**OTHER SUPPLEMENTARY MATERIAL**

**SUPPLEMENTARY Methods**

**Participants**

Participants were recruited from the university locale. Inclusion criteria were: age 18-35 years; infrequent (≤2/month) recreational drug use (except caffeine, alcohol and tobacco), ≤112 g weekly alcohol, BMI 18.5-30 kg/m2, normal blood pressure, normal or corrected to normal vision and hearing, access to a smart/internet device and ability to complete the remote intrusion monitoring task on the first three days, and at least five of the seven monitoring days. To limit the effects of ovarian hormone fluctuation on intrusions or emotional responding, participants also had to be daily users of a hormone-based oral contraceptive, confirmed using their most recent personal (named) prescription or drug pack. Exclusion criteria were: known memory impairments, significant sleep problems, asthma, diabetes, chronic obstructive pulmonary disease, cardiac disease, low blood pressure, history of seizures or neurosurgery, impaired liver or kidney function, and history of severe anaphylactic reaction to a variety of allergens, current use of glucocorticoid/ cardiovascular/psychiatric medication use; self-declared history of psychiatric disorder; (in)direct experience of significant interpersonal violence; history of fainting; previous exposure to the trauma-film (‘Irreversible’, Studio Canal). Note, since only the general nature of the film, rather than its title, were disclosed during the screening procedure, we could only ascertain whether participants had previous exposure to the film on day 1, after film viewing.

Related intrusion-interference studies have shown large effect size estimates (d>0.8) for intrusion counts (Holmes, James, Coode-Bate, & Deeprose, 2009; James et al., 2015). Given uncertainty about the effects of propranolol and hydrocortisone on intrusive memories, we assumed a more conservative, medium effect (*f*=0.25). With α=0.05 and 1-β=0.8, n=93 was required to detect a main effect of drug (Faul, Erdfelder, Lang, & Buchner, 2007). Of n=186 screened participants, n=111 reported meeting inclusion criteria and n=92 attended day 1. Of these, four participants could not be included because: n=1 had previously seen the film; n=1 found film too distressing; n=1 disclosed severe depression on day 1, n=1 inaccurately reported use of contraceptive at screening. This left n=88 who completed day 1 and the intrusion diaries (achieved power=0.78). All those who completed the diaries attended day 8.

Randomisation was performed using an online random number generator (Randomizer.org), using 30 consecutive ‘blocks’ of triplets, corresponding to each of the three conditions. Participants were assigned to condition at screening and coded envelopes containing the capsules were retained by the PI (SKK) until day 1. No experimenter had access to the treatment-participant code, which was held by the medical consultant and senior investigators (none of whom were involved in any data collection and had no access to the data during the study).

**Questionnaire and physiological assessments**

Baseline mood and trait measures were the Beck Depression Inventory-II (BDI; (Beck, Steer, & Brown, 1996), the Trait version of the State-Trait Anxiety Inventory (STAI; (Spielberger, 2010) and the Dissociative Experiences Scale-II (DES; (Carlson & Putnam, 1993). State positive and negative affect was assessed using the Positive-Negative Affect Schedule (PANAS; (Watson & Clark, 1999), with instructions to indicate *current* (“right now”) feelings. In addition, numerical rating scales of negative emotions were used (prior to PANAS). However, since these loaded onto a single factor which correlated highly with PANAS-negative scores (*r*(88)=0.769, *p*<0.001 – correlation between T1 scores), only PANAS-negative scores are reported. Similarly a single NRS item for happiness was strongly correlated with total PANAS-positive (*r*(88)=0.506, *p*<0.001), and so only PANAS-positive scores are reported.

The Bodily Symptoms Scale (BSS; (Bond & Lader, 1974), was used to assess drug-related psychological and physical states. Thirteen bodily/mental state items are included in the BSS: anxiety, depression, memory impairment, palpitations, nausea, emotional numbness, euphoria, drowsiness, muscle-tension, headache, loss of concentration, shaking/trembling and confusion). Each is scored on a 0 (no symptom) to 100 (very strong/severe) range.

