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The incidence of unpleasant dreams after sub-anaesthetic ketamine

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Abstract
Rationale Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist with psychotogenic effects and for which there are diverse reports of whether pleasant or unpleasant dreams result during anaesthesia, post-operatively or after sub-anaesthetic use.
Objective To assess in healthy volunteers the incidence of unpleasant dreams over the three nights after receiving a sub-anaesthetic dose of ketamine, in comparison to placebo, and with retrospective home nightmare frequency as a covariate.
Method Thirty healthy volunteers completed questionnaires about retrospective home dream recall and were then given either ketamine (n=19, males=9, mean age=23.5 years; mean ketamine blood plasma=175.29 ng/mL) or placebo (n=11, males=5, mean age=25.4 years). Dream recall and pleasantness/unpleasantness of dream content were recorded by questionnaire at home for the three nights after infusion.
Results Ketamine resulted in significantly more mean dream unpleasantness relative to placebo and caused a threefold increase in the odds ratio for the incidence of an unpleasant dream. The number of dreams reported over the three nights did not differ between the groups. The incidence of unpleasant dreams after ketamine use was predicted by retrospectively assessed nightmare frequency at home.
Conclusions Ketamine causes unpleasant dreams over the three post-administration nights. This may be evidence of a residual psychotogenic effect that is not found on standard self-report symptomatology measures or a result of disturbed sleep electrophysiology.

Keywords Ketamine · Abuse · Sleep · REM sleep · Dream · Dreaming · Nightmare · Sub-acute · Schizotypy · Dissociation · Schizophrenia · NMDA

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Introduction

Ketamine is a dissociative anaesthetic that blocks the *N*-methyl-D-aspartate (NMDA) receptor. It is used for anaesthesia or sedation, usually for brief procedures; as an analgesic and also as an illegal recreational drug. It can result in a dissociative state, and as a result of the increase in schizotypy and psychotic symptoms that it and other NMDA antagonists (e.g. phencyclidine [PCP]) can cause (e.g. Krystal et al. 2005; Lahti et al. 2001; Pomarol-Clotet et al. 2006; Radant et al. 1998; Stone and Pilowsky 2006), an NMDA receptor hypofunction model of schizophrenia has been proposed (Fletcher and Honey 2006; Olney et al. 1999).

Although these acute effects have been studied extensively, according to Kennedy and McAllister (2000), little is known of the medium- to long-term sequelae of ketamine sedation. Recent experimental work indicates that schizotypal and dissociative effects are not found 48 h (Newcomer et al. 1999) or 3 days after ketamine is taken by ketamine-naïve volunteers (Morgan et al. 2004a) nor in ketamine users assessed 3 days after use (Curran and Monaghan

2001). For clinical studies, although some mild emergence reactions have been found, for example, in children up to 15 days after surgery with ketamine (Erk et al. 2007), Fine and Finestone (1973) report just two cases of floating hallucinations and one of being surrounded by faceless people during the weeks after operations with ketamine, from 1,400 operations in total.

The aim of the current paper is to investigate possible residual effects of ketamine over the days after ingestion by an assessment of the number and emotional tone of dreams in the home environment, compared to a placebo group. Dream recall is chosen in this study as an index of any prolonged effect of ketamine because increased dream recall has been found to result during ketamine anaesthesia (e.g. Grace 2003), in a dose-dependent manner (Edwards et al. 1993), and lasting for at least 24 h post-operation (Klausen et al. 1983). Also, there are significant associations between dream recall frequency and dissociation and schizotypy in the normal population (Watson 2001). The emotional tone of dreams is used because frequent nightmares are associated with schizotypy and dissociation (Blagrove 2007; Hartmann et al. 1981, Kales et al. 1980; Levin 1998; Levin and Fireman 2002; Watson 2001, 2003). The mediating factor for these relationships has been described by Watson (2001) as the ease with which a person can pass between different (reality-based and fantasy-based) states of consciousness.

There have been some case reports of hallucinations and unpleasant dreams in the days after ketamine administration (e.g. Hersack 1994; Perel and Davidson 1976), but those reports have emphasised the rarity of these. Table 1 presents a review of the quantitative literature on the effects of ketamine on dreaming for periods of 24 h to 3 months after use and shows that the number of nightmares or unpleasant dreams in the nights after ketamine is low in most, but not all, studies.

There is a similar range of findings concerning whether unpleasant dreams or nightmares result during ketamine anaesthesia with some reports of frequent nightmares (e.g. Freuchen et al. 1976; Coppel et al. 1973), a 'possible' association with nightmares (Pagel and Helfter 2003), all dreams being unpleasant (Figallo et al. 1977), that there are more unpleasant than pleasant dreams (e.g. Krissel et al. 1994; Ellingson et al. 1977; Handa et al. 2000), that 'terrifying dreams are infrequent' (Khorramzadeh and Lofty 1976; Lofty et al. 1970) or that there are predominantly pleasant dreams (e.g. Grace 2003; Hejja and Galloon 1975; Hersack 1994; Sklar et al. 1981; Sechzer 1984; Fine and Finestone 1973; Downing et al. 1976; White et al. 1980, 1982). There is no systematic difference in ketamine dose between these acute studies, despite the large differences in dream characteristics. For example, 2 mg/kg was used by Freuchen et al. (1976), Handa et al. (2000) and Hejja and Galloon (1975) with findings of frequent nightmares, mostly unpleasant dreams and predominantly pleasant dreams, respectively.

Findings are thus mixed as regards any acute and subacute effects of ketamine on the emotional content of dreams. However, this may be due to three areas of methodological differences between or problems with the studies:

1. Obviously, differences in dream pleasantness under medical conditions might be caused by factors other than ketamine dose, making it inappropriate to rely on the comparison of findings from different studies with their different populations and procedures. For example, Cunningham and McKinney (1983) state that rapport with the anaesthetist may reduce any unpleasant vivid imagery. More appropriate for dose comparisons is that two studies have assessed different doses of ketamine within one study. One (Torvaldsson et al. 2005) found vivid dreams, nightmares and mild hallucinations after 350 mg ketamine but not after 120 mg, whereas the other (Sechzer 1984) found no ketamine dose differences between those with pleasant and those with unpleasant dreams.
2. Most of the above studies did not have a control group. It may thus be that negative dream emotions in some of the medical studies may be due to concerns about having an operation. For example, Kain et al. (1996) report 54% of children exhibited some negative behavioural responses 2 weeks after anaesthesia with O_2–N_2O and halothane, but without ketamine, and these responses included nightmares, anxiety and eating problems. Also, Sechzer (1984) found a higher percentage of unpleasant dreams in obstetric patients not given ketamine (52%) than in those given ketamine (35%), although the former did have a lower amount of dream recall (5.6%) than did the ketamine group (35%).
3. None of the above studies on dreams and nightmares after ketamine controlled for background home level of reporting of nightmares, although the association with home dream recall has been investigated. In Hejja and Galloon (1975), 45% of patients were home-dreamers ('defined as those patients who ordinarily dream at home'), and the incidence of dreams during ketamine anaesthesia among them was 75%, whereas only two of the 82 non-home-dreamers had a dream during the anaesthetic. Also, White et al. (1982) state that the incidence of emergence reactions are higher in people who normally dream, as well as in those with a history of personality problems.

