

Where there's smoke, is there fire?

Daniel W. Bowles, MD. University of Colorado
Targeted Therapies in Lung Cancer
Patient Forum

for ALK, ROS1, & EGFR Lung Cancers - August 20, 2016



What have you heard?



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Objectives

- Examine some cannabinoid biology
- Learn about marijuana and cancer risks
- Investigate cannabinoids and cancer care



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What is cannabis (marijuana)?

- Cannabis refers to the dried flower tops of the cannabis plant.
- Indica, Sativa, and Ruderalis
- Cannabis contains over 600 chemicals, about 80 of which are considered cannabinoids.
- Others are terpenoids and non psychoactive chemicals related to plant growth.



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Main chemical components

- The rock star: THC
- The silent hero: CBD
- The goofy side kicks: CBN, CBG, THCV, THCA, CBDA
- Back up dancers: Terpenoids

SPECIAL REPORT



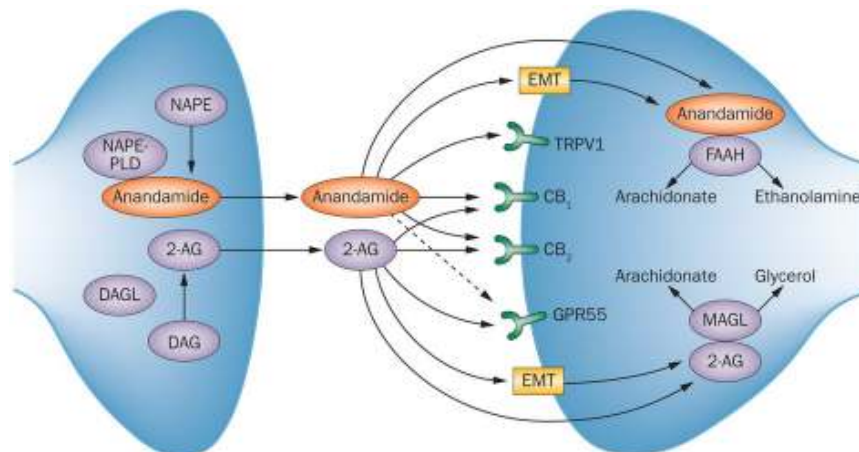
CBD in Colorado: Pushing ahead while seeking a marijuana miracle

www.denverpost.com accessed 12/14/14

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Endocannabinoid system



Reprinted with permission. Nat Rev Gastroenterol Hepatol. 2014;11(3):142-3

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Marijuana's physiologic effects

Marijuana's Effects on the Brain

- HYPOTHALAMUS:** Controls hunger, thirst, body temperature, and sexual behavior.
- HYPOPHYSEAL GLANDS:** Regulate the release of hormones that control the function of other glands.
- ENTORHINAL CORTEX:** Involved in learning and memory.
- AMYGDALA:** Responsible for emotion, aggression, and fear.
- STRIATUM AND SUBSTANTIA NIGRA:** Regulate movement, posture, and the dopamine system.
- CEREBELLUM:** Controls the movement and balance of the body.
- NEOCORTEX:** Involved in higher-level thinking and planning.
- VENTRAL STRIATUM:** Involved in the reward system and learning of new behaviors.

© Mark Chen, 2008. Adapted from Scientific American

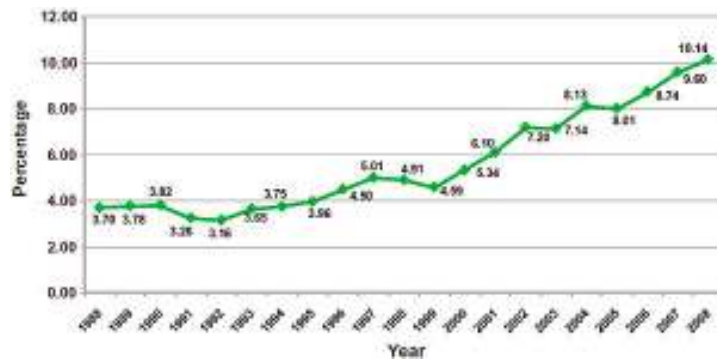
When marijuana is smoked, its active ingredient, THC, travels throughout the body, including the brain, to produce its many effects. THC attaches to sites called cannabinoid receptors on nerve cells in the brain, affecting the way those cells work. Cannabinoid receptors are abundant in parts of the brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgment, and pleasure.

