



2006; Radat and Lanteri-Minet, 2010; Fuh and Wang, 2012). It is unlikely that MOH is caused by the specific analgesic action of any single agent (Diener et al., 2016). Withdrawal from the offending medications is the treatment of choice, and approximately 2 out of 3 MOH patients experience headache improvement after having overcome the withdrawal phase (Chiang et al., 2016).

In addition to the association with MOH, however, there are other negative consequences associated with long-term overuse of analgesics such as harmful and potentially life-threatening side-effects and interactions. Concern has been voiced about the increased analgesic consumption among pain patients in Europe, as well as in the United States where more than 2 million people are estimated to be addicted to prescription opioid medications and where associated overdose deaths have greatly increased (Giraudon et al., 2013; Murthy, 2016).

Theoretical considerations as well as the many clinically observed similarities between dependence-like behavior in MOH and other more clearly defined addictions have prompted us and others previously to use the Severity of dependence scale (SDS) in MOH (Gossop et al., 1995; Calabresi and Cupini, 2005; Grande et al., 2009; Biagianni et al., 2012; Lundqvist et al., 2012). These studies have shown that the SDS picks up behavior associated with MOH with high precision in general population samples. The principles of the SDS are that it focuses not on drug-specific physical withdrawal symptoms but rather on general dependence-like behavior. The SDS is simple and quick to use in a clinical setting, and is generally not seen as provocative by the patients (Frich et al., 2014).

The rationale for this study was to assess the severity of analgesic dependence in MOH using the SDS, validated against formal DSM-IV substance dependence diagnosis in the same population, and whether the SDS score is a predictor of successful withdrawal.

## METHODS

### Design

The study was undertaken in South-eastern Norway in 2011 and 2012. We analyzed data from participants recruited through a previously reported randomized controlled trial of a brief intervention for MOH (the “BIMOH”-study) (Kristoffersen et al., 2012; Kristoffersen et al., 2015).

### Participants and Data Collection

Each individual in the Norwegian population is listed on one specified GPs patient list. A short screening questionnaire for headache and medication use was posted to all 18 to 50 year old patients (25,486) on such patient lists of 50 participating general practitioners (GPs). GPs were selected based on their Continuous Medical Education (CME) groups and the geographical location; of 18 CME groups invited from the surroundings of Oslo, 10 responded and were included (50 GPs in all). Patients with probable MOH were invited to take part in the brief intervention (BI) study. This study has previously been described in detail (Kristoffersen et al., 2012; Kristoffersen et al., 2015). Briefly, screening positive MOH patients of GPs randomized to the BI intervention arm were invited by their GP to a single BI intervention session including the SDS. This was

done within the GP's ordinary clinical out-patient consultation framework. The relationship between the patients' medication overuse and their headache was addressed, and an agreement to terminate analgesics was aimed for. Patients, whose GP was randomized to the control group, continued to receive ordinary care: business as usual (BAU) as their GP had not been taught the BI scheme. As part of the ordinary pragmatic treatment of chronic headache patients, both groups could, if the GP felt it to be motivated, receive headache prophylactic medication (eg, beta-blockers, anti-epileptics or amitriptyline). In addition, 2 other groups: chronic headache without medication overuse, and people without chronic headache, were drawn randomly from the same, screened GP population. In all 119 participants were invited. At the main data collection time point, 3 months after the intervention, all included patients were interviewed by a headache expert and given a headache diagnosis according to the International Classification of Headache Disorders 3rd ed. (Headache Classification Committee of the International Headache Society [IHS], 2018). This interview also included the SDS (Gossop et al., 1995) and the module of substance dependence in the Mini International Neuropsychiatric Interview (MINI) interview for DSM-IV substance dependence (American Psychiatric Association, 2000; Sheehan et al., 1998). The participants, including the 2 control groups, were at the interview classified as (i) MOH (with medication overuse defined according to the ICHD-3 criteria), (ii) chronic headache controls without medication overuse (CHC); patients on the list reporting chronic headache (> 14 days per month) but without medication overuse, and (iii) population controls (PC); patients also on the GPs list but without chronic headache. For all groups, use of analgesics and non-analgesic medication was monitored. The case mix as described enabled the blinding of the outcome assessor who was not aware of which group the patients belonged to. For MOH patients, the main MOH defining medication group was noted even if there was some minor use of other analgesics in addition. If patients overused both simple analgesics and centrally acting analgesics, they were classified as belonging to the latter group.

