is
28 18 located in a more advantaged area. The second level included patient characteristics: gender
29 19 (males/females), age in groups (18-34, 35-49, 50-64, 65-79, 80+ years), aboriginality
30 20 (Aboriginal or Torres Strait Islander: No, Yes, not recorded), and the patient’s IRSAD (divided
31 21 in quintiles).

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42 22 Results of the logistic regression models were expressed as marginal predicted probabilities
43 23 (i.e. adjusted cumulative incidence) instead of odds ratio to facilitate interpretation of the
44 24 results, as many medical doctors, researchers and health policymakers are not familiar with
45 25 these measures of association.⁴² Wald tests for heterogeneity or trend were used to estimate the
46 26 p-values due to the use of clustered data (i.e. practice defined as the cluster).

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51 27 Quantile regression models were used to investigate the variables associated with the median
52 28 duration (in days) of the long-term opioid prescription among incident cases, considering the
53 29 same levels of adjustment as above.

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57 30 All analyses were performed using the statistical software STATA 15.0 (StataCorp, Texas,
58 31 USA) and conditioned to the patient’s probability of being in the sample to minimise selection
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1 bias (i.e. the likelihood of receiving medical treatments or diagnosis increase with the number
2 of visits to the practice).⁴³

3 *Ethics approval*

4 The Human Research Ethics Committee of the University of Adelaide exempted this study of
5 an ethical review as only non-identifiable data was used. Access to the data for this study was
6 approved by the MedicineInsight Data Governance Committee (project 2016–004 and 2019-
7 029).

8 *Patient and public involvement*

9 Patients or the public were involved in the design, or conduct, or reporting, or dissemination
10 plans of our research. The provision of information for the study underwent a formal approval
11 process guided by the MedicineInsight independent external Data Governance Committee that
12 includes GPs, consumer advocates, privacy experts and researchers. Moreover, two of the
13 authors are active GPs regularly attending patients affected by MSK, which also supported the
14 design of the study.

15 **RESULTS**

16 The sample consisted of 811,174 unique regular adult patients with MSK attending one of the
17 MedicineInsight practices between 2012 and 2018 (Figure 1). The total number of regular
18 patients with MSK per year is shown in Figure 2. The sample ranged between 160,834 and
19 299,431 over the period.

20 The overall ‘prevalence’ of long-term opioid prescribing (i.e. patients with MSK on opioids,
21 either because they started that year or in previous years) increased from 5.5% in 2012 to 9.1%
22 in 2018 [annual change OR=1.09 IC95% 1.08-1.09; p-value for trend <0.001]. Figure 2 shows
23 the increase was related to a higher proportion of patients starting opioids in previous years,
24 rather than a rise in incident cases (i.e. those who started opioids in that year).

25 *[FIGURE 2 HERE]*

26 Table 1 shows males represented 44.5% of the sample, 28.4% had 65+ years, and 1.9% were
27 Aboriginal or Torres Strait Islanders. Individuals from different socioeconomic settings were
28 all represented in the study, and 40.0% were for regional or remote areas. The cumulative
29 incidence of long-term opioid prescription (i.e. excluding those who were already on opioids)

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5 1 among regular patients with a MSK ranged between 3.6% and 3.8% between 2012-2016,
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7 2 dropping to 3.0% in 2018 [3.0%; annual change OR=0.99 IC95% 0.98-0.99; p-value for trend
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9 3 0.002].

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11 4 The same table also shows the sociodemographic factors associated with the cumulative
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13 5 incidence of long-term opioid prescribing. In any investigated year, the cumulative incidence
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15 6 was 37%-52% higher among individuals attending practices located in rural Australia or areas
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17 7 with a very low IRSAD, compared to those attending practices located in major cities or areas
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19 8 with a higher IRSAD. Individual risk factors associated with a higher incidence of long-term
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21 9 opioid prescribing included increasing age (3.4 times higher among those aged 80+ years than
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23 10 the 18-34-year group in 2012, increasing to 4.8% in 2018), identifying as an Aboriginal or
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25 11 Torres Strait Islander (1.7-1.9 higher incidence than their peers), or living in areas with a lower
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27 12 IRSAD (36%-57% more likely than among those living in wealthiest areas). Neither the state
28
29 13 where the practice was located nor the patient's gender was associated with this outcome.

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31 14 [TABLE 1 HERE]

32
33 15 The average duration of the long-term opioid prescriptions among incident cases ranged from
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35 16 287 to 301 days between 2012-2016, reducing to 229 days in 2017 and 140 days in 2018 (Table
36
37 17 2). The most consistent pattern observed over the investigated years was an increased duration
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39 18 of prescribing among individuals attending practices located in lower socioeconomic areas (i.e.
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41 19 up to 152 days longer than those attending practices located in the wealthiest areas) or females
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43 20 (i.e. up to 77 days longer than in males). However, these differences were not evident in 2018.

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45 21 [TABLE 2 HERE]

46 47 22 **DISCUSSION**

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49 23 To the best of our knowledge, this is the first Australian study that uses EMR from a national
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51 24 general practice database to investigate patterns of long-term opioid prescriptions for patients
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53 25 with MSK.²⁷ Three main findings can be highlighted from the results. Firstly, the overall
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55 26 prevalence of long-term opioid prescriptions increased between 2012 and 2018 as a
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57 27 consequence of the progressive rise of patients starting opioids in previous years rather than
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59 28 for an upsurge of incident cases. Secondly, factors associated with a higher incidence of long-
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30 29 term opioid prescription included increasing age, identifying as Aboriginal or Torres Strait
Islander, living in a lower socioeconomic area, or attending practices located in a rural setting

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5 1 or more disadvantaged areas. Finally, a longer duration of these episodes was observed among
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7 2 females or patients attending practices in lower socioeconomic areas.

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9 3 The increase in the prevalence of long-term opioid prescriptions is consistent with other
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11 4 Australian studies using PBS data (9, 22).^{9 20 27} Some authors suggest the increase in opioid
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13 5 use/prescription is related to the ageing population with higher rates of MSK, availability of
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15 6 slow-release opioid formulations and aggressive marketing of opioids by pharmaceutical
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17 7 companies.^{1 2 21} Moreover, the observed increase in Australia is probably related to the
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19 8 prescription of potent opioids. A previous study using PBS data found that between 2006-2015
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21 9 weaker opioid use remained stable or declined, while there was a 238% increase in persons
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23 10 dispensed only strong opioids.²⁰ Nonetheless, there is evidence that long-term opioid
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25 11 prescription for patients with MSK in the UK and North America reached a plateau around
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27 12 2009-2011.^{21 22 44}

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29 13 Previous studies have also reported the incidence of opioid use has either decreased or
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31 14 remained unchanged in recent years, despite a rise in the prevalence.⁴⁵⁻⁴⁷ In consonance with
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33 15 these studies, we found a steady incidence between 2012-2016, followed by a lower incidence
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35 16 in 2018. Interestingly, the duration of long-term opioid prescription also declined in newly
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37 17 incident cases in 2017 and 2018 compared to the previous five years. Although results for
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39 18 2018 might reflect an insufficient follow-up of incident cases in that year, it would not explain
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41 19 the findings observed in 2017. Recent education strategies among GPs and health policy
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43 20 changes may have helped reduced opioid initiation and duration when prescribing to someone
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45 21 affected by MSK.^{8 13 15 39} However, the increasing prevalence between 2012-2018 with an
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47 22 upsurging number of patients starting opioids in previous years (i.e. 'prevalent' cases) may
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49 23 suggest insufficient pro-active opioid de-prescribing is being undertaken. Factors such as
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51 24 limited time of clinicians, insufficient training on de-prescribing, or restricted access to
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53 25 resources for monitoring patients using opioids are recognised barriers that affect strategies
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55 26 aiming to improve opioid prescription practices in primary care.⁴⁸

56
57 27 Our finding that the elderly, patients living in lower socioeconomic areas, attending practices
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59 28 located in more disadvantaged settings or from rural and remote Australia have higher rates of
60
1 long-term opioid prescription is consistent with British and American studies,^{21 22 49} as well as
2 with results based on PBS data.^{9 30 31} These groups are also more likely to be affected by chronic
3 MSK conditions^{5 21}. Perhaps a maldistribution of support services or access to tertiary based

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5 1 pain clinics could partially explain these differences⁴⁸, but further studies would be necessary
6
7 2 to investigate the underlying causes in the Australian context.

8 9 3 **Strengths and limitations**

10
11 4 The study has significant strengths: a national sample including adult patients of all age groups,
12
13 5 ethnicity, or sex, and practices from all Australian states, socioeconomic areas, or remoteness.
14
15 6 Despite the novelty in the use of a national general practice database that allows the
16
17 7 identification of patients with MSK and the reason for opioid prescription, differentiates
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19 8 between incident and prevalent cases, and provides data on different associated factors, some
20
21 9 limitations have to be recognised. First, our study did not distinguish between the strength of
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23 10 preparations (i.e. presented as either morphine equivalent doses or defined daily dose).
24
25 11 However, previous studies found that up to 40% of the dispensed pain medications for non-
26
27 12 cancer pain are potent opioids, and their use has increased over the years.^{14 17 20} Second,
28
29 13 individuals attending multiple clinics for prescriptions are not tracked by MedicineInsight, and
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31 14 this may underestimate the real frequency of long-term opioid prescriptions. However, the
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33 15 observed trends and associations are consistent with the available literature.^{9 20-22 27 44} Third,
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35 16 the place/professional that initiated the prescriptions (e.g. Emergency Department, hospital,
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37 17 private specialist) cannot be investigated. Nonetheless, according to PBS data, half of the
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39 18 opioids prescribed in Australia are initiated by general practitioners¹⁷ and most patients with
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41 19 chronic pain requiring long-term opioid prescriptions are managed in primary care settings.⁴⁸
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43 20 Finally, medicine-use information from MedicineInsight relates to records of GP prescribing,
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45 21 and not all prescriptions and repeats will be dispensed or taken by the patient. Therefore, results
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47 22 from this study reflect prescription patterns rather than opioid use.

