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Prescription stimulant use during long-term opioid therapy and risk for opioid use disorder

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ABSTRACT

Background: Concurrent therapeutic prescribing of prescription stimulants with opioid analgesics is increasing in the United States. Stimulant medication use is associated with increased risk for long-term opioid therapy (LTOT), and LTOT is associated with increased risk for opioid use disorder (OUD).

Aims: To determine if stimulant prescriptions among those with LTOT (≥90 days) are associated with greater risk for opioid use disorder (OUD).

Methods: This retrospective cohort study from 2010 to 2018 used a United States, nationally distributed Optum© analytics Integrated Claims-Clinical dataset. Patients ≥18 years of age, and free of prevalent OUD in the two years prior to index were eligible. All patients had a new ≥90-day opioid prescription. The index date was day 91. We compared risk for new OUD diagnoses in patients with and without a prescription stimulant overlapping LTOT. Entropy balancing and weighting controlled for confounding factors.

Results: Patients (n = 5,712), were 57.7 (SD±14.9) years of age on average, majority female (59.8%) and 73.3% White race. Among patients with LTOT, 2.8% had overlapping stimulant prescriptions. Before controlling for confounding, dual stimulant-opioid prescriptions, compared to opioid only, were associated with OUD risk (HR = 1.75; 95%CI:1.17-2.61). After controlling for confounding, this association was no longer present (HR = 0.89; 95%CI:0.47-1.71). Results did not differ in sensitivity analyses limiting the cohort to those <56 years of age.

Conclusions: Dual stimulant use among patients with LTOT does not increase risk for OUD. Stimulants prescribed for ADHD and other conditions may not worsen opioid outcomes for some patients with LTOT.

1. Introduction

In the United States and elsewhere, prescriptions for stimulants that overlap with opioid prescriptions are increasing. About 5% of adult Medicaid patients with attention-deficient/ hyperactivity disorder (ADHD) had long-term dual stimulant-opioid use (Wei et al., 2018). In Denmark, a 4-fold increase in dual use was observed between 2000 and 2012 (Ormhøj et al., 2018).

Consistent with increasing rates of dual use, Quinn et al. (2017) observed patients prescribed a stimulant medication, compared to those

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who were not, were more likely to start a prescription opioid and transition to long-term opioid therapy (LTOT). Although speculative, this finding may be partly due to the higher prevalence of common chronic pain conditions, such as arthritis, headache, back and neck pain in those with ADHD (the primary indication for stimulant therapy) as compared to controls (Kutuk et al., 2018; Kasahara et al., 2021). Patients with ADHD, compared to without, experience greater pain sensitivity and pain interference and are more likely to have multisite pain and fibromyalgia (Stray et al., 2013; Lensing et al., 2015; Skrove et al., 2015; Stickley et al., 2016; Van Rensburg et al., 2018).

Beyond the generally increased risk of substance use disorder among patients with ADHD, (Charach et al., 2011; Lee et al., 2011) the high burden of pain in ADHD, likely contributes to risk for LTOT and opioid use disorder (OUD), specifically. However, front-line stimulant medications for ADHD, such as methylphenidate, increase pain tolerance in controlled human laboratory studies (Pud et al., 2017) and adult patients with ADHD treated with stimulants, compared to those not treated, have a lower prevalence of chronic pain (Asztély et al., 2019). Therefore, stimulant treatment may reduce risk for OUD by limiting need for LTOT. We are not aware of studies that have investigated whether stimulant prescriptions for any reason, not just ADHD, among adult patients receiving prescription opioids are associated with increased risk for OUD.

Given the uncertain association between stimulant prescribing during LTOT and OUD risk, paired with evidence that dual stimulant-opioid prescribing is increasing, it is important to public health and clinical care to determine the relationship between dual prescription stimulant-LTOT and risk for OUD. Among patients with non-cancer pain and >90-day opioid prescriptions, we first determined if patients who had stimulant prescriptions overlapping with LTOT, compared to LTOT alone, had a greater risk for OUD. Second, we determined if stimulant prescriptions overlapping with LTOT, compared to LTOT alone, was associated with lower risk for OUD, independent of ADHD, other conditions for which stimulants are prescribed, and other potential confounding factors. Because stimulant medications are associated with greater risk for LTOT (Quinn et al., 2017), we hypothesized that risk for OUD would be greater in patients with concurrent stimulant prescriptions and LTOT, compared to LTOT alone.