Body effects of Cannabis

- Eyes:**
 - Reddening
 - Decreased intra-ocular pressure
- Mouth:**
 - Dryness
- Skin:**
 - Sensation of heat or cold
- Heart:**
 - Increased heart rate
- Muscles:**
 - Relaxation

www.drugabuse.gov/publications/marijuana-abuse/how-does-marijuana-produce-its-effects
 Accessed March 3, 2014

THC concentration is increasing



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www.drugprevent.org.uk

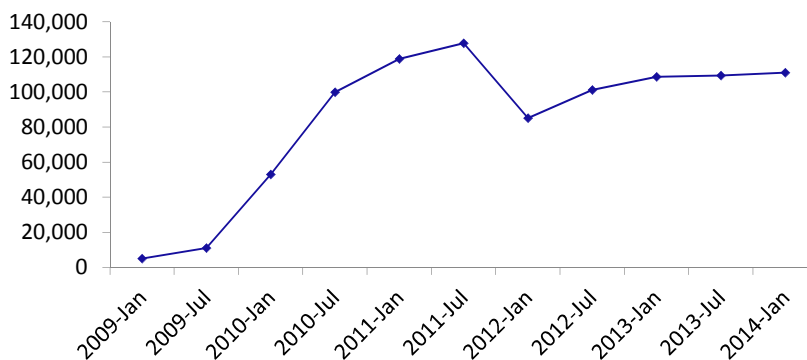
Routes of administration



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Colorado Medical Marijuana Registry

Active Patients
2009-2014



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Colorado Reported Conditions

Condition	Number	Percent*
Severe Pain	103,825	94%
Muscle Spasms	14,714	13%
Severe Nausea	11,023	10%
Cancer	3,079	3%
Seizures	2,098	2%
Cachexia	1,165	1%
Glaucoma	1,113	1%
HIV/AIDS	657	1%

*Does not add to 100% as some patients report more than one condition
MMWR Monthly Report – December 31, 2013



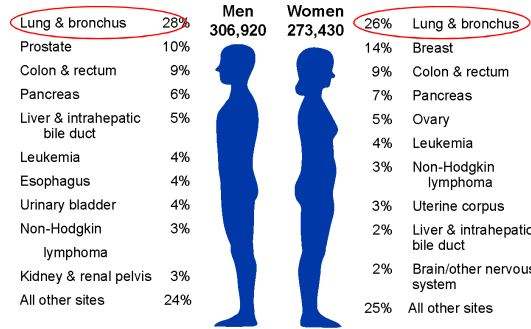
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How are cannabis and cancer related?

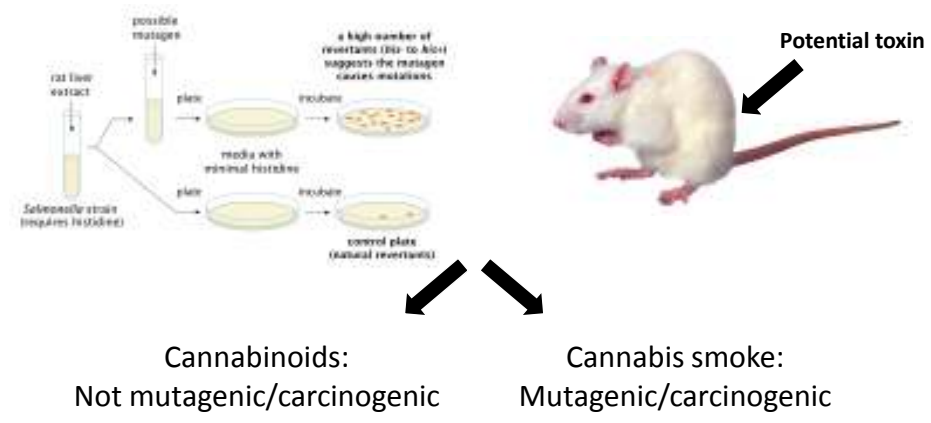


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Cannabis and cancer

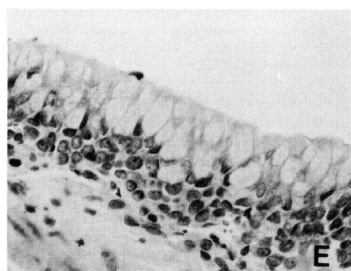
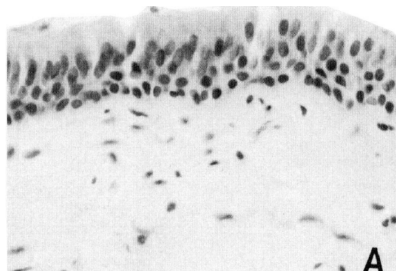


Separate the weed from the chaff



Cannabis Smoke

- Similar carcinogens to tobacco smoke
- Increased tar compared to tobacco smoke
- Causes pre-cancerous changes to respiratory mucosa



Fligel et al. Chest 1997.
Maertens et al. Chem Res Toxicol 2009.