It should also be noted that many of the post-operative studies reviewed above involved children. As adults tend to have worse experiences with ketamine than do children (Green and Johnson 1990; Green and Sherwin 2005; Green et al. 1990; Sherwin et al. 2000; Sussman 1974), they may be having frequent nightmares or unpleasant dreams during

Table 1 Effects of ketamine on dream reports for periods of 24 h to 3 months after use

Authors (date)	Dose	Age category	Finding
Dal et al. (2007)	0.5 mg/kg	Children	Three out of 60 children had bad dreams during the first post-operative night, which is no higher than controls
Erk et al. (2007)	7 mg/kg	Children	Nightmares occurred to 7.1% of children over the 24 h after surgery, but not at all after this
Funk et al. (2000)	6 mg/kg	Children	Parents were interviewed 1 and 7 days after their children (age 2–10 years) had surgery. Of the 36 children receiving ketamine, four had nightmares on the first night and five had nightmares between the first and seventh nights. [For the 39 children receiving midazolam, the numbers with nightmares were two on the first night and one between the first and seventh nights.]
Hostetler and Davis (2002)	0.5–2.5 mg/kg+midazolam and atropine	Children	Studied 301 children (6 months–18 years). Night 1: five bad dreams and three severe awakenings, over first week: eight bad dreams/nightmares and three children had unpleasant awakenings, over first month: five nightmares/bad dreams, two children having unpleasant awakenings (i.e. 1.7% bad dreams on first night, 2.7% in first week and 1.7% in first month)
Klausen et al. (1983)	2.2 mg/kg (range 1.7–4.5 mg/kg)	Adults	Twenty patients interviewed 3 months after low-dose ketamine infusion, only one of them had had nightmares, which had lasted 2 weeks from discharge
Krystal et al. (1994)	0.5/0.1 mg/kg	Adults	No psychological effects, including no nightmares, at follow-up on the day after being given low- or high-dose sub-anaesthetic ketamine. On the test day, those given low doses (0.1 mg/kg) found the experience pleasant, whereas at 0.5 mg/kg, responses ranged from enjoyment to fear with this dose being anxiogenic and causing paranoia in some subjects
Kwok et al. (2004)	0.15 mg/kg	Adults	No post-operative hallucinations or bad dreams
McGlone et al. (2004)	2–2.5 mg/kg	Adults	Two percent nightmares or disturbed sleep on the night after discharge, not persisting longer than this
Meyers and Charles (1978)	3.0 and 3.3 mg/kg	Children	Present 'to our knowledge … the first reported cases of prolonged problems following ketamine administration in children.' One 3-year-old with nightmares for 1 year after 3.0 mg/kg ketamine and one 3-year-old awakening screaming two to four times per night for a month after 3.3 mg/kg
Valentin and Bech (1996)	Cochleography group: 8–10 mg/kg induction, maintained with 0.5–1 mg/kg doses. Higher doses with squint group	Children	Seventeen percent of patients (median age 2.25 years) had nightmares later than 3 days after having ketamine anaesthesia for cochleography. This occurred for 5% of children having surgery for squints
Wathen et al. (2000)	1 mg/kg	Children	Over 2 weeks at home, nightmares occurred in 10.3% of cases and in 9.6% of those also given midazolam. Only 3.4% had pleasant dreams

the post-operative nights. Any such worse reactions in adults would occur despite the fact that idiopathic nightmares are more frequent in children (Muris et al. 2001) and adolescents (Nielsen et al. 2000) than in adults.

Aims of this study

Aim 1. To assess whether the incidence of all dreams, incidence of unpleasant dreams or mean dream unpleasantness differs between ketamine and placebo groups in the three nights after ketamine is given. As surgery itself can result in a rebound of rapid eye movement (REM) sleep two to four nights after the operation with heavy density of eye movements and vivid nightmares (Knill et al. 1990), we studied healthy volunteers so as to remove this confound and to test the specific effects of ketamine.

Aim 2. To use home nightmare frequency as a covariate in the comparison of dream unpleasantness between the ketamine and control groups.

Aim 3. To investigate whether individual differences in nightmare frequency at home or on-drug schizotypy or dissociation are predictive of the presence of unpleasant dreams after ketamine use. This will test the statement of Mattila et al. (1979) that unpleasant or terrifying dreams due to ketamine cannot be predicted.

Aim 4. To assess any differences between the ketamine and placebo conditions across the three post-treatment days in anxiety and depression. This is because anxiety and depression have small but significant associations with nightmare frequency (Blagrove et al. 2004), and hence, may mediate the effects of ketamine on dream unpleasantness.

Materials and methods

Design

An independent groups design was used in which male and female participants were randomly allocated to treatment of an infusion with one of two doses of ketamine or with placebo. The three groups were balanced for gender with eight females and eight males in each. Double-blind procedures were used throughout.

Participants

Participants were recruited through an advertisement and were paid for their participation. The study was carried out in accordance with the Declaration of Helsinki and was approved by the UCL/UCLH ethics committee. All participants gave written, witnessed, informed consent on two occasions: at screening and then at the beginning of the testing session. Screening of participants followed the same procedures as used in a previous study (Morgan et al. 2004b). Participants underwent a semi-structured interview to investigate psychiatric history, and drug use was verified by urinalysis. Inclusion criteria were that participants were between 18 and 35 years old and native English speakers. Exclusion criteria were current, past or a family history of psychiatric disorders, substance misuse and general health problems. Forty-eight participants completed the ketamine infusion stage of the study, one participant dropped out of the study during infusion of high-dose ketamine.