2. Materials and methods

2.1. Source of data

For this retrospective cohort study, we identified the eligible sample from a leased Optum© analytics database. The Optum database available to investigators contained de-identifed electronic health records (EHR) from a random sample of 5 million adult (≥18 years of age) patients with medical encounters in health systems across the United States that occurred between 2010-2018. The last year of available data was 2018. Of these patients, approximately 18% are part of Optum's de-identified Integrated Claims-Clinical dataset (n = 897,513) which includes data from EHR and medical claims.

The EHR and claims data included outpatient and inpatient encounters from academic and non-academic healthcare systems. The data included patients with private, government or no health insurance. Study variables were created from diagnoses measured with ICD-9-CM and ICD-10-CM codes, pharmacy fills, prescription orders, vital signs, laboratory results, demographics and geographic region.

2.2. Eligible cohort

Patients entered the cohort at the start of a new LTOT period (i.e., > 90-day opioid prescription). The index date was the 91st LTOT day. The earliest cohort entry was 1/1/2012 (index date = 3/31/12) to allow for a 2-year look-back period and the last date of cohort entry was 9/30/16 (index date = 12/31/16) to allow all patients at least 2 years to develop OUD. Eligible subjects had ≥ 1 health care encounter in the 2-years prior to cohort entry and were free of opioid use for 6-months prior to a new opioid prescription. The 6-month period without an opioid is a standard time frame to define a new episode of opioid use (Edlund et al., 2014; Salas et al., 2020; Scherrer et al., 2020). We required at least one opioid fill between 1/1/2012 and 9/30/2016 and eligible patients' new episode of opioid prescription must have continued for >90 days. Prescription opioids were considered to be continuously prescribed if there was no gap > 30 days between fills. We measured days covered, (i.e., days with an available prescribed opioid) and counted overlapping opioid prescriptions once. For any early refills we counted days covered from date of fill.

In the 2-year look-back period through index date, we excluded patients with prevalent OUD, cancer, or HIV. The latter two exclusions were designed to focus on opioid prescriptions for non-cancer pain. Patients must have been ≥ 18 years of age at cohort entry. Patients must have had ≥ 1 clinic encounter(s) or medical claim(s) after index. We excluded 5 patients with missing demographic measures resulting in an analytic cohort of 5,712 patients free of prevalent OUD and starting a new period of LTOT. The study design is illustrated in Fig. 1 and the sampling approach is shown in Fig. 2.

2.3. Variables

Detailed definitions for all variables used in this study are shown in supplementary e- table 1.

2.4. Outcome

New onset OUD, not in remission, was defined by any of the following ICD-9 codes: 304.00, 304.01, 304.02, 305.50, 305.51, 305.52, or any of the following ICD-10 codes: F11.1x, F11.20, F11.22x, F11.23, F11.24, F11.25x, F11.28x, F11.29.

2.5. Exposures

Prescription opioids included immediate and extended-release formulations for the following opioids: codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, tapentadol, and tramadol. We did not include buprenorphine but did include methadone. Compared to buprenorphine it is easier to determine when methadone is prescribed for OUD vs. pain. Methadone for OUD is a procedure code which means methadone prescriptions were for pain.

Stimulant medication included immediate and extended release formulations for amphetamine, dextroamphetamine, dexmethylphenidate, methylphenidate or lisdexamfetamine. For descriptive analyses, the average methylphenidate equivalent unit dose (MEU) was computed for each medication. We allowed stimulant prescriptions or fills to begin prior to opioid use. Dual stimulant-opioid use was considered present if the stimulant prescription or fill overlapped with the first 90 days of an active opioid prescription. Non-stimulant users were defined as those without a stimulant prescription or fill in the first 90 days of opioid use.

All patients had opioid fill data. We used opioid fill data from medical claims to compute LTOT because claims data contains days supply and date of fill. We used both prescription orders and claims to remove any prevalent opioid use prior to the new period of LTOT and to measure overlapping stimulant prescriptions.

