Nicotine Replacement Therapy During Pregnancy and Infantile Colic in the Offspring

WHAT'S KNOWN ON THIS SUBJECT: Infantile colic affects almost 10% of all infants and is characterized by crying and fussing in an otherwise healthy and well-fed infant. Prenatal exposure to tobacco smoking is a risk factor, but it is unclear whether nicotine causes the association.

WHAT THIS STUDY ADDS: Infants exposed to nicotine replacement therapy during pregnancy had elevated infantile colic risk of the same magnitude as infants exposed to tobacco smoking. Intrauterine exposure to nicotine may play a causal role in the pathogenesis of infantile colic.

abstract

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OBJECTIVE: To investigate the associations between use of nicotine replacement therapy (NRT) and smoking during pregnancy and infantile colic in the offspring.

METHODS: We used data from maternal interviews (from pregnancy and at 6 months post partum) from the Danish National Birth Cohort (1996–2002). We included 63 128 live-born singletons with complete information on nicotine exposure during pregnancy and infantile colic symptoms as recorded at 6 months of age.

RESULTS: A total of 46 660 infants (73.9%) were unexposed to nicotine during pregnancy; 207 (0.3%) were exposed to NRT, 15 016 (23.8%) were exposed to smoking, and 1245 (2.0%) to both. A total of 4974 (7.9%) infants fulfilled Wessel's modified criteria for infantile colic. Prenatal nicotine exposure was associated with elevated risk for infantile colic in the offspring. Compared with the unexposed, NRT users had an adjusted odds ratio (OR) (95% confidence interval) of 1.6 (1.0–2.5; $P = .03$), smokers had OR = 1.3 (1.2–1.4), and women who both smoked and used NRT had OR = 1.6 (1.3–1.9). Partners' smoking was not associated with infantile colic after adjustment for maternal smoking.

CONCLUSIONS: We corroborated the association between smoking and infantile colic after adjustment for several possible confounders in a large cohort study. Moreover, we found that infants exposed to NRT prenatally had an increased risk for infantile colic of the same magnitude as those exposed to tobacco smoke. Thus, nicotine may play a role in the pathogenesis of infantile colic. *Pediatrics* 2012;129:e652–e658

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KEY WORDS

infantile colic, smoking, nicotine replacement therapy

ABBREVIATIONS

BW—birth weight
CI—confidence interval
DNBC—Danish National Birth Cohort
GA—gestational age
NRT—nicotine replacement therapy
OR—odds ratio

The idea for the study on infantile colic came from Dr Søndergaard; Dr Olsen helped establish the Danish National Birth Cohort, and Dr Søndergaard participated in the planning of the cohort and edited the questions concerning infantile colic; Drs Milidou and Jensen performed the data analyses, and Dr Milidou wrote the first draft of the paper and edited the following versions; Drs Milidou, Henriksen, Olsen, Søndergaard, and Jensen discussed the design, edited the manuscript, and agreed on the final version; Dr Milidou is guarantor; and all authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Wessel defined infantile colic as paroxysms of crying and fussing for more than 3 hours per day for more than 3 days per week for more than 3 weeks in an otherwise healthy and well-fed infant.[1] In Western countries up to 8% to 10% of infants fulfill this definition in the first 3 months of life. Infantile colic is generally considered a benign and self-resolving condition,[2] yet it poses a burden on the affected families and may even trigger violent behavior toward the child.[3] Causal hypotheses relate to a gastrointestinal or a neurodevelopmental origin, such as altered gut microflora,[4,5] altered gastrointestinal motility,[6] lactose intolerance,[7,8] or a disorder in behavior regulation mechanisms.[1,9] Some consider infantile colic as an outlier in the developmental variation.[10–12] Maternal smoking has repeatedly been shown to increase the risk of infantile colic by a factor of almost 2,[13–16] and this association does not seem to be confounded by maternal education, socioeconomic status, obstetric history, gestational age (GA), or birth weight (BW).[13,17]

Smoking cessation has become a priority in recent years for many Western countries, and the use of nicotine replacement therapy (NRT) has proven effective.[18] U.S. Food and Drug Administration approved the first NRT (nicotine gum) in 1984, and the same year it became available over the counter in Denmark. An increasing number of pregnant women use NRTs[19] because NRT is generally considered to be a better alternative than continued smoking. However, NRTs are characterized as drugs that may pose a risk to the fetus, and some studies question their use in pregnancy.[19–21] Nicotine may be involved in the pathogenesis of infantile colic because it affects the gastrointestinal function[6] as well as the development of the fetal central nervous system.[22,23] Because NRTs release only nicotine, studying NRT users may be useful for examining whether the association between smoking and infantile colic is due to nicotine.