Thirty participants returned their baseline pre-testing session retrospective dream questionnaires and their post-testing session dream diaries (low-dose ketamine, $n=8$; high-dose ketamine, $n=11$; placebo, $n=11$). As there were no significant differences on any variables between the low- and high-dose ketamine groups and in order to provide a larger group for the analysis of predictor variables, the ketamine groups are combined in most statistical analyses. Demographic data for the study are thus: ketamine group, $n=19$, females=10, males=9, mean age=23.53 (SD=4.51); placebo group, $n=11$, females=6, males=5, mean age=25.36 (SD=4.50).

Procedure

Initial screening session

Participants completed demographic details, Beck Depression Inventory, Spielberger State Trait Anxiety Inventory Form Y-2 (Trait Anxiety), Dissociative Experiences Scale and the Retrospective Dream Questionnaire.

Before drug administration

Testing began at either 9 A.M. or 1 P.M. and the time of testing was matched across groups. Participants arrived at the hospital after completing an overnight fast for morning testing or a minimum of 6 h fasting for afternoon testing. They were assessed on the pre-drug subjective effects battery for 20 min, then allowed to rest for 15 min and were then cannulated. Approximately 5 min after cannulation, the anaesthetist began the infusion.

Drug administration

A 16-gauge intravenous cannula was inserted in the non-dominant forearm. Ketamine infusion was via a Graseby intravenous infusion pump controlled by the Stanpump programme (Schafer et al. 1990). The programme uses a bolus–elimination–transfer (BET) infusion scheme which aims to achieve the target plasma concentration almost instantaneously by taking into account ketamine pharmacokinetics using a three-compartment model (Domino et al. 1984). Participants received either ketamine (low-dose or high-dose) or placebo (0.9% NaCl solution). A peripheral venous blood sample was taken 50 min after commencing the infusion. The blood sample demonstrated that target concentrations (originally 100 and 200 ng/mL) were exceeded. For the participants included in the present paper, blood plasma concentrations were: low-dose ketamine ($n=8$), 114.97 ng/mL (SD=36.55); high-dose ketamine ($n=11$), 219.17 ng/mL (SD=35.20). Throughout the 60-min infusion, each participant's pulse, blood pressure and electrocardiogram were monitored.

After drug administration

On-drug subjective effects questionnaires were completed 40 min after the start of infusion. Participants were then provided with light refreshments, were assessed 30 min later and then at hourly intervals by the medical staff as to their 'street readiness' and were discharged approximately 2 h following infusion. Participants were given the telephone number of a clinical psychologist and an anaesthetist in case of adverse after effects; none were reported. Participants took home the three-night dream and mood questionnaire.

Assessments

Retrospective dream questionnaire

Participants rated their frequency of dream recall in answer to the question 'How often do you wake up and remember a dream' by indicating one of six response boxes: four to seven times per week; one to three times per week; one to three times per month; less than once per month; about once per year or less and never.

Participants were then given definitions of night terrors and of nightmares, so that they could distinguish the two and estimate their frequency of nightmares without confounding them with night terrors. They were told: 'A night terror is a sudden awakening in fear, possibly accompanied by a scream, but where you do not remember a dream'. The definition of a nightmare was given as: 'A vivid dream that is frightening or disturbing, the events of which you can remember clearly and in detail on awakening'. They were asked to estimate their nightmare frequency using the same six categories as for the question on dream recall.

Subjective effects questionnaires

Adapted Dissociative States Scale The Adapted Dissociative States Scale (ADSS) questionnaire consists of the subjectively rated items of the Clinician Administered Dissociative States Scale (Bremner et al. 1998).

Schizotypal Symptomatology Questionnaire The 26-item, self-rated Schizotypal Symptomatology Questionnaire (SSQ) was employed to assess state schizotypal positive symptomatology (Curran and Morgan 2000).

Visual analogue scales (VAS) mood assessments were conducted of contented/discontented, troubled/tranquil, tense/relaxed, happy/sad and withdrawn/gregarious. Each VAS was scored 0 (first adjective) to 100 (second adjective).

Dream and mood questionnaire (completed post-drug at home for 3 days and nights)

Ratings of anxiety and depression were made in the evening on two scales, one for the dimension relaxed–anxious and one for happy–depressed, anchored as very relaxed (1), quite relaxed (2), neither or mixed (3), quite anxious (4) and very anxious (5) and as very happy (1), quite happy (2), neither or mixed (3), quite depressed (4) and very depressed (5), respectively. Responses halfway between these five points were allowed (i.e. 1.5, 2.5, 3.5 and 4.5).

After waking, participants rated the presence of individual emotions in any dreams that had occurred, following the method of Fosse et al. (2001). The instructions were:

'For each dream, please indicate whether any of the following emotions occurred in the dream. If an emotion occurred, use a number from 1 to 3 to show how intense it was, where 1 is low, 2 is medium and 3 is high'. The emotions were listed as: anger; anxiety/fear; sadness; shame; joy/elation; love/erotic; surprise; other (please specify).

Participants then rated 'the overall mood of the dream' on a pleasantness/unpleasantness scale, anchored as very pleasant (1), quite pleasant (2), neither or mixed (3), quite unpleasant (4) and very unpleasant (5), adapted from the dream hedonic tone scale of Foulkes et al. (1966). Responses halfway between these five points were allowed (i.e. 1.5, 2.5, 3.5 and 4.5).

After having completed these ratings for any other dream that was recalled, they then completed the relaxed–anxious and happy–depressed scales again for how they were feeling that morning.

Cognitive assessments were also performed for semantic priming tasks, which are reported elsewhere (Morgan et al. 2006b).

Results

There were no significant differences between the high- and low-dose ketamine conditions for any variable. For example, on-drug schizotypy [means (SD): low-dose=9.25 (SD=9.25); high-dose=12.22 (15.02)] and on-drug dissociation [low-dose=14.38 (12.07); high-dose=14.22 (14.19)]. The low- and high-dose groups are thus combined for statistical analyses that compare the ketamine and placebo conditions. There were no sex differences on any of the variables, except for baseline schizotypy [means (SD): males=13.77 (16.41), females=2.25 (3.36), Mann–Whitney U=35.5, z=3.14, p=0.002].

Retrospective dream measures

Table 2 shows the retrospective dream recall frequencies of the ketamine/placebo groups. The groups did not differ significantly on dream recall frequency (chi square (4)=

Table 2 Retrospective dream recall frequencies for the ketamine and placebo groups

	Retrospective dream recall frequency					Total
	Four to seven times per week	One to three times per week	One to three times per month	Less than once per month	Once a year or less	
Placebo	3	7	0	1	0	11
Ketamine	4	10	2	2	1	19
Total	7	17	2	3	1	30

Groups do not differ significantly on dream recall frequency, chi square (4)=2.02

2.02). From this categorical data, retrospective dream recall frequency can be calculated as approximately 9.9 dreams per month for the ketamine group and 12.1 dreams per month for the placebo group.

