

# Single Versus Repeated Sessions of Ketamine-Assisted Psychotherapy for People with Heroin Dependence<sup>†</sup>

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**Abstract**— A prior study found that one ketamine-assisted psychotherapy session was significantly more effective than active placebo in promoting abstinence (Krupitsky et al. 2002). In this study of the efficacy of single versus repeated sessions of ketamine-assisted psychotherapy in promoting abstinence in people with heroin dependence, 59 detoxified inpatients with heroin dependence received a ketamine-assisted psychotherapy (KPT) session prior to their discharge from an addiction treatment hospital, and were then randomized into two treatment groups. Participants in the first group received two addiction counseling sessions followed by two KPT sessions, with sessions scheduled on a monthly interval (multiple KPT group). Participants in the second group received two addiction counseling sessions on a monthly interval, but no additional ketamine therapy sessions (single KPT group). At one-year follow-up, survival analysis demonstrated a significantly higher rate of abstinence in the multiple KPT group. Thirteen out of 26 subjects (50%) in the multiple KPT group remained abstinent, compared to 6 out of 27 subjects (22.2%) in the single KPT group ( $p < 0.05$ ). No differences between groups were found in depression, anxiety, craving for heroin, or their understanding of the meaning of their lives. It was concluded that three sessions of ketamine-assisted psychotherapy are more effective than a single session for the treatment of heroin addiction.

**Keywords**—hallucinogens, heroin addiction, ketamine, psychedelics, psychotherapy, treatment

Psychedelic-assisted psychotherapy utilizes the acute psychological effects of psychedelic, or hallucinogenic, drugs to enhance the normal mechanisms of psychotherapy. Many studies carried out in the 1950s and 1960s suggested that psychedelic-assisted psychotherapy might be an efficient

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treatment for alcoholism and addictions (Grinspoon & Bakalar 1979). However, it is difficult to generalize across these studies because of differences in methodology. After they were scheduled in 1970, the use of psychedelic drugs in research was strictly limited, significantly curtailing

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the development of studies employing more sophisticated methods. However, data collected in the 1950s and 1960s provide some important insights about treatment effects of psychedelic psychotherapy, which have been summarized in Halpern's (1996) comprehensive review.

One of the insights gained from previous research concerns the transient psychotherapeutic and psychological effects of psychedelic psychotherapy. The effects of psychedelic psychotherapy are often very pronounced within several days or weeks after a treatment session, but then these effects quickly decline (Halpern 1996). This phenomenon was termed a "psychedelic afterglow." Pahnke and colleagues (1970) described an afterglow as a positive post-hallucinogen state occurring in subjects after they have a transcendent psychedelic peak experience:

If a psychedelic-peak experience has been achieved and stabilized during the session, a clinical picture which we have termed the psychedelic afterglow can be observed in the days after the session. Mood is elevated and energetic; there is a relative freedom from concerns of the past and from guilt and anxiety, and the disposition and capacity to enter into close interpersonal relationships is enhanced. These psychedelic feelings generally persist for from two weeks to a month and then gradually fade into vivid memories that hopefully will still influence attitude and behavior. During this immediate postdrug period, there is a unique opportunity for effective psychotherapeutic work on strained family or other interpersonal relationships.

Ketamine is a drug used for anesthesia that acts as an NMDA receptor antagonist. Sub-anesthetic doses produce profound transformative experiences that share many elements with some near-death experiences (Jansen 2001). Previous studies have found that this experience often causes important insights about the self and the world, and can help people accept a new meaning of life, new values and new purpose in life related to abstinence from drugs and alcohol (Krupitsky et al. 2002; Krupitsky & Grinenko 1997).

Recent studies that employed a single-session ketamine psychotherapy (KPT) paradigm for alcohol and heroin-dependent patients have demonstrated that KPT is an effective treatment in promoting abstinence in alcoholics (Krupitsky & Grinenko 1997) and heroin addicts (Krupitsky et al. 2002). However, these studies did not clarify whether the effect of a single KPT session might be further enhanced by repeated sessions.

The major aim of this study was to compare the efficacy of a single session of ketamine-assisted psychotherapy with a multiple (three session) KPT regime in people with heroin dependence. The authors sought to determine whether the repeated sessions of KPT carried out over one-month intervals would improve the efficacy of a single KPT session, as reflected in objective measures of treatment outcome, such as abstinence from heroin on follow-up. In other words, could the efficacy of KPT in treating heroin dependence be

increased by administering multiple KPT sessions and thus stabilizing the afterglow?

