# CANCER CACHEXIA & MEGESTROL ACETATE

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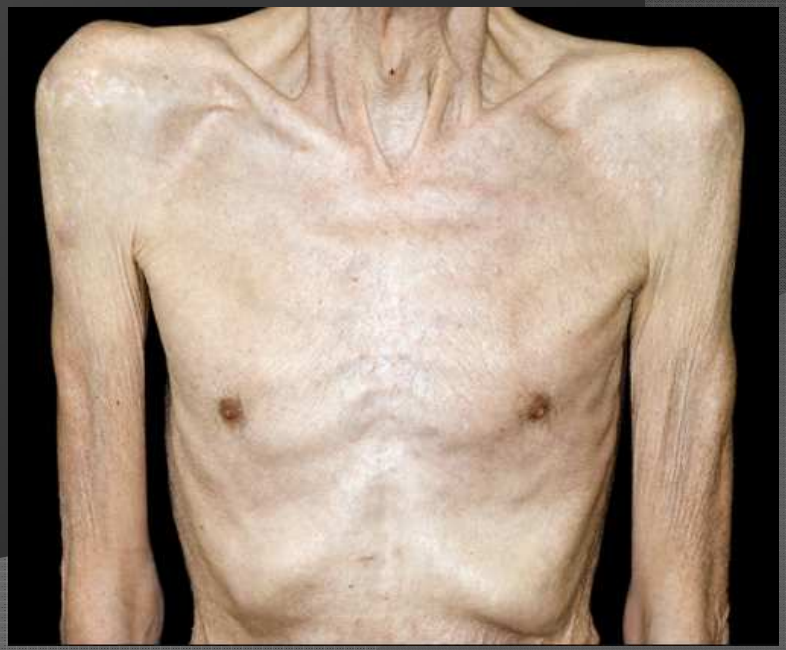
Date: 2019/9/7



# Outline

- Cancer Cachexia
  - Introduction
  - Pathophysiology
  - Clinical Management
- Megestrol acetate

# CANCER CACHEXIA: INTRODUCTION

# Proportion of Cancer Patients with Cachexia by Cancer Type

| Cancer type | Cancer patients with cachexia ICD-9 code only | Cancer patients with any cachexia ICD-9 code | Cancer patients taking prescription medication indicative of cachexia | Cancer patients with ≥5% weight loss | Cancer patients with any one of the cachexia definitions |
|---|---|---|---|---|---|
| Breast, $n = 2112$ | 0.8% | 3.1% | 5.3% | 18.6% | 24.8% |
| Colorectal, $n = 905$ | 2.5% | 6.1% | 6.2% | 16.4% | 25.5% |
| Esophagus, $n = 117$ | 12.8% | 20.5% | 13.7% | 16.2% | 41.9% |
| Gastric, $n = 142$ | 8.4% | 15.5% | 19.0% | 19.7% | 41.5% |
| Head/neck, $n = 246$ | 6.1% | 17.1% | 6.1% | 19.9% | 37.0% |
| Liver, $n = 153$ | 3.3% | 6.5% | 3.9% | 17.0% | 24.2% |
| Lung, $n = 1291$ | 6.4% | 9.7% | 14.2% | 15.2% | 31.1% |
| Pancreas, $n = 221$ | 3.6% | 7.2% | 19.5% | 12.7% | 34.8% |
| Prostate, $n = 3354$ | 0.8% | 3.2% | 2.6% | 11.0% | 15.1% |

**Upper GI cancer, HNN, lung cancer為主!**

*Fox KM et al. J Oncol Online 2009 Jul 1*

# Body Composition in Cancer Cachexia

TABLE 1. *Comparison of body composition of cachectic cancer patients with normal controls*

| Parameter | Normal, kg | Cachectic, kg |
|---|---|---|
| Total body weight | 65.6 | 44.9 ↓ |
| Total fat | 17.3 | 3.1 ↓ |
| Muscle protein | 2.8 | 0.7 ↓ |
| Nonmuscle protein | 8.3 | 8.1 |
| Intracellular water | 19.1 | 12.9 |
| Extracellular water | 15.1 | 17.5 |
| Minerals | 3.0 | 2.6 |

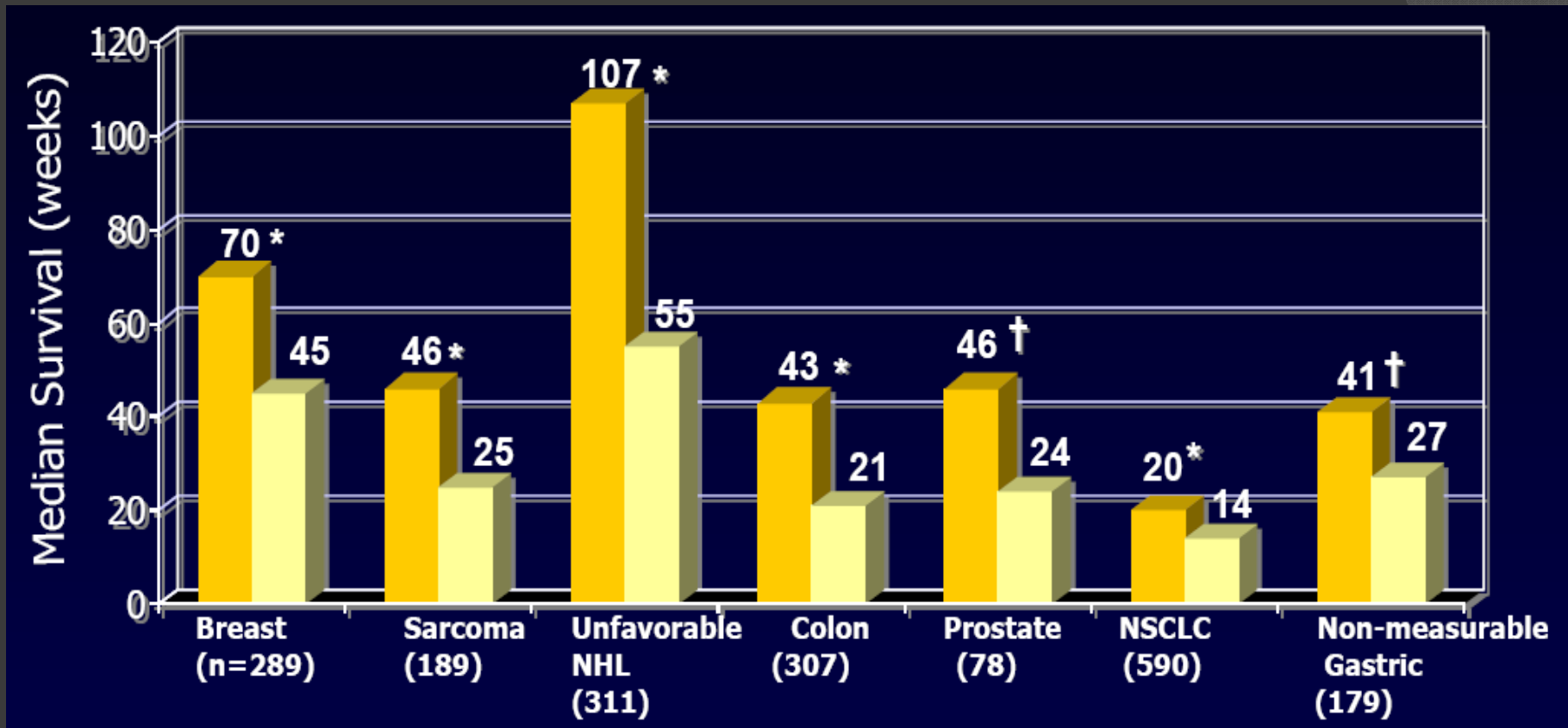
*Cohn SH et al. Metabolism 1981;30-222-9*

# 體重減輕增加死亡的危險性

**20% 的病患**
**是死於營養不良**
**而不是本身腫瘤疾病**

*De Wys et al: Am J Med 1980.*
*Andreyev et al: Eur J Cancer 1998*
*Kondrup, AJCN 2002*

# Impact of BWL and Survival




All patients were beyond the scope of curative surgery or radiation therapy.
Adapted from DeWys WD et al. *Am J Med* 1980;69:491-497.

# Consequences of Sarcopenia

Sarcopenia (severe muscle wasting) predicts key health outcomes

| | |
|---|---|
| **Survival** | • Prado et al. *Lancet Oncol*. 2008;9:629-3<br>• Prado et al. Int J Body Comp Research. 2010 8(1):7-15 |
| **Toxicity** | • Prado et al:<br>  • *Clin Cancer Res*. 2007; 13:3264<br>  • Clin Cancer Res 2009:15:2920<br>  • Cancer Chem Pharmacol. 2011: 67:93<br>• Antoun et al. Ann Oncol. 2010;21:1594 |
| **Time to Tumor Progression** | • Prado et al. Clin Cancer Res 2009:15:2920 |

And physical disability, infections, complications during hospitalization, length of hospital stay……

# Definition

- Historically, defined by involuntary weight loss of > 10% premorbid body weight
- Cachexia consensus conference (2007)
  - "Complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass"
  - Common findings: anorexia, inflammation, insulin resistance, increased muscle protein breakdown

*Davis MP, et al. Support Care Cancer. 2000*
*Evens WJ et al. Clin Nutr 2008;27:793-9*

# New Definition

## Definition and classification of cancer cachexia: an international consensus

*Kenneth Fearon*, Florian Strasser*, Stefan D Anker, Ingvar Bosaeus, Eduardo Bruera, Robin L Fainsinger, Aminah Jatoi, Charles Loprinzi, Neil MacDonald, Giovanni Mantovani, Mellar Davis, Maurizio Muscaritoli, Faith Ottery, Lukas Radbruch, Paula Ravasco, Declan Walsh, Andrew Wilcock, Stein Kaasa, Vickie E Baracos*

- **weight loss ≥ 5% over past 6 months (in absence of simple starvation)**
- **weight loss ≥ 2% in BMI <20 kg/m2**
- **weight loss ≥ 2% in skeletal muscle mass (sarcopenia)**

