

Prescription of antidepressants to patients on opioid maintenance therapy – a pharmacoepidemiological study

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ABSTRACT

Background and aims: Depression and anxiety are commonly reported among patients in opioid maintenance treatment (OMT). The aim of the present study was to describe aspects of prescription of antidepressant drug therapy among patients on OMT. Our research questions were: 1) What is the prevalence of antidepressant use according to age and gender? 2) Which antidepressants are used? 3) How are antidepressants used in terms of reimbursement codes, dispensed dose and duration of therapy?

Methods: Pharmacoepidemiological data were retrieved from the complete national Norwegian Prescription Database which contains information on all prescription drugs (such as Anatomical Therapeutic Chemical (ATC)-code, Defined Daily Dose (DDDs)), dispensed at pharmacies to individual patients. Norwegian OMT-patients (N=4374, 3035 men and 1339 women) who received methadone mixture, buprenorphine capsules or combined buprenorphine-naloxone capsules for at least 6 months in 2009 were included. Prevalence of antidepressant use in the studied patients was measured in terms of retrieval of prescriptions.

Results: During 2009 21.7% of the studied patients filled at least one prescription for an antidepressant drug (men: 21.2%; women: 22.9%). The subgroup of antidepressants most frequently dispensed was selective serotonin reuptake inhibitors (SSRIs) (33%), followed by the sedative antidepressants mianserin and mirtazapin (22%) and tricyclic antidepressants (TCAs) (20%). Except for TCAs, prescriptions of all antidepressant subgroups were reimbursed for either anxiety or depression in 90% of the cases. Overall, 46.9% of the antidepressant users were prescribed antidepressants in the category < 1 DDD per day and/or treatment < 3 months, with no gender difference.

Conclusions: About one out of five OMT-patients filled a prescription for an antidepressant drug in 2009. Above 90% had their prescriptions reimbursed for either depression or anxiety. Use at low doses and/or sporadic use among half of the antidepressant users may reflect poor compliance or use for other maladies than the reimbursed disease code. Drug therapy for depression and anxiety among OMT-patients seems to be in line with recommendations for use; the SSRIs constitute the recommended drugs of choice due to their better effect/side effect profile, compared to the older antidepressants such as the TCAs.

INTRODUCTION

Depression is one of our most common psychiatric disorders with an estimated 12 month prevalence of 7-10% of the adult population^{1,2}. Among drug and alcohol abusing individuals the prevalence rates are reported to be as high as 25-50%^{3,4}. Prevalence rates of major depression among opiate-dependent patients enrolled in treatment programs range between 10-30% in international studies⁵. This relatively large variation in prevalence may be explained by different study designs such as a varying length of participation in opioid maintenance (OMT)-programs at the time of diagnosis. Thus, depression and substance-dependencies commonly co-occur. This comorbidity has been associated with worse prognosis, poorer treatment outcomes, and increased risk of suicide⁶⁻⁸.

OMT is the most common treatment for opiate addiction in Europe⁹. In Norway there are approximately 6000 patients in OMT¹⁰. A survey of Norwegian OMT patients in 2009 indicated an approximate prevalence

rate of depressive symptoms of 16%, and about 20% had an anxiety disorder or symptoms that could point to this¹⁰. There were, however, large regional variations in the prevalence rates, e.g. for depression ranging from 7% in the county of Buskerud to 30% among OMT-patients in the county of Hedmark. These estimates must be interpreted with great caution; information was missing in 8% of the patients, and the results were not based on the use of clinically validated questionnaires. Still, it isn't reasonable that the prevalence of depressive disorders in OMT patients should vary to this extent across the country.

According to data from the Norwegian Prescription Database (NorPD), 9.3% of all adult women and 5.0% of all men in Norway had at least one prescription of an antidepressant drug dispensed in 2004 and prevalence increased with age¹¹. These figures resemble to a high degree the rates of depression in the population^{1,2}. Antidepressants, however, are used also for several other conditions like anxiety disorders, eating disorder, pain management and to induce sleep. Thus, the preva-

lence figures indicate that not all episodes of major depression are treated with antidepressants.