We therefore compare the association between intrauterine exposure to tobacco smoke and infantile colic with the possible association between NRT and infantile colic, on the basis of the hypothesis that any nicotine exposure would increase the risk of infantile colic.

METHODS

The Danish National Birth Cohort: Study Population

Our study was based on data from the Danish National Birth Cohort (DNBC), a nationwide population-based cohort of pregnant women recruited from 1996 to 2002.[24] Approximately 50% of the pregnant population was invited by their general practitioner to join the cohort at the first antenatal visit, and nearly 60% of those consented.[25] The original cohort included 101 042 pregnancies. The establishment of the original cohort was approved by the Danish Science Ethical Committee system (j.nr. [KF] 01-471/94). The current study was approved by the Danish Data Protection Agency (j.nr. 2009-41-3755).

Exposures during pregnancy, the mother's health status, medical and obstetric history, lifestyle and diet, working and living conditions, psychosocial stress, and socioeconomic status were assessed through 2 computer-assisted telephone interviews at ~17 and 32 gestational weeks (designated second- and third-trimester interviews, respectively). A similar interview concerning the last part of pregnancy and the infant's behavior, development, nutrition, and frequency and duration of cry episodes was conducted when the child was 6 months old (postpartum interview).

Exposure Assessment

We defined exposure to nicotine as self-reported smoking or use of NRT during pregnancy. In the second-trimester interview the women were asked about their smoking habits and use of NRTs during the entire pregnancy. Questions were: "Did you smoke during pregnancy (please also consider the very beginning of the pregnancy)?" and "Did you use nicotine gum, patches, or an inhalator while pregnant?". The entire questionnaire is available at http://www.dnbc.dk/. Combining mothers' replies (yes/no) in both questions, 4 mutually exclusive categories were created: NRT users, smokers, smokers using NRT (combination), and unexposed. Cigarette smoking was reported as cigarettes per week or as cigarettes per day, and women that used other types of tobacco (n = 15) reported number of pipes/cheroots/cigars smoked per day, which was converted to number of cigarettes according to estimated nicotine content. NRT users were asked whether they used gum, patch, or inhalator, alone or in combination. At the time of the study nicotine gum (2 and 4 mg), 16- and 24-hour patches, inhalators (10 mg), lozenges (1 and 2 mg), nasal spray (0.5 mg per dose), and sublingual tablets (2 and 4 mg) were available in Denmark. However, only use of the 3 most common NRTs was specifically assessed in the interview. The dose and frequency of NRT use was not assessed.

We used interview data from the second and third trimesters to identify exclusive NRT users who continued to be nonsmokers at least well into the third trimester. Maternal smoking but not NRT use during the postnatal period was assessed in the postpartum interview; hence only postnatal smoking status was available for secondary analyses.

Outcome Assessment

Infantile colic was reported by the mothers in the interview 6 months post partum, and identification of cases was based on the modified Wessel's criteria: crying or fussing for more than 3 hours

a day for more than 3 days a week. Because some infants had more than 1 period with crying and fussing, their first crying period had to start before the age of 3 months. The reported unease or crying had to be unrelated to teeth cutting or any recognized disease. For each reported period the mothers were asked "How many hours all together was he/she at unease/crying during 24 hours?" and "How many days a week was he/she at unease or crying for more than 3 hours during 24 hours?" They were asked to report the duration of the crying/unease period either as an interval with minimum and maximum or as an average.

Statistical Analysis

Infantile colic was modeled as a binary outcome using logistic regression, with prenatal exposure to smoking and NRT as the independent variables. We calculated odds ratio (OR) (with 95% confidence interval [CI]) for infantile colic in the offspring for the different exposures to nicotine. Statistical significance was defined as 2-sided *P* value of <0.05.