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Lung Ca: Swedish Military Study

- Longitudinal study of 49,321 men
- Conscripted 1969-1970
- Assessed for baseline health factors
- Followed until 2009



Callaghan et al. Cancer Causes Control 2013.
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Risk adjusted for tobacco smoking

Cannabis smoking	Crude HR (95% CI)	Tobacco-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Never (reference)	1	1	1
Ever	1.9 (1.3-2.75)	1.25 (0.85-1.83)	1.25 (0.84-1.87)
Once	2.07 (1.06-4.06)	1.48 (0.75-2.91)	1.52 (0.77-3.01)
2-4 times	0.95 (0.39-2.33)	0.65 (0.26-1.58)	0.66 (0.27-1.62)
5-10 times	1.02 (0.32-3.20)	0.66 (0.21-20.9)	0.68 (0.21-2.16)
11-50 times	2.69 (1.26-5.74)	1.68 (0.78-3.62)	1.69 (0.77-3.66)
More than 50 times	3.72 (1.96-7.06)	2.24 (1.17-4.29)	2.12 (1.08-4.14)
1-10 cigs/day	2.29 (1.48-3.57)		
>10 cigs/day	5.16 (3.45-7.73)		

Callaghan et al. Cancer Causes Control 2013.

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Other lung studies

Study	Findings	Limitations
Hashibe (2006)	OR 0.62 (NS)	Young age pts, unmeasured confounders
Mehra (2006)	NS	Systematic review
Berthiller (2008)	OR 2.4	Inconsistent tobacco reporting
Aldington (2008)	RR 5.7 in highest uses adjusted for tobacco	Limited cases (79)

Hashibe M et al. Cancer Epi Biomark Prev. 2006. Mehra et al. Arch Int. Med. 2006
Berthiller J et al. J Thoracic Oncol 2008. Aldington et al. Eur Respir J 2008.

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Meta-analysis: lung cancer

- Multi-site: US, Canada, UK, New Zealand
- Matched controls (2985)/cases (2159)
- No association between marijuana and cancer
 - Habitual vs. occ/never: OR 0.96
 - >10 joint years vs non-habitual/never: OR 0.88



Int J Cancer. 2015;136:894-903
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Head and Neck Cancer

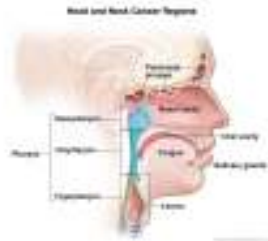
- Major risk factors
 - Tobacco
 - Alcohol
 - Human papillomavirus (HPV) infection
- Previous studies have been mixed



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INHANCE Consortium

- Over 2000 patients and 7800 controls
- Multiple sites in US and Latin America
- Mixed prospective and case-control



Marks MA et al. Cancer Epi Biomark Prev 2013.
www.cancer.gov

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HNSCC Risk and Marijuana Use

- Risk varies with location
 - Increased in oropharynx cancer (24%)
 - Decreased in oral tongue (53%)
- Dose dependent
- Oropharynx results may be confounded by HPV status



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 Marks MA et al. Cancer Epi Biomark Prev 2013

Does it do *anything* helpful?



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Pain



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Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review

Fiona A Campbell, Martin R Tramèr, Dawn Carroll, D John M Reynolds, R Andrew Moore, Henry J McQuay

- Five single-dose trials in cancer patients (9 total studies)
- Cross-over designs, single dose studies
- Cannabinoids as effective as codeine 50-120 mg
- Adverse events were common
- Problems: does not address smoked products, chronic use, adjunctive use

BMJ 2001; 323: 1-6



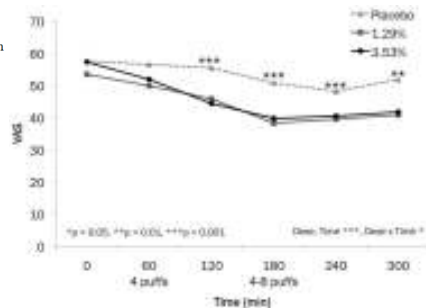
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Cannabis for neuropathic pain