Table 3 shows the retrospective nightmare frequencies of the two drug groups. The groups did not differ significantly on nightmare frequency (chi square (4)=4.96). From this categorical data, retrospective nightmare frequency can be calculated as approximately 1.1 nightmares per month for the ketamine group and 1.6 nightmares per month for the placebo group.

State and trait psychopathology measures

Table 4 shows the descriptive statistics for the data collected before drug administration and the state schizotypy, dissociation and VAS mood data before and during drug administration for the ketamine and placebo groups. The only significant differences between the two groups were for pre-drug VAS tense/relaxed (Mann–Whitney U=46.50, z=2.36, p<0.05), on-drug VAS tense/relaxed (Mann–Whitney U=39.00, z=2.70, p<0.01), on-drug VAS withdrawn/gregarious (Mann–Whitney U=40.00, z=2.65, p<0.01), on-drug schizotypy (Mann–Whitney U=54.00, z=2.03, p<0.05) and on-drug dissociation (Mann–Whitney U=28.00, z=3.136, p=0.002). From the results of the contented/discontented; troubled/tranquil; tense/relaxed, and happy/sad VAS, the experience was marginally more unpleasant for the ketamine group.

Effects of ketamine on anxiety and depression over the 3 days after drug use

There were no significant differences in anxiety or depression between any of the 3 days for either group. The scores for the 3 days were thus combined to produce a mean score for anxiety and a mean score for depression at each of the times of testing: evening and morning. Table 5 shows that there were no significant differences between the ketamine and placebo groups on these depressed–happy [F(1, 28)=0.50] or anxious–relaxed [F(1,28)=2.35] scores. Depression and anxiety were each significantly higher in the morning than in the evening [depression: F(1,28)=5.93, p=0.022; anxiety: F(1,28)=10.27, p=0.003]. The differences between morning and evening did not interact with drug condition for either anxiety or depression.

Effects of ketamine on dream recall and dream hedonic tone during the three post-drug administration nights

Shapiro–Wilk tests showed that home nightmare frequency, home dream frequency and mean hedonic tone were not normally distributed, and so non-parametric statistics are used. Kendall's correlation of concordance is used so as to allow for partial correlations. Critical values for p of partial correlation tau-b are taken from Maghsoodloo and Pallos (1981).

The ketamine and placebo groups did not differ on the number of dreams over the three nights after treatment [ketamine: n=19, mean (SD)=2.63 (1.89); placebo: n=11, mean (SD)=2.36 (1.69): Mann–Whitney U=98.00, z=0.284, n.s.]. Twenty-five participants reported at least one dream (ketamine low-dose, n=5; ketamine high-dose, n=11; placebo, n=9); dream content analyses are conducted on the two groups: ketamine, n=16 and placebo, n=9. There were no differences in dream unpleasantness between the three nights for the placebo (Friedman's test, chi square (2)=0.29) or ketamine group (chi square (2)=0.54) and for the low- and high-dose ketamine groups assessed separately

Table 3 Retrospective nightmare frequencies for the ketamine and placebo groups

	Retrospective nightmare frequency					Total
	Four to seven times per week	One to three times per week	One to three times per month	Less than once per month	Once a year or less	
Placebo	1	4	2	4	0	11
Ketamine	1	4	8	3	3	19
Total	2	8	10	7	3	30

Groups do not differ significantly on nightmare frequency, chi square (4)=4.96

Table 4 Pre-drug and on-drug descriptive statistics for trait and state psychopathology and mood measures

	Ketamine (n=19)		Placebo (n=11)	
	Mean	SD	Mean	SD
Beck Depression Inventory	4.53	4.94	3.55	5.68
Trait anxiety	18.00	7.91	13.45	13.13
Dissociative experiences	24.21	14.68	23.09	19.23
Contented/discontented pre-drug[a]	25.06	19.42	20.82	18.16
Contented/discontented on-drug[a]	21.67	16.39	13.18	12.54
Troubled/tranquil pre-drug[a]	72.39	17.09	82.18	14.23
Troubled/tranquil on-drug[a]	72.39	18.74	84.55	11.01
Tense/relaxed pre-drug[a]	61.94*	19.91	79.91*	16.68
Tense/relaxed on-drug[a]	63.89**	24.05	84.82**	12.17
Happy/sad pre-drug[a]	20.89	10.13	14.00	10.08
Happy/sad on-drug[a]	23.44	16.72	21.00	28.63
Withdrawn/gregarious pre-drug[a]	66.50	16.18	66.36	17.48
Withdrawn/gregarious on-drug[a]	50.72**	21.90	74.18**	20.97
State schizotypy pre-drug[a]	4.89	4.75	11.55	19.14
State schizotypy on-drug[a]	10.78*	11.99	7.91*	12.76
State dissociation pre-drug[a]	1.00	2.59	1.36	3.64
State dissociation on-drug[b]	14.29 ***	12.82	1.82***	2.86

*p<0.05; **p<0.01; ***p=0.002
[a] Ketamine group n=18 due to missing data
[b] Ketamine group n=17 due to missing data

(chi square (2)=3.00 and 0.67, respectively), and so data for the three nights are combined. Table 6 shows that the ketamine group scored significantly higher on dream unpleasantness on the dream hedonic tone scale than did the placebo group [Mann–Whitney U=37.00, z=2.002, p=0.045; Kendall's tau=0.35, p=0.045; for the sexes analysed separately, females (n=14), tau=0.52, p=0.03, males (n=11), tau=0.19] and became more significant when home retrospective nightmare frequency was partialled out (Kendall's partial tau=0.45, p=0.002). The Kendall correlation coefficient between ketamine blood plasma level and mean dream unpleasantness was negligible for the low-dose ketamine group (tau=0.00, n=5) but was significant for the high-dose group (tau=0.50, p=0.039, n=11).

The amounts of positive and negative emotions in the dreams were calculated according to the method of Fosse et al. (2001). Dream emotions were categorised as either positive (joy/elation; love/erotic; other positive emotions) or negative (anger; anxiety/fear; sadness; shame; other negative emotions). The intensities of the positive emotions and the negative emotions were each summed and then divided by the total number of dreams. This produced the total positive emotions and total negative emotions measures. Following Fosse et al., surprise was not included in either total positive emotions or total negative emotions and is calculated as the sum of intensities of surprise divided by the total number of dreams. The results for total positive emotions, total negative emotions and surprise are shown in Table 6.

