

# Centrally acting stimulants in patients receiving opioid agonist therapy; a national prospective cohort study in Norway from 2015 to 2017

Jørn Henrik Vold (✉ [jorn.vold@uib.no](mailto:jorn.vold@uib.no))

Universitetet i Bergen Det medisinsk-odontologiske fakultet <https://orcid.org/0000-0001-8701-7638>

Christer Aas

Universitetet i Bergen Det medisinsk-odontologiske fakultet

Svetlana Skurtveit

Folkehelseinstituttet

Ingvild Odsbu

Karolinska Institutet

Fatemeh Chalabianloo

Universitetet i Bergen Det medisinsk-odontologiske fakultet

Anne Halmøy

Universitetet i Bergen Det medisinsk-odontologiske fakultet

Kjell Arne Johansson

Universitetet i Bergen Det medisinsk-odontologiske fakultet

Lars Thore Fadnes

Universitetet i Bergen Det medisinsk-odontologiske fakultet

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## Research article

**Keywords:** Opioid agonist therapy, central stimulants, hyperkinetic disorder, Attention Deficit Hyperactivity Disorder, substance-related disorders, dispensation drugs, register data

**Posted Date:** September 12th, 2019

**DOI:** <https://doi.org/10.21203/rs.2.14354/v1>

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**Version of Record:** A version of this preprint was published at BMC Psychiatry on March 12th, 2020. See the published version at <https://doi.org/10.1186/s12888-020-02526-y>.

## Abstract

**Background** It is estimated that about a third of patients on opioid agonist therapy (OAT) have Attention Deficit Hyperactivity Disorder (ADHD). Treatment by centrally acting sympathomimetics (CAS) is one of the essential approaches. This study evaluates the use of CAS in the Norwegian OAT population in the period from 2015 to 2017. Types and doses of CAS, and co-dispensations of other addictive drugs like benzodiazepines, z-hypnotics, gabapentinoids, and non-OAT opioids, as well as direct-acting antivirals (DAA) against hepatitis C infection, are evaluated.

**Methods** Information about all dispensed CAS, OAT opioids, and the defined addictive drugs were recorded from the Norwegian Prescription Database. The number and the doses of dispensed drugs were used to estimate dispensation rates, the types, and the doses of dispensed CAS. Logistic regression analyses were employed to assess the associations between CAS and OAT opioid use, and dispensations of other addictive drugs and DAA against hepatitis C infection.

**Results** A total of 9,235 OAT patients were included. The proportion of patients who used both CAS and OAT opioids increased from 4 % to 5 % during the study period. The three most dispensed CAS were methylphenidate (59 %), lisdexamphetamine (24 %), and dexamphetamine (17 %). Buprenorphine as OAT opioid (adjusted odds ratio: 1.59, CI: 1.24-2.05) was associated with being dispensed CAS. Among patients who received CAS annually throughout the study period, the dispensed doses of methylphenidate increased from 63 mg/day in 2015 to 76 mg/day in 2017 ( $p = 0.01$ ). About 60 % of these patients were also dispensed other addictive drugs concomitantly in 2017.

**Conclusion** Co-dispensation of CAS was low among patients on OAT in Norway, considering a higher prevalence of ADHD in this patient group. On the other hand, concurrent dispensations of multiple addictive drugs are common in this population. Understanding the underlying causes of such prescribing is essential, and research on how to optimize CAS treatment of people with ADHD receiving OAT is needed.

## Background

The strong association between opioid addiction and Attention Deficit Hyperactivity Disorder (ADHD) is well known [1]. Studies indicate that around a third of patients receiving opioid agonist therapy (OAT) meet the criteria for ADHD [1–5]. Both opioids used in OAT and centrally acting sympathomimetics (CAS) as a treatment for ADHD have properties associated with euphoria and addiction. Current treatment guidelines, therefore, recommend careful considerations about the combined prescription of these high-potent drugs to stable psychosocial surroundings and close follow-ups by health professionals are ensured [6–9]. The prescription of other reinforcing addictive drugs such as benzodiazepines, z-hypnotics, non-OAT opioids, and gabapentinoids should be considered carefully to prevent adverse interactions and risk of additional addictions [10, 11]. About 50 % of patients receiving OAT and CAS concomitantly discontinue CAS during the first two years after the start of the treatment [12]. Reasons for discontinuation include illicit drug use, craving, side effects, and lack of psychosocial stability [12]. Long-term therapy of CAS seems to have the highest chance of success when combining psychosocial treatment with CAS and OAT in the absence of other reinforcing addictive drugs [13, 14].