48 49 23 **CONCLUSION**

50
51 24 The overall prevalence of long-term opioid prescribing for MSK conditions has increased in
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53 25 Australia between 2012 and 2018, despite a lower incidence and duration of these prescriptions
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55 26 in the last couple of years. This trend towards an increase in the prevalence of long-term opioid
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57 27 prescribing is of great concern, as current literature reports an overall escalation in the rates of
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59 28 opioid harms and deaths.^{8 9 13 15} Our study highlights the need for ongoing efforts to reduce the
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61 29 opioid burden, especially among those living and attending practices in more disadvantaged
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63 30 areas and considering the higher risk of adverse effect in elderly patients. This should come
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65 31 not only by reducing opioid initiation but also by proactively de-prescribing for suitable
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4 1 patients.^{8 13} While GPs are in an optimal position for this role⁴⁸, opioid stewardship is the
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6 2 responsibility of all prescribing medical practitioners and allied health professionals dealing
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8 3 with MSK pain management.
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Table 1. Cumulative incidence of long-term opioid prescription for the management of musculoskeletal conditions according to practice and patient's characteristics. regular patients^a aged 18+ years. Australia, 2012-2018.

Long-term opioids - incidence (%)								
Year	2012	2013	2014	2015	2016	2017	2018	
regular patients with a MSK 'at risk'^a	157,528	185,358	210,089	231,961	253,648	281,655	190,079	
	3.6	3.6	3.8	3.7	3.8	3.5	3.0	
Overall incidence - % (95%CI)	(3.4;3.8)	(3.4;3.8)	(3.6;4.0)	(3.5;3.9)	(3.6;4.0)	(3.4;3.7)	(2.8;3.1)	
Practice characteristics^c	% ^d							
State								
NSW	36.2	3.6	3.5	3.8	3.7	3.7	3.4	2.8
VIC	21.5	3.7	3.6	3.9	3.9	3.9	3.7	3.1
QLD	14.3	3.3	3.5	3.8	3.6	3.5	3.6	2.7
WA	11.3	3.7	3.8	3.9	3.8	4.3	4.1	3.5
TAS	10.4	3.3	3.3	3.4	3.4	3.4	3.1	2.8
SA	3.0	3.2	3.8	3.2	3.9	3.7	3.8	2.9
ACT	2.7	6.0	4.6	5.1	4.8	4.2	4.5	3.3
NT	0.6	2.6	3.6	3.5	2.5	3.7	2.6	2.6
Rurality								
Major cities	60.0	3.1	3.2	3.4	3.4	3.3	3.2	2.7
Inner regional	26.7	3.8	4.0	4.0	3.9	4.1	3.9	3.2
Outer regional/Remote	13.3	4.9	4.5	5.0	4.8	5.0	4.5	3.7
IRSAD Quintile								
Very high	25.8	2.8	2.9	3.1	2.9	3.1	2.8	2.4
High	16.7	3.4	3.4	3.4	3.4	3.6	3.4	3.0
Middle	22.8	3.8	3.6	3.9	4.0	4.0	3.9	3.1
Low	15.6	3.8	3.7	4.0	4.0	3.8	3.6	3.0
Very Low	19.1	4.0	4.3	4.5	4.4	4.4	4.1	3.3
Patient's characteristics^e								
Gender								
Male	44.5	3.4	3.4	3.6	3.7	3.7	3.4	3.0

Female	55.5	3.7	3.7	3.9	3.8	3.8	3.6	2.9
Age								
18-34 years	18.9	1.9	2.0	1.8	1.7	1.7	1.5	1.3
35-49 years	23.9	2.9	2.9	3.0	2.9	2.8	2.6	2.2
50-64 years	28.8	3.2	3.1	3.2	3.1	3.2	3.0	2.4
65-79 years	21.9	4.4	4.4	4.6	4.5	4.5	4.2	3.6
80+ years	6.5	6.5	6.5	7.0	7.4	7.6	7.3	6.2
Aboriginal/Torres Strait Islander								
No	77.9	3.6	3.6	3.8	3.8	3.8	3.5	3.0
Yes	1.9	6.5	6.0	6.5	7.3	7.0	6.5	5.3
Not recorded	20.2	3.0	3.1	3.1	3.0	3.3	3.3	2.7
IRSAD Quintile								
Very high	23.9	2.8	2.8	2.9	2.8	3.0	2.8	2.5
High	16.9	3.3	3.4	3.8	3.7	3.6	3.4	2.7
Middle	23.0	3.8	3.6	3.8	4.0	3.8	3.8	3.0
Low	17.3	3.7	3.7	4.0	3.8	4.2	3.7	3.2
Very Low	18.7	4.1	4.4	4.3	4.3	4.4	3.9	3.4

^a At least three consultations in any two consecutive years from 2012 to 2018. Numbers (n) represent the number of regular patients with a musculoskeletal condition in that year, excluding those who were already on opioids (i.e. patients “at risk”)

^b Values in parenthesis represent the 95% confidence intervals of the incidence

^c Logistic regression models with all practice characteristics mutually adjusted. Values in ‘bold’ represent those associations with a p-value <0.01

^d Values represent the sample distribution according to these characteristics

^e Logistic regression models with all patient characteristics mutually adjusted + adjustment for practice characteristics. Values in ‘bold’ represent those associations with a p-value <0.01

MSK: Musculoskeletal condition; IRSAD: Index of Relative Socioeconomic Advantage and Disadvantage.

Table 2. Average time on long-term opioid prescription for the management of musculoskeletal conditions among incident cases according to practice and patient's characteristics. regular patients^a aged 18+ years. Australia, 2012-2018.

	Time on long-term opioids among incident cases (days)						
	2012	2013	2014	2015	2016	2017	2018
Incident cases	5,621	6,647	7,944	8,652	9,572	9,958	5,672
	287	301	295	288	294	229	140
Median duration (95%CI)^b	(266;308)	(281;321)	(279;311)	(272;304)	(281;307)	(221;237)	(135;145)
Practice characteristics^c							
State							
NSW	266	299	308	273	292	210	134
VIC	283	309	312	313	268	230	141
QLD	342	243	264	278	297	244	146
WA	294	288	281	333	336	246	141
TAS	339	367	205	367	292	241	138
SA	269	393	255	292	402	214	154
ACT	327	299	431	338	321	267	186
NT	249	683	261	206	237	116	108
Rurality							
Major cities	301	327	288	309	290	221	137
Inner regional	309	313	319	290	316	234	142
Outer regional/Remote	242	243	310	309	284	240	148
IRSAD Quintile							
Very high	203	214	244	203	247	186	128
High	231	300	285	299	263	221	143
Middle	263	319	290	302	320	222	142
Low	393	341	361	341	293	259	145
Very Low	349	346	322	355	333	251	141
Patient's characteristics^d							
Gender							
Male	278	272	272	259	271	211	137
Female	311	349	329	336	323	238	143

Age							
18-34 years	230	361	276	363	247	233	147
35-49 years	335	361	345	327	350	257	154
50-64 years	299	337	320	293	306	221	142
65-79 years	278	257	277	279	242	203	132
80+ years	336	371	326	336	379	249	143
Aboriginal/Torres Strait Islander							
No	302	319	308	303	303	224	139
Yes	442	376	415	405	381	274	158
Not recorded	245	315	278	296	279	232	146
IRSAD Quintile							
Very high	238	287	236	268	277	230	127
High	249	315	258	296	292	218	140
Middle	278	315	306	297	319	233	139
Low	358	333	360	323	303	216	134
Very Low	343	337	343	330	308	232	159

^a At least three consultations in any two consecutive years from 2012 to 2018.

^b Values in parenthesis represent the 95% confidence intervals of the median time on opioids. The corresponding interquartile values are 2012=91-1177; 2013=98-1214; 2014=98-1145; 2015=94-989; 2016=97-759; 2017=91-474; 2018=78-255.

^c Quantile regression models with all practice characteristics mutually adjusted. Values in 'bold' represent those associations with a p-value <0.01

^d Quantile regression models with all patient characteristics mutually adjusted + adjustment for practice characteristics. Values in 'bold' represent those associations with a p-value <0.01

MSK: Musculoskeletal condition; IRSAD: Index of Relative Socioeconomic Advantage and Disadvantage.