The ketamine and placebo groups did not differ significantly on total negative emotions (Mann–Whitney

Table 5 Drug effects on anxiety and depression, assessed in the evening and in the morning and averaged across the three post-drug days

	Ketamine (n=19)		Placebo (n=11)	
	Mean	SD	Mean	SD
Depression in evening[a]	2.25	0.65	2.09	0.79
Depression in morning[a]	2.54	0.52	2.39	0.71
Anxiety in evening[b]	2.22	0.54	1.91	0.80
Anxiety in morning[b]	2.60	0.61	2.23	0.73

[a] Depressed–happy scale: very happy=1, very depressed=5
[b] Anxiety–relaxed scale: very relaxed=1, very anxious=5

Table 6 Effects of ketamine on dream hedonic tone, total positive and negative emotions and surprise

Data from participants who reported at least one dream	Ketamine (n=16)		Placebo (n=9)	
Dream hedonic tone[a]	3.25*	0.67	2.71*	0.69
Total positive emotions	0.34**, ***	0.56	1.21**	0.88
Total negative emotions	1.35***	0.98	1.54	2.55
Total surprise	0.42	0.53	1.20	1.12

*p<0.05, differs between groups; **p=0.005, differs between groups; ***p<0.01, differs within subjects
[a] 1=very pleasant, 5=very unpleasant

U=55.50, z=0.94) nor on total surprise (Mann–Whitney U=39.00, z=1.92). However, total positive emotions was significantly higher for the placebo group than for the ketamine group (Mann–Whitney U=25.0, z=2.78, p=0.005). For the placebo group, total positive emotions and total negative emotions did not differ significantly (Wilcoxon, z=0.18), whereas the ketamine group had significantly higher total negative emotions than total positive emotions (Wilcoxon, z=2.61, p=0.009). Within the low-dose ketamine group, all correlations between ketamine dose and total positive emotions, total negative emotions and total surprise were not significant. Within the high-dose group, there was a significant correlation only between dose and total negative emotion (tau=0.67, n=11, p=0.005).

Effects of ketamine on incidence of unpleasant dreams during the three post-drug administration nights

Incidence of unpleasant dreams was defined as whether participants had at least one dream over the three nights rated at least 4 on the pleasantness/unpleasantness scale. Table 7 shows the contingency table for the presence/absence of an unpleasant dream over the three nights after drug administration for the ketamine and placebo groups. Ketamine did not have a significant effect on incidence of unpleasant dreams (tau=0.25), but when home nightmare frequency was partialled out, the effect became significant (Kendall's partial tau=0.35, p=0.008). Odds ratio of effect of ketamine on the presence of an unpleasant dream was 2.96 (95%CI=0.596, 14.729). The effect of ketamine was greater for females (n=16, tau=0.33) than for males (n=14, tau=0.15).

The Kendall correlation coefficient between ketamine blood plasma level and unpleasant dream incidence were negligible for the low-dose ketamine group (tau=−0.09, n=8) but was larger for the high-dose group (tau=0.44, p=0.10, n=11).

Predictors of dream variables for the ketamine group

Home dream recall predicted post-drug dream recall for the ketamine group (Kendall's tau=0.49, p=0.01). The association was not significant for the placebo group (Kendall's tau=0.26). Unpleasant dream incidence was significantly associated with home nightmare frequency for the ketamine group [tau=0.58, p=0.008; females (n=10) tau=0.45, males (n=9) tau=0.75 (p=0.022)]: participants given ketamine who reported having one nightmare per year or less on the retrospective questionnaire had no unpleasant dreams over the three post-ketamine nights.

Table 8 shows that there were non-significant associations between unpleasant dream incidence and on-drug schizotypy and dissociation scores and negligible relationships between unpleasant dream incidence and baseline schizotypy and dissociation. There were no significant relationships between incidence of unpleasant dreams and on-drug VAS measures of the unpleasantness/pleasantness of the experience; the association of incidence of unpleasant dreams with VAS withdrawn/gregarious (tau=−0.41, p<0.05) was not significant after correction for family-wise type 1 error due to multiple correlations.

Ketamine-induced deficits in semantic priming for this study are reported in Morgan et al. (2006b): scores on semantic priming variables were not predictive of incidence of unpleasant dreams (all taus<0.20).

Discussion

Administration of a sub-anaesthetic dose of ketamine resulted in a greater incidence of unpleasant dreams and more mean unpleasantness of dreams compared to placebo over the three nights after administration. This effect seems to be due to the diminishing of positive dream emotions, rather than an intensification of negative emotions; the results of the placebo condition accorded with findings in the literature that positive and negative dream emotions are balanced across participants (Fosse et al. 2001; Schredl and

Table 7 Contingency tables reporting effect of ketamine on incidence of unpleasant dreams over the three nights after ketamine administration

For all participants	Ketamine n=19	Placebo n=11
At least one unpleasant dream	10	3
No unpleasant dreams	9	8

Kendall's tau association between drug condition and presence/absence of at least one unpleasant dream=0.25; Kendall's partial tau association between drug condition and presence/absence of at least one unpleasant dream when home nightmare frequency was partialled out=0.35, p=0.008

Table 8 Kendall's tau correlations between incidence of unpleasant dreams after ketamine and pre-drug and on-drug schizotypy and dissociation measures and on-drug mood measures

	Tau
State schizotypy pre-drug	−0.08
State schizotypy on-drug	0.33
State dissociation pre-drug	0.01
State dissociation on-drug[a]	0.34
Contented/discontented on-drug	0.03
Troubled/tranquil on-drug	−0.10
Tense/relaxed on-drug	−0.40
Happy/sad on-drug	0.05
Withdrawn/gregarious on-drug	−0.41

Data for ketamine group, n=18 due to missing data from one participant

[a] Ketamine group n=17 due to missing data

Doll 1998). The effect of ketamine is not due to state anxiety or depression over the three post-drug days, as the ketamine and placebo conditions did not differ on these variables, and is unlikely to be due to any general unpleasantness of the ketamine experience, as there was little difference between the ketamine and placebo conditions on VAS measures of the unpleasantness of the experience.