### Assessment of Dependence and Validity of the SDS

The 5 questions of the SDS were adapted for headache medication such that “your drug” in the original scale was substituted with the relevant headache medication (Gossop et al., 1995; Grande et al., 2009). The SDS questions were thus: (1) Do you think your use of [headache medication] is out of control? (never/almost never = 0, sometimes = 1, often = 2, always/nearly always = 3); (2) Does the prospect of missing a dose make you anxious or worried? (scoring as for question 1); (3) Do you worry about your use of your [headache medication]? (scoring as for question 1); (4) Do you wish you could stop? (scoring as for question 1); (5) How difficult do you find it to stop or go without your [headache medication]? (not difficult = 0, quite difficult = 1, very difficult = 2, impossible = 3).

As a “gold standard” for the validity of the SDS, we asked about substance dependence using the 7 criteria defined in the DSM-IV with questions from the substance dependence module of the MINI interview. Results were dichotomized according to the DSM-IV definition into substance dependent versus not substance dependent.

**TABLE 1.** Baseline Characteristics of Patients

	N	Males n (%)	Co-occurrence of Migraine n (%)	Age Years (95% CI)	Headache Days/Month (95% CI)	Medication Days/Month (95% CI)
MOH	60	8 (13)	42 (70)	42.1 (40.2–43.9)	25.0 (23.8–26.3)	22.9 (21.2–24.5)
CHC	15	1 (7)	8 (53)	37.9 (34.3–41.4)	23.7 (20.6–26.9)	3.3 (1.8–4.8)
PC	25	7 (28)	10 (40)	38.5 (35.1–41.9)	3.3 (1.8–4.9)	4.1 (1.3–6.9)
<i>P</i> (test)		0.14 ( $\chi^2 = 4.0$ )	0.031 ( $\chi^2 = 6.9$ )	0.041 (ANOVA, post hoc: MOH v. CHC*)	<0.001 (ANOVA, post hoc: MOH v. PC**, CHC v. PC**)	<0.001 (ANOVA, post hoc: MOH v. CHC**, MOH v. PC**)

CHC, chronic headache controls without medication overuse; MOH, medication overuse headache; PC, population controls (without chronic headache).

Post hoc tests are Bonferroni corrected – only significant post hoc comparisons are shown.

\**P* < 0.05.

\*\**P* < 0.01.

\*\*\**P* < 0.001.

## Measures

The outcome measures were mean SDS score (as continuous variable) and substance dependence (yes/no) in chronic headache patients with or without medication overuse, and in controls without chronic headache. Successful withdrawal was defined as no longer having medication overuse according to the International Headache Classification (ie, <15 days per month of medication overuse for most substances, <10 days for triptans or opioids) (Headache Classification Committee of the International Headache Society [IHS], 2018).

## Statistical Analysis

Students' *t* test and  $\chi^2$  tests were used to test 2-group differences for continuous and categorical data, respectively. Fisher's exact test was used when appropriate. Pre-defined significance levels were set to *P* < 0.05. Unless otherwise stated, 95% confidence intervals are given.

Analysis of variance (ANOVA) with Bonferroni corrections was used for post hoc comparisons and multi group comparisons of continuous data. Logistic regression analysis was performed to determine if the SDS score is a good predictor for DSM-IV defined dependence in MOH. The SDS score was treated as a continuous predictor variable and dependence and MOH as dichotomous outcome variables. Age, gender, and presence of migraine were included as possible confounders.

A receiver operating characteristics (ROC) analysis was performed to evaluate the relationship between sensitivity and specificity of the SDS score for the identification of DSM-IV defined dependence in MOH. The area under the ROC curve gives the diagnostic utility of the test, that is, the proportion of cases that are correctly discriminated by the SDS score. The optimal cutoff score was defined to be the one that yields the highest  $\chi^2$  value.

Statistical analyses were performed using SPSS 24.0.

## Ethical Issues

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services (NSD). Patients received posted written information before they consented.

## RESULTS

The overall response rate of the screening questionnaire was 42% (10 579/25,486). Those who responded to the screening questionnaire were older than the non-responders, and more

often female. One hundred of the 119 invited participants including the control groups fulfilled inclusion criteria and were interviewed. Sixty of the included patients were classified as medication-overuse headache (MOH), 15 patients as chronic headache controls without medication overuse (CHC) and 25 patients as population controls (PC) at baseline.

Patient characteristics are given in Table 1.

