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Research paper

The relationship between early administration of morphine or nitrous oxide gas and PTSD symptom development

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ABSTRACT

Background: Posttraumatic Stress Disorder (PTSD) is a debilitating mental health disorder. Certain drugs, such as morphine and nitrous oxide gas (N_2O), are administered to individuals who just experienced a traumatic event (e.g., soldiers, injured civilians). It is therefore crucial to understand if they incidentally affect PTSD symptom development. Furthermore, such observations could pave the way for the development of pharmacological prevention strategies of PTSD.

Methods: In this prospective population-based cohort study ($n = 2{,}070$), we examined the relationship between morphine or N_2O administration during childbirth, and subsequent childbirth-related PTSD symptoms at eight weeks postpartum. Pain during labour, prior PTSD symptoms, and birth medical severity were included as covariates in the analyses.

Results: In women who developed PTSD symptoms, N_2O administration during childbirth predicted reduced PTSD symptom severity ($p < .001$, small to medium effect size). A similar tendency was observed for morphine, but was not significant ($p < .065$, null to small effect size). Both drugs predicted increased PTSD symptoms when combined with severe pain during labour.

Limitations: This study was observational, thus drug administration was not randomised. Additionally, PTSD symptoms were self-reported.

Conclusions: Peritraumatic N_2O administration may reduce subsequent PTSD symptom severity and thus be a potential avenue for PTSD secondary prevention. This might also be the case for morphine. However, the role of severe peritraumatic pain in context of drug administration deserves further investigation.

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1. Introduction

Posttraumatic[1] stress disorder (PTSD) is a mental health disorder, which may occur after experiencing or witnessing a traumatic event (American Psychiatric Association, 2013), and has a lifetime prevalence of 3.9% (Koenen et al., 2017). Symptoms include re-experiencing, avoidance of trauma-related reminders, alterations in arousal, and negative cognitions and mood (American Psychiatric Association, 2013). They are present at least one month after the traumatic event (American Psychiatric Association, 2013) and have a mean duration of six years (Kessler et al., 2017). PTSD is comorbid with depression, anxiety, and substance abuse disorders (Brady et al., 2012). Even at subclinical levels, PTSD symptoms are associated with substantial functional impairment (Brancu et al., 2016), distress and suicidal ideation (McLaughlin et al., 2015). While evidence-based treatments for PTSD exist (Lewis et al., 2020), preventive interventions are lacking (Qi et al., 2016). Yet, PTSD onset is linked to an identifiable and temporally defined causative event, making it an ideal candidate for secondary prevention approaches (Qi et al., 2016).

The evidence of successful drug treatments for PTSD is mixed (Hoskins et al., 2015). However, when administered during the early posttraumatic period, certain drugs are associated with reduced subsequent PTSD symptoms (Astill Wright et al. 2019). Preliminary evidence suggesting such a protective relationship has, for instance, been reported for morphine, a pain relief medication of the opiate family. Two retrospective studies found that military personnel had a reduced likelihood of developing PTSD if they received morphine within the first hours following their brain or limb injuries (Holbrook et al., 2010; Melcer et al., 2014). However, one did not find such a relationship (Mion et al., 2017). Amongst civilians, receiving opiates or elevated morphine dose within 48 h following a traumatic injury was also associated with milder PTSD symptoms (Bryant et al., 2009; Mouthaan et al., 2015), although contradictory results were reported with opiate doses after lung injury (Bienvenu et al., 2013).

Another widely used pain relief is nitrous oxide gas (N_2O). Unlike morphine, the relationship between N_2O inhalation in the early posttraumatic period and PTSD development has received little attention. Yet, compared to medical air, N_2O inhalation after an analogue trauma significantly sped up the reduction of trauma-related intrusive memories (Das et al., 2016), a core symptom of PTSD. Importantly, results suggested that early inhalation of subanesthetic levels of N_2O may reduce PTSD symptoms while preserving voluntary memory. However, this relationship has never been investigated in the context of real-life trauma, nor beyond the first posttraumatic week.

Morphine and N_2O are used in a variety of contexts, such as intensive care units, labour wards, and in military medicine. Hence, they are administered to populations at high risk of PTSD. It is thus critical to assess whether these drugs have unsuspected effects on PTSD symptom development when administered in the early posttraumatic period. Such observations could also be a first step towards secondary pharmacological prevention of PTSD (Astill Wright et al., 2019; Maccani et al., 2012). On the contrary, they may reveal that morphine and N_2O cause iatrogenic harm (Fluegge, 2018). In any case, prospective studies on real-life traumas are lacking, especially for N_2O.

The underlying mechanisms of the association between early drug administration and PTSD symptom development are not well understood. One hypothesis is that morphine and N_2O impact memory consolidation, a time-dependent process of stabilisation of memories into long-term memory (McGaugh, 2000). During the consolidation window, lasting several hours after the event, memories are malleable and sensitive to interference (Nader et al., 2000). As PTSD is assumed to result from maladaptive memories and excessive fear learning (Pitman, 1989; van Marle, 2015), drugs disrupting the consolidation of trauma memories may prevent PTSD symptom development (Astill Wright et al., 2019). Morphine, for instance, impairs learning and reduces fear responses when administered after fear conditioning in rodents (e.g., McNally and Westbrook, 2003; Szczytkowski-Thomson et al., 2013). Similarly, N_2O inhalation can impair learning in both rodents (Rabat et al., 2004) and humans (Dunlosky et al., 1998). N_2O is, inter alia, an antagonist of N-methyl D-aspartate receptors (Emmanouil and Quock, 2007), which are implicated in long-term potentiation (LTP) (Luscher and Malenka, 2012). As LTP is one of the hypothesised mechanisms of memory consolidation (Nader and Hardt, 2009), N_2O is likely to disrupt memory consolidation. In terms of memory processes, it is also possible that morphine and N_2O, if administered very early, interfere with encoding. In this case, they could contribute to memory disorganization, which is frequently found in patients with PTSD (Brewin, 2018), and thus potentially trigger or worsen PTSD symptomatology.

