Correspondence

Patterns of Recovery From Early Posttraumatic Stress Symptoms After a Preventive Intervention With Oxytocin: Hormonal Contraception Use Is a Prognostic Factor

To the Editor:

In a previous issue of *Biological Psychiatry*, we reported on the efficacy of repeated intranasal oxytocin administration early after emergency department admission in preventing posttraumatic stress disorder (PTSD) symptoms, assessed 1.5, 3, and 6 months posttrauma (1). In a randomized, placebo-controlled trial, we demonstrated beneficial effects in patients with high symptom levels before treatment onset (1,2). While this indicates that oxytocin administration might be an effective preventive intervention for recently traumatized individuals with high early symptoms, the accompanying commentary to our study emphasized that it remains an ongoing challenge to identify and target individuals at risk for persistent symptoms (3). Indeed, as trauma-related symptoms constitute a major public health issue (4) and currently only few effective early interventions exist (5), it is crucial to target those patients who are at increased risk of developing adverse outcomes and who are most likely to benefit from treatment.

We addressed this by means of secondary data analyses, investigating the influence of differences in gonadal steroid status on PTSD symptom courses and treatment efficacy. This yielded interesting results that we believe are an important add-on to our previous publication.

Women experience PTSD more often, with higher severity, chronicity, and comorbidity (6–8). This disparity can partly be explained by gender-specific factors, including socioeconomic and coping-related risks (9,10), but sex-specific, especially endocrine, factors also contribute (11). Therefore, we previously investigated sex as a possible prognostic factor for different PTSD symptom courses, irrespective of treatment, and as a possible prescriptive factor of treatment efficacy. Results revealed neither a prognostic nor a prescriptive effect.

Etiological models explaining the development of PTSD after traumatic events comprise maladaptive neurocognitive processes, including facilitated acquisition and consolidation and impaired extinction of traumatic memories (12,13). These processes are also regulated by gonadal steroids, including progesterone and estrogens (14,15). Estrogens, including endogenous estradiol, facilitate extinction learning: higher estradiol during extinction learning enhanced subsequent extinction recall after classical fear conditioning (16). Moreover, women with PTSD and low estradiol concentrations showed deficient extinction learning, compared with trauma-exposed control subjects with low estradiol concentrations and patients with high estradiol concentrations (17). The constellation of high progesterone and low estradiol concentrations characterizing the luteal menstrual cycle phase facilitates fear acquisition and consolidation: women who viewed an emotional film during the luteal phase subsequently reported more intrusions than women in the follicular phase or men (18). Moreover, intrusive memory frequency was positively correlated with progesterone concentrations (19). Another study reported more intrusive memories of emotional film material viewed during the midluteal phase than the early follicular phase or ovulation and detected a negative association between intrusion frequency and estradiol-to-progesterone ratio (20). Women using hormonal contraception exhibit low but relatively stable levels of endogenous estradiol and progesterone and elevated levels of exogenous estrogens. Thus, high levels of estrogens, promoting traumatic memory extinction, and low levels of progesterone, preventing memory consolidation, might prevent PTSD symptom development in these women (14). Preliminary evidence for this hypothesis shows that emergency and regular hormonal contraception use at the time of trauma exposure was associated with fewer intrusive symptoms 6 months posttrauma in female sexual assault victims (21).

Therefore, we investigated prognostic and prescriptive effects of different gonadal steroid–related statuses on PTSD symptom courses, reanalyzing the dataset of our previous publication. We differentiated the original intention-to-treat sample (n = 107) into three groups: 54 men (mean age = 37.94 ± 13.68 years), 27 women using hormonal contraception (mean age = 28.74 ± 9.30 years), and 19 naturally cycling women (mean age = 31.58 ± 10.71 years). The following hormonal contraception methods were present, all delivering female gonadal steroids: oral contraceptives (n = 19), hormonal intrauterine device (n = 6), hormonal injection (n = 1), and vaginal ring (n = 1). Six menopausal women were excluded, as their small number did not allow for valid group comparisons, and 1 woman was excluded because of unknown menopausal status. We implemented the same data-analytic approach as in our previous publication (22): a mixed-effects model based on 40 multiple imputed datasets, testing main and interaction effects of time, treatment condition, and participant group on square root–transformed PTSD severity scores, measured by the Clinician-Administered PTSD Scale (23,24). We added baseline symptoms, age, and time between trauma and treatment initiation as covariates, the latter two because of significant group differences. The significant time effect indicated that overall symptom severity declined from 1.5 to 6 months posttrauma. The effect of hormonal contraception use on the intercept was nonsignificant, but its effect on the slope was significant: although there were no group differences 1.5 months posttrauma, women using hormonal contraception showed significantly stronger midterm to long-term recovery (from 1.5 to 6 months posttrauma) compared with cycling women and men, independently of baseline symptoms and treatment condition (Table 1, Figure 1).

