

Trauma reactivation under the influence of propranolol: an examination of clinical predictors

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Background: In two recent studies conducted by our group, a treatment combining propranolol with a brief reactivation session subsequently reduced posttraumatic stress disorder (PTSD) symptom severity and diagnosis, as well as reducing psychophysiological responses during trauma-related script-driven imagery. One likely explanation for those results is that memory reconsolidation was blocked by propranolol.

Objective: We explored the influence of various predictors on treatment outcome (i.e., PTSD severity), and whether the treated individuals improved in other important domains of functioning associated with PTSD.

Method: Thirty-three patients with longstanding PTSD participated in a 6-week open-label trial consisting of actively recalling one's trauma under the influence of propranolol, once a week.

Results: Treated patients reported a better quality of life, less comorbid depressive symptoms, less negative emotions in their daily life and during trauma recollections. Women were also found to improve more than men. Type of trauma (childhood vs. adulthood), time elapsed since trauma, borderline personality traits, depressive symptoms severity, Axis I comorbidity, and age did not influence treatment outcome.

Conclusion: These results must await publication of a randomized-controlled trial to further delineate effectiveness with this novel treatment approach.

Keywords: *reconsolidation; memory; beta-blockers; traumatic stress; PTSD; treatment outcome; gender differences*

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In a series of three open-label trials, we recently showed that one brief trauma reactivation session per week for 6 weeks under the influence of propranolol reduced Posttraumatic Stress Disorder (PTSD) diagnosis by 71–86% and symptom severity by 50–56% at follow-up (Brunet et al., 2011), with very large effect sizes (Cohen's $d=1.32-2.19$). In contrast, symptoms of a non-randomized control group of individuals declining the treatment improved by only 7%. Although alternate explanations are possible (see Brunet, Ashbaugh et al., 2011), this finding is consistent with reconsolidation theory. Indeed, reconsolidation blockade

using the β -adrenergic receptor blocker propranolol, has been shown to subsequently reduce the fear response in animals (Przybylski, Roulet, & Sara, 1999), in healthy humans (Kindt, Soeter, & Vervliet, 2009), and in PTSD patients (Brunet et al., 2008).

In this paper, we aimed to extend our finding that six weekly trauma reactivation sessions under the influence of propranolol reduced PTSD diagnosis and symptom severity (Brunet, et al., 2011), (1) by exploring the influence of variables in predicting treatment outcome, i.e., predictors of the effect of the treatment in reducing PTSD symptoms over time, and (2) by

examining whether the treated individuals improved in other important domains beyond their PTSD symptomatology. This work is much needed in order to further delineate the possibilities of this potentially novel treatment approach in psychiatry.

First objective: predictors of treatment outcome

Many variables can have an impact on the treatment of PTSD (Karatzias et al., 2007; Tarrrier, Sommerfield, Pilgrim, & Faragher, 2000; Taylor, 2003). We will thus examine whether there are predictors which have an influence on clinical improvement from pre- to post-treatment. It is important to identify predictors of outcome when developing a new treatment, to identify which patients would be more likely to benefit from treatment, and it becomes even more important since this treatment is based on reconsolidation blockade, which is a new emerging theory. A literature review suggested three families of variables (potential predictors): (1) sociodemographic variables; (2) trauma-related variables; and (3) psychiatric comorbidity.

Sociodemographic variables

According to a body of literature, age has generally no impact on PTSD treatment outcome (e.g., Karatzias et al., 2007), but gender may have such an effect. Cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR) have often shown to be more effective in women (Karatzias et al., 2007; Tarrrier et al., 2000), although some studies did not find such gender differences (e.g., Ehlers, Clark, Hackmann, McManus, & Fennell, 2005). In pharmacological treatments, results are inconsistent; for example, women may respond better than men to SSRI's, at least in MDD studies (Baca, Garcia-Garcia, & Porrás-Chavarino, 2004; Kornstein et al., 2000; Seedat, Stein, & Carey, 2005), although in PTSD patients, there would be no gender differences in outcome with other drugs such as venlafaxine, a serotonin-norepinephrine reuptake inhibitor (Rothbaum et al., 2008).