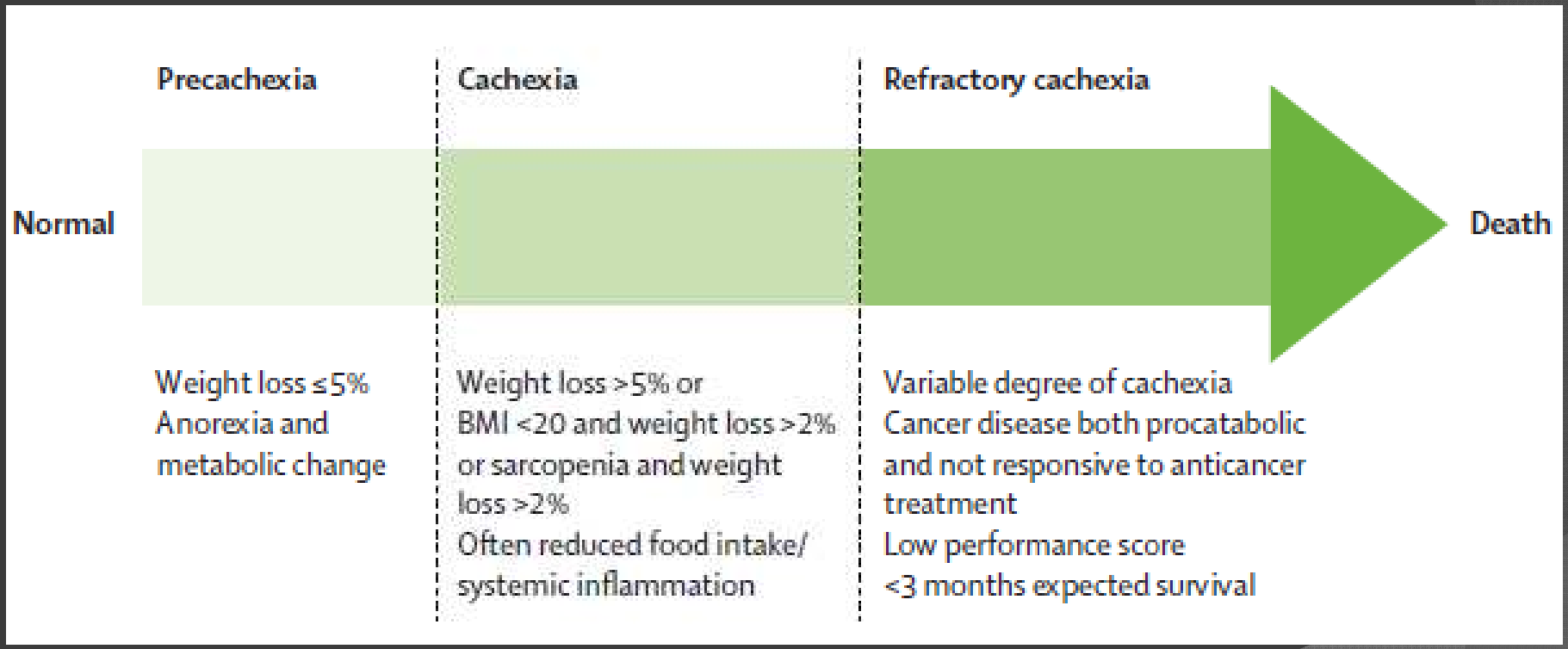
*Fearon K et al. Lancet Oncol 2011;12:489-95*

# Cachexia vs Starvation

| | Cachexia | Starvation |
|---|---|---|
| Body Weight | – / ↓ | ↓ |
| Body Cell Mass (Lean Body Mass) | ↓↓↓ | ↓ |
| Body Fat | ↓↓ | ↓↓↓ |
| Caloric Intake | ↓↓↓ | ↓↓↓ |
| Total Energy Expenditure (TEE) | – | ↓↓ |
| Resting EE (REE) | ↑↑ | ↓↓↓ |
| Protein Synthesis | ↓ | ↓↓↓ |
| Protein Degradation | ↑↑↑ | ↓↓↓ |
| Proteolysis-Inducing Factor (PIF) | YES | NO |

