Prescribing of drugs for attention-deficit hyperactivity disorder in opioid maintenance treatment

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Running head: Use of ADHD drugs in opioid maintenance treatment

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Abstract

Background:
Attention-deficit hyperactivity disorder (ADHD) is a risk factor for development of substance use disorders. Treatment of ADHD with psychostimulants in patients on opioid maintenance treatment (OMT) has been restricted in Norway. We examined use of prescribed drugs for ADHD in OMT patients, and assessed co-medication with other psychotropics.

Methods:
Data were drawn from the nationwide Norwegian Prescription Database (NorPD), which includes all prescriptions filled at pharmacies. The study population was people ≥18 years on OMT during 2008-2010.

Results:
In 2010, 6,116 patients received OMT and 2.8% of these patients also received ADHD drugs. This is seven times greater than in the gender- and age-specific general population of Norway. Prevalence was higher in the youngest patients, while there was no gender difference. Methylphenidate was the most commonly used drug for ADHD in OMT patients, followed by atomoxetine. 60% of OMT patients filled at least one prescription for antidepressants, anxiolytics or hypnotics and percentages were similar for users and non-users of ADHD drugs.

Conclusion:
Treatment with ADHD drugs was higher in OMT patients than expected from the general population, but was relatively low compared to the prevalence of ADHD in patients with substance use disorders reported in the literature.

Keywords:
ADHD, Opioid maintenance, Prescribed drugs, Psychotropic medicines, Stimulants, Prescription database, Pharmacoepidemiology
1 Introduction

Attention-deficit hyperactivity disorder (ADHD) is reported as a risk factor for developing a substance use disorder (SUD) [1;2]. The link between ADHD and SUD has a familial association also, as children of parents that suffer from SUD have higher rates of several mental disorders, including ADHD [3;4]. SUD patients who have comorbid ADHD tend to have initiated illegal drug use at an earlier age and have a reduced likelihood of going into remission, compared to SUD patients without ADHD [5-8]. Comorbid ADHD is associated with greater addiction severity, lower quality of life and a greater risk of having other psychiatric disorders [8-11]. There are few studies of the effects of ADHD in SUD populations like opioid-dependent patients, and there is great variation in the estimated prevalence of ADHD [11].

Although methylphenidate and other ADHD drugs are proven to be effective for treating ADHD, studies on such treatment in SUD populations are few, especially on patients receiving opioid-maintenance treatment (OMT). Controlled and uncontrolled studies do not give supporting evidence that pharmacotherapy for ADHD is effective when used in SUD populations [8;12]. A summary report on experience from Norway on treating ADHD in opioid-maintained populations indicate some positive results [14], but larger studies specifically designed to study the effectiveness and safety of combined treatment of ADHD and opioid-dependence are clearly needed. The objective of the present study was to give an overview of the use of drugs for ADHD in adult patients on OMT in Norway by using the nationwide Norwegian Prescription Database (NorPD).

Aims of the study:
To examine 1) annual prevalence of prescribed drug use for ADHD in OMT patients during 2008-2010; 2) annual prevalence of prescribed drug use for ADHD in OMT patients compared to the prevalence in the Norwegian general population; 3) type of prescribed drugs used for ADHD; 4) persistence of use of prescribed ADHD drugs in OMT patients; and 5) co-medication with other psychotropic drugs among users and non-users of prescribed ADHD drugs.
2 Materials and methods

2.1 Study setting

The OMT programme was implemented on a national level in 1998, and is integrated into the tax-supported public health service covering all Norwegian citizens. The programme has a multimodal approach for treating opioid-dependent patients and involves the specialist healthcare system, general practitioners (GPs) and the social services. The programme was quite restrictive during the first 12 years [15], but more liberal government regulations and national guidelines were implemented in 2010 [16;17]. The aim of the programme is to improve the patients’ quality of life, facilitate changes in lifestyle, as well as harm reduction. The regulation acknowledges that it may not be possible for all patients to attain abstinence from opioid use. The indication for treatment is opioid-dependence and there is no longer any minimum age for inclusion in the programme. Termination of the drug treatment without the patient’s consent should be considered only if it is harmful to the patient. Initiation and termination of OMT treatment is managed by the specialized regional OMT centres. GPs have a central role in the regular follow-up of patients once they are stabilized, including prescribing of drugs. GPs managed the prescribing of OMT drugs for two-thirds of the patients in 2010, however with substantial regional differences [18]. Most patients take the OMT drugs under supervision, most frequently by pharmacy or social services personnel. Only patients that have been stabilized on treatment over a longer period may bring OMT drugs home and take the drug without supervision, and for a maximum of 7 days [17;18].

