Well-being, psychosocial factors, and side-effects among heroin-dependent inpatients after detoxification using buprenorphine versus clonidine

Alexander M. Ponizovsky a,*, Alexander Grinshpoon a, Anatoly Margolis b, Rami Cohen c, Paula Rosca a,b

a Mental Health Services, Ministry of Health, 2 Ben Tabai St., Jerusalem, 93591, Israel
b Department of Substance Dependence Treatment, Ministry of Health, Jerusalem, Israel
c Association for Public Health Services, Jerusalem, Israel

Abstract

Previous studies comparing buprenorphine and clonidine provided little information about subjective factors associated with the effective management of opioid withdrawal. This study sought to compare detoxification programs using these medications with regard to side-effects and related distress, general well-being, perceived self-efficacy and social support. A total of 200 treatment-seeking heroin-dependent patients, aged 18–50, were randomly assigned to buprenorphine or clonidine inpatient withdrawal treatments over 10 days followed by 11 days of relapse prevention measures. A semi-structured interview and a battery of self-rating scales assessing parameters of the interest were administered to the patients who completed the 10-day detoxification protocol with buprenorphine (n=90) and clonidine (n=50). Chi-square statistics and analysis of covariance were performed to examine between-group differences. Compared with patients treated with clonidine, patients who received buprenorphine developed significantly less side-effects and related distress, and had higher senses of well-being, self-efficacy and social support. The findings suggest that buprenorphine is preferable for inpatient detoxification due to its side-effects profile and positive effects on well-being and psychosocial variables. These early benefits of buprenorphine could enable consequent maintenance treatment.

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Keywords: Buprenorphine; Clonidine; Inpatient detoxification; Side-effects; Well-being; Self-efficacy; Social support

* Corresponding author. Tel.: +972 2 6727794; fax: +972 2 6719007.
E-mail address: alexander.ponizovsky@moh.health.gov.il (A.M. Ponizovsky).
1. Introduction

Heroin- and other opioid-dependent patients have become a burdensome problem for health and other social services. Medical problems (Cherubin & Sapira, 1993; O’Connor, Selwyn, & Schottenfeld, 1994; Sporer, 1999; Stein, 1990), psychiatric comorbidity (Brooner, King, Kidorf, Schmidt, & Bigelow, 1997; Darke & Ross, 1997; Ziedonis & Brady, 1997) and other behavior-related problems such as family dysfunction, unemployment, and legal problems (Brewer, Fleming, Haggerty, & Catalano, 1998; Liebschutz, Mulvey, & Samet, 1997; Regidor, Barrio, de la Fuente, & Rodriguez, 1996; Wyshak & Modest, 1996) are highly prevalent among heroin-dependent individuals.

The effective management of opioid withdrawal is a critical first step in treating patients and subsequent proper and effective management often depends on beneficial outcome of the primary detoxification (O’Connor & Fiellin, 2000). The opioid withdrawal syndrome consists of subjective symptoms and objective signs resulting from the neuro-physiological rebound in the organ systems affected by opioids. In order to address both components of the syndrome in the treatment program, the management of opioid withdrawal combines general supportive measures (a safe environment, adequate nutrition, and careful monitoring) and pharmacological treatment including non-opioid and opioid medication. Detoxification using non-opioids focused primarily on clonidine, a \( \alpha_2 \)-agonist, which diminishes norepinephrine activity during opioid withdrawal (Gossop, 1998). Detoxification using opioid agonists is based on the mechanism of cross-tolerance, in which one opioid (e.g., heroin) is replaced by another (e.g., methadone) that is consequently slowly tapered (O’Connor & Fiellin, 2000).

Recently, buprenorphine, a derivative of the morphine alkaloid thebaine, with a partial agonist effect on the \( \mu \)-receptor and a weak antagonist at the \( \kappa \)-opioid receptor has been studied as a treatment for opioid withdrawal (Amass, Bickel, Higgins, & Hughes, 1994; Nigam, Ray, & Tripathi, 1993). Partial stimulation of the former induces a positive psychoactive effect reducing craving and helping people to comply with treatment regimens (Jones et al., 2004). Buprenorphine showed an improved safety profile, with less respiratory depression, reduced risk of fatal overdosing, and milder withdrawal effects when compared with methadone (Lintzeris, Bammer, Rushworth, Jolley, & Whelan, 2003). The side-effect profile is similar to other opioid agonists; common side effects are nausea, headache, withdrawal syndrome, non-specific pain and constipation (Jones et al., 2004). These side effects are milder than with other opioid agonists and are easily manageable, often resolving within 3 weeks (Ling & Smith, 2002; Mello et al., 1995).

