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Impact of adherence to antidepressants on long-term prescription opioid use cessation

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Background

Depression contributes to persistent opioid analgesic use (OAU). Treating depression may increase opioid cessation.

Aims

To determine if adherence to antidepressant medications (ADMs) *v.* non-adherence was associated with opioid cessation in patients with a new depression episode after >90 days of OAU.

Method

Patients with non-cancer, non-HIV pain ($n = 2821$), with a new episode of depression following >90 days of OAU, were eligible if they received ≥1 ADM prescription from 2002 to 2012. ADM adherence was defined as >80% of days covered. Opioid cessation was defined as ≥182 days without a prescription refill. Confounding was controlled by inverse probability of treatment weighting.

Results

In weighted data, the incidence rate of opioid cessation was significantly ($P = 0.007$) greater in patients who adhered *v.* did not adhered to taking antidepressants (57.2/1000 *v.* 45.0/1000 person-years). ADM adherence was significantly associated with opioid cessation (odds ratio (OR) = 1.24, 95% CI 1.05–1.46).

Conclusions

ADM adherence, compared with non-adherence, is associated with opioid cessation in non-cancer pain. Opioid taper and cessation may be more successful when depression is treated to remission.

Declaration of interest

None.

Long-term prescription opioid analgesic use (OAU) for chronic non-cancer pain is defined as 'daily or near-daily' use for >90 days.[1,2] Between 1.4 and 10% of patients with a new opioid prescription develop chronic OAU,[2,3] and a majority, 65–80%, of patients who have >90 days OAU, are still taking opioids 3–5 years later.[4,5] These patients are more likely than those who take opioids short term to develop opioid use disorder and overdose. Chronic OAU is also associated with new depressive episodes (NDEs)[3,6,7] and treatment-resistant depression.[6] Because depression and OAU are mutually reinforcing,[8] these patients may be in a cycle of persistent OAU, depression and pain. Research on treating depression to improve outcomes for chronic non-cancer pain is sparse. In Kroenke *et al*'s[9] Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) study, where patients were randomised to optimal depression treatment *v.* usual care, treating depression led to reduced pain severity and anxiety, improved functioning and better health-related quality of life.[9] Although SCAMP was not designed to measure change in OAU, the findings raise the possibility that depression treatment could reduce use of opioids, possibly from reduced pain or improved functioning.[9–11] Improved functioning can occur independent of pain[11] and should follow depression treatment. Independent of changes in pain severity, the need for OAU to self-regulate mood should dissipate following reduction in depression.

We are not aware of any studies that report changes in OAU following adherence to antidepressant medication (ADM) treatment in patients with chronic non-cancer pain. Using a retrospective cohort design, it is possible to test the hypothesis that adherence to ADM treatment *v.* non-adherence is associated with OAU cessation without the ethical barrier of randomising to inadequate treatment. Adherence serves as an indicator of depression improvement because patients who are non-adherent are less likely to have decreasing depression symptoms.[12] Among patients initiating ADMs, response to treatment by 24 weeks is much lower in non-adherent *v.* adherent patients (55.8 *v.* 82.5%).[13] Although it would be ideal to have 9-item Patient Health Questionnaire (PHQ-9)[14] scores for all patients at the time of ADM initiation and opioid cessation, such data was available from only a subset of patients. Therefore, we used adherence as a proxy for depression improvement. In a large cohort of Veterans Health Administration patients with NDE following >90 days of OAU, we tested the hypothesis that depression treatment adherence was associated with OAU cessation. Specifically, the objective of the current study was to determine whether patients who developed depression following chronic OAU were more likely to stop using opioids if they adhered to ADM treatment compared with patients who did not adhere to ADM treatment. In addition, exploratory analysis in a subset of patients with sufficient data was computed to assess the change in depression symptoms and pain scores over time in patients adherent to treatment with ADM compared with those who were non-adherent who did and did not stop OAU.

Method

This retrospective cohort analysis used patient data extracted from the Veterans Health Administration electronic medical record for 1 Jan 2000 to 31 Dec 2012. Data included ICD-9-CM diagnostic codes,[15] in-patient stays, out-patient visits, prescriptions dispensed records, vital signs and demographic information.

Cohort identification

A random sample of 500 000 patients was taken from a cohort of 2 910 335 identified with at least one out-patient visit in both fiscal years 1999 and 2000, and aged 18–80 years. We excluded patients over 80 because they are more likely to receive prescription opioids for end-of-life pain management and cancer pain and the risk of misclassifying depression increases because of the greater prevalence of vascular depression and depression related to

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dementia. From this sample, we excluded 151 500 patients with a cancer and/or HIV diagnosis. Patients must have had at least one yearly visit in the 2-year 'washout' period (2000–2001) during which they must have been free of a medical record depression diagnosis ($n = 266\,901$). We then selected patients with a NDE beginning in 2002–2011 and not occurring on the last out-patient visit date ($n = 31\,224$). Because our previous reports indicate >90-day OAU is associated with up to twice the risk of NDEs,[3,7] we limited the cohort to patients with >90 days of OAU or by the date of the NDE ($n = 3075$).