The pattern of antidepressant drug use in the general population is characterized by both an increasing use by age, and a higher level of use among women compared to men. To our knowledge, there is limited information on antidepressant drug therapy among patients enrolled in OMT-programs. Based on information from the nationwide NorPD, the aim of our study was to describe aspects of prescription of antidepressant drug therapy among patients on opioid maintenance therapy.

Our research questions were:

1. What is the prevalence of antidepressant use according to age and gender?
2. Which antidepressants are used?
3. How are antidepressants used in terms of reimbursement codes, dispensed dose (defined daily doses) and duration of therapy?

MATERIAL AND METHODS

Data source

Data were drawn from the NorPD¹². From January 1st 2004, all pharmacies in Norway have been obliged by law to submit data electronically to the NorPD on all dispensed prescriptions. The NorPD contains information on all prescription drugs, reimbursed or not, which are dispensed at pharmacies to individual patients outside institutions. Each record contains a unique person-identifier, which makes it possible to follow all prescriptions chronologically for each individual patient. Data on the prescribers are also collected, and each physician is identified by a unique identification code. Data on both patients and physicians are anonymized. Because data are collected from pharmacies, only prescribed drugs that are actually dispensed are captured in the NorPD. The data collected for our study were patients unique identifying number (encrypted), sex, age, the date of dispensing, and drug information (Anatomical Therapeutic Chemical (ATC)-code, Defined Daily Dose (DDDs)), and information on reimbursement codes. Reimbursement codes are wide categories of diseases, according to ICD-10 or ICPC coding, linking the prescribing to reimbursement. The following reimbursement codes were used: anxiety and depression: ICD code F3, F4 and ICPC code P73, P74, P76, P79, -74, -74, pain: ICD code -71, ICPC code -71, and other indications: ICD code -70.

All medicines dispensed in Norway are classified according to the ATC-classification system¹³. Quantities of dispensed drugs are measured in terms of the number of defined daily doses (DDDs). The basic definition of a DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults¹³. The DDD for each drug is determined by the WHO collaborating centre for drug statistics¹³. See Table 1 for all antidepressant substances included in this study with assigned defined daily doses (DDDs).

OMT in Norway

The Norwegian OMT model was implemented during 1998. To qualify for entry to the program, heroin users should have been dependent on heroin for several years and have had previous contact with abstinence-oriented treatment. OMT has only been available through a public funded program run by specialized centers¹⁴. According to the National Directorate of Health 4900 patients were included in OMT programs in Norway by the end of 2008¹⁵. Generally, OMT is provided as high-dose medication in Norway, and mean dosages for OMT medications in 2008 constituted 106 mg/day for methadone and 18 mg/day for buprenorphine¹⁶.

Study population

The study population was defined from retrieval of prescriptions of drugs used in OMT-programs during 2009. Due to relatively high numbers of patients entering and leaving OMT programs each year, our study population were restricted to include patients on OMT for six months or longer only. It has been reported that most patients who quit OMT, quit within the first year¹⁷.

The study was based on prescription data from January 1st 2009 to December 31st 2009. Figure 1 presents a flow chart of the study population, with inclusion and exclusion of patients. To be included in the study patients had to meet the following criteria: being dispensed either methadone mixture (ATC code N07BC02), buprenorphine capsules (Subutex®;

Table 1. Antidepressant substances registered in Norway in 2009, and included in the study, with assigned defined daily doses (DDDs).

ATC code	Name	1 DDD
<i>Tricyclic antidepressants (TCAs)</i>		
N06AA04	clomipramine	100 mg
N06AA06	trimipramine	150 mg
N06AA09	amitriptyline	75 mg
N06AA10	nortriptyline	30 mg
N06AA12	doxepin	100 mg
<i>Selective serotonin reuptake inhibitors (SSRIs)</i>		
N06AB03	fluoxetine	20 mg
N06AB04	citalopram	20 mg
N06AB05	paroxetine	20 mg
N06AB06	sertraline	50 mg
N06AB08	fluvoxamine	100 mg
N06AB10	escitalopram	10 mg
<i>Sedative antidepressants</i>		
N06AX03	mianserin	60 mg
N06AX11	mirtazepin	30 mg
<i>Others</i>		
N06AG02	moclobemide	300 mg
N06AX12	bupropion	300 mg
N06AX16	venlafaxine	100 mg
N06AX18	reboxetine	8 mg
N06AX21	duloxetine	60 mg