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5 **Figure 1. Algorithm of data extraction from MedicineInsight database for the diagnosis**
6 **of MSK and opioid prescriptions. Period 2012-2018**
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10 **Figure 2. Frequency of long-term opioid prescription for the management of**
11 **musculoskeletal conditions. regular patients^a aged 18+ years. Australia, 2012-2018.**
12 Number in parenthesis (n) represent the total number of regular patients with a musculoskeletal
13 condition in that year from a total of 811,174 regular patients investigated over the whole
14 period.
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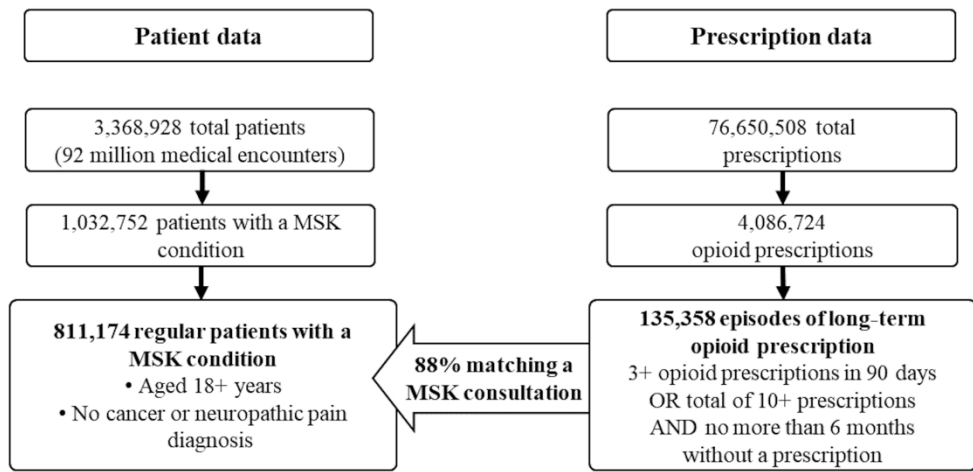


Figure 1. Algorithm of data extraction from MedicineInsight database for the diagnosis of MSK and opioid prescriptions. Period 2012-2018

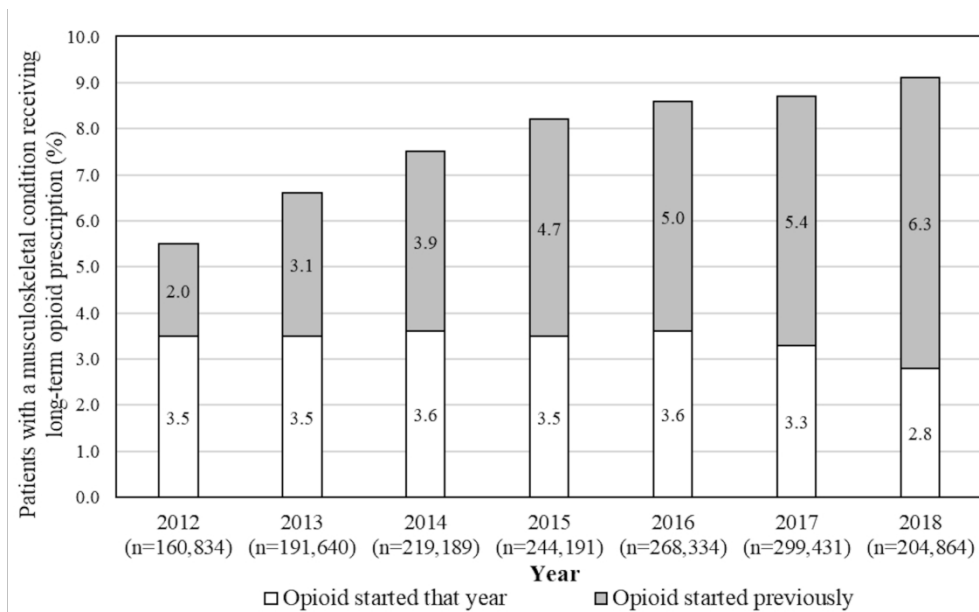


Figure 2. Frequency of long-term opioid prescription for the management of musculoskeletal conditions. regular patients aged 18+ years. Australia, 2012-2018. Number in parenthesis (n) represent the total number of regular patients with a musculoskeletal condition in that year from a total of 811,174 regular patients investigated over the whole period.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(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	1,2 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	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	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(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) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8 - 6-7 - -
Results			
Participants	13*	(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	6,9, Tables 1,2 - Fig. 1
Descriptive data	14*	(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) Summarise follow-up time (eg, average and total amount)	9, Table 1 9, Table 1 9, Table 1

1	Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 10, Fig. 2, Tables 1,2
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1 2 3 4 5 6 7 8 9 10	Main results	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	9-10, tables 1,2 9-10, tables 1,2 9-10, tables 1,2
11 12 13	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
14	Discussion			
15	Key results	18	Summarise key results with reference to study objectives	10
16 17 18	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	12
19 20	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
21 22	Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
23	Other information			
24 25 26 27	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	13

*Give information separately for exposed and unexposed groups.

Note: 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 <http://www.strobe-statement.org>.

BMJ Open

Trends in long-term opioid prescriptions for musculoskeletal conditions in Australian general practice: a national longitudinal study using MedicineInsight, 2012-2018

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics, Epidemiology, General practice / Family practice, Medical management, Public health
Keywords:	Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, PAIN MANAGEMENT, EPIDEMIOLOGY, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, PRIMARY CARE, PUBLIC HEALTH

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4 **1 Trends in long-term opioid prescriptions for musculoskeletal conditions in Australian**
5 **2 general practice: a national longitudinal study using MedicineInsight, 2012-2018**

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9 3 Short Title: Trends in long-term opioid prescribing in Australia

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1 ABSTRACT

2 **Objective:** Describe trends and patterns in long-term opioid prescriptions among adults with
3 musculoskeletal conditions (MSK).

4 **Design:** Interrupted time-series analysis based on an open cohort study

5 **Setting:** A representative sample of 402 Australian general practices contributing data to the
6 MedicineInsight database.

7 **Participants:** 811,174 patients aged 18+ years with a MSK diagnosis and three or more
8 consultations in any two consecutive years between 2012 and 2018. Males represented 44.5%
9 of the sample, 28.4% had 65+ years, and 1.9% were Aboriginal or Torres Strait Islanders.

10 **Primary and secondary outcome measures:** Annual prevalence and cumulative incidence
11 (%) of long-term opioid prescribing (3+ prescriptions in 90 days) among patients with a MSK.
12 Average duration of these episodes in each year between 2012 and 2018.

13 **Results:** The prevalence of long-term opioid prescribing increased from 5.5% (95%CI 5.2-5.8)
14 in 2012 to 9.1% (95%CI 8.8-9.7) in 2018 [annual change OR=1.09 IC95% 1.08-1.09], but a
15 slightly lower incidence was observed in 2018 [3.0% vs 3.6-3.8% in other years; annual change
16 OR=0.99 IC95% 0.98-0.99]. The incidence was between 37%-52% higher among practices
17 located in rural Australia or lower socioeconomic areas. Individual risk factors included
18 increasing age (3.4 times higher among those aged 80+ years than the 18-34-year group in
19 2012, increasing to 4.8% in 2018), identifying as Aboriginal or Torres Strait Islander (1.7-1.9
20 higher incidence than their peers), or living in disadvantaged areas (36%-57% more likely than
21 among those living in wealthiest areas). Long-term opioid prescriptions lasted in average 287-
22 301 days between 2012-2016, reducing to 229 days in 2017 and 140 days in 2018. A longer
23 duration was observed in practices from more disadvantaged areas and females in all years,
24 except in 2018.

25 **Conclusions:** The continued rise in the prevalence of long-term opioid prescribing is of
26 concern, despite a recent reduction in the incidence and duration of opioid management.

27 **Keywords:** Narcotic Analgesics, Electronic Health Records, Musculoskeletal Diseases,
28 Chronic Pain, Incidence

1 ARTICLE SUMMARY

2 Strengths and limitations of this study

- 3 • A national sample including 135,358 instances of long-term opioid prescriptions (3+ opioid
4 prescriptions in 90 days) and 811,174 adult patients with musculoskeletal conditions from
5 Australian general practice over seven years.
- 6 • Patients and practices from all Australian states, with different socioeconomic and
7 demographic profiles, and from urban and rural regions are included in the study.
- 8 • The study explores the incidence and duration of long-term opioid prescriptions over time
9 and their association with sociodemographic characteristics.
- 10 • Individuals attending multiple clinics for prescriptions are not tracked by MedicineInsight,
11 which may underestimate the real frequency. Moreover, the findings reflect prescribing
12 patterns rather than medication use, and the available data does not allow the investigation
13 of the place/professional that initiated these prescriptions.