*Kotler DP. Ann Intern Med 2000*

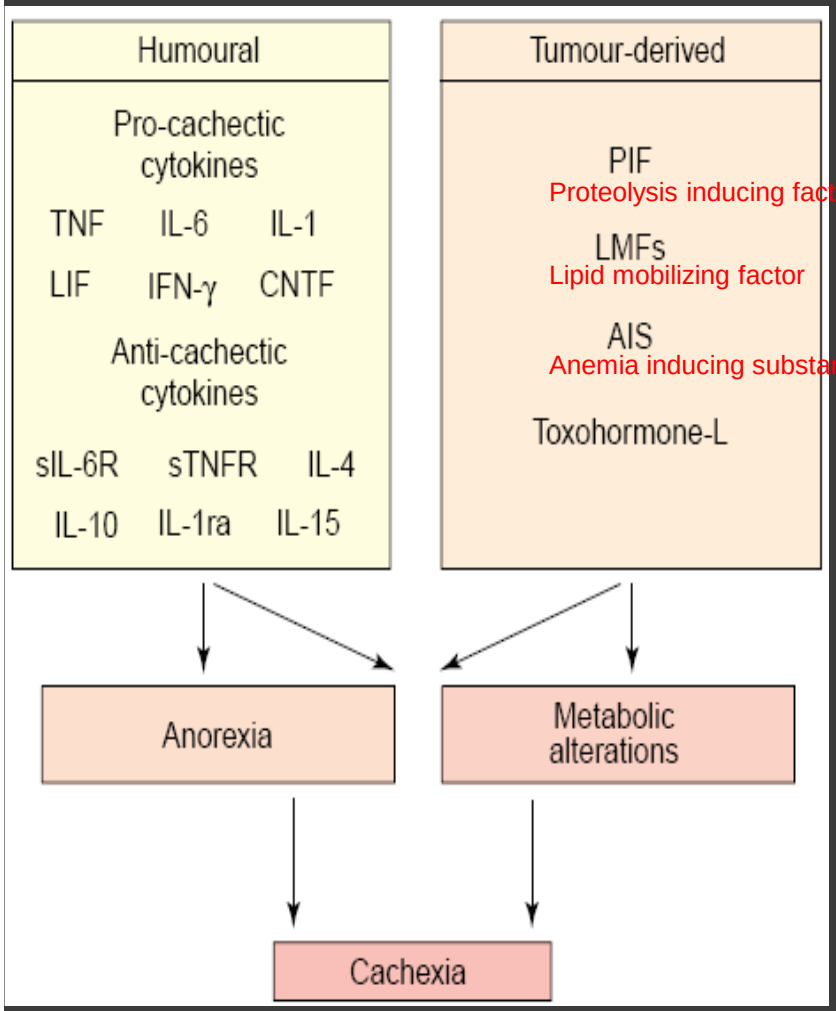
# Stages of Cancer Cachexia

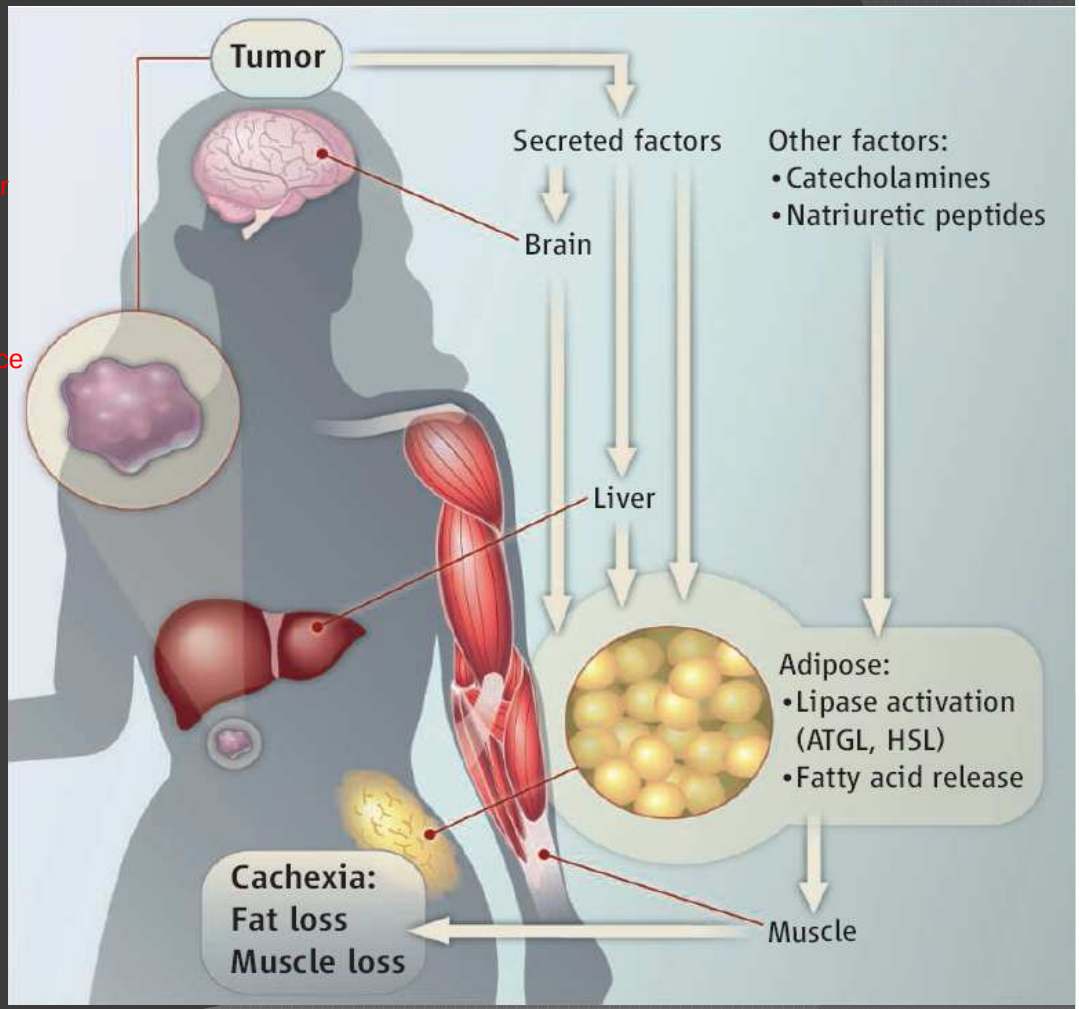



*Fearon K et al. Lancet Oncol 2011;12:489-95*

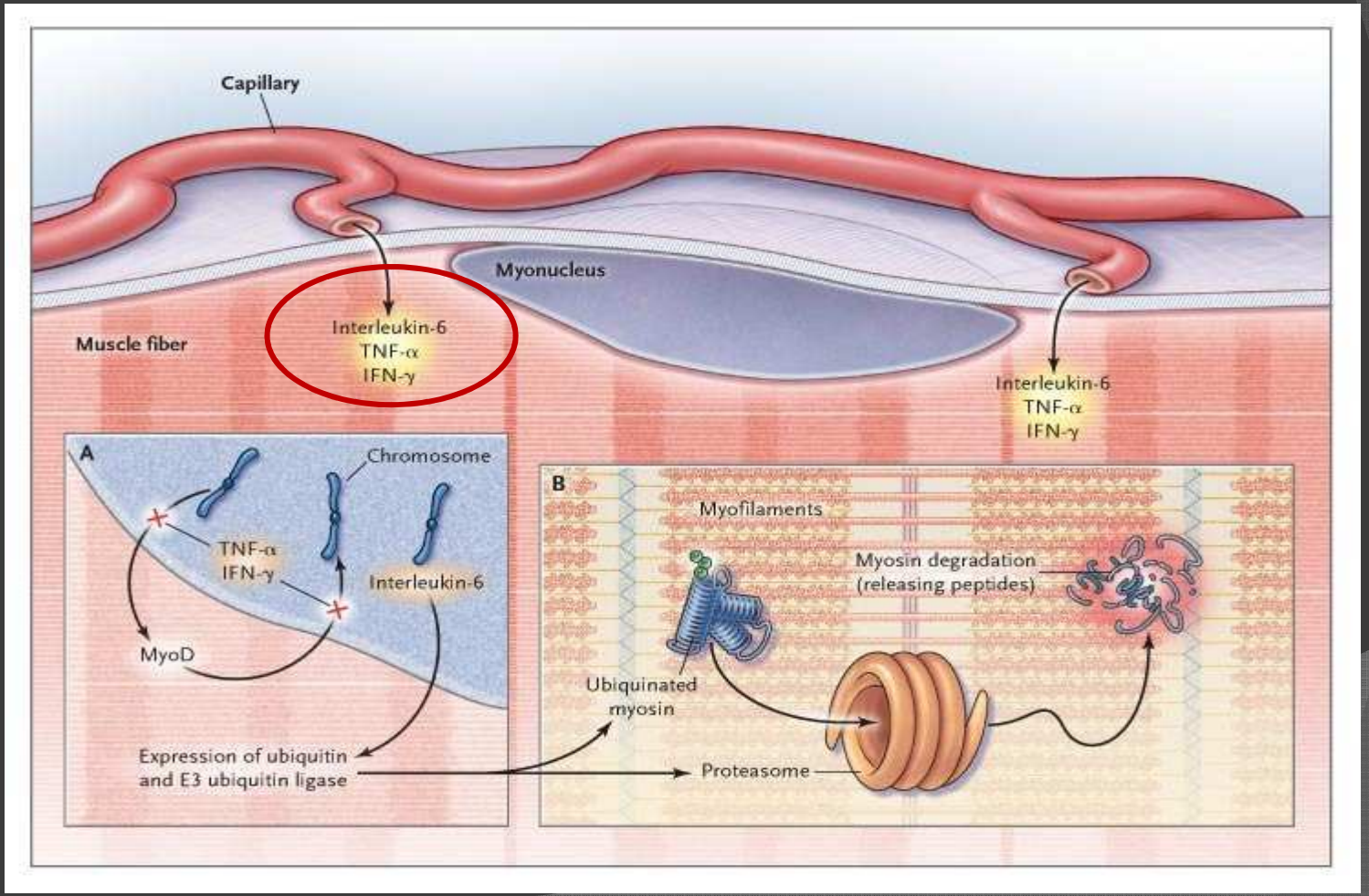
# PATHOPHYSIOLOGY

# Mechanism of Cachexia

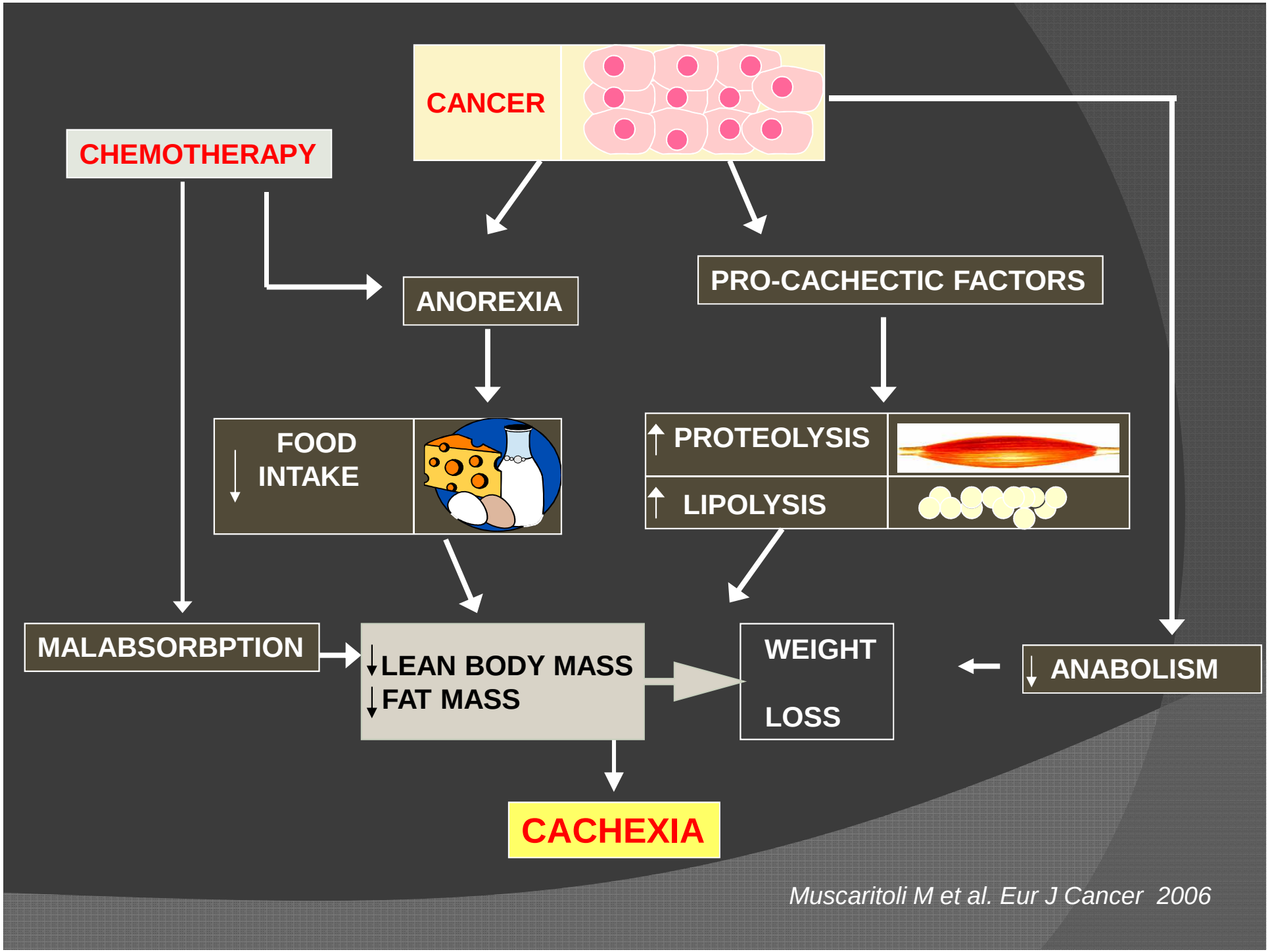


# Cytokines Mediated Myosin Degradation Proteasome-mediated Pathway




*Jeffrey S. Chamberlain. NEJM 2004*




*Muscaritoli M et al. Eur J Cancer 2006*

# MANAGEMENT OF CANCER CACHEXIA

Majorly treat underlying illness…

# Clinical Management of Cachexia

- Appetite stimulants
  - Corticosteroids
  - Progesterone analogs
  - Cannabinoids
- Cytokine inhibitors
  - EPA (fish oil)
  - Thalidomide
- Anabolic Agents
  - Androgens
  - Growth hormones
- Miscellaneous
  - Insulin
  - Melatonin
  - Mirtazapine
  - Serotonin antagonists
  - Metoclopramide
  - Amino acid supplements
  - Combination therapy

# MEGESTROL ACETATE

# History

- Megestrol Acetate was synthesized for the first time in 1963

1963 Contraceptive in England

1967 Breast cancer and Endometrial cancer

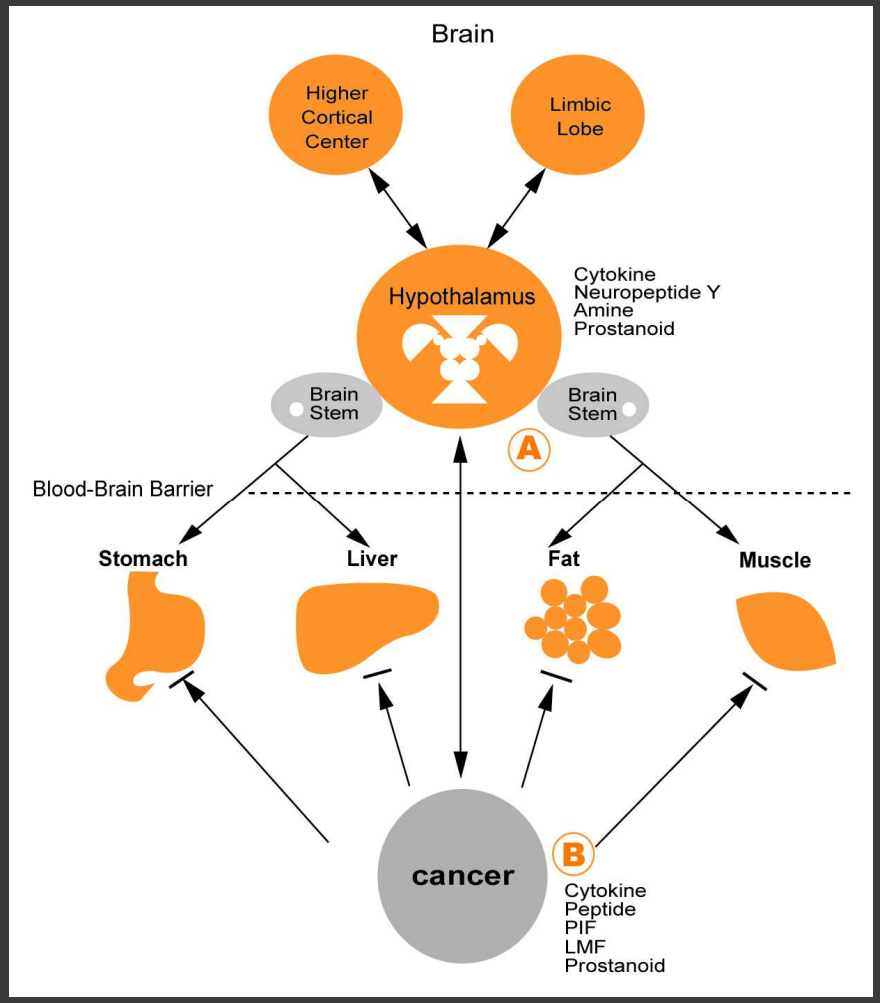
1993 Orexigenic effect

MA was approved by **FDA**

Indication: anorexia, cachexia, or weight loss due to unknown cause in **AIDS** patients