2.6. Potential confounding variables

Potential confounders were measured in the two-years prior to cohort entry through the index date, unless otherwise indicated, see supplementary e-table 1 for detailed variable definitions. We controlled for patient characteristics previously shown, or posited, to be associ-

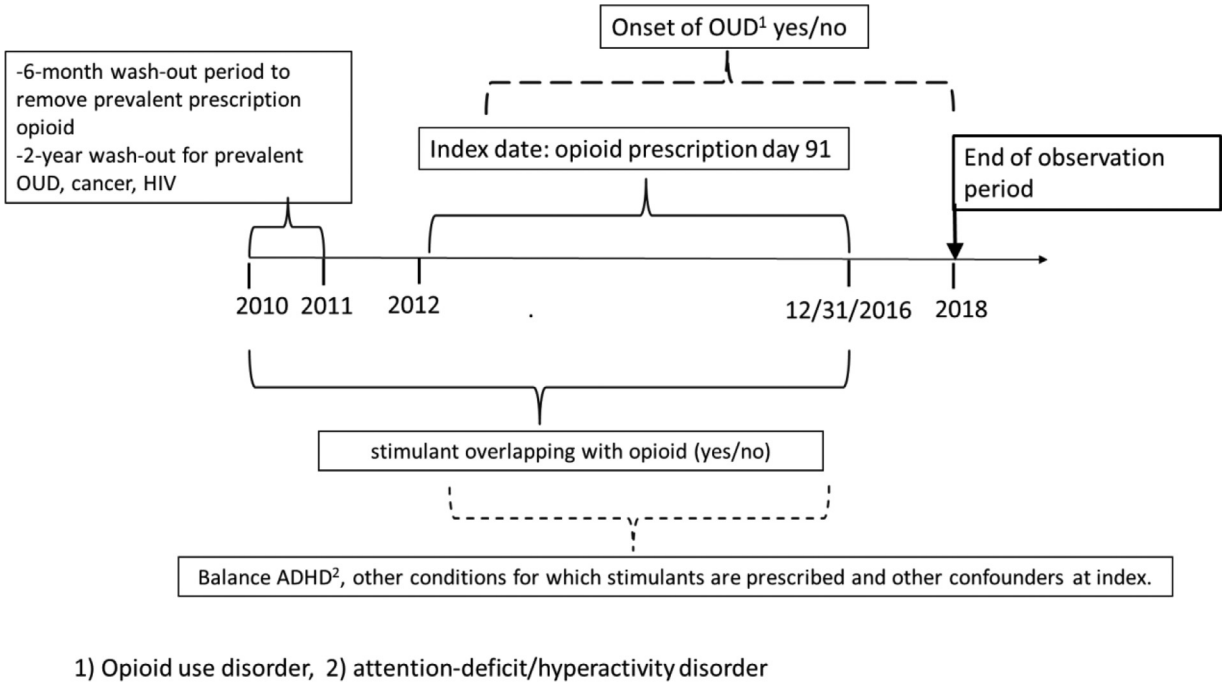

Fig. 1. Dynamic Retrospective cohort design.

ated with dual stimulant-opioid use and OUD. Demographic variables included age, sex and race. We controlled for the year of index date because of the changing prevalence of opioid and stimulant prescribing during this time. Because prescribing practices vary across the United States, we controlled for geographic regions defined as Midwest, Northeast, South, West and other/unknown. Patients who use more health care may be more likely to receive a diagnosis; therefore, we controlled for volume of health care use. This was measured by categorizing the top 25th percentile of the distribution of average visits per month in the 2 years prior to index as high utilization vs. low utilization (bottom 75th percentile).

The maximum morphine milligram equivalent (MME) opioid dose during the first 90 days was computed for each type of opioid prescription and categorized into 1-50 MME, 51-90 MME, 91-180 MME and >180 MME. We followed Seal et al's (Seal et al., 2012) definition of pain conditions for which an opioid can be prescribed and combined pain conditions into the following categories: arthritis, back pain, musculoskeletal pain, neuropathy and headache. The Charlson Comorbidity index was used to adjust for morbidity and mortality risk (Charlson et al., 1987, Quan et al., 2005, Sharabiani et al., 2012).

Conditions for which stimulants may be prescribed and for which we adjusted included ADHD, depression, obesity, traumatic brain injury, fatigue, narcolepsy and sleep disorders. We also adjusted for comorbid psychiatric disorders including any anxiety disorder, dysthymia, bipolar disorder, schizophrenia, personality disorder, alcohol abuse/dependence, drug abuse/dependence and nicotine dependence/smoking. Lastly, we controlled for benzodiazepine co-medication during the first 90 days of opioid use.

