Is there evidence for the use of buprenorphine in treating methamphetamine use disorder?

Dr Tom English

Addiction Psychiatry Advanced Trainee, St Vincent's Hospital

Referral question from community

"James" is a 45 year old homeless man with schizophrenia. He is case managed on a community treatment order. He has a good relationship with his long term case manager and is prescribed oral antipsychotic medication.

He has been smoking methamphetamine several times per week for the last 3 years. He is intermittently adherent to his antipsychotic medication, resulting in frequent psychotic relapses and subsequent admissions to the psychiatric inpatient ward to re-establish treatment. He was recently switched from depot medication to oral per his preference.

He wants to abstain from using methamphetamine but tells me that he has found it impossible EXCEPT for when he has been using illicit suboxone.

Can we prescribe him suboxone to reduce his methamphetamine use?

Initial thoughts

- Complex patient
- Very difficult to treat methamphetamine use disorder in schizophrenia
  - No evidence based pharmacotherapy for MUD
  - ?efficacy of psychosocial interventions (eg Contingency Management, CBT, Matrix Model, Community Reinforcement Approach) for patients with schizophrenia + MUD
    - Usually excluded from trials
    - Eg no mention of schizophrenia in latest American guidelines for treatment of Stimulant Use Disorder (2023)
  - Capacity of community MH services to deliver these interventions
- Does he have an undiagnosed OUD?
- Is he seeking to divert the BPN?
- Is the BPN reducing his MA withdrawal symptoms?
- Is the BPN reducing his psychotic symptoms?

BPN and schizophrenia

- Is the BPN reducing his psychotic symptoms?
  - BPN acts on
    - Mu-opioid receptor partial agonist
    - Kappa-opioid receptor (KOR) antagonist
  - KOR and schizophrenia
    - Dopamine hypothesis: symptoms of schizophrenia and non-schizophrenic psychosis are the result of dopamine abnormalities in the mesolimbic and PFC.
    - Preclinical studies suggest that KOR stimulation may contribute to the positive symptoms of schizophrenia by increasing dopamine release
    - Thus, KOR antagonism (by BPN) may reduce psychosis
    - Single 10 patient study in 1987 (Schmauss et al) found acute reduction in positive psychotic sx after BPN 0.2mg.

BPN and schizophrenia

Journal of psychiatry and brain science
Author Manuscript HHS Public Access

Relevance of the Kappa Dynorphin System to Schizophrenia and Its Therapeutics

Anissa Abi-Dargham

J Psychiatr Brain Sci. 2021; 6: e210015.

Antipsychotic Effect of Buprenorphine in Schizophrenia

Claudia Schmauss, M.D., Alexander Yassouridis, Ph.D., and Hinderk M. Emrich, M.D.

The antipsychotic potency of the partial opiate agonist buprenorphine was evaluated in 10 neuroleptic-free schizophrenic patients suffering from frequent hallucinations, delusions, and severe formal thought disorders. Buprenorphine had a pronounced antipsychotic effect, which lasted about 4 hours, in patients with schizophreniform disorders (N=4) and paranoid schizophrenia (N=3).
(Am J Psychiatry 1987; 144:1340–1342)

obtained. None had an organic illness. All patients had been free of neuroleptic medication for at least 5 weeks. Of the 10 patients, four were suffering from a first manifestation of a schizophreniform disorder, three were experiencing a repeat episode of paranoid schizophrenia and had been exposed previously to neuroleptic treatment, and the remaining three fulfilled the criteria for residual schizophrenia (i.e., continuously ill, blunted or inappropriate affect, and social withdrawal) and were experiencing acutely exacerbated paranoid and hallucinatory symptoms (DSM-III

Literature

The Effect of Buprenorphine on Methamphetamine Cravings

Mehrdad Salehi, MD, Alireza Emadossadat, MD,* Gholam Reza Kheirabadi, MD,† Mohammad Reza Maracy, PhD,‡ and Mohammad Reza Sharbafchi, MD**

(*J Clin Psychopharmacol* 2015;35: 724–727)

ST VINCENT'S HEALTH AUSTRALIA

Background: Methamphetamine (METH) abuse and dependence present a major global problem. We investigated the efficacy of adding buprenorphine in reducing METH cravings during treatment with the Matrix program.