## MATERIAL AND METHODS

### Design

After detoxification, 59 heroin-dependent participants were assigned to one of two groups on a random selection basis. The randomization was done after the first KPT session, but prior to the second session of KPT or counseling.

The participants in the multiple KPT group received three KPT sessions with a psychedelic (hallucinogenic) dose of ketamine (2.0 mg/kg i.m.), with one-month intervals between sessions. They received their first KPT session as inpatients after detoxification, just before being discharged from a psychiatric hospital. They came to the same hospital one and two months later for the second and third KPT sessions as outpatients. An individual addiction counseling session was conducted every time before the repeated (second and third) KPT sessions.

The participants in the single KPT group received only one KPT session with the same dose of ketamine and the same psychotherapeutic technique and environment as participants in the multiple KPT group. They received the KPT session as inpatients after detoxification, prior to being discharged from the psychiatric hospital. After one and two months, the same psychotherapist who carried out the KPT conducted an individual addiction counseling session at the psychiatric hospital.

All participants were treated alike and were given the same preparation for KPT. The KPT sessions, regardless of their number, were given under uniform circumstances at the same psychiatric hospital. Clinical evaluators blind to whether participants had received one or three KPT sessions performed psychological and clinical evaluations on all participants during treatment and follow-up periods.

### Participants

Out of 73 heroin-dependent patients screened, 59 of them (mean age  $M \pm SD = 22.6 \pm 3.9$  years, duration of heroin abuse  $38.8 \pm 30.4$  months, 49 males and 10 females) met inclusion criteria and were included in the study. Participants were recruited from the inpatient department of the Leningrad Regional Center of Addictions, a 300-bed hospital for treating patients with alcoholism and chemical dependencies who are living in the Leningrad Region. Informed consent was obtained from all participants prior to acceptance into the study. The study was approved by the Human Experimentation Ethical Committee at St. Petersburg Pavlov State Medical University.

### Psychotherapist

A psychotherapist specially trained by the investigator in conducting KPT provided psychotherapy to study

participants. All KPT and addiction counseling sessions for participants in both single and multiple KPT groups were done by the same psychotherapist.

### Participant Selection

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

- Inclusion criteria: ICD-10/DSM-IV criteria of current heroin dependence present for at least one year; age between 18 and 35; at least 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 within St. Petersburg or nearest district of Leningrad Region; participant has a home telephone number at which he/she can be reached; not currently on probation; and competency to give informed consent and otherwise participate.
- Exclusion criteria: ICD-10/DSM-IV criteria of organic mental disorder, schizophrenic disorder, paranoid disorder, major affective disorder, or seizure disorder; ICD-10/DSM-IV criteria for alcoholism or polydrug dependency; advanced neurological, cardiovascular, renal, or hepatic diseases; pregnancy; family history of psychiatric disorders listed above; clinically significant cognitive impairment; active tuberculosis or current febrile illness; AIDS; significant laboratory abnormality such as severe anemia, unstable diabetes, or liver function tests more than three times above normal; pending legal charges with potential impending incarceration; concurrent participation in another treatment study; or concurrent treatment in another substance abuse program.

### Participant's Evaluation

The participant's evaluation included a formal psychiatric and clinical examination and a battery of psychiatric and psychological scales.

Formal psychiatric and clinical examination included a standard medical examination, with blood chemistry panel (including hepatic functions), urine analysis, pregnancy test, electrocardiogram, and review of previous medical and psychiatric records.

The psychological assessment consisted of two parts, psychiatric assessments and psychological assessments. Psychiatric symptoms were assessed with Zung Self-Rated Depression Scale (ZDS; Zung 1965), Spielberger Self-Rated State-Trait Anxiety Scale (SAS; Spielberger et al. 1976), and the Visual Analog Scale of Craving for Heroin (VASC; Krystal et al. 1998). Psychological assessment consisted of the Purpose-in-Life Test (PLT; Crumbaugh 1968) based on Frankl's (1978) concept of people's aspiration for the meaning of life, intended to assess the participant's understanding of the meaning of his/her life. All international rating scales

mentioned above had been specially adapted and validated in Russia before the study.