The proportion of patients on OAT receiving CAS is low, considering the estimated prevalence of ADHD in this group [2]. One reason may be the use of illicit drugs and prescribed addictive drugs. Fatal or non-fatal overdoses [10, 11, 15], cognitive impairment caused by the drugs [6, 16], cardiac arrhythmias [17], and leakage of CAS to the illicit drug market are reported as consequences when these drugs are combined [8, 18]. Reinforcing effects of various addictive drugs makes co-prescribing of CAS and OAT opioids medically unsafe, complicate the ADHD diagnostics, and postpone treatment start with CAS [14]. Nevertheless, several studies showed that prescribed addictive drugs are frequently used among patients receiving OAT, including those who are dispensed CAS concomitantly [1, 19, 20]. High levels of psychiatric comorbidities, including major depressive disorder, anxiety disorders, post-traumatic stress disorders, and psychotic disorder may partly explain the high dispensation rates of addictive drugs in this population [4, 21–23].

Inappropriate use such as injection of illicit CAS exceeding recommended doses is common among patients with addiction to stimulant drugs [24]. Psychosis, seizures, and cardiovascular events are well-documented consequences in the case of intoxications by stimulants [9]. The use of contaminated injection equipment also significantly increases the risk of being transmitted with severe infectious diseases such as hepatitis C infection [25, 26]. The illicit use of CAS may be an expression of the low coverage of CAS among patients with ADHD. Overall, there is a lack of knowledge about how to facilitate a proper treatment approach in patients on OAT with comorbid ADHD. As an attempt to improve treatment of ADHD in this population, it is necessary to get an overview of the current dispensation rates of CAS, as well as other prescribed addictive drugs among patients on OAT, to could evaluate whether the prescription practice is in line with current guidelines for ADHD [27–29].

Thus, this observational study was aimed to evaluate dispensation rates of CAS and other addictive drugs among patients receiving OAT and CAS in the period from 2015 to 2017 in Norway. The following objectives were defined:

1. Assess the annual dispensation rates of CAS, and the types of CAS dispensed.
2. Evaluate whether the annual dispensations of CAS and OAT opioids were associated with dispensations of benzodiazepines, z-hypnotics, gabapentinoids, non-OAT opioids, as well as direct-acting antivirals (DAA) against hepatitis C infection, types of OAT opioids, the number of dispensed OAT opioids, gender, and age in the study period.
3. Evaluate the mean doses of dispensed CAS and the dispensation rates of benzodiazepines, z-hypnotics, gabapentinoids, and non-OAT opioids in 2017 among patients who received CAS annually throughout the period 2015 to 2017.

## Methods

## 2.1 Data source

All data were drawn from the Norwegian Prescription Database (NorPD). From January 1, 2004, all pharmacies are obliged to submit data for all dispensed drugs electronically to NorPD underlying the Norwegian Institute of Public Health. The NorPD contains information on all drugs dispensed from pharmacies, except for drugs administrated at hospitals, nursing homes, and outpatient clinics [30]. The Anatomical Therapeutic Chemical (ATC) classification system was employed in accordance with the World Health Organization (WHO) standards per October 2018 [31]. The STROBE checklist was applied in the preparation of the study (Additional file 1).

## 2.2 Opioid agonist therapy (OAT) in Norway

Opioid agonist therapy has been applied increasingly as an available treatment approach for opioid addiction in the last decades. In 2017, about 7500 patients received OAT in Norway [32]. Since 2014, the Norwegian guidelines for ADHD have recommended the use of CAS among patients receiving OAT [8, 33]. The use of other illicit or prescribed addictive drugs is discouraged.