Methods: This was a randomized, double-blind, controlled clinical trial of 40 men between the age of 18 and 40 years who were referred to the addiction treatment center at Noor Hospital from December 2012 to September 2013. All of the selected subjects participated in the Matrix program and were randomly assigned into 2 groups and given either buprenorphine or a placebo. A 4-month intervention program with buprenorphine or a placebo was arranged for each group. Demographic variables of the 2 groups, descriptive indices from the cocaine craving questionnaire-brief (CCQ-Brief), the ratio of urine tests positive for METH, and the frequency of drug complications were regularly evaluated in both groups every 2 weeks and, if not possible, by the third or fourth week. All analyses were performed by SPSS20 using analysis of covariance, χ^2, and t tests.

Results: The average of indices from the cocaine craving questionnaire-brief score, except the 2 initial measurements, was significantly lower in the intervention group in all measurements ($P < 0.05$). Apart from weeks 3 and 28, the ratio of positive tests was significantly different in all measurements in both groups ($P < 0.05$).

Conclusions: Buprenorphine augmentation, in comparison with the placebo, significantly reduced the craving to use METH during treatment with the Matrix program.

- 2015, RCT, double blind
- 40 men, MA dependent (no other substances), members of "Matrix program" at an addiction treatment centre in Iran
- Exclusion criteria
  - Other substance use
  - Severe mood disorder, SI, **psychotic disorder**
- 2 groups: BPN 6mg or placebo, 4 month psychosocial program
- Measurement: MA cravings (CCQ-Brief) and urine tests
- Results: BPN augmentation significantly reduced MA cravings

The Effect of Buprenorphine on Methamphetamine Cravings

Mehrdad Salehi, MD, Alireza Emadossadat, MD,* Gholam Reza Kheirabadi, MD,† Mohammad Reza Maracy, PhD,‡ and Mohammad Reza Sharbafchi, MD**

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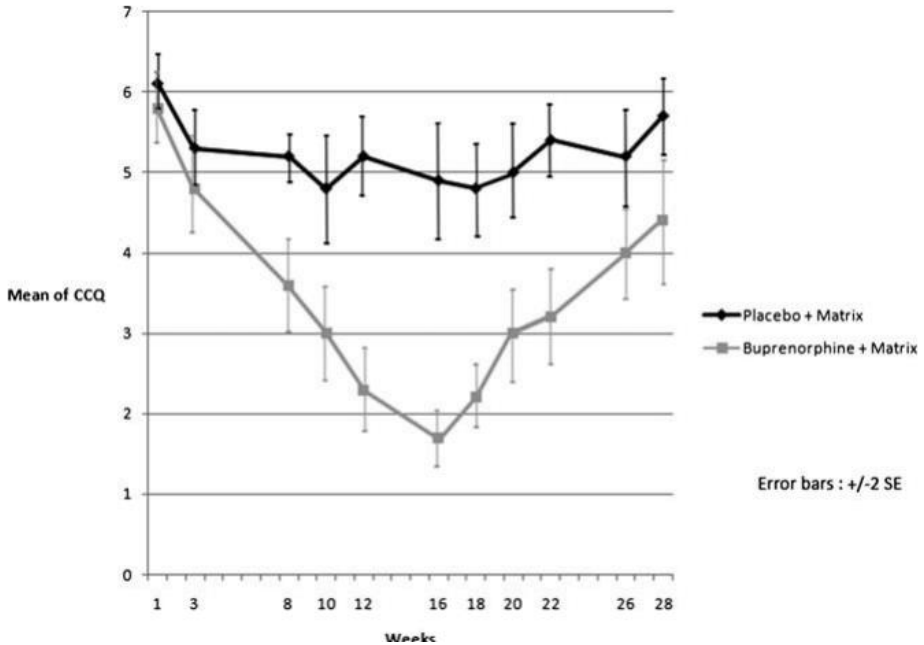
ST VINCENT'S HEALTH AUSTRALIA

TABLE 1. Results of *t* Test for Comparing CCQ Scores in Intervention and Placebo Groups in Measurement Times

	Placebo Group		Intervention Group		
CCQ	**n**	**Mean (SD)**	**n**	**Mean (SD)**	***P***
Baseline (first visit)	31	6.1 (0.89)	23	5.8 (1.1)	0.294
Week 3 (second visit)	29	5.3 (1.1)	22	4.8 (1.4)	0.134
Week 8 (third visit)	26	5.2 (0.7)	20	3.6 (1.3)	<0.001
Week 10 (fourth visit)	24	4.8 (1.5)	20	3.0 (1.3)	<0.001
Week 12 (fifth visit)	21	5.2 (1.0)	20	2.3 (1.2)	<0.001
Week 16 (sixth visit)	20	4.9 (1.5)	20	1.7 (0.8)	<0.001
Week 18 (seventh visit)	20	4.8 (1.2)	20	2.2 (1.0)	<0.001
Week 20 (eight visit)	20	5.0 (1.3)	20	3.0 (1.2)	<0.001
Week 22 (ninth visit)	20	5.4 (0.9)	20	3.2 (1.3)	<0.001
Week 26 (10th visit)	20	5.2 (1.3)	20	4.0 (1.2)	0.002
Week 28 (11th visit)	20	5.7 (1.0)	20	4.4 (1.6)	0.005