1 INTRODUCTION

2 Musculoskeletal conditions (MSK) represent a public health problem worldwide due to their
3 substantial impact on the quality of life, increasing prevalence, and contribution to the global
4 burden of disability.^{1 2} In Australia, MSK affect approximately 30% of adults (6.1 million
5 individuals), but its prevalence is even higher in lower socioeconomic groups and the elderly.³⁻⁵
6 In terms of health costs, MSK accounted for \$5,690 million in 2008-09, representing 9% of the
7 total Australian health-care expenditure in that year and the fourth most expensive group of
8 diseases in the country.⁶ MSK are among the ten most frequent problems managed by general
9 practitioners (GPs).⁴ The principal symptom associated with these visits is chronic pain.^{1 3 5-7}

10 Countries such as Australia, the United States, Canada, Belgium and the United Kingdom
11 recognise MSK and chronic pain management as a public health priority and have developed
12 national policies aiming to improve prevention and management.^{1 8} The strategies and actions
13 include models of care orientated toward high-value care options for MSK pain management,
14 as well as regular monitoring of their prevalence, patterns of medication use/prescription, and
15 side effects related to the use of these medications.^{1 2 8} Current guidelines recommend non-
16 pharmacological interventions as the primary initial approach for managing MSK pain.
17 Simultaneously, non-steroidal anti-inflammatory drugs (NSAIDs) represent the first-line
18 pharmacological therapy.⁸⁻¹⁰ The use of opioids for pain management is discouraged due to the
19 increased risk of severe side effects, especially in elderly patients or among long-term users.
20 ⁸⁻¹⁵ Harmful effects associated with opioid use include sedation, falls, respiratory depression,
21 and death, as well as an increased risk of dependence and diversion. Moreover, long-term use
22 of opioids can potentiate chronic pain mechanisms, reducing the effect of these drugs at
23 standard doses.^{8 9 14}

24 Despite their recognised harmful effects, opioid use has increased in the last decades, especially
25 among high-income countries such as the United States, Canada, the United Kingdom,
26 Germany, Norway, Australia and New Zealand.¹⁶⁻²⁰ In the United States, for example, the use
27 of opioids (licit and illicit) escalated 10-14 times in the last two decades, while in Australia
28 there was a 238% increase in the number of people receiving potent opioids between 2006 and
29 2015.^{19 20} However, some countries have reported an apparent plateau of opioid use among
30 patients with MSK in recent years.^{15 21-26} In Australia, a systematic review showed a significant
31 rise in opioid use up to 2017, mainly driven by oxycodone.²⁷ Nonetheless, most data regarding
32 opioid use in Australia analysed data from the Pharmaceutical Benefits Scheme (PBS)

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5 1 database.²⁷ PBS data represent an efficient and cost-effective way to monitor dispensed
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7 2 medicines and trends over time²⁸. However, studies based on dispensed medications tend to
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9 3 underestimate opioid use²⁹, the investigation of patterns is usually restricted to age and sex
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11 4 distribution, and the use of aggregated data cannot distinguish between incident users,
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13 5 prevalent users or long-term users.²⁷ Understanding the determinants and patterns of long-term
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15 6 opioid prescription/use is fundamental to inform stakeholders and propose targeted
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17 7 interventions aiming to reduce their use for MSK management.^{11-13 18 27} In Australia, only a
18
19 8 few studies have examined opioid prescribing and its association with sociodemographic
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21 9 characteristics at the local level but not across states or including urban and rural areas.^{30 31}

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23 10 In this sense, MedicineInsight is a national longitudinal database established in 2011 by NPS
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25 11 MedicineWise to collect comprehensive, de-identified patient data from GP electronic medical
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27 12 records (EMR) across Australia.³² Data from MedicineInsight has been previously used to
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29 13 assess trends and patterns of preventive activities, medication prescriptions and laboratory
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31 14 requests for acute and chronic conditions managed in Australian general practice.^{5 32-37} This
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33 15 study aims to utilise MedicineInsight data to estimate the prevalence and cumulative incidence
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35 16 of long-term opioid prescriptions among adult patients with MSK. Furthermore, it describes
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37 17 trends in opioid prescriptions between 2012-2018 and investigates associations with patient
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39 18 and practice characteristics.

40 **METHODS**

41 *Study design*

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44 22 This is an interrupted time-series study analysing data from MedicineInsight, a large general
45
46 23 practice database including patients from 662 general practices (8.2% of all general practices
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48 24 in Australia) and over 2,700 GPs across Australia.³² Although practices participating in
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50 25 MedicineInsight were recruited using a non-random process, all Australian states and regions
51
52 26 are represented, and the database includes practices vary in size and type of services offered.
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54 27 Patients in the database have been found to be comparable with the general population as
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56 28 measured by sociodemographic variables and clinical conditions.^{5 32} The information extracted
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58 29 from MedicineInsight for the present study include EMR dating between 1 January 2011 and
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60 30 31 December 2018.

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5 1 Patients within a practice have a unique identifying number which allows all the EMR held in
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7 2 the database for an individual to be linked and tracked over time. Patients' EMR are collected
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9 3 monthly, de-identified and securely transferred to NPS MedicineWise's data warehouse.
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11 4 Routinely collected information includes: demographics (gender, aboriginality, year of birth,
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13 5 patient postcode and area of residence), clinical information (diagnoses, reasons for
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15 6 consultation, immunisations), prescribed medications (generic and brand names, doses, active
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17 7 ingredient and number of repeats reasons for prescription, known allergies, drug reactions),
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19 8 pathology test results, clinical measurements (temperature, blood pressure, weight, height,
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21 9 waist circumference), and smoking status.³²

22 *Participants*

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24 11 To improve data quality, only practices established for at least two years before the end of the
25
26 12 analysis period, with recorded data (i.e., diagnosis, reason for encounter, or reason for
27
28 13 prescription) in at least 10% of clinical encounters, an average of 30 or more prescriptions per
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30 14 week and a consistent number of consultations over time (i.e. ratio between the highest and
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32 15 lowest number of annual total consultations lower than five, no gaps of more than six weeks in
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34 16 the previous two years in practice data) were included.

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36 17 The sample included all regular patients (i.e. individuals with three or more consultations in
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38 18 any two consecutive years) aged 18 years or older (Figure 1). The sample was further restricted
39
40 19 to patients with at least one recorded visit in the 12 months preceding the initial opioid
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42 20 prescription and follow-up time ended six months after the last medical encounter, in order to
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44 21 differentiate between past and current patients on opioids.²¹ Therefore, despite data in
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46 22 MedicineInsight was available since 2011, the analyses were restricted to the period 2012-
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48 23 2018. Patients were also excluded if they had a record of cancer or neuropathic pain up to 12
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50 24 months before or six months after the start date of the initial long-term opioid prescription
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52 25 episode. Therefore, we used data from 811,174 regular adult patients with MSK attending 402
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54 26 general practices across Australia.

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57 27 *[FIGURE 1 HERE]*

58 *Musculoskeletal conditions*

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60 29 Data regarding MSK conditions were extracted from the database using previously published
30
31 30 algorithms.⁵ The diagnosis, reason for encounter and reason for prescription fields were used

1 to identify patients with a potentially painful MSK condition, as these are typical fields used
2 by GPs to record morbidity in Australian general practice.³² Most general practices use coding
3 systems (i.e. 'Docle', 'Pyefinch' or the International Classification of Primary Care 2), and
4 these were mapped to the Systematized Nomenclature of Medicine - Clinical Terms
5 (SNOMED-CT).^{5 32 38} The list of MSK conditions included i) osteoarthritis, ii) osteoarthritis,
6 iii) spondylarthritis, iv) fibromyalgia, v) polymyalgia rheumatica, vi) rheumatoid arthritis, vii)
7 myofascial pain, viii) chronic fatigue syndrome, ix) gout, x) Paget disease, xi) osteoporosis,
8 xii) tenosynovitis, xiii) chronic back pain and xiv) other conditions recorded as 'chronic
9 musculoskeletal pain'. Synonyms and misspellings of these terms were also used, considering
10 that GPs can also use free-text in the completion of the diagnosis. The data extraction
11 algorithms used in this study are available from the authors by request.

12 *Prescription data*

13 Data regarding opioid prescriptions (i.e. codeine, tramadol, tapentadol, oxycodone, morphine,
14 fentanyl, buprenorphine, hydromorphone) were extracted from the prescription dataset using
15 generic and brand names.³⁹ Using recommendations from the literature,^{21 40} a new 'episode of
16 opioid prescription' was defined as a prescription provided to the patient where no opioid was
17 prescribed within six months from the 'end of the last episode'. The 'end date' of an 'episode
18 of opioid prescription' was considered as being 28 days after the last prescription was provided
19 (i.e. in Australia, opioids can be prescribed for up to 28 days without repeats).^{8 39} An episode
20 of 'long-term opioid prescription' was defined as patients receiving i) three or more scripts
21 (including the initiating script) within 90 days of the initial script or ii) a total of 10 or more
22 consecutive scripts with an interval lower than 180 between 'episodes of opioid prescription',
23 even though the first three were not provided within 90 days. An episode of 'long-term opioid
24 prescription' ended when the patient had not received a prescription for opioids for six or more
25 months.^{8 39} A total of 135,358 instances of long-term opioid prescriptions were identified over
26 the period (Figure 1), with 88% of them matching a consultation when the GP recorded a MSK
27 as the reason for diagnosis, reason for encounter and/or reason for prescription (i.e. excluding
28 cancer or neuropathic pain) within a period lasting from 30 days before the initial opioid
29 prescription, or up to 120 days after it.^{8 39}

30 *Data analysis*

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4 1 The prevalence of long-term opioid prescriptions was estimated as the percentage of regular
5 2 patients with MSK attending the practice that year that were on opioids (i.e. long-term opioid
6 3 prescription), either because these prescriptions started in that year or previous years. The
7 4 cumulative incidence of long-term opioid prescription was estimated as the percentage of
8 5 regular patients with MSK in any year between 2012 and 2018 starting opioids that year (i.e.
9 6 patients “at risk” not on opioids). The average annual change in the prevalence or incidence of
10 7 long term opioid prescription was investigated using logistic regression, and the results
11 8 expressed as odds ratios (OR) with their respective 95% confidence intervals (95% CI).