In controlled clinical trials, buprenorphine has been found superior to clonidine plus symptomatic treatment in retaining patients in treatment programs, reducing their opioid abuse and decreasing dropouts after detoxification (Digiusto et al., 2005; Fingerhood, Thompson, & Jasinski, 2001; Gowing, Ali, & White, 2004; Ling et al., 2005; Lintzeris, Bell, Bammer, Jolley, & Rushworth, 2002; Palmstierna, 2004). Likewise, it has been widely used to manage withdrawal providing good symptomatic relief and little rebound withdrawal on discontinuation (Cheskin, Fudala, & Johnson, 1994; DiPaula, Schwartz, Montoya, Baret, & Tang, 2002; Gibson, Doran, Bell, Ryan, & Lintzeris, 2003). Even low doses are better than clonidine but higher doses (6 to 16mg/day) appear to be necessary to achieve patient improvement. Cheskin et al. (1994) found mean peak urge for an opioid during the first 3 days of detoxification to be lower with buprenorphine; and flexible rather than fixed drug regimen has been recommended with buprenorphine (Lintzeris et al., 2002). Entry rates into post-detoxification programs were found to be higher in patients on buprenorphine (Digiusto et al., 2005; Kakko, Svanborg, Kreek, & Heilig, 2003), and it was suggested that buprenorphine might improve quality of life (Giacomuzzi, Ertl, Kemmler, Riener, & Vigl, 2005).
Most comparative studies focused on objective outcomes of detoxification such as retention rate, treatment completion, and illicit drug use; little information is provided about subjective factors, which could enable the effective management of opioid withdrawal and consequent treatment. Pacini and Maremmani (2005) pointed out that addiction should not be faced as split into two different pictures, one individual and one social but be interpreted as a single disease active on two different levels of clinical expression rooted in a common neurobiological core, implying that subjective-psychosocial features play an important role in treatment. To our knowledge, no studies have been conducted, which in addition to clinical effectiveness and side-effect profiles, would compare subjective outcomes of the detoxification programs with clonidine and buprenorphine. These subjective outcomes would be useful predictors for the post-withdrawal care preventing relapse by using maintenance medication and psychosocial services.

The present study is designed for cross-sectional, open-label comparison contrasting the detoxification program using buprenorphine and the conventional detoxification using clonidine with regard to subjective outcomes, such as general well-being, feelings of self-efficacy and perceived social support. In addition, the number of adverse symptoms of the medication and related distress were quantified. In other areas of clinical psychiatry, these factors have been shown to play an important role in the adaptation of patients to their social environment (Kessler, Price, & Wortman, 1985; Turner & Marino, 1994; Wethington & Kessler, 1986), treatment compliance and effectiveness (Koivumaa-Honkanen, Honkanen, Antikainen, Hintikka, & Viinamaki, 1999; Tollefson & Andersen, 1999). We hypothesized that heroin-dependent patients would experience less adverse/withdrawal symptoms and related distress, more feelings of self-efficacy and social support, and better well-being following completion of the detoxification program using buprenorphine compared with the standard detoxification with clonidine.

2. Methods

2.1. The clinical setting

Up to 2001 only conventional inpatient detoxification program using clonidine had been available in Israel. Because of dissatisfaction with clonidine due to its pronounced hypotensive and sedative effects, the Ministry of Health introduced buprenorphine in 2001 for use in detoxification and maintenance treatment of opioid-dependent subjects, restricting its ambulatory use to specialist centers under the Ministry supervision.

For this study, the inpatient opioid detoxification program was run in two different specialist settings: the conventional program using clonidine was performed at the inpatient department of Beersheba Addiction Center, and the buprenorphine detoxification program at the inpatient department of Jaffa Addiction Center. Both settings belong to the Ministry of Health, Israel, and are audited by the Department for the Treatment of Addictions. To produce study groups comparable with respect to known and unknown risk factors, and to remove investigator bias in the allocation of participants we used a random number generator to each incoming participant for treatment decision-making (Rosenberger & Lachin, 2002).