The Effect of Add-on Buprenorphine to Matrix Program in Reduction of Craving and Relapse Among People With Methamphetamine Use Disorder

A Randomized Controlled Trial

Gholam Reza Kheirabadi, MD, Mabobeh Bahrami, MD,† Ali Shariat, MD,† and Mohammadjavad Tarrahi, PhD‡*

Journal of Clinical Psychopharmacology • Volume 41, Number 1, January/February 2021

Abstract:

Background: Methamphetamine addiction is a global issue. Buprenorphine might have beneficial roles in reducing craving to methamphetamine use via altering neurotransmission signaling and dopaminergic system-related reward mechanisms.

Procedures: This clinical trial was performed in 2019 to 2020 in Khorshid Hospital, Isfahan, Iran. The study was conducted on patients with methamphetamine use disorder. The intervention group received sublingual buprenorphine for 8 weeks, and the other group also received placebo tablets. Patients were followed up and visited every month for the next 4 months. Both groups were treated simultaneously by matrix program for 2 months and observed for the next 4 months. Patients filled out the Cocaine Craving Questionnaire-Brief (CCQ-Brief) every week during intervention time (first 2 months) and every month during follow up visits (4 months). The Depression Anxiety Stress Scale (DASS-21) was also filled out before and after interventions for all of the patients. Data were analyzed using SPSS software using χ^2, independent t test and repeated-measure analysis of variance tests.

Results: Our data indicated significantly lower CCQ-Brief scores in the intervention group compared with the placebo group ($P < 0.05$). It was also indicated that changes in CCQ-Brief scores were also significant among both groups ($P < 0.001$). We also showed that the anxiety, depression, and stress scores reduced significantly after interventions ($P < 0.001$). These scores were also significantly lower in the intervention group compared with placebo group ($P < 0.05$).

Conclusions: Buprenorphine may be effective and may have positive potential roles in reducing methamphetamine craving. This drug is also helpful in reducing the anxiety, depression, and stress of patients with methamphetamine use disorders.

- 2020, RCT, double blind
- 40 men/women, MA dependent (no other substances), doing Matric Program
- 2 groups: BPN 4mg or placebo for 8 weeks + Matrix Program.
- Exclusion criteria: major mental illness (including psychotic disorder)
- Measurement: MA cravings (CCQ-Brief) + MA use, 4 months follow up.
- Results: BPN significantly reduced MA craving + MA usage occasions

Association between methamphetamine use and retention among patients with opioid use disorders treated with buprenorphine

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Journal of Substance Abuse Treatment 109 (2020) 80–85

ABSTRACT

Background: Methamphetamine use is increasing in parts of the U.S., yet its impact on treatment for opioid use disorder is relatively unknown.
Methods: The study utilized data on adult patients receiving buprenorphine from Washington State Medication Assisted Treatment-Prescription Drug and Opioid Addiction program clinics between November 1, 2015 and April 31, 2018. Past 30-day substance use data were collected at baseline and 6-months, as well as date of program discharge. Cox proportional hazards regression was used to estimate the relative hazards for treatment discharge comparing methamphetamine users at baseline with non-users, adjusting for site, time period, age, gender, race, ethnicity, and education. For a subset of patients with data, we describe the proportion of individuals reporting methamphetamine use at baseline versus 6-months.
Results: The sample included 799 patients, of which 237 (30%) reported using methamphetamine in the past 30 days; of those, 156 (66%) reported 1–10 days of use, 46 (19%) reported 11–20 days of use, and 35 (15%) reported 21–30 days of use. Baseline methamphetamine use was associated with more than twice the relative hazards for discharge in adjusted models (aHR = 2.39; 95% CI: 1.94–2.93). In the sub-sample with data (n = 516), there was an absolute reduction of 15% in methamphetamine use: 135 (26%) reported use at baseline versus 57 (11%) at follow-up.
Conclusions: In summary, this study found that patients who concurrently used methamphetamine were less likely to be retained in buprenorphine treatment compared to non-users. For persons who were retained, however, methamphetamine use decreased over time.