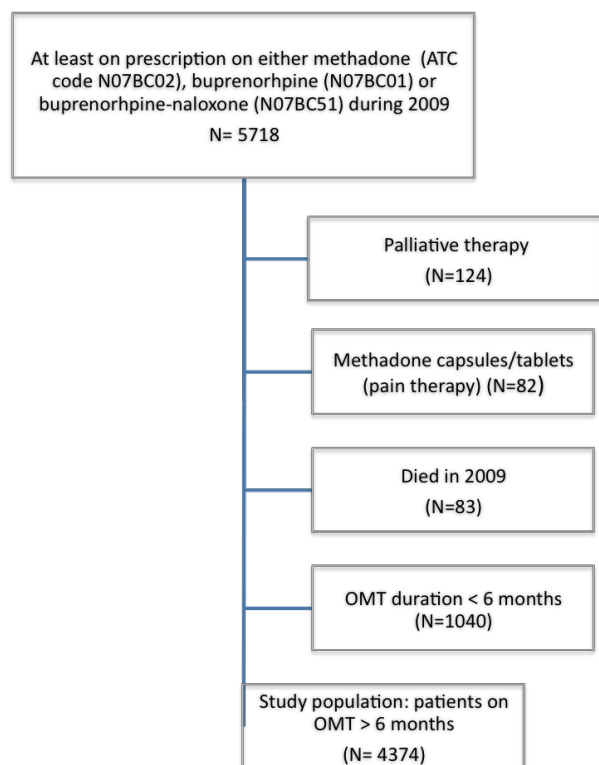


Figure 1. Flow chart of the study population, with inclusion and exclusion of patients. OMT = Opioid maintenance therapy.

Table 2. Characteristics of Norwegian patients in opioid maintenance therapy (OMT) more than six months in 2009 according to age and type of therapy.

	OMT-patients
Study population, N	4374
Men, n (%)	3035 (69.4)
Age (mean, SD)	41.6 (SD 8.0)
Methadone, n (%)	2489 (56.9)
Buprenorphine, n (%)	1603 (36.6)
Buprenorphine-naloxone combination; n (%)	819 (18.7)
Two or more opioids*, n (%)	517 (11.8)

*Patients who received two or more different opioids for maintenance therapy during the year.

N07BC01) or buprenorphine-naloxone combined capsules (Subuxone®; N07BC51) during the study period. Patients who had been dispensed methadone mixture with the reimbursement code for palliative treatment of malignant disease or methadone capsules were not included in the study. Patients who were dispensed tablets or capsules of methadone were excluded because these formulations of methadone are in Norway primarily used in pain therapy. Patients who died during 2009 and patients who received opioid maintenance therapy for a short time (less than 6 months) were excluded from the study.

Patients who received their OMT-drug in specialized centers and institutions during the study period were not available for inclusion in our study because their OMT drugs dispensed in institutions are not captured by NorPD.

Antidepressants available in Norway

In Norway antidepressants are available as prescription drugs only. Registered antidepressants in Norway were categorized into 4 groups: 1) selective serotonin reuptake inhibitors (ATC code N06AB) 2) tricyclic antidepressants (N06AA) 3) sedative antidepressants; mianserin (N06AX03) and mirtazapin (N06AX11) and 4) others.

Analyses and statistics

One-year prevalences of antidepressant use is presented and defined as retrieval of at least one prescription of an antidepressant drug during 2009. Distribution of antidepressant subgroups and reimbursement codes among antidepressant users in 2009 are presented as proportions. Further, the amount of antidepressant drugs dispensed (DDDs per day) was calculated as follows: Total DDDs dispensed in 2009 divided by (the number of days between last and first OMT drug dispensed + number of DDDs at the last dispensed prescription of antidepressant). Aspects of antidepressant use according to dispensed dose (DDDs) per day and duration of therapy were explored using the following four categories:

- > 1 DDD/day and treatment > 3 months
- > 1 DDD/day and treatment < 3 months
- < 1 DDD/day and treatment > 3 months
- < 1 DDD/day and treatment < 3 months

The software SPSS 17.0 for Windows was applied for data management and descriptive statistics.