NDE was defined by the presence of a primary diagnosis (ICD-9-CM: 296.2, 296.3, 311) of depression in at least one in-patient stay or two out-patient visits within the same 12-month period. This algorithm has been shown to be a valid measure of depression when compared with self-report or written medical record information.[16,17] Patients without ADM treatment on or after the NDE were excluded ($n = 138$). Patients must have had >3 months follow-up after NDE diagnosis to allow for the possibility of the occurrence of least one acute-phase depression treatment period (≥84 days)[18] ($n = 2843$). The final sample included patients with complete demographic data ($n = 2821$). The cohort selection process is shown in Fig. 1.

Outcome – opioid cessation

Opioids included codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, oxycodone, oxymorphone, morphine and pentazocine. Both short-acting and long-acting formulations were included. Opioid prescription information included days supplied, quantity (e.g. pills or liquid volume) and unit dose (mg). OAU cessation was defined as a gap of at least 182 days from the end date of the last prescription.[5] OAU cessation date was the first day of this gap.

Exposure – ADM adherence

ADMs included monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclics (TCAs) and non-classified ADMs. ADM adherence was defined using proportion of days covered (PDC) from NDE to opioid cessation or censor date.[19,20] ADM prescriptions dispensed were used to create time arrays to identify days of follow-up that an ADM was available. If multiple ADMs were available in a day, that particular day was only counted once as a covered day. The PDC was calculated by taking the total number of covered days in follow-up by the total number of days in follow-up. PDC was dichotomised to standard thresholds for adherence (≥80%) and non-adherence (<80%).[19–21] To determine if patient adherence was correlated with duration of ADM treatment, we computed the number of continuous weeks of treatment. ADM use was considered continuous if there was no gap of >30 days between prescriptions dispensed and duration for all periods of continuous use in follow-up were assessed to categorise duration as ever ≥24 weeks, 12 to <23 weeks or <12 weeks.

Covariates

We included an OAU duration variable to control for duration of use at the date of NDE (3–6 months, >6 to 12 months, >12 to 24 months, >24 months). Duration was computed from the months of continuous OAU (no gap >30 days between prescriptions dispensed). The opioid morphine equivalent dose (MED) was calculated using standard conversion tables. Days supplied and quantity variables were used to calculate daily MED in follow-up. We modelled the maximum daily MED before the end of follow-up (1–50 mg, 51–100 mg, >100 mg). We controlled for comedication with benzodiazepines, which are associated with long-term opioid use,[22] and muscle relaxants, which could improve pain and functioning. Benzodiazepines included alprazolam, clonazepam, diazepam, lorazepam, chlordiazepoxide and clorazepate. Muscle relaxants included carisoprodol, cyclobenzaprine, baclofen, dantrolene, metaxalone, methocarbamol, chlorzoxazone, tizanidine and orphenadrine. Demographic variables included age, gender, ethnicity (white *v.* other), marital status (married *v.* other) and insurance coverage (Veterans Health Administration only *v.* other sources).

To control for detection bias related to more healthcare encounters, we created a healthcare utilisation variable defined as average number of out-patient clinic visits per month in follow-up. The distribution of the mean was then dichotomised into high utiliser, >75th percentile, *v.* low utiliser, ≤75th percentile. We controlled for psychiatric and physical comorbidities associated with depression[23] and/or OAU.[24–26] Comorbidities were defined using ICD-9-CM diagnostic codes. Psychiatric comorbidities included post-traumatic stress disorder and any other anxiety disorder, a composite of panic disorder, generalised anxiety disorder, social phobia, obsessive–compulsive disorder and anxiety disorder not otherwise specified. We controlled for alcohol misuse or dependence; illicit drug misuse or dependence, including opioids; and nicotine dependence. Chronic physical conditions included type 2 diabetes mellitus, hypertension, cerebrovascular disease, obesity, low testosterone, sleep apnoea and cardiovascular disease. Cardiovascular disease was a composite of hyperlipidaemia, ischaemic heart disease, disease of pulmonary circulation, other heart disease, hypertensive heart disease and myocardial infarction.

Five separate pain condition variables were created based on over 900 ICD-9-CM codes.[7,24] These conditions were arthritis, back pain, musculoskeletal pain, headaches and neuropathic pain. Pain scores, collected during routine care in the Veterans Health Administration, were on a numerical rating scale ranging from 0 to 10, with higher scores indicating greater pain intensity. In propensity score models, we adjusted for a time invariant maximum pain score before the end of follow-up to control for the highest pain level. As variability in pain scores in the Veterans Health Administration have been previously reported,[27] a time-varying pain score for each month of follow-up was used in final survival models. For the time-varying pain score assessment, the pain score was assumed to be consistent across subsequent months until a new monthly assessment was available.