2.2 Data source: the Norwegian Prescription Database (NorPD)

Data were drawn from the Norwegian Prescription Database (NorPD), which covers the entire population (~4.9 million) of Norway since 2004 [19]. NorPD contains information on all prescribed drugs, reimbursed or not, that have been dispensed from pharmacies to patients in ambulatory care. Prescriptions can be linked to individual patients by the personal identity number (encrypted identity). Drugs are classified according to the Anatomical Therapeutic Chemical classification system (ATC) [20]. Variables included in this study were the patient’s unique identity number,
gender, age, date of dispensing the drug, ATC code and the Nordic article number for drug packages.

2.3 Study population: patients receiving OMT drugs

The study population included people ≥18 years who received OMT drugs on prescription during 2008-2010. Since 2008, OMT drugs have mainly been dispensed by pharmacies and are registered on the individual patient in NorPD. OMT drugs used when patients are admitted in institutions are not registered on an individual level in NorPD. Methadone, especially tablets, may be used for pain relief in Norway. To minimize inclusion of non-OMT patients in our study population, patients that exclusively received methadone as tablets were not included (258 patients) [21]. In 2010, we identified 6,116 OMT patients ≥18 years in NorPD, while one patient aged 17 years was excluded from analysis (Table 1).

2.4 Definition of OMT drugs, ADHD drugs, and other psychotropic drugs

OMT drugs: Methadone mixture (ATC code N07BC02), buprenorphine tablets (N07BC01), and buprenorphine-naloxone combined tablets (N07BC51). Methadone tablets were not included when defining the study population of OMT patients.

ADHD drugs: Methylphenidate (N06BA04), atomoxetine (N06BA09), racemic amphetamine (N06BA01), and dexamphetamine (N06BA02). ADHD drugs may also be used for narcolepsy. We checked that none of the OMT patients in 2010 received ADHD drugs for narcolepsy by examining the drug reimbursement codes (ICD-10 and ICPC-2), which have been included in NorPD from 2008 and fully implemented from 2009.

Other psychotropic drugs: Antidepressants (N06A), anxiolytics (N05B), and hypnotics (N05C).

2.5 Prescribing restrictions for narcotic drugs

Prescribing of narcotic drugs requires a specific prescription form («class A drug prescription»), and applies to strong opioids (all OMT drugs) and psychostimulants (all ADHD drugs except atomoxetine). Prescribing of OMT drugs is strictly regulated in the OMT programme, and prescribing of psychostimulants is also restricted; specialists in psychiatry, paediatrics or neurology can prescribe to all patients after
given a general permission, while other physicians have to apply for permission to prescribe psychostimulants to specific, named patients. Unlike the psychostimulants used in the treatment of ADHD, atomoxetine is not defined as a narcotic drug and does not have the same prescribing restrictions. If concomitant use of psychostimulants with OMT drugs is considered appropriate for a patient, a specific application for such use is required [22].

2.6 Analysis strategy and statistics

Data for the period 2008-2010 were retrieved from NorPD and analysed as one-year cross sections. The main analysis was based on OMT patients in 2010. For the calculation of Standardized Morbidity Ratio (O/E), the observed number of patients treated with ADHD drugs in 2010 was compared to the expected number, by applying the prevalence of ADHD drug use for each gender- and age- specific group in the Norwegian general population (standard population) on the one-year age- and gender- specific distribution in the OMT population (study population). The denominator for the prevalence in the standard population is the gender- and age- specific total population of Norway, retrieved from Statistics Norway. Age-adjusted odds ratios (OR) for use of antidepressants, anxiolytics and hypnotics for users versus non-users of ADHD drugs among OMT patients were estimated by logistic regression. Data analysis was performed with Stata version 11.

3 Results

3.1 Annual prevalence of ADHD drugs used by OMT patients

The number of patients that received at least one prescription for OMT drugs during one calendar year increased over the period 2008-2010 in both men and women (Table 1). In 2010, 6,116 patients received OMT drugs, and 170 (2.8%) patients also received ADHD drugs the same year. The proportion receiving ADHD drugs in 2010 was higher in the youngest men and women, but there was no gender difference within the two age strata (Table 2).
3.2 Annual prevalence of ADHD drug use in OMT patients compared to the general population of Norway

The gender- and age- specific prevalence of ADHD drug use in the Norwegian general population was used as a reference in Table 2. The prevalence of ADHD therapy was seven times greater among OMT patients than expected from the general population, and this increase was observed within different gender and age strata (O/E range 5.8-7.5).