 General trauma symptoms (previous 7 days) were assessed using the 22-item Impact of Events Scale (IES; (Weiss, 2007) adapted for the trauma-film (Holmes et al., 2009). Heart rate (HR) was recorded using a BodyGuard-2 ECG device (FirstBeat Technologies, Finland), and episodic blood pressure with a BM40 XL device (Beurer UK) as outlined elsewhere (Kamboj et al., 2017). Event markers corresponding to the start of the film and end of the 1 hr filler period were recorded to identify the 5-min pre-film and post-drug periods (T1 and T3 as described in the main paper and Figure 1).

**Salivary cortisol levels**

Participants were instructed to avoid consuming any foods for >2 hr prior to the session and any drinks other than water for >1 hr. After a mouth rinse with water, passive drool (approximately 500 µl) was collected into cryovials. Samples were frozen immediately and stored at -80°C until analysis.

Prior to assay, samples were thawed completely at room temperature, vortex mixed, and centrifuged at 1500 x g for 15 minutes to remove precipitated mucins and particulate matter. Samples were later analysed using the Expanded Range, High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit (Salimetrics LLC, CA, USA), according to the manufacturer’s instructions.

**Drugs**

Drug doses were based on previous research demonstrating reliable effects on hormonal/physiological indices (Kuhlmann, Kirschbaum, & Wolf, 2005), which might not be observed at lower doses (Maheu, Joober, Beaulieu, & Lupien, 2004). Propranolol (2x40 mg; Accord Healthcare, Middlesex, UK) and hydrocortisone (1x10 mg + 1x20 mg; Auden Mckenzie Pharma Division, Ruislip, UK) tablets were mechanically crushed and re-encapsuled in opaque gelatine capsules, with additional lactose powder. Identical placebo capsules contained only lactose. Capsule preparation was performed by two trained researchers who were not otherwise involved in the study. Participants took these with water. Participants were aware of the side effect profile of the active drugs (based on information provided in the study information sheet) and provided a guess on treatment at the end of day 1, entered directly onto the computerised survey tool, allowing the experimenter to make independent guesses. This occurred before BP assessment at T3 to limit the influence of interoceptive signals (e.g. from the tightened BP cuff among participants) and device readings (experimenters).

**Intrusive memory recording**

At the end of the day 1 lab session, the importance of completing diary entries on each day was stressed to participants. They were provided with a detailed description of the nature of intrusive memories as ‘…*spontaneously occurring memory. By ‘spontaneous’ we mean memories of the film that suddenly pop into your mind automatically….not .....when you deliberately think about it. The spontaneous memories may pop into your mind when you are doing or thinking about something completely unrelated. The main thing is that you didn’t mean to think about the film but recalled something about it out of the blue.*’

**Voluntary memory assessment**

For free recall, participants were asked to recall “as much information and detail as possible including information about where things happen, when they happen, who they happen to, what the people and scenes look like, etc.,” typing this directly into a text box with no time limit. Performance was determined by counting the number of recalled ‘idea units’. For cued recall task (11), participants provided responses to 19 questions about events in the two clips.

Free and cued recall were independently scored either 0 (inaccurate), 0.5 (partially accurate), or 1 (highly accurate) by two treatment-blind researchers. Freely recalled items were classified as gist or detail (Kamboj & Curran, 2006). High interrater agreement was achieved (>90%) across recall metrics, with disagreements resolved through discussion.

**Statistical analysis**

Analyses were conducted on IBM SPSS (version 24) and Stata (version 14). Descriptive statistics are *means* + *SDs* (except where indicated). Outliers (studentised residuals >|3|) were winsorised $\left(x\_{(highest non-outlier)}+1\right)$. Data was checked for normality and homogeneity of variance, and where appropriate (IES score), log transformation applied prior to analysis (untransformed data are presented in the results for clarity). One-way ANOVAs were used to analyse baseline variables, voluntary memory and IES. Physiological and subjective data with limited missing values (due to recording failures, as reflected in lower-than-expected *dfs*: HR, BP, state affect/ bodily symptoms) were analysed using repeated measures ANOVA. Where assumptions of sphericity were violated, Greenhouse-Geisser correction was applied to *dfs* and *ps* adjusted accordingly. Correlation coefficients are Pearson’s *r* and case-wise diagnostics were used to determine the presence of outliers that might have influenced any significant effects*.* Day 1 intrusion counts were transformed $\left(Log\_{10}x\_{i}+1\right)$ for correlation analyses.

