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'The entire pharmaceutical compendium' in the treatment of substance use disorders

PERSPECTIVES

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Norway has had a restrictive prescription practice for habit-forming drugs. Several trends point in the direction of liberalisation, while problems arising from drug prescriptions are increasing in many countries – including Norway.

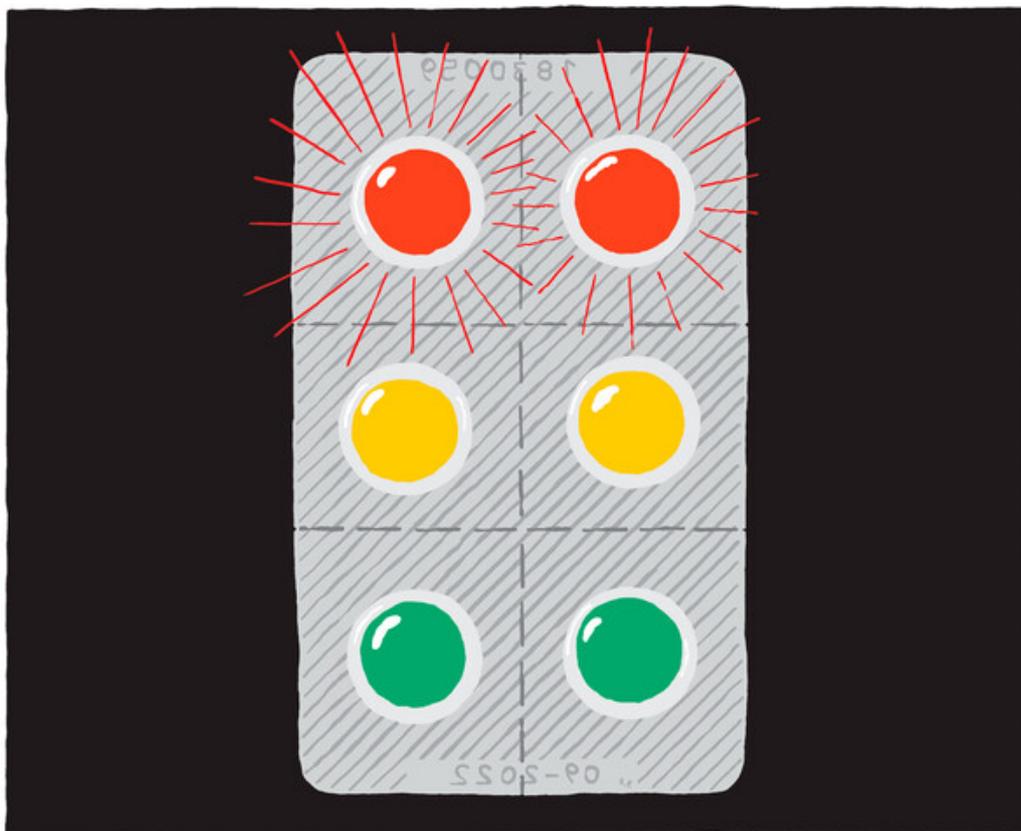


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Norway has traditionally had strict guidelines for prescribing habit-forming drugs. Sedatives and hypnotic drugs should generally only be prescribed for short periods in connection with demonstrable conditions. Except for terminal illness, strong analgesics should only be prescribed for a limited time in the event of injury and postoperative and acute pain, while caution must be shown with regard to chronic diseases. Particular restraint should be exercised when prescribing habit-forming drugs for substance use disorders (1,2). In such instances, the general rule is that the doctor's choice of medication is based on guidelines and instructions, but of course the patient must have a say in the matter as far as possible – just as in other parts of the health services.

A restrictive drug policy on shaky ground?

Several aspects of Norwegian drug policy are presently challenged. The public health services and the social services have had a decades-long statutory responsibility for treating substance use disorders. Since the Vagrancy Act was abolished in 2006, there has been no legal basis on which to impose criminal sanctions for intoxicated behaviour. There has long been widespread agreement that the health and care services are responsible when substance abuse results in ill health. Drug dependent subjects should be treated, not punished. Therefore, the key issues are not *whether* a person with substance use disorder should be treated, but *when* and *how*. Some signals from the political sphere and professional field give cause for concern.