## 2.3 Study population

All patients above 18 years of age who received at least one annual dispensation of OAT opioids, including methadone, levomethadone, buprenorphine, and buprenorphine-naloxone from January 1, 2015, to December 31, 2017, were included. Dispensation rates were calculated for each calendar year, as the cases recorded in years without any dispensations of OAT opioids, were censored. In addition, due to some patients in palliative care use methadone tablets to achieve pain relief, those who only were dispensed methadone tablets without any history of receiving other OAT opioids or methadone mixture were excluded.

## 2.4 Analysis strategy and statistical analyses

### 2.4.1 Definitions of drugs, including centrally acting sympatomimetics and opioid agonist therapy opioids, number of dispensations, prescribed daily drug doses and diagnoses.

CAS were defined as all stimulants that had marketing authorizations in Norway in the period 2015 to 2017, including racemic amphetamine, dexamphetamine, methylphenidate, and lisdexamphetamine. In addition, we included the non-stimulant atomoxetine, which is also authorized and a commonly used drug in the treatment of ADHD. All included OAT opioids, CAS, non-OAT opioids, benzodiazepines, z-hypnotics, gabapentinoids including gabapentin and pregabalin, and DAA, were defined according to their ATC codes (Additional file 2).

The number of dispensed drugs of OAT opioids was defined as the number of dispensations per patient from the pharmacies annually recorded in the NorPD. The number of dispensed drugs were stratified according to four categories: 1–6, 7–12, 13–51, and  $\geq 52$  dispensations per year. Patients with 52 or more dispensations were assumed to have a high tolerance for opioids and to be medical continuity in their OAT treatment.

The mean doses of dispensed CAS were calculated using defined daily doses (DDD) [34]. Because the total dose dispensed were listed in DDD in NorPD, DDD of each dispensed CAS were converted to milligrams according to WHO's standards (Additional file 3).

All reimbursable and non-reimbursable CAS dispensations were included. To get public drug expenses reimbursed in Norway, the prescribing physician needs to specify the medical condition that is treated by the respective drug, using codes from the 10<sup>th</sup> revision of International Classification of Diseases (ICD–10) or International Classification of Primary Care 2 (ICPC–2). The diagnostic codes of reimbursed drugs are recorded in the NorPD. Only two medical conditions are approved for CAS expense reimbursements in Norway: Hyperkinetic disorder/ADHD (ICD–10: F90 and ICPC–2: P81) or narcolepsy (ICD–10: G47 and ICPC–2: P81). The diagnostic codes for non-reimbursable dispensations are not specified in the NorPD.

### 2.4.2 Analysis strategy according to the aims

One-year's dispensation rates of CAS during the study period were assessed by summing all annual dispensed CAS stratified on two groups: "all medical indications," and "ADHD." The group "all medical indications" included all patients who received dispensations of CAS either they were reimbursed or not, and less than five patients who used reimbursable CAS due to narcolepsy in the study period. Each type of dispensed CAS was evaluated by calculating the proportion of patients being dispensed the respective drugs annually.

To evaluate the dispensations of benzodiazepines, z-hypnotics, gabapentinoids, and non-OAT opioids to the patients who were dispensed CAS and OAT opioids, all dispensations of these drugs were identified annually. Patients who received at least one dispensation of one or more of these drugs were included. Dispensations of DAA were also evaluated due to the frequent use of illicit stimulant drugs in the OAT population and the fact that annual dispensations of DAA against hepatitis C infection have increased the last years significantly [32, 35]. The dispensed OAT opioids were stratified according to the predefined categories. To estimate types of dispensed OAT opioids annually, the type of the last annual dispensed OAT opioid was used.

To assess the mean doses of dispensed CAS, only patients who had dispensed CAS annually throughout the study period were included. These patients were assumed to have achieved medical continuity in their ADHD treatment.

## 2.4.3 Statistical analyses

SPSS version 24 was used for all analyses. Means, medians, percentiles, percentages, 95 % confidence intervals (CI), odds ratios (OR), and p-values are presented when appropriate. The Chi-square test, and paired sample t-test were used to estimate differences in proportions and changes in doses. Multivariable analyses for categorical variables were performed by binary logistic regression. Level of statistical significance was defined as  $p < 0.05$ . We censored all patients from the calendar year they died.