RESULTS

Study population

4374 patients were included in the study, of whom 69% were men (table 2). Overall, mean age was 41.6 (SD 8.0) years and median age was 42 years, and the men were on average older than the women. More than half of the study population received methadone for opioid maintenance therapy, whereas the remaining patients received either buprenorphine or buprenorphine-naloxone in combination (no gender difference) (table 2).

Prevalence of antidepressants dispensed to patients on OMT

During 2009, 21.7% (949 out of 4374) of the study population filled at least one prescription for an antidepressant drug (men: 21.2%; women: 22.9%). Figure 2 shows prevalences of antidepressant drug use by age. The highest prevalence of antidepressant use was ob-

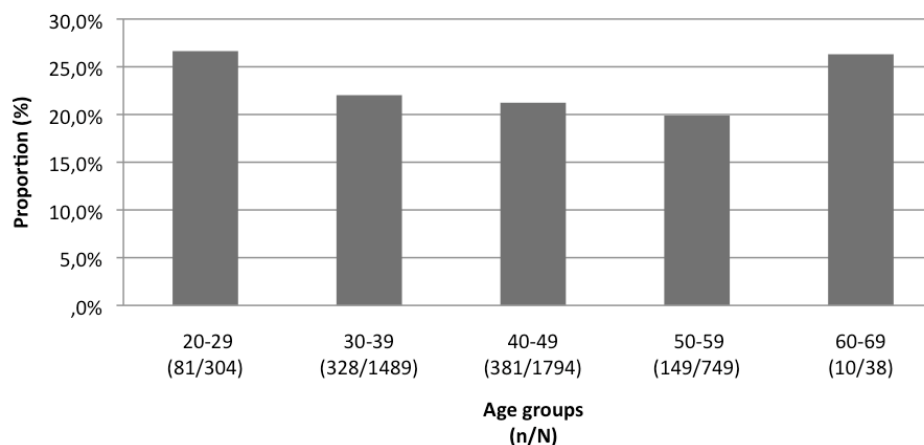


Figure 2. Proportion of patients on opioid maintenance therapy who had at least one antidepressant drug dispensed in 2009, according to age. Percent.

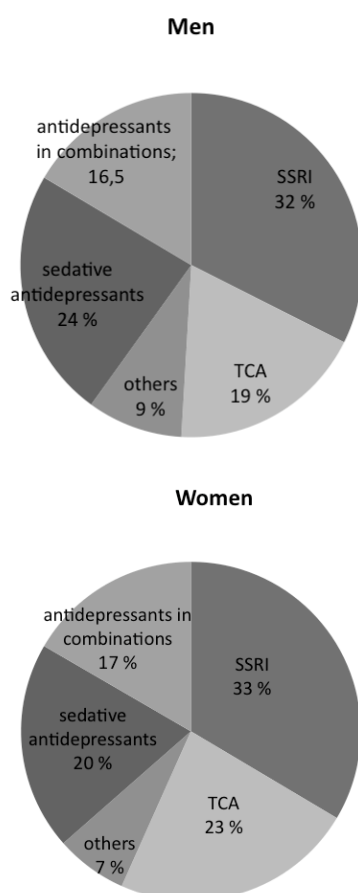


Figure 3. Distribution of antidepressant subgroups among patients on opioid maintenance treatment who had at least one antidepressant drug dispensed in 2009. Percent.

served among the youngest, aged 20-29 years, and oldest OMT patients, aged 60-69 years.

Figure 3 shows choice of antidepressant subgroups among OMT patients who had dispensed at least on one prescription of antidepressant drug in 2009. The subgroup of antidepressants most frequently dispensed was SSRI (33%), followed by the sedative antidepressants mianserin and mirtazapin (22%), TCA (20%),

antidepressants in combination during the year (17%) and others (8%). A similar pattern of use was observed among men and women (figure 3).

Antidepressants use according to reimbursement codes, dispensed dose and duration of therapy

Table 3 shows antidepressant use according to reimbursement codes. Prescriptions of all antidepressant subgroups were reimbursed for either anxiety or depression in 90% of the cases, except TCAs in which about three out of four of all prescriptions were reimbursed for anxiety or depression (men: 74.6%, women: 76.1%).