Comorbidity

Most individuals with longstanding PTSD also suffer from one or more comorbid disorders. Although the relationship of DSM-IV (APA, 2000) Axis I comorbidity with treatment outcome is complex to the point where no consensus has been reached, some studies suggest that Axis I comorbidity (including depression) does not influence treatment outcome (Davis, Barlow, & Smith, 2010; Forbes, Creamer, Hawthorne, Allen, & McHugh, 2003; Taylor, 2003). With respect to the Axis II disorders, previous studies have shown that PTSD treatments can be less effective with borderline personality disorder (BPD) patients, or that CBT can suffer from high drop-out rates (e.g., Cloitre & Koenen, 2001;

McDonagh et al., 2005; but see Clarke, Rizvi, & Resick, 2008). Despite these inconsistencies in the literature, BPD patients are assumed by clinicians to benefit less from treatments for Axis I disorders, and BPD is typically an exclusion criterion in randomized controlled trials for PTSD (Clarke, et al., 2008).

Trauma-related variables

Longstanding PTSD may be more difficult to treat than acute PTSD (Foa, Keane, Friedman, & Cohen, 2008), despite inconsistent results on that matter (e.g., Ehlers, Clark, Hackmann, McManus, & Fennell, 2005). Also, trauma type may have an impact on treatment outcome: despite some positive results in the treatment of adults suffering from childhood trauma (Taylor & Harvey, 2010), it remains that childhood trauma is rarely addressed in randomized controlled trials (Bradley, Greene, Russ, Dutra, & Westen, 2005), and that complex PTSD seems to have a less favourable prognosis (Ford & Kidd, 1998) because of a more severe clinical profile.

Second objective: going beyond the core PTSD symptoms

According to several authors (Gladis, Gosch, Dishuk, & Crits-Christoph, 1999; Schnurr & Lunney, 2008; Wilson & Cleary, 1995), a sound treatment should not only reduce the disorder's core symptoms, but should also improve other domains of functioning. For instance, quality of life is a central element in psychopathology and its improvement should be a treatment goal (Schnurr & Lunney, 2008). Depressive symptoms are also particularly prevalent in patients suffering from PTSD, and some treatments geared primarily at PTSD reduction have been shown to also reduce depressive symptom severity (e.g., Foa et al., 2005). Finally, since emotions affect memory in PTSD (Sotgiu & Galati, 2007), and since we believe that the treatment effectiveness is explained by reconsolidation blockade, we examined whether patients report less negative emotions in their daily life, and whether they experience less negative emotions when actively recollecting the traumatic event at the end of their treatment.

Study Hypotheses

Objective one

Using an open-label study design, we formulated the following hypotheses about the influence of sociodemographic variables on the effectiveness of the treatment: (1) age would have no impact on treatment effectiveness, and (2) women would improve more than men on PTSD symptoms during the treatment. With comorbidity, we hypothesized that (3) the number of current Axis I comorbidities, and (4) that depressive symptom

scores would have no impact on treatment effectiveness, and that (5) higher scores on BPD traits would reduce treatment effectiveness. With respect to trauma-related variables, we hypothesized that (6) higher time elapsed since trauma would reduce treatment effectiveness, and that (7) trauma type would impact treatment effectiveness, where patients with childhood trauma would improve less than those with adult trauma on PTSD symptoms.

Objective two

We hypothesized that the following domains of functioning would also improve with the treatment: (1) quality of life, (2) comorbid depressive symptoms, (3) negative emotions in daily life, and (4) negative emotions when recollecting the traumatic event.

Method

Participants

Inclusion/exclusion criteria

The study participants met the DSM-IV criteria for chronic PTSD, were 18–65 years old, and fluent in either French or English. Exclusion criteria included a history of traumatic brain injury; a current or past psychotic, bipolar, or substance dependence disorder; severe dissociative tendencies; a previous adverse reaction to a β -blocker; current use of a medication that could involve dangerous interactions with propranolol, including antidepressants that are cytochrome P450 2D6 inhibitors; a medical condition that contraindicated propranolol administration (e.g., asthma, heart problems, diabetes); pregnancy or breast-feeding; or participation in any form of psychotherapy other than supportive.

Sociodemographic

Thirty-six participants were recruited via newspapers. Two were excluded because of invalid answers (filling out questionnaires at random), and one because of a possible traumatic brain injury history. Thirty-three participants were included in the analyses. Of those, 26 participants were recruited from the open label study (Brunet, et al., 2011), and seven others were recruited via additional newspaper advertisements. These 33 participants were mostly Caucasian (91%), female (70%), with a mean age of 37.7 (SD = 11.2) years, and mean time elapsed since trauma was 16.06 (SD = 13.38) years. They reported the following index traumatic events: motor vehicle accident (4), participation in a United Nation peacekeeping mission (4), physical assault (7), sexual abuse (4), incest (6), severe physical abuse during childhood (4), or other traumatic experiences (4).