We first estimated the risk of infantile colic among infants exposed prenatally to NRT, tobacco smoke, or both, using unexposed infants as a reference. We also identified a subgroup of NRT users who reported no smoking in both prenatal interviews and compared the risk of infantile colic in their offspring with the risk among unexposed infants. Because of the small number of exclusive NRT users we could not further stratify by type of NRT. Subsequently, we analyzed the risk for infantile colic by level of daily smoking during pregnancy (0, <1, 1–3, 4–9, 10–14, and 15+ cigarettes per day), excluding infants exposed to NRT. We also combined level of daily smoking (0, <1–4, 5–9, and 10+ cigarettes per day) and use of NRT (yes/no) in a single eight-level variable combining both sources of nicotine. The risk for offspring infantile colic for the exposure groups was compared with the reference of nonsmokers and no NRT users.

We estimated the risk of infantile colic according to partners' smoking habits to address whether the association between maternal smoking and infantile colic could be due to uncontrolled confounding from family conditions and socioeconomic status.[26] If such confounding is present, we would expect to observe an association between partners' smoking and offspring infantile colic. The mothers reported their partners' smoking habits (smoker or nonsmoker) in the second-trimester interview, and for this analysis women living alone ($n = 1135$) were regarded as having a nonsmoking partner. In a subanalysis we identified pairs of siblings discordant in their exposure to tobacco smoking during pregnancy and compared their risk of infantile colic.

We decided a priori, based on a directed acyclic graph, to adjust all analyses for the following covariates: maternal age (in 7 equally sized groups), parity at the birth of the index child (1 and 2+), daily coffee consumption during pregnancy (0, <1–4, and 5+ cups), weekly alcohol consumption (0, <1–2, 3–4, and 5+ units; 1 unit corresponds to 12 g of alcohol), binge drinking episodes (consumption of more than 5 alcohol units on a single occasion) during pregnancy (0 and 1+), and the couple's combined educational and occupational status (in 4 categories, Table 1). All information was collected during the interviews. Because the infantile colic assessment was based on maternal report and could be influenced by social conditions, we decided a priori to both create 2 different models, adjusted and unadjusted for the couple's combined educational and occupational status, and repeat our analyses restricted to the 2 upper socioeconomic categories. For all our analyses each of the covariates included a separate category for missing values (proportions shown in Table 1).

Low BW has been associated with infantile colic[27] and is closely linked to GA. Because nicotine exposure is a risk factor for low BW and early delivery, these were considered potential intermediate variables and were not included in the main analysis. To explore this further, we repeated all analyses restricted to infants born between 37 and 41 completed gestational weeks with a BW above 2500 g. Moreover, we performed regression analyses, adding BW and GA as a linear, as a polynomial, and as a categorical variable.

RESULTS

From the 101 042 pregnancies registered in the DNBC, a total of 92 676 resulted in singleton live births. Among those, 66 823 completed both the second-trimester and postnatal interviews with an assessment of nicotine use in pregnancy and symptoms of infantile colic in the offspring. The main analysis was based on first child in the cohort, excluding 3695 younger siblings. Thus, the study population consisted of 63 128 mother-infant dyads.

A total of 46 660 infants (73.9%) were unexposed to nicotine during pregnancy; 207 (0.3%) were exposed to NRT, whereas 15 016 (23.8%) were exposed to smoking and 1245 (2.0%) to a combination of smoking and NRT. Among NRT users, 194 used one type of NRT, and 13 two different types (158 used gum, 26 patches, and 35 an inhalator). Inhalator and gum was the most popular combination ($n = 10$). More than 70% of all NRT users preferred short-release products, primarily nicotine gum alone (almost 50%) or in combination with an inhalator ($<0.5\%$). Despite the usual recommendations, almost half of all NRT users ($n = 802$) continued active smoking over a longer period,

TABLE 1 Maternal and Child Characteristics in 4 Prenatal Nicotine Exposure Groups According to Tobacco Smoke and Use of NRT, the DNBC, 1996–2002