Pairwise comparisons of the effects of four potencies of smoked cannabis on average daily pain

Potency, % of THC	Potency, % of THC, mean difference (95% CI)			
	0	2.5	6.0	9.4
0	-	-	-	-
2.5	-0.13 (-0.83 to 0.56)	-	-	-
6.0	-0.09 (-0.78 to 0.60)	0.04 (-0.64 to 0.73)	-	-
9.4	-0.71 (-1.40 to -0.02)	-0.58 (-1.27 to 0.11)	-0.63 (-1.30 to 0.06)	-

Note: CI = confidence interval, THC = tetrahydrocannabinol.



CMAJ. 2010; 182: E694-E701
J Pain. 2013; 14: 136-148.



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Placebo controlled pain trials

Patients	Route	THC%	Better than placebo?
HIV neuropathy	Smoked	3.56	Yes
Neuropathic	Smoked	2.5-9.4	Yes
Neuropathic	Vaporized	1.29-3.53	Yes
Multiple sclerosis muscle stiffness	Cannabis extract	--	Yes
MS pain	Smoked	4	Yes



Neurology 2007; 68:515-21. CMAJ. 2010; 182: E694-E701. J Pain. 2013; 14: 136-148. J
Neurol Neurosurg Psychiatry. 2012;83:1125-32. CMAJ 2012; 184: 1143-1150. Patient Forum

Nausea & Vomiting



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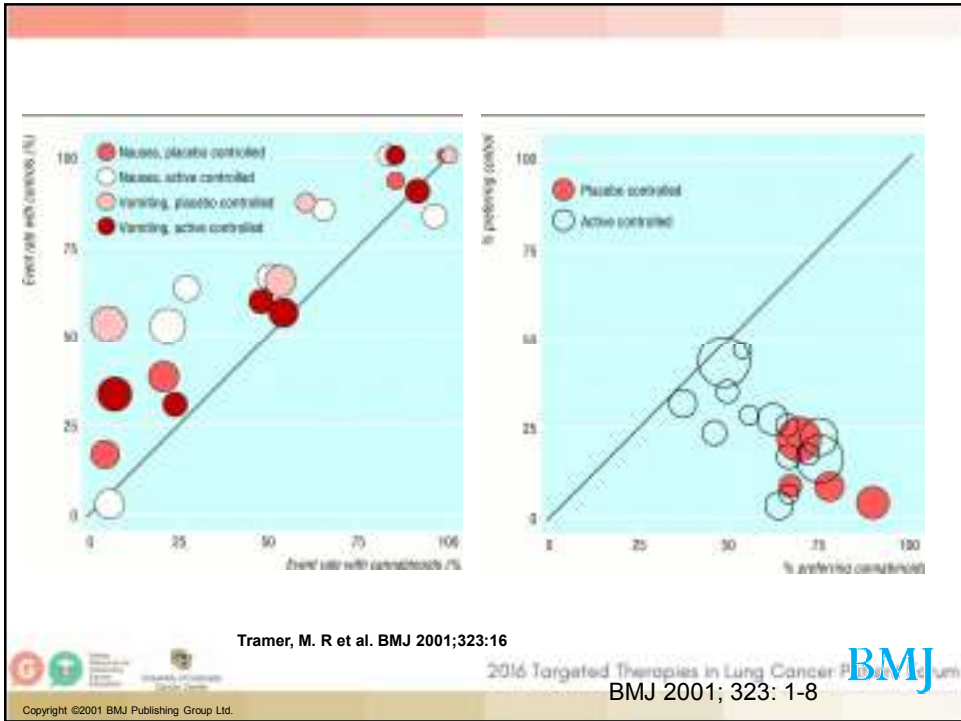
Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review

Martin R Tramer, Dawn Carroll, Fiona A Campbell, D John M Reynolds, R Andrew Moore, Henry J McQuay

- 198 reports whittled to 30 evaluable trials
- Efficacy data on 1366 patients
- Average trial size was 46 patients
- 83% of trials used a cross over design
- Nabilone (16), dronabinol (13), levonantradol (1)
- All evaluated acute CINV

