A fifteen-year overview of increasing tramadol utilisation and associated mortality and the impact of tramadol classification in the United Kingdom

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Keywords:	tramadol classification, drug utilisation, interrupted time series analysis, tramadol-related mortality
Abstract:	<p>Purpose This study aimed to develop hypotheses to explain the increasing tramadol utilisation, evaluate the impact of tramadol classification and explore the trend between tramadol utilisation and related deaths in the United Kingdom.</p> <p>Methods This cross-sectional study used individual patient data, the Clinical Practice Research Datalink from 1993 to 2015, to calculate monthly Defined Daily Dose (DDD)/1000 registrants, monthly prevalence and incidence of tramadol users, annual supply days and mean daily dose of tramadol. Aggregated-level national statistics and prescribing reimbursement data from 2004 to 2015 were also used to quantify annual and monthly tramadol DDD/1000 inhabitants and rate of tramadol-related deaths in England and Wales. Interrupted time-series analysis was used to evaluate the impact of tramadol classification in June 2014.</p> <p>Results Prevalence of tramadol users increased from 23 to 97.6/10000 registrants from 2000 to 2015. Both annual dose and annual supply days of existing tramadol users were higher than new users. Level and trend of monthly utilisation (β_2: -12.9, β_3: -1.6) and prevalence of tramadol users (β_2: -6.4, β_3: -0.37) significantly reduced after classification. Both annual tramadol utilisation and rate of tramadol-related deaths increased before tramadol classification, and decreased thereafter.</p>

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	<p>Conclusions</p> <p>Increasing tramadol utilisation was influenced by the increase in prevalence and incidence of tramadol users, mean daily dose and day of supply. Prevalence of tramadol users, tramadol utilisation and reported deaths declined after tramadol classification. Future studies need to evaluate the influencing factors to ensure the safety of long-term tramadol use.</p>

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Title: A fifteen-year overview of increasing tramadol utilisation and associated mortality and the impact of tramadol classification in the United Kingdom

Running head: Tramadol utilisation and related mortality

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Keywords: tramadol classification, drug utilisation, interrupted time series analysis,

20 tramadol-related mortality

21 **Key points:**

- 22 1. The marked increase of tramadol utilisation in the UK primary care setting from
23 2000 to 2015 was influenced most by increasing prevalence, mean daily dose and
24 supply days for existing tramadol users.
- 25 2. The level and trend of monthly prevalence of tramadol users and tramadol
26 utilisation reduced after the classification of tramadol in June 2014.
- 27 3. From 2004 to 2013, the annual tramadol utilisation doubled and coincidently the
28 number of tramadol-related deaths increased almost six times in England and
29 Wales, but their trends declined in 2014 and 2015.

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Abstract

Purpose

This study aimed to develop hypotheses to explain the increasing tramadol utilisation, evaluate the impact of tramadol classification and explore the trend between tramadol utilisation and related deaths in the United Kingdom.

Methods

This cross-sectional study used individual patient data, the Clinical Practice Research Datalink from 1993 to 2015, to calculate monthly Defined Daily Dose (DDD)/1000 registrants, monthly prevalence and incidence of tramadol users, annual supply days and mean daily dose of tramadol. Aggregated-level national statistics and prescribing reimbursement data from 2004 to 2015 were also used to quantify annual and monthly tramadol DDD/1000 inhabitants and rate of tramadol-related deaths in England and Wales. Interrupted time-series analysis was used to evaluate the impact of tramadol classification in June 2014.

Results

Prevalence of tramadol users increased from 23 to 97.6/10000 registrants from 2000 to 2015. Both annual dose and annual supply days of existing tramadol users were higher than new users. Level and trend of monthly utilisation (β_2 : -12.9, β_3 : -1.6) and prevalence of tramadol users (β_2 : -6.4, β_3 : -0.37) significantly reduced after

classification. Both annual tramadol utilisation and rate of tramadol-related deaths increased before tramadol classification, and decreased thereafter.