12 9 The association between sociodemographic characteristics and the incidence of long-term
13 10 opioid prescription was also explored using logistic regression, and the variables were included
14 11 in the models considering two hierarchical levels. The first level included practice
15 12 characteristics: state, rurality (i.e. major cities, inner regional, or outer regional/remote
16 13 Australia) and the practice’s Index of Relative Socioeconomic Advantage and Disadvantage
17 14 [IRSAD, as provided by MedicineInsight (based on the postcode of the practice) and divided
18 15 in quintiles]. IRSAD is a relative indicator of economic and social advantage/disadvantage of
19 16 people and households within an area generated by the Australian Bureau of Statistics and
20 17 based on a range of census variables.⁴¹ Higher IRSAD scores indicate that the practice is
21 18 located in a more advantaged area. The second level included patient characteristics: gender
22 19 (males/females), age in groups (18-34, 35-49, 50-64, 65-79, 80+ years), aboriginality
23 20 (Aboriginal or Torres Strait Islander: No, Yes, not recorded), and the patient’s IRSAD (divided
24 21 in quintiles).

25 22 Results of the logistic regression models were expressed as marginal predicted probabilities
26 23 (i.e. adjusted cumulative incidence) instead of odds ratio to facilitate interpretation of the
27 24 results, as many medical doctors, researchers and health policymakers are not familiar with
28 25 these measures of association.⁴² Wald tests for heterogeneity or trend were used to estimate the
29 26 p-values due to the use of clustered data (i.e. practice defined as the cluster).

30 27 Quantile regression models were used to investigate the variables associated with the median
31 28 duration (in days) of the long-term opioid prescription among incident cases, considering the
32 29 same levels of adjustment as above.

33 30 All analyses were performed using the statistical software STATA 15.0 (StataCorp, Texas,
34 31 USA) and conditioned to the patient’s probability of being in the sample to minimise selection
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1 bias (i.e. the likelihood of receiving medical treatments or diagnosis increase with the number
2 of visits to the practice).⁴³

3 *Ethics approval*

4 The Human Research Ethics Committee of the University of Adelaide exempted this study of
5 an ethical review as only non-identifiable data was used. Access to the data for this study was
6 approved by the MedicineInsight Data Governance Committee (project 2016–004 and 2019-
7 029).

8 *Patient and public involvement*

9 Patients or the public were not directly involved in the design, conduct, reporting, or
10 dissemination plans of our research. However, the provision of information for the study
11 underwent a formal approval process guided by the MedicineInsight independent external Data
12 Governance Committee that includes GPs, consumer advocates, privacy experts and
13 researchers. Moreover, two of the authors are active GPs regularly attending patients affected
14 by MSK, which also supported the design of the study.

15 **RESULTS**

16 MedicineInsight included a total sample of 3,368,928 total patients, with 1,936,573 of them
17 aged 18 years or older (Figure 1). Most practices were from New South Wales (35.5%) and
18 Victoria (21.7%) and located in major cities (60.5%), but practices from all regions and with a
19 different socioeconomic profile were included (Supplementary Table 1). Males represented
20 42.2% of the adults in the database, while 28.7% were 65 years or older and 2.0% Aboriginals
21 or Torres Strait islanders. The most common MSK among patients aged 18+ years were chronic
22 back pain (16.6%), osteoarthritis (13.7%), tenosynovitis (6.7%) osteoporosis (4.2) and gout
23 (4.0%). The rest of the conditions showed a prevalence lower than 1%.

24 The analysed sample of unique regular adult patients with MSK attending one of the
25 MedicineInsight practices between 2012 and 2018 consisted of 811,174 individuals. As shown
26 in Figure 2, the number of these patients per year ranged between 160,834 and 299,431
27 individuals.

28 The overall ‘prevalence’ of long-term opioid prescribing (i.e. patients with MSK on opioids,
29 either because they started that year or in previous years) increased from 5.5% (95% CI 5.2-
30 5.8) in 2012 to 9.1% (95% CI 8.8-9.7) in 2018 [annual change OR=1.09 IC95% 1.08-1.09; p-

1 value for trend <0.001]. Figure 2 shows the increase was related to a higher proportion of
2 patients starting opioids in previous years, rather than a rise in incident cases (i.e. those who
3 started opioids in that year).

4 [FIGURE 2 HERE]

5 The MSK with the highest rate of long-term opioid prescribing were spondyloarthritis (13.8%)
6 and fibromyalgia (13.3%) in 2012, and Paget disease (22.2%) and fibromyalgia (21.4%) in
7 2018 (Supplementary Figure 1). Patients with fatigue syndrome or gout were less likely to be
8 on long-term opioids (4.4% and 3.4% in 2012; 8.6% and 6.9% in 2018, respectively).

9 Table 1 shows males represented 44.5% of the sample, 28.4% had 65+ years, and 1.9% were
10 Aboriginal or Torres Strait Islanders. Individuals from different socioeconomic settings were
11 all represented in the study, and 40.0% were for regional or remote areas. The cumulative
12 incidence of long-term opioid prescription (i.e. excluding those who were already on opioids)
13 among regular patients with a MSK ranged between 3.6% and 3.8% between 2012-2016,
14 dropping to 3.0% in 2018 [3.0%; annual change OR=0.99 IC95% 0.98-0.99; p-value for trend
15 0.002].

16 The same table also shows the sociodemographic factors associated with the cumulative
17 incidence of long-term opioid prescribing. In any investigated year, the cumulative incidence
18 was 37%-52% higher among individuals attending practices located in rural Australia or areas
19 with a very low IRSAD, compared to those attending practices located in major cities or areas
20 with a higher IRSAD. Individual risk factors associated with a higher incidence of long-term
21 opioid prescribing included increasing age (3.4 times higher among those aged 80+ years than
22 the 18-34-year group in 2012, increasing to 4.8% in 2018), identifying as an Aboriginal or
23 Torres Strait Islander (1.7-1.9 higher incidence than their peers), or living in areas with a lower
24 IRSAD (36%-57% more likely than among those living in wealthiest areas). Neither the state
25 where the practice was located nor the patient's gender was associated with this outcome.

26 [TABLE 1 HERE]

27 The average duration of the long-term opioid prescriptions among incident cases ranged from
28 287 to 301 days between 2012-2016, reducing to 229 days in 2017 and 140 days in 2018 (Table
29 2). The most consistent pattern observed over the investigated years was an increased duration
30 of prescribing among individuals attending practices located in lower socioeconomic areas (i.e.

1 up to 152 days longer than those attending practices located in the wealthiest areas) or females
2 (i.e. up to 77 days longer than in males). However, these differences were not evident in 2018.

3 [TABLE 2 HERE]

4 Figure 3 shows that 74.4% (CI 95% 72.9-75.8) of those that started long-term opioid
5 prescriptions in 2012 were still receiving these prescriptions after one year, while for those
6 starting opioids in 2017, the proportion was 76.3% (95% CI 75.0-77.6). The proportion of
7 patients in each cohort still on these prescriptions decreased to 54%-56% in year two and to
8 48-51% in year three after starting long-term opioid prescriptions, remaining steady at around
9 48% in subsequent years.

10 [FIGURE 3 HERE]

11 DISCUSSION

12 To the best of our knowledge, this is the first Australian study that uses EMR from a national
13 general practice database to investigate patterns of long-term opioid prescriptions for patients
14 with MSK.²⁷ Three main findings can be highlighted from the results. Firstly, the overall
15 prevalence of long-term opioid prescriptions increased between 2012 and 2018 as a
16 consequence of the progressive rise of patients starting opioids in previous years rather than
17 for an upsurge of incident cases. Secondly, factors associated with a higher incidence of long-
18 term opioid prescription included increasing age, identifying as Aboriginal or Torres Strait
19 Islander, living in a lower socioeconomic area, or attending practices located in a rural setting
20 or more disadvantaged areas. Finally, a longer duration of these episodes was observed among
21 females or patients attending practices in lower socioeconomic areas.

22 The increase in the prevalence of long-term opioid prescriptions is consistent with other
23 Australian studies using PBS data (9, 22).^{11 20 27} The observed increase in opioids prescriptions
24 represents a substantial ongoing burden for Australia. In 2015-16, the total direct cost related
25 to opioid use in Australia (i.e. premature mortality, health care, criminal justice) was estimated
26 in \$15.76 billion, with additional \$26.8 associated the loss of quality of life of users and co-
27 residents.⁴⁴ Some authors suggest the increase in opioid use/prescription is related to the ageing
28 population with higher rates of MSK, availability of slow-release opioid formulations and
29 aggressive marketing of opioids by pharmaceutical companies.^{1 2 21} Moreover, the observed
30 increase in Australia is probably related to the prescription of potent opioids. A previous study

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5 1 using PBS data found that between 2006-2015 weaker opioid use remained stable or declined,
6 2 while there was a 238% increase in persons dispensed only strong opioids.²⁰ Nonetheless, there
7 3 is evidence that long-term opioid prescription for patients with MSK in the UK and North
8 4 America reached a plateau around 2009-2011.^{21 22 45}

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12 5 Previous studies have also reported the incidence of opioid use has either decreased or
13 6 remained unchanged in recent years, despite a rise in the prevalence.⁴⁶⁻⁴⁸ In consonance with
14 7 these studies, we found a steady incidence between 2012-2016, followed by a lower incidence
15 8 in 2018. Interestingly, the duration of long-term opioid prescription also declined in newly
16 9 incident cases in 2017 and 2018 compared to the previous five years. Although results for
17 10 2018 might reflect an insufficient follow-up of incident cases in that year, it would not explain
18 11 the findings observed in 2017. Recent education strategies among GPs and health policy
19 12 changes may have helped reduce opioid initiation and duration when prescribing to someone
20 13 affected by MSK.^{8 9 14 39} However, the increasing prevalence between 2012-2018 with an
21 14 upsurging number of patients starting opioids in previous years (i.e. 'prevalent' cases) may
22 15 suggest insufficient pro-active opioid de-prescribing is being undertaken. This conclusion is
23 16 reinforced by the findings that four years or after starting long-term opioid prescriptions, half
24 17 the patients continued to receive these prescriptions. Therefore, after all that time receiving
25 18 opioids, it is likely that a considerable number of these patients became either dependent or
26 19 possibly addicted to opioids.^{8 11 19}