## Severity of Dependence Scores Versus DSM-IV Substance Dependence Among Medication-overuse Headache Patients and Controls

Half of the patients with a diagnosis of MOH (30/60) were, using DSM-IV criteria based on the MINI-interview, diagnosed as having substance dependence. Of those 40 participants (40/100) that did not receive a clinical MOH diagnosis, 8% (3/40) were given a DSM-IV substance dependence diagnosis ( $\chi^2 = 19.6$ , *P* < 0.001).

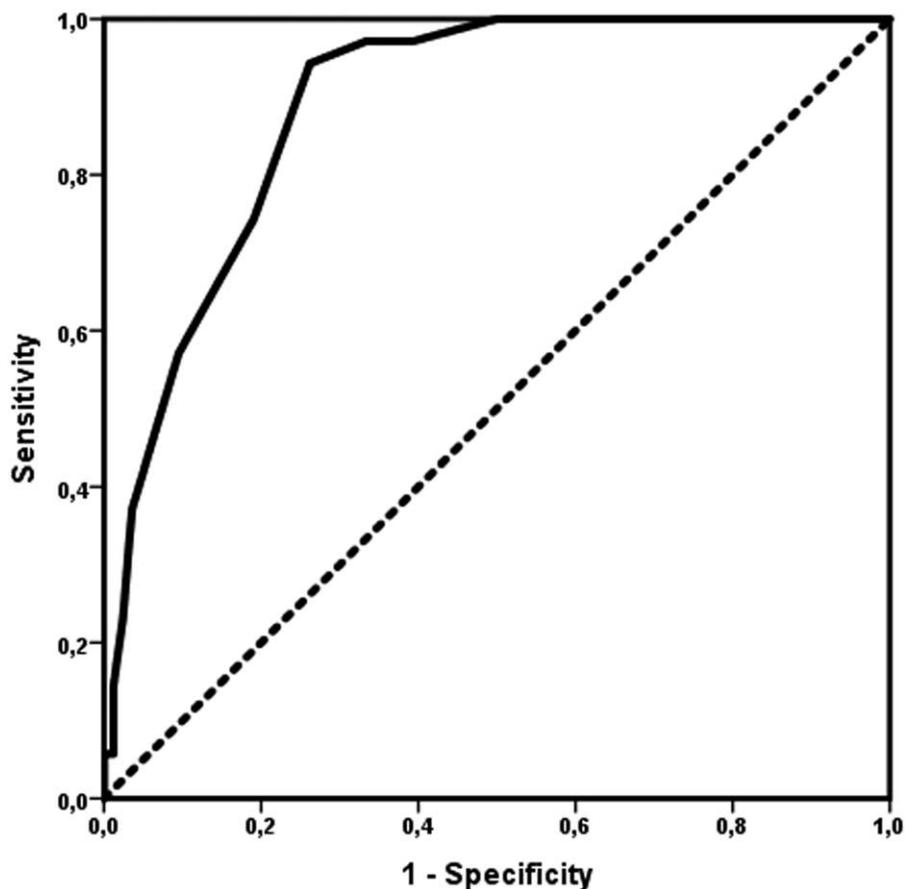
The SDS score was significantly higher for patients who were classified as substance dependent according to the DSM-IV, as compared to non-dependent patients (7.1 vs 2.7, *P* < 0.001). The ROC curve analysis of SDS score for detecting DSM-IV dependence among all included patients (ie, including controls) gave Area Under Curve (AUC) of 88% (Fig. 1). Using the optimal cutoff with the highest  $\chi^2$  value (SDS  $\geq 5$ ,  $\chi^2 = 46.1$ , *P* < 0.001) gave sensitivity of 94% and specificity of 72% for detecting dependence in the whole study sample (n = 100).

MOH patients had significantly higher SDS scores than controls that were not overusing medication (F = 37.1, *P* < 0.001; post hoc: MOH vs CHC *P* < 0.001, MOH vs PC *P* < 0.001, CHC vs PC *P* = 1.0) (Fig. 2, Table 2). Among the 60 patients who were clinically diagnosed as having MOH, SDS scores were also significantly higher if they were classified as substance dependent than if they were not dependent (7.1 vs 4.8, *P* < 0.001). Also, in this case ROC analysis (not shown) showed that the SDS detected DSM-IV dependence but with slightly lower precision (AUC 76%, sensitivity 93%, specificity 47%).