2.7. Analytic approach

All primary analyses were performed with SAS v9.4 (SAS Institute, Cary, NC) at a two-tailed alpha = 0.05. Variable distributions are presented as means (±standard deviation (sd)) or frequency and percent. This was an intention to treat analyses where stimulant use was assigned at index as if randomized to dual use or not.

2.8. Entropy balancing and weighting

Dual stimulant-opioid use is not random because patient characteristics (e.g., ADHD, depression) are associated with odds of receiving prescriptions. Therefore we weighted data via entropy balancing (e-balance) to balance potential confounders (i.e. all variables shown in Table 1) between those who were and were not dual stimulant-opioid users (Hainmueller, 2012; Hainmueller and Xu, 2013). This method can achieve better balance over other commonly used methods (e.g., propensity scores and inverse probability of treatment weighting) because e-balance does not rely on correctly specifying propensity score models. In contrast to propensity score weighting, e-balance reweights the non-stimulant group by deriving weights so that specified covariate moments (e.g., mean, variance) match the stimulant user group. E-balance was conducted in STATA v16.1 using the 'ebalance' command (StataCorp, College Station, TX). Balance was evaluated using the standardized mean difference percent (SMD% = 100*SMD). Well-balanced covariates have an SMD% < 10% (Austin and Stuart, 2015).

2.9. Primary analysis

Bivariate comparisons between covariates and dual vs. no dual stimulant use were performed using chi-square tests for categorical variables and independent samples t-tests for continuous variables. SMD% before and after e-balance assessed covariate balance. Cox proportional hazard models before and after weighting were used to calculate hazard ratios and 95% confidence intervals for the association of dual stimulant-LTOT, compared to LTOT alone, and risk of new OUD. Crude, bivariate models were computed to estimate the association of each covariate with time to OUD prior to controlling for confounding. Weighted models used robust, sandwich-type variance estimators for confidence intervals.(Austin and Stuart, 2015) The 'zph' option was used in 'Proc Phreg' to request diagnostics for checking the proportional hazards assumption using global tests. The assumption was met for both unweighted ($p = .154$) and weighted models ($p = .111$) as well as each crude bivariate model (all $p > 0.10$).

Table 1
Demographic and Baseline characteristics (%) of new long-term OAU users, overall and by dual stimulant use.

Covariates	Overall (n = 5,712)	No STIM (n = 5,554)	Dual STIM (n = 158)	p-value	SMD%
Index date year					
2012	1000 (17.5)	978 (17.6)	22 (13.9)		-10.1
2013	1166 (20.4)	1137 (20.5)	29 (18.4)		-5.4
2014	1189 (20.8)	1157 (20.8)	32 (20.3)	.269	-1.4
2015	1014 (17.8)	976 (17.6)	38 (24.1)		16.0
2016	1343 (23.5)	1306 (23.5)	37 (23.4)		-0.2
Sociodemographic-related					
Age, mean (±sd)	57.7 (±14.9)	58.1 (±14.8)	46.7 (±14.1)	<.0001	-78.2
Female sex	3415 (59.8)	3306 (59.5)	109 (69.0)	.017	19.8
Race					
White	4187 (73.3)	4052 (73.0)	135 (85.4)		31.1
Black	483 (8.5)	482 (8.7)	< 5	.0002	-38.9
Other/Unknown	1042 (18.2)	1020 (18.4)	22 (13.9)		-12.1
Region					
Midwest	1920 (33.6)	1876 (33.8)	44 (27.9)		-12.9
Northeast	544 (9.5)	529 (9.5)	15 (9.5)		-0.1
South	2353 (41.2)	2284 (41.1)	69 (43.7)	.405	5.2
West	683 (12.0)	658 (11.8)	25 (15.8)		11.5
Other/unknown	212 (3.7)	207 (3.7)	5 (3.2)		-3.1
High healthcare utilization	1428 (25.0)	1382 (24.9)	46 (29.1)	.226	9.5
OAU-related					
Maximum daily MME (mg) [a]					
1-50	2831 (49.6)	2765 (49.8)	66 (41.8)		-16.1
51-90	1403 (24.6)	1354 (24.4)	49 (31.0)	.026	14.9
91-180	941 (16.5)	920 (16.6)	21 (13.3)		-9.2
> 180	537 (9.4)	515 (9.3)	22 (13.9)		14.6
Comorbidities [b]					
Arthritis	3772 (66.0)	3684 (66.3)	88 (55.7)	.005	-21.9
Back pain	3893 (68.2)	3772 (67.9)	121 (76.6)	.021	19.5
Muscle pain	3605 (63.1)	3505 (63.1)	100 (63.3)	.962	0.4
Neuropathy	1095 (19.2)	1065 (19.2)	30 (19.0)	.953	-0.5
Headache	1139 (19.9)	1102 (19.8)	37 (23.4)	.267	8.7
Charlson index, mean(±sd)	1.6 (±2.1)	1.6 (±2.1)	0.9 (±1.7)	<.0001	-38.4
Obese	1553 (27.2)	1519 (27.3)	34 (21.5)	.104	-13.6
Traumatic brain injury	308 (5.4)	298 (5.4)	10 (6.3)	.597	4.1
Fatigue	1340 (23.5)	1290 (23.2)	50 (31.6)	.014	18.9
ADHD	137 (2.4)	49 (0.9)	88 (55.7)	<.0001	153.4
Depression	1094 (19.2)	1041 (18.7)	53 (33.5)	<.0001	34.2
Anxiety disorders[c] and or PTSD	1101 (19.3)	1047 (18.8)	54 (34.2)	<.0001	35.3
Dysthymia	188 (3.3)	179 (3.2)	9 (5.7)	.086	12.0
Bipolar disorder	220 (3.9)	204 (3.7)	16 (10.1)	<.0001	25.7
Schizophrenia	53 (0.9)	52 (0.9)	< 5	.695	-3.4
Personality disorder	39 (0.7)	34 (0.6)	5 (3.2)	.0001	18.8
Narcolepsy	11 (0.2)	< 5	7 (4.4)	<.0001	29.7
Other sleep disorder	1442 (25.3)	1397 (25.2)	45 (28.5)	.342	7.5
Alcohol abuse/dependence	195 (3.4)	193 (3.5)	< 5	.132	-14.6
Drug abuse/dependence	155 (2.7)	150 (2.7)	5 (3.2)	.724	2.8
Nicotine dependence/smoking	1575 (27.6)	1545 (27.8)	30 (19.0)	.014	-21.0
Benzodiazepine co-medication[d]	1593 (27.9)	1522 (27.4)	71 (44.9)	<.0001	37.1