Now Majority of **European** countries and **Taiwan** has approved the MA in AIDS and cancer patients

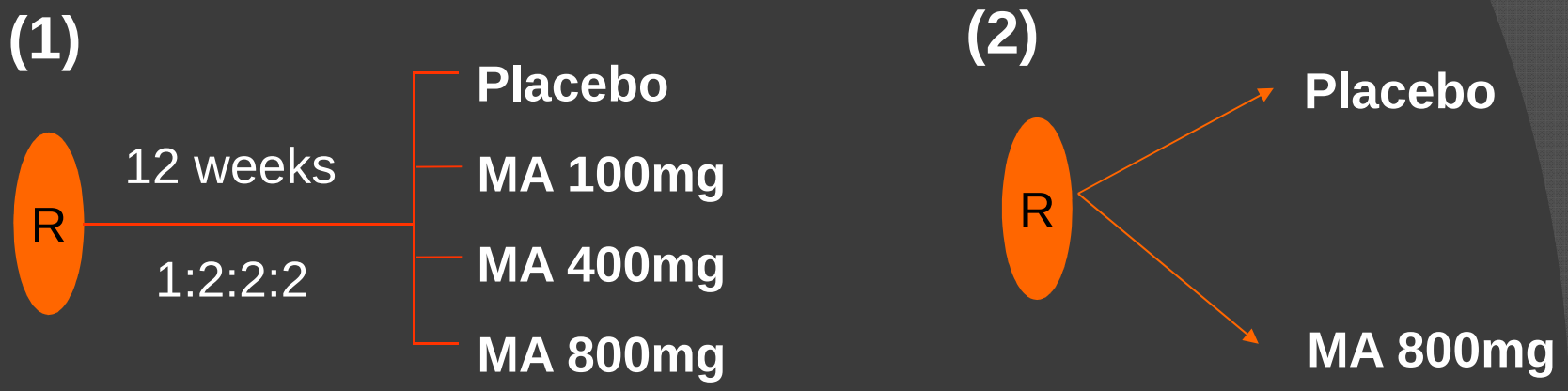
# Pharmacology




- It is related to glucocorticoid activity and similar to corticosteroids.
- It may stimulate appetite via Neuropeptide Y in CNS
- It may down-regulating the synthesis and release of pro-inflammatory cytokine, eg: TNF-a, IL-1, IL-6…

*CA Cancer J Clin 2002; 52:72-91*

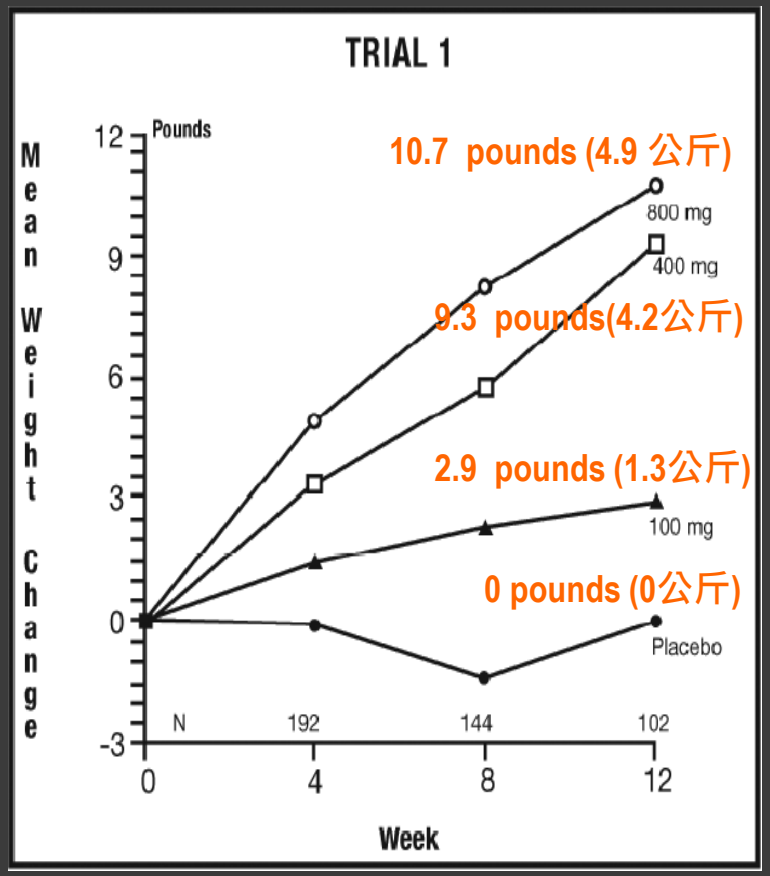
# Study for Optimal Dosage of MA (in AIDS-related Cachexia)

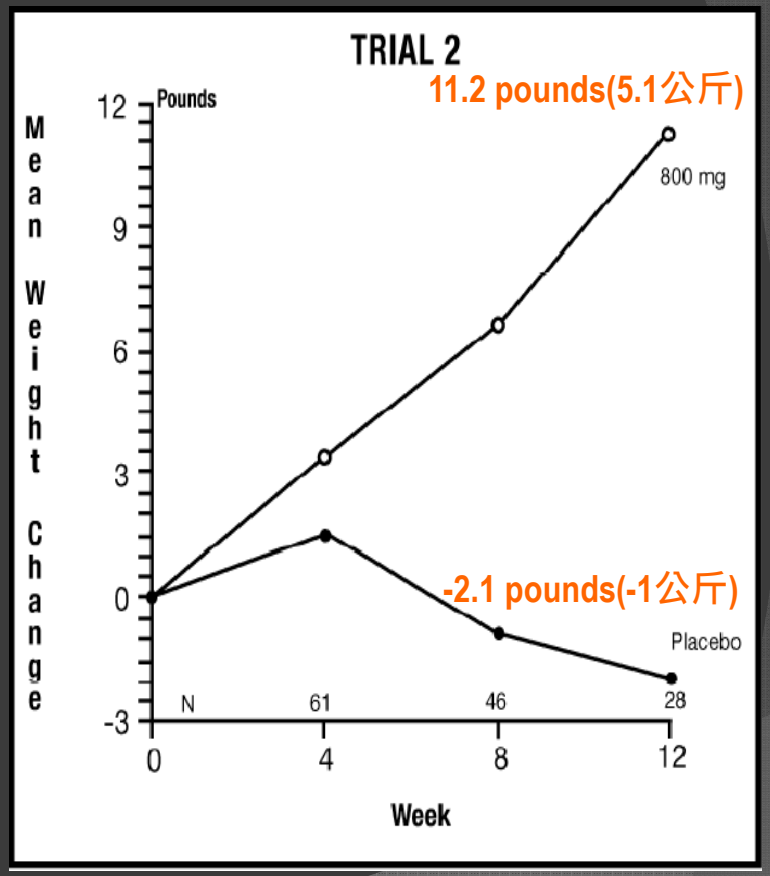



- Randomized, double-blind, placebo-control trial
- **Endpoints :**
  - Primary : weight gain
  - Secondary : the changes in weight and body composition, caloric intake, sense of well-being, toxic effects and appetite.

*Annuals of Internal Medicine 1994; Volume 121, Number 6*
*Oncology 1994 ; 51 (suppl I):19-24*

# Weight Gain (1EP) under MA use




*Prod Info Megace® Oral Suspension 2007 PDR@*
*Oncology 1994 ; 51 (suppl I):19-24*

# Change in Appetite (2EP)

| Treatment group | Patients with improved appetite at time of maximum weight change, % |
|---|---|
| Four-arm trial | |
| Placebo | 50 |
| Megace 100 mg | 70.5 |
| 400 mg | 71.7 |
| 800 mg | 92.5** |
| Two-arm trial | |
| Placebo | 48.3 |
| Megace 800 mg | 69.5* |

*Oncology 1994 ; 51 (suppl I):19-24*

# Safety (2EP)

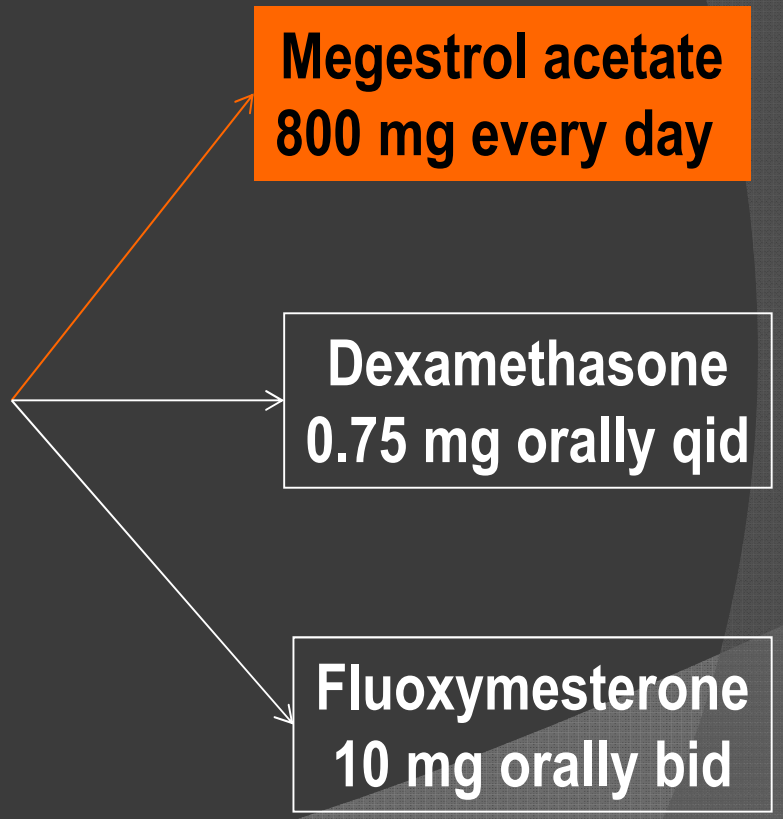
| Adverse experience | Experiences, n | | | |
|---|---|---|---|---|
| | placebo | megestrol acetate, mg | | |
| | | 100 | 400 | 800 |
| | (n=86) | (n=82) | (n=75) | (n=127) |
| Deep-vein thrombosis | 0 | 0 | 1(1.2) | 0 |
| Edema | 7(8.2) | 4(4.9) | 9(12.0) | 2(1.5) |
| Impotence | 1(1.2) | 3(3.7) | 4(5.3) | 11(8.7) |
| Rash | 4(4.7) | 6(7.3) | 3(4.0) | 9(7.1) |