### Treatment Assessment, Outcome and Follow-Up

During the treatment phase, the investigators performed urine drug testing before the first KPT session in both groups, before each successive KPT and counseling session in the multiple KPT group, and before each addiction counseling session in the single KPT group. The ZDS, SAS, VASC, and PLT were administered before and after the first KPT session in both groups, before and after the second and third KPT and addiction counseling sessions in the multiple KPT group, and before and after each of the two addiction counseling sessions in the single KPT group.

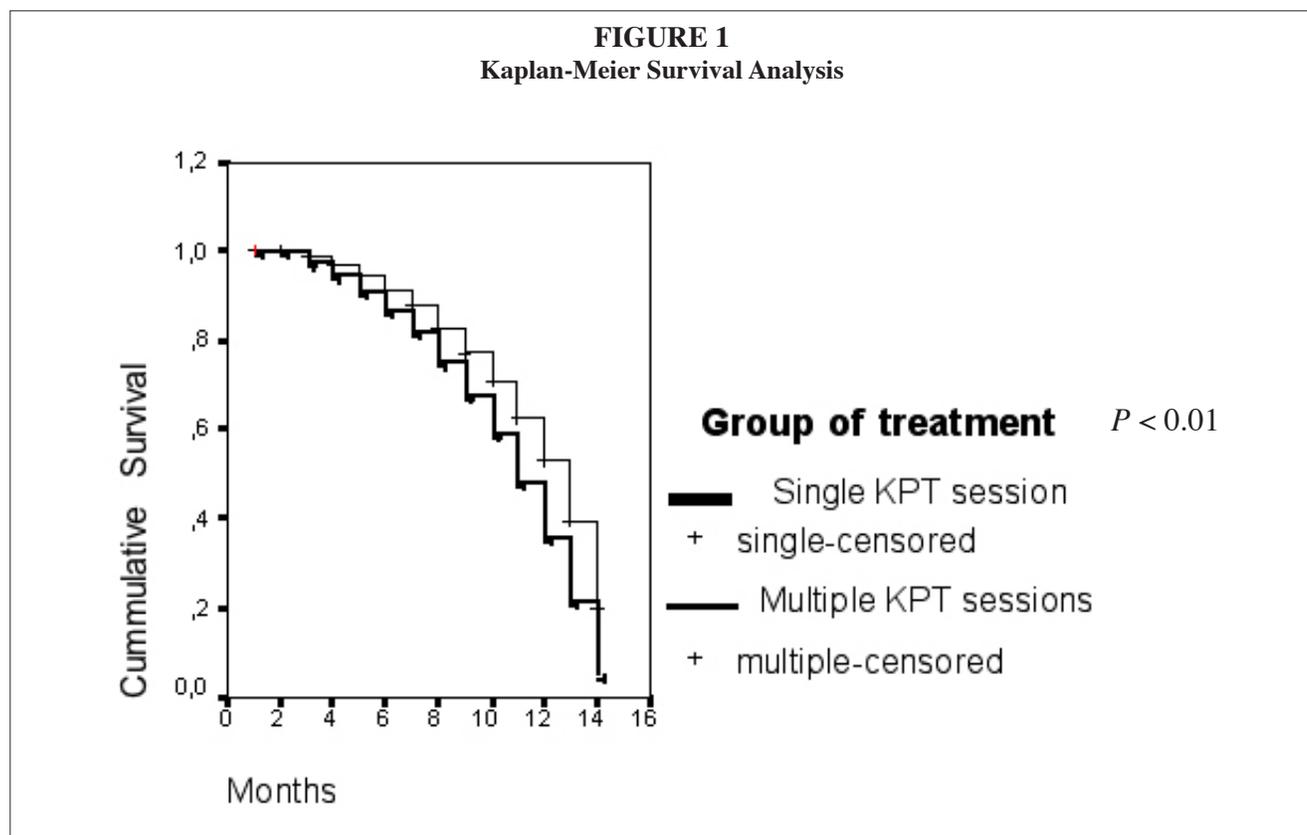
One month after the final treatment, and then at three-month intervals for the remainder of the year, participants completed a follow-up interview in person with a research assistant. Each participant underwent a physical examination to determine the presence or absence of traces (marks) of injections on his or her veins, and a urine sample was collected for drug testing. Information from the physical examination was used to determine whether a participant had abstained from heroin. Abstinent participants completed the ZDS, SAS, VASC, and PLT during this examination.