One such signal is that several important politicians seem to want to decide how drug-assisted rehabilitation (DAR) should develop. The Norwegian government states in its current political platform that it wishes to include more medications and ensure greater freedom of choice in DAR, as well as conduct trials with heroin-assisted treatment within DAR (3). The drug users are supposed to have more influence over which medications should be prescribed for them. It is not clear what this means, but the fundamental conditions underlying DAR are not mentioned. The most important aspect is that the drug-dependent patient can be stabilised with a medication that works so slowly over such a

long period of time that he or she can be treated with a drug that is taken once every 24 hours. The goal is that the patient can live his or her life in society without being dominated by swings between abstinence and intoxication.

Norway currently uses methadone and buprenorphine, two internationally approved and recommended drugs. One possible option is slow-release morphine, which is used in Austria and some other countries (4). Treatment results from this are on par with methadone, and some patients report a slightly improved quality of life (5). However, the drug is more difficult to manage and much more expensive. Treatment with short-term drugs such as heroin (diacetylmorphine) requires 2–3 doses per day, and clinics must therefore be established where patients come several times a day, seven days a week, for an unlimited period of time (6). DAR is currently being imposed as a cost-reduction regime, and there is no indication that more resources will accompany the new medications.

The user organisations have signalled the expectation that patients will have increased influence on chosen medications, including other opioids such as morphine chloride and oxycodone. However, the immediate subjective high following drug intake is a central motivation in heroin addiction. This craving, which intensifies with repeated use, is critical for understanding a substance use disorder (7). Usually, popular abused drugs have a rapid, intense effect – not a delayed one due to slow absorption and gradual uptake into the brain, such as methadone. This can easily lead to conflict and dissatisfaction between patients and doctors if treatment is developed with the expectation that the user's wishes and experience of the drug's effect will be a determining factor in the choice of medications.

There is also reason to expect difficulties relating to control measures. In Denmark, where control is less stringent, the number of deaths linked to methadone is higher than the number of heroin-related deaths (8). In England, the number of fatal overdoses caused by heroin is lower than the number caused by prescription opioids with methadone as the main contributor (9). The percentage of methadone-related deaths in Norway continued to increase up to 2012 (10). As a result, more emphasis was placed on various types of controls over the drug's distribution and use, and the percentage of methadone deaths has since declined (10). The percentage of heroin-related deaths has also dropped significantly, but mortality resulting from opioid use is still relatively unchanged due to the increase in deaths from other opioids, including medications requested by users (10).

A concern in this regard is that individual doctors have also begun to prescribe other opioids, especially morphine sulphate, as well as oxycodone. An example of this is that the doctor in charge of a low-threshold intervention in Oslo city centre recommends 'drawing on the entire pharmaceutical compendium in the effort to help the most down-and-out users' (11). The expression 'use the entire pharmaceutical compendium' has gained popularity in the media and is heard in political debates as well. But what does this really mean? Like other patients, those with substance use disorders will of course get drug-related help as indicated by their medical condition. By the same token, the risk of complications and issues of safety must be taken into account. However, the expression is often interpreted to mean that people with substance use disorders should be treated with the opioid of their choice based on their own experiences. Some user organisations now also require maintenance treatment for users of CNS stimulants and benzodiazepines. Treatment of alcohol addiction is mentioned in this context as well (12). On this basis, it is not surprising that we are currently seeing an increase in prescriptions for habit-forming drugs, especially opioids such as oxycodone and tramadol (12, 13). Mortality statistics show that these drugs are increasingly contributing to fatal overdoses (10).

The problem of benzodiazepines

Another aspect is that many users want to take benzodiazepines. As we now know, the risk of developing a dependency on these drugs is high. Despite recommendations that all treatment with benzodiazepines should be short term, studies of the Norwegian Prescription Database show that 7 % of those who used anti-anxiety drugs and 15 % of those who took hypnotics overused these drugs, defined as more than 365 defined drug doses per year (14). This corresponds to more than daily use throughout an entire year. A Swedish study shows that prescriptions for children and adolescents tend to last over an extended period time and are difficult to stop (15).