2.2. The detoxification protocols

Both programs last up to 3 weeks and consist of the specific pharmacological treatments (10 days) and similar relapse prevention measures (11 days) including occupational and recreational activities, physical training program, and group supportive therapies.
The conventional detoxification protocol included the administration of clonidine in tablets (0.15 mg) according to the schedule of one tablet 4 times (every 4 h) on days 1–4, the same dose 3 times on days 5–8, and 1/2 tablet 3 times on days 9 and 10. Because clonidine may be less effective in managing subjective withdrawal symptoms, adjuvant therapy with promethazaine (max 150 mg/bedtime), dipyrone (max 1500 mg/day), trazodone (100 mg/bedtime), phenobarbital (200 mg/bedtime), and antiemetics were used when indicated.

The buprenorphine detoxification program included the use of buprenorphine hydrochloride (Subutex) 2 mg sublingual tablets manufactured by Reckitt Benckiser (Berks, UK) and supplied through the Schering-Plough and Trading Pharma (Petch-Tikva, Israel) and partially financed by the Ministry of Health. All subjects received the same number of tablets according to the schedule of three tablets at 9 am and two tablets at 4 pm on day 1, two and two at the same time on days 2 and 3, two and one on day 4, two on day 5, one on days 6 and 7, and a half on days 8 and 9. In addition, two extra tablets on days 1 and 2, and one on days 3–6 were added if needed. The mean stabilization dose was 21.3 mg (median 10 mg).

2.3. Participants

From January 2003 throughout December 2004, the potential participants were either self-referred or referred from one of the outpatient drug treatment centers across the country and were assessed at the specialist clinics. Routine inquiry about past and current use of heroin and other drugs was performed in all patients. The sample comprised 200 heroin-dependent patients who were randomly assigned to Jaffa AC where they received buprenorphine (n = 100) or to Beersheba AC where they received clonidine (n = 100). Inclusion criteria were as follows: age 18–50, fulfilling ICD-10 criteria for diagnosis of heroin dependence, intention-to-detoxification, and capacity to provide a written informed consent. Patients with co-morbid serious physical illness, suicide risk, acute psychosis, severe depression, organic brain syndrome, dependence on benzodiazepines or alcohol, pregnancy or breast-feeding were excluded. All participants gave written informed consent according to the study protocol approved by the Institutional Review Board for human studies.

2.4. Assessment

On day 10, a clinical structured interview including the administration of the Clinical Global Impression scale (Guy, 1976) and the Distress Scale for Adverse Symptoms (DSAS; Ritsner et al., 2002) was performed with all patients who completed medical withdrawal protocol. In addition, these patients filled the study questionnaires: General Health Questionnaire-12 (GHQ-12; Goldberg & Williams, 1988); General Self-Efficacy Scale (GSES; Jerusalem & Schwarzer, 1986), and Multidimensional Scale of Perceived Social Support (MSPSS; Zimet, Dahlem, Zimet, & Farley, 1988). Time frame for all the questionnaires was the 10 days preceding the interview.

The DSAS evaluates patients’ objective and subjective aspects of adverse events related to drug therapy and is described in more detail elsewhere (Ritsner et al., 2002). Briefly, it is an observer-administrated rating scale consisting of a checklist of the 22 most frequently observed side effects during treatment with psychotropic medication. Each item rated on a 5-point scale ranging from 0 (none or questionable symptom) to 4 (extreme expression of the symptom). 11 items cover adverse events of mental or neurological nature (e.g., headache, fatigue, nervousness, dizziness, sleep disturbances, etc.) and the
remaining items cover somatic or autonomic dysfunctions (e.g., hypersalivation/dry mouth, nausea/vomiting, appetite disturbances, gastric discomfort, constipation/diarrhea, weight loss/gain, tachycardia/bradycardia, hypotension/hypertension, etc.). After an adverse event is revealed by the clinician’s standard techniques, the patient is asked: “How much discomfort has this event caused you during the past 10 days?” Responses are scored on a 5-point scale, with higher scores indicating greater distress attributed to the given adverse event. The total number of adverse symptoms (NAS) and general distress index (DI) were computed. In the present sample, internal consistency of the DSAS indices was satisfactory (Cronbach’s $\alpha = 0.84$ for NAS and 0.82 for DI).

