

# Methadone and buprenorphine effects on driving abilities

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## 5. Summary

### *Background/aims*

Driving under the influence of drugs and alcohol are major contributors to the high frequency of road traffic crashes globally. Methadone and buprenorphine are among the twenty drugs most frequently detected in apprehended drivers suspected of drug driving in Norway. However, research investigating drug induced traffic impairment after use of methadone and buprenorphine has hardly been performed.

We aimed to provide an overview of the current scientific literature studying the effects of these drugs on crash risk and driving-related performance. We further performed a clinical study with actual on-road driving to investigate the acute effects of two single, analgesic doses of both methadone and buprenorphine on driving performance in opioid-naïve subjects, including neurocognitive tests and pharmacokinetic measures.

### *Methods*

For Paper I, we performed a systematic literature review of the current scientific literature on traffic-related effects of methadone and buprenorphine. Epidemiological studies on traffic risk and experimental studies on performance of traffic relevant skills were included.

For Papers II and III a clinical trial was performed , using a five-way, double-blind, randomized, placebo-controlled, double-dummy, cross-over design, to study on-road driving and driving relevant neurocognitive tests in healthy subjects after a single dose of methadone (5 or 10 mg) and buprenorphine (0.2 or 0.4 mg). Blood and oral fluid were collected throughout the test days. Paper II describes the effects of both drugs on driving and neurocognitive tests. In Paper III we analyzed the correlations between drug concentrations in blood and effects on the neurocognitive tests including driving, and report drug concentrations in blood and oral fluid as well as oral fluid/blood concentration ratios.

### *Results and conclusions*

The review revealed that recent epidemiological studies found an increased crash risk in male patients treated with methadone and an increased odds ratio for being responsible for the crash in injured drivers exposed to either methadone or buprenorphine. Studies on patients in opioid maintenance treatment found that both drugs to some degree impaired

performance relevant to safe driving. Few studies had investigated the acute effects of methadone and buprenorphine on driving related skills in healthy volunteers, and none of these tested on-road driving.

Our clinical trial showed some dose-dependent effects of both drugs on driving related skills, even though the administered doses are considered to be low. Buprenorphine 0.4 mg significantly impaired driving measured with the standard deviation of lateral position (SDLP). Mild effects on driving related skills were measured, but large individual variations were observed. For both drugs, four out of 22 subjects terminated the driving test due to sleepiness. Some significant positive correlations between drug concentration in blood and effects on neurocognitive testing were found for buprenorphine, but not for methadone. Large individual differences in pharmacokinetics were observed for both drugs, in blood as well as in oral fluid. Concentrations of buprenorphine in blood were in general very low and concentrations above the limit of qualification were found only in one third of the blood samples.

Our results imply that caution regarding driving is required when initiating opioid treatment and adjusting opioid doses, and patients should thus be informed accordingly, to avoid impaired driving and being involved in traffic accidents.

## 6. Sammendrag

### *Bakgrunn/formål*

Kjøring i påvirket tilstand er medvirkende årsak til et stort antall trafikkulykker globalt. Metadon og buprenorfin er blant de tjue psykoaktive stoffene som oftest påvises i prøver fra bilførere mistenkt av politiet for ruspåvirket kjøring i Norge. Det er imidlertid gjennomført svært få studier når det gjelder trafikkrelevant påvirkning etter bruk av metadon og buprenorfin.

Vi har undersøkt hva som foreligger av vitenskapelige studier hvor effekten av disse stoffene på kjørerelaterte ferdigheter og risiko for trafikkulykker er studert. Videre gjennomførte vi en klinisk studie hvor de akutte effektene av lave smertestillende doser av metadon eller buprenorfin hos opioid-naive personer ble undersøkt ved reelle kjøring på motorvei, inkludert nevrokognitive tester og farmakokinetiske målinger.

### *Metode*

Artikkel I er en systematisk litteraturgjennomgang av studier som har undersøkt trafikkrelaterte effekter av metadon og buprenorfin. Epidemiologiske studier av trafikkrisiko og eksperimentelle studier av effekter på trafikkrelevante ferdigheter ble inkludert.

Artikkel II og III omfatter en femveis, dobbelt blindet, randomisert, placebokontrollert, dobbelt dummy, overkrysningsstudie for å studere effektene på kjøring og kjørerelevante ferdigheter av enkeltdoser med metadon (5 eller 10 mg) og buprenorfin (0,2 eller 0,4 mg) gitt til friske frivillige. Det ble tatt blod- og spyttprøver i løpet av testdagene. Artikkel II beskriver virkningene av begge legemidler på bilkjøring og nevrokognitive tester. I artikkel III analyserte vi sammenhengen mellom stoffkonsentrasjoner i blod og effekter på de nevrokognitive testene inkludert kjøring. Konsentrasjoner av metadon og buprenorfin ble målt i både blod og spytt, samt spytt/blod konsentrasjonsratio, ble rapportert.

### *Resultater og konklusjon*

Oversiktsartikkelen viste at nyere epidemiologiske studier har avdekket en økt risiko for å være involvert i trafikkulykker for mannlige pasienter som behandles med metadon, og en økt sannsynlighet for å være skyld i trafikkulykker for skadde sjåførere som hadde brukt metadon eller buprenorfin. Studier av pasienter i vedlikeholdsbehandling med opioider viste

at både metadon og buprenorfin til en viss grad svekket trafikkrelevante ferdigheter. Det er få studier som har undersøkt de akutte effektene av metadon og buprenorfin når det gjelder kjørerelaterte ferdigheter hos friske frivillige, og ingen kjørestudier var gjennomført.