Values in parentheses are percentages

*Oncology 1994 ; 51 (suppl I):19-24*

# Randomized Comparison of Megestrol Acetate Versus Dexamethasone Versus Fluoxymesterone for the Treatment of CAC

- Adult patients with incurable advanced cancer
- losing at least 5 pounds within the previous 2 months
- estimated daily caloric intake of less than 20 cal/kg




*J Clin Oncol 1999 Oct;17(10):3299-306.*

# Megestrol Acetate Increase Appetite

| Question | Megestrol Acetate (% of patients, n = 158) | Dexamethasone (% of patients, n = 159) | Fluoxymesterone % of patients, n = 158) | P | |
|---|---|---|---|---|---|
| | | | | M v D | M v F |
| Compare appetite to before present illness | | | | .4 | .05 |
| Missing responses, no. of patients | 79 | 68 | 70 | | |
| Worse | 5 | 9 | 13 | | |
| Same | 22 | 30 | 27 | | |
| Better | 73 | 61 | 60 | | |
| Food intake compared to before present illness | | | | .4 | .03 |
| Missing responses, no. of patients | 79 | 67 | 71 | | |
| Worse | 7 | 6 | 14 | | |
| Same | 22 | 30 | 30 | | |
| Better | 71 | 64 | 56 | | |

*J Clin Oncol 1999 Oct;17(10):3299-306.*

# Weight Gain Data

| | Megestrol Acetate (n = 114) | Dexameth-asone (n = 120) | Fluoxymes-terone (n = 114) | P | |
|---|---|---|---|---|---|
| | | | | M v D | M v F |
| MD-determined maximal weight gain of ≥ 10% from baseline, % of patients | 10 | 7 | 4 | .42 | .08 |
| MD-determined maximal weight gain, kg | | | | .55 | .68 |
| median | 0.46 | 0.15 | 0.39 | | |
| mean | 2.50 | 2.01 | 1.77 | | |

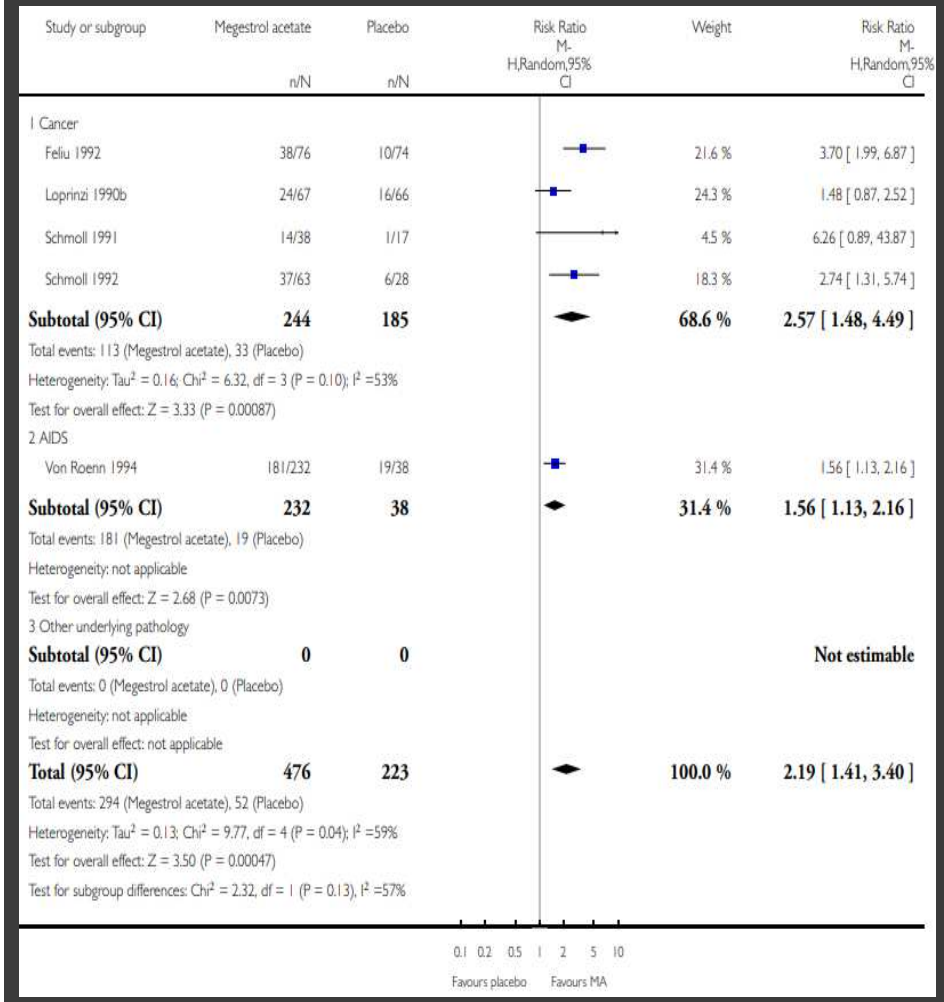
Abbreviations: M, megestrol acetate; D, dexamethasone; F, fluoxymesterone; MD, physician.

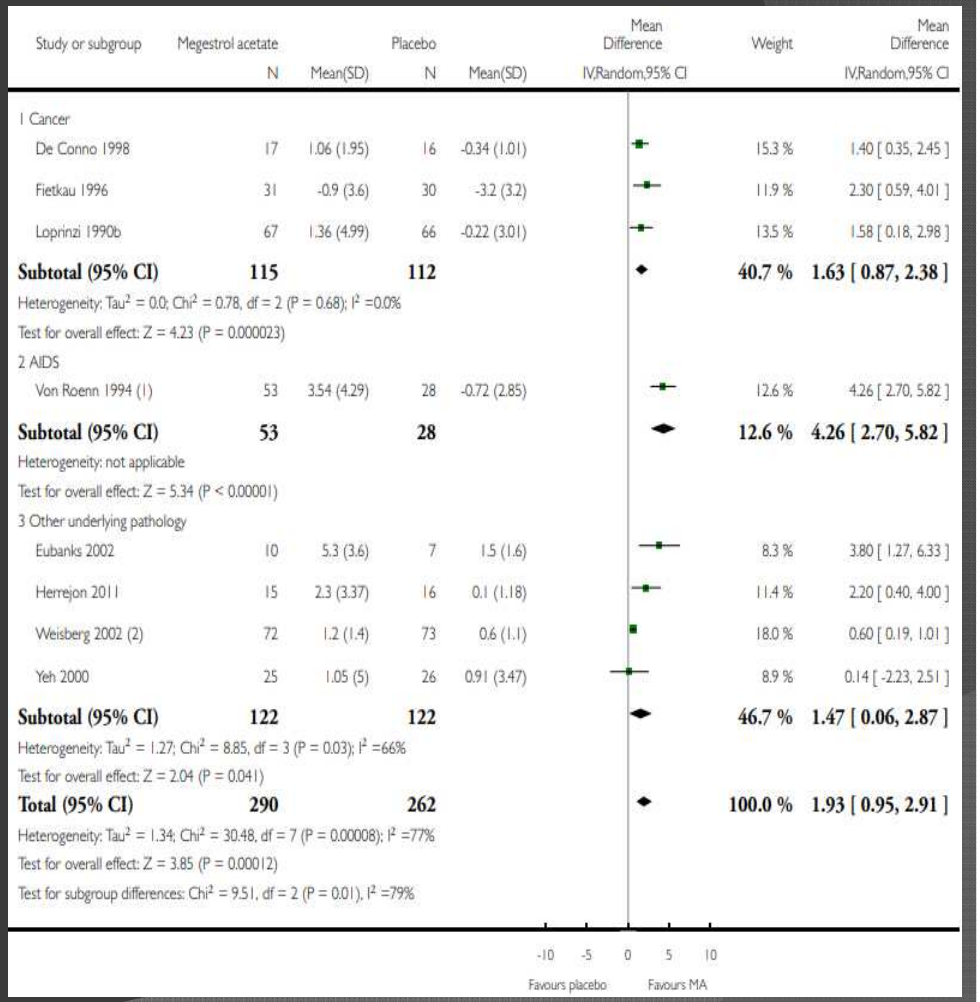
- A trend for increased non-fluid weight gains for the megestrol acetate arm compared with both fluoxymesterone and dexamethasone.