- 2020
- Prospective cohort study. 800 patients on BPN.
- Measurement: impact of MA use on OAT program retention at 6 months.
- Results:
  - MA users (30% cohort) ~2.5x more likely to drop out of OAT
  - For those MA users retained, 73% no longer using MA at 6 months (ie MA use decreased over time)

Cravings

Ahmadi and Razeghian Jahromi *Trials* (2017) 18:259
DOI 10.1186/s13063-017-2007-3

Trials

RESEARCH Open Access

Comparing the effect of buprenorphine and methadone in the reduction of methamphetamine craving: a randomized clinical trial

Jamshid Ahmadi* and Leila Razeghian Jahromi

Abstract

Background: We sought to test the effectiveness of methadone and buprenorphine in the treatment of methamphetamine withdrawal craving over a 17-day treatment period.

Methods: Patients were randomized into one of two groups. The study sample comprised 40 male subjects dependent on methamphetamine who met criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, for methamphetamine dependence and withdrawal and were seeking treatment. Furthermore, they should have a history of daily methamphetamine use for at least 6 months and should have discontinued their use just before starting the protocol. Patients received 40 mg of methadone or 8 mg of buprenorphine per day and were treated in an inpatient psychiatric hospital. We used methamphetamine craving score, negative urine drug screening test (thin-layer chromatography) during the study, and retention in treatment.

Results: All 40 patients completed the study. Both drugs were effective in decreasing methamphetamine craving during methamphetamine withdrawal. Reduction of craving in the buprenorphine group was significantly more than in the methadone group ($P < 0.05$).

Conclusions: The results favor the efficacy and safety of buprenorphine as a short-term treatment for methamphetamine withdrawal craving. We should mention that it is to be expected that craving declines over time without any medication. Therefore, the conclusion may not be that methadone and buprenorphine both reduce the craving. Because buprenorphine is superior to methadone, only buprenorphine surely reduces craving.

Trial registration: Iranian Registry of Clinical Trials identifier: IRCT2015112125160N1. Registered on 4 June 2016.

- 2017
- 40 outpatients, MA dependent (daily use for 6 months prior to trial, then asked to cease immediately prior)
- Randomised to receive either methadone 40mg or buprenorphine 8 mg (no control group)
- Measurement: MA cravings
- 17 day follow up, daily interview and cravings measurement
- Result: craving reduced in both groups, significantly more in buprenorphine group (**consistent with natural history)**
- Conclusion: recommended buprenorphine to reduce cravings

Ahmadi *et al. Trials* (2019) 20:468
https://doi.org/10.1186/s13063-019-3554-6

Trials

ST VINCENT'S HEALTH AUSTRALIA

RESEARCH Open Access

A randomized clinical trial on the effects of bupropion and buprenorphine on the reduction of methamphetamine craving

Jamshid Ahmadi*, Ali Sahraian and Mehdi Biuseh

Abstract

Background: The purpose of this study was to compare the effect of 300 mg of bupropion and 8 mg of buprenorphine per day on the treatment of methamphetamine withdrawal cravings over a 2-week treatment interval.

Method: Sixty-five methamphetamine-dependent men who met the DSM-IV-TR (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision) criteria for methamphetamine dependence and withdrawal were randomly divided into two groups. Subjects randomly received 300 mg of bupropion or 8 mg of buprenorphine per day in a psychiatric ward. Of the 65 subjects, 35 (53.8%) received buprenorphine and 30 (46.2%) received bupropion. The subjects were assessed by using methamphetamine craving score, interview, and negative urine drug test.

Findings: There were no statistically significant differences between the two groups in regard to age, education, duration of methamphetamine dependency, marital status, employment, and income. The mean ages were 32.8 years (standard deviation (SD) = 7.26, range = 22 to 59) for the buprenorphine group and 32.21 years (SD = 8.45, range = 17 to 51) for the bupropion group. All 65 patients completed the 2-week study. Both medications were effective in the reduction of methamphetamine cravings. Reduction of craving in the buprenorphine group was significantly more than the bupropion group ($P = 0.011$). Overall, a significant main effect of day ($P < 0.001$) and group ($P = 0.011$) and a non-significant group-by-day interaction ($P > 0.05$) were detected.

Conclusions: The results support the safety and effectiveness of buprenorphine and bupropion in the treatment of methamphetamine withdrawal craving. Administration of 8 mg of buprenorphine per day can be recommended for the treatment of methamphetamine withdrawal cravings. We should note that it is to be expected that craving decreases over time without any medication. So the conclusion may not be that bupropion and buprenorphine both lower the craving. As the buprenorphine is superior to bupropion, only buprenorphine does so for sure.

Trial registration: Iranian Registry of Clinical Trials (IRCT) registration number: IRCT2015010320540N1. Date registered: April 10, 2015.