## Characterization of Dependence Among MOH Cases

### Type of Overused Medication

The majority (37/60, 62%) of MOH patients were overusing simple analgesics; of these 83% used paracetamol,



**FIGURE 1.** ROC analyses Severity of Dependence Scale (SDS) scores versus DSM-IV dependence.

81% ibuprofen, and 72% used both). For other medications, groups were too small to analyze separately and were grouped together as “centrally acting analgesics”, including both codeine/opiate containing medications (10 and 3 patients, respectively) and triptans (10 patients), which were overused by 38% (23/60). Of all patients, 8% (3/40) of non-MOH patients, 46% (17/37) of those overusing simple analgesics and 57% (13/23) overusing centrally acting analgesics were classified as substance dependent based on DSM-IV criteria ( $\chi^2 = 20.3$ ,  $P < 0.001$ ). Figure 3 shows the SDS scores by main medication group. There were statistically significant differences in the SDS score between those not overusing analgesics, those overusing only simple analgesics and those overusing centrally acting medications (codeine-containing medications, triptans or opiates) (Fig. 3, Table 2).

### Severity of Dependence and Withdrawal

The SDS was significantly higher among MOH patients who had not managed to withdraw from their medication overuse at follow-up as compared to patients who had managed this (6.7 vs 4.7,  $P < 0.001$ ) (Table 2). There was still a difference, albeit smaller, between failed withdrawal patients with a substance dependence diagnosis who had a higher score (7.6, 95% CI 6.6–8.5) as compared to those without

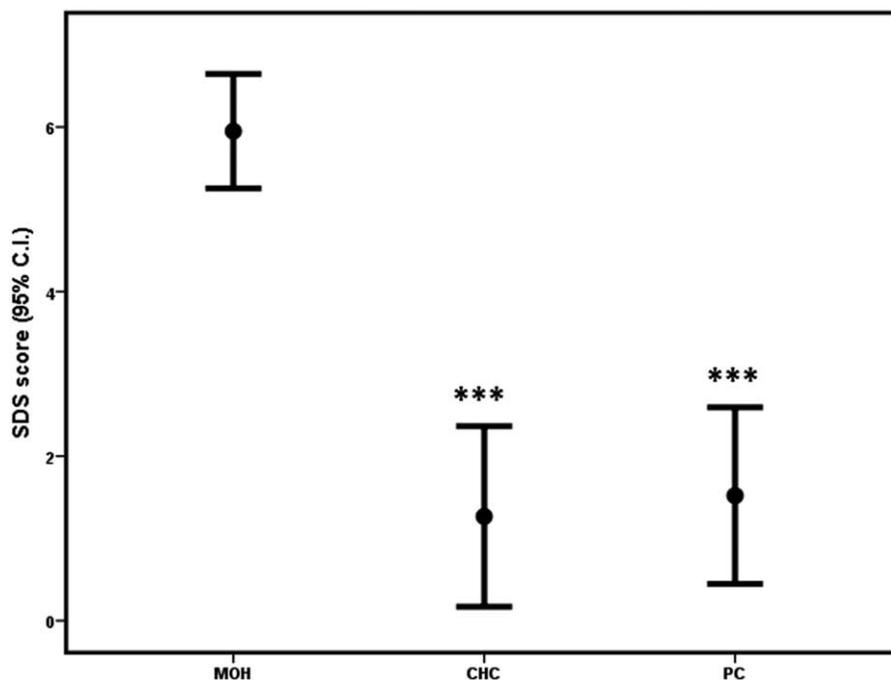
substance dependence (5.6, 95% CI 4.7–6.4,  $F = 1.0$ ,  $P = 0.002$ ).

Even if we select those 24 who actually received the defined brief intervention, SDS was significantly associated with successful withdrawal (Table 2). Of these 24, 73% (11/15) overusing simple analgesics and 56% (5/9) overusing centrally acting analgesics managed to withdraw from their overuse.

### DISCUSSION

In the present study, we found that even though the majority of MOH patients overuse simple analgesics such as paracetamol and ibuprofen, they fulfilled the DSM-IV criteria for substance dependence. In addition, the SDS score was associated with a DSM-IV dependence diagnosis and characterizes dependence-like behavior among such patients.

A clear majority of MOH patients in the general population overuse only simple analgesics (paracetamol and ibuprofen) which in many countries are available as OTC (Colas et al., 2004; Jonsson et al., 2011). The hypothesis that overuse of such non-centrally acting medication represents dependence-like behavior is often challenged by the idea that overuse of pain killers is purely motivated by a desire to reduce the intensity somewhat of a continuously present,



**FIGURE 2.** Severity of Dependence Scale (SDS) scores at the main data collection interview for all cases split by diagnosis. Significant differences between groups: ANOVA,  $P < 0.001$ ; \*\*\*post hoc test:  $P < 0.001$  versus MOH. Patient groups: CHC, chronic headache (without medication overuse) controls; MOH, medication-overuse headache; PC, population controls (without chronic headache).

debilitating headache (Scher et al., 2017). This view may be expected to lead to a constant search for new and more potent pain killers and does not address the possibility that this behavior *per se* may be headache inducing.

