TOPAMAX® (topiramate)
Use of TOPAMAX in Pregnancy and Lactation

SUMMARY

- TOPAMAX® can cause fetal harm when administered to a pregnant woman.[1]
- Consider the benefits and the risks of TOPAMAX when administering this drug in women of childbearing potential, particularly when TOPAMAX is considered for a condition not usually associated with permanent injury or death.[1]
- TOPAMAX should be used during pregnancy only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.[1]
- Data from pregnancy registries and routinely collected healthcare encounters indicate that infants exposed to topiramate in utero have an increased risk of major congenital malformations (MCMs), including but not limited to cleft lip and/or cleft palate (oral clefts [OCs]), small for gestational age (SGA) [1-3,4,5-11] and may be associated with cardiovascular malformations and neurodevelopmental disorders.[12-15]
    - The prevalence of SGA is greater in infants of women who received higher doses of TOPAMAX during pregnancy. The prevalence of SGA in infants of women who continued topiramate use until later in pregnancy is higher compared to the prevalence in infants of women who stopped TOPAMAX use before the third trimester.[1]
- The effect of topiramate-induced metabolic acidosis has not been studied in pregnancy; however, metabolic acidosis in pregnancy (due to other causes) can cause decreased fetal growth, decreased fetal oxygenation, and fetal death, and may affect the fetus' ability to tolerate labor. Pregnant patients and their newborns should be monitored for metabolic acidosis and treated as in the nonpregnant state.[1]
- TOPAMAX is excreted in human milk. The effects of TOPAMAX on milk production are unknown. Diarrhea and somnolence have been reported in breastfed infants whose mothers receive TOPAMAX treatment. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TOPAMAX and any potential adverse effects on the breastfed infant from TOPAMAX or from the underlying maternal condition.[1]
- To provide information regarding the effects of in utero exposure to TOPAMAX, physicians are advised to recommend that pregnant patients taking TOPAMAX enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number, 1-888-233-2334, and must be done by the patients themselves. Information about the NAAED can be found at www.aedpregnancyregistry.org.[1]

CLINICAL AND DATABASE ANALYSES

Bjork et al (2022)[12] described a population-based cohort study using health and social register data from Denmark, Finland, Iceland, Norway, and Sweden from 1996-2017 to estimate the risks of autism spectrum disorder (ASD) and intellectual disability (ID) after prenatal exposure to the most frequently used antiseizure medications. Approximately 4.5 million children were included;16,170 were born to mothers with epilepsy that were prenatally exposed to antiseizure medications. The 8-year cumulative incidences of ASD and ID in children of mothers unexposed were 1.5% and 0.8%, respectively while those exposed to topiramate was 4.3% and 3.1%, respectively. The adjusted hazard ratios (aHR) for children of women with epilepsy exposed to topiramate compared to children of women with epilepsy not exposed were 2.77 (95% CI, 1.35-5.65) for ASD and 3.47 (95% CI, 1.40-8.63) for ID. Combination therapy with lamotrigine and topiramate was associated with an increased risk of neurodevelopmental disorders (ASD and/or ID) in children of women with epilepsy: 8-year cumulative incidence, 7.5%; aHR, 2.4 (95% CI, 1.1-4.9).

Blotiere et al (2019)[11] reported an observational cohort analysis of pregnancies ≥20 weeks exposed to one of 10 different antiepileptic drugs (AED) collected from French nationwide healthcare databases, January 2011-March 2015. Exposure was defined as an AED dispensed 1 month before and 2 months after the beginning of pregnancy. A sensitivity analysis was also conducted, which limited the dispensing window to the first 2 months of pregnancy. There were 517 pregnancies exposed to topiramate out of a cohort of 1,886,825 pregnancies, where exposure to topiramate was associated with an increased risk of cleft lip, with or without cleft palate (OR 6.8, 95% CI, 1.4-20.0). In the sensitivity analysis, exposure to topiramate was associated with an increased risk of hypospadias (OR 4.9, 95% CI, 1.0-14.6). This is consistent with previous literature.