Table 4 shows antidepressant use according to doses per day and duration of treatment. Overall, 46.9% of the antidepressant users were prescribed antidepressants in the category < 1 DDD per day and/or treatment < 3 months. This was similar in both genders (men 46.7%; women 47.2%). Among TCA users, 92.6% of the patients were prescribed antidepressants at doses < 1 DDD per day and/or treatment < 3 months.

DISCUSSION

Overall; 22% of Norwegian OMT patients were on antidepressant drug therapy, in which about 90% were reimbursed for either depression or anxiety disorders. According to annual assessments of all OMT-centers in Norway in 2009, 16% of all OMT-patients had symptoms of depression, and about 20% had an anxiety disorder or symptoms that could point to this¹⁰. However, we do not know the extent to which these symptoms are overlapping in these patients. Thus, the present study cannot conclude on a divergence between the prevalence depression and anxiety morbidity and the drug treatment among OMT-patients.

Interestingly, approximately half of the antidepressant drug users were prescribed drugs at low daily doses (less than a DDD per day) or over a short period of time. These aspects of antidepressant drug use among OMT-patients could have several explanations. First,

Table 3. Distribution of antidepressants according to reimbursement code among patients on opioid maintenance treatment in 2009. Number and percent.

Reimbursement code	depression/ anxiety		pain	other	without reim- bursement code	
	N (%)	n (%)			n (%)	n (%)
Men						
SSRI*	208 (100)	200 (96.2)	0	1 (0.4)	8 (3.9)	
TCA**	119 (100)	90 (75.6)	4 (3.4)	0	25 (21.0)	
new sedative antidepressants	151 (100)	138 (91.4)	0	0	13 (8.6)	
others	58 (100)	52 (89.7)	1 (1.7)	0	6 (10.3)	
combinations	106 (100)	103 (97.2)	1 (0.9)	0	3 (2.8)	
Women						
SSRI*	103 (100)	102 (99.0)	0	0	1 (1.0)	
TCA**	71 (100)	54 (76.1)	4 (5.6)	0	13 (18.3)	
new sedative antidepressants	61 (100)	56 (91.8)	0	0	5 (8.2)	
others	21 (100)	21 (100)	1 (4.8)	0	0	
combinations	51 (100)	50 (98.0)	4 (7.8)	0	1 (2.0)	

* SSRI- selective serotonin reuptake inhibitors

** TCA- tricyclic antidepressants

Table 4. Distribution of antidepressants according to daily doses and duration of treatment among patients on opioid maintenance treatment in 2009. Number and percent.

	Use of antidepressants	doses <1DDD/day and treatment <3 months	doses >1DDD/day and treatment <3 months	doses <1DDD/day and treatment >3 months	doses >1DDD/day and treatment >3 months
		N (%)	n (%)	n (%)	n (%)
Men					
SSRI*	208 (100)	0	21 (10.1)	34 (16.3)	153 (73.6)
TCA**	119 (100)	12 (10.1)	43 (36.1)	58 (48.7)	6 (5.0)
sedative antidepressants	151 (100)	5 (3.3)	39 (25.8)	26 (17.2)	81 (53.6)
others	58 (100)	2 (3.4)	15 (25.9)	9 (15.5)	32 (55.2)
antidepressants in combination	106 (100)	0	6 (5.7)	30 (28.3)	70 (66.0)
Women					
SSRI*	103 (100)	1 (1.0)	8 (7.8)	22 (21.4)	71 (69.9)
TCA**	71 (100)	3 (4.2)	28 (39.4)	32 (45.1)	8 (11.3)
sedative antidepressants	61 (100)	2 (3.3)	18 (29.5)	10 (16.4)	31 (50.8)
others	21 (100)	0	5 (23.8)	6 (28.6)	10 (47.6)
antidepressants in combination	51 (100)	0	3 (5.9)	7 (13.7)	41 (80.4)

* SSRI- selective serotonin reuptake inhibitors

** TCA- tricyclic antidepressants

antidepressants may also be used at lower doses to alleviate sleep problems or as adjunctive therapy for pain. Even if more than 90% of the prescriptions were reimbursed for depression or anxiety disorders, we know from earlier observations that reimbursement (disease) codes that trigger reimbursement are used to help the patient, rather than being exact codes for the disease at hand. Thus the relatively high frequency use of low doses and/or more sporadic use may reflect use for other maladies than indicated by the reimbursement code. Second, in addition to diagnosis, prescribed antidepressant drug dose depends on patients' age and body weight, and treatment duration depends on therapeutic efficacy and adverse side effects, which all constitute rational reasons for some patients to be prescribed lower daily doses than a DDD per day and/or stop therapy. Third, poor compliance with prescribed anti-

depressant therapy may also contribute to patterns of sporadic retrieval of antidepressant drug prescriptions observed in this study. In this context, although prescribed antidepressants may be dispensed, prescription data do not reveal any information on the extent to which the dispensed drugs actually are ingested.