Propensity scores and inverse probability of treatment weighting (IPTW) were used to balance potential confounders listed in Table 1 between ADM adherent and non-adherent treatment groups to reduce the effect of bias by indication and other sources of confounding. The propensity score is the probability of ADM adherence, given covariates and was calculated using a binary logistic regression model. Propensity scores were used to apply IPTW approaches using stabilised weights.[28–33] A stabilised weight is the marginal probability of ADM adherence divided by the propensity score for the adherent group, and (1 – marginal probability of ADM adherence) divided by (1 – propensity score) for the non-adherent group. It helps reduce bias associated with extreme weights of either individuals in the ADM adherent group with low propensity scores or those in the non-adherent group with high propensity scores. Extreme weights are associated with increased variability of the exposure effect, thus, stabilising weights helps reduce type II error rate.[34] Stabilised IPTW also preserves original sample size (i.e. does not inflate sample size in pseudo-data) in analysis thereby also preserving the type I error rate.[33] Stabilised weights were trimmed if they were ≥10, as well-behaved weights have a mean close to 1 and a maximum <10.[30,35] The mean of stabilised weights should be close to 1, extreme values indicate the propensity-score model poorly specified predictors of treatment exposure. IPTW resulted in pseudo-populations

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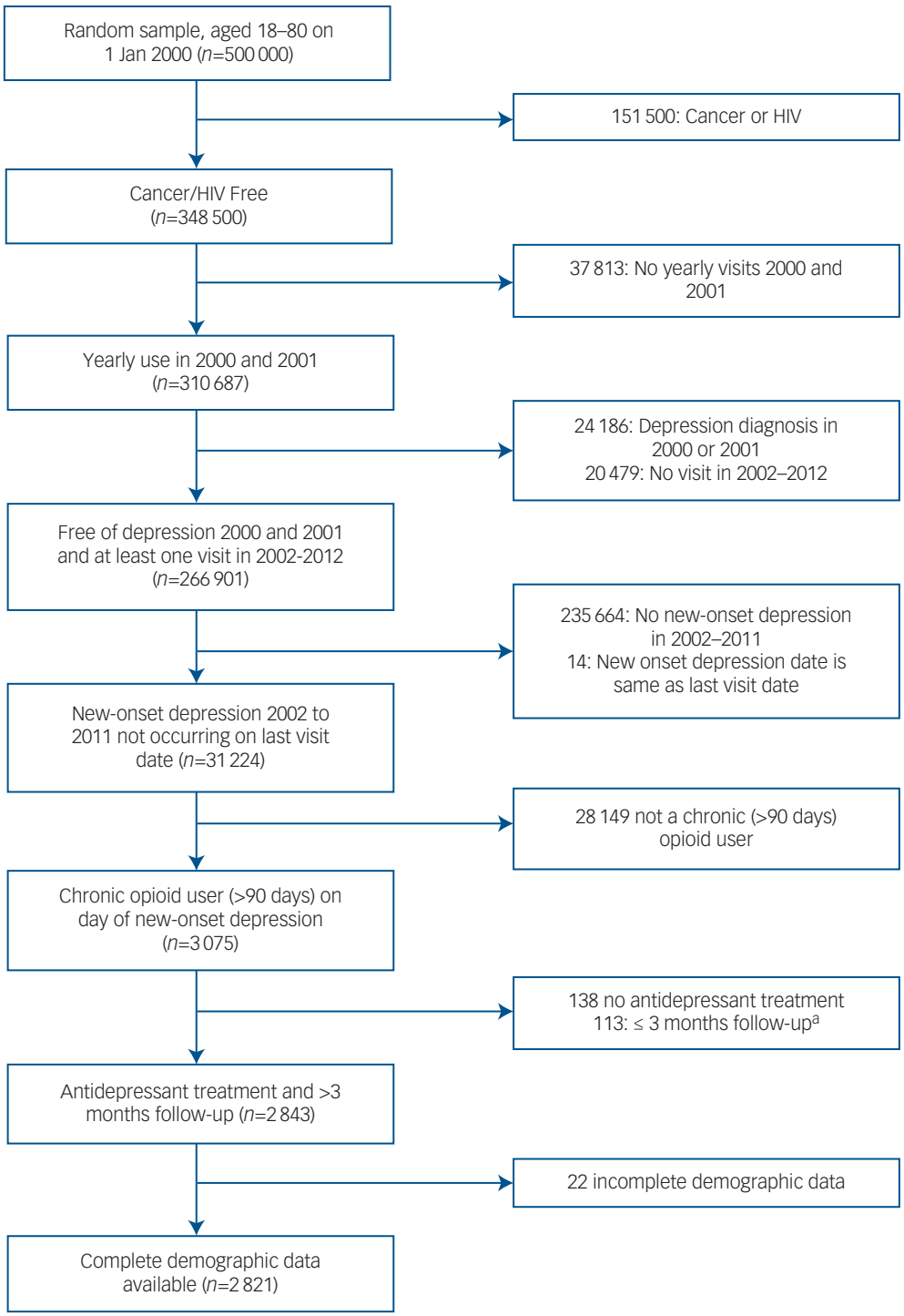

Fig. 1 Cohort selection.