To conclude, while considering dichotomous sex did not divulge a prognostic effect, more detailed consideration of gonadal steroid–related statuses revealed distinct patterns of recovery from early PTSD symptoms in women using hormonal contraception. Our analyses were exploratory and hypothesis generating rather than hypothesis testing. Moreover, it would have been interesting to additionally evaluate effects of specific hormonal contraception methods and menstrual

https://doi.org/10.1016/j.biopsych.2019.01.014
ISSN: 0006-3223

Table 1. Exploration of Possible Prognostic or Prescriptive Effects of Sex and Hormonal Contraception Use

Predictor	*B* (SEM)	*t*	*p*	95% CI
Intercept	4.35 (0.17)	25.80	.00[a]	4.02 to 4.69
Control Variables				
Age	0.42 (0.16)	2.68	.01[a]	0.11 to 0.73
Time between traumatic event and treatment initiation	−0.15 (0.16)	−0.93	.35	−0.46 to 0.16
Baseline symptoms	1.01 (0.16)	6.30	.00[a]	0.70 to 1.33
Treatment				
Oxytocin	−0.51 (0.35)	−1.49	.14	−1.19 to 0.16
Time	−0.26 (0.04)	−6.39	.00[a]	−0.34 to −0.18
Treatment × Time				
Oxytocin × Time	0.08 (0.08)	0.92	.36	−0.09 to 0.24
Sex and Hormonal Contraception Use				
Women using hormonal contraception	0.08 (0.31)	0.26	.79	−0.52 to 0.68
Cycling women	−0.21 (0.37)	−0.57	.57	−0.93 to 0.51
Time × Sex and Hormonal Contraception Use				
Time × women using hormonal contraception	−0.16 (0.07)	−2.39	.02[a]	−0.28 to −0.03
Time × cycling women	0.05 (0.09)	0.53	.59	−0.12 to 0.22

Final model resulting from the stepwise approach to identify prognostic and prescriptive variables according to Fournier *et al.* (22). As a first step, all possible main and interactive effects of a metric variable for time (0 = 1.5 months posttrauma, 1.5 = 3 months posttrauma, 4.5 = 6 months posttrauma), an unweighted-effect coded variable for treatment (comparing oxytocin with placebo condition: −0.50 = placebo, 0.50 = oxytocin), and two weighted-effect coded variables for sex and hormonal contraception use (one comparing women using hormonal contraception with men and cycling women: −0.50 = men, 0 = cycling women, 1 = women using hormonal contraception; and one comparing cycling women with men and women using hormonal contraception: −0.35 = men, 0 = women using hormonal contraception, 1 = cycling women) were included to predict square root–transformed Clinician-Administered Posttraumatic Stress Disorder Scale scores. In the following steps, main and interactive effects were excluded according to predefined *p* thresholds. The resulting final model was controlled for age, time between traumatic event, and treatment initiation and baseline symptoms. The results are based on data from *n* = 100 patients.

CI, confidence interval.

[a]Effect was considered as statistically significant.

cycle–related fluctuations of gonadal steroids. However, that would have reduced group sizes and impeded meaningful conclusions.

Nevertheless, important implications can be derived from these results. We provide further evidence that hormonal contraception use, altering endogenous and exogenous gonadal steroid hormone concentrations, promotes recovery from traumatic stress until at least 6 months posttrauma. Interestingly, the faster recovery became apparent after the first few weeks posttrauma had passed. Our findings open up a promising line of research and should undergo long-term follow-up. Moreover, they clearly demonstrate that women cannot simply be merged into one participant group. Even statistically controlling for contraception use or menstrual cycle phases still impedes such differential conclusions for women depending on gonadal steroid–related status. We sincerely hope that our finding will not lead to further exclusion of women from psychiatric research, but instead