Mother and Child Characteristics	Maternal Smoking and Use of NRT (%)			
	Unexposed (*n* = 46 660)	NRT Users (*n* = 207)	Smokers (*n* = 15 016)	Smoking + NRT (*n* = 1245)
Primiparous[a]	48.5	57.0	50.6	57.4
Social class[b]				
High-grade professionals and managers	38.7	39.6	23.4	29.6
Middle-grade professionals	32.7	35.8	29.9	34.3
Skilled workers, students	26.1	22.2	39.7	31.7
Unskilled workers, unemployed, social security	2.6	2.4	7.0	4.4
Mother's age, y[a]				
<25	4.3	1.0	9.8	7.0
25–29	32.9	24.3	34.4	30.4
30–34	41.8	49.0	36.6	37.9
35–39	18.2	20.9	16.6	21.0
≥40	2.9	4.9	2.6	3.8
Coffee consumption (cups per d)[a]				
0	61.1	38.7	40.3	31.4
<1–4	34.7	48.8	41.4	45.9
≥5	4.2	12.6	18.3	22.7
Alcohol consumption (units per wk)[a]				
0	55.1	47.3	56.1	50.7
<1–2	34.2	32.9	30.6	33.5
3–4	10.0	18.8	11.7	14.1
≥5	0.7	1	1.7	1.8
≥1 Binge drinking episode during pregnancy[b]	22.3	28.0	33.4	35.3
Married or cohabitating[a,c]	98.6	98.1	94.8	95.4
Major concern about the birth and the child's health while pregnant[b]	5.1	6.3	7.7	9.1
Child exposed to environmental tobacco[a,c]	5.7	2.9	28.5	23.7
GA[b]				
<37 wks	4.0	2.9	4.9	5.2
37–40 wks	86.9	85.9	86.0	85.4
≥41 wks	9.1	11.2	9.1	9.4
BW <2500 g[b]	2.4	2.9	4.3	4.8
5 min Apgar score <7[d]	0.6	0	0.6	0.7
Girls[a]	49.0	43.0	49.2	45.9
Child never had formula milk[c,e]	28.0	28.4	20.6	19.9

[a] Percentage of missing values for each covariate ≤0.1%.
[b] Percentage of missing values for each covariate ≤0.5%.
[c] Refers to the 6 months postpartum interview (all prenatal exposures were assessed in the second-trimester interview).
[d] Percentage of missing values for each covariate ≤1%.
[e] Percentage of missing values for each covariate ≤10%. One unit of alcohol corresponds to 12 g of alcohol.

and many of them (*n* = 255) combined smoking with a slow-release NRT (patch).

Mothers who smoked, exclusively or in combination with NRT, tended to be less educated, slightly younger, and more concerned about the current pregnancy and the health of their child (Table 1). Their infants were smaller at birth, more often exposed to environmental tobacco smoking and less often exclusively breastfed. All types of nicotine exposure were associated with higher coffee consumption. NRT users who did not smoke were similar to the nonsmokers on many characteristics.

A total of 4974 (7.9%) infants fulfilled the criteria for infantile colic. All 3 types of prenatal nicotine exposure were associated with elevated risk for infantile colic compared with unexposed (Table 2). Notably, the OR for infantile colic among infants exposed to NRT was comparable to that of infants exposed to tobacco smoke. Adjustment for the potential confounders had negligible impact on the point estimates, and including the socioeconomic status in the model left results unchanged. Similar associations between prenatal exposure to nicotine and infantile colic were found across strata of socioeconomic status (data not shown). The risk for offspring infantile colic among NRT users compared with nonsmokers remained elevated (OR = 1.5 [0.9–2.4]), when we restricted the analysis to the subgroup of NRT users who reported no smoking in both prenatal interviews (*n* = 176), but was nonsignificant.

An increasing number of cigarettes smoked per day was associated with an increasing risk for infantile colic (Table 3). For the combination variable, the highest OR was observed in women who smoked 5 to 9 cigarettes, alone (OR = 1.5 [1.3–1.6]) or in combination with NRT (OR = 1.8 [1.4–2.3]) (Fig 1).

In a subpopulation of 3658 pairs of siblings, 349 pairs were discordant for smoking exposure in pregnancy and 444 for infantile colic. However, only 46 pairs were informative, and this small number did not allow for meaningful comparisons.