Comorbidity

Current DSM-IV axis I comorbid psychiatric disorders, as measured with the Mini International Neuropsychiatric Interview (MINI), included: major depressive disorder (24%), social phobia (24%), generalized anxiety disorder (18%), obsessive-compulsive disorder (15%), panic disorder with (9%) and without (15%) agoraphobia, agoraphobia without panic (6%), bulimia (6%), and anorexia nervosa (3%).

Ethics approval, informed consent, and participants' compensation

The study was approved by the ethics committee of the Douglas Mental Health University Institute, and by Health Canada. Participants gave written informed consent. A compensation of \$250 was provided for the assessment sessions. All assessments and treatments were conducted by a supervised doctoral-level candidate in clinical psychology.

Psychodiagnostics and psychometrics

The main outcome measures were the PTSD Checklist (PCL) (Weathers, Litz, Herman, Huska, & Keane, 1993) and the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995). The self-report PCL was selected in order to monitor weekly change (Miles, Marshall, & Schell, 2008) in PTSD symptoms; it was employed at pre-treatment, during all six treatment sessions, at post-treatment and follow-up. One should note that the PCL ranges from 17 (no PTSD symptoms whatsoever) to 85. Because we had few Anglophone patients, we report here only Cronbach alphas of the French versions of all questionnaires. With the PCL, a Cronbach alpha of 0.87 was found in this study. The CAPS is considered to be the gold standard semi-structured interview for PTSD, it provides both a PTSD diagnosis and a severity score (range: 0–136), and was administered at pre-treatment, post-treatment and follow-up.

The other questionnaires used are: (1) the self-report Borderline Personality Inventory (BPI) (Leichsenring, 1999), which provides both a continuous score and a cut-off score for BPD, at pre-treatment only; in our study, a Cronbach alpha of 0.90 was found; (2) the self-report Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), which assesses for current severity of depressive symptoms, at pre-, post-treatment, and follow-up; it had a Cronbach alpha of 0.90 at pre-treatment; (3) the self-report World Health Organization Quality of Life (WHOQOL-BREF) (WHOQOL Group, 1998), which assesses current quality of life in four domains, physical, psychological, social and environmental, at pre-, post-treatment and follow-up; Cronbach alphas were the following: 0.67 for physical, 0.62 for psychological, 0.53 for social, 0.73 for environmental; (4) the self-report Differential Emotions Scale IV

(DES-IV) (Izard, Libero, Putnam, & Haynes, 1993), which provides a general score for levels of emotions in daily life, and a score for interest, joy, surprise, disgust, contempt, hostility, fear, sadness, shame, anger, shyness, and guilt, at pre-, post-treatment and follow-up; a Cronbach alpha of 0.85 was found for negative emotions; (5) the self-report Traumatic Emotions Questionnaire to assess the emotional intensity of the traumatic memory, based on a questionnaire developed by Sotgiu and Galati (2007). We kept eight of the 13 emotions assessed by Sotgiu and Galati (2007), which were most appropriate for traumatic memories, precisely fear, anger, sadness, disgust, guilt, shame, proudness and serenity, but instead of a 4-point scale, we used a 11-point scale ranging from 0 (no emotion) to 10 (the most intense emotion one could imagine) in order to avoid floor and ceiling effects. The participants indicated to what extent they felt each of a series of emotions, *today, in the here and now*, when thinking about their traumatic event. This questionnaire was used at pre- and post-treatment and at follow-up. It had a very high internal consistency for negative emotions, with a Cronbach alpha of 0.88 at pre-treatment; only negative emotions were used in this study. Finally, we used (6) the structured interview Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), to assess DSM-IV axis I psychiatric comorbidity, at pre-treatment only.

Study medication and dosage

Propranolol hydrochloride is a non-selective synthetic β_1 and β_2 -adrenoreceptor antagonist that crosses the blood brain barrier. We used a first dose of 0.67mg/kg of propranolol short-acting (SA). Ninety minutes later, if systolic blood pressure had not fallen by 30% or more from its original value, a dose of 1 mg/kg propranolol long-acting (LA) was given, followed by the first treatment session. Because all subjects tolerated the doses well in the first treatment session, both doses were given simultaneously for the remaining treatment sessions.