An alternative explanation of the relationship between early drug administration and PTSD symptoms is pain relief. Indeed, morphine and N_2O reduce peritraumatic pain, a well-known risk factor for PTSD (Ayers et al., 2016). Given that the severity of the patients' medical situation may impact pain relief drug administration, peritraumatic pain may also reflect the severity of patients' medical situations. Both the severity of the patients' medical situation and peritraumatic pain are thus important to consider within this hypothesis. Importantly, the pain hypothesis is challenged by research on rodents, suggesting that morphine still reduces fear responses when administered after the end of the painful stimuli (e.g., RaiseAbdullahi et al., 2019). So far, few clinical studies included pain in their analyses. Even if these tend to support the hypothesis of an independent action of morphine on PTSD development (Bryant et al., 2009), the lack of data from prospective studies precludes firm conclusions.

The relationship between early drug administration and PTSD symptom development has never been studied in the context of childbirth. Yet, childbirth seems an opportune context: firstly, childbirth-related PTSD (C-PTSD) affects four to six per cent of mothers in community samples, and 18.5% in high-risk samples (e.g., emergency caesarean sections (ECS)) (Yildiz et al., 2017). Second, morphine and N_2O are routinely administered during birth. Third, childbirth is one of the most standardised real-life traumas, with a relatively homogeneous population and a similar peritraumatic environment (a care setting). Finally, since women have medical appointments during pregnancy, it is possible to obtain reliable measures of prior PTSD symptoms, a crucial risk factor for PTSD (Delahanty and Nugent, 2006).

To summarise, early morphine and N_2O administration might have an unexpected preventive effect on PTSD symptom development. However, there is a need for more prospective studies, taking the role of peritraumatic pain into account. This population-based cohort study firstly focused on the relationship between morphine or N_2O administration during childbirth and C-PTSD symptoms at eight weeks postpartum. In addition, we explored the role of pain during labour as a potential covariate, whilst controlling for prior PTSD symptoms and birth medical severity. We hypothesized that receiving morphine or N_2O during childbirth would predict reduced C- PTSD symptoms.

2. Method

2.1. Design and study population

Data were derived from a large population-based prospective cohort study: the Akershus Birth Cohort (ABC). Thus, the results of this study stem from secondary analyses.

The ABC targeted all women scheduled to give birth at Akershus University Hospital (Norway), which serves around 350,000

[2] ABC = Akershus Birth Cohort; AIC = Akaike Information Criterion; C-PTSD = Childbirth-related PTSD; ECS = Emergency caesarean Section; IES = Impact of Event Scale; IRM = Item Response Model; ISS = Injury Severity Score; MINI = Mini-International Neuropsychiatric Interview; N_2O = Nitrous oxide gas; RESI = Robust Effect Size Index; VIF = Variance Inflation Factor.

inhabitants. Recruitment took place between November 2008 and April 2010, during the 17-week pregnancy routine examination. Women were eligible to participate if they could complete the questionnaires in Norwegian.

Participants completed questionnaires during pregnancy, at 17 weeks and 32 weeks of gestation, and at eight weeks and two years postpartum. Medical information relating to the birth was registered in the hospital birth record. Participants who gave birth between May 2009 and September 2010 completed an additional questionnaire on pain at 48 hours postpartum. The ABC obtained ethical approval from the Regional Committees for Medical and Health Research Ethics (approval number S-08013a), and all participants provided written informed consent. Of the eligible women, 80% (n = 3,752) agreed to participate and returned the first questionnaire. Detailed information on participants and drop out in the ABC can be found in Garthus-Niegel et al. (2018).

In this study, we used data from the 17-weeks of gestation questionnaires, the eight weeks postpartum questionnaires, and the hospital birth record. Out of the 3,752 women who returned the 17-week questionnaire, we excluded those for which the hospital birth record was not available (n = 189). We also excluded women who received pethidine, which is an opioid (n = 2), or general anaesthetics (n = 73) during childbirth, because these drugs might independently affect PTSD symptom development. Women who received opiates other than morphine (n = 8) were excluded, too: since data on the type of opiate and mode of administration were not available, their inclusion would have made interpretation of the results difficult. Finally, we excluded women who did not return the questionnaires of interest at eight weeks postpartum (n = 1,395), or did not fully complete them (n = 15). Our final sample consisted of 2,070 women (Fig. 1).

2.2. Measures

2.2.1. Childbirth-related PTSD symptoms

The 15-item self-rating Impact of Event Scale (IES) (Horowitz et al., 1979) was used to measure C-PTSD symptoms at eight weeks postpartum. The IES has been validated in postpartum women (Olde et al., 2006). Participants were instructed to complete the scale in relation to their childbirth. Each item concerns one symptom, with four response categories (usually recoded with the following weightings: 0 = not at all, 1 = rarely, 3 = sometimes, and 5 = often). Sum scores of the overall scale can be computed (range 0–75), and scores above 34 indicate probable PTSD (Neal et al., 1994). In this study, we took into account the ordinal nature of the response scale by using a polytomous Item Response Model (IRM) (Hambleton et al., 1991), to estimate a global IES

