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Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up

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Abstract

Seventy detoxified heroin-addicted patients were randomly assigned to one of two groups receiving ketamine psychotherapy (KPT) involving two different doses of ketamine. The patients of the experimental group received existentially oriented psychotherapy in combination with a hallucinogenic (“psychedelic”) dose of ketamine (2.0 mg/kg im). The patients of the control group received the same psychotherapy combined with a low, non-hallucinogenic (non-psychedelic), dose of ketamine (0.2 mg/kg im). Both the psychotherapist and patient were blind to the dose of ketamine. The therapy included preparation for the ketamine session, the ketamine session itself, and the post session psychotherapy aimed to help patients to integrate insights from their ketamine session into everyday life. The results of this double blind randomized clinical trial of KPT for heroin addiction showed that high dose (2.0 mg/kg) KPT elicits a full psychedelic experience in heroin addicts as assessed quantitatively by the Hallucinogen Rating Scale. On the other hand, low dose KPT (0.2 mg/kg) elicits “sub-psychedelic” experiences and functions as ketamine-facilitated guided imagery. High dose KPT produced a significantly greater rate of abstinence in heroin addicts within the first two years of follow-up, a greater and longer-lasting reduction in craving for heroin, as well as greater positive change in nonverbal unconscious emotional attitudes than did low dose KPT.

Keywords: Ketamine; Heroin Addiction; Psychotherapy; Psychedelics; Hallucinogens; Treatment

1. Introduction

Evidence suggests that psychedelic psychotherapy is a promising approach to the treatment of addiction. The method of drug-assisted psychotherapy utilizes the acute psychological effects of hallucinogenic, or psychedelic, drugs to enhance the normal mechanisms of psychotherapy, and at times, partakes of less traditional psychotherapeutic processes. The results of our recent study using ketamine psychotherapy (KPT) in the treatment of detoxified alcoholic patients (Krupitsky & Grinenko, 1997), as well as a recent review of previous studies carried out in the 1960s and early 1970s (Halpern, 1996), support this hypothesis. However, not all studies demonstrated positive outcomes and different methodologies make it difficult to generalize results across studies (Grinspoon & Bakalar, 1979). Ketamine, normally used for general anesthesia, but in smaller doses producing a profound psychedelic experience (Bowdle et al., 1998), is a useful drug in this regard.

As an adjunct to the psychotherapeutic treatment of addiction, ketamine has several advantages over other psychedelics: it is safe and short acting; it is already an approved prescription medicine, and it has been shown to be an effective treatment for alcoholism (Krupitsky & Grinenko, 1997). Also, because of its influence on the NMDA receptor, it is similar to other NMDA receptor ligands such as acomprosate and ibogaine (Mash et al., 1998; Sass, Soyka, Mann, & Zieglgansberger, 1996), and may possess similar anti-craving properties.

Until now, treatments for a variety of addictions have included therapy and counseling, Alcoholics Anonymous, Narcotics Anonymous, different kinds of rehabilitation programs, drug substitution maintenance programs, and pharmacotherapy. However, in many cases these methods have

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relatively high rates of recidivism. There remains a pressing need for new, more successful treatments.

In the early 1970s, Savage and McCabe (1973) showed that LSD-assisted psychotherapy had a positive effect on treatment outcome in heroin-addicted individuals: 25% of the subjects treated with LSD remained abstinent from opiates for one year, as opposed to only 5% of the conventional weekly group psychotherapy. By the time their study was published, human research with these substances had become extraordinarily difficult due to changes in the legal status of these drugs, and duplication of their work was not possible.

Later in the 1980s and 1990s, both animal studies and anecdotal human reports suggested anti-craving properties of another psychedelic, ibogaine (''Endabuse'') (Lotsof, 1995; Mash et al., 1998). However, concerns about ibogaine toxicity halted further human research with it in the United States (Binienda, Scallet, Schmued, & Ali, 2001; Glick, Maisonneuve, & Szumlinski, 2000).

In order to extend our results using KPT for alcoholism, we now report our findings from a treatment protocol employing KPT in a group of detoxified intravenous heroin addicts within a double-blind protocol. Treatment of heroin addiction in Russia is important for two reasons. There was an epidemic of heroin addiction in Russia within the last decade, closely related to an HIV epidemic. In addition, all opioid agonists (methadone) and even partial agonists/antagonists (buprenorphine) are legally prohibited in Russia. The only available medication for heroin addiction in Russia is naltrexone, with its attendant problem of poor compliance.

2. Materials and methods

2.1. Design

Seventy detoxified heroin-addicted patients were randomly assigned to one of two groups. The subjects of the high dose group received psychotherapy in combination with a psychedelic dose of ketamine (2.0 mg/kg im). The subjects of the low dose group received the same psychotherapy combined with a sub-psychedelic dose of ketamine (0.20 mg/kg im). We have found that this dose induces some pharmacological effects without inducing a full psychedelic experience, thus acting as an active placebo condition (see Results section below). Both the psychotherapist and subject were blind to the dose of ketamine, and all subjects were treated similarly except for their dose of ketamine. A clinical evaluator, other than the psychotherapist providing KPT, performed all of the subjects' psychological and clinical evaluations during the treatment and follow-up period. This rater was also blind to the dose of ketamine. The low ketamine dose group was considered to be an ''active placebo'' which allowed a study to be performed within the rigorous scientific double-blind design.