These results can be interpreted as evidence for residual emergence effects of ketamine use with the decrease in positive dream emotions in the ketamine group possibly due to the anhedonia that is a component of schizotypy and dissociation. For example, Krystal et al. (1994) reported that subjects were emotionally blunted and dulled during the day of receiving ketamine, and anhedonia with anxiety and some suspiciousness is described by Duncan et al. (2001) for normal subjects given sub-anaesthetic ketamine. Although such residual effects have only been observed over some hours after ketamine administration, low-level effects might be present for longer but masked during wakefulness by the volume of other cognitive activity.

This explanation for the results accords with the proposal that ketamine may model aspects of psychosis. Although the literature on the association of schizotypy and nightmare frequency does not distinguish between positive and negative schizotypal symptoms, the present study found for the ketamine group that unpleasant dream incidence had an association with on-drug social withdrawal of tau=0.41, which is comparable in size to the association with on-drug (positive) schizotypy (tau=0.33). Given also that the ketamine group reported significantly higher on-drug schizotypy and withdrawal than placebo, the current study supports previous research showing that acute ketamine mimics both positive and negative psychosis-like symptoms (Krystal et al. 2005; Lahti et al. 2001).

One other possible explanation for these effects of ketamine on dream unpleasantness, however, concerns the effects of ketamine on sleep. Both racemic and S-ketamine result in an increase in high-frequency electroencephalogram (EEG; above 20 Hz) during anaesthesia (Maksimow et al. 2006), and there is electrocerebral and subjective activation in the wake state (Knott et al. 2006) after sub-anaesthetic ketamine. Campbell and Feinberg (1999) found that changes in EEG spectra following the NMDA antagonist MK-801 were similar to changes caused by sleep deprivation with large increases in non-rapid eye movement (NREM) delta and REM 10–20 Hz power. The enhancing of 10–20 Hz power during REM sleep by NMDA was also found by Lydic and Baghdoyan (2002). Ketamine also increases cortical acetylcholine (Kim et al. 1999), upon which REM sleep is dependent (Rye 1997), and there is a REM rebound following the increase in NREM delta over the 12 h after ketamine (Feinberg and March 1995). Such an activating effect on sleep would cause an intensification of dream imagery (Dement 1960; Nielsen et al. 2005). However, as the greater unpleasantness of the dreams of the ketamine group seems to result from a diminishing of positive emotions, rather than an intensification of negative emotions, it is unclear how an intensification of dream imagery could have resulted in such a profile of differences in dream emotions between the ketamine and placebo groups. Also, positive dream emotions have been found to be of equal intensity to negative emotions in dreams by St-Onge et al. (2005) and slightly less intense than negative emotions by Schredl and Doll (1998), and so arguably, negative emotions would not be preferentially augmented by an intensification of dreaming. It should also be noted that dream recall over the three nights after administration was anyway not higher in the ketamine group. However, neither self-ratings nor objective measures of sleep length and quality were taken in the present study, and so it remains possible that, in this study, the effects on dream unpleasantness were mediated by sleep variables.

Individual differences in the incidence of unpleasant dreams after ketamine were significantly associated with retrospective home nightmare frequency. It is possible that this is because those high in home nightmare frequency are high in associated traits (e.g. thin boundariness, absorption, neuroticism; Blagrove 2007) that might interact with the state effects of ketamine to produce unpleasant dreams. Although retrospective measures of nightmare frequency do provide lower estimates of nightmare frequency than do prospective diary measures (Blagrove et al. 2004), this measure may be useful in the medical use of ketamine as an indicator of increased likelihood of unpleasant dreams. The co-use of other drugs during anaesthesia [e.g. benzodiazepines (Grace 2003), clonidine (Handa et al. 2000), diazepam and midazolam (Hersack 1994)] can reduce the incidence of unpleasant dreams such that this prediction is in those circumstances not necessary, but prediction of the incidence of unpleasant dreams should be considered where ketamine is the sole agent used, such as in analgesia and minor surgery.

It is unclear how to interpret the finding that the effect of ketamine on dream unpleasantness was greater for females than males, given that this study also found, as did previous work (Morgan et al. 2006a), that there are no sex differences in on-drug psychotic symptoms or dissociation due to ketamine (although the latter authors did find that there are larger ketamine-induced memory deficits for males than for females). There have been findings that females report nightmares more often than do males (e.g. Levin 1994; Nielsen et al. 2006), but this has sometimes not been replicated (e.g. Chivers and Blagrove 1999). Future work should thus address whether this sex difference is a chance effect, a result of a more general propensity of

females to have unpleasant dreams or to be willing to report them (an effect not anyway present in our baseline retrospective data) or a novel neurochemical finding for ketamine.

In conclusion, sub-anaesthetic ketamine produces an increase in dream unpleasantness over the three nights after drug use, especially for females. This may be mediated by residual schizotypy and dissociative effects. Retrospective frequency of nightmares was a significant predictor of incidence of unpleasant dreams and should be controlled for in future studies of the effects of ketamine on dreaming.

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References

Blagrove M (2007) Personality and dreaming. In: Barrett D, McNamara P (eds) The new science of dreaming, volume 2: content, recall, and personality correlates. Praeger, Westport, CT, pp 115–158

Blagrove M, Farmer L, Williams E (2004) The relationship of nightmare frequency and nightmare distress to well-being. J Sleep Res 13:129–136

Bremner JD, Krystal JD, Putman FW, Southwick SM, Marmar C, Charney DS, Mazure CM (1998) Measurement of dissociative states with the Clinician Administered Dissociative States Scale (CADDS). J Trauma Stress 11:125–136

Campbell IG, Feinberg I (1999) Comparison of MK-801 and sleep deprivation effects on NREM, REM, and waking spectra in the rat. Sleep 22:423–432

Chivers L, Blagrove M (1999) Nightmare frequency, personality and acute psychopathology. Pers Individ Differ 27:843–851

Coppel DL, Bovill JG, Dundee JW (1973) The taming of ketamine. Anaesthesia 28:293–296

Cunningham BL, McKinney P (1983) Patient acceptance of dissociative anesthetics. Plast Reconstr Surg 72:22–26

Curran HV, Monaghan L (2001) In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. Addiction 96:749–760

Curran HV, Morgan C (2000) Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. Addiction 95:575–590

Dal D, Celebi N, Elvan EG, Celiker V, Aypar U (2007) The efficacy of intravenous or peritonsillar infiltration of ketamine for postoperative pain relief in children following adenotonsillectomy. Paediatr Anaesth 17:263–269

Dement W (1960) The effect of dream deprivation. Science 131:1705–1707

Domino EF, Domino SE, Smith RE, Domino LE, Goulet RJ, Domino KE, Zsigmond EK (1984) Ketamine kinetics in unmedicated and diazepam-premedicated subjects. Clin Pharmacol Ther 36:645–653