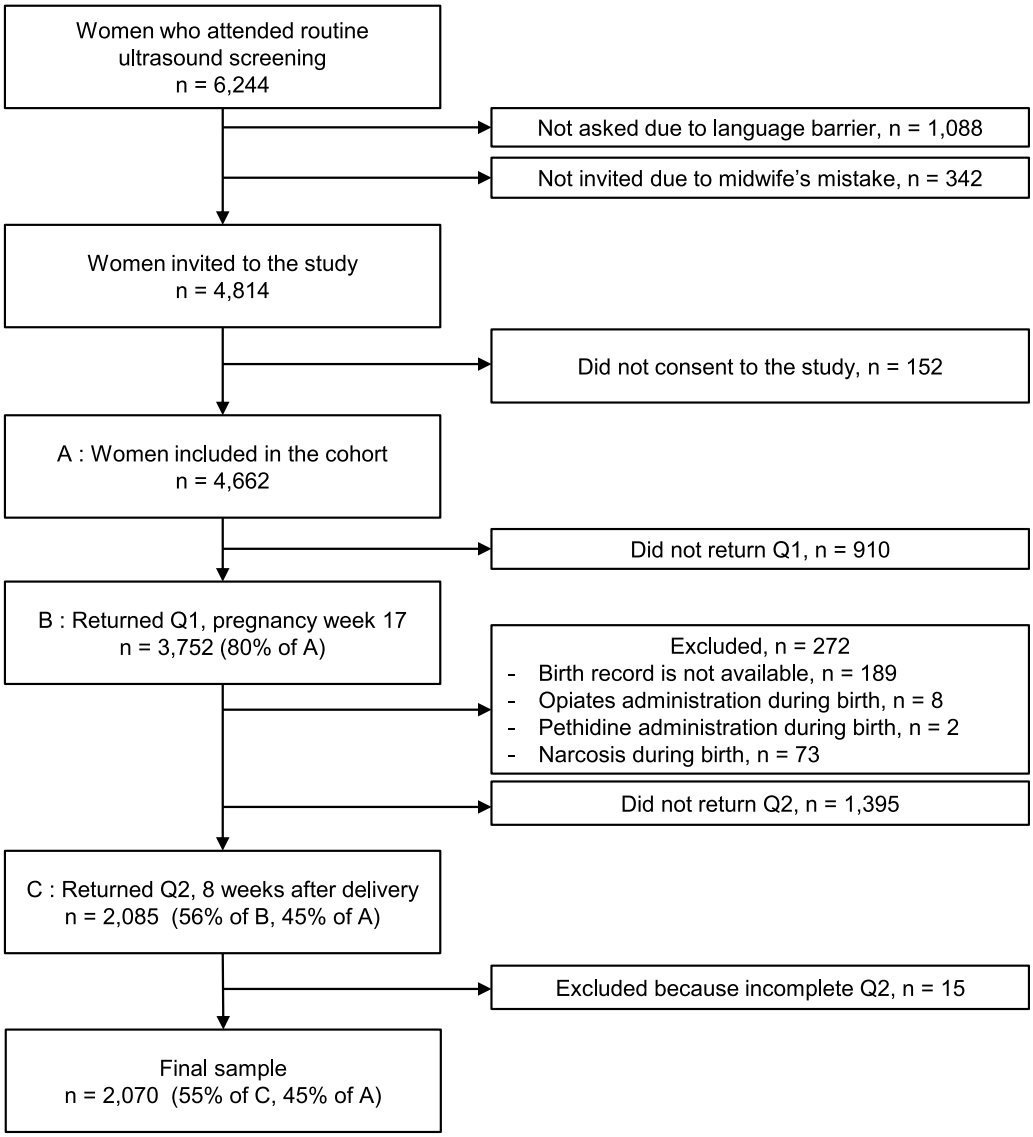

Fig. 1. Response and participation rates of the study.

score.

2.2.2. Prior PTSD symptoms

Prior PTSD symptoms were reported at 17 weeks of pregnancy. Women indicated whether they suffered from eight PTSD symptoms over the past month, in relation to a dramatic or terrifying event they potentially experienced. This PTSD symptom checklist was derived from the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Each item was scored 0 (symptom absent) or 1 (symptom present); the total scores ranged from 0 (no symptoms) to 8. See Garthus-Niegel et al. (2018) for a detailed description of this scale. In the present study, the prior PTSD symptoms score was computed with a dichotomous IRM (Hambleton et al., 1991).

2.2.3. Pain relief administered during childbirth

Data regarding morphine or N_2O administration during childbirth was extracted from the hospital birth record. Each drug was treated as a dichotomous variable, depending on whether it was used (1) or not (0). Both morphine and N_2O, if needed, were given during labour. Morphine was administered intramuscularly. N_2O was given through an inhalation mask. Participants were instructed to breathe in the mask as needed, and received 30 to 50% N_2O.

2.2.4. Pain during labour

Pain during labour was measured at 48 hours and eight weeks postpartum, with the following question: "How much pain did you feel during labour?". Participants replied using a numerical rating scale from 0 ("no pain at all") to 10 ("most intense imaginable pain"), which is a valid way of measuring pain intensity (Ferreira-Valente et al., 2011). Not all participants completed the questionnaire at 48 hours, but the pain ratings from both time points were highly correlated ($r = .76$, $p < .01$) and indicated good test–retest reliability (intraclass correlation = .88, $p < .001$). Therefore, due to the larger sample size available at eight weeks (2,070 vs 682 participants), we used the eight-weeks assessment.

2.2.5. Birth medical severity

Based on hospital birth records, a dichotomous variable was created, depending on whether the birth involved the use of forceps, vacuum, ended in an ECS (1) or not (0). ECS were considered as such if they were planned less than eight hours before delivery. This variable aimed to reflect birth medical severity, just as scores like the Injury Severity Score (ISS) reflect the severity of patients' medical situations in other populations (Holbrook et al., 2010). To our knowledge, a validated equivalent of the ISS does not exist in obstetrics. Thus, we used operative birth as a proxy for medical severity, as it indicates an urgency for the birth to occur quickly. Although they are operative, planned caesarean sections were coded "0", as they do not reflect medical emergency *during* birth. Besides, planned caesarean sections are not associated with as poor maternal adjustment outcomes as ECS (Alderdice et al., 2019), nor with comparable PTSD prevalence (Orovou et al., 2020).