The abridged 12-item version of the GHQ is a valid and reliable measure of non-specific psychological distress or demoralization (Dohrenwend, Shrout, Egri, & Mendelsohn, 1980; Goldberg & Williams, 1988). The scale evaluates whether the respondent had experienced a particular symptom or behavior within the past 10 days. The responses are rated on a five-point Likert frequency scale ranging from “never” (weighted as 0) to “very often” (weighted as 4). It is scored by adding responses to the 12 items and diving by the number of completed items, with higher score indicating more emotional distress.

The GSES measures the person’s belief in his/her ability to cope with stressful situations. The scale consists of 10 items (e.g., “Usually I am able to control a situation” or “In unexpected situations, I always know how I must behave myself”). Responses are rated on a 4-point Likert-scale ranging from “absolutely not true” (weighted as 1) to “absolutely true” (weighted as 4), where the higher GSES total scores indicate stronger self-efficacy feelings. Good internal reliability consistency ($\alpha = 0.92$) and test–retest reliability over 6 months have been reported (Cheung & Sun, 1999; Skaret, Kvale, & Raadal, 2003). This scale has been used among mentally ill inpatients (Ritsner et al., 2000) as well as physicians and nurses in primary care in Israel (Idel et al., 2003; Rabin et al., 2000).

The MSPSS is a self-report tool for assessing emotional help and the level of satisfaction with the social support obtained from three sources—family, friends and significant others. The scale includes 12 items, each of which refer to the people to whom the respondent would turn if he/she had problems in the past 10 days of a personal, health or family nature, as well as financial and employment problems (e.g., “I get the emotional help and support I need from my family”, or “I have friends with whom I can share my joys and sorrows”, or “There is a special person who is around when I am in need”). Responses are scored on a 7-point scale from 1 (‘completely disagree’) to 7 (‘completely agree’). The MSPSS index and three subscales—family, friends and significant others—are computed, with a higher score indicating greater satisfaction with social support. This scale was used among Israeli university students as well as adult students with schizophrenia in a supported education program; in both cases it was found to be reliable, with Cronbach’s alpha from 0.90 (Ponizovsky, Grinshpoon, Sasson, & Levav, 2004) to 0.94 (Ben-Ari & Gil, 2002).

2.5. Data analysis

All analyses were performed using the STATISTICA-6.0 software packet (StatSoft, Inc., Tusla, OK, USA). Between-group differences in proportions were tested using Chi-square statistics or Mann–Whitney two-sample (non-matched) test, if indicated. Analysis of covariance (ANCOVA) was used to examine how interaction effects among an array of acting factors can affect the between-group differences in clinical and psychosocial characteristics (response variables). For all analyses, the level of statistical significance was established as $P < .05$. 

3. Results

Only 90 of the 100 patients assigned to detoxification with buprenorphine completed the medical withdrawal protocol, while the corresponding figure for clonidine was 50 of the 100; this difference in 40% (95% CI 28–51) is highly statistically significant (Mann–Whitney two-sample (non-matched) test: z-value=6.17, P=.0000). There were no significant differences in socio-demographic characteristics studied between completers and non-completers within each group (data not shown) as well as between the completers of both groups in gender ($\chi^2=0.39, df=1, P=.53$), age ($\chi^2=2.45, df=3, P=.48$), marital status ($\chi^2=0.64, df=2, P=.72$), length of education ($\chi^2=0.66, df=2, P=.72$), employment status ($\chi^2=0.67, df=1, P=.41$), and religious affiliation ($\chi^2=0.39, df=1, P=.53$) (Table 1).

Table 2 shows the results of the between-group comparisons in clinical and psychosocial outcomes as assessed by the standardized questionnaires administered on day 10 of the detoxification programs.