Even though there is evidence that depression among opiate-dependent patients has been associated with worse prognosis, there is a debate on how to treat OMT-patients with concurrent depression. Firstly, studies of antidepressant drug therapy for depression during OMT have shown varied results¹⁸. A recent review concluded that there is mixed and possibly poor evidence supporting the clinical use of antidepressants for the treatment of depression in opioid addicts that are treated with opioid agonists¹⁹. It is not clear what accounts for the differences in response to anti-

depressant drug therapy, and more research is needed to determine how to select opiate-dependent patients most likely to benefit from antidepressants.

Secondly the debate concerns the complex relationship between depression and opioid dependence. Depression may be a primary disorder, or may be secondary to the toxic and withdrawal effects of drugs, or of psychosocial stress associated with addiction^{18,20}. Entry into OMT-programs, and reduction of drug use, has in several studies been associated with improvement in depressive symptoms in many OMT-patients with major depression^{18,20}. However, not all patients will have such a favorable response to entry into OMT-programs. Our study population included OMT-patients on long term stable OMT (6 months or longer), most likely belonging to the latter group.

Among the OMT-patients in our study SSRIs constituted the antidepressant drug of choice. Only one out of five of the antidepressant users were prescribed TCAs, of whom about a quarter had their TCAs reimbursed for other indications than depression or anxiety. Further, only 5-10% of all TCA users had TCAs dispensed at daily doses over a duration of time indicative of use for depression or anxiety, compared to 70% of all SSRI users. Thus, this observation may reflect that TCAs, when prescribed, probably mainly are used for other problems than anxiety or depression. A reasonable conclusion from this may be that drug therapy for depression and anxiety among OMT-patients seems to be in line with recommendations for use; the SSRIs constitute the recommended drugs of choice due to their better effect/side effect profile, compared to the older antidepressants such as the TCAs.

Patterns of use of antidepressant drugs in the general population in Norway is characterized by both an increasing use by age, and a higher level of use among women compared to men¹¹. According to the NorPD, 7.9% of all women and 4.2% of all men in Norway had at least one prescription of an antidepressant drug

dispensed in 2009¹². Further, 4.1% of all 20-29 year olds had at least one prescription of an antidepressant drug dispensed in 2009, increasing to 9.6% of all 60-69 year olds. Compared to the general population, a higher proportion of OMT-patients were dispensed antidepressants, with no gender difference, or an increasing use by age. A higher level of use may be as expected, and in agreement with the higher prevalence of depression and anxiety (and other maladies) among OMT-patients compared to the general population. Similar level of use irrespective of age and gender among OMT-patients, may also reflect different patterns of morbidity among OMT-patients compared to the general population.

The major strength of this study is that all dispensed drugs, both opioid maintenance drugs and antidepressants are captured at an individual level, and that each individual can be followed over time with data on all dispensed drugs. On the other hand, as mentioned, there may be several limitations using information from NorPD as a datasource to describe patterns of drug use in the population; the dispensed drugs may not necessarily be consumed, the reimbursement code may not reflect the true reason for prescribing a drug, and the DDD may deviate from the actual prescribed daily dose.

In conclusion, about one out of five long-term OMT-patients had an antidepressant drug dispensed in 2009, of whom above 90% had their prescriptions reimbursed for either depression or anxiety. Use at low daily doses and/or sporadic use among half of the antidepressant users may reflect poor compliance or use for other maladies than the reimbursed disease code. Drug therapy for depression and anxiety among OMT-patients seems to be in line with recommendations for use; the SSRIs constitute the recommended drugs of choice due to their better effect/side effect profile, compared to the older antidepressants such as the TCAs.

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