Conclusions

Increasing tramadol utilisation was influenced by the increase in prevalence and incidence of tramadol users, mean daily dose and day of supply. Prevalence of tramadol users, tramadol utilisation and reported deaths declined after tramadol classification. Future studies need to evaluate the influencing factors to ensure the safety of long-term tramadol use.

62 Introduction

63 Tramadol is indicated for moderate to severe pain in the United Kingdom (UK).

64 In the past decade, the utilisation of tramadol has consistently increased in

65 many countries, including the United States (US), Germany¹ as well as the

66 UK². According to the UK National Health Service (NHS) Business Services

67 Authority (BSA), the annual tramadol utilisation in England increased from 5.9

68 to 11.1 million Defined Daily Doses (DDD) between 2005 and 2012²;

69 coincidentally, there was a marked increase in the number of tramadol-related

70 deaths during the same period.

71

72 In the US, prolonged opioid use for persistent pain has been identified as the

73 main reason for increasing opioid utilisation,³ although several clinical

74 guidelines⁴⁻⁶ suggest the long-term opioid use for chronic non-cancer pain

75 (CNCP) remains controversial.^{7, 8} However, the reasons attributable to the

76 increasing opioid utilisation, such as tramadol have not been investigated in

77 the UK.

78

79 Currently, there is no direct evidence to infer the relationship between

80 increasing tramadol utilisation and related mortality in the UK. At the

81 population level, the NHS BSA only presented tramadol utilisation without
82 adjusting for population size, and tramadol utilisation in Wales was not
83 included in the report;² but the published mortality figures from the Office for
84 National Statistics (ONS) covered both England and Wales.⁹ Consequently,
85 the correlation between tramadol utilisation and tramadol-related deaths has
86 not been established.²

87
88 Due to the concerns about safety and potential risk of misuse, tramadol was
89 classified as a Schedule 3 Controlled Substance in June 2014 in the U.K.²
90 Thereafter, tramadol prescribing needs to follow stricter prescription
91 requirements with clear defined dose and the maximum supply days should
92 not exceed 30 days². For such a medication with high usage and potential
93 harm, the effectiveness of policy intervention on utilisation and
94 tramadol-related mortality is an important public health issue. However, the
95 effect of tramadol classification has not been explored.

96
97 Therefore, this study aimed to develop hypotheses to explain the increasing
98 tramadol utilisation and evaluate policy changes in the UK. The objectives
99 were to (1) identify potential reasons for increasing tramadol utilisation from

100 individual utilisation patterns; (2) evaluate the impact of tramadol classification
101 on prevalence of tramadol users and tramadol utilisation; and (3) explore the
102 trend between tramadol utilisation and tramadol-related deaths.

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103 **Methods**

104 **Study design and data source**

105 This cross-sectional study used several data sources which cover information from
106 different geographical region and time frames, including aggregated-level and
107 publically available data from the UK government sources as well as individual patient
108 data (IPD) from a UK primary care database to address multiple research questions
109 and compensate limitation of each database (Table 1).

110

111 To explore potential reasons for the increasing tramadol utilisation from individual
112 utilisation patterns, validate findings about the impact of tramadol classification on
113 monthly tramadol utilisation from aggregate-level data and evaluate the impact of
114 tramadol classification on prevalence of tramadol users and tramadol utilisation, a UK
115 primary care database, the Clinical Practice Research Datalink (CPRD) from January
116 1993 to December 2015 was used after receiving approval from the Independent
117 Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory
118 Agency (Protocol number: 12_007RA).