Partners' smoking was not associated with offspring infantile colic after adjustment for maternal exposure to nicotine (OR = 1.1 [1.0–1.1]; *P* = .10). Moreover, the positive association between maternal smoking and infantile colic was not modified by partners' smoking habits (Table 3).

We observed results similar to those already presented in a secondary analysis restricted to children born between 37 and 41 completed gestational weeks with a BW above 2500 g (*n* = 53 906). None of the reported results changed when BW was added to the model as a linear, a quadratic, or as a categorical term. The ORs for offspring infantile colic in mutually exclusive

TABLE 2 Crude and Adjusted OR With 95% CIs for Infantile Colic According to Maternal Use of NRT and Tobacco Smoking During the First and Second Trimester of Pregnancy

Nicotine Exposure	Infantile Colic				
	N	*n* (%)	Crude OR	Adjusted OR_1 (95% CI)	Adjusted OR_2 (95% CI)
Unexposed	46 660	3397 (7.3)	1[a]	1[a]	1[a]
NRT users	207	23 (11.1)	1.6	1.6 (1.0–2.5)	1.6 (1.0–2.5)
Smokers	15 016	11 417 (9.4)	1.3	1.3 (1.2–1.4)	1.3 (1.2–1.4)
Smoking and NRT	1245	137 (11.0)	1.6	1.5 (1.3–1.9)	1.5 (1.3–1.8)

N, number; OR_1, adjusted for maternal age, first parity, daily coffee consumption, weekly consumption, and binge-drinking episodes; OR_2, further adjusted for couple's combined educational and occupational status.
[a] Reference group.

TABLE 3 Crude and Adjusted OR With 95% CIs for Infantile Colic According to Level of Maternal Smoking and Partners' Smoking Habits

Level of Maternal Smoking[a] (Cigarettes Per D)	Infantile Colic				
	N	*n* (%)	Crude OR	Adjusted OR (95% CI)	
				Partner Nonsmoker	Partner Smoker
Unexposed	46 660	3397 (7.3)	1[b]	1[b]	1.0 (1.0–1.1)
<1	1066	86 (8.0)	1.1	1.1 (0.9–1.4)	1.1 (0.9–1.4)
1–4	2727	230 (8.4)	1.2	1.1 (1.0–1.3)	1.2 (1.0–1.3)
5–9	4616	455 (9.9)	1.4	1.3 (1.2–1.5)	1.3 (1.2–1.5)
10–14	3757	369 (9.8)	1.4	1.3 (1.2–1.5)	1.3 (1.2–1.5)
≥15	2707	260 (9.6)	1.4	1.3 (1.1–1.5)	1.3 (1.1–1.5)

Adjusted for maternal age, first parity, daily coffee consumption, weekly alcohol consumption, binge-drinking episodes, and couple's educational and occupational status.
[a] Among non-NRT users.
[b] Reference group.

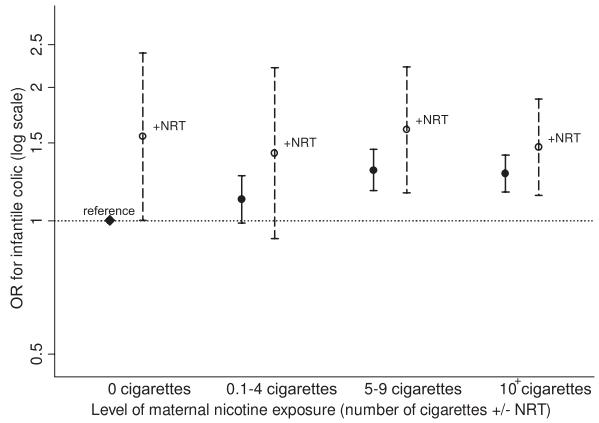

FIGURE 1
Adjusted ORs with 95% CI for infantile colic according to level of maternal nicotine exposure, defined as number of cigarettes daily, with (dashed lines) and without (solid lines) additional use of NRT. The reference group (0 cigarettes/no NRT) is marked with a diamond.

groups of smokers (smoking in pregnancy and not during lactation, smoking only during lactation, continuous smoking during both pregnancy and lactation) were all higher than in nonsmokers, with continuous smokers having a slightly higher OR for offspring infantile colic (data not shown).