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39 20 It is also overwhelming that sedative-hypnotics drugs (i.e. benzodiazepines and Z-drugs) are
40 21 being concomitantly prescribed with of opioids, increasing the risk of addiction,
41 22 hospitalisations and deaths.^{19 49 50} Preliminary findings using MedicineInsight data show that
42 23 the proportion of patients with MSK on long-term opioids prescriptions also receiving long-
43 24 term benzodiazepines/Z-drugs prescriptions increased from 24.4 % (95% CI 23.3-25.5) in 2012
44 25 to 30.0% (95% CI 29.0-30.9%). In contrast, among patients with MSK not receiving opioids,
45 26 only 7.1% received long-term benzodiazepines/Z-drugs prescriptions in 2012 or 2018
46 27 (unpublished results). These findings help explain the substantial increase of opioid-induced
47 28 deaths in Australia, which raised from 2.67 per 100,00 people in 2001 (514 out of 1,038 total
48 29 drug-induced deaths) to 4.36 per 100,000 people in 2018 (1,088 out of 1,740 total drug-induced
49 30 deaths).^{44 49}

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58 31 Factors such as limited time of clinicians, insufficient training on de-prescribing, restricted
59 32 access to resources for monitoring patients using opioids are recognised barriers that affect

1 strategies aiming to improve opioid prescription practices in primary care.^{1 51} Moreover,
2 pharmaceutical companies' aggressive marketing strategies also influence opioid prescription
3 practices. In 2019, the Therapeutic Goods Administration fined Mundipharma \$302,400 for
4 infringement notices related to misleading, imbalanced and inaccurate claims of promotional
5 materials directed to Australian health professionals, all of them related to nine opioid
6 medicines marketed under the name Targin®.⁵²

7 Our finding that the elderly, patients living in lower socioeconomic areas, attending practices
8 located in more disadvantaged settings or from rural and remote Australia have higher rates of
9 long-term opioid prescription is consistent with British and American studies,^{21 22 53} as well as
10 with results based on PBS data.^{11 30 31} These groups are also more likely to be affected by
11 chronic MSK conditions^{5 21}. Perhaps a maldistribution of support services or access to tertiary
12 based pain clinics could partially explain these differences⁵¹, but further studies would be
13 necessary to investigate the underlying causes in the Australian context.

14 **Strengths and limitations**

15 The study has significant strengths: a national sample including adult patients of all age groups,
16 ethnicity, or sex, and practices from all Australian states, socioeconomic areas, or remoteness.
17 Despite the novelty in the use of a national general practice database that allows the
18 identification of patients with MSK and the reason for opioid prescription, differentiates
19 between incident and prevalent cases, and provides data on different associated factors, some
20 limitations have to be recognised.

21 First, medicine-use information from MedicineInsight relates to records of GP prescribing, and
22 not all prescriptions and repeats will be dispensed or taken by the patient. Therefore, results
23 from this study reflect prescription patterns rather than opioid use.

24 Second, our study did not distinguish between the strength of preparations (i.e. presented as
25 either morphine equivalent doses or defined daily dose). However, previous studies found that
26 up to 40% of the dispensed pain medications for non-cancer pain are potent opioids, and their
27 use has increased over the years.^{15 17 20}

28 Third, individuals attending multiple clinics for prescriptions are not tracked by
29 MedicineInsight, and this may underestimate the real frequency of long-term opioid
30 prescriptions. However, the observed trends and associations are consistent with the available
31 literature.^{11 20-22 27 45}

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5 1 Finally, the place/professional that initiated the prescriptions (e.g. Emergency Department,
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7 2 hospital, private specialist) cannot be investigated. Moreover, MedicineInsight does not
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9 3 provide details on the size and type of practices or characteristics of the doctors prescribing
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11 4 opioids (e.g. junior doctor, specialist, or GPs; years of experience, etc.) Nonetheless, according
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13 5 to PBS data, half of the opioids prescribed in Australia are initiated by general practitioners¹⁷
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15 6 and most patients with chronic pain requiring long-term opioid prescriptions are managed in
16
17 7 primary care settings.⁵¹

17 8 **CONCLUSION**

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20 9 The overall prevalence of long-term opioid prescribing for MSK conditions has increased in
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22 10 Australia between 2012 and 2018, despite a lower incidence and duration of these prescriptions
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24 11 in the last couple of years. This trend towards an increase in the prevalence of long-term opioid
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26 12 prescribing is of great concern, as current literature reports an overall escalation in the rates of
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28 13 opioid harms and deaths.^{8 9 11 14} Our study highlights the need for ongoing efforts to reduce the
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30 14 opioid burden, especially among those living and attending practices in more disadvantaged
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32 15 areas and considering the higher risk of adverse effect in elderly patients. This should come
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34 16 not only by reducing opioid initiation but also by proactively de-prescribing for suitable
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36 17 patients.^{8 14} While GPs are in an optimal position for this role⁵¹, opioid stewardship is the
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38 18 responsibility of all prescribing medical practitioners and allied health professionals dealing
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40 19 with MSK pain management.
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5 **AUTHOR CONTRIBUTIONS**

6 All authors made significant contributions to the manuscript and are responsible for its content.
7 NS and SBT conceived the idea and planned this study. DGC was responsible for data
8 extraction and analysis, interpreting and presenting the results. SBT and DGC wrote the first
9 draft and the revisions. NS contributed to the manuscript refinement. All authors have read and
10 approved the final manuscript.

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13 not-for-profit sectors.

14 **COMPETING INTERESTS**

15 None declared.

16 **ETHICS APPROVAL**

17 The Human Research Ethics Committee of the University of Adelaide exempted this study of
18 an ethical review as only non-identifiable data was used. Access to the data for this study was
19 approved by the MedicineInsight Data Governance Committee (project 2016–004 and 2019-
20 029).

21 **DATA SHARING STATEMENT**

22 Data may be obtained from MedicineInsight and are not publicly available. Third parties may
23 express an interest in the information collected through MedicineInsight. The provision of
24 information in these instances undergoes a formal approval process and is guided by the
25 MedicineInsight independent external Data Governance Committee. This Committee includes
26 GPs, consumer advocates, privacy experts and researchers.

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Table 1. Cumulative incidence of long-term opioid prescription for the management of musculoskeletal conditions according to practice and patient's characteristics. regular patients^a aged 18+ years. Australia, 2012-2018.

Year	Long-term opioids - incidence (%)							
	2012	2013	2014	2015	2016	2017	2018	
regular patients with a MSK 'at risk'^a	157,528	185,358	210,089	231,961	253,648	281,655	190,079	
	3.6	3.6	3.8	3.7	3.8	3.5	3.0	
Overall incidence - % (95%CI)	(3.4;3.8)	(3.4;3.8)	(3.6;4.0)	(3.5;3.9)	(3.6;4.0)	(3.4;3.7)	(2.8;3.1)	
Practice characteristics^c	% ^d							
State								
NSW	36.2	3.6	3.5	3.8	3.7	3.7	3.4	2.8
VIC	21.5	3.7	3.6	3.9	3.9	3.9	3.7	3.1
QLD	14.3	3.3	3.5	3.8	3.6	3.5	3.6	2.7
WA	11.3	3.7	3.8	3.9	3.8	4.3	4.1	3.5
TAS	10.4	3.3	3.3	3.4	3.4	3.4	3.1	2.8
SA	3.0	3.2	3.8	3.2	3.9	3.7	3.8	2.9
ACT	2.7	6.0	4.6	5.1	4.8	4.2	4.5	3.3
NT	0.6	2.6	3.6	3.5	2.5	3.7	2.6	2.6
Rurality								
Major cities	60.0	3.1	3.2	3.4	3.4	3.3	3.2	2.7
Inner regional	26.7	3.8	4.0	4.0	3.9	4.1	3.9	3.2
Outer regional/Remote	13.3	4.9	4.5	5.0	4.8	5.0	4.5	3.7
IRSAD Quintile								
Very high	25.8	2.8	2.9	3.1	2.9	3.1	2.8	2.4
High	16.7	3.4	3.4	3.4	3.4	3.6	3.4	3.0
Middle	22.8	3.8	3.6	3.9	4.0	4.0	3.9	3.1
Low	15.6	3.8	3.7	4.0	4.0	3.8	3.6	3.0
Very Low	19.1	4.0	4.3	4.5	4.4	4.4	4.1	3.3
Patient's characteristics^e								
Gender								
Male	44.5	3.4	3.4	3.6	3.7	3.7	3.4	3.0