119

120 CPRD is the largest verified primary care database of anonymised clinical records in
121 the UK. IPD in CPRD were prospectively collected from general practitioners' daily

122 records and it represents about 8.3% of the UK population up to March 2016.¹⁰⁻¹² The
123 population is representative of the UK general population in terms of the age and
124 gender distribution, and hence, CPRD has been widely used in drug utilisation
125 research in UK primary care.^{13, 14}

126

127 Monthly practice-level dispensing data from October 2010 to September 2015 was
128 used as the primary data source to evaluate the impact of tramadol classification on
129 monthly tramadol utilisation in England.¹⁵ To explore the correlation between annual
130 tramadol utilisation and tramadol-related deaths between 2004 and 2015, this study
131 used mortality data which is originally recorded by the International Classification of
132 Diseases-the tenth version (ICD-10) diagnosis codes⁹, annual aggregated-level
133 dispensing data from Prescription Cost Analysis (PCA) in England¹⁶ and Wales¹⁷ and
134 the annual number of mid-year population estimates from the ONS¹⁸. Those
135 aggregate-level data are publically available and use requires no ethical review.

136

137 <Insert Table 1>

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139 **Study population**

140 For the IPD analysis, adult CPRD registrants (age >18 years) prescribed tramadol

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141 between January 2000 and December 2015 were included. For monthly
142 practice-level dispensing data, practices which issued any tramadol prescriptions
143 between October 2010 and September 2015 in England were included.

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145 **Outcomes measured using aggregated-level data**

146 The annual number of tramadol-related deaths/100000 inhabitants and annual and
147 monthly DDDs of dispensed tramadol/1000 inhabitants were measured in
148 aggregated-level statistics and datasets. The number of tramadol related deaths was
149 directly extracted from government reports.⁹ The annual quantity of tramadol
150 preparations reported in the PCA was used to calculate the annual number of DDDs
151 dispensed in England¹⁶ and Wales¹⁷. While the quantity of tramadol preparations
152 extracted from monthly practice-level dispensing data were used to calculate the
153 monthly number of DDDs dispensed in England.¹⁵

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155 The annual number of tramadol-related deaths was divided by the mid-year number
156 of population in England and Wales and then multiplied by 100000 to calculate the
157 annual number of tramadol-related deaths/100000 inhabitants. The total dose of each
158 tramadol preparation was calculated by multiplying strength (in milligrams) and
159 quantity, and then summed in annual or monthly basis, and then divided by 300 (as

defined by the World Health Organisation¹⁹) to calculate the number of DDDs of tramadol. The annual or monthly DDD was adjusted by the mid-year number of population¹⁸ to derive the annual or monthly number of DDDs of dispensed tramadol/1000 inhabitants.

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165 **Outcomes measured using individual patient data**

166 The monthly prevalence and incidence of tramadol users/10000 registrants, monthly
167 DDDs/1000 registrants and annual supply days and mean daily dose for each
168 tramadol user were measured by using tramadol prescription records from CPRD.

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170 Adult patients who received their first tramadol prescription during the study period
171 were identified as new tramadol users in that calendar year, and if the patients
172 received tramadol in the subsequence years, they will be classified as existing users
173 in the subsequence years. The number of new and existing tramadol users were
174 calculated in each calendar month, and adjusted by the total number of active
175 patients in the CPRD to derive the monthly incidence and prevalence of tramadol
176 users/10000 registrants.

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178 The total dose of each tramadol prescription was calculated by multiplying strength

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179 and quantity, and then converted to the monthly number of DDDs; which was further
180 adjusted by the number of active patients in the particular calendar month to calculate
181 the monthly number of DDDs of tramadol/1000 registrants.
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183 For each tramadol prescription, the dose was divided by numerical daily dose
184 (recorded by physicians and available in the CPRD therapy file) to derive the number
185 of supply days. If the interval between two consecutive prescriptions was shorter than
186 the supply day of the anterior prescription, then the supply day was replaced by
187 interval between the two prescriptions.
188
189 For each patient, the total doses of tramadol prescriptions and annual number of
190 supply days were summed in each calendar year. If the annual number of supply
191 days was more than 365 days, then it was capped to 365 days. The annual dose was
192 divided by annual number of supply days to derive the annual mean daily dose in
193 particular calendar year.