Given the absence of valid vividness and distress ratings later in the week, when intrusion counts tended towards 0, linear mixed models were used to analyse these variables. Missing intrusion counts were rare (1.1%) and conservatively replaced with the next day’s value (usually ‘0’). Given the non-zero inflated, over-dispersed nature of the intrusion counts (dispersion parameter *α*>0, *p*<0.001), mixed effects negative binomial regression was used to analyse counts. ‘Participant’ and Day were random factors and day was treated as continuous. Random intercept models were compared to random slopes models, with and without covariates, and interaction terms. Sequential change in model-fit was assessed using Akaike’s Information Criterion (AIC). Peri-film (T2) HR and cortisol were of special interest as covariates based on their demonstrated influence on intrusion characteristics(Chou, La Marca, Steptoe, & Brewin, 2014; Chou, Marca, Steptoe, & Brewin, 2014) and their potential interaction with subsequent propranolol and hydrocortisone treatment respectively. The influence of baseline anxiety (STAI) and depression (BDI) were also explored, given their reliable association with intrusive memories (Marks, Franklin, & Zoellner, 2018). Since STAI and BDI scores did not improve model fit, the effects of these are not discussed further.

**SUPPLEMENTARY RESULTS**

**Baseline characteristics**

Groups were well matched on demographic and psychological variables (Table 1 in the main paper). Due to the large number of cells, ethnicity data (South Asian, (South) East Asian, Black, White or mixed race/other) is not presented in Table 1 (main paper). However, ethnicity was balanced across groups (Fisher’s exact test=12.150, *p*=0.099).

Critically, the number of hours between film viewing and diary completion on day 1 (i.e. the period over which intrusive memories could be retrieved and rehearsed; ‘post-film period on day 1’ in Table 1) did not differ between groups. Neither was there a difference in quality (Fisher’s Exact Test=4.387, *p*=0.654) or amount of sleep (*F*(2,86)=0.196, *p*=0.822) on the night of day 1.

**Subjective and physiological response to film and drugs**

As in most previous studies with these drugs(Sijbrandij, Kleiboer, Bisson, Barbui, & Cuijpers, 2015), no adverse effects were reported. PANAS-negative scores showed no Group effects (*F* values ≤1.70, *p* values≥0.153), but a main effect of Time (*F*(1.47, 124.56)=205.062, p<0.001, *ηp2=*0.707), reflecting an increase from T1: 12.51 + 3.19 (*M* + *SD*) to T2: 24.61 + 7.87 (*p*<0.001), and return to baseline at T3 (13.48 + 4.32). PANAS-positive also showed no Group effects (*F* values ≤0.358, *ps*≥0.716), but a main effect of Time (*F*(2,170)=93.566, *p*<0.001, *ηp2=*0.524), with deterioration in positive affect between T1 (28.36 + 7.80) and T2 (19.59 + 5.99; *p*<0.001), maintained at T3 (20.74 + 7.85; *p*=0.247). No significant Group x Time interactions were found on any BSS items, which, with the exception of drowsiness (which increased equivalently in all groups), were generally at floor level (i.e. <10 on a 0-100 scale) across T1-T3. The absence of reported changes in bodily symptoms was consistent with chance level correct guessing on treatment by participants, (29.54%; *χ2*(4)=2.513, *p*=0.642) and experimenters (37.5%; *χ2*(4)=3.206, *p=*0.524).