2.2. Subjects

All 70 subjects were screened, evaluated and randomized in the study. They were recruited from the inpatient department of the Leningrad Regional Center of Addictions, an alcohol and drug abuse treatment center with a 300-bed hospital located in the Leningrad Region, an administrative territory around the city of St. Petersburg. After they completed acute detoxification, informed consent was obtained from all subjects prior to acceptance into the study. The study was approved by the Institutional Review Board at the Leningrad Regional Center of Addictions. All subjects were treated as inpatients and discharged from the hospital after they completed KPT.

There were 35 subjects (27 male and 8 female) in the high dose group and 35 subjects (28 male and 7 female) in the low dose group. There were no statistically significant differences between the high dose and low dose groups with respect to age (High [Mean ± *SD*] = 23.0 ± 4.4 vs. Low = 21.6 ± 3.0 years), duration of heroin addiction (31.7 ± 24.1 vs. 37.4 ± 23.0 months, respectively), and duration of abstinence from heroin (25.3 ± 14.8 vs. 24.5 ± 10.1 days, respectively).

The subjects participating in the study were mostly young adults, consistent with the fact that the typical age of heroin-addicted individuals in Russia is between 17 and 26. In addition, the average duration of addiction is from three to four years. Many individuals die because of overdose or become incarcerated within the first few years of heroin abuse.

2.3. Psychotherapist

Psychotherapy was provided by a psychiatrist specially trained in KPT. Only one KPT session was carried out for each subject. The details of KPT sessions and psychotherapeutic techniques are described below in Treatment Procedure.

2.4. Patient selection

The following inclusion and exclusion criteria were employed for patient selection:

2.4.1. Inclusion criteria

ICD-10/DSM-IV criteria of current Heroin Dependence present for at least one year, age between 18 and 30, at least a high school education, abstinence from heroin and other substances of abuse for at least two weeks, not currently on psychotropic medication, at least one relative willing to assist in follow-up and provide outcome data, stable address in St. Petersburg or Leningrad region, home telephone number at which the subject could be reached, not currently on probation, and competency to give informed consent and otherwise participate.

2.4.2. Exclusion Criteria

ICD-10/DSM-IV diagnosis of organic mental disorder, schizophrenic disorder, paranoid disorder, major affective disorder, or seizure disorder; family history of psychiatric disorders listed above; ICD-10/DSM-IV diagnosis for alcoholism or polydrug dependency; advanced neurological, cardiovascular, renal, or hepatic diseases; pregnancy; clinically significant cognitive impairment; active tuberculosis or current febrile illness; AIDS-defining illness; significant laboratory abnormality such as severe anemia, unstable diabetes, or liver function tests three times above normal; pending legal charges with potential incarceration; concurrent participation in another research study; or concurrent treatment in another substance abuse program.

2.5. Screening evaluation

The screening evaluation included: (1) Formal psychiatric examination; (2) Complete medical examination, including blood chemistry panel (including hepatic functions), urine analysis, HIV-test, pregnancy test, and EKG; and (3) Review of previous medical and psychiatric records.

2.6. Assessment instruments

In order to provide comparability with our previous studies of KPT for alcoholism (Krupitsky & Grinenko, 1997), we used the same battery of assessment instruments,. We also used instruments widely used in psychotherapy outcome research. Finally, due to the specific nature of ketamine psychotherapy, instruments were considered desirable that might indicate changes in the areas of personality, life values and goals, spiritual development, and unconscious emotional attitudes.We used specially adapted Russian versions of the international scales and questionnaires mentioned below.

2.6.1. Psychiatric symptoms and psychopathology assessments

- ICD-10 Structured Clinical Interview for Psychiatric Disorders (SIDI)
- Zung Self-rating Depression Scale (ZDS) (Zung, 1965) - to assess depression
- Spielberger Self-rating State-Trait Anxiety Scale (SAS) (Spielberger, Anton, & Bedell, 1976) - to assess state and trait anxiety
- Visual Analog Scale of Craving (VASC) - 100 mm line marked by subjects relative to the intensity of craving experienced while completing the scale
- Scale of Anhedonia Syndrome (SA) (Krupitsky, Burakov, Romanova, Vostrikov, & Grinenko, 1998) - to assess the severity of the syndrome of anhedonia. Many detoxified heroin addicts report that the termination of withdrawal leads to a syndrome of anhedonia, which includes affective symptoms (mostly depression), anxiety, tension, irritability, feeling as if life is dull and empty, passivity, sleep disturbance, and craving for heroin. SA has affective, cognitive, and behavioral subscales
- Hallucinogenic Rating Scale (HRS) (Strassman, Qualls, Uhlenhuth, & Kellner, 1994) - to assess acute subjective responses to a psychoactive drug challenge

2.6.2. Psychological assessments

- Minnesota Multiphasic Personality Inventory (MMPI) (Dahlstrom, Welsh, & Dahlstrom, 1972) - to assess personality characteristics
- Locus of Control Scale (LCS) developed by Rotter (Phares, 1976) and adapted in Russia by Bazhin, Golynkina, and Etkind (1993) - to assess the perception by subjects of their ability to control and manage different situations in their lives
- Color Test of Attitudes (CTA) (Etkind, 1980) - to assess nonverbal unconscious emotional attitudes. The methodology of CTA has been described in detail previously (Krupitsky & Grinenko, 1997)
- Purpose-in-Life Test (PLT) (Crumbaugh, 1968), based on Frankl's (1978) concept of the individual's aspiration for meaning in life (PLT was adapted in Russia by Leontiev (1992)
- Spirituality Changes Scale (SCS) based on the combination of the Spirituality Self-Assessment Scale developed by Whitfield (1984), who studied the importance of spirituality in Alcoholics Anonymous; and the Life Changes Inventory developed by Ring (1984), to estimate psychological changes produced by near-death experiences. The SCS has been shown to be sensitive to changes in spirituality in our studies of KPT in alcoholism (Krupitsky & Grinenko, 1997)

2.7. Treatment assessment, outcome and follow-up

2.7.1. Assessment schedule

ZDS, SAS, VASC, SA, MMPI, LCS, CTA, and PLT were administered pre-therapy (baseline) and post-therapy (during the week after the ketamine session). SCS and HRS were administered only post-therapy to assess spiritual changes and acute subjective effects of the drug treatment. ZDS, SAS, and VASC were administered also at 1, 3, 6, 12, 18 and 24 months after treatment was completed, in those subjects abstaining from heroin. Those who relapsed were unavailable for assessment.