The disadvantage of long-term drug prescription is substantial, and involves a high incidence of falls, reduced cognition, functional impairment and, in reality, episodic memory loss as well. These users also find it difficult to meet the requirements of driving licence regulations. Alzheimer's disease has been shown to be associated with use of benzodiazepines (16). There are currently no accepted indications of long-term treatment with these drugs for mental disorders or sleep disorders. They bring immediate relief from agitation and tension, but their long-term use leads to problems with stress intolerance and disruption of circadian rhythms. Many patients with substance use disorders self-medicate a variety of health problems and want to continue to have their prescriptions.

A major Norwegian literature review clearly shows a lack of documentation of the benefits of long-term use of benzodiazepines for people with substance use disorders and that the drug increases the incidence of irritability, dysphoria and weak impulse control (17). It also shows that use of benzodiazepines is incorporated in the substance abuse dynamics whereby the medication intensifies the feeling of inebriation or intoxication from other drugs. The drugs requested by users are usually those resulting in rapid increases in blood drug concentrations and quick uptake into the brain with the target GABA receptors – leading to more pronounced inebriation.

'Is it really so dangerous?'

How dangerous are benzodiazepines? The pharmacodynamic synergy not only intensifies the feeling of intoxication of, for example, opioids; it also weakens the respiration even further. Studies in forensic toxicology show that benzodiazepines are involved in more than two-thirds of opioid-dominated overdose fatalities (18). They are also involved in a significant amount of violent crime and various types of accidents. Thus, there is good reason to limit their use as much as possible and to have a restrictive policy on prescribing benzodiazepines to patients with substance use disorders.

Opioid use has increased dramatically in the US and some other countries. First came an increase in oxycodone, which was launched as a safe, non-habit-forming drug in an extensive marketing campaign by Purdue Pharma in the late 1990s. This was followed by a substantial rise in fatal drug overdoses, as shown in a major US scientific analysis of the correlation between opioid prescriptions and fatal overdoses (19).

Further, analyses of prescription patterns and deaths have shown that when opioids are prescribed in combination with benzodiazepines in pain therapy, the percentage of patients who develop a dependency increases dramatically (19). Benzodiazepines have also been found to be involved in many of the deaths. Mortality increases systematically with simultaneous prescription of benzodiazepines (20).

Kindness is not always kindness

In summary, there are many reasons to defend the relatively strict Norwegian prescription practice for habit-forming medications such as opioid analgesics, benzodiazepines and benzodiazepine-like sedatives and hypnotics. Doctors in the US often experience a strong

expectation to prescribe medications according to their patients' wishes – as long as the patient can pay. Few effective restrictions are in place, and until recently there has been relatively little support within society for such regulations.

Demand for medications to relieve various forms of discomfort is growing in Norway as well. However, anxiety, sadness and pain are all phenomena that serve as important signals in both an individual's life and in society at large. To date, Norwegian doctors have worked within a regulatory framework and with recommendations that support prescribing habit-forming medications only when a clear medical indication is present. It is important that Norwegian doctors retain such support – from both medical and political arenas. This does not mean that the use of medication cannot and should not be expanded, but like other areas of medical treatment, this must be done on the basis of information from systematic literature reviews or as a part of well-planned, controlled clinical trials.

Note: Following acceptance of the manuscript in the Journal of the Norwegian Medical Association, the Norwegian Institute of Public Health published mortality statistics for 2017, which show an overall decline in the number of drug overdoses. Analyses of forensic toxicology findings suggest that deaths caused primarily by heroin use continue to decrease, while the percentage of methadone-related deaths has increased. According to this analysis, more people die from methadone and buprenorphine than from heroin in Norway, as in Denmark. The same applies to opioids such as morphine and oxycodone. It is too early to know whether this indicates a trend, but the findings emphasise the importance of having a restrictive prescription practice and the best possible control of DAR medications (<https://www.fhi.no/nyheter/2018/nakotikautlostedodsfall-2017/>).

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