## 2.5. Ethical considerations

The Regional Committee for Medical and Health Research Ethics, REC vest, Norway, has approved the use of registry data for the study (approval number 2018/939/REK Vest, June 19, 2018). No informed consent from included patients was necessary.

### Results

## 3.1 Basic characteristics

A total of 9,235 patients received at least one OAT opioid from pharmacies in Norway in the period 2015 to 2017. In 2017, 69 % were male, and the mean age was 45 years (Table 1). A total of 376 participants died during the study period.

## 3.2 One-year prevalence and the types of dispensed centrally acting sympathomimetics

The proportions of OAT patients who received at least one annual dispensation of CAS increased from 4 % in 2015 to 5 % in 2017 (Table 1). A vast majority of them, i.e., 74 % received buprenorphine or buprenorphine-naloxone, whereas the remaining 26 % were dispensed methadone or levomethadone (Table 2). In 2017, the most dispensed CAS was methylphenidate (59 %), followed by lisdexamphetamine (24 %), dexamphetamine (17 %), atomoxetine (6 %), and racemic amphetamine (2 %) (Table 3a, Table 3b).

## 3.3 Dispensations of addictive drugs to patients receiving both opioid agonist therapy opioids and centrally acting sympathomimetics

In the period from 2015 to 2017, dispensations of CAS were associated with dispensation of buprenorphine as OAT opioid (2017: adjusted odds ratio (aOR): 1.6, 95 % confidence interval (CI): 1.2–2.1) (Table 4). Being dispensed non-OAT opioids (aOR 1.5, 95 % CI: 1.1–1.9) and DAA against hepatitis C infection (aOR 1.6, 95 % CI: 1.2–2.2) was associated with being dispensed CAS (in 2017). The odds ratio (OR) of being dispensed DAA increased steadily during the study period. Being dispensed CAS was no statistical significance with being dispensed gabapentinoids, benzodiazepines, or z-hypnotics in this study population.

## 3.4 Doses of dispensed centrally acting sympathomimetics (CAS), and dispensation rates of other addictive drugs among those who received CAS and opioid agonist therapy opioids throughout the study period

We identified 142 patients who received both CAS and OAT opioids annually throughout the period from 2015 to 2017. We found a large increase in the dispensed mean doses of methylphenidate from 63 mg/day in 2015 to 76 mg/day in 2017 ( $p = 0.01$ ) (Figure 1). The mean doses of other dispensed CAS were not statistically significantly different in 2017 compared to 2015, although the power of these assessments was limited by infrequent dispensations of several CAS other than methylphenidate. Nevertheless, it is noteworthy that mean doses of lisdexamphetamine increased from 21 mg/day in 2015 to 83 mg/day in 2017. The mean doses of amphetamine, dexamphetamine, methylphenidate, and lisdexamphetamine were near the highest recommended doses for each drug according to the Norwegian Medicines Agency. Furthermore, about 60 % of patients who used CAS and OAT annually during the study period received at least one dispensation of z-hypnotics or benzodiazepines, gabapentinoids, or non-OAT opioids in 2017 (Figure 2). The most dispensed combination of drugs was OAT opioid, CAS, and benzodiazepines or z-hypnotics. Seven patients received all addictive drugs from all the assessed categories of drugs.

### Discussion

In the period 2015 to 2017, the proportion of patients receiving CAS in the OAT population increased from 4% to 5%. Methylphenidate and lisdexamphetamine were the most frequently dispensed CAS. Dispensation of buprenorphine as OAT opioid was associated with being dispensed CAS. In addition, in the last year of the study period (2017), being dispensed non-OAT opioids and DAA against hepatitis C infection were associated with being dispensed CAS. For four out of five CAS, the mean doses were near the highest recommended dose of the respective CAS. Among patients who received CAS throughout the study period, a significant increase in the dose of methylphenidate was identified, and about 60 % were dispensed benzodiazepines, z-hypnotics, gabapentinoids, or non-OAT opioids.