Female	55.5	3.7	3.7	3.9	3.8	3.8	3.6	2.9
Age								
18-34 years	18.9	1.9	2.0	1.8	1.7	1.7	1.5	1.3
35-49 years	23.9	2.9	2.9	3.0	2.9	2.8	2.6	2.2
50-64 years	28.8	3.2	3.1	3.2	3.1	3.2	3.0	2.4
65-79 years	21.9	4.4	4.4	4.6	4.5	4.5	4.2	3.6
80+ years	6.5	6.5	6.5	7.0	7.4	7.6	7.3	6.2
Aboriginal/Torres Strait Islander								
No	77.9	3.6	3.6	3.8	3.8	3.8	3.5	3.0
Yes	1.9	6.5	6.0	6.5	7.3	7.0	6.5	5.3
Not recorded	20.2	3.0	3.1	3.1	3.0	3.3	3.3	2.7
IRSAD Quintile								
Very high	23.9	2.8	2.8	2.9	2.8	3.0	2.8	2.5
High	16.9	3.3	3.4	3.8	3.7	3.6	3.4	2.7
Middle	23.0	3.8	3.6	3.8	4.0	3.8	3.8	3.0
Low	17.3	3.7	3.7	4.0	3.8	4.2	3.7	3.2
Very Low	18.7	4.1	4.4	4.3	4.3	4.4	3.9	3.4

^a At least three consultations in any two consecutive years from 2012 to 2018. Numbers (n) represent the number of regular patients with a musculoskeletal condition in that year, excluding those who were already on opioids (i.e. patients “at risk”)

^b Values in parenthesis represent the 95% confidence intervals of the incidence

^c Logistic regression models with all practice characteristics mutually adjusted. Values in ‘bold’ represent those associations with a p-value <0.01

^d Values represent the sample distribution according to these characteristics

^e Logistic regression models with all patient characteristics mutually adjusted + adjustment for practice characteristics. Values in ‘bold’ represent those associations with a p-value <0.01

MSK: Musculoskeletal condition; IRSAD: Index of Relative Socioeconomic Advantage and Disadvantage.

Table 2. Average time on long-term opioid prescription for the management of musculoskeletal conditions among incident cases according to practice and patient's characteristics. regular patients^a aged 18+ years. Australia, 2012-2018.

	Time on long-term opioids among incident cases (days)						
	2012	2013	2014	2015	2016	2017	2018
Incident cases	5,621	6,647	7,944	8,652	9,572	9,958	5,672
	287	301	295	288	294	229	140
Median duration (95%CI)^b	(266;308)	(281;321)	(279;311)	(272;304)	(281;307)	(221;237)	(135;145)
Practice characteristics^c							
State							
NSW	266	299	308	273	292	210	134
VIC	283	309	312	313	268	230	141
QLD	342	243	264	278	297	244	146
WA	294	288	281	333	336	246	141
TAS	339	367	205	367	292	241	138
SA	269	393	255	292	402	214	154
ACT	327	299	431	338	321	267	186
NT	249	683	261	206	237	116	108
Rurality							
Major cities	301	327	288	309	290	221	137
Inner regional	309	313	319	290	316	234	142
Outer regional/Remote	242	243	310	309	284	240	148
IRSAD Quintile							
Very high	203	214	244	203	247	186	128
High	231	300	285	299	263	221	143
Middle	263	319	290	302	320	222	142
Low	393	341	361	341	293	259	145
Very Low	349	346	322	355	333	251	141
Patient's characteristics^d							
Gender							
Male	278	272	272	259	271	211	137
Female	311	349	329	336	323	238	143

Age							
18-34 years	230	361	276	363	247	233	147
35-49 years	335	361	345	327	350	257	154
50-64 years	299	337	320	293	306	221	142
65-79 years	278	257	277	279	242	203	132
80+ years	336	371	326	336	379	249	143
Aboriginal/Torres Strait Islander							
No	302	319	308	303	303	224	139
Yes	442	376	415	405	381	274	158
Not recorded	245	315	278	296	279	232	146
IRSAD Quintile							
Very high	238	287	236	268	277	230	127
High	249	315	258	296	292	218	140
Middle	278	315	306	297	319	233	139
Low	358	333	360	323	303	216	134
Very Low	343	337	343	330	308	232	159

^a At least three consultations in any two consecutive years from 2012 to 2018.

^b Values in parenthesis represent the 95% confidence intervals of the median time on opioids. The corresponding interquartile values are 2012=91-1177; 2013=98-1214; 2014=98-1145; 2015=94-989; 2016=97-759; 2017=91-474; 2018=78-255.

^c Quantile regression models with all practice characteristics mutually adjusted. Values in 'bold' represent those associations with a p-value <0.01

^d Quantile regression models with all patient characteristics mutually adjusted + adjustment for practice characteristics. Values in 'bold' represent those associations with a p-value <0.01

MSK: Musculoskeletal condition; IRSAD: Index of Relative Socioeconomic Advantage and Disadvantage.

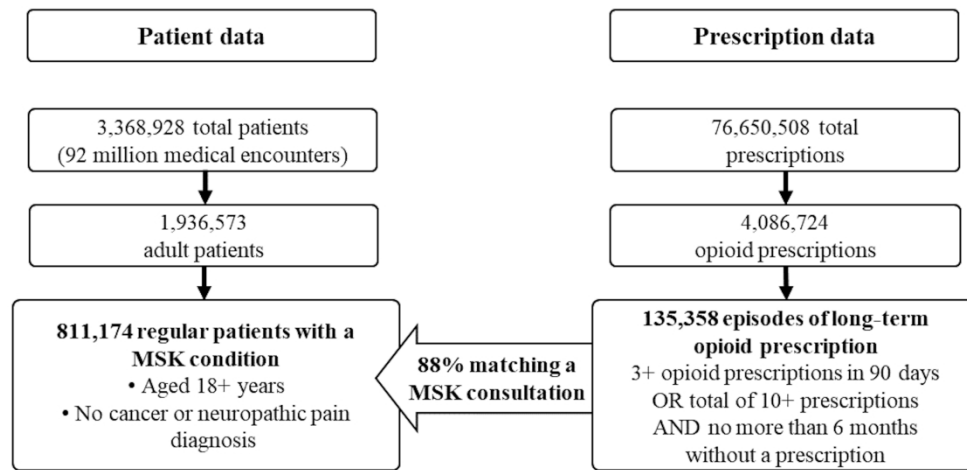
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4 **Figure 1. Algorithm of data extraction from MedicineInsight database for the diagnosis**
5 **of MSK and opioid prescriptions. Period 2012-2018**
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9 **Figure 2. Frequency of long-term opioid prescription for the management of**
10 **musculoskeletal conditions. Period 2012-2018.** Number in parenthesis (n) represent the total
11 number of regular patients with a musculoskeletal condition in that year from a total of 811,174
12 regular patients investigated over the whole period.
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17 **Figure 3. Proportion of patients starting long-term opioid prescriptions in any year that**
18 **were still receiving these prescriptions in subsequent years. Period 2012-2018.** Each
19 connected line represents a different cohort followed over time. Numbers in parenthesis (n)
20 represent the total number of regular patients with a musculoskeletal condition that started long-
21 term opioid prescriptions in that year.
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26 **Supplementary Table 1. Practice and patient characteristics in the whole sample. Regular**
27 **patients^a aged 18+ years. MedicineInsight data, 2018.**
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31 **Supplementary Figure 1. Rate of long-term opioid prescribing for different**
32 **musculoskeletal conditions in 2012 and 2018.**
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23 Figure 1. Algorithm of data extraction from MedicineInsight database for the diagnosis of MSK and opioid
24 prescriptions. Period 2012-2018

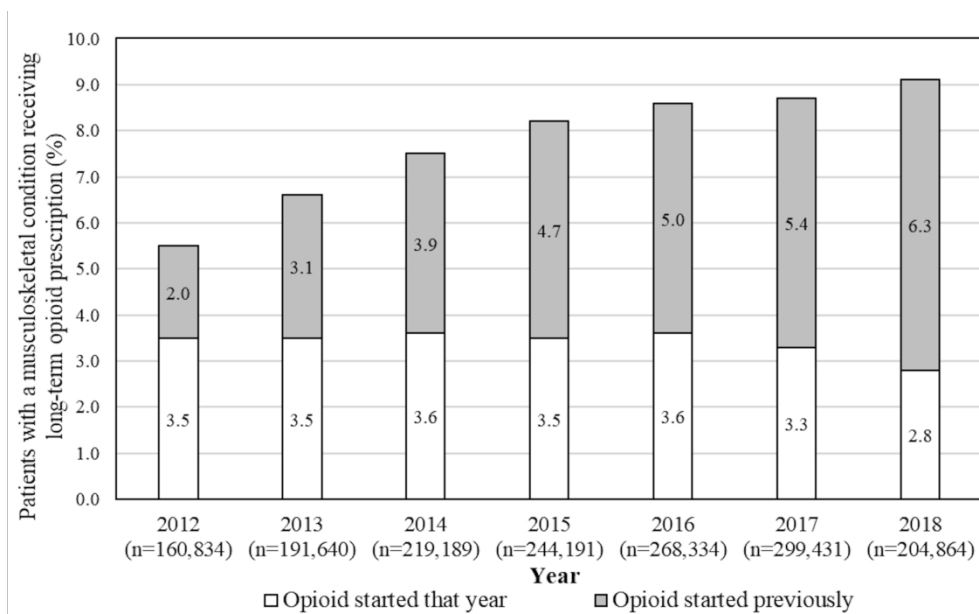


Figure 2. Frequency of long-term opioid prescription for the management of musculoskeletal conditions. regular patients aged 18+ years. Australia, 2012-2018. Number in parenthesis (n) represent the total number of regular patients with a musculoskeletal condition in that year from a total of 811,174 regular patients investigated over the whole period.