Using data from Medicaid Analytic eXract (MAX), **Hernandez-Diaz et al (2018)**[16] evaluated if topiramate exposure in the first trimester increases the risk of OCs, based on ICD-9 codes, in a population of pregnant women exposed to high and low does for epilepsy and non-epilepsy indications compared to untreated women between last menstrual period and end of first-trimester and women treated with lamotrigine. The risks of OCs and adjusted risk ratios are described in Table: Risks of Oral Clefts (OCs) in Topiramate Exposed, Unexposed, and Lamotrigine Exposed Pregnancies. Unadjusted demographics of the various groups showed that women on topiramate were older, more likely to be white and obese, were smokers, had chronic illnesses, and used concomitant medications compared to unexposed women. After propensity score adjustments, all groups were similar.

Risks of Oral Clefts (OCs) in Topiramate-Exposed, Unexposed, and Lamotrigine-Exposed Pregnancies[16]

Oral Clefts	Topiramate-Exposed (n=2425)	Lamotrigine-Exposed (n=2796)	Unexposed (n= 1,322,955)
Events[a], n	<11	<11	1501
Risk (per 1000)	4.1	1.5	1.1
Unadjusted RR (95% CI)	3.63 (1.95-6.76)	1.89 (0.85-4.21)	Reference
Propensity-Score Adjusted RR (95% CI)	2.9 (1.56-5.4)	1.89 (0.85-4.21)	
[a]no reported information for <11 cases			

Tennis et al (2015)[13] screened for potential safety signals of MCMs after first-trimester topiramate use during pregnancy (excluding OCs) using claims and administrative data from four separate healthcare databases. The goal of this retrospective cohort analysis was to estimate the prevalence ratio of MCMs compared to women without first-trimester topiramate exposure and to obtain pooled estimates. The results showed that the cardiovascular and genitourinary systems were most frequently affected by MCMs. The overall prevalence of MCMs was 55 per 1000 infants (95% CI, 44.9-65.1) for the topiramate cohort versus 33.9/1000 (30.9-37.0) for the unexposed cohort. Pooled prevalence ratios for selected MCMs is presented in Table: Prevalence Ratios for Major Congenital Malformations (MCMs): First-Trimester Topiramate Exposure vs Non-Exposure. The authors caution that these data are intended to identify potential safety signals and are subject to limitations associated with unvalidated health claims data.

Prevalence Ratios for Major Congenital Malformations (MCMs): First-Trimester Topiramate Exposure vs Non-Exposure[13]

Most Frequent MCMs (based on the general population)[a]	Prevalence Ratio - topiramate cohort (N = 1945) vs. non-exposed cohort (N = 13,614)
Ventricular septal defect	1.63 (1.02-2.62)
Atrial septal defect	1.88 (1.35-2.61)
Conotruncal heart defects	2.55 (0.81-7.99)
Pulmonary valve stenosis	0.80 (0.28-2.25)

Coarctation of the aorta	1.91 (0.53-6.84)
Pyloric stenosis	1.22 (0.55-2.73)
Congenital dislocation or dysplasia of the hip	0.78 (0.28-2.18)
Hypospadias[b]	1.91 (1.04-3.51)
Hydrocephalus	0.00 (0-1.81)
Patent ductus arteriosus[c]	2.76 (1.45-5.23)
Obstructive genitourinary defect	1.46 (0.72-3.00)
[a]excludes oral clefts [b]only among males – cohort sizes are 1015 for topiramate, and 7037 in the non-exposed cohort [c]included as malformation only when no claim for premature birth was associated with the infant.	

An earlier study from this data set reported a prevalence for OCs of 0.36% in newborns of mothers who were exposed to topiramate during the first trimester versus 0.07% for those not exposed to topiramate.[17]