Assessment and treatment sessions

There was a pre-treatment assessment session, followed by six treatment sessions and a post-treatment session, all eight sessions held on a weekly basis. Follow-up was three months after post-treatment. This time course of the treatment was homogeneous for all patients.

First treatment session

At the onset of treatment, a physician examined patients, and then authorized the administration of propranolol along with a light snack (Walle et al., 1981). A registered nurse monitored vital signs every 30 minutes for 3 hours while the participant sat quietly into a small private hospital room.

After receiving the second dose of propranolol, participants described in writing the event(s) that led to their current PTSD, with as many contextual and emotional details as possible, and involving all sensory modalities. Participants also circled from a list of bodily responses those they remembered as having accompanied their experience. The interviewer reviewed the participant responses, and asked them to clarify or expand on certain details as necessary. Trauma narratives had a mean number of 1000.5 words ($SD = 657.4$). These narratives were typed and subsequently used to reactivate the traumatic memory during the following treatment sessions.

Following treatment sessions

Ninety minutes after taking propranolol, participants read aloud their trauma narrative once to the interviewer, as if they were back into the experience once again. The interviewer facilitated this process by asking occasional questions; preventing the participant from wandering off the traumatic event, and encouraging participant to focus on aspects of the traumatic event that either continued to provoke emotional distress, or had not yet been described. More specifically, the interviewer asked: Would you please tell me what occurred? What did you think would happen to you? How did you feel about that? How do you feel right now? What happened next? Is there anything particular about the memory of this event that continues to upset you? Is there anything about the event, or your reactions at the time, that you haven't told me about so far? Has your memory changed since last week? How so? Additional or missing parts of the memory were thereafter included into the trauma narrative.

Data and statistical procedures

The data approximated normal distribution; qq-plots, skewness and kurtosis tests confirmed normality. Some participants had missing data on an entire questionnaire. Out of 297 self-report questionnaires on PTSD, only five were missing and no computation strategy was employed, as mixed models are particularly efficient at handling missing data (Gueorguieva & Krystal, 2004; West, Welch, & Galecki, 2006).

Five participants did not fill out the borderline personality traits questionnaire. Also, 12 participants did not fill out the other questionnaires used to test the second objective of this study. We started to use these questionnaires after the 12 first participants in our study, at pre-, post-treatment and follow-up. Again, no computation strategy was employed to impute data, as mixed models are efficient at handling missing data.

First objective

A linear mixed model with a random intercept (Brown & Prescott, 2006) was employed to model the change in PTSD symptoms over time. Two measures of PTSD were used as dependant variables, the PCL (8 data points: pre-treatment, six sessions of treatment, post-treatment) and the CAPS (2 data points: pre-treatment and post-treatment). Basic measures of model fit (AIC, BIC) (Brown & Prescott, 2006) were used in order to assess the necessity of using a random slope to model the effect of time. The influence of all variables (potential predictors) on treatment outcome (i.e., on the change of PTSD symptoms over time) was tested one-by-one, using an interaction term crossing the variable with time. All analyses were controlled for age. The estimated coefficients (β) of the interaction terms are reported. These estimates were based on standardized variables betas to permit the comparison between variables for their modifying effect. Alpha inflation was controlled using the false discovery rate technique (Benjamini & Hochberg, 1995), with the following three families of variables: (1) sociodemographic variables, (2) trauma-related variables, and (3) comorbidity. All the statistical tests performed were two-tailed, with an alpha level of 0.05, using SPSS (PASW) version 18.

Second objective

Multiple linear mixed models with a random intercept were used to examine if the following dependant variables significantly improved during the treatment: quality of life in psychological, environmental, physical and social domains, depressive symptoms, negative emotions in daily life, and negative emotions when recollecting the traumatic event. The variables were alternately entered as dependant variables in a mixed model, with three data points: pre-treatment, post-treatment, and follow-up. Alpha inflation was controlled using the false discovery rate technique (Benjamini & Hochberg, 1995).