[a] MME = morphine milligram equivalent – maximum dose reached in first 90 days of new long-term OAU use (OAU start to index date)
[b] Comorbidities measured from 2-years prior to index to index date
[c] Anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS
[d] Benzodiazepine co-med = Fill or prescription during first 90 days of new long-term OAU (OAU start to index date)

2.10. Follow-up time

Follow-up time was defined as months from index date to new onset OUD or censoring. Among patients not developing OUD in follow-up, censoring was defined as the last available claim or encounter.

2.11. Sensitivity analysis

Because the risk for prescription stimulant and opioid misuse and OUD are more prevalent in younger patients, we conducted sensitivity analyses by limiting the cohort to the <75th percentile for age in dual stimulant-opioid users (< 56 years of age; n = 2,534). Data were reweighted using e-balance and weighted Cox proportional hazard models were conducted to assess the dual stimulant-risk for OUD association in this younger cohort.

Post-hoc sensitivity analyses were computed to adjust for the number of different types of opioids prescribed in the first 90 days of opioid use and to determine if risk for OUD differed after accounting for receipt of immediate release (IR) vs. extended release (ER) formulations.

2.12. Ethics statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human

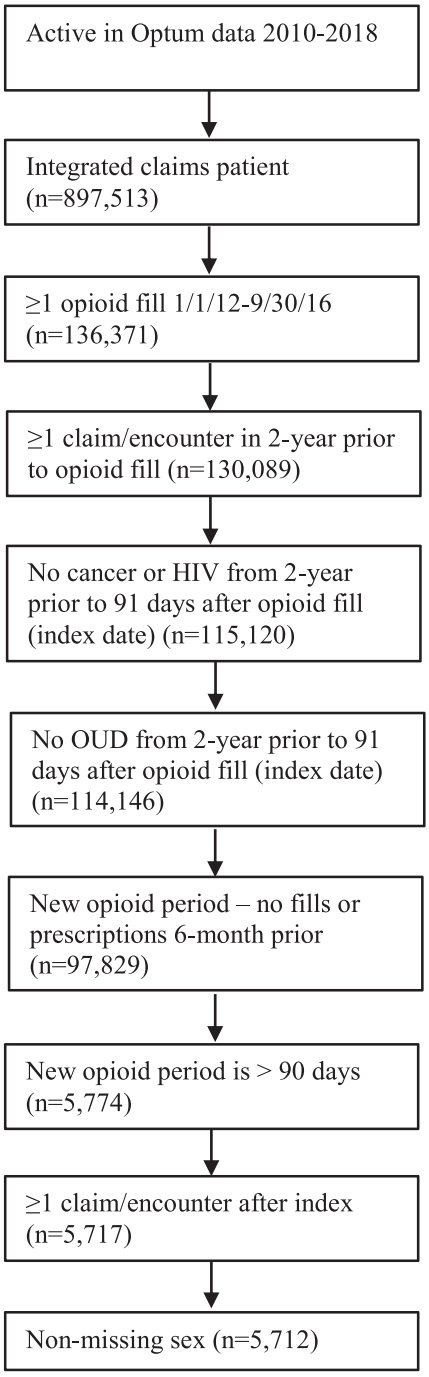

Fig. 2. Sampling CONSORT diagram.

subjects/patients were approved by the Saint Louis University IRB and deemed non-human subjects research because all data was de-identified.

3. Results

Patients were, on average, 57.7 (SD ± 14.9) years of age; a majority were female (59.8%) and white (73.3%). Among all patients who had new LTOT (i.e., >90-day opioid prescriptions), 2.8% had an overlapping stimulant prescription (n = 158). Among prescription stimulant users, 22.8% were receiving methylphenidate, 76.0% amphetamine containing products and 1.3% received both types of medications during the dual use period. The average methylphenidate equivalent unit dose (MEU) was 71.4 mg (± 43.9) and 25.9% were prescribed an MEU >100 mg per day. During the first 90 days of opioid prescriptions, 93.4% of patients had IR formulations only, 0.9% had ER formulations and 5.8% had both. Most (63.6%) patients received only one type of opioid, 29.0% received two types of opioids and 7.5% received 3 or more different opioid types in the first 90 days.