DISCUSSION

Exposure to nicotine exclusively from NRT during pregnancy was associated with an increased risk of infantile colic in the infant of the same magnitude as cigarette smoking. This finding indicates that nicotine may be the component in tobacco smoke responsible for the increased risk for infantile colic.

Although this is 1 of the largest studies of NRT use in pregnancy, the number of exclusive NRT users was still limited, and some estimates have large CIs. The results are based on a large population-based follow-up study after adjusting for several covariates, and the exposure assessment was carried out prospectively during pregnancy, which precludes differential reporting in relation to the outcome.

Maternal smoking at any time during pregnancy was associated with increased risk for infantile colic in the offspring, as seen in most[13–16] but not all studies.[28] Some authors argue that the association between smoking and infantile colic is entirely attributable to uncontrolled confounding by factors related to smoking behavior, such as social class.[28] In our study the 2 models, adjusted and unadjusted for socioeconomic status, yielded similar results. The magnitude of association between nicotine exposure and infantile colic was similar across strata of socioeconomic status categories. Furthermore, if the observed association is indeed confounded by lifestyle or any other unknown factors associated with smoking, we would expect maternal and partners' smoking during pregnancy to be equally good proxy measures of these factors, which was not seen. The dose-response like association seen between level of nicotine exposure and risk for infantile colic might indicate a causal link. In addition, NRT users in our sample were quite similar to the unexposed population with respect to other characteristics, which reduces the risk of confounding. Even so, we cannot rule out unmeasured or residual confounding due to our observational study design.

Data did not allow us to distinguish between early, late gestational, and postnatal exposure to nicotine because most exposed women were exposed to some

extent throughout and after the pregnancy. The association between smoking during the first and second trimester and infantile colic was weaker compared with smoking throughout pregnancy. The limited numbers and the lack of postnatal assessment did not allow for such a comparison among NRT users.

Women tend to change their smoking habits during pregnancy, and many have several attempts to quit and relapses, especially light smokers.[29] By assessing nicotine exposure twice during pregnancy and by asking about the entire pregnancy up to the interview and not only the current status we expect to identify the majority of exposed infants. Indeed, very few nonsmokers changed their smoking status (n = 360) or NRT use (n = 3) after the second-trimester interview, and our results were similar regardless of whether their infants were coded as exposed or not. Some women may have discontinued their exposure late in pregnancy, but this would most likely lead to bias toward no association. Some of the observed association between NRT and infantile colic could be due to nonreported tobacco exposure among NRT users. However, when we restricted our analysis to women who reported to have remained tobacco-free during pregnancy, point estimates were unchanged for the association between NRT and infantile colic. Underreported smoking during pregnancy is possible,[30,31] but women would probably disclose their NRT use because there is no public awareness of negative effects of NRT use to the fetus in Denmark. Nonjudgmental attitude of the interviewer combined with several questions addressing smoking as in the DNBC should facilitate a rather accurate disclosure.[31]

Infantile colic was assessed after resolution of the symptoms, and the prevalence of infantile colic in our study was comparable to that reported by a prospective assessment in the same source population.[32] We adjusted for relevant covariates that may affect perceptions of abnormal cry behavior, such as parity and social status.[33] We furthermore attempted to use siblings as controls in the sibling subpopulation analysis, but the number of siblings discordant for exposure was insufficient.

CONCLUSIONS

The mechanisms responsible for the association between prenatal exposure to tobacco smoking and infantile colic are unknown, but our data indicate that nicotine may play a role. A causal role of nicotine in the pathogenesis of infantile colic is biologically plausible. Nicotine acts as a neurotransmitter to the nicotinic acetylcholine receptors and upregulates them.[22] It also modifies the function of serotonin receptors in the fetus[23] and thus interferes with the actions of critical neurotransmitter signals in the developing brain. Similar receptors exist in the adult intestinal epithelial cells, and they were recently found to be involved in inflammatory conditions and diseases such as ulcerative colitis.[34,35] Furthermore, nicotine causes vasoconstriction in the gastrointestinal system[22] and increases serotonin secretion from the intestinal chromaffinic cells,[36] stimulating gastrointestinal motility and secretion.

Our study does not warrant a contraindication for using NRT for women who cannot stop smoking while pregnant but calls for more studies on the safety of NRT use in pregnancy.

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