In addition, psychiatrists blind to condition collected follow-up data on a monthly basis for up to 12 months after the end of the treatment phase (the last session). During monthly telephone interviews, the psychiatrists collected self-reported information from the participant about his/her drug use during the follow-up period, using the Time Line Follow Back technique (Sobell & Sobell 1992). Information from the participant's relatives about the participant's drug use was collected in the same manner.

### Treatment Procedure

Before the first ketamine session, participants received five hours of psychotherapy focused on the participants' addictions to prepare them for the ketamine session, and they received five hours of psychotherapy after the first ketamine session to help them to interpret their experience during the ketamine session and integrate it into everyday life. One hour of addiction counseling was provided before the second and third KPT sessions to prepare participants to explore issues related to their chemical dependence during those sessions. After the second and third KPT sessions, participants in the multiple KPT group received an additional hour of psychotherapy after each session to help them integrate their experience during these sessions.

An anesthesiologist was available throughout all ketamine sessions to treat any possible complications. Ketamine was injected intramuscularly at the dose of 2 mg/kg. The length of a ketamine session was between 1.5 and two hours. The participant was instructed to recline on a couch with eye-shades. The participant listened to a preselected program of music throughout the session. The psychotherapist provided



emotional support for the participant and carried out psychotherapy during the ketamine session. The psychotherapy was existentially-oriented, focusing on assisting the participant to consider and formulate a purposeful or meaningful life, but also took into account the participant's individuality, and his or her specific personality problems. This therapy aimed to establish a strong personal motivation for a sober life without drugs.

The ketamine experience is similar to some near-death experiences (Jansen 2001), and it may produce a positive shift in the participant's understanding of the meaning of life, life purposes, and spiritual development through mechanisms similar to those seen with near-death experiences (Krupitsky et al. 2002; Krupitsky & Grinenko 1997). The major goal of the psychotherapy provided before, during, and after KPT sessions was to assist the participant in reaching this positive shift. The details of KPT technique and psychotherapeutic intervention have been described in previous publications (Krupitsky et al. 2002; Krupitsky & Grinenko 1997).

Ketamine produces diverse experiences ranging from spiritual rapture to fear and even horror, sometimes all in the same person and during the same session. People have reported experiencing violent or rapid travel through tunnels or corridors, derealization, extreme depersonalization associated with intense fear or euphoria, and feeling connected to God or a higher power. The transformative experiences often began with extreme fear, including fear of the world

ending or apocalypse, and often ended in an experience of rebirth associated with oceanic, or positively experienced, ego loss and boundlessness. All of these experiences were emotionally intense and compelling. Many people reported great difficulty in expressing their experiences in words. It should be noted that despite these common themes, the patient almost always experienced individually specific themes that reflected the individual's case history and personality problems in symbolic form.

After the first KPT session, all participants received an addiction counseling session at their second and third monthly scheduled appointments. These sessions included manualized addiction counseling procedures used in Russia, which include elements of cognitive-behavioral therapy and a motivational enhancement approach. Participants in the multiple KPT group also received brief instructions preparing them for additional KPT during these addiction counseling sessions.

#### Data Management and Statistical Analysis

Data management and analysis were performed with SPSS 11.0 statistical software package. The rate of abstinence was considered the primary outcome variable. The psychometric data were treated as secondary outcome variables, with each scale considered independent of other scores. Survival analysis (Kaplan-Meier survival function) was employed to assess differences in the rate of abstinence between the single and multiple KPT groups.

MANOVA within-subjects repeated measures of analysis design with Tukey test for post-hoc comparisons were employed to assess the effect of single versus repeated KPT and counseling sessions and changes in psychometrics over the treatment and follow-up periods. Independent variables were participant's condition (single or multiple KPT) and follow-up time point, and dependent variables were ZDA, SAS, VASC, and PLT scores.