Den kliniske studien viste doseavhengige effekter av begge legemidler på enkelte av de nevrokognitive testene selv om dosene som ble gitt anses lave. Buprenorfin 0,4 mg medførte signifikant økning av «vingling i vegbanen» (SDLP). Generelt ble det funnet moderate kliniske effekter av legemidlene, men store individuelle forskjeller ble observert. Fire av 22 deltakere avsluttet imidlertid kjøringen på grunn av søvnighet etter inntak av både metadon og buprenorfin. Signifikant korrelasjon mellom konsentrasjon i blod og noen av effektene på de nevrokognitive testene ble vist for buprenorfin, men ikke for metadon. Det ble observert store individuelle forskjeller i farmakokinetikk for begge legemidlene, både i blod og spytt. Konsentrasjonene av buprenorfin i blod var generelt veldig lave og bare en tredjedel av blodprøvene hadde konsentrasjoner av buprenorfin over påvisningsgrensen.

Resultatene viser at det bør utvises forsiktighet med hensyn til kjøring ved oppstart av behandling med opioider og ved justering av opioid-doser. Pasienter som behandles med disse legemidlene bør informeres om dette, for å unngå påvirket kjøring og ikke bli involvert i trafikkulykker.

## 7. Samenvatting

### *Achtergrond/doel*

Rijden onder invloed van alcohol of drugs dragen in belangrijke mate bij aan het hoge aantal verkeersongevallen wereldwijd. Methadon en buprenorfine behoren tot de twintig geneesmiddelen/drugs die het vaakst worden aangetoond bij bestuurders aangehouden op verdenking van het rijden onder invloed in Noorwegen. Onderzoek naar verkeersgerelateerde effecten na het gebruik van methadon en buprenorfine is echter nauwelijks uitgevoerd.

We wilden meer te weten te komen over de bestaande kennis over de effecten van deze geneesmiddelen op rijvaardigheid en verkeersongevallen. We wilden ook een klinisch onderzoek uitvoeren met een rijtest om de acute effecten van analgetische doseringen van methadon en buprenorfine bij opiaat-naïeve personen te onderzoeken, inclusief neurocognitieve tests en farmacokinetische metingen.

### *Methode*

In paper I werd een overzicht gegeven van de huidige wetenschappelijke literatuur over verkeersgerelateerde effecten van methadon en buprenorfine. Een systematisch literatuuronderzoek werd uitgevoerd om epidemiologische studies en experimentele studies naar de invloed van deze stoffen op ongevalsrisico en rijvaardigheid te beoordelen.

Vervolgens werd een 5-wegs, dubbelblind, gerandomiseerd, placebo-gecontroleerd, dubbel dummy crossover onderzoek uitgevoerd (paper II en III) om rijvaardigheid en relevante neurocognitieve functies te bestuderen in gezonde personen na een enkele dosering methadon (5 of 10 mg) of buprenorfine (0,2 of 0,4 mg). In paper II worden de effecten van beide geneesmiddelen op rijvaardigheid en de neurocognitieve tests beschreven. In papier III analyseerden we de correlaties tussen geneesmiddelconcentraties in bloed en effecten op de neurocognitieve tests en rijvaardigheid, en geneesmiddelconcentraties in bloed en speeksel evenals speeksel / bloed-concentratieratio werd gerapporteerd.

### *Resultaten en conclusies*

De review bracht aan het licht dat recente epidemiologische studies vonden een verhoogd risico op verkeersongevallen bij mannelijke patiënten die werden behandeld met methadon

en een verhoogd risico op schuld bij verkeersongevallen na gebruik van methadon en buprenorfine. Onderzoek bij patiënten die een onderhoudsbehandeling met opioïden ontvangen wees uit dat beide geneesmiddelen tot op zekere hoogte de verkeersgerelateerde vaardigheden negatief beïnvloedden. Verder zijn er weinig studies uitgevoerd naar de acute effecten van methadon en buprenorfine op rijvaardigheid bij gezonde vrijwilligers, en geen rijstudies zijn uitgevoerd.

De klinische studie toonde enkele dosisafhankelijke effecten van beide geneesmiddelen op rijvaardigheid. Buprenorfine 0,4 mg verslechterde aanzienlijk de rijvaardigheid zoals gemeten met de standaard deviatie van de laterale positie (SDLP), een maat voor slingergedrag. De invloed van opiaten op rijvaardigheid was over het algemeen mild, maar individuele variantie was hoog. Vier van de 22 proefpersonen beëindigden voortijdig hun rijtest vanwege slaperigheid na beide medicijnen. Enkele correlaties tussen geneesmiddelconcentratie in bloed en effecten op neurocognitieve testen werden gevonden voor buprenorfine, maar niet voor methadon. Grote individuele variaties werden ook waargenomen met betrekking tot de farmacokinetiek van beide geneesmiddelen. Concentraties van buprenorfine in het bloed waren in het algemeen laag en in slechts een derde van de bloedmonsters was de buprenorfine concentraties boven de bepaalbaarheidsgrens.

De resultaten impliceren dat voorzichtigheid met betrekking tot autorijden vereist is bij het initiëren van behandeling met opioïden en bij het aanpassen van opioïde doses, en patiënten moeten hierover worden geïnformeerd om rijden onder invloed en verkeersongevallen te voorkomen.