

# Benzodiazepine treatment for drug-dependent subjects

This is an excerpt from the full technical report, which is written in Norwegian.

The excerpt provides the report's main messages in English.

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We would like to thank all contributors for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services  
Oslo, January 2007

# Key messages

## Benzodiazepine treatment for drug-dependent subjects

**Background** Benzodiazepines are drugs used in treatment of anxiety and insomnia, in addition to muscle pain and seizures. Benzodiazepines are widely used by the general population and the sales figures correspond to a daily consumption of therapeutic doses of benzodiazepines in 4-5% of the population. Benzodiazepines are effective drugs with low toxicity. Benzodiazepines are also popular as drugs of abuse and its consumption may contribute to exacerbate an existing drug abuse problem. The cost benefit considerations are therefore especially interesting when these drugs are prescribed to subjects with pre-existing problems of drug abuse.

**Methods** The systematic review was performed according to general principles of HTA. The work was carried out together with a review team of professionals from the drug abuse field. Systematic searches were performed after published systematic reviews and randomised controlled trials in international databases.

**Results** The report includes 38 studies; one systematic review, 33 randomised controlled trials and four observational studies. There were only two randomised controlled trials involving drug-dependent subjects. The other studies involve long-term users of therapeutic doses of benzodiazepines (14 studies), non-dependent subjects with a history of drug abuse (12 studies) and subjects with alcohol-dependence (6 studies). The focus of the report is therefore concentrated on subjects with general drug abuse problems or with long-term users of therapeutic doses of benzodiazepines. No studies were found on the therapeutic effects of benzodiazepines for the usual indications (anxiety, insomnia, epilepsy) in subjects with drug abuse problems. The studies showed that benzodiazepines have abuse liability in this population and may lead to dependence problems. In addition, benzodiazepines impaired psychomotor skills and cognitive functions in drug abusers as well as in long-term users of benzodiazepines. The report showed that even though benzodiazepines reduce symptoms related to alcohol withdrawal, this could as well be achieved with other drugs without abuse potential.

**Conclusion** The systematic review did not find any studies on the therapeutic effect of benzodiazepines in drug-dependent subjects. Our report documents evidence of negative effects in subjects with drug problems. Benzodiazepines have abuse liability and may lead to dependence problems. The studies showed that benzodiazepines impaired psychomotor skills and cognitive functions in drug abusers as well as in long-term users of benzodiazepines. The magnitude of the effects on psychomotor and cognitive functions is less apparent for oxazepam and roughly equivalent for other benzodiazepines.

# Executive summary

## Benzodiazepine treatment for drug-dependent subjects

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### BACKGROUND

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Benzodiazepines are drugs used in treatment of anxiety and insomnia, in addition to muscle pain and seizures. The benzodiazepines bind to gamma-aminobutyric acid (GABA) receptors located in the central nervous system.

Benzodiazepines are widely used in the general population and the sales figures correspond to a daily consumption of therapeutic doses of 4-5% of the population. Benzodiazepines are effective drugs with low toxicity. Benzodiazepines are also popular as drugs of abuse and its consumption may contribute to exacerbate an existing drug abuse problem. The cost benefit considerations are therefore especially interesting when these drugs are prescribed to subjects with pre-existing problems of drug abuse. Seven different benzodiazepines are on the market in Norway.

The Norwegian Knowledge Centre for the Health Service (NOKC) was requested by the Medical Faculty at the University of Oslo to do a health technology assessment (HTA) on benzodiazepine treatment for drug-dependent subjects.

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### OBJECTIVE

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The report is a systematic review of the literature on benzodiazepine treatment for drug-dependent people.

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### METHODS

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The work was carried out together with a review team of professionals from the drug abuse field. Systematic searches were performed after published systematic reviews and randomized controlled trials in international databases. Observational studies were included for the endpoints death and car-accidents. The literature is evaluated in a step-wise manner according to general principles of HTA. Studies that fulfilled our predetermined inclusion criteria are assessed and summarized.

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### RESULTS

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The report includes 38 studies; one systematic review, 33 randomised controlled trials and four observational studies. There were only two randomised controlled trials involv-

ing drug-dependent subjects. The other studies involve long-term users of therapeutic doses of benzodiazepines (14 studies), non-dependent subjects with a history of drug abuse (12 studies) and subjects with alcohol-dependence (6 studies). The report is therefore focused on subjects with general drug abuse problems or long-term users of therapeutic doses of benzodiazepines.

No studies were found on the therapeutic effects of benzodiazepines for the usual indications (anxiety, insomnia, epilepsy) in subjects with drug abuse problems. Use of benzodiazepines in treatment of drug dependent subjects therefore often takes place without documented effect and on uncertain indications.

Our report documents negative effects of benzodiazepines in drug-dependent subjects. The studies showed that benzodiazepines have potential of abuse liability in this population and may lead to dependence problems. In addition, benzodiazepines impaired psychomotor skills and cognitive functions in drug abusers as well as in long-term users of benzodiazepines. These problems are present with all known benzodiazepines and are dependent on dosesize, treatment period, high absorption speed and high bioavailability. Diazepam, flunitrazepam and alprazolam are benzodiazepines with these two last characteristics and the studies reported problems with those drugs. On the other side, oxazepam had slow absorption and gave fewer problems. Clonazepam is less well characterized but it has characteristics similar to diazepam and alprazolam.

Our report shows that even though benzodiazepines reduce symptoms related to alcohol withdrawal, this could as well be achieved with other drugs without abuse potential.

- No studies were found on effect of benzodiazepines on the indications anxiety, insomnia or epilepsy in drug-dependent subjects
- Randomised controlled trials (12 studies) showed that benzodiazepines had potential of abuse liability and could cause dependence in people with a history of drug abuse
- Randomised controlled trials (12 studies) showed that benzodiazepines gave reduced psychomotoric and cognitive functions in drug-dependent people, as in persons with a history of drug abuse
- Diazepam showed greater abuse liability than oxazepam
- Diazepam, lorazepam, flunitrazepam and triazolam showed similar effects on psychomotoric and cognitive functions. Oxazepam had some more favourable profile on these two endpoints
- Withdrawal from benzodiazepines gave significant better psychomotoric function compared to the control group remaining on benzodiazepines
- There were no studies on withdrawal from benzodiazepines in drug dependent people. The studies included long-term users of benzodiazepines
- Slow withdrawal was better than fast withdrawal
- The studies showed improved effect of diazepam compared to placebo as symptom relieving agent and as seizure prophylactic in withdrawal from alcohol
- The studies showed no improved effect of benzodiazepines compared to other agents as symptom relieving agent or as seizure prophylactic in withdrawal from alcohol

- The effect of benzodiazepines in opioid maintenance treatment are not systematic investigated

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## CONCLUSION

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The systematic review did not find any studies that could document the effect of benzodiazepines in drug dependent subjects. The report documents evidence of negative effects in subjects with drug abuse problems. Benzodiazepines have abuse liability and may lead to dependence problems. The studies showed that benzodiazepines impaired psychomotor skills and cognitive functions in drug abusers as well as in long-term users of benzodiazepines. The magnitude of the effects on psychomotor and cognitive functions is less apparent for oxazepam and roughly equivalent for other benzodiazepines.

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