[a]Groups are not mutually exclusive.

for ADM adherence groups such that covariates balanced across the two groups. Covariate balance was assessed by comparing covariate distributions between ADM adherence groups. Balance is indicated with no significant differences in the distribution of covariates between groups and by standard mean differences <10%.[34,36]

Statistical analysis

Analyses were performed with SAS v9.4 at an alpha of 0.05. Bivariate analyses, using independent samples *t*-tests for continuous variables and chi-square tests for categorical variables, assessed the relationship of covariates with ADM adherence in unweighted and weighted data. A Poisson regression model was used in unweighted and weighted data to compare opioid cessation incidence rate (person-years) between ADM adherence groups. Unweighted and weighted Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals for the relationship of ADM adherence and time to opioid cessation. Weighted analyses used stabilised weights in probability weighting. Confidence intervals and *P*-values in weighted analyses were

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Table 1 Characteristics of patients with long-term opioid use with a new depression episode (NDE) by antidepressant medication (ADM) adherence status in unweighted data, 2002–2012 ($n = 2821$)

Covariates	Overall ($n = 2821$)	ADM adherence <80% ($n = 1744$)	ADM adherence ≥80% ($n = 1077$)	*P*	SMD %
Opioid duration at time of NDE, months, *n* (%)					
3–6	404 (14.3)	272 (15.6)	132 (12.3)		–9.65
>6 to 12	519 (18.4)	334 (19.2)	185 (17.2)	**0.017**	–5.11
>12 to 24	576 (20.4)	354 (20.3)	222 (20.6)		0.77
>24	1322 (46.9)	784 (44.9)	538 (49.9)		10.02
Maximum dose, mg: *n* (%)					
1–50	449 (15.9)	285 (16.3)	164 (15.2)		–3.04
51–100	595 (21.1)	363 (20.8)	232 (21.5)	0.704	1.79
>100	1777 (63.0)	1096 (62.8)	681 (63.2)		0.81
Benzodiazepine	1570 (55.6)	935 (53.6)	635 (59.0)	**0.006**	10.80
Muscle relaxants	1559 (55.3)	956 (54.8)	603 (56.0)	0.543	2.41
Psychiatric comorbidities, *n* (%)					
Post-traumatic stress disorder	990 (35.1)	570 (32.7)	420 (39.0)	**0.001**	13.21
Other anxiety[a]	1069 (37.9)	646 (37.0)	423 (39.3)	0.235	4.61
Nicotine misuse/dependence	1761 (62.4)	1109 (63.6)	652 (60.5)	0.104	–6.29
Alcohol misuse/dependence	982 (34.8)	643 (36.9)	339 (31.5)	**0.004**	–11.38
Any illicit drug misuse/dependence	997 (35.3)	684 (39.2)	313 (29.1)	**<0.0001**	–21.55
Metabolic/cardiovascular comorbidities, *n* (%)					
Diabetes type 2	1177 (41.7)	702 (40.3)	475 (44.1)	**0.044**	7.80
Hypertension	2341 (83.0)	1425 (81.7)	916 (85.1)	**0.022**	8.98
Cardiovascular disease[b]	2471 (87.6)	1502 (86.1)	969 (90.0)	**0.003**	11.89
Cerebrovascular disease	628 (22.3)	377 (21.6)	251 (23.3)	0.295	4.05
Obesity diagnosis	1242 (44.0)	745 (42.7)	497 (46.2)	0.075	6.91
Other comorbidities					
Low testosterone	263 (9.3)	146 (8.4)	117 (10.9)	**0.027**	8.45
Sleep apnoea	543 (19.3)	308 (17.7)	235 (21.8)	**0.007**	10.46
Painful conditions, *n* (%)					
Arthritis	2640 (93.6)	1632 (93.6)	1008 (93.6)	0.987	0.04
Back pain	2612 (92.6)	1610 (92.3)	1002 (93.0)	0.478	2.76
Headaches	1111 (39.4)	686 (39.3)	425 (39.5)	0.947	0.27
Musculoskeletal pain	2304 (81.7)	1433 (82.2)	871 (80.9)	0.388	–3.35
Neuropathic pain	1467 (52.0)	890 (51.0)	577 (53.6)	0.189	5.09
Maximum pain score, mean (s.d.)	9.6 (0.9)	9.6 (0.9)	9.5 (1.0)	**0.011**	–10.02
High healthcare utilization, *n* (%)	1602 (56.8)	943 (54.1)	659 (61.2)	**<0.001**	14.44
Age, mean (s.d.)	48.9 (10.0)	48.5 (10.2)	49.7 (9.7)	**0.002**	11.84
Gender, male: *n* (%)	2576 (91.3)	1590 (91.2)	986 (91.6)	0.727	1.35
Ethnicity, White: *n* (%)	2375 (84.2)	1406 (80.6)	969 (90.0)	**<0.0001**	26.63
Insurance, Veterans Health Administration only: *n* (%)	2046 (72.5)	1294 (74.2)	752 (69.8)	**0.012**	–9.77
Marital status, married: *n* (%)	1444 (51.2)	820 (47.0)	624 (57.9)	**<0.0001**	22.00

Results in bold are significant.
SMD %, standardised mean difference per cent.
a. Other anxiety disorders: panic disorder, obsessive–compulsive disorder, social phobia, generalised anxiety disorder, anxiety not otherwise specified.
b. Cardiovascular disease, hyperlipidaemia, ischaemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction.

calculated using robust, sandwich-type variance estimators. Follow-up time was defined as months from date of NDE to date of OAU cessation or censor date, which was the last available Veterans Health Administration encounter.