195 **Data analysis**

196 Descriptive statistics were used to report annual dose and number of supply days.
197 The trend of (1) monthly incidence and prevalence of tramadol users from January

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4 198 2000 to December 2015; (2) annual mean daily dose stratified by new and existing
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7 199 users; (3) annual number of DDDs of dispensed tramadol/1000 inhabitants and the
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10 200 rate of tramadol-related deaths in England and Wales from 2004 to 2015 were
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12 201 reported graphically. Cross-correlation between the two time-series, i.e. annual
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15 202 number of tramadol-related deaths/100000 inhabitants and annual number of DDDs
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18 203 of dispensed tramadol/1000 inhabitants, was investigated at no lag time effect and
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21 204 presented as cross-correlation coefficient (ranged from -1 to 1).
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27 206 Interrupted time-series analysis (ITSA)²⁰ was used to evaluate the impact of tramadol
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30 207 classification in June 2014 on the levels and trends of two series between October
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33 208 2010 and September 2015: (1) monthly prevalence and incidence of tramadol users
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36 209 estimated from CPRD; (2) monthly DDD/1000 registrants estimated from both
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39 210 monthly practice-level dispensing data and CPRD. In CPRD, monthly DDD/1000
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42 211 registrants was further stratified by new and existing users to identify the impact of
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45 212 tramadol classification on different patient groups.
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50 214 The Durbin Watson test was used to test first-order autocorrelation in each time
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53 215 series, as no first-order autocorrelation was found²¹, and hence auto-regressive
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56 216 integrated moving-average (ARIMA) model was not applied in the ITSA²². In the
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217 regimented regression model, baseline trend before classification (β_1), change in the
218 level (β_2) and change in trend after classification (β_3) were tested and reported for
219 each time series. Additional time points in the policy development were tested in
220 sensitivity analysis (Appendix 1). All analysis was performed using STATA 14
221 (Stata-Corp, Texas, USA, 2015).

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222 Results

223 Trend of prevalence and incidence of tramadol users from 2000 to 2015

224 The IPD extracted from CPRD showed that the monthly prevalence and incidence of
225 tramadol users increased from 23 to 99.3/10000 registrants and 4.1 to 7.7/10000
226 registrants respectively between January 2000 and May 2014 (Figure 1).

227

228 <Insert Figure 1>

229

230 Annual dose, supply days and mean daily dose from 2000 to 2015

231 For all adult tramadol users in CPRD, most tramadol prescriptions were issued for
232 existing tramadol users. In 2000, 69.2% of the annual tramadol dose was prescribed
233 to existing tramadol users, and this proportion increased to 91.4% in 2015 (Appendix
234 2). In addition, between 2000 and 2015, the annual dose per existing tramadol user in
235 each calendar year (range: 37910.8 to 40218.2 mg) was consistently higher than the
236 annual dose per new users (range: 9717.8 to 11642.6 mg). Furthermore, the annual
237 supply days per existing tramadol users in each calendar year (range: 134.3 to 150.7
238 days) was consistently higher than new users (range: 35.7 to 47.9 days) (Appendix
239 3).

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241 From 2000 to 2013, the annual mean daily tramadol dose increased in both existing

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242 and new users. After 2007, new users had greater annual mean daily dose than
243 existing users, however, since tramadol classification, the annual mean daily dose of
244 new users decreased in 2014 and 2015 (Figure 2).

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246 <Insert Figure 2>

247
248 **Impact of tramadol classification on monthly tramadol utilisation**

249 Tramadol classification had similar impacts on its utilisation in the results of ITSA
250 using aggregated-level data and IPD. In the monthly practice-level dispensing data,
251 the ITSA revealed that the level (β_2 : -12.9, $p=0.017$) and the trend (β_3 : -1.6, $p=0.002$)
252 of monthly tramadol utilisation significantly decreased after tramadol classification,
253 despite there was a significant increase in the baseline trend (β_1 : 0.79, $p<0.001$)
254 before tramadol classification (Figure 3).