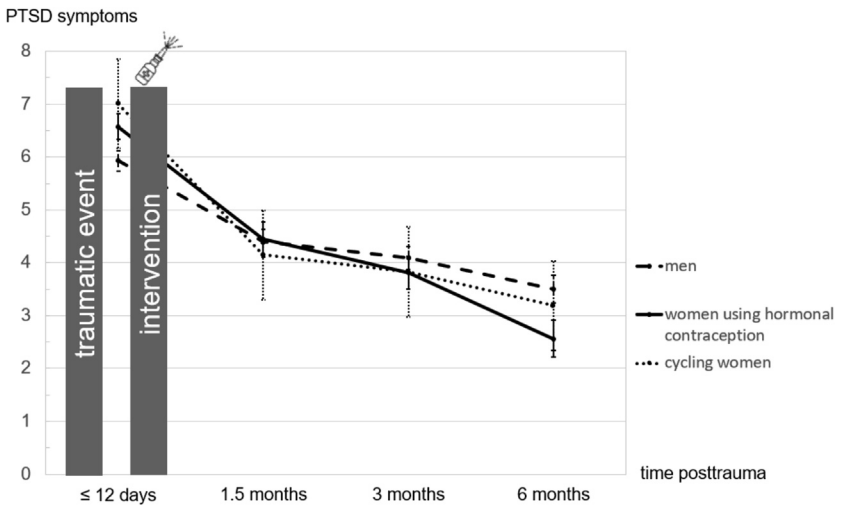

Figure 1. Predicted courses of posttraumatic stress disorder (PTSD) symptoms over follow-up time points, irrespective of treatment condition (intranasal oxytocin or placebo), differentiated for men (broken lines), women using hormonal contraception (full lines), and cycling women (dotted lines). PTSD symptom severity is presented as observed (≤12 days) and estimated (1.5, 3, 6 months) square root–transformed Clinician-Administered PTSD Scale mean ± SE.

encourages researchers to design studies and analyze data in a way that enables detection of differential effects of menstrual cycle phases and hormonal contraception use (25).

Sinha Engel
Mirjam van Zuiden
Jessie L. Frijling
Saskia B.J. Koch
Laura Nawijn
Sarah Schumacher
Christine Knaevelsrud
Dick J. Veltman
Miranda Olff

Acknowledgments and Disclosures

This study was supported by the Netherlands Organization for Health Research and Development Grant No. 91210041 (to MO); Academic Medical Center Research Council Grant No. 110614 (to MO); and doctoral funding from "Stiftung der Deutschen Wirtschaft" (to SE). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

We thank Kim van Dijk, MSc, and Saleha Tariq, MSc, for their valuable assistance in data collection.

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the Department of Psychiatry (SE, MvZ, JLF, SBJK, LN, MO), Amsterdam University Medical Centers, Location Academic Medical Center, University of Amsterdam; and Department of Psychiatry (LN, DJV), Amsterdam University Medical Centers, Location VU University Medical Center, VU University, Amsterdam; Donders Institute for Brain, Cognition and Behaviour (SBJK), Centre for Cognitive Neuroimaging, Radboud University Nijmegen, Nijmegen; and Arq Psychotrauma Expert Group (MO), Diemen, the Netherlands; and the Division of Clinical Psychological Intervention (SE, SS, CK), Freie Universität Berlin, Berlin, Germany.

SE and MvZ contributed equally to this article as joint first authors.

Address correspondence to Mirjam van Zuiden, Ph.D., Amsterdam University Medical Centers, Location Academic Medical Center, University of Amsterdam, Department of Psychiatry, PO Box 22660, 1100 DD Amsterdam, the Netherlands; E-mail: m.vanzuiden@amc.nl.

Received Jan 17, 2019; accepted Jan 18, 2019.