The final model included variables to control for pain diagnoses and changing pain score after the initiation of ADM treatment. All pain variables and ADM adherence were modelled as time dependent. This allows ascertainment of exposure status over the multiyear observation period and permits new diagnoses and change in pain scores to contribute to the outcome. Initial evaluation of each interaction term of each covariate and follow-up time confirmed that the proportional hazards assumption was met for ADM adherence ($P = 0.11$) and pain covariates ($P > 0.05$).

This project was approved by the institutional review boards of participating institutions.

Exploratory analysis

In unweighted data, the average monthly change in PHQ-9 score and pain score across follow-up was computed using random intercept longitudinal mixed models (Proc Mixed, SAS v9.4) for four groups; (a) ADM adherent with OAU cessation ($n = 5$ PHQ-9; $n = 213$ pain scores), (b) ADM adherent without OAU cessation ($n = 96$ PHQ-9; $n = 864$ pain scores), (c) ADM non-adherent with OAU cessation ($n = 14$ PHQ-9; $n = 354$) and (d) ADM non-adherent without OAU cessation($n = 147$ PHQ-9; $n = 1390$ pain scores). Because of the lack of PHQ-9 data prior to 2008, monthly changes in PHQ-9 scores in follow-up were computed for a subset of 262 patients with NDE occurring in 2008–2012 and with at least one PHQ-9 score before end of follow-up. Time was modelled as months since NDE and models included all available pain and PHQ-9 data in follow-up.

Results

In unweighted data, a Fisher's exact test of independence revealed ADM adherence and duration were highly related ($P < 0.0001$, results not shown). Among 1077 patients who were adherent, 0.2% received continuous ADM for less than 12 weeks, 4.4%

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received an ADM for 12 to <24 weeks and 95.5% for at least 24 weeks. Among 1744 patients who were non-adherent, 15.0% received ADM for less than 12 weeks, 19.0% for 12 to <24 weeks and 66.1% for at least 24 weeks.

Figure 2 shows that the overall unweighted incidence rate for OAU cessation was 48.4 per 1000 person-years, with no significant differences between ADM adherent (50.2/1000 person-years) and non-adherent (47.4/1000 person-years) groups ($P = 0.496$). However, after weighting data using IPTW techniques, the incidence rate of OAU cessation was higher for ADM adherent (57.2/1000 person-years) compared with non-adherent (45.0/1000 person-years) groups ($P = 0.007$).

Unweighted distributions of covariates by ADM adherence are shown in Table 1. Among those individuals taking opioids for >90 day with a NDE receiving ADM treatment, almost half (46.9%) had taken opioids for more than 2 years (>24 months) at the time of the NDE. Almost two-thirds (63.0%) reached a maximum MED of >100 mg. Maximum dose achieved was similar ($P = 0.704$) in ADM adherent and non-adherent groups. Benzodiazepine comedication with ADM was significantly more prevalent among ADM adherent (59.0%) *v.* non-adherent (53.6%) groups. Comorbidities that were significantly more prevalent among ADM adherent compared with non-adherent groups were post-traumatic stress disorder, type 2 diabetes, hypertension, cardiovascular disease, low testosterone and sleep apnoea. Alcohol and illicit drug misuse/dependence were more prevalent among the non-adherent group. Patients in the ADM adherent compared with the non-adherent group were significantly older, White, married, more likely to have other insurance in addition to Veterans Health Administration insurance and have higher healthcare utilisation.

After applying IPTW, all covariates balanced and were not significantly different between the ADM adherent and non-adherent groups (Table 2). IPTW stabilised weights ranged from 0.54 to 3.15, with a mean of 1.00 (s.d. = 0.25) and median of 0.95 (interquartile range (IQR) = 0.83–1.11). The standardised mean differences (SMDs) after weighting were all <10%. Good balance was achieved given differences between treatment groups were all non-significant and all SMDs were <10%.

Results of unweighted and weighted Cox proportional hazards models estimating the association between ADM adherence and time to OAU cessation are shown in Table 3. In unweighted data, there was no relationship of ADM adherence and time to OAU cessation (hazard ratio (HR) = 1.05, 95% CI = 0.88–1.24). However, after weighting and adjusting for changes in pain scores and pain diagnoses that could occur after ADM initiation, adherence was associated with a 24% increased likelihood of OAU cessation compared with non-adherence (HR = 1.24, 95% CI = 1.05–1.46)

Longitudinal linear growth curves for PHQ-9 score among a subset of 262 patients by ADM adherent and OAU cessation groups are shown in Fig. 3(a). At time of NDE, mean PHQ-9 scores were not significantly different between groups ($P = 0.995$). Overall, there was a trend for a monthly decrease in PHQ-9 score ($P = 0.08$). Average monthly decrease in PHQ-9 scores was largest for the ADM adherent group with OAU cessation ($\beta = -0.60$, 95% CI −1.33 to 0.12) followed by the ADM non-adherent group with OAU cessation ($\beta = -0.21$, 95% CI −0.53 to 0.10), ADM adherent group without OAU cessation ($\beta = -0.13$, 95% CI = −0.21 to −0.04), and ADM non-adherent group without OAU cessation ($\beta = -0.06$, 95% CI −0.12 to 0.01). However, time trend slopes were not statistically different ($P = 0.23$).