*J Clin Oncol 1999 Oct;17(10):3299-306.*

# Meta-analysis:

## MA Improved Appetite and BW gain (vs Placebo)

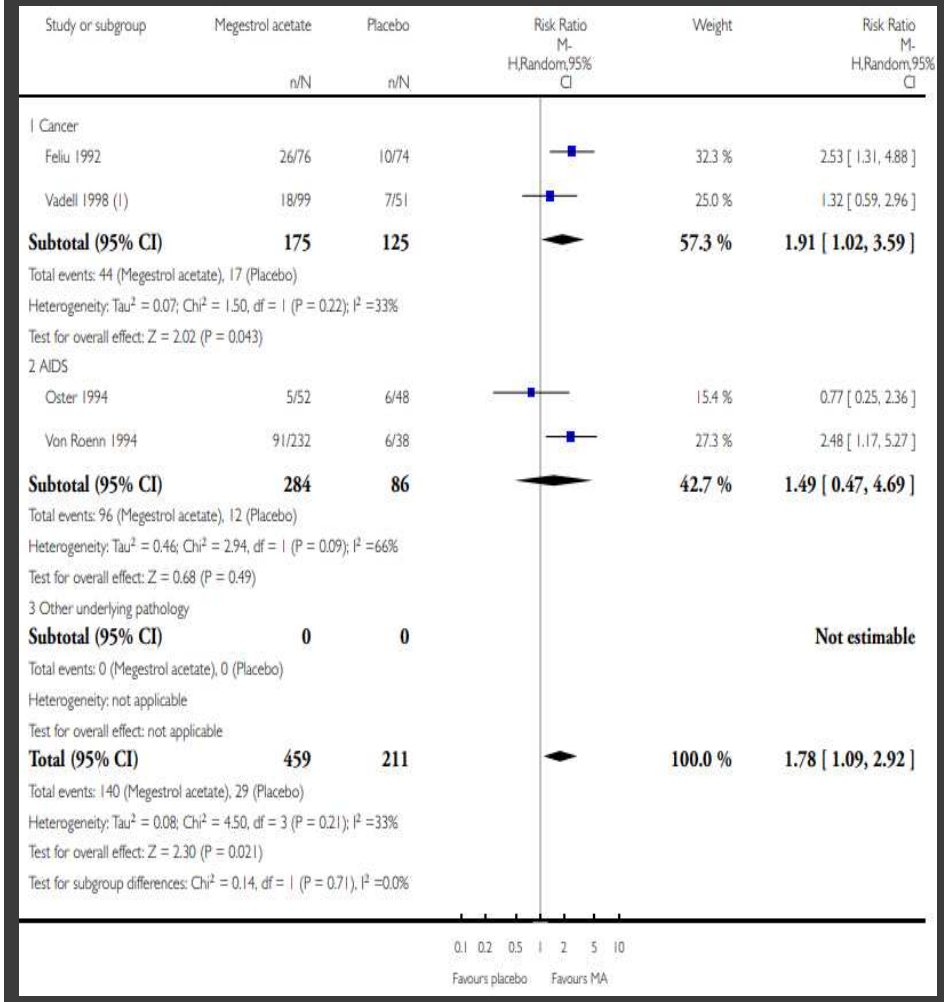


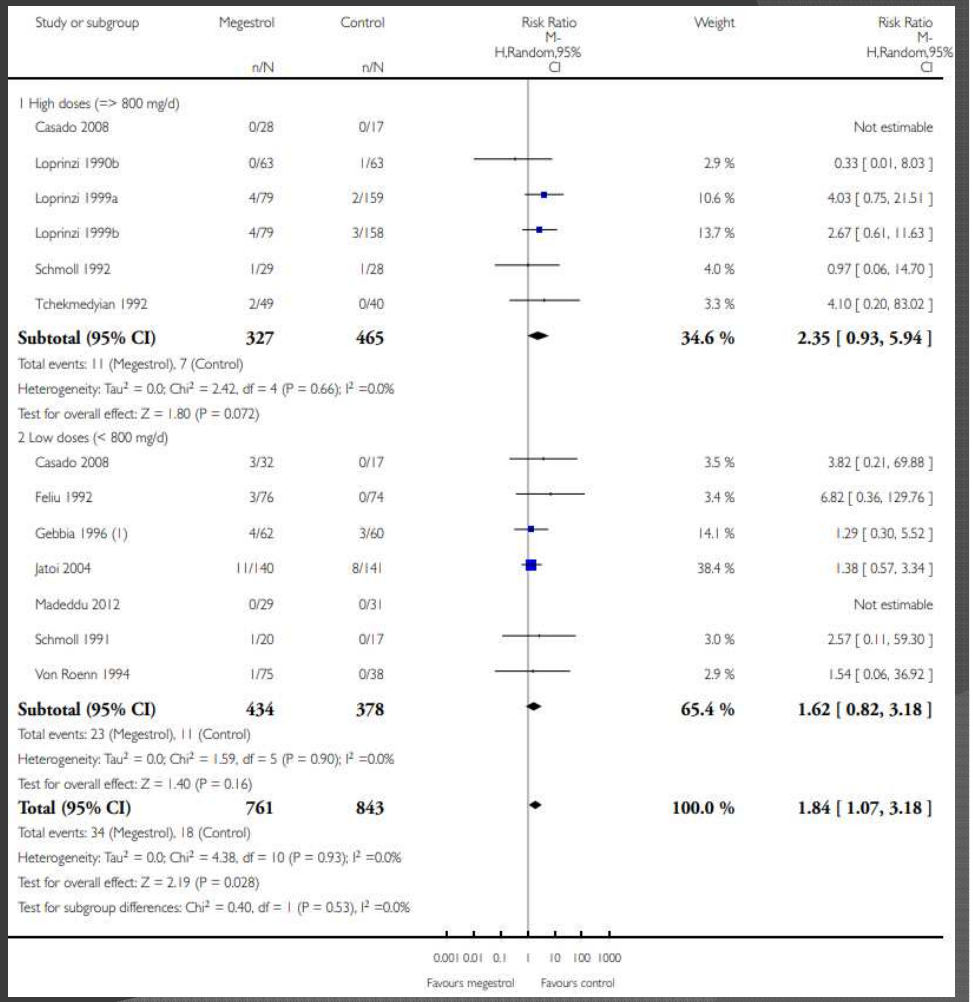




*Ruiz Garcia V et al. Cochrane Database Syst Rev. 2013*

# Meta-analysis:

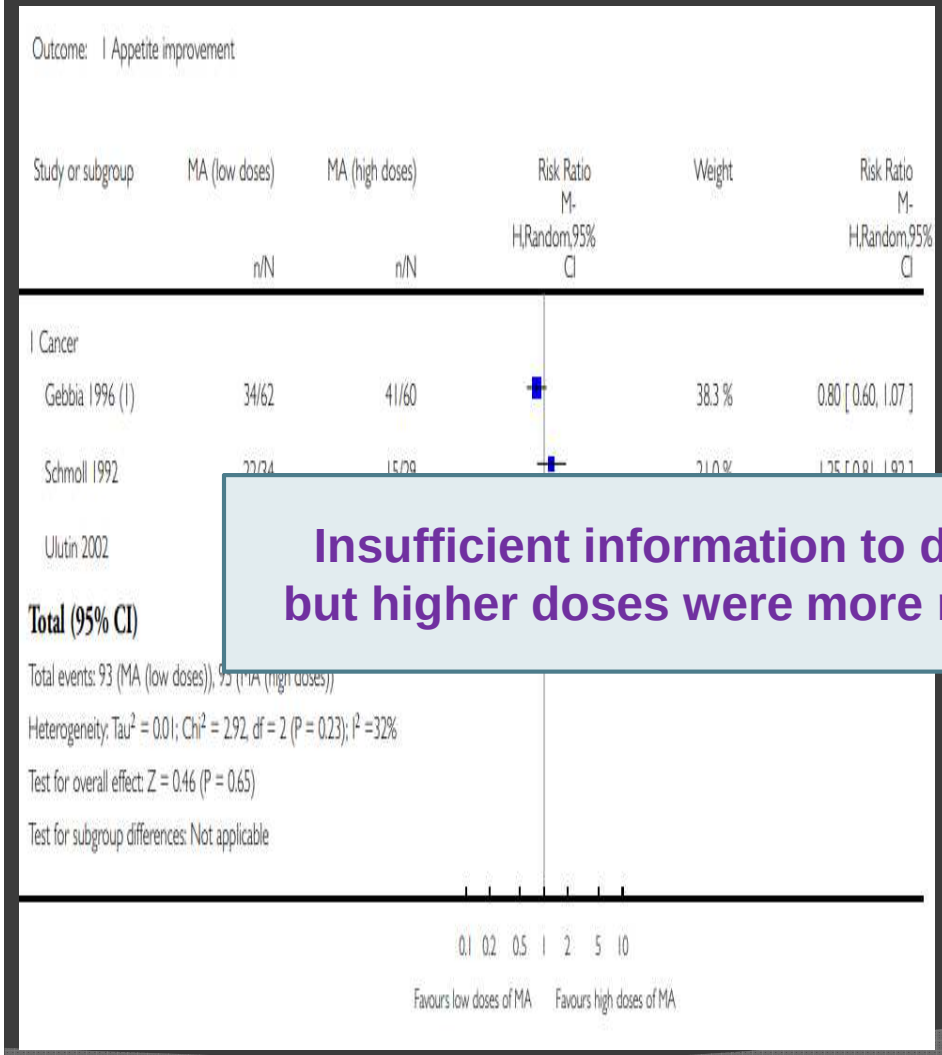
## MA Improved QoL *but Increased VTE* (vs Placebo)