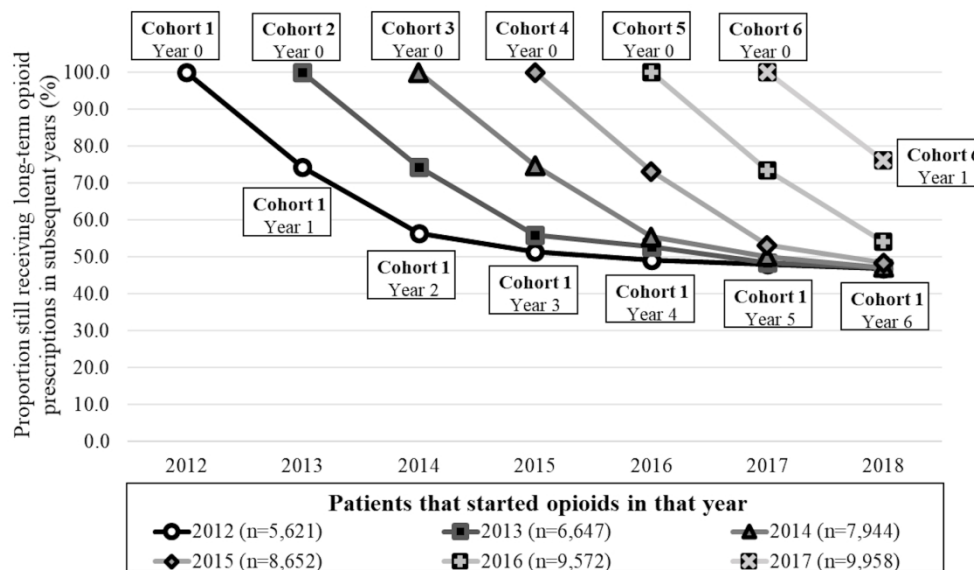


Figure 3. Proportion of patients starting long-term opioid prescriptions in any year that were still receiving these prescriptions in subsequent years. Period 2012-2018. Each connected line represents a different cohort followed over time. Numbers in parenthesis (n) represent the total number of regular patients with a musculoskeletal condition that started long-term opioid prescriptions in that year.

Supplementary Table 1. Practice and patient characteristics in the whole sample. Regular patients^a aged 18+ years. MedicineInsight data, 2018.

Practice characteristics	% ^b	95% CI
State		
NSW	35.5	30.1-41.2
VIC	21.7	17.1-27.2
QLD	14.4	10.9-18.8
WA	12.0	8.5-16.6
TAS	10.0	6.8-14.4
SA	2.6	1.4-5.0
ACT	2.8	1.3-6.1
NT	1.0	0.4-2.4
Rurality		
Major cities	60.5	54.7-66.1
Inner regional	25.9	21.1-31.4
Outer regional/Remote	13.5	10.2-17.8
IRSAD Quintile		
Very high	27.0	22.0-32.7
High	16.4	12.6-21.0
Middle	22.6	18.0-28.1
Low	18.8	11.3-18.9
Very Low	18.8	14.5-24.1
Patient's characteristics		
Gender		
Male	42.2	41.7-42.8
Female	57.7	57.1-58.2
Age		
18-34 years	23.0	22.1-23.9
35-49 years	23.2	22.6-23.9
50-64 years	25.1	24.7-25.5
65-79 years	15.4	14.9-16.0
80+ years	13.3	12.6-14.0
Aboriginal/Torres Strait Islander		
No	76.9	73.9-79.6
Yes	2.0	1.1-2.3
Not recorded	21.1	18.4-24.2
IRSAD Quintile		
Very high	25.0	21.3-29.2
High	16.9	14.6-19.4
Middle	22.7	19.5-26.3
Low	16.5	13.9-19.5
Very Low	18.1	15.0-21.8
Chronic musculoskeletal conditions^c		
Chronic back pain	16.6	15.9-17.2
Osteoarthritis	13.7	13.1-14.3
Tenosynovitis	6.7	6.4-7.1
Osteoporosis	4.2	4.0-4.4
Gout	4.0	3.8-4.1
Rheumatoid arthritis	0.89	0.85-0.94
Fibromyalgia	0.69	0.64-0.73

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3	Polymyalgia_rheumatica	0.68	0.63-0.74
4	Osteoarthritis	0.38	0.34-0.43
5	Spondyloarthritis	0.28	0.26-0.31
6	Fatigue syndrome	0.22	0.20-0.24
7	Paget disease	0.11	0.01-0.12
8	Myofascial pain	0.03	0.02-0.05
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10 ^a At least three consultations in any two consecutive years

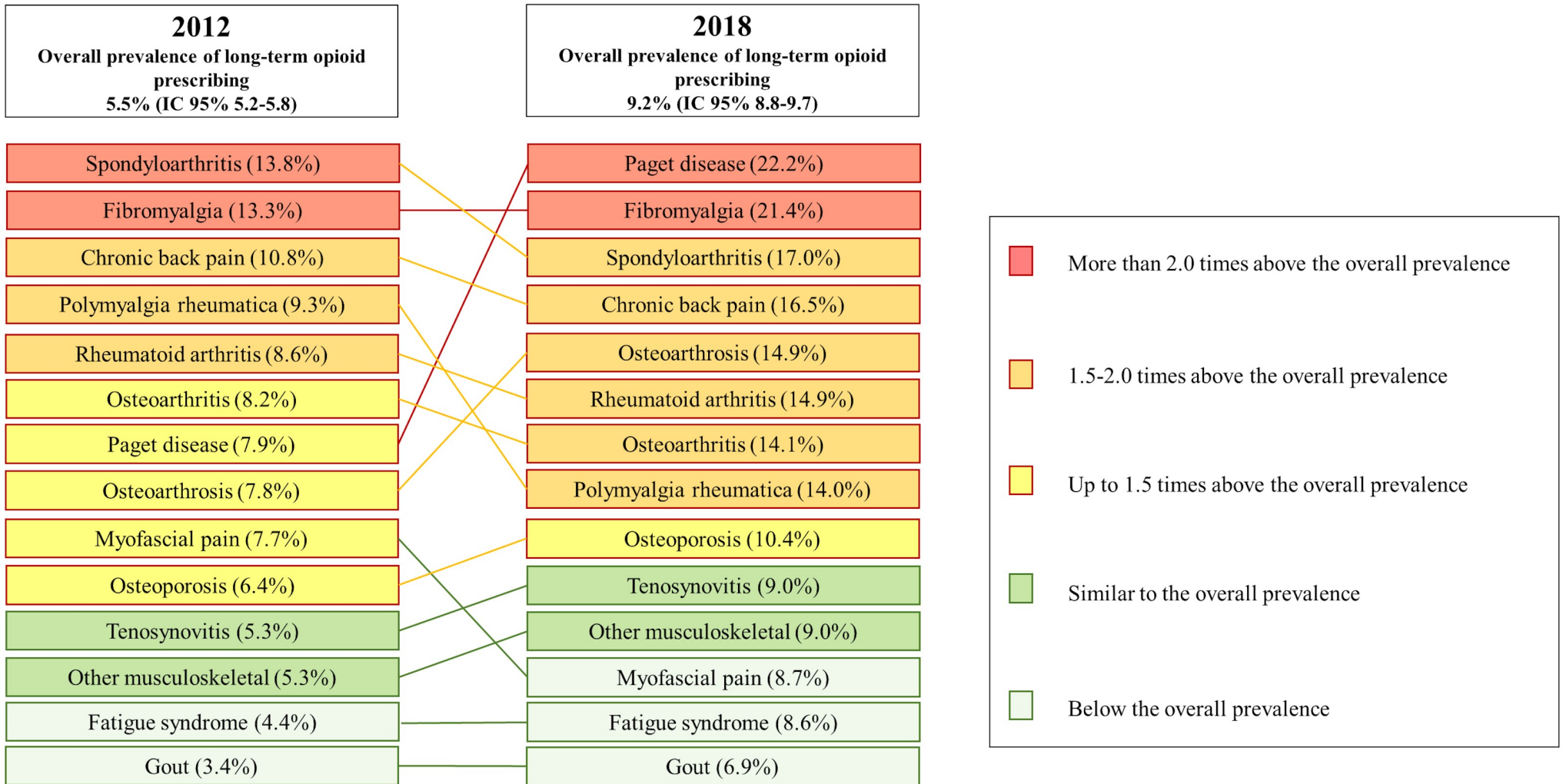
11 ^b Values represent the distribution (prevalence) in the whole sample of regular patients aged 18+ years
 12 according to these characteristics

13 ^c List of chronic musculoskeletal conditions diagnosed at any time between 2011 and 2018
 14 IRSAD: Index of Relative Socioeconomic Advantage and Disadvantage.

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(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	1,2 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	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	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(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) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8 - 6-7 - -
Results			
Participants	13*	(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	6,9, Tables 1,2 - Fig. 1
Descriptive data	14*	(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) Summarise follow-up time (eg, average and total amount)	9, Table 1 9, Table 1 9, Table 1

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Outcome data

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Report numbers of outcome events or summary measures over time

9, 10,
Fig. 2,
Tables
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1	Main results	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	9-10, tables 1,2
2			(b) Report category boundaries when continuous variables were categorized	9-10, tables 1,2
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10, tables 1,2
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10	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	10
13	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	12
14	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
15	Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
16	Other information			
17	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	13

27 *Give information separately for exposed and unexposed groups.

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30 **Note:** 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 <http://www.strobe-statement.org>.