2.7.2. Follow-up data

Psychiatrists who were blind to the dose of ketamine collected follow-up data on a monthly basis for up to 24 months, if the subject had not relapsed before that.

Follow-up data included: Information from the subject about his/her drug use during the follow-up period; examination for evidence of injection sites over the subject's veins; information from the subject's relatives and/or colleagues about his/her drug use; urine drug testing at 1, 3, 6, 12, 18, and 24 months after completion of therapy; ZDS, SAS, and VASC data at 1, 3, 6, 12, 18, and 24 months. We were unable to follow patients after they relapsed to heroin due to poor compliance. None of the subjects received continued care or other treatment for their addiction or psychiatric problems after their participation in the KPT study, until they completed participation in the follow-up study or relapsed.

2.8. Treatment procedure

Witnessed informed consent was obtained from all patients before inclusion into the study.

Ten hours of psychotherapy were provided before the ketamine session in order to prepare subjects for the session. Five hours of psychotherapy were provided after the ketamine session to help subjects interpret and integrate their experiences during the session into everyday life.

An anesthesiologist was present throughout the ketamine session to respond to any complications. The length of the ketamine session was about 1.5–2 hr. Only one ketamine session was carried out for each subject. The subject was instructed to recline on a couch with eyeshades. Music preselected by psychotherapist was used throughout the ketamine session. The psychotherapist provided emotional support for the subject and carried out psychotherapy during the session. Psychotherapy was existentially oriented, but also took into account the subject's individual and personality problems (Krupitsky & Grinenko, 1997). Subjects were discharged from the hospital soon after the KPT (within 3 to 5 days).

2.9. Description of the psychotherapeutic technique provided

There are three main stages in our method of KPT (Krupitsky & Grinenko, 1997). The first stage is preparation. In this stage, preliminary psychotherapy is carried out with subjects. During these psychotherapeutic sessions it is explained to the subjects that the relief of their dependence from heroin will be attempted in an altered state of consciousness. They will have particular experiences that will help them to realize the negative effects of heroin abuse, and the positive aspects of life without drugs. We explain that the ketamine session may induce insights concerning their personal problems. It could modify their system of values, their notions of self and the world around them, and possibly contribute to discovering their purposes in life. They were told that these processes might positively effect changes in their personality, facilitating the development of a life without heroin.

During the ketamine sessions, subjects often experience an altered state that has been described as the separation of consciousness from the body and the dissolving of the ego. Therefore, it is very important to prepare subjects carefully for such an unusual experience. The therapist pays close attention to such issues as the subject's personal motives for treatment, his goals for his new life without drugs, and his theory about the cause of his disease and its consequences. An individually tailored psychotherapeutic set is formed during this phase of treatment. This psychotherapeutic set includes the patient's ideas about his/her personal reasons for addiction and how KPT might help them. This becomes the most salient factor influencing the psychological content of the second stage of the KPT. It is also important to create an atmosphere of confidence and mutual understanding between the psychotherapist and patient during this first stage of KPT.

The second stage of KPT is the ketamine session itself. With a background of special music (we used mostly soothing instrumental music intended to promote relaxation and abreaction), the subject is administered the assigned dose of ketamine. While under the influence, the subject is then treated psychotherapeutically. The content of these psychotherapeutic sessions is based on the data of the subject's case history. The session is directed toward the resolution of their personality problems and the formation of a stable orientation to a future without drugs. We try to help our subjects create new meaning and purpose in life during this session. We clearly direct the subject's experiences by verbal influences and guiding the musical background toward the symbolic resolution of the personality conflicts during the ketamine session. Two physicians, one a psychotherapist and one an anesthesiologist, conduct this second stage of KPT, because some complications and side effects (such as increased blood pressure and depression of breath) are possible, though very rare. No such complications occurred in our study. After the session, the subject rests. The subjects write a detailed self-report of their experience later that evening.

In the third stage, special psychotherapeutic sessions are carried out within several days after the KPT session. This discussion is directed toward helping the subject establish a connection between their ketamine experience and their intra- and interpersonal problems, especially those that reinforce the subjects desire for a life without drugs. We try also to assist subjects to integrate the insights from the ketamine session into everyday life.

2.10. Data management and statistical analysis

All subject-related information was filed under a study code number for purposes of confidentiality and to maintain the double-blind design.