3.3 Type of ADHD drugs used by OMT patients

Table 3 presents the type of ADHD drugs used by the 170 OMT patients who received ADHD drugs in 2010. Methylphenidate was by far the most commonly used ADHD drug, followed by atomoxetine. Delayed release formulations of methylphenidate were more commonly used than immediate release formulations. Racemic amphetamine and dexamphetamine were used by 15 patients. In total, 138 patients (81%) received at least one of the psychostimulants (methylphenidate, amphetamine or dexamphetamine) and 5 of these patients received two different psychostimulants.

3.4 Persistence of use of ADHD drugs in OMT patients

In total 4,020 patients received OMT drugs in all three years 2008-2010. In this group, 110 patients received drugs for ADHD in 2008. 81 (74%) of these received ADHD drugs also in 2009, while 62 (56%) received these drugs all three years. Corresponding figures in the general population with the same gender and age distribution as the OMT population and who had received ADHD drugs in 2008 were 80% and 67%, respectively.

3.5 Co-medication with other psychotropic drugs

Co-medication with other psychotropic drugs was common in OMT patients (Table 4). In total, 60% of the OMT patients received at least one prescription for antidepressants, anxiolytics or hypnotics in 2010. Odds ratios (OR) for use of psychotropics in users versus non-users of ADHD drugs did not show any consistent pattern for higher or lower use of psychotropics. The only statistically significant OR
was that fewer of the female users of ADHD drugs received anxiolytics than female non-users (age-adjusted OR 0.43 [0.23-0.81]).

4 Discussion

The main finding of this nationwide study in Norway was that 2.8% of patients on OMT in the outpatient setting received ADHD drugs in 2010. This is seven times higher than expected from ADHD drug use in the general population. The prevalence was higher in the youngest patients, while there was no gender difference. Co-medication with antidepressants, anxiolytics and hypnotics was high in the OMT population but showed no consistent pattern between ADHD drug users and non-users.

An overall ADHD prevalence of 23% in SUD patients (different types of substances) was reported in a meta-analysis [23]. There are few studies of ADHD in opioid-dependent patients but, as summarized by Carpentier et al. [11], prevalence in the range 11-29% have been reported in clinical, treatment-seeking populations from Switzerland, Germany and the USA. One study reported an ADHD prevalence of 4-5%, but the opioid- and/or cocaine-dependant study population was not necessarily seeking treatment [7]. Carpentier and co-workers [11] also conducted their own comprehensive study in the Netherlands among patients in long-term methadone maintenance treatment. 35% had childhood ADHD and 25% had ADHD persisting into adulthood, while an additional 6-7% had suspected ADHD.

These prevalence estimates for ADHD in opioid-dependent patients from four different countries are high compared to the percentage of OMT patients who received pharmacotherapy for ADHD in Norway (2.8%). Deleterious effects of ADHD on outcomes of SUD have been reported, but there is limited evidence of the benefits and harm for treatment with different ADHD drugs in SUD populations, and results are conflicting [8;12-14]. Risk of misuse and diversion of psychostimulants may contribute to restrictive pharmacotherapy, although this may be less of a problem in the context of therapeutic use and with slow release formulations [8;14]. Norwegian guidance on treatment of ADHD has not recommended concomitant use of
psychostimulants and OMT drugs. In addition to the general restrictions for prescribing psychostimulants, physicians need to apply for a permit for a specific patient before initiating concomitant treatment with psychostimulants and OMT drugs [22]. Psychostimulants have only been sanctioned for use after three months of documented abstinence from drug abuse but may be considered earlier for individual patients admitted in institutions. Permission for concomitant use of OMT and psychostimulants has been granted to a few projects that were established to evaluate the effects of this treatment option. A conference evaluating these projects has been arranged and the conference summary report recommends that psychostimulants should be a treatment option offered also to OMT patients [14].