Margulis et al (2012)[18] focused on the association between topiramate monotherapy use during the first trimester of pregnancy and the development of OCs (cleft lip with or without cleft palate - CL/P) in the newborn. The study examined data from two case-control studies: (1) the Boston University Slone Epidemiology Center Birth Defects Study (BDS) and (2) the Centers for Disease Control and Prevention's National Birth Defects Prevention Study (NBDPS). The study population from the BDS (1997-2009) consisted of 10,618 infants with MCMs, and 6983 controls (defined as infants without MCMs). There was a total of 785 cases of CL/P. A total of 7 infants (5 infants with malformations and 2 controls) were exposed to topiramate, of which 3 cases had CL/P. The odds ratio (OR) of first trimester topiramate exposure versus no AED use for MCM was 1.22 (95% CI, 0.19-13.01) vs 10.13 (95% CI, 1.09-129.21) for CL/P. The NBDPS dataset (1997-2007) consisted of 23,333 MCM, and 8494 controls. There were a total of 2283 cases of CL/P. Fourteen infants were exposed to topiramate (10 infants with malformations and 4 controls), of which 4 infants had CL/P. The OR for MCM in first trimester exposure to topiramate versus no AED use was 0.92 (95% CI, 0.26-4.06) vs 3.63 (95% CI, 0.66-20.00) for CL/P. The pooled study found overall that first trimester topiramate monotherapy exposure was not associated with an increase in the risk of MCM (OR, 1.01; 95% CI, 0.37-3.22). However, there is an elevated risk of CL/P (OR, 5.36; 95% CI, 1.49-20.07) compared with no use of AEDs.

Green et al (2012)[19] conducted a retrospective cohort analysis examining patients' pharmacy and medical claims through a longitudinal database from 2002-2010. The study sought to evaluate the risk of MCM occurrence, including OC, in infants exposed to topiramate during the first trimester of pregnancy. This population of interest was compared to three cohorts, including the following: drug-exposed cohort (use of any other AEDs during pregnancy), disease-state cohorts including migraine, epilepsy and diabetes mellitus, as well as a random comparator group. First trimester exposure was based on the earliest probable conception date, prescription fill dates, and days' supply. The risk of OC and MCM in topiramate-exposed infants in the first trimester compared with other AEDs and disease-state cohorts are summarized in the table below.

Risk of OC and MCM in topiramate-exposed infants in the first trimester compared with other AEDs and disease-state cohorts[19]

	Patients (n)	OC (%)	RR Topiramate vs. Comparator (95% CI)	MCM (%)	RR Topiramate vs. Comparator (95% CI)
Drug-exposed cohorts					
Topiramate	870	2 (0.23)	-	37 (4.25)	-
Other AEDs	3615	6 (0.17)	1.39 (0.28-6.85)	116 (3.21)	1.33 (0.92-1.90)
Disease-state cohorts					
Migraine	26,865	42 (0.16)	1.47 (0.36-6.06)	1,017 (3.79)	1.12 (0.81-1.55)
Epilepsy	2607	8 (0.31)	0.75 (0.16-3.52)	113 (4.33)	0.98 (0.68-1.41)
Diabetes	13,062	34 (0.26)	0.88 (0.21-3.67)	859 (6.58)	0.65 (0.47-0.89)
Random Sample	99,761	159 (0.16)	1.44 (0.36-5.81)	3,758 (3.77)	1.13 (0.82-1.55)

Abbreviations: AEDs, antiepileptic drugs; CI, confidence interval; MCM, major congenital malformations; OC, oral cleft; RR, relative risk.

The OC events were too few to detect an effect of maximum daily dose on the frequency of OC events. The MCM rate was highest (6.13%) in the cohorts with the lowest daily dose (≤50 mg). The frequency of MCM was lowest (3.03%) in the cohorts receiving the most common daily doses (51-100 mg) and increased (to 5.05%) in cohorts receiving the highest daily dose (≥201 mg).

Ornoy et al (2008)[20] followed the outcomes of pregnancies reported to the Israeli Teratogen Information Service (TIS). Data from 52 pregnancies exposed to topiramate were compared with 212 controls. In the topiramate group, 29 patients were on monotherapy and 23 were on polytherapy. There were 41 live births in the topiramate group compared with 198 in the control group. Key results are reported below Table: Pregnancy outcomes for topiramate versus controls.