The software package "Statistica" ("STATISTICA for Windows", release 5.0 A, StatSoft, Inc., Tulsa, OK, USA) was used. Independent variables were treatment group (dose

Table 1
Acute effects of two ketamine doses on hallucinogen rating scale subscales

Dose of ketamine		Subscales of Hallucinogenic Rating Scale (HRS)					
		Intensity	Somaesthesia	Affect	Perception	Cognition	Volition
High	Mean	1.84[a,***]	1.7[a,***]	2.22[a,***]	1.74[a,**]	2.31[a,***]	2.39
	SD[b]	0.45	0.38	0.45	0.55	0.39	0.74
Low	Mean	1.11	0.98	1.43	0.86	1.28	2.05
	SD[b]	0.54	0.57	0.43	0.57	0.72	0.69

[a] Statistical significance of differences between the high dose and low dose group: * - $p < .05$; ** - $p < .01$; *** - $p < .001$.
[b] SD- Standard Deviation.

of ketamine), and time of assessment (pre- and post-therapy, or during the follow-up; see assessment schedule). Dependent variables were clinical and psychological ratings, and rate of abstinence and relapse. The rate of abstinence and relapse was considered the primary outcome variable. The psychometric data were treated as secondary outcome variables independent from each other. Data were analyzed using within subjects repeated measures ANOVA for within groups comparisons (with an LSD test for post-hoc comparisons), and Student's *t*-test for between group comparisons.

3. Results

3.1. Components of the ketamine experience

Acute psychological responses to the ketamine experience were evaluated with the Hallucinogen Rating Scale, an instrument developed using N,N-dimethyltryptamine (DMT), as the normative agent (Strassman et al., 1994) (Table 1). HRS scores provided evidence that patients in the high dose group had a full psychedelic experience, comparable to a psychedelic dose of DMT. HRS scores in the low dose group suggest that patients experienced some drug effects, but these fell short of a full psychedelic effect. Differences between the scores of high and low dose groups were statistically significant for all HRS scales except Volition.

3.2. Treatment outcome: Follow-up data for 24 months

The follow-up data included information from subjects, their relatives, and urine drug testing results. Follow-up data for 24 months are presented in Fig. 1. The rate of abstinence in the high dose group was significantly higher than that of the low dose group (Fig. 1), while the corresponding rate of relapse was lower. The differences between the high dose and low dose group in rates of both abstinence and relapse were statistically significant starting from the first month and then for almost all of the 24 months of follow-up (Fig. 1).

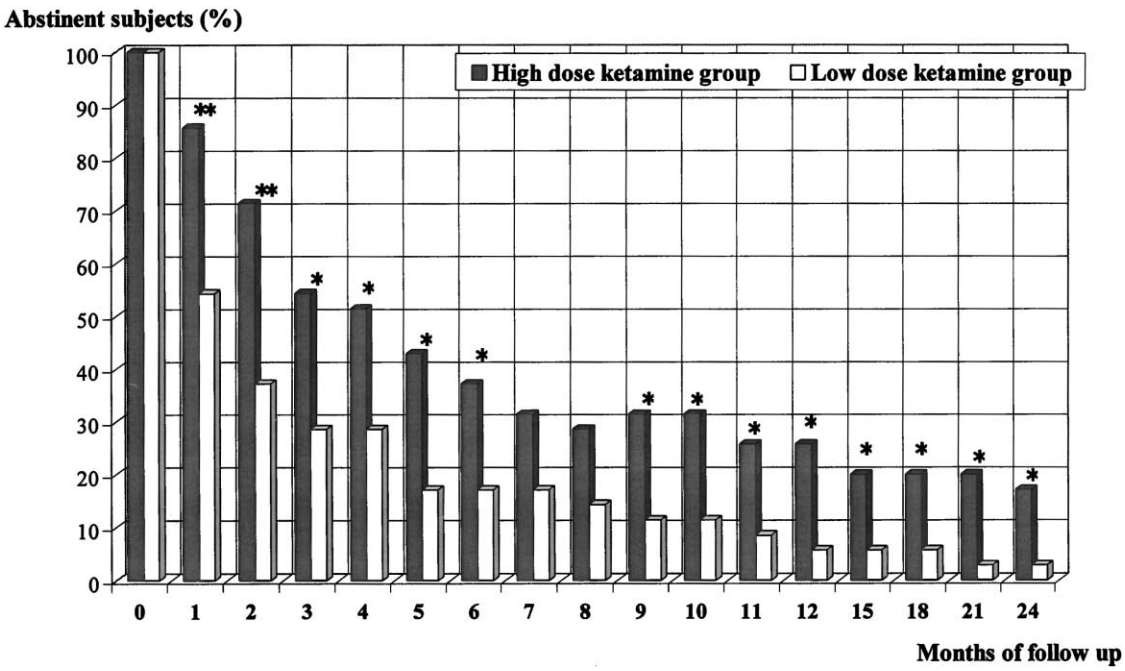

Fig. 1. Rate of abstinence: relapse free proportion. * $p < .05$; ** $p < .01$.

Table 2
KPT influence on craving, anxiety, and depression

Scales	Dose of ketamine		Before KPT	After KPT	1 month	3 months	6 months	12 months	18 months	24 months
Visual Analog Scale of Craving	High	Mean	29.24	3.97***,+++	7.72*,+++	5.40**,+++	9.25++	3.17+++	0.57+++	1.71+++
		SD	27.32	5.04	13.25	13.35	15.67	4.52	0.98	4.53
	Low	Mean	36.34	15.06+++	20.18++	28.33	19.75	27.00	12.50	0.00[a]
		SD	24.88	16.54	22.41	27.93	14.54	24.04	2.12	—[a]
Spielberger State Anxiety Scale	High	Mean	41.17	35.71+	35.81+	36.36	38.00	37.00	33.57	37.14
		SD	11.55	8.64	9.69	7.46	9.3	10.75	11.98	9.37
	Low	Mean	45.11	38.06++	35.26+++	37.17+	35.88+	28.50+	25.00++	31.00[a]
		SD	11.86	10.62	8.38	7.49	7.83	7.78	2.83	—[a]
Spielberger Trait Anxiety Scale	High	Mean	45.97	42.23+	39.54++	38.71+	37.33++	37.44+	38.86	40.86
		SD	9.9	9.12	9.21	7.17	5.68	8.45	9.99	7.77
	Low	Mean	46.69	40.74++	40.13++	37.58++	36.50++	33.50+	36.50	34.00[a]
		SD	8.73	8.35	8.09	7.05	7.50	3.54	4.95	—[a]
Zung Depression Scale	High	Mean	46.20	42.66	39.88+	39.57+	40.50	39.44+	35.00++	37.66+
		SD	8.96	9.21	9.81	8.10	9.40	10.63	9.45	6.89
	Low	Mean	49.31	41.71+++	40.87+++	38.00+++	37.50+++	35.00+	37.00	30.00[a]
		SD	9.26	10.28	6.81	9.02	6.41	1.41	1.41	—[a]