Although we did not rate withdrawal severity during the detoxification period, following completion of the 10-day protocol both groups had similar ratings on the Clinical Global Impression scale, ranging from normal to borderline mentally ill score (CGI mean score=2.01, S.D.=0.45 vs. 1.78, S.D.=0.63, $F=0.20, df=1$, NS). The patients developed a significantly less number of adverse symptoms during the detoxification with buprenorphine than with clonidine (DSAS adverse symptom mean score=1.81, S.D.=1.32 vs. 6.01, S.D.=1.41; $F=22.70, df=1, P<.001$) and, correspondingly, they reported

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substantially lower levels of side effects-induced distress (DSAS Distress Index mean score=1.92, S.D.=1.51 vs. 5.31, S.D.=1.63; \( F=10.15, df=1, P<.01 \)). Likewise, the patients detoxified with buprenorphine reported significantly lower levels of general nonspecific distress than those detoxified with clonidine (GHQ mean score 2.65, S.D.=0.19 vs. 2.90, S.D.=0.21; \( F=3.27, df=1, P<.05 \)).

The patients from the buprenorphine group compared with those from the clonidine group scored significantly higher on the GSES (mean score 2.77, S.D.=0.18 vs. 2.50, S.D.=0.19; \( F=4.63, df=1, P<.05 \)) indicating more feelings of self-efficacy when faced stress. Another important psychosocial resource, perceived social support, also was scored higher by the patients treated with buprenorphine than those of the clonidine group (MSPSS total mean score=5.22, S.D.=0.38 vs. 4.61, S.D.=0.41; \( F=6.17, df=1, P<.01 \)). Although both groups reported similar levels of support perceived from their families and friends, the buprenorphine-detoxified patients were more satisfied with support from significant others than the clonidine-detoxified (MSPSS significant others mean score=5.19, S.D.=0.47 vs. 4.48, S.D.=0.51, \( F=5.33, df=1, P<.05 \)).

### 4. Discussion

Our findings indicate that among the patients who completed the medical withdrawal phase of the detoxification programs those treated with buprenorphine had better well-being, more perceived social support and feelings of self-efficacy, and they showed substantially less side-effects and associated distress than those who were detoxified in the standard program using clonidine.

This is the first study in Israel that compares some clinical and psychosocial outcomes of two demographically homogeneous groups of heroin-dependent inpatients randomly assigned to detoxifi-
cation either with buprenorphine or clonidine. Unlike earlier studies that focused on the influence of the analogous detoxification programs with regard to objective behavioral aspects of withdrawal syndrome such as retention and completion of treatment (Cheskin et al., 1994; Nigam et al., 1993; Gibson et al., 2003), we investigated more subjective manifestations of heroin withdrawal that combined adverse events and related distress together with general well-being and some psychosocial resources. This approach attempts to reveal the factors that would be potential predictors of effective post-withdrawal treatment. Indeed, the between-group differences that were found in this study favor buprenorphine with regard to the subjective components of withdrawal syndrome.

Our finding that patients had a substantially less number of adverse/withdrawal symptoms and associated distress after the detoxification with buprenorphine than with clonidine is consistent with data of clinical trials on acute detoxification using the same medications, which mostly favored buprenorphine (Cheskin et al., 1994; Lintzeris et al., 2002; Nigam et al., 1993; O’Connor, Carroll, Shi, Schottenfeld, Kosten, & Rounsaville, 1997; Oreskovich et al., 2005).

The fact that heroin-dependent individuals are more vulnerable to psychological stressors than members of the general population is a well-documented clinical issue (Kosten & George, 2002). The stressors trigger drug craving in addicted subjects and subsequent compulsion to keep taking the drug (Shaham, Erb, & Stewart, 2000). Therefore our finding of lower levels of distress in the buprenorphine-treated group suggests that this treatment might be more effective than clonidine one in reducing craving and compulsion during post-withdrawal care. It is a possible explanation for a lower dropout rate in the buprenorphine group compared with the clonidine group (10% vs. 50%).

In turn, social support has been the focus of extensive research as a determinant of well-being and mental health, as a buffer of the noxious effects of environmental stress (Kessler et al., 1985; Wethington & Kessler, 1986), and as significant adaptive resource (Turner & Marino, 1994). A buffer function of social support, which was found to be higher among patients in the buprenorphine than the clonidine group, is a possible explanation for reduced distress among these patients. These results suggest that buprenorphine may promote the patient’s confidence and improve compliance with this treatment at the next stage of maintenance therapy. They are consistent with research showing that more than 70% of the patients treated with buprenorphine remained within the healthcare system for a 2-year follow-up period and that these patients had significantly improved social status, a significant decrease in drug intake, and an improvement in the severity of drug abuse (Duburcq, Charpak, Blin, & Madec, 2000; Fhima, Henrion, Lowenstein, & Charpak, 2001; Fingerhood et al., 2001). Likewise, the more feeling of self-efficacy associated with buprenorphine seems to further contribute to patient social rehabilitation by reducing emotional distress.

