PRC

Drugs to treat and relief patients with cancer cachexia

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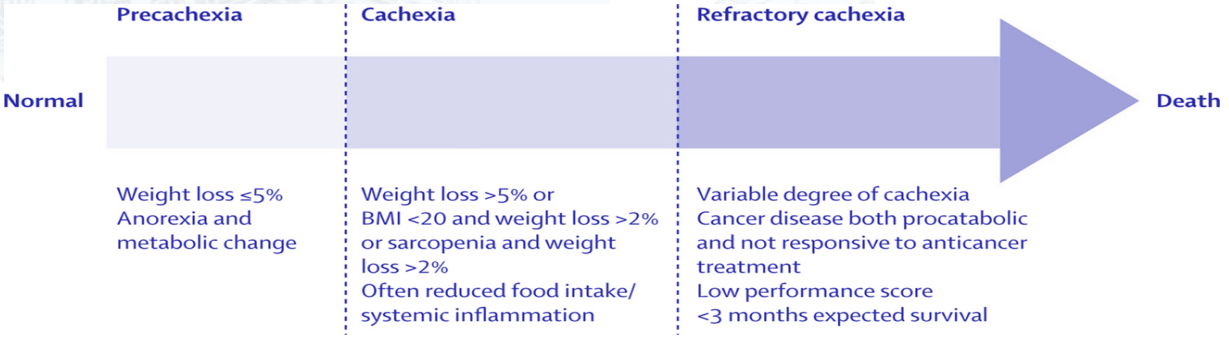
EAPC ONLUS

NORWEGIAN CANCER SOCIETY

- Aim of pharmacological symptom relief in cachexia
- Current pharmacological management
  - Nutritional Impact Symptoms
  - Targeted to treat appetite or weight
- New cachexia based mechanisms
- Optimal outcomes in clinical trials
- Future

Treatment aim depends on stage



ref. Fearon, Strasser, et al. 2011

Aim – in refractory cachexia

- Refractory cachexia impairs QoL, food intake, physical function and causes psychosocial distress

- The aim of the pharmacological treatment in refractory cachexia is immediate symptom relief
  - The ability to eat more or to appreciate the meal/eating situation
  - Improve QoL and reduce eating-related distress
  - The ability to maintain physical function

Aim – in precachexia and cachexia

- Stabilise/improve:
  - Weight
  - Muscle mass
  - Physical performance
  - Appetite
  - Nutritional intake
  - Quality of life
  - Eating related distress

Current pharmacological management - Nutritional Impact Symptom

- Patients with advanced cancer have a multitude of symptoms

Symptom	%	Symptom	%	Symptom	%
Pain	84	Sleep problems	49	Dizziness	19
Easy fatigue	69	Depression	41	Dyspepsia	19
Weakness	66	Cough	38	Dysphagia	18
Anorexia	66	Nausea	36	Lack of energy	18
Belching	61	Edema	28	Bloating	18
Dry mouth	57	Taste change	28	Wheezing	13
Constipation	52	Hoarseness	24	Memory problems	12
Early satiety	51	Anxiety	24	Headache	11
Dyspnea	50	Vomiting	23	Sedation	10
10% weight loss	50	Confusion	21		

Current pharmacological management

- Patients with advanced cancer have a multitude of symptoms
  - and a wealth of these have impact on nutritional aspects

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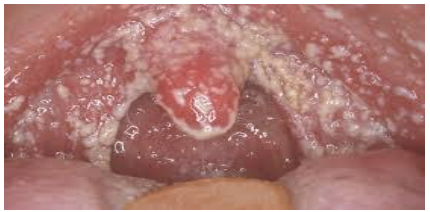
ref: Walsh et al 2000

Pharmacological symptom relief

- It is imperative that symptoms or conditions that can interfere with nutritional intake are addressed and treated
  - It is for instance not to be expected that one is to improve nutritional intake in patients undergoing pain or who are suffering from severe oral stomatitis
    - *ref Del Fabbro et al 2011*



Pharmacological symptom relief

- We all know our medical armamentarium, and it should be used
  - Laxantia, opioids, PPI, antiemetics etc.