Pregnancy outcomes for topiramate versus controls[20]

	Topiramate	Control	*P* value
Reported Pregnancies	52	212	n/a
Live births	41	198	n/a
Gestational age at delivery (weeks)	40 (38-40)	39 (38-41)	0.828
Birth weight, median (g)	2932 (2615-3512)	3300 (2900-3653)	0.024
Birth weight - term infants without multiple gestations, median (g)	3084±90	3356±455	0.001
Major anomalies	4/41 (9.8%)	7/206 (3.4%)	0.090
Nongenetic anomalies	2/41 (4.9%)	5/206 (2.4%)	0.328

Major anomalies were not statistically different between topiramate and control groups. Topiramate was associated with reduced birth weight, but not decreased gestational age at time of delivery. There was no increased risk for major anomalies identified, however, the small number of topiramate exposures presented here is not sufficient to rule out the potential for structural defects.

PREGNANCY REGISTRIES

Background

The primary role of the various registries is to assess the in-utero risks of AED exposure to the newborn. The focus has been on MCM with some data available on minor malformations as well. Due to significant methodological differences, general pooling across the registries would not provide meaningful data. Because of obvious ethical concerns in studying women in pregnancy, the observational data provided by the registries creates an efficient way to evaluate the teratogenic potential of AEDs.[21,22]

North American Registry

Pregnant patients receiving treatment with AEDs, including TOPAMAX®, are advised to enroll in the NAAED Pregnancy Registry at 1-888-233-2334. The registry is located at the Genetics and Teratology Unit at the Massachusetts General Hospital in Boston, Massachusetts. All calls are kept confidential and participants are provided with educational materials concerning perinatal care for women with epilepsy. Enrolled women are asked to provide information about the health status of their infants. The findings are analyzed to assess the fetal risk of all AEDs in pregnancy. Further information may be found at the following NAAED Pregnancy Registry web site: http://www.aedpregnancyregistry.org/.

In the NAAED pregnancy registry, when topiramate-exposed infants with only OCs were excluded, the prevalence of MCMs (4.1%) was higher than that in infants exposed to a reference AED (1.8%) or in infants with mothers without epilepsy and without exposure to AEDs (1.1%). The prevalence of OCs among topiramate-exposed infants (1.4%) was higher than the prevalence in infants exposed to a reference AED (0.3%) or the prevalence in

infants with mothers without epilepsy and without exposure to AEDs (0.11%). It was also higher than the background prevalence in United States (0.17%) as estimated by the Centers for Disease Control and Prevention (CDC). The relative risk of OCs in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 12.5 (95% CI, 5.9-26.37) as compared to the risk in a background population of untreated women.[1]

Data from the NAAED pregnancy registry and a population-based birth registry cohort indicate that exposure to topiramate *in utero* is associated with an increased risk of SGA newborns (birth weight <10th percentile). In the NAAED pregnancy registry, 19.7% of topiramate-exposed newborns were SGA compared to 7.9% of newborns exposed to a reference AED and 5.4% of newborns of mothers without epilepsy and without AED exposure.[1]

UK Epilepsy and Pregnancy Register

The UK Epilepsy and Pregnancy Register is an independent, prospective, observational, registration, and follow-up study of pregnant women with epilepsy. Cases are included in the registry if they are referred before the pregnancy outcome is known, regardless of whether there was exposure to an AED (i.e., monotherapy or polytherapy).[2,6,7,23]

Data collected in the UK Epilepsy and Pregnancy Register as of August 2007 were evaluated by Hunt et al in a study focusing on women who became pregnant while receiving treatment for epilepsy with topiramate alone, or in combination with another AED.[2] The primary study outcome assessment was the rate of MCMs. Among 203 pregnancies, 178 resulted in live births. Sixteen (9.0%; 95% CI, 5.6-14.1) of the 178 births were associated with MCM. Three MCM (4.8%; 95% CI, 1.7-13.3) were observed after fetal exposure to monotherapy (n=70 monotherapy), and 13 MCM (11.2%; 95% CI, 6.7-18.2) after fetal exposure to polytherapy (n=133 polytherapy). Overall, four cases of OC were reported in infants exposed to topiramate (2.2%); two of these cases were in monotherapy (3.2%). The observed rate of OCs in monotherapy was 16 times higher than the background rate in the UK, which is approximately 0.2%.[1] Out of 78 live male births, four cases of hypospadias were reported (5.1%; 95% CI, 0.2-10.1). Concomitant valproate and topiramate administration was associated with the highest rates of MCM. The authors express the relevance of these data for women of childbearing potential, regardless of indication, and encourage careful interpretation due to the small sample size and wide confidence intervals.[2]