As shown in Table 1, as indicated by an SMD%>10, younger age, female sex, and white race were more prevalent among dual users. The lowest MME category (1-50 MME) was less prevalent while >180 MME opioid use was more prevalent among dual users. Arthritis was more common in opioid only users and back pain was more common among dual users. The average Charlson Comorbidity Index score was higher in opioid only users.

Obesity was more common among opioid only users and fatigue, ADHD, depression, anxiety, dysthymia, bipolar disorder, personality disorder and narcolepsy were more prevalent among dual users. Alcohol abuse/dependence and nicotine dependence were more prevalent among opioid only users. Benzodiazepine co-medication was more prevalent among dual users.

In unweighted data, the cumulative incidence of OUD was nearly twice as great in dual prescription stimulant-LTOT compared to LTOT alone (15.8% vs. 9.9%). The incidence of OUD per 1,000 Person Years (PY) was 55.5/1000PY among stimulant-LTOT and 31.6/1000PY among LTOT only. The median follow-up time from index to incident OUD or end of follow-up did not differ between stimulant-LTOT (median = 35 months (IQR: 16–50) and LTOT alone (median = 35 months (IQR: 23–55)).

Results from crude bivariate Cox proportional hazard models are shown in Table 2. The risk for OUD increased with greater maximum MME. Arthritis was inversely associated with risk for OUD, while back pain and headache were positively associated with OUD. ADHD was associated with more than a 2-fold risk for OUD. Depression, anxiety disorders, dysthymia, bipolar disorder and personality disorder were each significantly associated with greater OUD risk. Alcohol and drug abuse/dependence, nicotine dependence/smoking and benzodiazepine co-medication were positively associated with OUD risk.

As shown in supplementary e-table 2, entropy weighting successfully balanced all covariates as evidenced by SMD%<10.

The results from Cox Proportional Hazard models estimating the association between dual stimulant-LTOT, compared to LTOT only, and new onset OUD are shown in Table 3. Prior to controlling for confounding in unweighted data, dual stimulant-LTOT, compared to LTOT alone, was associated with a 75% increased risk for new onset OUD (HR = 1.75; 95%CI:1.17-2.61). After weighting data, there was no association between dual stimulant-LTOT and new onset OUD (HR = 0.89; 95%CI:0.47-1.71). Sensitivity analyses among patients < 56 years of age showed similar associations (see Table 3). After adjusting for the number of different opioids prescribed and receipt of IR vs. ER opioid formulations in the final model, results remained largely unchanged (HR = 0.90; 95%CI:0.46-1.76).