Longitudinal linear growth curves for pain scores in follow-up among the entire sample of 2821 patients are shown in Fig. 3b. The ADM non-adherent group with OAU cessation had significantly higher pain scores than the other three groups at time of

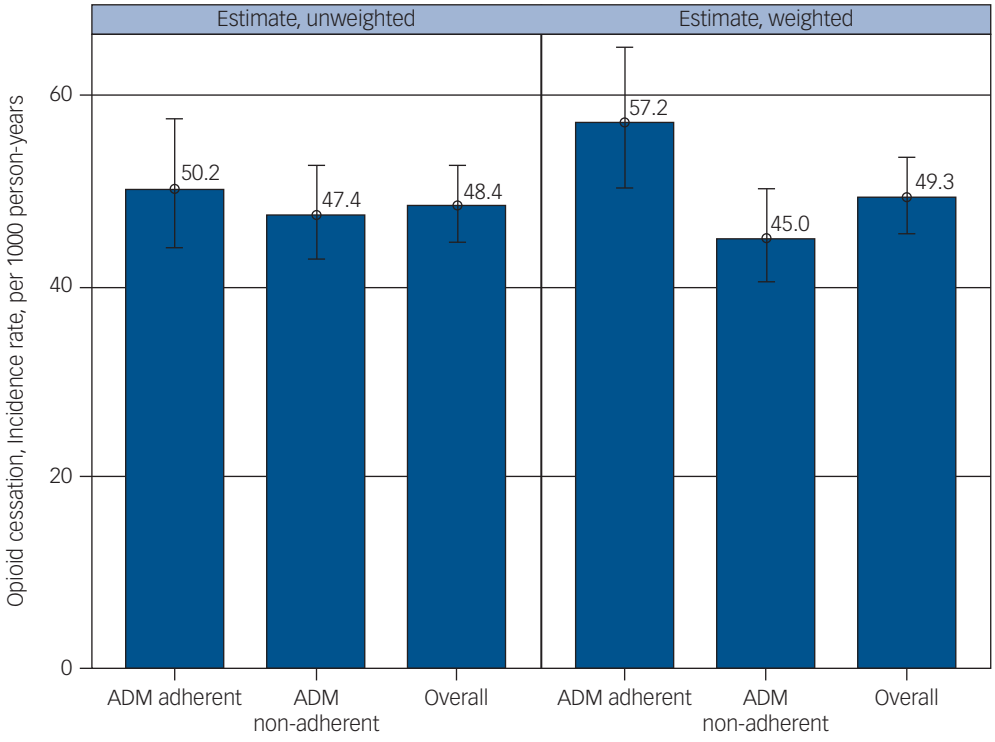

Fig. 2 Antidepressant adherence, non-adherence and prescription incidence of opioids.

ADM, antidepressant medication.

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Table 2 Weighted association of covariates with antidepressant medication (ADM) treatment adherence, weighted by inverse probability of ADM treatment adherence, in patients with chronic opioid use (>90 days) at time of new depression episode (NDE, 2002–2012; *n* = 2821)

Covariates	ADM adherence <80% (*n* = 1744)	ADM adherence ≥80% (*n* = 1077)	*P*	SMD %
Opioid duration at time of NDE, months: %				
3–6	14.2	13.7		−1.38
>6 to 12	18.4	18.2	0.982	−0.36
>12 to 24	20.4	20.7		0.57
>24	47.0	47.4		0.80
Maximum dose, mg: %				
1–50	15.9	15.5		−1.13
51–100	21.1	21.4	0.952	0.73
>100	63.0	63.2		0.21
Benzodiazepine	55.7	55.7	0.973	0.14
Muscle relaxer	55.2	54.8	0.828	−0.80
Psychiatric comorbidities, %				
Post-traumatic stress disorder	34.9	34.8	0.959	−0.10
Other anxiety[a]	37.9	38.2	0.891	0.60
Nicotine misuse/dependence	62.1	61.4	0.722	−1.34
Alcohol misuse/dependence	34.6	34.4	0.890	−0.52
Any illicit drug misuse/dependence	35.4	35.5	0.949	0.12
Metabolic/cardiovascular comorbidities				
Diabetes type II	41.8	42.1	0.894	0.55
Hypertension	83.0	83.3	0.864	0.72
Cardiovascular disease[b]	87.6	87.8	0.887	0.52
Cerebrovascular disease	22.0	21.7	0.834	−0.77
Obesity diagnosis	43.8	43.9	0.957	0.26
Other comorbidities, %				
Low testosterone	9.4	9.5	0.883	0.55
Sleep apnoea	19.0	18.6	0.773	−1.13
Painful conditions, %				
Arthritis	93.5	93.5	0.982	0.04
Back pain	92.5	92.6	0.901	0.34
Headaches	39.4	39.5	0.952	0.24
Musculoskeletal pain	81.7	81.6	0.938	−0.28
Neuropathic pain	52.0	52.4	0.845	0.80
Maximum pain score, mean (s.d.)	9.6 (0.9)	9.6 (0.9)	0.973	−0.18
High healthcare utilisation, %	56.7	56.7	0.993	−0.06
Age, years: mean (s.d.)	48.9 (10.3)	49.0 (9.7)	0.923	0.43
Gender, male: %	91.2	91.3	0.967	0.14
Ethnicity, White: %	84.2	84.2	0.988	0.08
Insurance, Veterans Health Administration only, %	72.7	72.8	0.963	0.13
Marital status, married, %	51.2	51.6	0.843	−5.52