2.2.6. Parity

Parity was reported by participants at 17 weeks of pregnancy, and recoded as 0 for nulliparous and as 1 for parous.

2.2.7. Sociodemographic characteristics

Education, marital status, and age at the time of birth were retrieved from the hospital birth record. Education had three categories, reflecting the highest achieved degree: elementary school (0), high school (1), and higher degree (2). Marital status was recoded into a dichotomous variable, distinguishing married/cohabiting women (1) versus singles (0).

2.3. Data analysis

2.3.1. Sample description

Descriptive analyses for the sociodemographic and obstetric variables, as well as PTSD-related scores were carried out for the total study sample. For C-PTSD symptoms, prior PTSD symptoms, pain during labour, and birth medical severity (the main study variables of interest), the sample was divided into four groups, based on drug administration during labour. Women either received no pain relief drug, morphine, N_2O, or a combination of morphine and N_2O. For all the analyses, we checked if the appropriate statistical assumptions were met and, if not, non-parametric tests were used. Group differences were investigated through chi-square analyses (categorical variables) or Kruskal-Wallis tests (continuous variables). Post-hoc comparisons with a Bonferroni correction were used to assess group differences in pain during labour, across the four drug-administration groups.

Given that ageing may increase the risk of obstetrical complication (Schummers et al., 2018) and thus affect drug administration, a post-hoc one-way between-subjects ANOVA was carried out to evaluate if age differed across the drug-administration groups. Group comparisons with a Bonferroni correction were used to assess drug group differences in age. Similarly, an independent sample t-test was conducted to compare age depending on birth medical severity. IBM SPSS 24 was used for all analyses in relation with sample description (Tables 1 and 2).

2.3.2. Prior PTSD and C-PTSD scores

For the total scores of both the IES and MINI-based prior PTSD symptom checklist, we took into account the ordinal nature of the response scale by using an Item Response Model (IRM). IRM are a class of statistical models designed to model categorical responses using probabilities (Hambleton et al., 1991). These models allow proper quantification of subject responses without a priori assuming equidistant response categories. By contrast with factor techniques, they explicitly incorporate person parameters (i.e., locations on some latent dimension) that directly model individual specificities in the response process, which is especially relevant for patient-reported outcomes (see Supplementary material, section I, "IRM and calculation of symptom scores" for details on scores computation).

2.3.3. Generalized linear regression models

A series of generalized linear regression models were fitted to explain IES scores at eight weeks from our main predictors: prior PTSD symptoms, pain during labour, birth medical severity, and morphine or N_2O administration. The latter were coded as present or absent because we wanted to quantify drug effects rather than group differences. An advantage of this coding is its ability to reveal more fine-grained interaction effects, in particular a potential interaction between both drugs, for women who received a combination of morphine and N_2O.

A zero-inflated Tweedie compound Poisson model (Zhang, 2013) was used, including two components: a logistic part discriminating between the zero and non-zero scores (absence vs. presence of symptoms), and a Tweedie compound Poisson model accounting for the non-null score variance (i.e., modelling stress intensity) (see Supplementary material, section II, "Zero-inflated Tweedie compound Poisson model" for details on the reasoning behind this model choice). Note that two sets of regression coefficients result from this analysis, one for each part of the model. All analyses were performed using the 'cplm' R package (Zhang, 2013).

A model comparison approach, where models of varying complexity are considered in turn, was adopted. In our modelling strategy, for statistical but also interpretability reasons, no interaction effect was included without adding the corresponding main effects or lower order interactions. The four following structures have been fitted on both zero-inflated and Tweedie components: i) a full model including all variables and their interactions up to second order (third order interactions were not included to avoid zero counts cells); ii) a reduced model (reduced model 1) including all effects and first order interactions; iii) a reduced model (reduced model 2) including only main effects; iv) a restricted model where only significant predictors from the full model were included. Combining these hypothetical structures on both parts of the

model resulted in a set of 16 models that were compared using the Akaike Information Criterion (AIC) (Akaike, 1973). Note that AIC model selection is relatively robust to collinearity, provided that the sample size is large enough (i.e. N ≥ 2000) (Brewer et al., 2016). Robust Effect Size Indices (RESI) (Vandekar et al., 2020) were calculated for each coefficient within the retained model.

3. Results

3.1. Characteristics of the study sample

In our sample, mean maternal age at birth was 31.33 years ($SD = 4.6$) (Table 1). Most participants had obtained a higher educational degree. A majority of women received N_2O during birth, while a minority received morphine (Table 1). The mean number of PTSD symptoms before childbirth was low ($M = 0.25$; $SD = 0.76$). At eight weeks postpartum, according to the IES original weighted scoring, 1.9% of our sample had probable C-PTSD (Table 1).

Table 2 reports each of the main study variables of interest, according to the drugs received by women during childbirth. Groups differed in terms of pain during labour ($H(3) = 137.08, p < .001$). A post-hoc pairwise comparison revealed that women receiving no pain relief reported significantly less pain than those who received N_2O ($p < .001$) or both morphine and N_2O ($p < .01$) (Table 2). Groups also significantly differed in terms of age ($F(3, 2066) = 3.124$, $p < .05$). A post-hoc pairwise comparison showed that the only difference was that women who received no pain relief ($M = 31.68$, $SD = 4.54$) were slightly older than those who received N_2O ($M = 31.09$, $SD = 4.6$) ($p < .05$). However, since the age difference was only seven months, it is unlikely to have led to a substantial increase of obstetrical complications. Women who received morphine ($M = 31.4$, $SD = 3.8$) or both morphine and N_2O ($M = 32.26$, $SD = 5.05$) did not differ from the others. Furthermore, women whose birth involved vacuum, forceps, or ECS ($M = 31.4$, $SD = 4.46$) were similar in age compared to the others ($M = 31.32$, $SD = 4.32$); $t(2068) = 0.302$, $p = .762$. Thus, age did not appear as a relevant variable and was not included in our model.