Notes: 1. Statistical significance of differences between the scores before KPT and later scores: + - $p < .05$; ++ - $p < .01$; +++ - $p < .001$.
2. Statistical significance of differences between the high dose and low dose group: * - $p < .05$; ** - $p < .01$; *** - $p < .001$.
3. SD - Standard Deviation.
4. [a] - There is only one subject in this group.

3.3. Craving for heroin

There were no statistically significant baseline differences in craving (as well as in all other psychometrics) between groups. Both doses of ketamine in KPT sessions significantly reduced craving for heroin as evaluated by the Visual Analog Scale of Craving (Table 2). This effect on craving in the high dose group was significantly greater than in the low dose group immediately after KPT, as well as at 1 and 3 months after the ketamine session. Also, craving in the high dose group was significantly reduced at the two year follow-up, but only for the first month in the low dose group.

3.4. Syndrome of anhedonia

In both high and low dose groups, KPT significantly reduced the severity of all three components of the syndrome of anhedonia (Fig. 2). While scores for each subscale show a positive effect for the high dose group, these differences were not statistically significant.

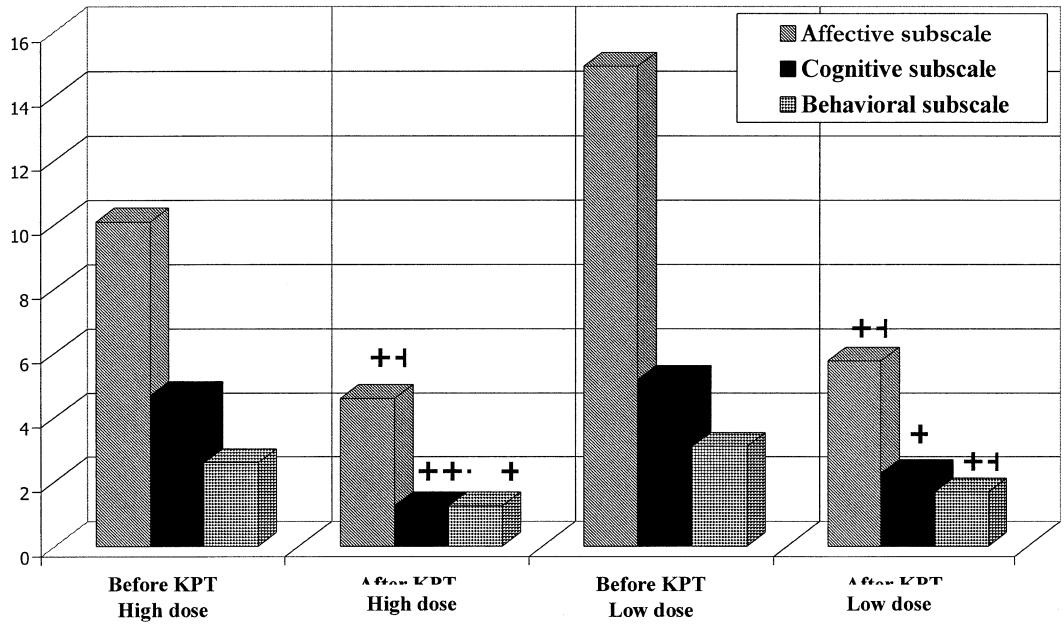

Fig. 2. KPT influence on the syndrome of anhedonia. + $p < .05$; ++ $p < .01$; +++ $p < .001$.

3.5. Anxiety

Follow-up revealed that both KPT groups demonstrated significantly reduced state and trait anxiety compared to baseline, measured with the Spielberger Anxiety Scale (Table 2). The level of anxiety was within normal limits by 3, 6, 12, and 24 months of abstinence in both groups. There were no significant differences between the high and low dose groups.

3.6. Depression

Both high and low dose KPT significantly reduced elevated levels of pre-treatment depression relative to baseline values, measured by the Zung Depression Scale (Table 2). There were no significant differences between the two groups.

3.7. MMPI

Relative to baseline values, high dose KPT produced a decrease in scores for the following MMPI scales: depression, conversion hysteria, paranoia, schizophrenia, and the Taylor scale of anxiety (Fig. 3). The self-sufficiency score also significantly increased. Low dose KPT decreased scores of the following scales: hypochondriasis, depression, conversion hysteria, masculinity-femininity, paranoia, psychasthenia, schizophrenia, sensitivity-repression, and the Taylor scale of anxiety. The self-sufficiency score also significantly increased. There were no significant differences in the MMPI scores between the two groups either before or after the KPT session.