Downing JW, Mahomedy MC, Jeal DE, Allen PJ (1976) Anaesthesia for cesarian section. Anaesthesia 31:883–892

Duncan EJ, Madonick SH, Parwani A, Angrist B, Rajan R, Chakravorty S, Efferen TR, Szilagyi S, Stephanides M, Chappell PB, Gonzenbach S, Ko GN, Rotrosen JP (2001) Clinical and sensorimotor gating effects of ketamine in normals. Neuropsychopharmacology 25:72–83

Edwards ND, Fletcher A, Cole JR, Peacock JE (1993) Combined infusions of morphine and ketamine for postoperative pain in elderly patients. Anaesthesia 48:124–127

Ellingson A, Haram K, Sagen N (1977) Ketamine and diazepam as anaesthesia for forceps delivery. A comparative study. Acta Anaesthesiol Scand 21:37–40

Erk G, Örnek D, Donmez NF, Taspinar V (2007) The use of ketamine or ketamine–midazolam for adenotonsillectomy. Int J Pediatr Otorhinolaryngol 71:937–941

Feinberg I, March JD (1995) Observations on delta homeostasis, the one-stimulus model of NREM-REM alternation and the neurobiologic implications of experimental dream studies. Behav Brain Res 69:97–108

Figallo EM, McKenzie R, Tantisira B, Wadhwa RK, Sinchioco CS (1977) Anaesthesia for dilatation, evacuation and curettage in outpatients: comparison of subanaesthetic doses of ketamine and sodium methohexitone-nitrous oxide anaesthesia. Can Anaesth Soc J 24:110–117

Fine J, Finestone SC (1973) Sensory disturbances following ketamine anesthesia: recurrent hallucinations. Anaesth Analg 52:428–430

Fletcher PC, Honey GD (2006) Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. Trends Cogn Sci 10:167–174

Fosse R, Stickgold R, Hobson JA (2001) The mind in REM sleep: reports of emotional experience. Sleep 24:947–955

Foulkes D, Spear PS, Symonds JD (1966) Individual differences in mental activity at sleep onset. J Abnorm Psychol 71:280–286

Freuchen I, Østergaard J, Kűhl JB, Mikkelsen BO (1976) Reduction of psychotomimetic side effects of Ketalar* (Ketamine) by Rohypnol* (Flunitrazepam). Acta Anaesthesiol Scand 20:97–103

Funk W, Jakob W, Riedl T, Taeger K (2000) Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine *vs* midazolam or ketamine alone. Br J Anaesth 84:335–340

Grace RF (2003) The effect of variable-dose diazepam on dreaming and emergence phenomena in 400 cases of ketamine-fentanyl anaesthesia. Anaesthesia 58:874–910

Green SM, Johnson NE (1990) Ketamine sedation for pediatric procedures: part 2, review and implications. Ann Emerg Med 19:1033–1046

Green SM, Sherwin TS (2005) Incidence and severity of recovery agitation after ketamine sedation in young adults. Am J Emerg Med 23:142–144

Green SM, Nakamura R, Johnson NE (1990) Ketamine sedation for pediatric procedures: part 1, a prospective series. Ann Emerg Med 19:1024–1032

Handa F, Tanaka M, Nishikawa T, Toyooka H (2000) Effects of oral clonidine premedication on side effects of intravenous ketamine anesthesia: a randomized, double-blind, placebo-controlled study. J Clin Anesth 12:19–24

Hartmann E, Russ D, van der Kolk B, Falke R, Oldfield M (1981) A preliminary study of the personality of the nightmare sufferer: relationship to schizophrenia and creativity? Am J Psychiatry 138:794–797

Hejja P, Galloon S (1975) A consideration of ketamine dreams. Can Anaesth Soc J 22:100–105

Hersack RA (1994) Ketamine's psychological effects do not contraindicate its use based on a patient's occupation. Aviat Space Environ Med 65:1041–1046

Hostetler MA, Davis CO (2002) Prospective age-based comparison of behavioral reactions occurring after ketamine sedation in the ED. Am J Emerg Med 20:463–468

Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV (1996) Preoperative anxiety in children. Predictors and outcomes. Arch Pediatr Adolesc Med 150:1238–1245

Kales A, Soldatos CR, Caldwell AB, Charney DS, Kales JD, Markel D, Cadieux R (1980) Nightmares: clinical characteristics and personality patterns. Am J Psychiatry 137:1197–1201

Kennedy RM, McAllister JD (2000) Midazolam with ketamine: who benefits? Ann Emerg Med 35:297–299

Khorramzadeh E, Lofty AO (1976) Personality predisposition and emergence phenomena with ketamine. Psychosomatics 17:94–95

Kim SH, Price MT, Olney JW, Farber NB (1999) Excessive cerebrocortical release of acetylcholine induced by NMDA antagonists is reduced by GABAergic and 2-adrenergic agonists. Mol Psychiatry 4:344–352

Klausen N-O, Wiberg-Jørgensen F, Chræmmer-Jørgensen B (1983) Psychomimetic reactions after low-dose ketamine infusion. Br J Anaesth 55:297–301

Knill RL, Moote CA, Skinner MI, Rose EA (1990) Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. Anesthesiology 73:52–61

Knott V, McIntosh J, Millar A, Fisher D, Villeneuve C, Ilivitsky V, Horn E (2006) Nicotine and smoker status moderate brain electric and mood activation induced by ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist. Pharmacol Biochem Behav 85:228–242

Krissel J, Dick WF, Leyser K-H, Gervais H, Brockerhoff P, Schranz D (1994) Thiopentone, thiopentone/ketamine, and ketamine for induction of anaesthesia in caesarean section. Eur J Anaesthesiol 11:115–122

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB, Charney DS (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214

Krystal JH, Perry EB, Gueorguieva R, Belger A, Madonick SH, Abi-Dargham A, Cooper TB, MacDougall L, Abi-Saab W, D'Souza DC (2005) Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. Arch Gen Psychiatry 62:985–995

Kwok RF, Lim J, Chan MT, Gin T, Chiu WK (2004) Preoperative ketamine improves postoperative analgesia after gynecologic laparoscopic surgery. Anesth Analg 98:1044–1049

Lahti AC, Weiler MA, Michaelidis T, Parwani A, Tamminga CA (2001) Effects of ketamine in normal and schizophrenic volunteers. Neuropsychopharmacology 25:455–467

Levin R (1994) Sleep and dreaming characteristics of frequent nightmare subjects in a university population. Dreaming 4:127–137