Table 1
Characteristics of the study sample (n = 2,070).

Sample characteristics (*time point measured;range*)	Frequency (%)	Mean (*SD*)
Sociodemographic characteristics		
Age (*at time of childbirth;18–45*)		31.33 (4.6)
Education (*at time of childbirth*)		
Elementary	62 (3[a])	
High school	579 (28[a])	
Higher degree	1362 (65.8[a])	
Marital status (*at time of childbirth*)		
Married or cohabiting	2009 (97.1[a])	
Single	46 (2.2[a])	
Obstetrical factors		
Parity (*pregnancy week 17*)		
Nulliparous	1009 (48.7)	
Parous	1061 (51.3)	
Pain during labour (*8 weeks postpartum;0–10*)		
Pain relief (*at time of childbirth*)		7.73 (2.4)
No pain relief	796 (38.5)	
Morphine	17 (0.8)	
N_2O	1225 (59.2)	
Morphine and N_2O	32 (1.5)	
Birth medical severity (forceps, vacuum, ECS)	384 (18.6)	
PTSD symptoms		
Prior PTSD symptoms (*pregnancy week 17*)		
Raw score (*0–8*)		0.25 (0.76)
IRM score[b] (*-0.25–3.19*)		-0.04 (0.54)
C-PTSD symptoms (*8 weeks postpartum*)		
Score (*0–65*)		6.82 (8.11)
Score>34, probable C-PTSD[c]	39 (1.9)	
IRM score[b] (*0–4.97*)		1.28 (0.91)

Note. N_2O = Nitrous oxide gas; ECS = Emergency caesarean section; IRM = Item Response Model; C-PTSD= Childbirth-related PTSD

[a] Total of % does not equal 100 because of missing values ($n = 2,003$ for education and $n = 2,055$ for marital status).

[b] Scores computed using an IRM. It is these scores that are used in our analysis.

[c] Scores derived from the original weighted IES scoring. Reported for descriptive purposes only.

Table 2
Characteristics of the main study variables grouped by method of pain relief.

	No pain relief ($n = 796$)	Morphine ($n = 17$)	N_2O ($n = 1,225$)	Morphine and N_2O ($n = 32$)	*P*-value
Prior PTSD symptoms (*IRM score*[a]) (Mean (*SD*))	-0.01 (0.58)	0.10 (0.83)	-0.06 (0.51)	0.05 (0.6)	.22[b]
Pain during labour (Mean (*SD*))	6.73 (3.07)	8.18 (2.13)	8.35 (1.66)	8.66 (1.2)	<.001[b]***
Birth medical severity (forceps, vacuum, ECS) (Number (%))	134 (16.83)	3 (17.65)	239 (19.51)	8 (25)	.36[c]
C-PTSD symptoms (*IRM score*[a]) (Mean (*SD*))	1.25 (0.88)	1.27 (1.21)	1.29 (0.92)	1.6 (0.8)	.09[b]

Note. N_2O = Nitrous oxide gas; IRM = Item Response Model; ECS = Emergency caesarean section; C-PTSD = Childbirth-related PTSD

[a] Scores computed using an IRM.

[b] Statistical significance was computed via Kruskal-Wallis test.

[c] Statistical significance was computed via Chi-square test.* $p < .05$** $p < .01$*** $p < .001$

3.2. Associations with C-PTSD scores

The best model retained included only main effects on the zero inflation model, and main and first order interactions in the Tweedie regression model (see Supplementary material, section III, "Model comparison and selection" for the AIC of each model). Corresponding model coefficients are displayed in Table 3, along with RESI (Vandekar et al., 2020) and Variance Inflation Factors (VIF). Although a strong collinearity (VIF > 10) is apparent for six terms out of 20, the use of AIC model selection and the RESI allows to identify relevant predictors.

The zero inflation model (Table 3.a) showed that few prior PTSD symptoms, mild pain during labour, and low birth medical severity (neither vacuum nor forceps nor ECS) were all significant predictors of a zero response to IES, thus reinforcing the relevance of these covariates in our analyses. However, only pain was close to a noticeable effect size ($S = 0.0978$).

Coefficients in the Tweedie regression model (Table 3.b) showed that N_2O inhalation during childbirth decreased the IES score ($\beta = -0.4062$, $p < .001$), i.e., reduced C-PTSD symptom severity. The effect size was small to medium ($S = 0.1121$). A similar tendency was apparent for morphine, although the corresponding coefficient was not significant ($\beta = -0.8454$, $p = .064$) and the effect size was null to small ($S = 0.0290$) (Table 3.b). Significant first order interactions of both N_2O and morphine with pain during labour were found, with positive coefficients. The effects sizes were respectively small to medium ($S = 0.1179$) and null to small ($S = 0.0326$). This result suggests that women who received N_2O during birth were likely to develop more severe C-PTSD symptoms if the pain level was high, and log-proportionally to pain level. The same pattern of opposite effects, with pain as a moderator, was observed for morphine, although the main protective effect of morphine did not reach significance (Table 3.b). Scatter plots of pain severity and IES scores in the four drug-administration groups can be

Table 3
Estimated coefficients on the Zero Inflated Tweedie Compound Poisson model of IES.