Power analysis

Power analyses were performed in order to estimate the probability of not rejecting a null hypothesis in the case of an actual predicting effect on treatment outcome. The mixed model and the associated parameter estimates were used as a basis for digitally simulating data. Multiple potential predictors' effect sizes were simulated, and their power to detect an effect was obtained from 1,000 iterations.

All obtained measures of power were based on a 95% significance level. The power to detect a significant predicting effect on the treatment outcome was found to be higher with one dependant variable (PCL) than with the other (CAPS). The following considered modifying effects on treatment outcome are based on a variation of one standard deviation of a continuous covariate,

or one level of a categorical variable. When considering the interaction effect with a continuous variable, and using a power of 80%, a difference of 12% of the effect of treatment over time (i.e., a difference of 12% of the treatment slope) could be detected for the PCL, and a difference of 52% for the CAPS. These correspond to standardized betas of 0.6 and 13 for PCL and CAPS respectively. When considering the interaction effect with a categorical variable, and using a power of 80%, a difference of 25% of the effect of treatment over time could be detected for the PCL, and a difference of 104% for the CAPS. These correspond to standardized betas of 1.25 and 26 for PCL and CAPS respectively. These values can be used in evaluating the possibility of type II errors in our results.

Results

Recruitment

A first series of advertisement in Montreal's free newspapers yielded approximately 175 phone calls, out of which 52 participants' candidates were invited and came for a PTSD diagnostic assessment. Five candidates did not meet criteria for PTSD, eight met an exclusion criterion and five did not show up for their first treatment session. Six dropped out after the first treatment session. None dropped-out during the remainder of the treatment. Two patients who completed the treatment were removed from the analyses, as they had invalid data on many self-report questionnaires. The treatment completers data was analyzed ($n=26$). The remaining seven patients that were added to the 26 were also recruited via newspapers. However, recruitment data is not available for these additional patients.

All patients suffered from chronic PTSD, with a mean time elapsed since trauma of 16.06 (SD = 13.38) years. The mean PCL score was 58.3 (SD = 10.5) at pre-treatment, 36.3 (SD = 13.5) at post-treatment, and 35.5 (SD = 14.1) at follow-up. The mean CAPS score was 70.3 (SD = 19.5) at pre-treatment, 45.8 (SD = 23.5) at post-treatment, and 43.4 (SD = 24.9) at follow-up.

T tests for paired samples revealed no significant differences between post-treatment and follow-up for all repeated variables, i.e., PTSD symptoms, depressive symptoms, quality of life, negative emotions when recollecting the traumatic event and in life in general.

Objective one: predictors of treatment outcome

We used a linear mixed model with random intercept, and all results are shown in Table 1. Diagnostics of the mixed models confirmed normality of residuals and of random intercepts, and found satisfactory variance components in all the analyses.

It is important to note that the β from the PCL cannot be compared with those from the CAPS. Indeed,

Table 1. The influence of predictors on PTSD clinical improvement

Predictors	Self-reported PTSD symptoms of the past week ^a		Interviewer-based PTSD symptoms of the past month ^b	
	β for interaction*	<i>p</i> -value	β for interaction*	<i>p</i> -value
Sociodemographic variables				
Age	0.01	n.s.	-0.58	n.s.
Gender	0.99	0.025	23.27	0.01
Trauma-related variables				
Time elapsed since trauma	0.41	n.s.	6.11	n.s.
Type of trauma	0.79	n.s.	5.93	n.s.
Comorbidity				
No. of Axis I disorders	0.16	n.s.	-0.24	n.s.
Depression score	0.38	n.s.	8.26	n.s.
Borderline personality score	0.25	n.s.	-1.95	n.s.

Notes: n.s., Not significant; β , coefficients are standardized for the continuous predictors (not the categorical predictors).

^aPTSD Checklist (PCL).

^bClinician-Administered PTSD Scale (CAPS).

the calculation of a beta is the division of the change on the Y-axis by the change on the X-axis; the PCL has eight measurement times and thus the division is by eight, while the CAPS has two measurement times and thus the division is by two. It is therefore expected for the β of the CAPS to be higher than the β of the PCL, which would reflect the difference in measurement points rather than a true difference between the improvement on the CAPS and PCL variables.

We selected three families of variables (potential predictors). The first family is related to sociodemographic variables, age and gender. Using the mixed model, both hypotheses were confirmed, as age did not influence treatment outcome, but gender did, whereby women improved more than men on the PCL, $\beta=0.99$, $p=0.025$, and on the CAPS, $\beta=23.27$, $p=0.01$. Using the false discovery rate technique (Benjamini & Hochberg, 1995), these p values are still significant.