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256 <Insert Figure 3>

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258 Similarly, the IPD from CPRD showed a significant increase trend (β_1 : 0.56, $p<0.001$)
259 before tramadol classification, and the level significantly reduced at the launch of
260 classification (β_2 : -16.3, $p=0.021$) but there was no significant change in the trend of

261 tramadol utilisation after classification.

262

263 When stratifying monthly tramadol utilisation into existing and new tramadol users,
264 before the classification, the trend significantly increased in existing users (β_1 : 0.63,
265 $p<0.001$) (Figure 4) but decreased in new users (β_1 : -0.07, $p<0.001$) (Figure 5). After
266 the launch of tramadol classification, the level significantly decreased in both existing
267 users (β_2 : -13.8, $p=0.041$) and new (β_2 : -2.6, $p<0.001$) users. However, there was no
268 significant change in the trend of tramadol utilisation for both existing and new users
269 after tramadol classification.

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271 <Insert Figure 4>

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273 <Insert Figure 5>

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275 **Impact of tramadol classification on monthly prevalence and incidence of** 276 **tramadol users**

277 In addition to the decrease in monthly tramadol utilisation, tramadol classification also
278 decreased the prevalence of tramadol users. In the IPD from CPRD, the baseline
279 trend significantly increased in prevalence (β_1 : 0.21, $p<0.001$) but decreased in

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incidence (β_1 : -0.04, $p<0.001$) of tramadol users between October 2010 and May 2014. The level of both prevalence (β_2 : -6.4, $p=0.001$) and incidence (β_2 : -1.7, $p<0.001$) decreased significantly after the launch of tramadol classification. However, only the trend of prevalence decreased significantly (β_3 : -0.37, $p=0.028$) and there was no significant change in the trend of incidence (Figure 1). All sensitivity analysis models found that other intervention time points had no significant effect on tramadol utilisation, prevalence and incidence.

Trend of annual tramadol utilisation and tramadol-related deaths from 2004 to 2014

Before tramadol classification, the annual tramadol utilisation summarised in PCA in England and Wales increased from 1190.4 to 2714.7 DDDs/1000 inhabitants during 2004 and 2013; meanwhile the number of tramadol-related deaths/100000 inhabitants increased from 0.08 in 2004 to 0.42 in 2014 (Figure 6). After tramadol classification, tramadol annual utilisation decreased, and the number of tramadol-related deaths/100000 inhabitants decreased to 0.36 in 2015. A strong positive correlation was found between tramadol annual utilisation and related deaths (cross-correlation coefficient=0.9090).

299 <Insert Figure 6>

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Discussion

This study found monthly tramadol utilisation consistently increased before tramadol classification and the increasing trend did not act as a substitution of other more potent opioids because the utilisation of all strong opioids and codeine consistently increased since 2004.² Furthermore, the withdrawal of co-proxamol in 2005 did not change the increasing trend of tramadol utilisation and tramadol-related death from 2000.²³

From the IPD, the monthly incidence of tramadol users doubled and the monthly prevalence increased four-fold. The mean daily dose of tramadol prescriptions increased and more than 70% of tramadol users were existing users who had greater number of supply days than new users. Therefore, the increasing prevalence and incidence of tramadol users, higher mean daily dose and the prolonged use of tramadol were the main causes of increasing tramadol utilisation over time.

From the monthly practice-level dispensing data, the monthly tramadol utilisation decreased after tramadol classification. Once tramadol users were stratified into new and existing users in the IPD, the level of tramadol utilisation and the prevalence of tramadol users decreased after classification, but only the trend of prevalence of

319 tramadol users changed significantly after June 2014.

320

321 Overall, a similar trend between annual tramadol utilisation and the rate of
322 tramadol-related deaths was found, which is consistent with government
323 publications.^{2, 9} In short, after the launch of tramadol classification, monthly
324 prevalence and incidence, overall tramadol utilisation and the number of
325 tramadol-related deaths decreased reversing the upward trend from 2004.