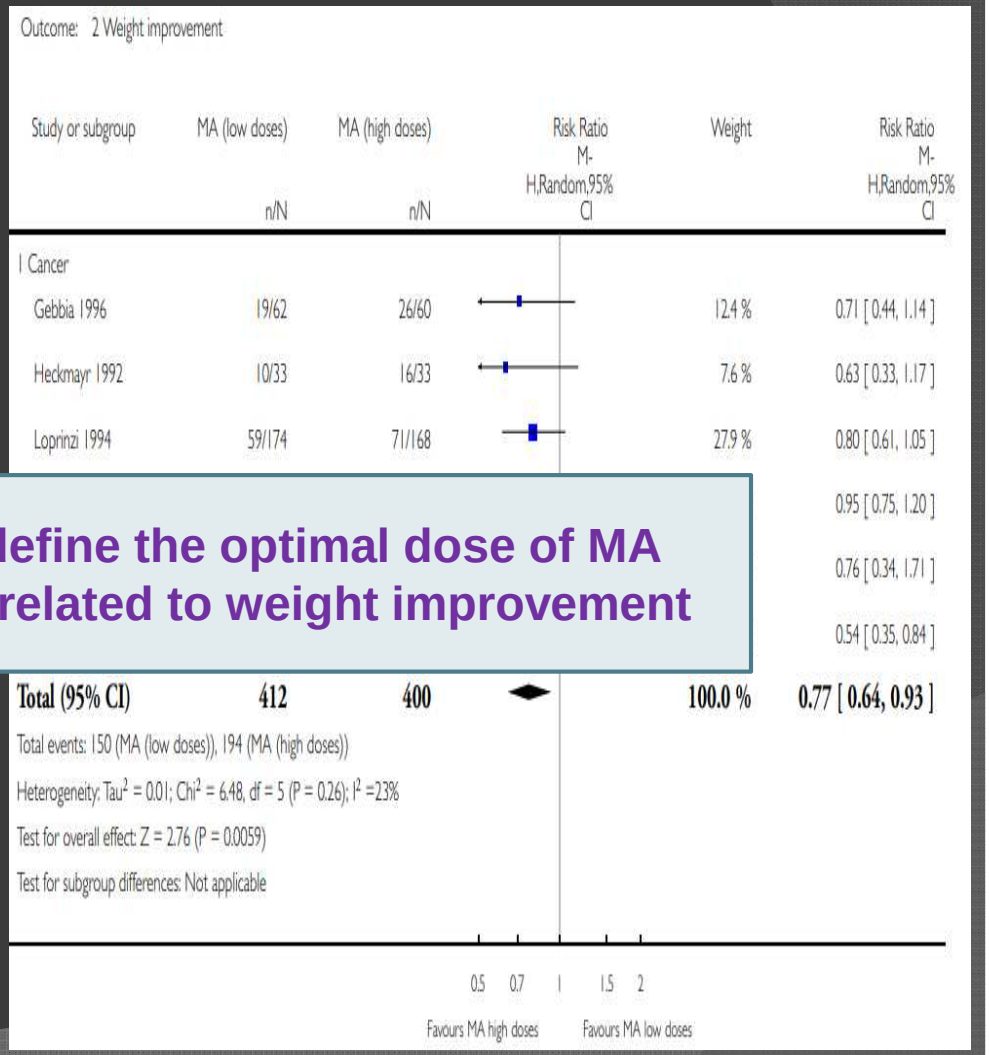



*Ruiz Garcia V et al. Cochrane Database Syst Rev. 2013*

# Meta-analysis:
## LD vs HD MA in BW Gain and Appetite Enhancement




**Insufficient information to define the optimal dose of MA but higher doses were more related to weight improvement**

*Ruiz Garcia V et al. Cochrane Database Syst Rev. 2013*

# Megestrol Acetate：劑量

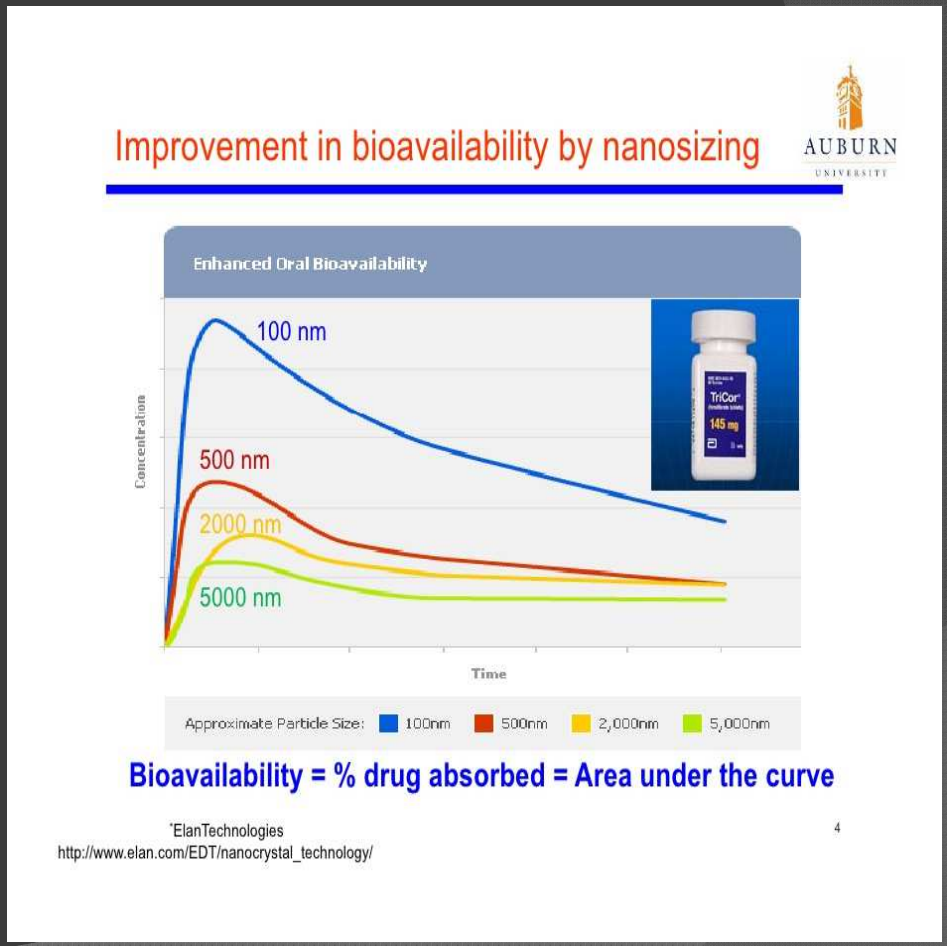
- 臨床效果與劑量有相關性(每日400 ~ 800 mg)
- 劑量增至800 mg左右有最大療效
- 現有錠劑(每錠20mg,40mg及160mg)及懸浮液(每 c.c. 40mg)兩種劑型

# Megestrol Acetate Suspension Advantages:

- 口服懸液劑較方便使用
- 病人順從性高 (good compliance)
- 口感ok
- 促進食慾 (約兩星期內)
- 增加體重 (約一到三個月)
- 提升QoL

# Advantages of Nanoparticles

- Improved dissolution rate
- Improved solubility
- Enhanced bioavailability
- Reduced fed/fasted variation in bioavailability
- Fast onset action
- Dose reduction




*http://www.stanipharm.fr/technology/drug-nanoparticles/*

# Nanocrystal formulation vs Traditional oral suspension

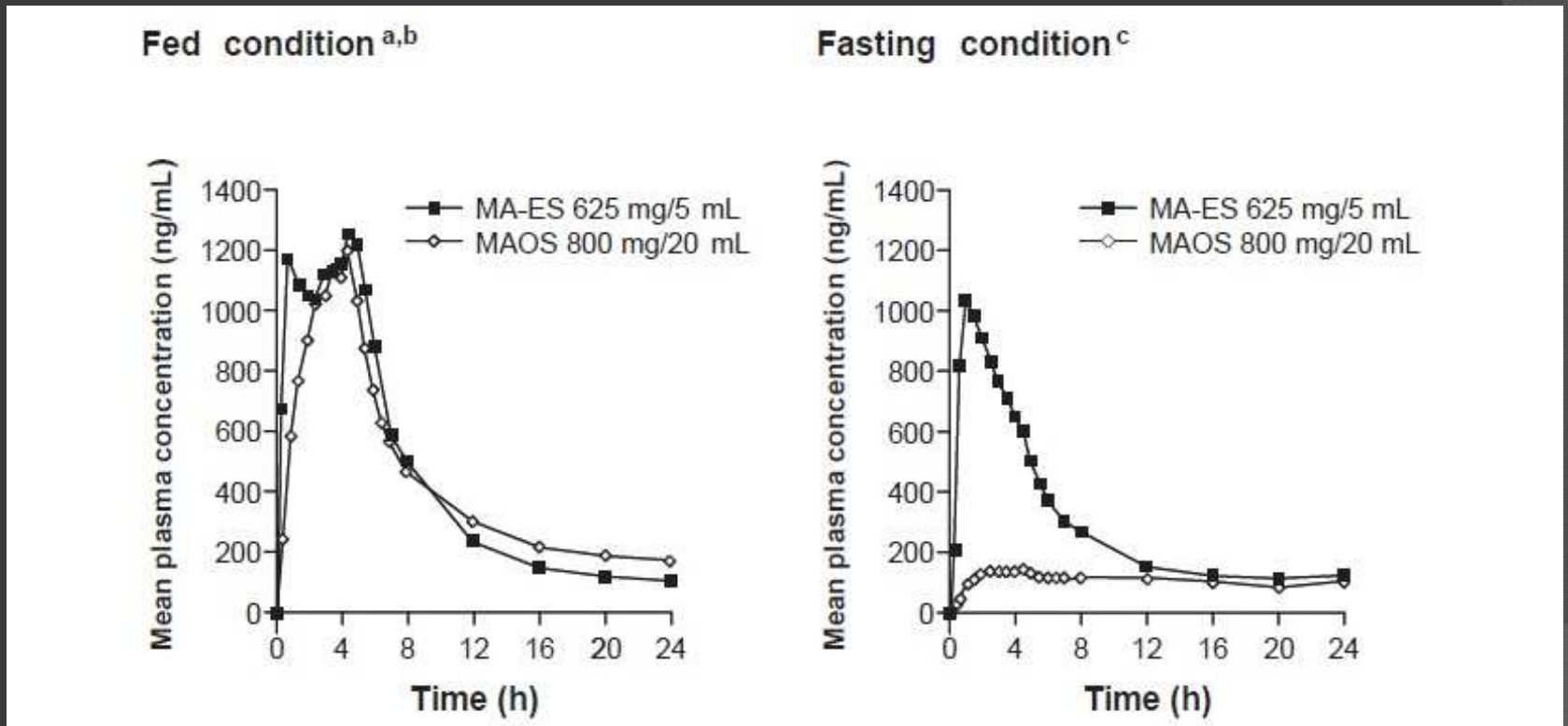



**Figure 4** Food effect differences between a nanocrystal dispersion of megestrol acetate (MA-ES) 625 mg/5 mL and a micronized formulation of megestrol acetate oral suspension (MAOS) 800 mg/20 mL.

[a]800 to 1000 calories, ~50% fat.

[b]Data in fed subjects from Study 1, MA-ES (N = 23), and Study 2, MAOS (N = 32).

[c]Data in fasting subjects from Study 1, MA-ES (N = 23), and Study 3, MAOS (N = 36).