Data from a 2009 update of the UK registry reported on 241 topiramate outcomes with a MCM rate of 7.1% (95% CI, 4.5-11.0%). Three of 79 cases were in topiramate monotherapy (3.8%; 95% CI, 1.3-10.6%) and 14 of 162 cases (8.6%; 95% CI, 5.2-14.0%) were in topiramate polytherapy. The number of reported OCs (four cases) remained the same as in the earlier UK report.[2,23]

Campbell et al (2013)[24] utilized the UK registry data to evaluate whether women who have had one child with a congenital malformation (major or minor congenital malformations CM) are at an increased risk of having recurrent malformations with additional pregnancies. Overall, there was a 16.8% risk of having a second child with a CM when looking at all AEDs studied. In patients taking topiramate, the recurrence risk of CM after one child was 50% (3/6; 1 monotherapy, 2 polytherapy). The recurrence rate in topiramate monotherapy and polytherapy were 33.3% and 66.6%, respectively. In addition, there was a 50% risk of recurrence for women who had two previous children with CM. Recurrence risks were also higher in women who had their AED dose increased after a first pregnancy and for women who were on polytherapy.

Australian Pregnancy Register

Data from a 2013 study under the Australian Pregnancy Register, evaluated fetal malformations and AED therapy taken during pregnancy. The Registry reported a statistically significant association between topiramate and hypospadias, and various brain

maldevelopments (n=3) based on exposure to poly and monotherapy with topiramate (P<0.05). There were four instances of hypospadias (6.67%) among 60 male infants who were exposed to topiramate which appeared to be dose related.[8]

Regarding seizure activity during pregnancy, **Vajda et al (2014)** reported a rate of seizure occurrence at 54.8% (from a cohort of 42 topiramate monotherapy cases), versus 31.7% (from a cohort of 82 levetiracetam monotherapy cases; P<0.05).[25]

In a subsequent analysis, **Vajda et al (2018)** reported that 15 fetuses had malformation in 93 topiramate-exposed pregnancies. There were significant dose-related increases in fetal malformation risk involving topiramate polypharmacy.[26]

In an analysis of 20 years of data collected by the Australian Registry**, Vajda et al (2019)** identified a dose-related increased occurrence of malformation-carrying pregnancies with valproate and topiramate in the presence of topiramate in AED polypharmacy.[27]

Danish Medical Birth Registry

A population-based cohort study from the Danish Medical Birth Registry evaluated pregnancy outcomes for infants exposed to newer AEDs.[28] The study evaluated outcomes from January 1996 through September 2008 and included first trimester polytherapy or monotherapy exposure to topiramate, lamotrigine, oxcarbazepine, or levetiracetam in 1532 infants. These results were compared with pregnancies from the registry that were not exposed to AEDs (n=836,263). Overall, the unexposed group experienced birth defects in 2.4% (19,911/836,263) of births compared with 3.2% (49/1532) of births in the group exposed to the newer AEDs. In the topiramate group, there were birth defects reported in 4.6% of pregnancies (5/108). When adjusted for diagnosis of epilepsy and first trimester use of older AEDs, the prevalence odds ratio (POR) for topiramate was 1.44 (95% CI, 0.58-3.58). A statistically significant association with major birth defects was not established.

Norwegian Registry

The Medical Birth Registry of Norway (MBRN) is a compulsory population-based registry which records deliveries in women who are at 12 or more weeks of gestation, with or without epilepsy or AED treatment. Data collection includes use of AED and folate supplementation, maternal health prior to pregnancy, complications during pregnancy, and perinatal outcomes.[1]

Data collected in the MBRN Registry was evaluated by **Veiby et al (2014)**[9] in a study assessing birth defects and fetal growth restriction in children and infants exposed to AEDs. Outcomes were available for 90 infants exposed to topiramate in utero, of which, 48 were exposed to topiramate monotherapy. Twenty five percent of newborns in the topiramate monotherapy exposure group were SGA compared to 9% in the comparison group unexposed to AEDs. The long-term consequences of the SGA findings are not known.[1,9]