326

327 The increasing tramadol utilisation may be attributed to long-term opioid utilisation
328 which is commonly observed in patients with CNCP.³ In the UK, higher doses and
329 prolonged use of strong opioids was related to increasing demands for pain relief in
330 CNCP.²⁴ In addition, a cross-sectional study conducted in Germany found that higher
331 tramadol utilisation was associated with CNCP diagnosis.¹ However, similar to other
332 opioids, there is currently no robust evidence to support the clinical effectiveness of
333 prolonged tramadol utilisation for CNCP.²⁵⁻²⁸ Moreover, evidence from post-mortem
334 toxicological analysis in the UK suggests that tramadol-related deaths were more
335 related to persistent tramadol users.²⁹⁻³¹

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337 Nevertheless, the ITSA found tramadol classification did not change the increasing

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338 trend of tramadol utilisation in existing tramadol users who had greater number of
339 supply days. In addition, the proportion of tramadol-related deaths in all opioid-related
340 deaths (10.5%) was still higher than codeine-related deaths (6.4%) in 2015, despite
341 more prescriptions for codeine being dispensed.⁹

342

343 Although indicators to monitor tramadol related deaths are needed, as tramadol has
344 been considered relatively safe comparing with other strong opioids⁸, only one of the
345 previous nested case-control studies which assessed the association between risk
346 factors and opioid-related deaths included tramadol.^{7, 8, 32, 33} Furthermore, tramadol
347 related deaths involved multiple risk factors²⁹⁻³¹, but there is currently no applicable
348 indicators to monitor tramadol utilisation and related deaths.

349

350 In the ITSA, the decreased trend in monthly tramadol utilisation was found in the
351 aggregated monthly practice-level dispensing data but not in IPD. Some reasons
352 might explain the different results derived from the two data sources. First, CPRD
353 contains prescribing records from general practices, but NHS Digital data included
354 community dispensing records, and prescriptions are not necessary always been
355 dispensed. Second, CPRD collects prescription records from selected practices
356 across the UK whereas NHS Digital obtains all dispensing data in England. There

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4 357 might be some variations in patients' characteristics and prescribers' clinical decision
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7 358 making between practices in CPRD and NHS Digital dispensing data. In fact,
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10 359 geographic variation in opioid prescribing has been found in the USA and
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12 360 Australia³⁴⁻³⁶, and it was possible that the interpretation and application of policy
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15 361 varied between practices in different regions.
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21 363 This is the first study to identify the influence of tramadol classification on its utilisation
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24 364 in the UK. To fully explore tramadol utilisation in the past 15 years, several national
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27 365 statistics and datasets as well as CPRD were used to compensate the limitations of
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30 366 each database. We used DDDs to quantify tramadol utilisation which is easy to
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33 367 compare with previous studies and understand the clinical implication as it can be
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36 368 converted into oral morphine equivalent dose by multiplying the potency ratio.³⁷
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39 369 Furthermore, to establish hypotheses for further analysis, potential reasons of
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42 370 increasing tramadol utilisation and tramadol-related deaths were identified by
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45 371 measuring both individual and population utilisation.
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50 373 There are some limitations to this research. CPRD does not included prescription
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53 374 records from secondary care and hence may underestimate tramadol utilisation,
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56 375 especially for acute tramadol use. Tramadol prescriptions outside the study period
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376 were not included and hence the new users might be over-estimated. Furthermore,
377 this cross-sectional study aimed to establish potential hypotheses for changes in
378 tramadol utilisation and deaths, but it was not intended to study the causal
379 relationship between particular utilisation patterns such as chronic use and changes
380 in tramadol utilisation. The number of tramadol-related deaths was an aggregated
381 summary retrieved from government reports and hence characteristics of
382 tramadol-related fatalities were not available to be explore.