*Deschamps et al. International Journal of Nanomedicine 2009:4*

# Nanocrystal formulation vs Traditional oral suspension

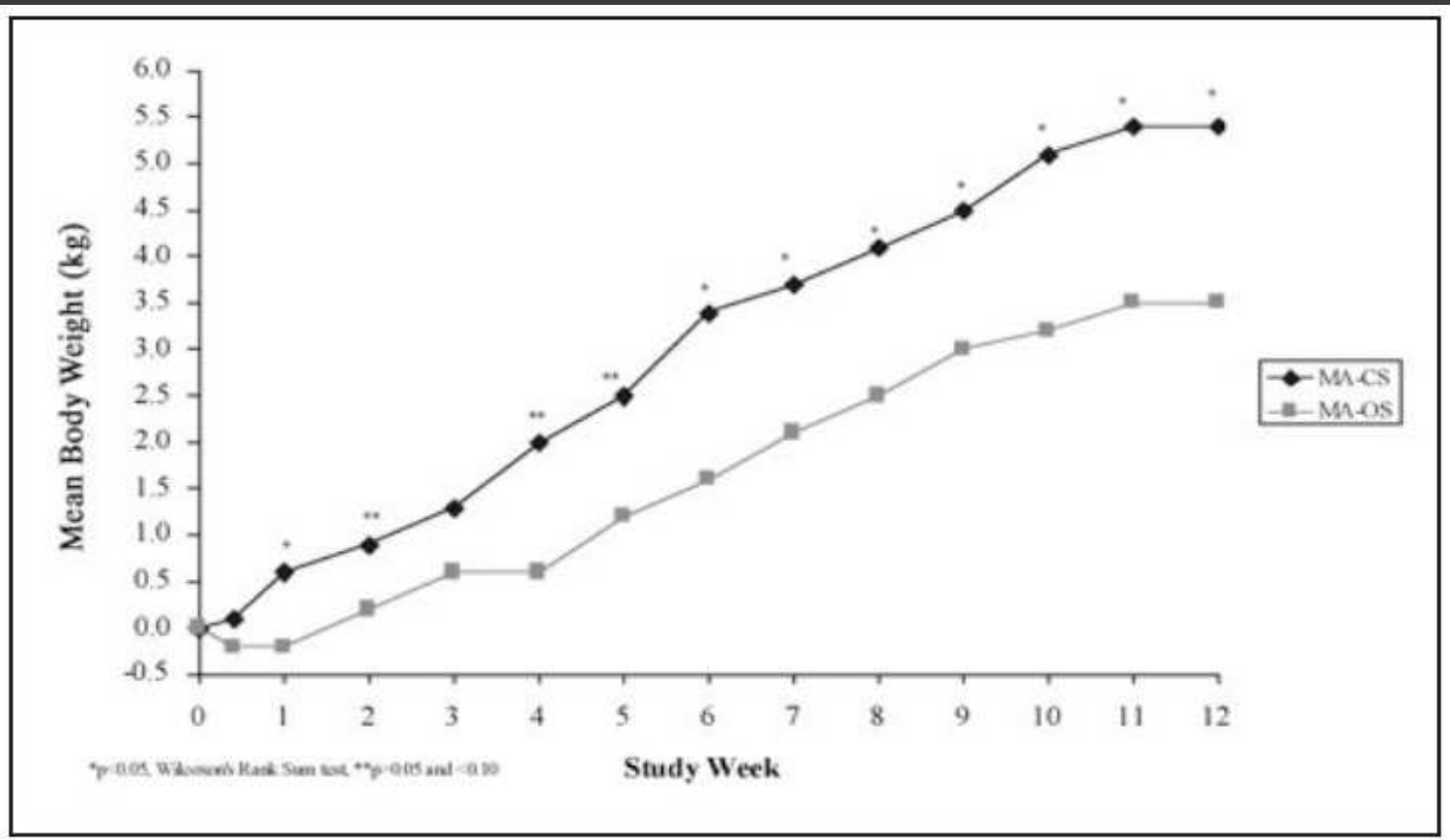



**Figure 1.** Mean body weight change from baseline.
*P<0.05, Wilcoxon's Rank Sum Test; **P>0.05 and <0.10
MA-CS = megestrol acetate concentrated solution; MA-OS = megestrol acetate oral suspension

*The Journal of Applied Research.Vol. 7, No. 3, 2007*

# Megestrol Acetate in CAC

| Author | Eligibility criteria | Drug Dose | Duration | Weight | Appetite | Side-effects |
|---|---|---|---|---|---|---|
| Loprinzi J Natl Cancer, 1990 | Advanced hormone-independent tumors<br>WL> 5 lb, ECOG<=2<br>CPS>3 months | 800 | Median time 7 weeks | >15 lb<br>**MA 11/67=16%**<br>**Placebo 1/66=2%** | **Appetite improvement**:<br>MA 42/67=63%<br>Placebo 26/66=39% | **Emesis (M:8%, P:25%,p=0.009), nausea (M:13%, P 38%, p=0.001)**, edema(M=29%, P=13%), irregular menses |
| Schmoll Oncology, 1992 | Advanced hormone-independent tumors<br>WL> 5%, CPS>2 ms | 480<br>960 | 8 weeks | **HMA 9/21=43%**<br>**LMA 8/27=30%**<br>Placebo 4/17=23.5% | **HMA 15/21=71%**<br>**LMA 22/27=81.5%**<br>Placebo 6/17=35% | Mild |
| Loprinzi et al, JCO, 1993 | Advanced incurable cancers, WL> 5 lb, ECOG<=2 | 160<br>480<br>800<br>1280 | Median survival 127 days | >=10%<br>**160mg =8%,**<br>**480mg =8%**<br>**800mg =15%**<br>**1280mg =13%** | Appetite increased as dose escalated up to 800mg | Nausea, vomiting (no statistically) |
| Vadell Am J Clin Oncol, 1998 | Advanced hormone-independent tumors<br>WL> 5%, KPS>=60<br>CPS>12 weeks | 160<br>480 | 8 weeks | **HMA 24/35=69%**<br>**LMA 14/37=38%**<br>Placebo 13/35=37% | Appetite increase from basal score | Minimal and reversible |
| Rowland JCO, 1996 | Advanced small-cell lung cancer ECOG PS<= 2 | 800 | 2 years | >=10%<br>**MA 26/122=21%**<br>**Placebo 8/121=7%** | | Edema , phlebitis |

# Adverse Effects of MA

- Thromboembolic event
- Fluid retention/Edema
- Weight gain (primarily through fat)
- Flushing
- Erectile dysfunction/Impotence
- Vaginal bleeding
- Adrenal insufficiency
- Cushing's syndrome

# Progesterone Analogs之藥品比較表

| | Megest | Megaxia ES | Farlutal |
|---|---|---|---|
| 成分 | megestrol | megestrol | medroxyprogesterone |
| 外觀 |  120 ml |  35 ml |   500mg/tab |
| 劑型 | Oral Suspension | Nanocrystal oral suspension | Oral tablet |
| 用法用量 | 成人建議劑量為400~800毫克/天 (每天10~20毫升) | 成人起始建議劑量為312.5 毫克/天(每天 2.5 毫升)至 625 毫克/天(每天 5 毫升) | 成人起始建議劑量為 早晚各1顆 |
| 健保價 | NT$ 796 / 120 ml (Bot) | NT$ 965 / 35ml (Bot) | NT$ 49 / Tab |
| 每日藥費 | NT$ 65/day起 (400mg) 26.5元/4ml | 約 NT$ 70/day起 (312.5mg) 27.6元/ml | NT$ 49 / day 起 (500mg) |
| 適應症 | 後天免疫缺乏症候群患者的厭食症，及後天免疫缺乏症候群患者及癌症患者之惡病體質引起的體重明顯減輕。 | 後天免疫缺乏症候群患者的厭食症，及後天免疫缺乏症候群患者及癌症患者之惡病體質引起的體重明顯減輕。 | 不能手術及復發性或轉移性之子宮內膜癌之輔助療法，停經後婦女之乳癌，攝護腺癌及伴有惡病體質之末期癌症病患使用。 |

**目前處方之Traditional oral suspension之 ml 數 ÷ 4 即為 Megaxia ES 建議劑量**

# Megaxia ES VS Megest

## 目前處方之Traditional oral suspension之 ml 數 ÷ 4 即為 Megaxia ES 建議劑量

| 商品名 | Megaxia ES Oral Suspension | MEGATUS ORAL SUSPENSION |
|---|---|---|
| 中文名 | 美適亞高濃度微粒懸液劑 | 美佳特口服懸液劑 |
| 製造廠 | 安成國際藥業股份有限公司 | 美時藥廠股份有限公司 |
| 成份 | Megestrol Acetate | Megestrol Acetate |
| 濃度 | 125 mg/ml | 40 mg/ml |
| 包裝規格 | 35ml/btl | 120ml、150ml、240ml |
| 健保價 | 35ml-NT$ 990 元<br>Daily cost: 28元/ml | 120ml-NT$796 元<br>Daily cost: 26元/4ml |
| 適應症 | 後天免疫缺乏症候群患者的厭食症，及後天免疫缺乏症候群患者及癌症患者之惡病體質引起的體重明顯減輕。 | |
| 用法用量 | 較無需考慮進食與否<br>成人起始建議劑量為 312.5 毫克/天(每天 2.5 毫升)至 625 毫克/天(每天 5 毫升) | 成人建議劑量為400~800毫克/天<br>(每天10~20毫升) |
| 劑型/顏色 | 奈米劑型，乳白色、檸檬口味之懸液劑 | 白色懸液劑 |
| 產品特色 | 1.國內第一支奈米製劑megestrol acetate suspension，可避免因進食與否而影響藥物吸收。<br>2.因生物可用率提高，可減少服用劑量。<br>3.高濃度懸液劑可減少服用mL數。<br>4.根據藥動學，藥物血中濃度較快達到峰值。(Tmax較快，AUC較高)<br>5.增加體重之效果較佳。<br>6.為TFDA核准新療效複方之新藥。<br>7.美國FDA核准上市（ANDA）203139 | |

# NCCN Guideline 2019.v2

| PALLIATIVE CARE DRUG APPENDIX | |
|---|---|
| Anorexia/ Cachexia (PAL-13) | Life Expectancy: Years; Year to Months<br>• Depression/anorexia: Mirtazapine, 7.5–30 mg PO QHS<br>• Gastroparesis (early satiety): Metoclopramide 5–10 mg PO QID 30 min before meals and at bedtime<br>• Low/no appetite: Megestrol acetate, 400–800 mg/d PO |
| Anorexia/ Cachexia (PAL-14) | Life Expectancy: Months to Weeks; Weeks to Days (dying patient)<br>• Offer education to patient<br>• Low/no appetite: Megestrol acetate, 400–800 mg/d PO OR olanzapine, 5 mg/d PO OR dexamethasone, 4–8 mg/d PO OR consider cannabinoid<br>• Depression: Mirtazapine, 7.5–30 mg PO QHS |

For patients with months-to-weeks or weeks-to-days life expectancy, appetite stimulants may be helpful (eg, megestrol acetate, dexamethasone, olanzapine) if increased appetite is an important aspect of quality of life.[191-195] A recent systematic review and meta-analysis of megestrol acetate revealed improved appetite and slight improvements in weight gain when using this drug to treat anorexia/cachexia in patients with cancer.[192] While one quarter of patients treated with megestrol acetate may have increased appetite and 1 in 12 may improve their weight, clinicians should be mindful of the increased risks of thromboembolic phenomena and death.[192]

# Megaxia ES之TFDA適應症與健保給付規範

- 適應症:

  後天免疫缺乏症候群患者的厭食症，及後天免疫缺乏症候群患者及癌症患者之惡病體質引起的體重明顯減輕。

- 健保給付規範（108/06/01):
  - 限用於已排除其他可治療之體重減輕（如全身性感染、影響吸收的腸胃道疾病、內分泌疾病、腎臟或精神病）之具惡病質的後天免疫缺乏症候群患者及癌症患者。
  - 惡病質之條件包括最近6個月以上體重流失>5%，或BMI<20且體重流失>2%。

# Take Home Message

- Cancer cachexia:
  - Majorly in upper GI cancer, HNN and lung cancer
  - Survival, Toxicity, Time to tumor progression
  - BWL ≥ 5%/6 m or BWL ≥ 2% in BMI < 20 or sarcopenia
  - Staging: precachexia→cachexia→refractory cachexia
  - Pathophysiology: pro-inflammatory cytokine + tumor releasing facotrs (PIF, LMF, AIS, etc)→proteolysis(hallmark!), lipolysis
  - Management: appetite stimulant (megestrol acetate)

# Take Home Message

- Megestrol acetate: nanoparticle form
  - Advantage:
    - Improved dissolution/solubility/bioavailability/onset
    - *Reduce fed/fast variation*
  - Side effect: thromboembolic event, edema, impotence, weight gain, etc
- Megexia ES: traditional suspension ml ÷ 4


Thanks for your attention