In a post-hoc analysis, considering the strength of the results with gender, we re-analysed the PCL and CAPS results as a function of gender. On the PCL, women improved from a pre-treatment score of 58.26 (SD=10.06) to a post-treatment score of 34.65 (SD=13.28), yielding a mean improvement of 57%, while men improved from a pre-treatment score of 58.40 (SD=12.14) to a post-treatment score of 40.10 (SD=13.81), yielding a mean improvement of 44%. On the CAPS, women improved from a pre-treatment score of 74.00 (SD=19.04) to a post-treatment score of 42.43 (SD=22.92), yielding a mean improvement of 43%, while men improved from a pre-treatment score of 61.80 (SD=18.64) to a post-treatment score of 53.50 (SD=24.23), yielding a mean improvement of only 13%. However, these differences in gender are lower at

follow-up: on the PCL, women improved by 61% and men by 43%, and on the CAPS, women improved by 44% and men by 24%.

The second family of variables is related to trauma-related variables, which are type of trauma (childhood or adult) and time elapsed since trauma. Using the mixed model, type of trauma did not influence treatment outcome, and time elapsed since trauma did influence treatment outcome on the PCL, $\beta=0.41$, $p=.046$, but not on the CAPS (see Table 1). All p -values became non-significant after using the false discovery rate procedure (Benjamini & Hochberg, 1995). Contrary to our hypotheses, trauma type and time elapsed since trauma did not influence treatment outcome.

The third family of variables is related to comorbidity: number of current comorbid Axis I mental disorders, current depression severity score, and borderline personality severity score. Confirming our hypotheses, the number of current Axis I disorders and current depression severity score did not influence treatment outcome (see Table 1). Contradicting our hypothesis, the borderline personality severity score did not influence treatment outcome. All p values were non-significant.

Objective two: improvement in domains other than PTSD

We used a linear mixed model with a random intercept, and diagnostics of the mixed models confirmed normality of the residuals and of random intercepts, and found satisfactory negative variance components with all variables, except with three subscales: disgust when recollecting the event, disgust and contempt in daily life, where the normality of residuals or random intercept was

not met. Therefore, the analysis of the improvement over time of these subscales is not reported.

All results are shown in Table 2. Using the false discovery rate technique (Benjamini & Hochberg, 1995), only the p -value of .044 is no longer significant (the emotion of shame in daily life). All hypotheses were confirmed, except with respect to the emotion of shame, and quality of life in the physical domain.

Discussion

Following-up on our previous papers showing that the combination of propranolol with brief reactivation sessions of a traumatic memory decreased PTSD symptom severity and diagnosis (Brunet et al., 2011), and reduced psychophysiological responding during script-driven imagery (Brunet et al., 2008), one objective in this study was to explore the extent of improvement in other health-related domains than PTSD symptoms. As hypothesized, depressive symptoms, negative emotions when recollecting the traumatic event, negative emotions in daily life, and quality of life in the psychological, social and environmental domains were significantly improved, with the exception of the physical

Table 2. Clinical Improvement in health domains other than PTSD symptoms

Variables	β	p -value
Quality of life ^a		
Psychological	0.20	0.001
Environmental	0.13	0.030
Social	0.27	0.006
Physical	0.07	n.s.
Depression ^b	-3.20	0.009
Negative emotions when recollecting the event ^c	-5.39	0.003
Fear	-1.09	0.001
Anger	-1.01	0.004
Shame	-0.80	0.024
Guilt	-1.00	0.010
Sadness	-0.62	n.s.
Negative emotions in daily life ^d	-6.28	0.001
Fear	-1.20	0.001
Sadness	-0.58	0.008
Shame	-0.52	n.s.
Guilt	-0.98	0.001
Hostility towards self	-0.62	0.018
Timidity	-0.75	0.007
Anger	-0.51	n.s.

Notes: n.s., Not significant.

^aWorld Health Organization Quality of Life (WHOQOL-BREF).

^bBeck Depression Inventory (BDI).

^cTraumatic Emotions Questionnaire.