The proportion of patients who received CAS and OAT opioids increased in the inclusion period. Nevertheless, the dispensation rates were still in the lower range of what could be expected. It is estimated that as much as a third of patients with drug addictions in Norway have comorbid ADHD [36], and the proportion among those with opioid use disorder is supposed to be 11–33 % [3–5]. Assuming that 40–50 % of patients with ADHD receive CAS in the general population [29], one would expect that about 4–16 % of those with opioid use disorder are dispensed CAS. Our findings showed that only 4–5 % of the patients on OAT also received CAS during the study period. This might have several explanations. A consensus report evaluating screening, diagnosis, and treatment of patients with drug addictions and ADHD, recommends use of CAS when potentially therapeutic benefits and disadvantages are considered in advance [29]. Further, since 2014, the Norwegian guidelines for ADHD have discouraged dispensations of CAS among patients in OAT who used other addictive drugs concomitantly [8]. Low dispensation rates of CAS in the OAT population may also be explained by medical illnesses or psychosocial conditions, and active illicit drug use, which may disturb the diagnostic assessment of ADHD and delay pharmacological treatment.

Retention to treatment is generally challenging in the treatment of drug addictions, particularly among patients with comorbid ADHD. Inadequate knowledge of pharmacological properties of various CAS may explain a low coverage of CAS. For example, unlike amphetamines, atomoxetine may need several weeks to give optimal clinical response [29]. Late-onset of the effect of atomoxetine or careful dose-escalation of methylphenidates and amphetamines may conflict with patient's expectations on a quick reduction of ADHD symptoms. In addition, to prevent discontinuation of CAS treatment may play an essential role in preventing relapse to illicit stimulant drug use and sustained stimulant injections, as well as improving the quality of life by keeping complications such as hepatitis C infection down [37]. Integrating CAS treatment in OAT, or vice versa may be a way to facilitate the diagnostics and treatment and improve follow-up approaches among marginalized patients with comorbid ADHD [38].

In this study, the mean doses of CAS were in the highest range of usual recommended doses. The benefits of high-dose CAS on the treatment of ADHD in OAT population are not clear. Two placebo-controlled randomized trials, including patients with ADHD and addictions to amphetamines or cocaine, have found a decrease of ADHD symptoms in doses up to 180 mg methylphenidate [25] and 80 mg racemic amphetamine daily compared to placebo [26]. The former study [25] also found that high-dose of methylphenidate reduced relapse to illicit stimulant use and contributed to higher retention in treatment. Previous research has also confirmed similar findings [39]. The latter study [26], evaluating racemic amphetamine to placebo showed that dosages on 60 mg and 80 mg racemic amphetamine per day inhibited cocaine-related craving, although, a dose on 80 mg racemic amphetamine did not seem to reduce ADHD symptoms more than a dosage of 60 mg per day. Overall, one can assume that using higher doses of methylphenidate or racemic amphetamine may improve the effect of these medications on ADHD by keeping patients in treatment, reducing the craving for illicit stimulant drugs, as well as by suppressing ADHD symptoms.

The proportion of patients who were dispensed lisdexamphetamine increased significantly from 2015 to 2017. In addition, the mean dose rose markedly in the same period, although not statistically significant. A meta-analysis evaluating the efficacy, acceptability, and tolerability of CAS among patients with ADHD without drug addiction favored amphetamines as the first drug group of choice in the short-term treatment of ADHD in adults [40]. Comparing to methylphenidate and amphetamines, the latter was more efficacious, and the only CAS where patients did not leave the studies for any reasons (acceptability). National Institute for Health and Care Excellence (NICE) guidelines [28] and a consensus report [29] evaluating patients with drug addictions and ADHD recommend methylphenidate or lisdexamphetamine as the first drug of choice in the treatment of ADHD in adults. A risk assessment of the potential of misuse of lisdexamphetamine and methylphenidate has been completed by the WHO, which pointed towards that methylphenidate and lisdexamphetamine have still low harmful profiles compared to stimulants such as racemic amphetamine and methamphetamine in treatment of ADHD [41]. The use of CAS in the Norwegian OAT population was in line with these recommendations. In addition, it is essential to mention that upcoming Norwegian facilitation in the pre-approved reimbursement of lisdexamphetamine was introduced in October 2018 [42], which may also explain some of the increasing dispensation rates found in this study.