A Time x Group interaction on HR (*F*(3.20, 132.71)=7.730, *p*<0.001, *ηp2=*0.157; Figure 2A), was driven by a drop between T2 and T3 (*p*<0.001) only after propranolol. Systolic BP also showed a Time x Group interaction (*F*(4,168)*=*3.766, *p*=0.006) driven by a reduction in systolic-BP only in the propranolol group between T2 and T3 (*p*<0.001). Baseline salivary cortisol levels (0.144 µg/dl) were in the expected range (Miller et al., 2016). A Time x Group interaction on cortisol levels (*F*(2.01, 80.37)=16.78, *p*<0.001, *ηp2=*0.296), reflected a T2 to T3 increase only after hydrocortisone (*p*<0.001; Figure 2B).

**Attention to film: Eye tracking**

There were no significant group differences in (pre-drug) attentional parameters during film viewing. The averaged dwell-time on AOI for placebo (2.54 + 1.84 s) was not significantly different to that for propranolol (1.88 + 2.18 s) or hydrocortisone (2.59 + 2.35 s; *F*(2,83)=0.983, *p*=0.379). Similarly, the number of fixations per AOI in the placebo group (8.02 + 5.99) did not differ relative to propranolol (5.79 + 6.29) or hydrocortisone (7.72 + 6.33; *F*(2,85)=1.132, *p*=0.327).

**Involuntary memory: intrusion frequency**

The main results section (Figure 3A) illustrates the predicted intrusion values based on a mixed effects model. Supplementary Table 1 shows the raw means (+ SEM) for the three groups (mean number of intrusions by Day).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | **Day** |  |  |  |
|  | D1 | D2 | D3 | D4 | D5 | D6 | D7 |
| **Placebo** | 4.97 + 0.70 | 5.10 + 1.21 | 2.62 + 0.63 | 1.59 + 0.40 | 1.31 + 0.32 | 1.03 + 0.27 | 1.07 + 0.28 |
| **Propranolol** | 3.00 + 0.62 | 2.97 + 0.68 | 1.73 + 0.43 | 0.97 + 0.23 | 0.63 + 0.21 | 0.43 + 0.15 | 0.23 + 0.12 |
| **Hydrocortisone** | 2.21 + 0.33 | 2.28 + 0.58 | 1.48 + 0.41 | 0.69 + 0.24 | 0.62 + 0.16 | 0.31 + 0.10 | 0.28 + 0.10 |

**Table S1.** Raw means + SEMs for intrusion counts per Group by Day.

A compact, random intercept model, with Day and Group as fixed factors was tested first (AIC=1788.57). In the absence of any covariates, this baseline model showed main effects of Group and Day (*p* values<0.01). Model fitwas improved by inclusion of a random slope (AIC=1780.23; Group and Day effects: *p* values <0.0183) and addition of peri-film cortisol and HR (but not their interaction, nor the interaction between Group and Day) substantially further improved this model (AIC=1660.21). Predicted intrusion counts based on this model are shown in Figure 3A and parameter estimates, described in the main results section of the paper.

The correlation between intrusion frequency (log transformed) and salivary cortisol at T3 was significant (*r*=0.48, *p*=0.01). This illustrated in Figure S1. Note, case-wise regression diagnostics showed that no residuals exceeded |1.88| suggesting an absence of influential cases.

**Figure S1**: Relationship between intrusion counts (log transformed) and salivary cortisol.

**Involuntary memory: vividness**

The baseline model for vividness also included Day and Group as fixed factors, with random intercepts for Participant (AIC=889.91). The model was improved by including a random slope and a Day x Group interaction (AIC=883.81; Day and Group main effects and their interaction were significant: *p*<0.037). However, the best fitting model, with random slopes, again also included peri-film HR and cortisol as covariates (as above for intrusion frequency), along with the Day x Group interaction term (AIC=827.758). Parameter estimates for this model are described in the main text.

**Involantary memory: distress**

The same model specifications as used in the vividness mixed effects model above were used to analyse intrusion-related distress. Again, the inclusion of a Day x Group interaction and covariates improved the model (AIC=775.44) relative to the fixed effects model without covariates (AIC=834.59). However, as noted in the main results section, the interaction was not significant. The best fit model is shown in Figure S2.

**Figure S2:** Predictedintrusion-related distress (mean + SEM). The fitted model included T2 HR and cortisol as covariates.

**References**

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Beck Depression Inventory-II (BDI-II). San Antonio, TX: Psychological Corporation.