Pharmacological symptom relief

- But symptom relief is not always *adding* a pharmacological treatment

- Always keep scrupulous attention to whether the patient really need the prescribed drug – or if the dose can be reduced

Symptom management

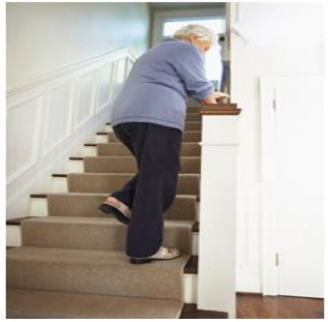
- A lot of side effects mimic common symptoms in advanced cancer / refractory cachexia
  - **Opioids:** nausea, constipation, sedation, dry mouth, reduced appetite
  - **Benzodiazepam:** sedation, dizziness
  - **5-HT3R antagonists:** constipation
  - **Dipyridamol:** dizziness, nausea
  - **Statins:** headache, difficulty sleeping, muscle aches, drowsiness, dizziness, myopathy

Current pharmacological management — Targeted to treat appetite or weight

- Only **progestins** and **corticosteroids** were found to have sufficient evidence to support their use in improvement of **appetite**

Ref: Yavuzsen 2005

Corticosteroids



- Can improve QoL, appetite, vomiting, wellbeing, fatigue
  - Weight is often not significantly affected
- Side effects: hyperglycaemia, myopathy, mood changes, pseudo rheumatism, immunosuppression etc.

ESPEN-guidelines

B5 – 1 Corticosteroids to improve appetite

Strength of recommendation

WEAK

We suggest considering corticosteroids to increase appetite of anorectic cancer patients with advanced disease for a restricted period of time (1-3 weeks) but to be aware off side effects.

Level of evidence

High

Ref: Arends et al 2016

Different corticosteroids

- Little evidence which compound to be recommended for improved appetite
- Rarely compared head to head
- Dexamethasone most investigated

Drug	Equivalent pharmacologic dose (mg)	Anti-inflammatory potency	Mineralocorticoid potency[a]	Biological half-life (hour)
Hydrocortisone	20	1	2+	8–12
Cortisone	25	0.7	2+	8–12
Prednisone	5	4	1+	24–36
Methylprednisolone	4	5	0–0.5	24–36
Dexamethasone	0.75	25	0	36–54

Progestines

- RR appetite improvement: 2.57 (1.48-4.49)
- RR weight improvement: 1.55 (1.08-2.26)
- RR QoL: 1.91 (1.02-3.59)

- Increased risk; impotence, dyspnoea, oedema, thromboembolism and death

Ref: Ruiz Garcia V et al 2013

ESPEN-guidelines

B5 – 2 Progestines to improve appetite

Strength of recommendation WEAK	We suggest considering progestines to increase the appetite of anorectic cancer patients with advanced disease but to be aware off potential serious side effects.
Level of evidence	High