## RESULTS

### Retention in Treatment and Abstinence Rate

Six out of 59 participants enrolled in the study (mean age  $M \pm SD = 23.0 \pm 5.5$  years, duration of heroin abuse  $48.3 \pm 48.0$  months, five males and one female) relapsed and dropped out of treatment within the first month after the initial KPT session. Prior to the second session, the 53 remaining participants were randomized into the two treatment groups. Twenty-six participants (mean age  $M \pm SD = 22.4 \pm 4.1$  years, duration of heroin abuse  $36.5 \pm 27.6$  months, 21 males and five females) were assigned to the multiple KPT group and received two more KPT sessions, including addiction counseling sessions before KPT, separated by one-month intervals. Twenty-seven participants (mean age  $M \pm SD = 22.7 \pm 3.5$  years, duration of heroin abuse  $38.9 \pm 29.2$  months, 23 males and four females) were assigned to the single KPT group and received two addiction counseling sessions separated by one-month intervals. There were no statistically significant differences between these groups in the mean age, duration of heroin addiction, and gender.

In the multiple KPT group, four out of 26 participants (15.4%) relapsed and dropped out of treatment after the second KPT session but prior to the third. In the single KPT group, seven out of 27 participants (25.9%) relapsed and dropped out of treatment after the first counseling session. The difference in the retention in treatment phase between the two groups was not statistically significant.

However, Kaplan-Meier survival analysis revealed statistically-significant differences in the follow-up abstinence rate between groups: the abstinence rate was significantly greater in the multiple KPT group throughout the year of the follow-up (Figure 1). At the end of the one-year follow-up, 13 out of 26 participants (50%) in the multiple KPT group remained abstinent compared to six out of 27 participants (22.2%) in the single KPT group ( $p < 0.05$ ).

### Psychometrics

Symptom intensity for all measures administered (depression, state and trait anxiety, and craving for heroin) were significantly reduced after the first KPT session in both groups, and then gradually decreased further in both groups in those participants who did not relapse and who showed up for scheduled appointments. There were no significant differences in these scores between the single and multiple KPT groups (see Table 1). Those who relapsed were

unavailable for psychometric evaluation. The understanding of the meaning of life measured by the PLT improved in both groups in a similar manner (Table 1), and there were no statistical differences between the two groups.

### Side Effects

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

## DISCUSSION

Results of this study showed that a three session KPT program is more effective in promoting abstinence from heroin addiction than a single KPT session followed by two counseling sessions. The rate of abstinence was significantly higher in the three KPT session group throughout a year of follow-up. At the end of one year, the rate of abstinence in the multiple KPT sessions group (50%) was more than twice as high as in the single KPT session group (22.2%). Furthermore, if we include the six participants who relapsed after a single KPT session but prior to condition assignment into the single KPT group, it lowers the rate of abstinence at 12 months to 18.2%, lending further support to the contention that a single KPT session does not provide the same benefits as multiple KPT sessions. These results correspond very well with the observations made in clinical studies with psychedelics carried out in the 1950s and 1960s that provided the rationale for the multiple session approach used in this study. In particular, Halpern (1996) noted that, "the longer follow-up, the less improvement was observed across the single dose studies." In the review of Grinspoon and Bakalar (1979), the authors wrote that "Some controlled studies show an improvement lasting from several weeks to several months . . . The obvious recourse of supplementary treatments every once in a while has been suggested but never taken seriously possibly because everyone is mesmerized by the vision of a quasi-miraculous single-shot cure . . ."

This study does not compare ketamine-assisted therapy with placebo, raising issues of separating effects resulting from ketamine-assisted therapy versus those arising from psychotherapy or from placebo effect. However, a previous investigation we conducted has addressed this issue, finding that high-dose ketamine produced a greater rate of abstinence from heroin than psychotherapy conducted with active placebo (Krupitsky et al. 2002). Building on these findings, we chose to examine whether multiple (three) psychotherapy sessions could produce greater benefits than a single session.