Keywords: Buprenorphine, Bupropion, Methamphetamine withdrawal craving

Ahmadi et al. Trials (2019) 20:468
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Trials

RESEARCH Open Access

A randomized clinical trial on the effects of bupropion and buprenorphine on the reduction of methamphetamine craving

Jamshid Ahmadi, Ali Sahraian and Mehdi Biuseh

ST VINCENT'S HEALTH AUSTRALIA

- 2015
- RCT: effects of bupropion and buprenorphine on methamphetamine cravings
- 65 participants (MA dependent, **not currently using**, psychiatric inpatients)
- Divided into 2 groups: given 300mg buproprion or 8mg buprenorphine for **2 weeks**
- Measurement: MA cravings, urine drug tests
- Results: both groups had significant reductions in cravings, BPN>buproprion, **consistent with natural history**
- Conclusion: buprenorphine recommended for MA cravings

- No mention of risks and side effects from iatrogenic neuroadaptation

Australas Psychiatry. 2023 Oct;31(5):690-693. doi: 10.1177/10398562231190211. Epub 2023 Jul 21.

Impact of long-acting buprenorphine injection on methamphetamine use: A retrospective cohort study

M Raza [1], H Abeysundera [2], G Branjerdporn [1]

Affiliations + expand

PMID: 37478293 DOI: 10.1177/10398562231190211

Objective: The aim is to assess the impact of long-acting buprenorphine (LAI-BNP) on frequency of methamphetamine (MA) use.

Methods: We undertook an observational, descriptive, retrospective cohort study of patients of a public, tertiary, community-based Alcohol and Other Drug Service (AODS) with opioid use disorder (OUD) treated with LAI-BNP who are current or past users of MA. We assessed the changes of frequency of use in their MA use at start (baseline), 3 and 6 months of LAI-BNP.

Results: Study included 59 participants. Based on their MA use at the commencement of LAI-BNP, the sample was further sub-grouped as active users (n = 30) and past users (n = 29). At 6 months of LAI-BNP, all the past users remained abstinent from MA use. 70% (n = 21) of participants with active MA use had reduced or ceased their MA use while 17% (n = 5) increased their MA use at 6 months.

Conclusions: The results favour the use of LAI-BNP as a potential treatment for MA use.

- Retrospective cohort study: 59 people with OUD + beginning treatment with LAI-BPN + current or past use of MA
    - Comorbid OUD + current/past MA use (common, up to 1/3rd of patients in opioid treatment programs)

- Measurement: change in MA use at baseline, 3 months, 6 months
- Results: all past MA users remained abstinent, 70% of active MA users reduced or ceased use
- Conclusion: consider using LAI-BPN as a treatment for MA use
- Consistent with clinical experience: **treatment of OUD often results in reduction in other substance use**

Literature summary

- Impact of suboxone on MA cravings: one promising reasonable quality RCT, other studies very low quality.
- Impact of treating OUD on MA use: good (matches clinical experience)
- Insufficient evidence to support hypothesis that OAT should be prescribed for methamphetamine use disorder in absence of OUD.
- Literature excludes patients with schizophrenia; unfortunate, given level of psychosocial dysfunction and distress and complexity of their care
- No mention of the risks of neuroadaptation in any study.
- BPN treatment for patients with schizophrenia may reduce MA use indirectly by reducing psychotic symptoms

Risks

- Iatrogenic neuroadaptation to opioids

- "Neuroadaptation"
  - The processes by which initial drug effects are either enhanced (sensitisation) or attenuated (counter-adaptation) by exposure to a drug
  - Inferred from observing changes in opioid tolerance and withdrawal phenomena
  - Can occur immediately following the administration of an opioid agonist (single dose of morphine to non-dependent person; can induce withdrawal reaction by giving large dose of naloxone, indicating neuroadaptation)
  - Certainly occurs when commenced on OAT

- Impact of neuroadaptation
  - Opioid tolerance and risk of withdrawal
  - Side effects of OAT
  - If OAT ceased, are sensitised and more rapidly neuroadapted to opioids thereafter

Side effects of OAT

- Overdose
- Prolonged QTc
- Hyperalgesia
- Hypogonotrophic hypogonadism
  - Osteoporosis (increased fracture risk)
  - Sarcopenia
  - Reduced libido, erectile dysfunction
  - Fatigue
  - Infertility and menstrual irregularity
- Immunosuppression
  - Variable for each opioid
  - NB: methadone has been shown to be immuno-restorative in humans

Side effects of OAT

- Peripheral oedema

- Dental issues (caries, abscesses) with SL BPN

- Constipation
- Miosis
- Headache
- Sweating

Questions

- Have you observed this or been told this by your clients?