^dDifferential Emotions Scale IV (DES-IV).

domain. This finding that the patients improved in all quality of life domains except the physical domain might be explained by the diversity of the seven facets included in this domain. For instance, while we would expect to find some improvement in some facets of the physical domain, such as with sleep, energy, and level of activities, we would not expect to find an improvement on the other facets of the domain, which are pain, physical mobility, dependence on medicinal substances, and work capacity. Therefore, this finding is not surprising.

Typically, a few clinical variables are expected to have a negative impact in psychological and pharmacological treatments for PTSD. In this study, only gender was found to have an impact on treatment outcome, where women improved more than men in the course of the treatment. This finding was consistent using self-report and clinician-administered measures. Interestingly, and contradicting our hypotheses, trauma-related variables such as type of trauma (childhood vs. adulthood) and time elapsed since trauma did not have a negative impact on treatment outcome. This is more surprising in the case of type of trauma, since repeated childhood abuse seems to have a lower treatment outcome, or at least is rarely addressed in treatment efficacy studies (Bradley et al., 2005; but see Taylor & Harvey, 2010). Also contradicting our hypotheses, the severity of BPD traits did not have a negative impact on treatment outcome. This was unexpected, since patients suffering from BPD are assumed to respond less to treatment and are typically excluded from treatment efficacy studies (Clarke, et al., 2008). As expected, age, as well as comorbidity variables such as depression severity and number of Axis-I comorbidities did not influence treatment outcome; these variables have shown to not typically predict treatment outcome in the literature.

In the case of gender, diverging results have been found in the past with treatment outcome; some studies did find women to improve more than men in psychological (e.g., Karatzias et al., 2007) or pharmacological treatments (e.g., Kornstein et al., 2000), although these results were not always replicated (e.g., Ehlers et al., 2005; Rothbaum et al., 2008). There is also another explanation which may shed light on our results. Literature on emotional memory shows a gender difference in the encoding of emotional memory, where emotional arousal improves memory of central aspects of the event with men and of peripheral aspects of the event with women (Chamberlain, Muller, Blackwell, Robbins, & Sahakian, 2006). Accordingly, one study showed that beta blockers such as propranolol blocked consolidation of central aspects of the event with men and of peripheral aspects with women (Cahill & van Stegeren, 2003). Also, propranolol is metabolized differently in women, compared to men (Walle, Fagan, Topmiller, Conradi, & Walle, 1994).

It is possible that these differences influenced our treatment effectiveness; for example, it may be harder to reduce the emotional strength of central aspects rather than peripheral aspects of a traumatic event.

Study limitations

In the absence of a placebo condition, the conclusion that propranolol was necessary for the observed improvement must await results of an ongoing double-blind, randomized, placebo-controlled trial (RCT). In fact, our results probably reflect both direct (specific) and general effects of treatment; we cannot disentangle these effects without a proper RCT.

Another limitation pertains to the fact that this study has a small sample size. It is possible that this reduced the chances of finding significant results in the case of our negative results. Even if a power analysis revealed that we had sufficient power to detect moderate-sized effects, we cannot exclude the possibility that some negative results could be better explained by lack of power. Also, women responded better to the treatment than men in our sample, but the smaller proportion of men in this sample ($n = 10$) reduces the generalizability of the findings. Another limitation pertains to the fact that all assessments and treatment sessions were conducted by a doctoral-level candidate in clinical psychology, who was nonetheless supervised by a licensed psychologist. Finally, there was a three-month follow-up in this study; future studies should investigate a longer-term outcome, to test the hypothesis that reduction in fear using reconsolidation blockade could be permanent.

Conclusions

Six reactivations sessions conducted under the influence of propranolol reduced PTSD symptom severity and diagnosis (see Brunet et al., 2011), and was shown in the current study to also improve other important health domains, i.e., quality of life, depressive symptoms, negative emotions when recollecting the traumatic event and in life in general. Particularly interesting is the finding that all variables but one did not have a negative impact on treatment outcome. Women improved more than men in our sample, and future studies could reveal whether this finding is generalizable or not to the population of patients suffering from PTSD. Finally, confirmation of the theoretical rationale, i.e., that the improvement noted in the patients was caused by reconsolidation blockade of the emotional aspects of the traumatic event, must await publication of a RCT on the topic.

Conflicts of interest and funding

Joaquin Poundja holds a doctoral scholarship from the CIHR. Alain Brunet holds a salary award from the Fonds de Recherche en Santé du Québec (FRSQ).

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