SMD %, standardised mean difference per cent.
a. Other anxiety disorders: panic disorder, obsessive–compulsive disorder, social phobia, generalised anxiety disorder, anxiety not otherwise specified.
b. Cardiovascular disease, hyperlipidaemia, ischaemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction.

Table 3 Results from Cox proportional hazards models estimating the association between antidepressant medication (ADM) adherence and opioid cessation among patients with chronic opioid use ((>90 days) with a new depression episode (NDE, 2002–2012) (*n* = 2821).

	Hazard ratio (95% CI)		
Variable	Model 1 – Crude[a]	Model 2 – Weighted[b]	Model 3 – Weighted + Pain[c]
ADM adherence ≥80%	1.05 (0.88–1.24)	**1.24 (1.05–1.46)**	**1.24 (1.05–1.46)**
Arthritis			0.97 (0.73–1.30)
Back pain			0.77 (0.59–1.01)
Headache			1.13 (0.95–1.33)
Musculoskeletal pain			1.09 (0.88–1.34)
Neuropathy			0.96 (0.81–1.13)
Pain score			1.02 (0.99–1.05)

Results in bold are significant.
a. Unweighted data.
b. Inverse probability of adherence weighted data to control for confounding factors shown in Table 1.
c. Additional adjustment for painful conditions and pain scores after date of ADM initiation.

NDE ($P = 0.0003$). Results indicated there was an overall significant monthly decrease in pain score across follow-up ($P = 0.002$) and that these monthly changes were different between groups ($P = 0.01$), however, these changes were relatively flat (β range −0.0004 to 0.009).

Discussion

In a cohort of 2821 Veterans Health Administration patients who developed NDE after >90 days of prescription OAU and who

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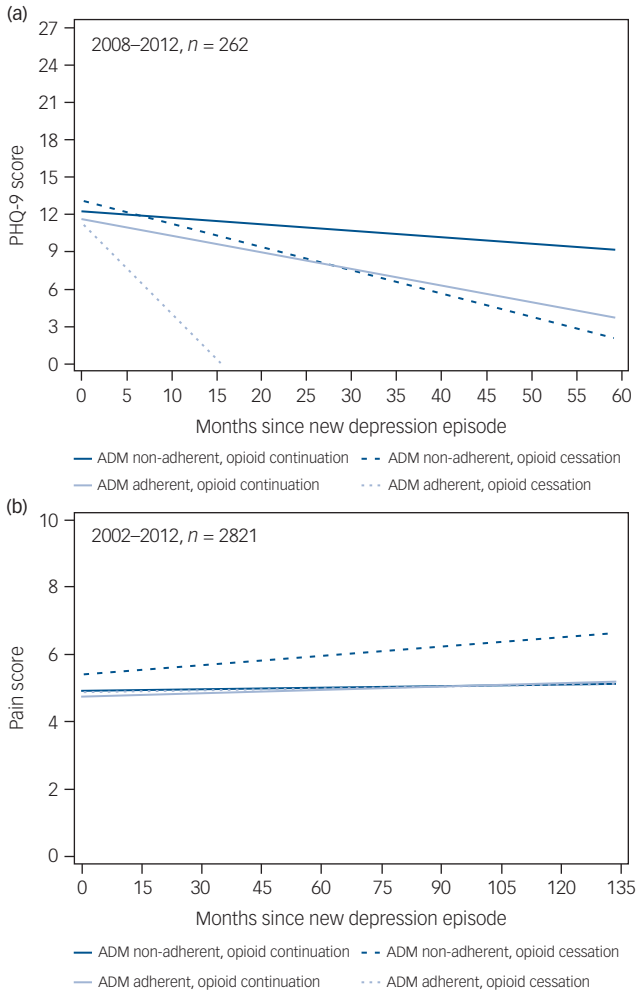

Fig. 3 Change in (a) 9-item Patient Health Questionnaire (PHQ-9) scores and (b) pain scores over time in the study groups.