4. Discussion

In a nationally distributed cohort of patients receiving LTOT, dual stimulant prescription use, compared to LTOT only, was not associated with increased risk for new onset OUD. To our knowledge, this is the first study of the association between stimulant use in LTOT and risk for OUD.

Prior to controlling for bias by indication and other sources of confounding, we observed stimulant use was positively associated with OUD. This is probably due to the higher prevalence of risk factors for OUD (Biederman et al., 1998, Faraone and Wilens, 2007; Young-Wolff et al., 2017; Sullivan, 2018; Klimas et al., 2019), including ADHD, depression, anxiety and or PTSD, other forms of substance use disorder, smoking/nicotine dependence and benzodiazepine co-medication in those with stimulant prescriptions and LTOT, compared to those with LTOT alone. This positive association became null after control-

Table 2
Crude, bivariate associations of each covariate and risk of OUD – Cox proportional hazard models.

Covariates	Crude HR (95% CI)
Index date year	
2012	1.00
2013	1.31 (1.01-1.71)
2014	1.36 (1.03-1.79)
2015	1.73 (1.29-2.32)
2016	2.31 (1.74-3.06)
Sociodemographic-related	
Age	0.98 (0.97-0.99)
Female sex	0.99 (0.84-1.17)
Race	
White	1.00
Black	1.03 (0.77-1.37)
Other/Unknown	0.72 (0.56-0.92)
Region	
Midwest	1.00
Northeast	0.96 (0.69-1.33)
South	1.46 (1.20-1.78)
West	1.54 (1.18-2.01)
Other/unknown	1.82 (1.22-2.71)
High healthcare utilization	1.20 (0.99-1.43)
OAU-related	
Maximum daily MME (mg) [a]	
1-50	1.00
51-90	1.82 (1.46-2.27)
91-180	2.60 (2.07-3.25)
> 180	4.34 (3.43-5.49)
Comorbidities [b]	
Arthritis	0.84 (0.71-0.99)
Back pain	1.59 (1.31-1.92)
Muscle pain	0.85 (0.72-1.01)
Neuropathy	1.10 (0.90-1.35)
Headache	1.23 (1.02-1.50)
Charlson index	0.97 (0.93-1.01)
Obese	0.84 (0.70-1.02)
Traumatic brain injury	0.87 (0.59-1.28)
Fatigue	1.03 (0.85-1.25)
ADHD	2.17 (1.46-3.21)
Depression	1.47 (1.21-1.78)
Anxiety disorders and or PTSD[c]	1.43 (1.18-1.73)
Dysthymia	1.62 (1.13-2.33)
Bipolar disorder	1.66 (1.17-2.36)
Schizophrenia	1.47 (0.73-2.95)
Personality disorder	2.38 (1.23-4.60)
Narcolepsy	0.87 (0.12-6.18)
Other sleep disorder	1.08 (0.89-1.30)
Alcohol abuse/dependence	1.59 (1.08-2.34)
Drug abuse/dependence	2.41 (1.71-3.41)
Nicotine dependence/smoking	1.44 (1.21-1.71)
Benzodiazepine co-medication[d]	1.78 (1.50-2.10)

[a] MME = morphine milligram equivalent – maximum dose reached in first 90 days of new long-term OAU use (OAU start to index date)
[b] Comorbidities measured from 2-years prior to index to index date
[c] Anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS
[d] Benzodiazepine co-med = Fill or prescription during first 90 days of new long-term OAU (OAU start to index date)

Table 3
Results from cox proportional hazard models estimating the association of dual stimulant use and OUD (n = 5,712).

	Model 1 – Crude/unweighted	Model 2 – Weighted
Stimulant Use	HR (95%CI)	HR (95%CI)
No STIM	1.00	1.00
Dual STIM	1.75 (1.17-2.61)	0.89 (0.47-1.71)
Sensitivity analysis – models among patients < 56 years of age (n = 2,534)		
No STIM	1.00	1.00
Dual STIM	1.62 (1.03-2.55)	0.72 (0.35-1.47)

Note: HR = hazard ratio; CI = confidence interval; OUD = opioid use disorder

ling for all measured confounding which is consistent with evidence that stimulant medications for ADHD are associated with a reduced risk for substance use disorders for at least 3 years after treatment starts (Chang et al., 2014).