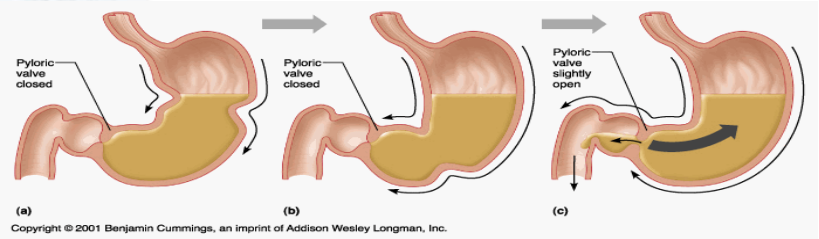
Ref: Arends et al 2016

Progestines

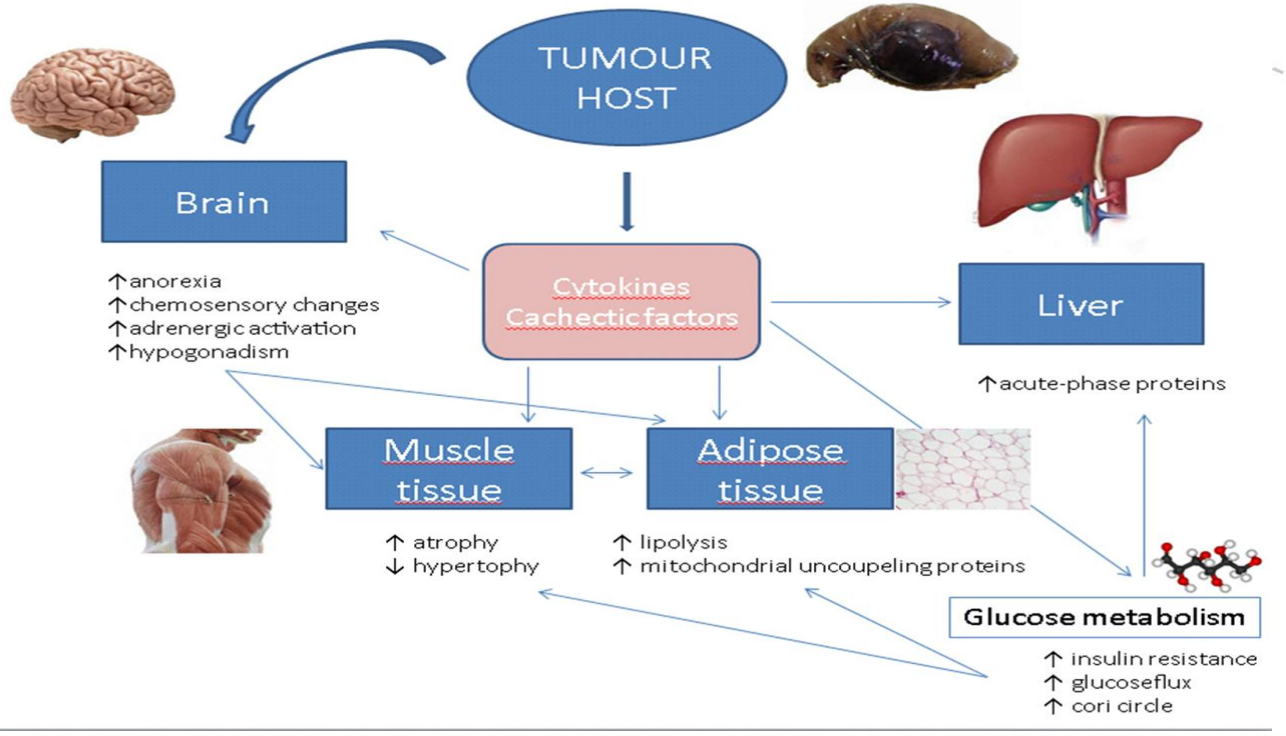
- Optimal dose is 160-800 mg/d (?)
- For short-intermediate term appetite stimulation and increase of weight but not muscle mass