A further explanation of the relatively low prevalence of ADHD drug use could be that patients with ADHD are less able to comply with the strict OMT programme due to nature of the disease and its symptoms. Thus, higher shares of the OMT patients with ADHD may have dropped out of the programme than in OMT patients without ADHD. Our prevalence estimate of ADHD drug use must be interpreted in light of these issues with ADHD treatment in this patient group, as well as the possibility of undiagnosed ADHD in this patient group. Thus, the prevalence of use of prescribed ADHD drugs reported in the present study cannot be considered as a prevalence estimate of ADHD in OMT patients.

There are more men than women in the OMT programme, but no gender difference was observed in the proportion of patients receiving drugs for ADHD in this adult population. This is also observed in the general population of Norway; while the prevalence of use of ADHD drugs is markedly higher in boys during childhood and adolescence, there is no gender difference in adults and the prevalence levels are substantially lower at this age [24].

For patients who are abstinent from drug abuse for at least three months, methylphenidate is the treatment of choice for ADHD in Norwegian OMT patients [22]. Racemic amphetamine and dexamphetamine may have a higher risk of relapse of drug abuse and is currently not recommended in previous drug abusers [22]. However, some experts have proposed that amphetamine and dexamphetamine
should be considered if methylphenidate does not have sufficient effect [14]. Atomoxetine, which is not classified as a narcotic drug, should also be considered in drug abusers even though it is only approved for use in children and adolescents with ADHD [22]. According to NorPD data from 2010 for the entire Norwegian population 20 years or older [24], 87% of ADHD drug users received methylphenidate and 9% received atomoxetine, compared to respectively 75% and 19% in the OMT population (Table 3). Thus, the guidance for ADHD treatment of this population seems to have had some impact on the type of drugs that are prescribed.

We found that co-medication with other psychotropic drugs, some with potential for misuse, was common in OMT patients. However, use of other psychotropics was not consistently higher or lower in users of ADHD drugs compared to non-users. Thus, our results do not provide a clear indication of different rates of psychiatric comorbidity in ADHD patients compared to the patients without ADHD. This high prevalence of co-medication with psychotropics has also been reported in previous NorPD studies in OMT patients. Hartz et al. [25] found a prevalence for antidepressants of 22%, with equal shares in men and women. Fredheim et al. [26] reported that 12% of OMT patients received prescriptions for another opioid in addition to the opioid used for OMT. Bramness and Kornør [27] reported a prevalence of 40% for prescribed benzodiazepines in OMT patients in 2005 and the prevalence of use was higher in women than in men. The annual report for the Norwegian OMT programme for 2010 also reported high use of benzodiazepines [18], as 23% of OMT patients were reported to have received prescribed benzodiazepines, while 41% were reported to use benzodiazepines during the last four weeks (prescribed and/or illegal) [18]. The national guidelines states that benzodiazepines should not be prescribed to OMT patients [17].

Strengths of the present study are that it is based on high quality data from a nationwide prescription database covering drugs dispensed from Norwegian pharmacies to all individuals in ambulatory care. Since 2008, OMT drugs have mainly been provided by pharmacies for all patients except when they are admitted to institutions. Thus, use of these drugs has been registered in NorPD for individual
patients (with encrypted personal identity number), and enable us to study the concomitant use of OMT and ADHD drugs on a nationwide scale.

The study population of OMT patients was identified by studying dispensed prescriptions for OMT drugs. We excluded patients that only received methadone tablets, as these are more likely to be Using methadone for treatment of pain. Furthermore, all physicians can in principle initiate use of OMT drugs before applying for enrolment in the OMT programme to stabilize specific patients during critical situations. Thus, some patients not enrolled in the OMT programme may have been included in our study and contribute to a slightly higher number of OMT patients. On the other hand, some patients admitted to institutions may only have received OMT drugs from the institutions, and are therefore not registered in NorPD. In 2010, 6,015 patients were enrolled in the OMT programme at the end of the year [18]. This corresponds quite well with our NorPD data that identified 6,116 patients who received OMT drugs during the same year.

We did not have access to diagnostic information or other clinical information like the extent of impairment from ADHD, which is important when deciding treatment for ADHD. The appropriateness of ADHD drug use could not be addressed. Furthermore, we could not assess whether patients were stabilized on the OMT drugs and whether they used any illegal substances. When using data from prescription databases, one does not know if the dispensed drugs are actually taken by the patients. It is common in Norway that OMT drugs have to be taken in the presence of pharmacy personnel or others, while taking psychostimulants is not supervised and diversion of these drugs to the illegal market is possible.