Levin R (1998) Nightmares and schizotypy. Psychiatry 61:206–216

Levin R, Fireman G (2002) Nightmare prevalence, nightmare distress, and self-reported psychological disturbance. Sleep 25:205–212

Lofty AO, Amir-Jahed AK, Moarefi P (1970) Anesthesia with ketamine: indications, advantages and shortcomings. Anesth Analg 49:969–974

Lydic R, Baghdoyan HA (2002) Ketamine and mk-801 decrease acetylcholine release in the pontine reticular formation, slow breathing, and disrupt sleep. Sleep 25:617–622

Maghsoodloo S, Pallos LL (1981) Asymptotic behavior of Kendall's partial rank correlation coefficient and additional quartile estimates. J Stat Comput Simul 13:41–48

Maksimow A, Särkelä M, Långsjö JW, Salmi E, Kaisti KK, Yli-Hankala A, Hinkka-Yli-Salomäki S, Scheinin H, Jääskeläinen SK (2006) Increase in high frequency EEG activity explains the poor performance of EEG spectral entropy monitor during S-ketamine anesthesia. Clin Neurophysiol 117:1660–1668

Mattila MA, Larni HM, Nummi SE, Pekkola PO (1979) Effects of diazepam on emergence from ketamine anaesthesia. A double-blind study. Anaesthesist 28:20–23

McGlone RG, Howes MC, Joshi M (2004) The Lancaster experience of 2.0 to 2.5 mg/kg intramuscular ketamine for paediatric sedation: 501 cases and analysis. Emerg Med J 21:290–295

Meyers EF, Charles P (1978) Prolonged adverse reactions to ketamine in children. Anesthesiology 49:39–40

Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV (2004a) Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose-response study. Psychopharmacology 172:298–308

Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV (2004b) Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacology 29:208–218

Morgan CJA, Perry EB, Cho H-S, Krystal JH, D'Souza DC (2006a) Greater vulnerability to the amnestic effects of ketamine in males. Psychopharmacology 187:405–414

Morgan CJA, Rossell SL, Pepper F, Smart J, Blackburn J, Brandner B, Curran HV (2006b) Semantic priming after ketamine acutely in healthy volunteers and following chronic self-administration in substance users. Biol Psychiatry 59:265–272

Muris P, Merckelbach H, Ollendick TH, King NJ, Bogie N (2001) Children's nighttime fears: parent–child ratings of frequency, content, origins, coping behaviors and severity. Behav Res Ther 39:13–28

Newcomer JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, Craft S, Olney JW (1999) Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neurospychopharmacology 20:106–118

Nielsen TA, Laberge L, Paquet J, Tremblay RE, Vitaro F, Montplaisir J (2000) Development of disturbing dreams during adolescence and their relation to anxiety symptoms. Sleep 23:727–736

Nielsen T, Stenstrom P, Takeuchi T, Saucier S, Lara-Carrasco J, Solomonova E, Martel E (2005) Partial REM-sleep deprivation increases the dream-like quality of mentation from REM sleep and sleep onset. Sleep 28:1083–1089

Nielsen TA, Stenstrom P, Levin R (2006) Nightmare frequency as a function of age, gender, and September 11, 2001: findings from an internet questionnaire. Dreaming 16:145–158

Olney JW, Newcomer JW, Farber NB (1999) NMDA receptor hypofunction model of schizophrenia. J Psychiatr Res 33:523–533

Pagel JF, Helfter P (2003) Drug induced nightmares—an etiology based review. Hum Psychopharmacol 18:59–67

Perel A, Davidson JT (1976) Recurrent hallucinations following ketamine. Anaesthesia 31:1081–1083

Pomarol-Clotet E, Honey GD, Murray GK, Corlett PR, Absalom AR, Lee M, McKenna PJ, Bullmore ET, Fletcher PC (2006) Psychological effects of ketamine in healthy volunteers: phenomenological study. Br J Psychiatry 189:173–179

Radant AD, Bowdle TA, Cowley DS, Kharasch ED, Roy-Byrne PP (1998) Does ketamine-mediated n-methyl-d-aspartate receptor antagonism cause schizophrenia-like oculomotor abnormalities? Neuropsychopharmacology 19:434–444

Rye DB (1997) Contributions of the pedunculopontine region to normal and altered REM sleep. Sleep 20:757–788

Schafer SL, Varvel JR, Aziz N, Scott JC (1990) Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. Anesthesiology 73:1091–1102

Schredl M, Doll E (1998) Emotions in diary dreams. Conscious Cogn 7:634–646

Sechzer PH (1984) Dreams with low-dose ketamine in obstetrical patients. Curr Ther Res 35:396–404

Sherwin TS, Green SM, Khan A, Chapman DS, Dannenberg B (2000) Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. Ann Emerg Med 35:229–238

Sklar GS, Zukin SR, Reilly TA (1981) Adverse reactions to ketamine anaesthesia: abolition by a psychological technique. Anaesthesia 36:183–187

Stone JM, Pilowsky LS (2006) Psychopathological consequences of ketamine. Br J Psychiatry 189:565–566

St-Onge M, Lortie-Lussier M, Mercier P, Grenier J, De Koninck J (2005) Emotions in the diary and REM dreams of young and late adulthood women and their relation to life satisfaction. Dreaming 15:116–128

Sussman DR (1974) A comparative evaluation of ketamine anesthesia in children and adults. Anesthesiology 40:459–464

Torvaldsson S, Grote L, Peker Y, Basum H, Hedner J (2005) A randomized placebo-controlled trial of an NMDA receptor antagonist in sleep-disordered breathing. J Sleep Res 14:149–155

Valentin N, Bech B (1996) Ketamine anaesthesia for electrocochleography in children: are psychic side effects really rare? Scand Audiol 25:39–43

Wathen JE, Roback MG, Mackenzie T, Bothner JP (2000) Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomized controlled, emergency department trial. Ann Emerg Med 36: 579–588

Watson D (2001) Dissociations of the night: individual differences in sleep-related experiences and their relation to dissociation and schizotypy. J Abnorm Psychol 110:526–535

Watson D (2003) To dream, perchance to remember: individual differences in dream recall. Pers Individ Differ 34:1271–1286

White PF, Ham J, Way WL, Trevor AJ (1980) Pharmacology of ketamine isomers in surgical patients. Anesthesiology 52: 231–239

White PF, Way WL, Trevor AJ (1982) Ketamine—its pharmacology and therapeutic uses. Anesthesiology 56:119–136