Bond, A., & Lader, M. (1974). The use of analogue scales in rating subjective feelings. Psychology and Psychotherapy: Theory, Research and Practice, 47(3), 211-218.

Carlson, E. B., & Putnam, F. W. (1993). An update on the dissociative experiences scale. Dissociation: Progress in the Dissociative Disorders 6(1), 16-27.

Chou, C.-Y., La Marca, R., Steptoe, A., & Brewin, C. R. (2014). Biological responses to trauma and the development of intrusive memories: an analog study with the trauma film paradigm. Biological Psychology, 103, 135-143.

Chou, C. Y., La Marca, R., Steptoe, A., & Brewin, C. R. (2014). Heart rate, startle response, and intrusive trauma memories. Psychophysiology, 51(3), 236-246.

Das, R., Tamman, A., Nikolova, V., Freeman, T., Bisby, J., Lazzarino, A., & Kamboj, S. (2016). Nitrous oxide speeds the reduction of distressing intrusive memories in an experimental model of psychological trauma. Psychological Medicine, 46(08), 1749-1759.

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G\* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods, 39(2), 175-191.

Holmes, E. A., James, E. L., Coode-Bate, T., & Deeprose, C. (2009). Can playing the computer game “Tetris” reduce the build-up of flashbacks for trauma? A proposal from cognitive science. PloS One, 4(1), e4153.

James, E. L., Bonsall, M. B., Hoppitt, L., Tunbridge, E. M., Geddes, J. R., Milton, A. L., & Holmes, E. A. (2015). Computer game play reduces intrusive memories of experimental trauma via reconsolidation-update mechanisms. Psychological Science, 26(8), 1201-1215.

Kamboj, S. K., & Curran, H. V. (2006). Neutral and emotional episodic memory: global impairment after lorazepam or scopolamine. Psychopharmacology, 188(4), 482-488.

Kamboj, S. K., Irez, D., Serfaty, S., Thomas, E., Das, R. K., & Freeman, T. P. (2017). Ultra-Brief Mindfulness Training Reduces Alcohol Consumption in At-Risk Drinkers: A Randomized Double-Blind Active-Controlled Experiment. International Journal of Neuropsychopharmacology, 20(11), 936-947.

Kuhlmann, S., Kirschbaum, C., & Wolf, O. T. (2005). Effects of oral cortisol treatment in healthy young women on memory retrieval of negative and neutral words. Neurobiology of Learning and Memory, 83(2), 158-162.

Maheu, F. S., Joober, R., Beaulieu, S., & Lupien, S. J. (2004). Differential effects of adrenergic and corticosteroid hormonal systems on human short-and long-term declarative memory for emotionally arousing material. Behavioral Neuroscience, 118(2), 420.

Marks, E. H., Franklin, A. R., & Zoellner, L. A. (2018). Can’t get it out of my mind: A systematic review of predictors of intrusive memories of distressing events. Psychological Bulletin, 144(6), 584.

Miller, R., Stalder, T., Jarczok, M., Almeida, D. M., Badrick, E., Bartels, M., . . . Donzella, B. (2016). The CIRCORT database: Reference ranges and seasonal changes in diurnal salivary cortisol derived from a meta-dataset comprised of 15 field studies. Psychoneuroendocrinology, 73, 16-23.

Sijbrandij, M., Kleiboer, A., Bisson, J. I., Barbui, C., & Cuijpers, P. (2015). Pharmacological prevention of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis. The Lancet Psychiatry, 2(5), 413-421.

Spielberger, C. D. (2010). State‐Trait Anxiety Inventory: Wiley Online Library.

Watson, D., & Clark, L. A. (1999). The PANAS-X: Manual for the Positive and Negative Affect Schedule-Expanded Form. https://ir.uiowa.edu/cgi/viewcontent.cgi?article=1011&context=psychology\_pubs

Accessed on 7th January 2019.

Weiss, D. S. (2007). The impact of event scale: revised. Cross-cultural assessment of psychological trauma and PTSD (pp. 219-238): Springer. Boston MA