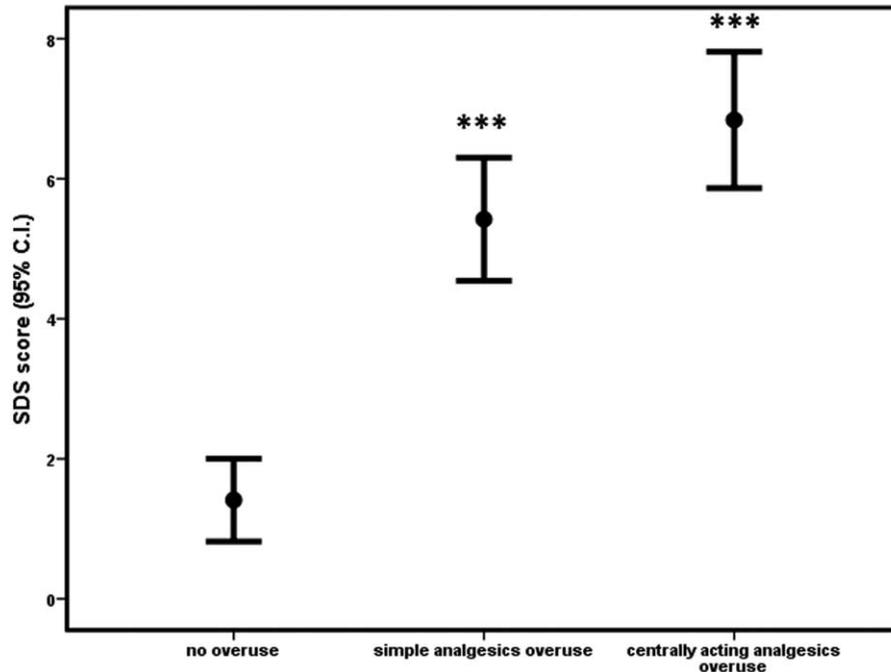
Theoretical considerations and preclinical studies show many similarities between MOH and drug addiction (Calabresi and Cupini, 2005; Cupini et al., 2010). However, it is still debated whether MOH should be regarded as dependence, whether or not the patient should be approached with this perspective and whether withdrawal from the offending medication should be the initial step (Radat and Lanteri-Minet, 2010; Scher et al., 2017). Alternative strategies suggested have

been simply to add various prophylactic pharmacological treatments, such as beta-blockers, topiramate, botulinum toxin, amitriptyline or valproate, directly without prior termination of overuse of the offending drugs (Diener, 2012; Olesen, 2012; Diener et al., 2016). Though some of these medications may carry the risk of new side-effects, this strategy has also been demonstrated to be effective and some patients may indeed spontaneously stop overusing acute headache analgesics over time when administered prophylactics (Diener et al., 2009; Hagen et al., 2009; Silberstein et al., 2013; Sarchielli et al., 2014). It thus becomes difficult to differentiate between improvement caused by addition of prophylactics and that

**TABLE 2.** Logistic Regression Showing Odds Ratios and Significance of Predictor Variables for (a) DSM-IV Dependence and (b) Un-successful Withdrawal (Age, Gender, and Presence of Migraine Included as (Non-significant) Predictors in All Analyses)

(a)			
Patients Included	Test Variable	OR	P
All patients (n = 100)	No medication overuse (reference)	1	
	Simple analgesics overuse	12.1	0.001
	Central analgesics overuse	19.5	0.001
	SDS score	1.8	<0.001
MOH patients (n = 60)	SDS score	1.6	0.001
(b)			
	Successful Withdrawal (Reference)	1	
MOH patients (n = 60)	SDS score	1.6	0.004
BI treated MOH patients (n = 24)	SDS score	2.1	0.04

MOH, medication-overuse headache; OR, odds ratios; SDS, Severity of Dependence Scale.



**FIGURE 3.** Severity of Dependence Scale (SDS) scores at the main data collection interview for all cases split by medication group. Significant differences between groups: ANOVA,  $P < 0.001$ ; \*\*\*post hoc test:  $P < 0.001$  versus no overuse.

achieved through termination of medication overuse. It is reasonable to assume that both mechanisms may contribute.