3.8. Locus of control

The locus of control in heroin addicts, evaluated with the Locus of Control Scale, became significantly more "internal" after KPT in both groups. In the high dose group the LCS index had increased from (Mean ± *SD*) 4.1 ± 1.5 before KPT to 5.2 ± 2.1 after KPT ($p < .01$); in the low dose group corresponding values were 3.8 ± 1.3 before KPT and 4.5 ± 1.4 after it ($p < .01$). In addition, locus of control in the area of failures became significantly more internal in the high dose group after KPT compared to baseline: 5.2 ± 1.8 and 4.2 ± 2.0, respectively ($p < .05$).

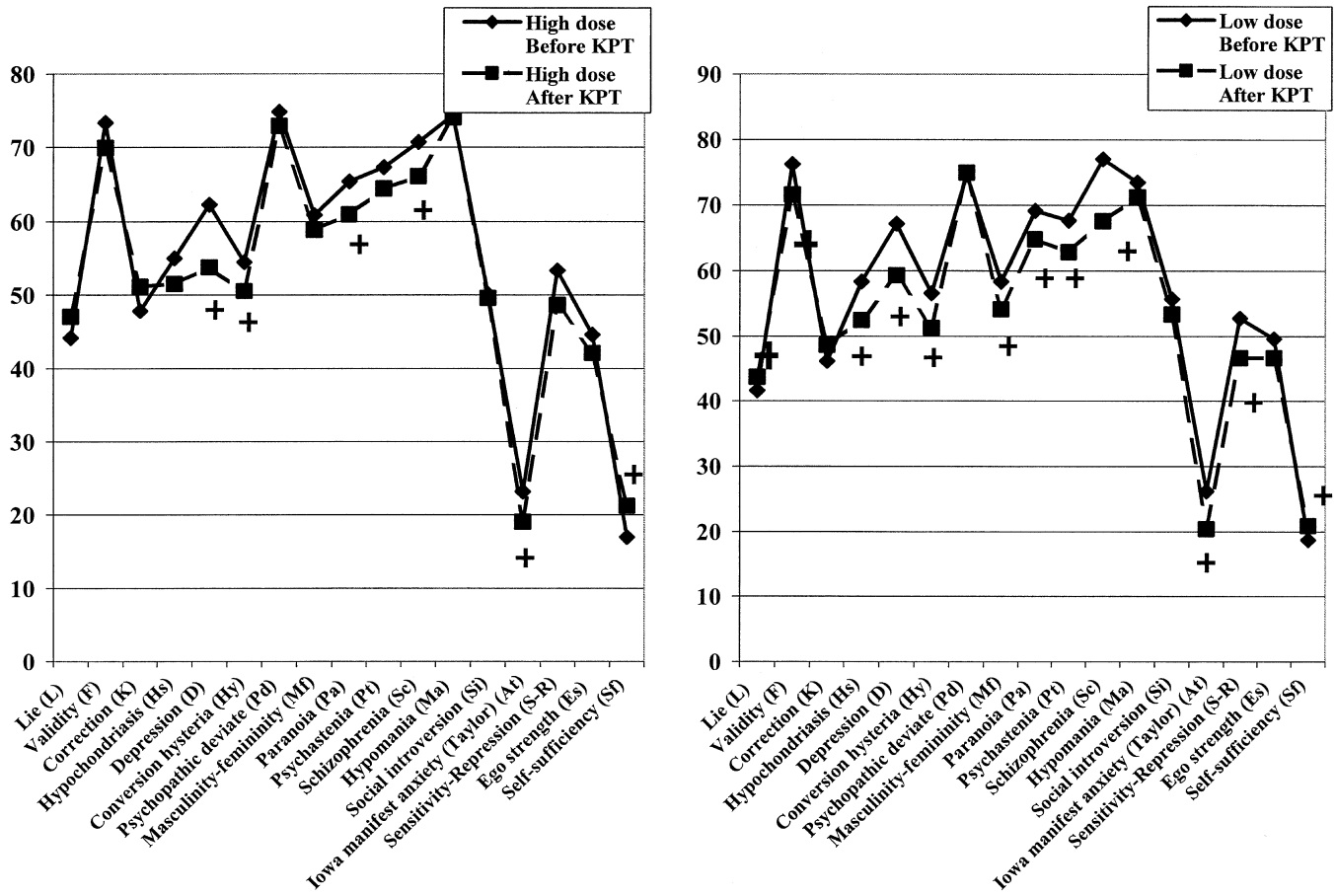

Fig. 3. MMPI. + $p < .05$.

Table 3
KPT influence on non-verbal emotional attitudes

		Attitude to the images of the Color Test of Attitudes (CTA)									
		Me now		The ideal image of self		Me in the past		Me in the future		My family	
Dose of ketamine		Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	Mean	16.11	10.51^{+++}	15.43	11.43^{++}	24.97	26.63	15.43	12.4^{++}	16.51	11.94^{++}
	SD	6.72	5.53	7.02	6.59	5.45	4.77	5.19	6.32	7.65	7.45
Low	Mean	14.00	8.00^{++}	11.09	9.66	24.23	26.60	14.69	11.66	14.69	10.91^{+}
	SD	8.05	5.35	6.48	7.69	7.87	6.85	8.21	8.13	8.86	8.03

		My job		Heroin addict		A man abstaining from drugs		Psychiatrist	
Dose of ketamine		Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	Mean	16.66	12.6^{+++}	24.00	25.03	14.23	11.66^{+}	14.86	12.17^{+}
	SD	7.33	6.36	6.96	7.01	6.89	6.71	7.98	7.45
Low	Mean	16.46	11.77^{++}	24.46	26.46	11.74	9.49	13.31	10.03^{+}
	SD	8.33	7.40	9.17	8.14	7.85	7.15	8.82	7.76

Note: 1.See notes for Table 2.
2. The lower the score, the more positive the attitude to the image is.