About 60 % of patients using the combination of CAS and OAT opioids were dispensed either benzodiazepines, z-hypnotics, gabapentinoids, or non-OAT opioids at least as frequent as in the remaining OAT population not using CAS. Our findings complement previous studies on the OAT population, showing that about a half were dispensed benzodiazepines or z-hypnotics, 18 % received non-OAT opioids, and 11 % used gabapentinoids in 2017 [19, 20]. The fact that only 40 % of the patients were dispensed CAS without dispensations of other addictive drugs may point towards the need of improving the prescribing practice of addictive drugs in this comorbid population by keeping the risk of adverse interactions down [10, 11, 15]. On the other hand, benzodiazepines, z-hypnotics, gabapentinoids, and non-OAT opioids may also be essential in the medical treatment of this high-risk population due to other psychiatric and somatic comorbidities. Additionally, in some cases, prescribing of these drugs may be used to keep the patients completely abstinent of other illicit addictive drugs provided strict follow-ups by health professionals and also medically sound prescribing practices [13, 14].

## 5. Strengths and limitations

The use of national registry data has some clear strengths, by capturing whole cohorts of the studied populations. Pharmacy records are considered more valid than both medical records and data collected from questionnaires and interviews. Because practically all dispensed drugs are registered in the NorPD database, completeness, and precision of all received information is high, and the potential for information biases is low.

This study also had some limitations. First, because non-reimbursed dispensations of CAS were not received through the Norwegian Health Economics Administration (HELFO), the medical indications for these dispensations are not available for the researchers through NorPD. Further, it is not possible to assess the causes of these dispensations from NorPD. Gabapentinoids, benzodiazepines, z-hypnotics, and non-OAT opioids have different medical indications and have not been evaluated in this study. Second, the number of dispensed OAT opioids may be incompletely registered by the pharmacies. The annual self-reporting survey of OAT in Norway showed that the mean dispensations of OAT opioids were four times a week [32]. This finding may indicate that the number of dispensations is underestimated. Third, the NorPD only receives information about dispensed drugs, and we cannot know whether the drugs have been consumed. All addictive drugs are coveted for illegal consumptions, and the drugs may be re-distributed. Illicit use is common in this population and cannot be

covered using register data. Fourth, slightly less than 10 % of OAT opioids are dispensed in addiction specialist outpatient clinics, and those are not necessarily registered in the NorPD. Some of these outpatient clinics ordered OAT opioids directly from pharmacies without linking to a personal identification number. These patients were missed in this study, and those could have higher dispensation rates of addictive drugs than patients included in this study [32].

## Conclusion

Co-dispensation of CAS was low in OAT in Norway, relative to the expected prevalence of ADHD in this patient group. Considering that up to a third of OAT population is estimated to have ADHD, only 4 to 5 % of patients received both CAS and OAT opioids in Norway in the period from 2015 to 2017. The mean doses of dispensed CAS among these were near the highest recommended dose range, and about 60 % of the patients with CAS and OAT were dispensed other addictive drugs concomitantly. Generally, the polydrug use of addictive drugs increases the risk of fatal and non-fatal overdoses in addicted patients; however, a treatment combining several addictive drugs in patients using CAS and OAT opioids has been only scarcely studied. Further, randomized-controlled trials evaluating CAS in different doses are needed to improve the treatment of ADHD in the OAT population.

## List Of Abbreviations

ADHD - Attention Deficit Hyperactivity Disorder

AOR - Adjusted odds ratio

ATC - Anatomical Therapeutic Chemical

CAS - Centrally acting sympathomimetic

CI - Confidence interval

DAA - Direct-acting antivirals

DDD - Defined Daily Doses

HELFO - The Norwegian Health Economics Administration

ICD-10<sup>th</sup> - revision of International Classification of Diseases

ICPC 2 - International Classification of Primary Care 2

NICE - National Institute for Health and Care Excellence

NorPD - The Norwegian Prescription Database

OAT - Opioid agonist therapy

OR - Odds ratio

WHO - World Health Organization

## Declarations

## Ethics approval and consent to participate and consent of publication

The Regional Committee for Medical and Health Research Ethics (REC), REC West, Norway, has approved the use of registry data for the study (reference number 2018/939/REK Vest, June 19, 2018). The REC committee is appointed by the Norwegian Ministry of Education and Research. No informed consent from the patients was necessary.