Several limitations of the study should be addressed here. First, a methodological problem common to all studies exploring patient complaints is the clear attribution of complaints by patients as due to medication. In our case, the problem of attribution has been complicated by the substantial overlap between typical features of the opioid withdrawal syndrome indistinguishable from adverse events attributed to pharmacological effect of the comparators. Headache, nervousness, anxiety/restlessness, tremor, insomnia, bradycardia/hypotension, sweetness, appetite inhibition, nausea/vomiting all are the examples of such symptom overlapping. Therefore we were limited by only general symptom counting, without attributing and attempting to differentiate a symptom profile of the treatment compounds studied.

Second, we were not able to perform baseline assessments with self-report instruments, and hence our study was inevitably restricted to aftercare assessments. In the absence of baseline data, one may suggest that patients in both groups initially differed in the factors, which showed clear differences at the
assessment time. We suggest, however, that this potential bias was precluded by the fact of the specialization of detoxification settings (buprenorphine vs. clonidine) as well as the random assignment of patients to one or another type of detoxification. As well known, such randomization equalizes groups with respect to known and unknown risk factors, and removes investigator bias in the allocation of participants (Rosenberger & Lachin, 2002) increasing external validity and allowing researchers to generalize their findings to the general population (Friedman, Furberg, & DeMets, 1998). In addition, we found that the groups were comparable in their socio-demographic characteristics; this homogeneity precludes demographic bias in interpreting the obtained findings.

There also could be factors other than the detoxification drug used affecting the study results, e.g., an open-label design of the study or potential differences in qualification levels of the specialists at each setting. Unlike a double-blind clinical trial, the open-label design is open for a clinician’s subjective bias during data collection and evaluation of study parameters, usually in favor of the efficacy of either experimental compound over comparator or vice versa. However, this is true mostly in respect to clinical impressions and assessments of symptoms, but not self-administered questionnaires, where the clinician’s impact on the outcome measurement practically excluded. As mentioned above, randomization increases the likelihood that patient attributes, such as demographic and baseline characteristics are balanced across treatment groups, minimizing their effects on treatment outcome. Also, to our knowledge, the clinicians of both participating centers were equivalently trained and experienced, and that precluded a potential bias regarding qualification level. Finally, the impact of supportive relapse prevention measures on our results can be excluded because the assessments were performed immediately after the pharmacological phase of treatment, and before the beginning of these interventions.

There are several reasons to suggest that the use of buprenorphine in detoxification programs is more preferable than the use of clonidine. First, it allows avoiding a polypharmacy regimen as is used with clonidine, a fact that is associated with better general feeling and less danger of potential drug–drug interactions. Second, a milder and better-tolerated side-effect profile with less subjective distress, and more positive subjective feelings may promote a more rapid social rehabilitation of the patients and enhance treatment completion rate. Recall here, although treatment completion was not the special goal of this study, we found that only a half of the clonidine-treated patients completed the detoxification program versus 90% of the patients treated with buprenorphine. It is very possible that the 50% of the patients who failed to complete in the clonidine group showed an even worse response than the completers who were included in the comparison. Therefore, given the absence of socio-demographic differences between the completers and non-completers as well as between reasons for dropout in both groups, the substantially higher completion rate for the buprenorphine versus clonidine protocol suggests an underestimate of the genuine effect size of the former. In general, the advantage for buprenorphine over clonidine in terms of completion of treatment amplifies, yet indirectly, the main findings of the study.

5. Conclusion

Taken together, the results of our study show the benefit of buprenorphine over clonidine in respect to the side-effects of medication and associated distress, well-being, feelings of self-efficacy and social support when used in inpatient detoxification program for heroin-dependent individuals. Further longitudinal maintenance studies are needed to test predictive validity of the factors linked to buprenorphine benefits.
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References