(a) Zero inflation logistic model	Estimate[a]	Std. Error	z value	Pr(>|z|)	RESI[b]	VIF
(Intercept)	-0.6147	0.1692	-3.6326	0.0003***	0.0788	
Prior PTSD	-0.5374	0.1348	-3.9876	0.0001***	0.0833	1.0030
Pain	-0.1030	0.0229	-4.5054	0.0000***	0.0978	1.1175
Birth Medical Severity	-0.6798	0.1677	-4.0544	0.0001***	0.0861	1.0025
N_2O	0.1314	0.1219	1.0781	0.2810	0.0080	1.1165
Morphine	-0.2916	0.4175	-0.6984	0.4849	0.0000	1.0035

(b) Tweedie regression model	Estimate[a]	Std. Error	z value	Pr (>|z|)	RESI[b]	VIF
(Intercept)	0.4168	0.0469	8.8948	0.0000***	0.2111	
Prior PTSD	0.0785	0.0521	1.5067	0.1319	0.0196	7.5925
Pain	-0.0004	0.0062	-0.0594	0.9527	0.0000	1.9691
Birth Medical Severity	0.0305	0.0917	0.3325	0.7395	0.0000	12.7208
N_2O	-0.4062	0.0841	-4.8291	0.0000***	0.1121	15.4729
Morphine	-0.8454	0.4568	-1.8507	0.0642	0.0290	41.0325
Prior PTSD x Pain	0.0072	0.0070	1.0286	0.3037	0.0000	8.8915
Prior PTSD x Birth medical severity	-0.0306	0.0451	-0.6776	0.4980	0.0000	1.2940
Prior PTSD x N_2O	-0.0402	0.0407	-0.9872	0.3236	0.0000	2.6150
Prior PTSD x Morphine	-0.0637	0.1210	-0.5260	0.5989	0.0000	1.2258
Pain x Birth medical severity	0.0217	0.0119	1.8258	0.0679	0.0373	15.2262
Pain x N_2O	0.0514	0.0101	5.0820	0.0000***	0.1179	17.5108
Pain x Morphine	0.0999	0.0508	1.9655	0.0494*	0.0326	39.9776
Birth medical severity x N_2O	-0.0580	0.0586	-0.9901	0.3221	0.0000	3.4923
Birth medical severity x Morphine	-0.0065	0.1575	-0.0411	0.9672	0.0000	1.3901
N_2O x Morphine	0.0390	0.1462	0.2668	0.7896	0.0000	3.2786
Dispersion parameter :	0.19617					
Index parameter :	1.8681					

Note. RESI = Robust Effect Size Index; VIF = Variance Inflation Factor; N_2O = Nitrous oxide gas.
[a] Estimates represent unstandardized β values.
[b] Interpretation of Robust Effect Sizes: [0;0.1]: None-Small,]0.10;0.25]: Small-Medium,]0.25;0.4]: Medium-Large (Vandekar et al., 2020). The RESI directly control for collinearity by using the parameter information matrix as its main metric (see Vandekar et al. (2020), formula 16): when covariances are high, parameter variances are high, and the RESI is low, such that effects with at least small-medium effect sizes ($0.10 < S < 0.25$) can be confidently interpreted*$p < .05$**$p < .01$***$p < .001$

found in Fig. 2. As illustrated by Fig. 3, the administration of morphine, N_2O or both was associated with more severe C-PTSD symptoms from a pain rating of about 9 out of 10. Note that morphine and N_2O administration did not statistically interact ($p = .79$).

In view of the moderating role played by N_2O in the final model, its impact was further investigated by performing two mediation analyses on the Tweedie part of the model, using the mediation package in R (Tingley et al., 2014). No significant mediating effect of N_2O in the pain/C-PTSD relationship, nor of pain in the N_2O/C-PTSD relationship, was found.

3.3. Discussion

In this large population-based cohort study, we examined the prospective relationship between morphine or N_2O administration during a real-life traumatic event, and PTSD symptoms eight weeks later. Pursuant to our hypothesis, N_2O administration during childbirth predicted milder C-PTSD symptoms when controlling for birth medical severity, prior PTSD symptoms, and pain during labour. Although not statistically significant ($p < .065$), a similar association was observed with morphine. We believe this latter result warrants attention given the low p-value, the number of studies reporting a protective effect of morphine, and the small number of women who received morphine in our sample ($n = 49/2{,}070$).

The second aim of this study was to explore the role of peritraumatic pain as a covariate. The significant interaction between drugs and peritraumatic pain indicates that women who received analgesics and reported intense pain during labour ($\geqslant 9/10$) had more severe C-PTSD symptoms, thus suggesting that pain does play a role. However, unlike N_2O, it should be noted that the effect size of the interaction between pain and morphine was null-small – which might be due to low power. Importantly, the above-mentioned results only apply to mothers reporting some C-PTSD symptoms, as neither morphine nor N_2O administration predicted the *absence* of C-PTSD symptoms.

3.4. Underlying mechanisms

Although our study remains observational, several elements could contribute to the debate on mechanisms underlying the relationship between early drug administration and PTSD.

3.4.1. Memory consolidation hypothesis

A priori, a drug can only disrupt memory consolidation if it is administered and active during the early *post*traumatic period, within the memory consolidation window. In our study, analgesics were administered *during* labour. Importantly, childbirth can be composed of several traumatic experiences (e.g., unexpected induction of labour, an ECS). Thus, some mothers may have received pain relief during the *post*traumatic period, whilst others may have received them during the pretraumatic period, i.e. outside of the memory consolidation window. This may explain why morphine was not significantly associated with milder C-PTSD symptoms although, since it has a half-life of a couple of hours (Berkowitz, 1976), the drug may still have been active in the posttraumatic period. This is less likely for N_2O, which has a half-life of three minutes (Hale, 1999). Finally, given that the drugs were sometimes given during the pretraumatic period, they may have, in addition to disrupting memory consolidation, affected stress response (Mouthaan et al., 2015).