## Consent for publication

Not applicable

## Availability of data and material

Supplemental tables and data sources in this observational study are available in this published article and its additional files.

## Competing interests

I. O. is employed at the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organizations) for performance of drug safety and drug utilization studies, unrelated to this work.

## Funding

The study was funded by The Norwegian Research Council (BEHANDLING, contract no 269855) and the Western Norway Regional Health Authority («Åpen prosjektstøtte») with Department of Addiction Medicine, Haukeland University Hospital as responsible institution. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Two of the authors are funded from the research grant BEHANDLING related to the project INTRO-HCV from the Norwegian Research Council. Their respective affiliations fund the other authors.

## Authors' contributions

J. H. V. was involved in the study design, led analysis, and writing the article preparation. C. A., S. S., F. C., I. O., A. H., K. A. J., and L. T. F. contributed in the study design, analysis, and writing the article preparation. All authors have read and approved the final article.

## Acknowledgments

Not applicable

## Authors' information

Jørn Henrik Vold, MD, Department of Addiction Medicine, Haukeland University Hospital, and Department of Public Health and Primary Care, University of Bergen. Mailing address: Department of Addiction Medicine, Haukeland University Hospital, Østre Murallmenningen 7, N-5012 Bergen, Norway. E-mail: [jorn.vold@uib.no](mailto:jorn.vold@uib.no).

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## Tables

Due to technical limitations, all Tables is only available as a download in the supplemental files section.