The four study groups were antidepressant medication (ADM) adherent, opioid continuation; ADM adherent, opioid cessation; ADM non-adherent, opioid continuation; and ADM non-adherent, opioid cessation.

received at least one ADM prescription, we observed adherence *v.* non-adherence to ADM treatment was associated with a 24% greater likelihood of opioid cessation. The ADM adherent *v.* non-adherent group had a significantly greater incidence rate of OAU cessation (57.2/1000 *v.* 45.0/1000 person years; $P = 0.007$). These results were observed after balancing factors associated with ADM. We also controlled for confounding by pain that could persist during ADM treatment.

Exploratory analysis indicates that the ADM adherent group who stopped taking opioids experienced a rapid and greater decline in depression symptoms compared with patients who did not stop taking opioids, regardless of adherence; however, these results are preliminary because cell sizes were very small for OAU cessation groups. Monthly pain scores were significantly higher among the ADM non-adherent group with OAU cessation compared with the other ADM adherent, non-adherent/opioid cessation-no cessation groups, but the size of the difference was not clinically meaningful. Adjusting for maximum pain scores after ADM initiation in the full Cox proportional hazard models did not change the association between ADM adherence and opioid cessation. Together, these results provide preliminary evidence that a reduction in depression may lead to OAU cessation. Stronger evidence indicates change in pain scores does not explain the association between ADM adherence and opioid cessation.

Interestingly, ADM adherent and non-adherent groups who stopped OAU had the steepest reductions in depression symptoms across follow-up. Because response to antidepressant treatment is markedly greater in those individuals who are adherent *v.* non-adherent,[12,13] we speculate people who are ADM non-adherent may have decreased PHQ-9 scores because of OAU cessation. This would be consistent with the evidence for a bidirectional relationship between OAU and depression.[8] Prospective studies are warranted to verify this finding.

Patients with comorbid pain and depression may remain on opioids in an attempt to self-medicate mood[37] and to avoid depression during opioid withdrawal.[38] Patients with depression are more likely to drop-out of opioid taper, and withdrawal symptoms are exacerbated in patients with current depression.[38] Thus, another explanation for our findings may be related to improved depression leading to decreasing attempts to self-medicate mood and greater probability of completing opioid taper.

ADM adherence may be a proxy for overall adherence to medical treatment, the 'healthy adherer' effect.[39] These patients may adhere to physician instructions to end OAU, adhere to other forms of pain management or begin opioid substitution treatment.

Limitations

It is possible that unmeasured confounders were not included in the propensity score and we violated the exchangeability assumption.[34] For instance we do not have personality measures or indicators of an orientation toward health that might predict both adherence to antidepressants and contribute to opioid cessation. Thus, unmeasured confounding is a limitation. The cohort was a majority male, Veterans Health Administration patient population, which could limit generalizability to non-Veterans Health Administration patients. However, we have previously found that the association between duration of OAU and NDEs in Veterans Health Administration patients was replicated in two private-sector cohorts,[3] and the association between opioid use *v.* no use and risk of depression recurrence in Veterans Health Administration patients was replicated in a private-sector cohort.[40] This suggests our findings could be replicated in private-sector cohorts. OAU was based on prescriptions dispensed and we were unable to determine whether patients took their medication as prescribed. Some OAU could be misclassified if patients transitioned to non-Veterans Health Administration or illicit sources for opioids.

Some antidepressants such as TCAs and duloxetine are used in pain management,[41,42] but ADM management for analgesia is not designed to treat depression. Our conclusions were consistent in *post hoc* analysis comparing adherence to TCAs/duloxetine only *v.* adherence to other ADMs, indicating our findings were not as a result of adherence to only ADMs commonly used in pain management.

Implications

ADM adherence was associated with increased likelihood of OAU cessation in individuals with chronic use of opioids and this association was independent of duration of opioid use, maximum MED, pain and numerous comorbid conditions. Several studies have reported that the majority of people who take opioids for >90 days remain on opioids for 3–5 years.[4,5] In our cohort, 47% took them for >2 years. Thus, OAU cessation following adherent ADM treatment occurred in a patient cohort with a low probability of OAU cessation. We computed the number-needed-to-treat and

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found for every 20 patients adherent to ADMs, one patient will stop OAU who would not have stopped if they were non-adherent.

Treatment of opioid dependence in patients with comorbid depression may be successful following effective depression treatment. Preliminary evidence suggests OAU cessation may also contribute to improvement in depression. Therefore, opioid taper paired with ADM could result in a faster reduction of depression symptoms and increase likelihood of successful OAU cessation. Prospective data collection to obtain detailed depression and functioning measures, change in OAU and treatment trials are needed to confirm our findings.

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poems

These halls

Charles Cooper

I think therefore I am,
I walk these halls alone,
my footstep's echo wanes
in this grand, vacant house.

I walk these halls alone,
the only comfort drawn
in this abandoned house
is my own absent mind.

The only comfort drawn,
was when I chose to doubt
in my own absent mind,
as I came to discern.

So long imprisoned by
'I think therefore I am,'
I soon came to discern
that I am not my thoughts.

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