It is interesting to note that the 22.2% rate of abstinence after one year in the single KPT session group in this study

**TABLE 1**  
Psychometric data

Symptom	Group	Psychometrics by Time Points (M±SE)												
		1st Session		2nd Session		3rd Session		1st Month		3rd Month		Follow-ups		
		Before	After	Before	After	Before	After	Before	After	Before	After	6th Month	9th Month	12th Month
Depression	1st	41.2±1.5	36.9±1.4	36.6±1.3	37.5±1.6	35.6±1.5	34.5±1.4	35.1±1.4	34.3±1.4	36.7±1.7	37.4±1.8	36.7±1.7	37.4±1.8	34.3±1.4
	2nd	44.7±2.0	39.9±1.8	40.8±2.0	38.0±1.6	35.8±1.3	35.0±1.3	35.4±1.6	36.8±1.3	37.9±1.2	34.5±1.2	37.9±1.3	34.5±1.2	37.9±1.3
State anxiety	1st	43.8±1.9	38.4±2.2	38.9±2.2	37.0±1.7	34.6±1.7	33.4±1.3	33.0±1.6	32.6±1.7	34.8±2.1	33.7±1.9	34.8±2.1	33.7±1.9	30.6±1.8
	2nd	42.7±1.5	39.9±1.8	39.6±1.6	38.4±1.8	35.3±1.0	33.3±1.3	33.0±1.7	32.5±1.3	31.1±1.4	31.1±1.4	32.4±1.4	31.1±1.4	28.1±0.6
Trait anxiety	1st	42.0±2.0	34.4±2.3	33.8±1.9	32.0±1.8	33.2±2.4	29.9±1.6	30.4±1.7	26.9±1.1	31.6±2.0	29.6±1.4	31.6±2.0	29.6±1.4	25.8±1.3
	2nd	41.5±1.9	33.3±1.6	36.4±2.0	34.3±1.9	31.15±1.5	29.2±1.3	30.5±1.9	29.6±1.1	26.4±1.6	26.4±1.6	23.6±0.8	23.6±1.6	24.7±0.5
Craving for heroin	1st	20.1±4.7	9.6±3.6	11.9±3.5	6.07±2.7	7.1±3.1	5.4±3.0	6.09±2.6	2.6±1.0	5.3±2.1	3.2±1.7	5.3±2.1	3.2±1.7	0.3±0.2
	2nd	22.8±5.4	4.6±1.6	8.9±3.3	7.3±2.8	4.7±1.5	3.3±1.1	7.2±2.9	3.7±1.4	3.9±1.3	1.9±0.5	3.9±1.3	1.9±0.5	0.0±0.0
Understanding the meaning of life	1st	92.0±3.6	106.5±3.6	108.8±3.2	110.3±2.9	112.8±3.1	113.8±2.6	115.2±3.7	115.2±3.3	114.9±2.8	115.7±3.8	114.9±2.8	115.7±3.8	119.6±3.4
	2nd	90.3±3.6	101.6±3.6	103.0±3.7	103.3±4.1	113.6±2.8	113.5±2.7	114.9±3.4	115.1±3.2	119.8±2.3	120.5±2.7	119.8±2.3	119.8±2.7	124±0.8

Notes: First group — multiple KPT, second group — single KPT. MANOVA results: All the psychometrics significantly improved over the time points. No significant differences in either one psychometric were found between the first and the second group.

was similar to the one year abstinence rate of 24% after a single KPT session in a previous study of KPT for heroin addiction (Krupitsky et al. 2002), in which a single KPT session was compared to a single active placebo session (a low, nonpsychedelic dose of ketamine). Due to the close similarities in rate of one year abstinence in the single KPT groups in this current study and in the previous study, it seems likely that the groups are well-matched. This supports the assumption that, were a placebo group to have been added to this current study, the rate of one year abstinence would have been somewhat similar to that in the earlier study, or 6%. It is also notable that the rate of abstinence for single KPT participants was similar to the rate of retention in treatment for people receiving the opioid antagonist naltrexone (Krupitsky et al. 2004), and the rate of abstinence in the multiple KPT was even higher than after naltrexone treatment. These findings suggest that multiple sessions of

KPT hold promise as a treatment for people with heroin dependence, and that multiple sessions are better than a single session of KPT, despite lack of significant differences between the two groups in self-reported depression, anxiety or cravings for heroin.

The lack of significant differences between single and multiple KPT groups on other outcome measures, including those for depression, anxiety, life purpose and heroin craving, suggests that increased rates of abstinence in the multiple KPT group is at least partly due to factors not measured in this study. This effect could be related to a specific shift in the participant's mind and his or her attitude to life that was described by Pahnke and colleagues (1970) as an "afterglow," and for which we do not yet have a rating scale to measure. In the future, we may employ measures more liable to capture this shift or change in attitude or life view.

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