3.9. Understanding the meaning and purpose of one's own life

Ketamine psychotherapy caused a significant increase in indices measuring understanding the meanings and purposes in life, as well as self-actualization, and the ability to control oneself and one's own life in accordance to those life purposes. In particular, understanding of the meaning of life increased in the high dose group from (Mean ± *SD*) 75.4 ± 21.0 to 99.6 ± 20.4 ($p < .001$), while in the low dose group it increased from 77.5 ± 20.4 to 95.9 ± 19.9 ($p < .001$). Understanding of purposes in life increased from 22.2 ± 8.6 to 30.1 ± 7.6 in the high dose group ($p < .001$), and from 23.6 ± 7.1 to 28.5 ± 7.0 in the low dose group ($p < .001$). Self-actualization increased from 16.8 ± 6.8 to 22.9 ± 6.7 ($p < .001$) in the high dose group, and from 16.1 ± 6.8 to 21.8 ± 6.5 ($p < .01$) in the low dose group. There were no statistically significant differences between groups.

3.10. Spirituality

The Spirituality Changes Scale (SCS) demonstrated a similar increase in the level of spiritual development after KPT in both groups of heroin addicts. In particular, the number of answers showing the increase of spiritual development after KPT in the high dose group was (Mean ± *SD*) 27.2 ± 9.3; in the low dose it was 25 ± 9.6. Changes in SCS scores in heroin addicts were similar to those induced by KPT in alcoholics in our previous studies (Krupitsky & Grinenko, 1997).

3.11. Non-verbal emotional attitudes

The methodology of the Color Test of Attitudes (CTA) has been described in detail previously (Krupitsky & Grinenko, 1997). According to the CTA data (Table 3), significant positive changes in the high dose group occurred in patients' nonverbal/unconscious assessments of seven of nine images: "Me now", "The ideal image of self", "Me in the future", "My family", "My job", "A man abstaining from drugs", and "Psychiatrist". This means that the patients emotionally accepted these images and, in turn, incorporated attitudes towards abstinence connected with them.

Low dose group effects were less than in the high dose group and involved only four images: "Me now", "My family", "My job", and "Psychiatrist" (Table 3). Thus, high dose KPT in heroin addicts produced greater changes in nonverbal unconscious emotional attitudes of heroin addicts than did low dose KPT.

3.12. Side effects and complications

There were no complications, such as protracted psychosis or flashbacks, after KPT. No subject participating in the study became addicted to ketamine. The only side effect noted in all subjects was an acute increase in systolic and particularly diastolic blood pressure of 20–30% during the session.

4. Discussion

This double-blind, active-placebo controlled study demonstrates that ketamine-assisted psychotherapy of heroin addicts is more effective when a high, psychedelic, dose of ketamine is administered than when a low, sub-psychedelic, dose is administered. However, many of the measured change variables did not differ significantly between high and low dose groups. This suggests that the psychotherapy common to both groups played an important role in the observed effects.

We confirm that acute psychological effects of ketamine in a sub-anesthetic doses are psychedelic in nature. For example, quantitative assessment of these effects in the high dose group using the Hallucinogen Rating Scale (HRS)

were similar to those induced by a dose of the tryptamine hallucinogen N,N-dimethyltryptamine described by experienced psychedelic users as fully psychedelic (Strassman, 1996). Average HRS scores in the high dose group are similar to those obtained by Bowdle and co-authors also using sub-anesthetic doses of ketamine (Bowdle et al., 1998). All but one HRS subscale scores differed significantly between the high dose and low dose groups. The single exception was Volition, a subscale with previously described problems in sensitivity to other experimental interventions (Strassman, Qualls, & Berg, 1996) (Table 1). Subjects in the high dose group had a typical psychedelic experience while patients in the low dose group experienced something that functions as ketamine-facilitated guided imagery (Leuner, 1977). However, subjects in the low dose group were often affected by their experiences and considered them as useful and therapeutic.

While HRS scores in the low dose group were significantly less, they still were substantially higher than those seen in placebo groups in Strassman's DMT and Bowdle's ketamine studies. Thus, subjects in the low dose group had experiences of what might be referred to as ''sub-psychedelic''. This could be the effect of set and setting combined with a relatively low dose of ketamine. Similar effects were noted in a previous study by Kurland, Savage, Pahnke, Grof, & Olsson, (1971). They used 500 mcg of LSD as their high dose, and 50 mcg as their low dose, in treating alcohol-dependent individuals. It was believed that 50 mcg would be an active placebo, but they found the frequency of ''peak experiences'' to be similar in both groups. This finding may relate to the important, and often ignored, interplay between set (state of the research subject), setting (physical and interpersonal circumstances in which the drug is taken), and dose of drug (Strassman, 1995).

Nevertheless, above certain dose levels psychedelic effects are usual; thus set and setting are more likely to play a role in lower dose conditions (Strassman et al., 1994). Future studies may therefore demonstrate a greater effect of ketamine as an adjunct to psychotherapy of addicted patients using even lower doses of ketamine or placebo.

Ketamine psychotherapy produced no significant adverse reactions in this study. This is in distinct contrast to reports from the first phase of psychedelic psychotherapy studies with other compounds in 1960s (Grinspoon & Bakalar, 1979). This might be because the mechanism underlying ketamine action (blockade of calcium channel within the NMDA receptor) is different from that of other psychedelics, which are primarily serotonin partial agonists. Also, excluding patients with co-morbid psychiatric disorders might have reduced the overall risk of adverse effects.