3.4.2. Pain hypothesis

In our study, N_2O predicted reduced C-PTSD symptoms, even when controlling for pain. Furthermore, pain did not predict C-PTSD symptom intensity, although low pain scores predicted their absence. Besides, the pain scores of women who received N_2O or a combination of morphine and N_2O were significantly higher than those of the control group, while women who received morphine had a score comparable to that of the

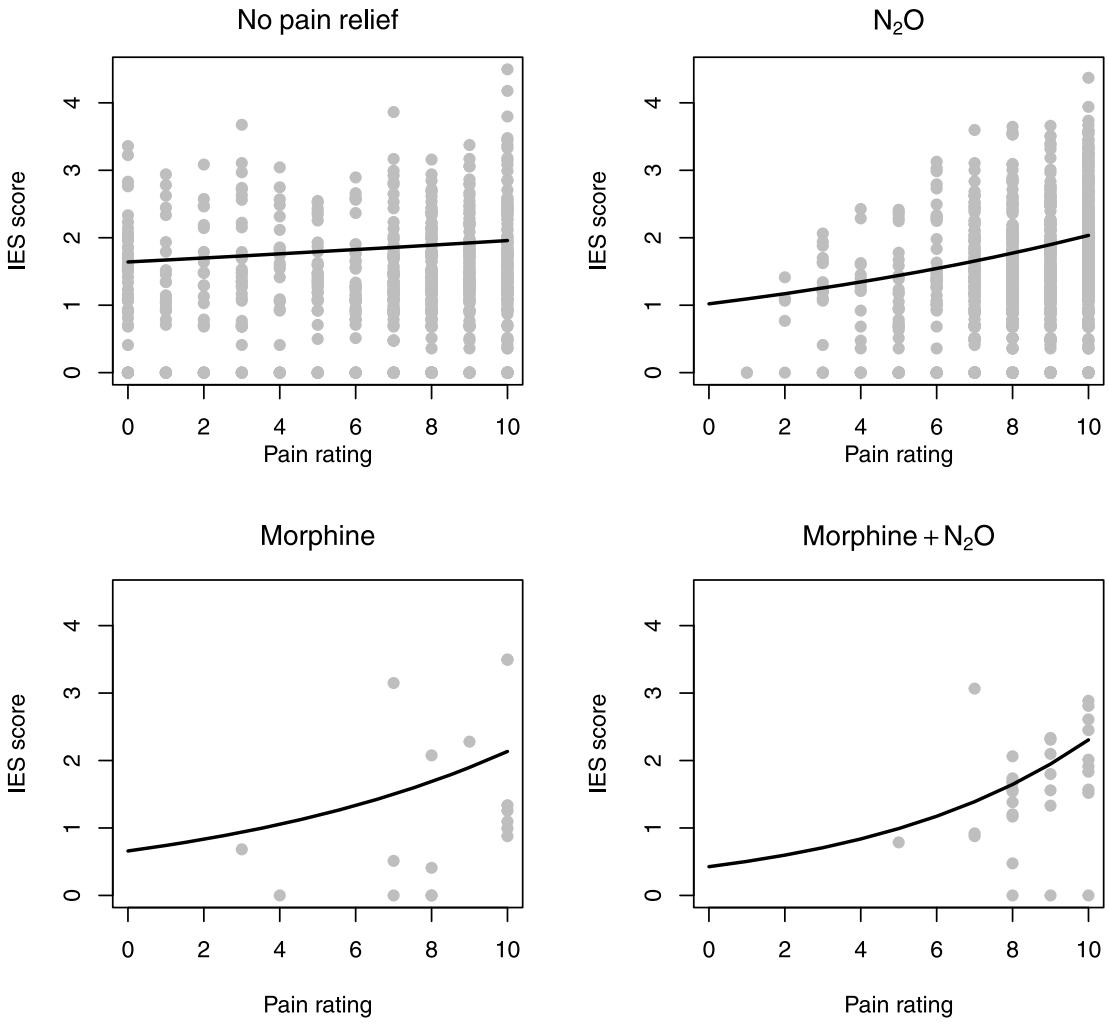

Fig. 2. Marginal model curves of the relationship between pain rating and IES score in the four pain relief groups, based on the full Tweedie regression model.
Note. IES = Impact of Event Scale; N_2O = Nitrous oxide gas.

control group. It does not appear that women who received analgesics thereby had a less painful experience than those who did not. This is probably explained by the fact that it was the pain intensity that led women to ask for pain relief. Besides, unless women reported highly intense pain, N_2O inhalation remained protective. Additionally, the mediation analysis did not show that the relationship between N_2O and C-PTSD symptoms severity was mediated by pain. Overall, these elements are not in favour of the pain hypothesis.

3.4.3. Non-pharmacological mechanisms

Aside from memory consolidation disruption or pain reduction, the observed association with PTSD symptoms could be due to indirect mechanisms. Firstly, the use of analgesics may enhance women's sense of control, or contribute to a sense of support from the staff, which both protect against C-PTSD (Ayers et al., 2016; Czarnocka and Slade, 2000). N_2O benefits could also come from its mode of administration, as focusing on breathing may help to relax (Richardson et al., 2019). Finally, all these non-pharmacological aspects could contribute to a reduction in PTSD symptoms through improved overall birth experience (Garthus-Niegel et al., 2014). They may also explain why N_2O and morphine both predicted more severe C-PTSD symptoms when combined with intense labour pain: since perceiving the midwife as in control of the situation is a protective factor for C-PTSD (De Schepper et al., 2016), inefficient pain relief may give the impression that the staff is powerless.

3.5. Study limitations

Despite the prospective, population-based design, the large sample size and the inclusion of important confounding variables, this study has several limitations. The first, which is inherent in observational clinical studies, is that drug administration was not randomised. While this is for obvious ethical and medical reasons, it may lead to biases. For that same reason, our sample included only a few women who received morphine, and thus we may have lacked statistical power for this drug.

Another limitation of our study concerns the type of measurement used. PTSD symptoms, whether pre-existing or childbirth-related, were self-reported. As for pain, it was measured at eight weeks postpartum, and thus may reflect pain memory, despite a strong correlation between pain at 48 hours and eight weeks postpartum. Additionally, since these analyses were not designed at the time of data collection, we do not have specific information on the intensity of pain relief provided by morphine and N_2O. Our measurement of pain thus remains a global indicator, which limits the mechanistic interpretations and notably the interpretation of the mediation analyses.