Mean birth weight, length, and head circumference were lower in infants exposed to topiramate compared to unexposed infants. Subjects receiving topiramate had a mean lesser weight of 393 grams (95% CI 259-526 grams), mean lesser length of 2.2 cm (95% CI, 1.6-2.9), and a mean lesser head circumference of 1.5 cm (95% CI, 1.1-1.9). Patients exposed to topiramate also had a substantial risk for SGA birth weight (OR, 3.1; 95% CI, 1.9-5.3) and microcephaly (OR, 4.8; 95% CI, 2.5-9.3).[9]

International Registry of Antiepileptic Drugs and Pregnancy – EURAP

EURAP is a consortium of independent research groups organized by a central project commission. The registry began in 1999 in two European countries and has now expanded to over 40 countries. Individual outcomes data for topiramate monotherapy are not presented in the report.[29]

Additional Pregnancy Registry Data

Additional registry citations have been identified in the published literature.[4,5,30-38] Specific reports on topiramate outcomes are limited. AED pregnancy registries that did not include topiramate data were beyond the scope of this communication.

CLINICAL DATA - USE IN LACTATION

Kacirova (2021)[39] reported levels of topiramate found in colostrum, mature maternal milk, and breastfed infants of 27 women treated with topiramate at delivery and/or during breastfeeding from 2004 to 2020. Maternal, umbilical cord, breast milk and infant serum topiramate levels were measured in three subgroups: delivery, colostrum (3-4 days postpartum) and mature milk (7-30 days postpartum).

Topiramate levels ranged from 1.0 to 7.1 mg/L in maternal serum and from 0.8 to 6.2 mg/L in umbilical cord serum. The mean umbilical cord/maternal serum ratio was 0.93±0.11 mg/L confirming transplacental passage of topiramate. There was a significant correlation between umbilical cord serum and maternal serum levels ($P< 0.0001$)

Topiramate concentrations 3-4 days post-delivery ranged from 1.4-8.4 mg/L in maternal serum, 1.5-8.6 mg/L in breast milk, and 0.3-4.4 mg/L in infant serum. Significant correlations were found between milk and maternal serum levels ($P=0.0001$) and infant serum and maternal levels ($P=0.0009$). The mean breast milk/maternal serum ratio was 0.99±0.45 and the infant/maternal serum ratio was 0.25±0.15. The infant/maternal serum ratio was significantly lower than the milk/maternal serum ratio ($P<0.0001$).

At 7-30 days post-delivery, maternal serum levels varied from 1.9 to 9.7 mg/L, milk levels ranged from 2.3 to 10.6 mg/L and infant serum levels ranged from 0.3 to 6.5 mg/L. Paired breast milk and maternal serum levels were not significantly different ($P=0.8712$). The mean milk/maternal serum ratio was 1.07±0.31, and the mean infant/maternal serum ratio was 0.51±0.27. Sixty percent of maternal serum concentrations were in the reference range used for the general epileptic population (5-20 mg/L).[40] One infant serum level (6.5 mg/L) was found to be in the reference range; the remaining were lower (2 were found below the lower limit of quantification).

Ohman (2002)[41] reported on topiramate concentrations in plasma and breast milk in 5 women with epilepsy treated with topiramate during lactation. Blood samples were collected from mothers at delivery, the umbilical cord and newborns at 24, 48 and 72 hours after delivery. Transplacental transfer of topiramate was evident as umbilical cord and maternal plasma levels were similar. At 24 hours, infant topiramate plasma levels were 33-45% lower than levels in the umbilical cord. Topiramate plasma levels and milk/plasma ratios at the time of breastfeeding, 2-3-weeks, 1 month and 3 months after delivery were collected. Three weeks after delivery, the mean milk/maternal plasma ratio was 0.86 (range, 0.67-1.1) before nursing. Topiramate concentrations in milk and maternal plasma levels were similar from 2 to 3 weeks up to 3 months (0.69) after delivery. The concentrations in the breastfed infants were approximately 10-20% of the mothers' plasma levels. The absolute approximate dose to infant was 0.1-0.7 mg/kg/day assuming a daily milk intake of 150 mL/day/kg.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 23 July 2024. Additional relevant citations identified in the published literature are provided here for your reference.[42-53]

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