383

384 In conclusion, the prolonged use by existing tramadol users and the increasing
385 prevalence of tramadol users led to increasing tramadol utilisation over the past
386 fifteen years in the UK. Although tramadol classification altered tramadol utilisation
387 and associated deaths, to optimise the use of tramadol in patients with CNCP, future
388 studies are needed to identify the causal relationship between patient characteristics,
389 long-term tramadol utilisation and tramadol-related deaths.

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Table

Table 1. A summary of aggregated-level data and individual patient data used in this study

Data source	Dataset	Countries and time	Extract information	Outcome measure
Aggregated-level statistics and datasets				
ONS	Deaths related to drug poisoning ⁹	England and Wales, 2004-2015	Annual number of tramadol-related deaths	Annual number of tramadol-related deaths/100000 inhabitants
ONS	Annual number of mid-year population estimates ¹⁸	England and Wales, 2004-2015	Annual number of mid-year population estimates	Annual and monthly DDD/1000 inhabitants Annual number of tramadol-related deaths/100000 inhabitants
NHS Digital	Annual Prescription Cost Analysis ¹⁶	England, 2004-2015	Annual quantity of dispensed tramadol preparations	Annual DDD/1000 inhabitants
NHS Wales*	Annual Prescription Cost Analysis ¹⁷	Wales, 2004-2015	Annual quantity of dispensed tramadol preparations	Annual DDD/1000 inhabitants
NHS Digital	Monthly practice-level dispensing data ¹⁵	England, October 2010 to September 2015	Monthly quantity of dispensed tramadol preparations	Monthly DDD/1000 inhabitants
Individual patient data				
CPRD	Therapy file	United Kingdom, January 1993 to December 2015	Tramadol prescriptions	Monthly DDD/1000 registrants Monthly incidence and prevalence/10000 registrants Annual supply days and mean daily dose
Note: ONS: Office for National Statistics, NHS: National Health Service, DDD: Defined Daily Dose, CPRD: Clinical Practice Research Datalink, *NHS Wales Shared Services Partnership				

Figure

Figure 1. Monthly prevalence and incidence of tramadol users per 10000 registrants between 2000 and 2015

Figure 2. Mean daily dose between existing and new tramadol users

Figure 3. Monthly tramadol utilisation in England between October 2010 and September 2015 in the national practice-level dispensing data

Figure 4. Monthly tramadol utilisation for existing tramadol users between October 2010 and September 2015 in the individual patient data retrieved from CPRD

Figure 5. Monthly tramadol utilisation for new tramadol users between October 2010 and September 2015 in the individual patient data retrieved from CPRD

Figure 6. Annual tramadol utilisation and the number of tramadol-related deaths in England and Wales from 2004 to 2015

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Appendices

Appendix 1. Segmented regression model

$$Y_t = \beta_0 + \beta_1 * time + \beta_2 * tramadol\ classification + \beta_3 * time\ after\ tramadol\ classification$$

Y_t is monthly tramadol utilisation, measured as monthly DDD between October 2010 and September 2015 from NHS digital practice-level dispensing data and CPRD (further stratified by incident and prevalent users).

time refers to time from October 2010 to September 2015 in a monthly base.

Tramadol classification is a binary variable and 1 to denote the time from June 2014.

Time after tramadol classification refers to time from June 2014 to September 2015 in a monthly base.

The baseline trend of monthly tramadol utilisation before classification (β_1), the change in the levels of monthly utilisation (β_2) and the change in trend of monthly tramadol utilisation after classification (β_3) were tested.

Additional time points in the policy development, including the publication of Advisory Council on the Misuse of Drugs recommendation (February 2013), commencing public consultation about tramadol classification (July 2013) and publishing results of the public consultation (March 2014) were included in the segmented regression model for sensitivity analysis.

Appendix 2. Proportion of the annual tramadol dose prescribed to existing users

Appendix 3. Annual dose and supply days between existing and new tramadol users