References

1. van Zuiden M, Frijling JL, Nawijn L, Koch SBJ, Goslings JC, Luitse JS, *et al.* (2017): Intranasal oxytocin to prevent posttraumatic stress disorder symptoms: A randomized controlled trial in emergency department patients. Biol Psychiatry 81:1030–1040.
2. Frijling JL (2017): Preventing PTSD with oxytocin: Effects of oxytocin administration on fear neurocircuitry and PTSD symptom development in recently trauma-exposed individuals. Eur J Psychotraumatol 8:1302652.
3. Garcia MA, Delahanty DL (2017): Oxytocin and other pharmacologic preventive interventions for posttraumatic stress disorder: Not a one-size-fits-all approach. Biol Psychiatry 81:977–978.
4. Magruder KM, Kassam-Adams N, Thoresen S, Olff M (2016): Prevention and public health approaches to trauma and traumatic stress: A rationale and a call to action. Eur J Psychotraumatol 7:29715.
5. Sijbrandij M, Kleiboer A, Bisson JI, Barbui C, Cuijpers P (2015): Pharmacological prevention of post-traumatic stress disorder and acute stress disorder: A systematic review and meta-analysis. Lancet Psychiatry 2:413–421.
6. Atwoli L, Stein DJ, Koenen KC, McLaughlin KA (2015): Epidemiology of posttraumatic stress disorder: Prevalence, correlates and consequences. Curr Opin Psychiatry 28:307–311.
7. McLean CP, Asnaani A, Litz BT, Hofmann SG (2011): Gender differences in anxiety disorders: Prevalence, course of illness, comorbidity and burden of illness. J Psychiatr Res 45:1027–1035.
8. Charak R, Armour C, Elklit A, Angmo D, Elhai JD, Koot HM (2014): Factor structure of PTSD, and relation with gender in trauma survivors from India. Eur J Psychotraumatol 5:25547.
9. Cromer LD, Smyth JM (2010): Making meaning of trauma: Trauma exposure doesn't tell the whole story. J Contemp Psychother 40:65–72.
10. Gavranidou M, Rosner R (2003): The weaker sex? Gender and posttraumatic stress disorder. Depress Anxiety 17:130–139.
11. Olff M, Langeland W, Draijer N, Gersons BPR (2007): Gender differences in posttraumatic stress disorder. Psychol Bull 133:183–204.
12. Pitman RK (1989): Post-traumatic stress disorder, hormones, and memory. Biol Psychiatry 26:221–223.
13. Wessa M, Flor H (2007): Failure of extinction of fear responses in posttraumatic stress disorder: Evidence from second-order conditioning. Am J Psychiatry 164:1684–1692.
14. Kornfield SL, Hantsoo L, Epperson CN (2018): What does sex have to do with it? The role of sex as a biological variable in the development of posttraumatic stress disorder. Curr Psychiatry Rep 20:39.
15. Li SH, Graham BM (2017): Why are women so vulnerable to anxiety, trauma-related and stress-related disorders? The potential role of sex hormones. Lancet Psychiatry 4:73–82.
16. Milad MR, Zeidan MA, Contero A, Pitman RK, Klibanski A, Rauch SL, *et al.* (2010): The influence of gonadal hormones on conditioned fear extinction in healthy humans. Neuroscience 168:652–658.
17. Glover EM, Jovanovic T, Mercer KB, Kerley K, Bradley B, Ressler KJ, *et al.* (2012): Estrogen levels are associated with extinction deficits in women with posttraumatic stress disorder. Biol Psychiatry 72:19–24.
18. Ferree NK, Cahill L (2009): Post-event spontaneous intrusive recollections and strength of memory for emotional events in men and women. Conscious Cogn 18:126–134.
19. Ferree NK, Kamat R, Cahill L (2011): Influences of menstrual cycle position and sex hormone levels on spontaneous intrusive recollections following emotional stimuli. Conscious Cogn 20: 1154–1162.
20. Soni M, Curran VH, Kamboj SK (2013): Identification of a narrow post-ovulatory window of vulnerability to distressing involuntary memories in healthy women. Neurobiol Learn Mem 104:32–38.
21. Ferree NK, Wheeler M, Cahill L (2012): The influence of emergency contraception on post-traumatic stress symptoms following sexual assault. J Forensic Nurs 8:122–130.
22. Fournier JC, DeRubeis RJ, Shelton RC, Hollon SD, Amsterdam JD, Gallop R (2009): Prediction of response to medication and cognitive therapy in the treatment of moderate to severe depression. J Consult Clin Psychol 77:775–787.
23. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, *et al.* (1995): The development of a Clinician-Administered PTSD Scale. J Trauma Stress 8:75–90.
24. Hovens JE, van der Ploeg HM, Klaarenbeek MT, Bramsen I, Schreuder JN, Rivero VV (1994): The assessment of posttraumatic stress disorder with the Clinician Administered PTSD Scale: Dutch results. J Clin Psychol 50:325–340.
25. Olff M (2016): Five years of European Journal of Psychotraumatology. Eur J Psychotraumatol 7:31350.