The rate of abstinence in the high dose group was significantly greater than that of the low dose group, while the corresponding rate of relapse was lower (Fig. 1). These differences emerged at the first month of follow-up and continued through the subsequent 23 months. The rate of abstinence in the high dose group also was higher than the typical rate of abstinence in conventional treatment programs for heroin addiction in Russia. These programs usually include only drug counseling, cognitive behavioral psychotherapy, and limited prescription of naltrexone (all agonists are legally prohibited in Russia). Almost 50% of patients in the high dose group and 60% of subjects in the low dose group relapsed within the first 3 months after KPT. Thus, repeated sessions carried out within the first few months after KPT might provide a higher rate of abstinence. Halpern (1996) in his review of the studies of psychedelic psychotherapy of addictions came to a similar conclusion. We are currently testing that hypothesis in an ongoing study.

High dose KPT produced greater and longer-lasting decrements in drug craving in heroin addicts than did low dose KPT. Other NMDA receptor antagonists, such as ibogaine and acamprosate, have a similar influence on craving (Sass et al., 1996; Mash et al., 1998). A long lasting anti-depressant effect of a single ketamine hallucinogenic experience has also been recently noted by Berman et al. (2000).

Both groups showed a significant reduction in the severity of the syndrome of anhedonia, which appears to be a protracted withdrawal syndrome, and occurred more quickly than did traditional treatment with selective serotonin reuptake inhibitors (SSRIs) which takes at least 3 weeks. The reduction in the severity of this syndrome contributes to relapse prevention (Krupitsky et al., 1998). Also, the severity of all components of the anhedonia syndrome was reduced, including the cognitive, while SSRIs influence primarily affective and behavioral components (Krupitsky, Burakov, Romanova, Vostrikov, & Grinenko, 1999).

Both groups showed a positive effect on anxiety, depression, mood, and activity in everyday life. All of those effects might favor abstinence since high levels of depression and anxiety may provoke relapse to heroin in heroin addicts (Nunes et al., 1998).

Both groups' MMPI scores changed similarly, suggesting that patients became more confident, more optimistic about their possibilities and their futures, less anxious, less depressed and neurotic, and more emotionally open after treatment. These changes are also similar to those noted in alcoholics after KPT (Krupitsky & Grinenko, 1997). Of note is that positive MMPI changes in the low dose group were similar to those in the high dose group and included even more scales. However, the scores for the Lie scale significantly increased while those for the Validity scale decreased in the low dose group. This result may mean that low dose group patients tried to present themselves in a more positive and socially acceptable way, rather than reflecting deeper personality effects.

Locus of control data suggest that both groups demonstrated an increase in patients' confidence in their ability to control and manage different situations in their lives. They felt more responsible for their lives and futures after treatment. The fact that locus of control in the area of

failures became significantly more internal after high dose KPT suggests that those patients assumed more responsibility for failures and problems of their lives after treatment.

Purpose in Life Test data revealed that both groups were better able to understand the meaning of their lives, their life purposes, and perspective. Both groups demonstrated positive changes in life values of heroin addicts reflecting the increased understanding and importance of life values other than the heroin ''high''. Relative to Frankl's approach (1978), which considers alcoholism and addictions as an ''existential neurosis'' resulting from loss of meaning of life (''existential void''), we believe treatment may have helped fill this void to some extent.

A psychedelic ketamine experience is to some extent similar to the near-death experience (NDE) (Jansen, 1997, 2001). And, similar to the NDE, it might be transformative and induce changes in spiritual development and worldview (Ring, 1984; Krupitsky and Grinenko, 1997). In addition, many reports suggest that religious or spiritual conversion is an important factor in ''spontaneous'' recovery from drug abuse. Indeed, Twelve Steps and Alcoholic Anonymous programs have a distinctly spiritual/religious orientation (Corrington, 1989; Whitfield, 1984). A therapy that enhances the likelihood of a conversion or spiritual experience therefore might have utility in the treatment of substance abuse. Ketamine-assisted psychotherapy may represent one method of eliciting spiritual experiences in subjects with chemical dependence and thus help promote abstinence.

High dose KPT elicited greater effects than low dose conditions on the non-verbal emotional attitudes measured with the CTA. These data suggest that high dose KPT modifies unconscious attitudes related to abstinence. The CTA data also support the hypothesis that enhancement of the relationship with the psychiatrist is salutary.

The results of this double-blind, randomized clinical trial of KPT for heroin addiction showed that high dose (2.0 mg/kg) ketamine psychedelic psychotherapy elicits a full psychedelic experience in heroin addicts. On the other hand, low dose KPT (0.20 mg/kg) elicits a ''sub-psychedelic'' experience which functions as ketamine-facilitated guided imagery. High dose KPT produced a significantly greater rate of abstinence in heroin addicts within the first 24 months of follow-up than did low dose KPT. High dose KPT brought about a greater and longer-lasting reduction in craving for heroin, as well as greater positive change in nonverbal unconscious emotional attitudes. Thus, it is possible that the higher rate of abstinence in the high dose group was to some extent due to positive effects of ketamine on craving, similar to other NMDA receptor ligands such as ibogaine and acamprosate.

Both treatment groups demonstrated changes in depression, anxiety, anhedonia, and psychological profile assessed with a battery of verbal tests. These results support the hypothesis that the effects of psychedelic psychotherapy on the verbal level do not necessarily lead to high rates of abstinence from drugs and alcohol (Grinspoon & Bakalar, 1979). These results might also reflect some common effects of our psychotherapy of heroin addiction provided to all patients independent of the psychedelic effects of high-dose ketamine. Future research will explore further how to utilize these unique psychological effects more effectively in promoting abstinence. The most pressing need is to assess whether repeated KPT treatments are more useful than single sessions.

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