Our results suggest that dual stimulant - LTOT is not associated with increased risk for OUD, compared to LTOT alone. One explanation is that stimulant use is not a risk factor for OUD among patients with LTOT. Alternatively, we speculate that stimulants were prescribed to treat ADHD, depression and other comorbidities (e.g., fatigue) in patients with LTOT, and may have contributed to improvement in these conditions which could reduce risk for OUD. Although this conclusion is speculative, it is consistent with findings reported in predominately younger samples (Boland et al., 2020); however, the present data, limited to adults, seem to show stimulants are inversely associated with development of OUD in adults with non-cancer pain who are co-administered opioids for therapeutic reasons.

The biological relationship between the most common reason for stimulant prescriptions, (i.e., ADHD), stimulants, opioids and OUD is complex. Catecholaminergic circuitry and dysfunction has been postulated in both OUD (Kosten and George, 2002) as well as ADHD (Tripp and Wickens, 2009). For instance, opioids have been found to stimulant mu opioid receptors in the brain activating release of dopamine and subsequent downstream feelings of pleasure (Kosten and George, 2002). Feedback from the prefrontal cortex may dampen this effect and appears compromised in persons with OUD (Kosten and George, 2002). ADHD is also associated with alterations in dopamine activity and reinforcement, salience, and reward (Tripp and Wickens, 2009). Interestingly, although the principal molecular targets of stimulants in the CNS are catecholamines, at sufficiently high doses they also activate the mu opioid receptor in the brain resulting in reinforcing effects such as is seen with opioids (and reversed with opioid blockers) (Zhu et al., 2011). Though speculative, it may be that by operating through similar opioid-related mechanisms, prescription stimulants co-administered with opioids attenuate opioid related euphoria and limit risk for OUD among patients with LTOT.

4.1. Limitations

Our study design allowed for prevalent stimulant use to occur prior to the new period of 90-day opioid prescriptions. Post-hoc analyses revealed that among the LTOT only group, 0.8% (n = 46) had a stimulant prior to the new period of LTOT, and among the stimulant-LTOT group, 53.8% (n = 85) had a stimulant prescription prior to the start of LTOT. Of the 5,554 patients in the LTOT only group, 1% (n = 56) became stimulant users after index. Therefore, it is unlikely that the minimal non-overlapping stimulant use in the LTOT only group significantly biased our results.

We did not have data to determine if patients took their prescription medication, although we expect nonadherence to medications was likely randomly distributed in the two exposure groups. We included methadone among eligible prescription opioids; however, we did not have data to confirm whether these prescriptions were for OUD treatment or for pain. Yet, it is unlikely that methadone maintenance clinics are included in the Optum data which is largely derived from provider networks and health care systems.

Our observation period ended in 2018 and we measured dual stimulant-opioid prescriptions through most of 2016. Because dual 30-day stimulant-opioid use is increasing in the United States (Wei et al., 2018) and in other countries (Ormhøj et al., 2018), our results may not generalize to the present rate and consequences of dual use.

Misclassification and residual confounding are potential limitations of retrospective cohort studies. We used integrated EHR and medical claims data which may improve correctly classifying exposure and outcomes because diagnoses are not necessarily limited to one source. Nonetheless, results may be biased due to misclassification. We controlled for a large number of confounding factors. For an unmeasured

confounder to completely explain our results, it would have to have had a strong association with the outcome and exposure and be uncorrelated with measured confounding factors. We do not believe such a variable was present.

4.2. Conclusions

Among patients with non-cancer pain and LTOT, overlapping prescription stimulant use was not associated with an increase in OUD. An important possibility that requires further exploration is that stimulant treatment mitigates the ultimate risk for OUD associated with untreated ADHD and other conditions for which stimulants are prescribed. The current evidence suggests that for most cases, prescribing stimulants for patients receiving LTOT should not increase risk for OUD. Further studies in separate cohorts are warranted to confirm the present findings. In addition, given the high prevalence of benzodiazepine prescriptions among dual stimulant-LTOT, research measuring consequences of concomitant use of benzodiazepines, stimulants and opioids is warranted.

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Declaration of Competing Interest

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Dr. Scherrer and Ms. Salas had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data analyses was conducted by Ms. Salas.

The first draft of the manuscript was written by Dr. Scherrer.

Data Availability: The data are not publicly available because the agreements of the data lease with Optum© analytics does not permit sharing the data outside of Saint Louis University.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dadr.2022.100122.

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