Furthermore, we acknowledge that using ECS, forceps, or vacuum as a proxy for birth medical severity is also a limitation. While it was necessary to take into account the severity of the obstetrical situation at the time of delivery, use of a validated index, had it been available, would have been preferable.

As shown by the VIF in Table 3, the important collinearity detected

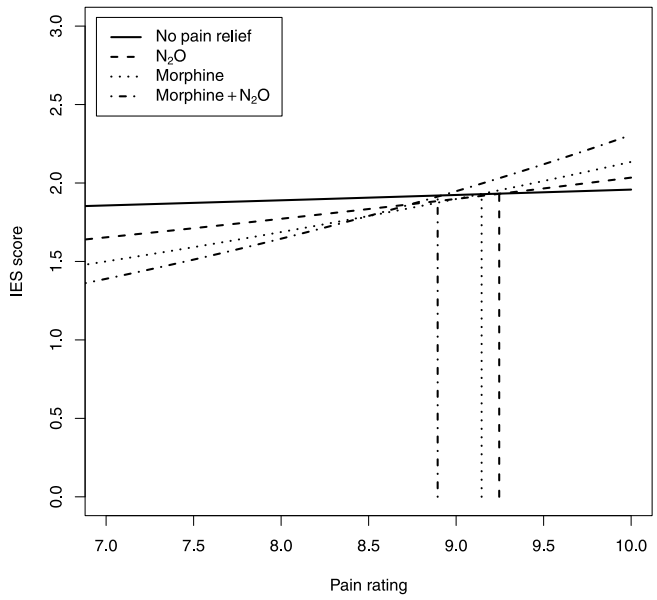

Fig. 3. Relationship between pain and IES score for pain ratings above 7 (on a scale from 0-10), as predicted by the full Tweedie regression model for each pain relief group. Vertical lines correspond to thresholds for which drugs are associated with more severe C-PTSD symptoms.
Note. IES = Impact of Event Scale; N_2O = Nitrous oxide gas.

for several terms of the Tweedie regression may also limit the interpretation of results, although this collinearity is taken into account in the RESI computation.

Finally, despite our exclusion criteria, other drugs may have been given during childbirth and thus influenced PTSD symptom development. Oxytocin and benzodiazepines, for example, may affect PTSD development if administered following the traumatic event (Frijling, 2017; Guina et al., 2015), although the evidence is mixed (Astill Wright et al., 2019; McGhee et al., 2009).

3.6. Implications and future directions

We believe that our results suggest that both N_2O and morphine merit further investigation about their use in the prevention of PTSD symptoms development. However, while most of the published studies are naturalistic, research would benefit from randomised controlled trials. Even if these are difficult to carry out in a clinical context, the trauma film paradigm seems to offer a good alternative for laboratory studies (James et al., 2016).

Future research should focus on the dose-response relationship between administered drugs and PTSD symptom development. Indeed, the effects of N_2O or morphine on memory (Good and Westbrook, 1995; Rabat et al., 2004) or PTSD (Bryant et al., 2009) may be dose-dependent. In our study, for instance, morphine dose may not have been sufficient to significantly affect PTSD symptoms. With a view to developing preventive interventions, greater clarity on this issue seems essential. In this respect, while morphine can be addictive and have psychotropic effects, N_2O has the advantage of having a short half-life, and moderate side effects (Likis et al., 2014). Besides, it seems to preserve the memory of the traumatic event (Das et al., 2016), which is a key aspect of the ethical debate on pharmacological prevention of PTSD (Jain et al., 2011). Overall, its use is considered safe and minimally invasive (Zafirova et al., 2018). However, its toxicity is still debated (Fluegge, 2018), and it could increase intrusions frequency in dissociated individuals (Das et al., 2016). Furthermore, while many studies suggest that timing is key (e.g., Bryant et al., 2009; RaiseAbdullahi et al., 2019), it has not been systematically investigated either.

Among injured or suffering populations, future studies should take into account the effects of anaesthesia provided during the peritraumatic period. Indeed, anaesthesia procedures may involve not only other drugs with singular effects on pain or memory, but also additional (locally administered) opioids and opiates. Thus, anaesthesia represents another gateway for drugs to enter the body, and its relationship with PTSD development remains unclear (Hernandez-Martinez et al., 2020; Lopez et al., 2017).

Furthermore, the protective effect of N_2O in the absence of severe pain suggests that it would be relevant to examine the preventive potential of analgesics for uninjured victims of traumatic events such as witnesses of assaults. On the contrary, since morphine and N_2O are commonly used to relieve injured patients, it would be important to clarify whether their administration actually worsens the severity of subsequent PTSD symptoms in those in extreme pain.

4. Conclusion

In this study, N_2O was associated with reduced C-PTSD symptoms when inhaled during the peritraumatic period. Although not significant, a similar trend was observed for morphine. Conversely, higher levels of pain predicted more severe C-PTSD symptoms in women who received morphine or N_2O. These results may be of interest to health professionals routinely using these two drugs in populations at risk of developing PTSD, by providing information on the associations between pain relief and mental health. Furthermore, they open up exciting prospects for research on N_2O as a potential pharmacological agent for PTSD prevention.

5. Author Statement

Contributors. C. Deforges, S. Stuijfzand and A. Horsch conceptualized the study. Y. Noël, S. Garthus-Niegel and C. Deforges performed all the analyses, in collaboration with S. Stuijfzand, and A. Horsch. C. Deforges drafted the initial manuscript, with the contribution of S. Garthus-Niegel for the method section and Y. Noël for the statistics. M. Eberhard-Gran designed and coordinated the original cohort study. T. Breines Simonsen supervised the data collection and data extraction of the hospital birth record. M. Robertson contributed with her expertise in anaesthesiology and the interpretation of the data. All authors approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work. A. Horsch is the PhD supervisor of C. Deforges.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.12.051.

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