The OMT programme is multimodal and the use of OMT drugs should enable patients to utilize the important psychosocial support provided through the programme. Diagnosing and treating ADHD in drug abusers is challenging and requires careful consideration of benefits and harm for the individual patient, but may assist in preventing relapse of drug abuse. Close monitoring of the use of psychostimulants is important for this patient group.
Acknowledgements
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References


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Table 1. Patients on opioid maintenance treatment (OMT) and OMT patients receiving drugs for attention-deficit hyperactivity disorder (ADHD) in 2008-2010. Norwegian Prescription Database (NorPD).

<table>
<thead>
<tr>
<th>Year</th>
<th>OMT N</th>
<th>ADHD n</th>
<th>% 95% CI</th>
<th>OMT N</th>
<th>ADHD n</th>
<th>% 95% CI</th>
<th>OMT N</th>
<th>ADHD n</th>
<th>% 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>3,473</td>
<td>104</td>
<td>3.0 2.5-3.6</td>
<td>1,502</td>
<td>31</td>
<td>2.1 1.4-2.9</td>
<td>4,975</td>
<td>135</td>
<td>2.7 2.3-3.2</td>
</tr>
<tr>
<td>2009</td>
<td>3,847</td>
<td>121</td>
<td>3.1 2.6-3.8</td>
<td>1,648</td>
<td>50</td>
<td>3.0 2.3-4.0</td>
<td>5,495</td>
<td>171</td>
<td>3.1 2.7-3.6</td>
</tr>
<tr>
<td>2010</td>
<td>4,316</td>
<td>120</td>
<td>2.8 2.3-3.3</td>
<td>1,800</td>
<td>50</td>
<td>2.8 2.1-3.6</td>
<td>6,116</td>
<td>170</td>
<td>2.8 2.4-3.2</td>
</tr>
</tbody>
</table>
Table 2. Observed number (O), prevalence (%), and expected number (E) receiving drugs for attention-deficit hyperactivity disorder (ADHD) in patients on opioid maintenance treatment (OMT) in 2010.

Standard population: population of Norway ≥18 years in 2010.
Norwegian Prescription Database (NorPD).

<table>
<thead>
<tr>
<th></th>
<th>Standard population</th>
<th></th>
<th>OMT population</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Total, 18+ yrs</td>
<td>3,805,931</td>
<td>14,077</td>
<td>0.37</td>
<td>6,116</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-39 yrs</td>
<td>734,750</td>
<td>5,773</td>
<td>0.79</td>
<td>1,780</td>
</tr>
<tr>
<td>40+ yrs</td>
<td>1,154,737</td>
<td>1,858</td>
<td>0.16</td>
<td>2,536</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-39 yrs</td>
<td>704,849</td>
<td>4,659</td>
<td>0.66</td>
<td>843</td>
</tr>
<tr>
<td>40+ yrs</td>
<td>1,211,595</td>
<td>1,787</td>
<td>0.15</td>
<td>957</td>
</tr>
</tbody>
</table>
Table 3. Type of drugs for attention-deficit hyperactivity disorder (ADHD) received by 170 patients on opioid maintenance treatment (OMT) in 2010. Norwegian Prescription Database (NorPD).

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18-39 yrs</td>
<td>40+ yrs</td>
<td>18-39 yrs</td>
</tr>
<tr>
<td></td>
<td>N=74</td>
<td>N=46</td>
<td>N=33</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>60</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Delayed release formulation**</td>
<td>50</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Immediate release formulation**</td>
<td>20</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>13</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Racemic amphetamine</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dexamphetamine</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Two types of ADHD drugs*</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Received two types of ADHD drugs during 2010 (methylphenidate, atomoxetine, racemic amphetamine, or dexamphetamine) and are counted on both of the drugs they received.

** Numbers in italics give details on the type of formulation of methylphenidate that patients received during 2010 (some patients received both types of formulations).
Table 4. Co-medication with psychotropics in patients on opioid maintenance treatment (OMT), with or without use of drugs for attention-deficit hyperactivity disorder (ADHD) in 2010.

Norwegian Prescription Database (NorPD).

<table>
<thead>
<tr>
<th>Received ADHD drugs</th>
<th>Odds Ratio of receiving psychotropics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>-------</td>
<td>---</td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>OMT patients</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>OMT patients</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>

* Age-adjusted Odds Ratio (OR) for use of psychotropics in users versus non-users of ADHD drugs among all OMT patients.

** Received at least one of the psychotropic drugs in 2010.