BMJ 2001; 323: 1-8

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Cannabis extract for N/V

Proportion of patients reaching secondary or exploratory end points

	CBM <i>n</i> = 7	Placebo <i>n</i> = 9	Difference (%) (95% CI)
No delayed emesis	5 (71.4%)	2 (22.2%)	49.2 (1.0, 75.0)
No delayed nausea [*]	4 (57.1%)	2 (22.2%)	34.9 (-10.8, 66.3)
No significant delayed nausea [†]	5 (71.4%)	4 (44.4%)	27.0 (-18.0, 59.7)
Not valued	1 [‡] (14.3%)	–	

Br J Clin Pharmacol. 2010;70:656-63

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Herbal cannabis for non-chemo N/V



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Cannabinoid hyperemesis

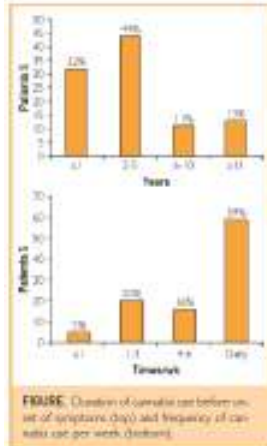


TABLE 3. Clinical Manifestations of Cannabinoid Hyperemesis in 88 Patients

Symptom	No. (%) of patients
Nausea	88 (100)
Vomiting	88 (100)
Time of symptoms (n=75)	
Morning	32 (43)
Progressive	14 (19)
During awakening	4 (5)
Midnight pain	23 (31)
Location of pain (n=75)	
Epigastric	46 (61)
Peri-umbilical	17 (23)
Distal	4 (5)
Other	8 (11)
Description of pain (n=66)	
Burning	15 (23)
Cramping	14 (21)
Sharp	11 (17)
Other	10 (15)
Gastrointestinal (n=81)	
Diarrhea	23 (28)
Constipation	7 (9)
Bleeding	3 (4)
Nausea	44 (54)
Pain with hot showers (n=57)	
Yes	32 (56)
No	25 (44)

Mayo Clin Proc. 2012;87:114-9.

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Does is cure cancer?

CURE YOUR OWN CANCER HIGH TIMES

PAX
THE WORLD'S BEST VAPORIZER

FEDERAL GOVERNMENT UNWITTINGLY ADMITS CANNABIS KILLS CANCER

CANNABIS OIL TREATMENT
This treatment method is experimental and used by cancer patients. Most are able to finish the entire treatment in 90 days.

WEEK 1
Start with 3 doses daily, about half the size of a short grain of rice.

WEEKS 2 - 5
At week 2 you will double your intake every 4 days.

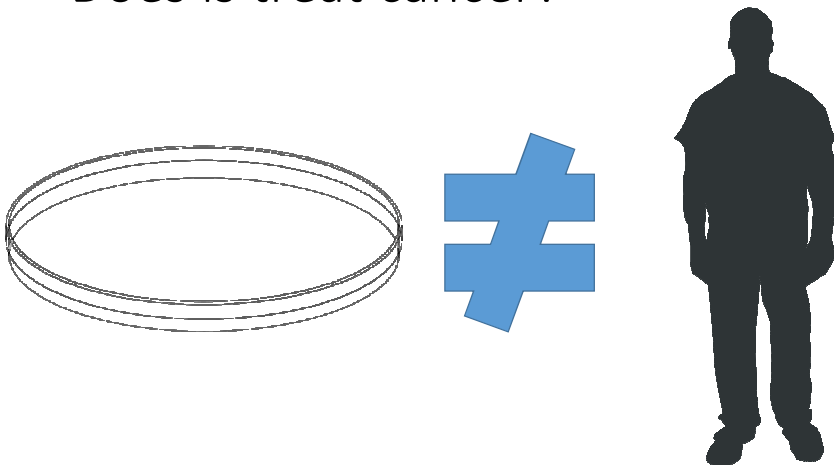
WEEKS 5 - 12
You should now be able to consume 1 gram per day. Ingest 1 gram / day until your 60 gram supply is gone.

THE GOAL
Consume 60 grams of Cannabis oil in 90 days.

Medical Science

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Does it treat cancer?



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The Colorado Perspective

- Lots of dispensaries: 497 medical, 292 retail
- Edibles present a particular challenge
- Possibly increased health care burden
 - Estimated 1-2% of U. Colorado Hosp ER visits
 - Marijuana-related burns
 - Increased marijuana N/V (prev. ratio 1.92)
 - Accidental ingestions among children

Moshe, Zane, Heard. JAMA 2014
JAMA Pediatr. 2013;167:630-633

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Why don't we know more?



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What to take home...

- Cannabis and cancer is a complicated subject
- A lot of the risks/benefits are not known
- Keep it away from children



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