The SDS (Gossop et al., 1995) is a much used instrument which has previously been validated for behavioral dependence among patients overusing both alcohol (Lawrinson et al., 2007), several illegal and legal drugs (Gossop et al., 1995; Topp and Mattick, 1997; De Las Cuevas et al., 2000; Kaye and Darke, 2002; Martin et al., 2006). The definition of substance dependence used here is from the DSM-IV definitions based on a structural diagnostic interview (MINI) (American Psychiatric Association, 2000; Sheehan et al., 1998). The DSM-IV has often been used as a “gold standard” for clinical diagnoses of substance dependence, not least in studies testing the validity of other instruments. Previous studies have shown that around 70% of MOH patients from headache clinics fulfil DSM-IV criteria for substance dependence (Fuh et al., 2005; Radat et al., 2008). Studies from such clinic populations generally have much higher proportions of severe overuse of more potent, centrally acting drugs. Based on this it is not surprising that these reports find even higher proportions of dependence than we have demonstrated here (Fuh et al., 2005; Radat et al., 2008). We find that in MOH patients, a high SDS score with high precision predicts substance dependence as defined by the DSM-IV. In addition, lower SDS scores are associated with successful termination of the analgesics overuse. We have previously reported that SDS scores predict prognosis related to “self-detoxification” and that they correlate with the type of medication that is overused (Lundqvist et al., 2012). Together with the present findings this suggests that the SDS is a valid instrument for characterizing dependence-like behavior among these patients in a research setting. It may add

useful information in a clinical setting with less chance of successful out-patient withdrawal for a patient with high SDS scores. This may suggest earlier referral to in-patient treatment or early prophylactic treatment. Patients with lower scores should initially be offered medication withdrawal as out-patients with referral still an option if this fails.

We demonstrate that a brief intervention strategy, applied by the GP to cases overusing simple analgesics identified in the general population, is effective treatment and is acceptable by both patients and GPs (Frich et al., 2014; Kristoffersen et al., 2015). It has been argued that patients overusing simple analgesics which are not centrally acting, cannot become dependent in the same manner as those overusing centrally acting drugs. Nevertheless, there are many examples of studies that have demonstrated dependence-like centrally rewarding effects even of placebo (Zubieta and Stohler, 2009; Petrovic et al., 2010). Dependence is therefore by no means excluded in the setting of MOH. The issue of whether the pain drives the medication intake or vice versa seems to have been partly settled through the very clear demonstration in several studies that removing the overuse leads to headache improvement for the majority of patients (Rossi et al., 2006; Tassorelli et al., 2014; Carlsen et al., 2017).

More importantly, whether patients with MOH are “dependent” or “dependent-like,” our studies support a positive effect of detoxification with significant positive consequences for the afflicted patients.

### Methodological Considerations and Limitations

The recruitment base for the study was from patient lists of representative GPs. We can, however, never be fully sure that such a small sample is completely representable of

the general population of Norway. As the population was not recruited for epidemiological purposes but rather for a treatment study, responder rate was not pursued further and was, consequently, lower than in most epidemiological studies. However, our MOH sample is also similar to samples recruited from the general population in recent studies (Colas et al., 2004; Jonsson et al., 2011). In addition, as previously suggested, characteristics of our recruited GPs (Kristoffersen et al., 2015) as well as the similarity of their patients compared to a much larger population-based Norwegian sample of chronic headache cases (Grande et al., 2009) suggest reasonable representativity. Even so, the validation of the SDS versus DSM-IV dependence provided here was not performed in a true general population but from a population sample consisting of the 3 described pre-defined groups. This may lead to an artificially high precision. Our participants were not aware of the focus of the study being medication overuse or the termination of this. They were only informed that the study focused on management of headache in primary care. We suggest this reduces risk of selection bias and over-recruitment of patients with less severe dependence-like behavior or patients who were more motivated for addressing their medication overuse. Clinical data and SDS scores were collected through interview by trained interviewers who were blinded to the diagnoses of the patients.

## CONCLUSIONS

The characteristics of MOH patients suggest that the dependence-like behavior of these patients has clinical implications which should be taken into account in treatment strategies.

Disadvantages of a focus on dependence-like behavior, rest on the assumption that the consequences of such a focus may be negative for the patient. If, on the contrary, negative stigmatization of the patient is avoided and the consequences are identification of the headache cause, increased likelihood of an effective treatment and a more careful prophylactic stance in the first place, then the advantages may well outweigh the disadvantages.

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