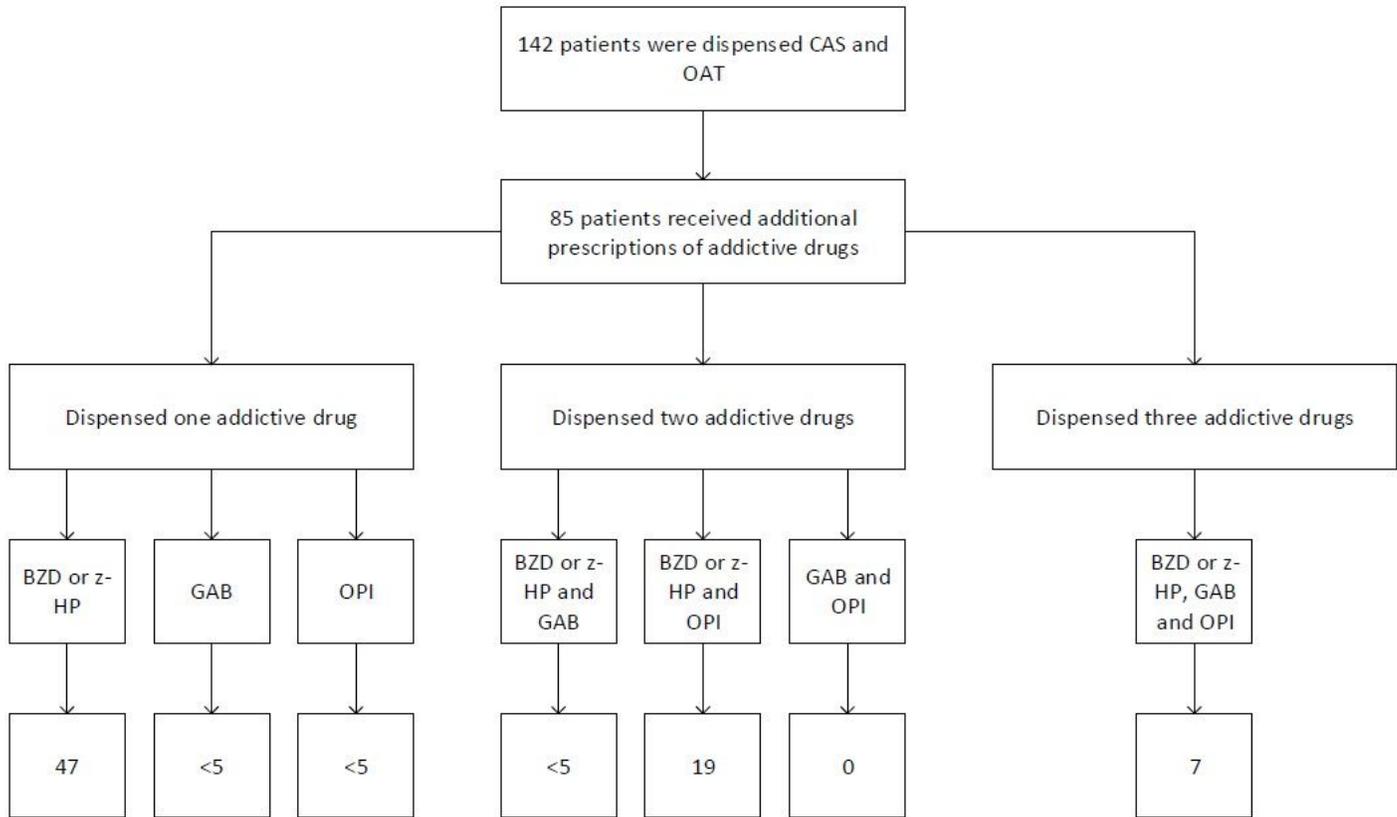
## Figures

All medical indications		Year			Upper recommended dose (mg)*	Δ mean (95 % CI)**	p-value
		2015	2016	2017			
Methylphenidate	Number of patients	88	88	88	80***	13 (4 - 22) <sup>1)</sup>	0.0
	Mean (mg/day)	63	82	76			
	Median (mg/day)	60	76	73			
	25 percentile (mg/day)	26	50	52			
	75 percentile (mg/day)	92	106	104			
Dex-amphetamine	Number of patients	27	27	27	40	8 (-3 - 19) <sup>2)</sup>	0.2
	Mean (mg/day)	42	48	50			
	Median (mg/day)	40	47	49			
	25 percentile (mg/day)	27	34	27			
	75 percentile (mg/day)	52	60	64			
Lisdex-amphetamine	Number of patients	6	6	6	70	62 (-6 - 131) <sup>3)</sup>	0.1
	Mean (mg/day)	21	82	83			
	Median (mg/day)	22	84	100			
	25 percentile (mg/day)	6	61	22			
	75 percentile (mg/day)	30	109	127			
Atomoxetine	Number of patients	5	5	5	100	-4 (-84 - 75) <sup>4)</sup>	0.9
	Mean (mg/day)	55	63	51			
	Median (mg/day)	48	69	69			
	25 percentile (mg/day)	24	25	7			
	75 percentile (mg/day)	89	98	85			
Racemic amphetamine	Number of patients	< 5	< 5	< 5	45	-	-
	Mean (mg/day)	60	42	65			
	Median (mg/day)	60	42	65			
	25 percentile (mg/day)	60	42	65			
	75 percentile (mg/day)	60	42	65			

Figure 1

Doses of dispensed CAS among patients who received OAT opioids from 2015 to 2017. Legends: Df = degree of freedom, CI = confidence interval 1) Paired-samples t-test, df = 87, 2) Paired-samples t-test, df = 26, 3) Paired-samples t-test, df = 5, and 4) Paired-samples t-test, df = 4. \* = Upper recommended doses according to The Norwegian Medicines Agency (NMA) per July 2019, \*\* = Calculation of the differences in doses between 2015 and 2017, and \*\*\* = Upper

recommended dose of short-acting methylphenidate according to the NMA. The figure displays the dispensed doses of CAS among those who received CAS annually in the period from 2015 to 2017.



**Figure 2**

Patients who received dispensations of other addictive drugs in 2017 Legends: BZD = benzodiazepines, CAS = Centrally acting sympathomimetics, OAT = Opioid agonist therapy, OPI = non-OAT opioids, and z-HP = z-hypnotics. The figure displays dispensations of BZD, z-HP, GAB, and OPI in 2017 among patients who were dispensed CAS and OAT opioids annually in the period from 2015 to 2017. Eighty-five patients were identified to be dispensed BZD or z-HP, GAB, or OPI.

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