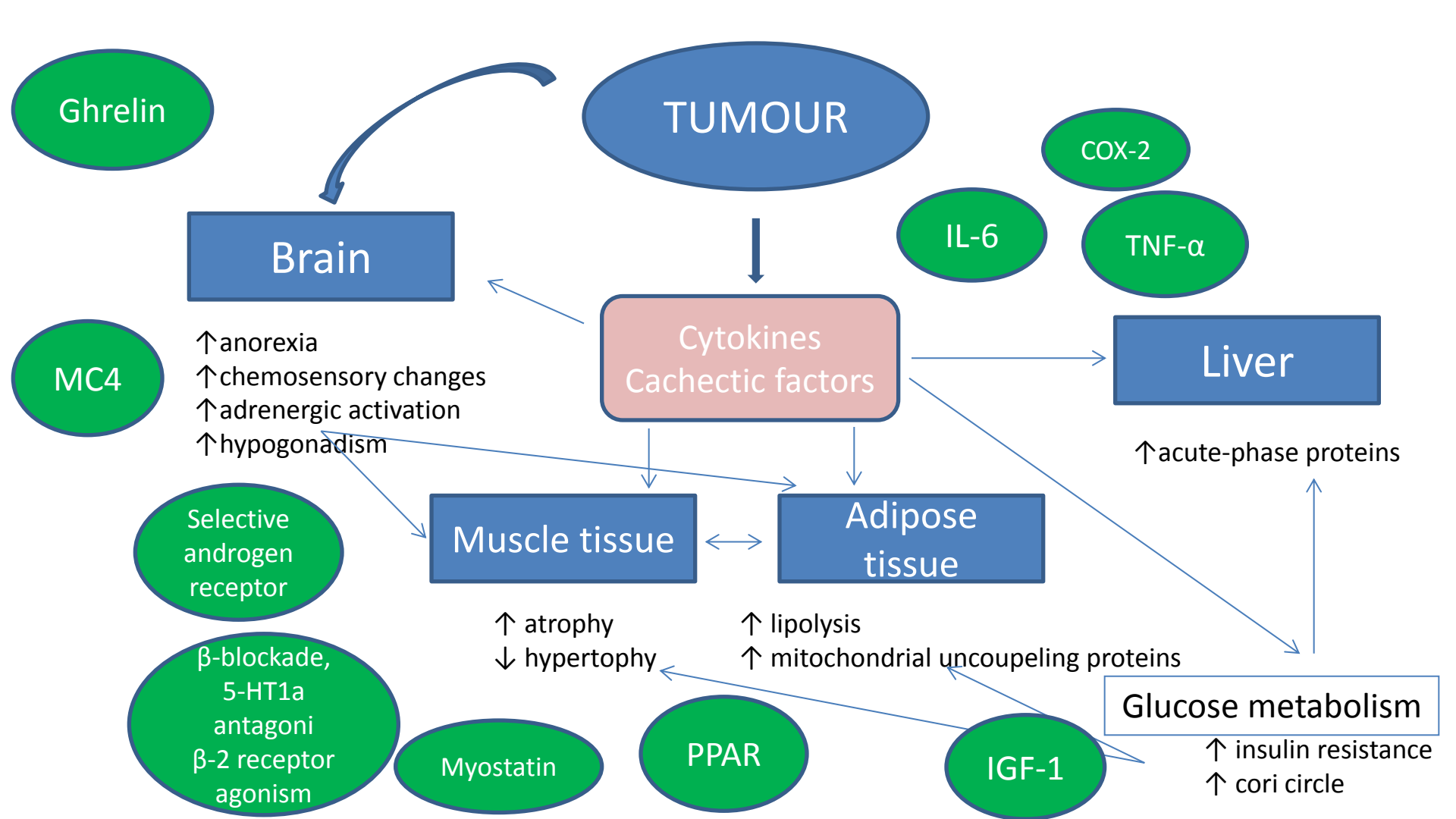
Prokinetic drugs

- Metoclorpramide and domperidone
- Fewer patients included in studies
- Can help in patients with early satiety and nausea
- But does it improve intake?



Newer, more targeted cachexia treatment




Ghrelin
TUMOUR
COX-2
IL-6
TNF-α
Brain
MC4
↑anorexia
↑chemosensory changes
↑adrenergic activation
↑hypogonadism
Cytokines
Cachectic factors
Liver
↑acute-phase proteins
Selective androgen receptor
Muscle tissue
Adipose tissue
↑ atrophy
↓ hypertophy
↑ lipolysis
↑ mitochondrial uncoupeling proteins
β-blockade, 5-HT1a antagoni β-2 receptor agonism
Myostatin
PPAR
IGF-1
Glucose metabolism
↑ insulin resistance
↑ cori circle

Targeted cachexia interventions the last few years

- There have been studies that showed few, inconsistent or no improvements

- Several agents might have shown inferior results
  - lack of multimodal interventions
  - lack of compliance
  - administrated to late in the disease trajectory

New cachexia based mechanisms

- Most ongoing studies are now designed to include patients at an early stage
  - There is more anabolic potential, most likely to succeed in improving muscle/function
  - Better compliance and less attrition
- Few studies are multimodal

New cachexia based mechanisms

- Drugs are mainly used to:
  - Decrease systemic inflammation
  - Increase muscle mass
  - Appetite stimulation

New cachexia based mechanisms

- Drugs are mainly used to:
  - **Decrease systemic inflammation**
  - Increase muscle mass
  - Appetite stimulation

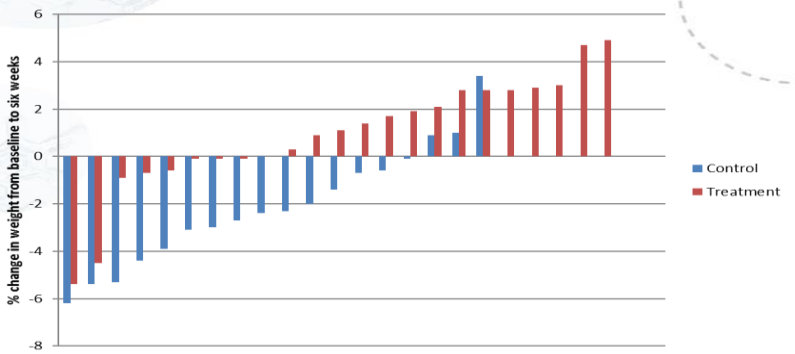
Decrease systemic inflammation

- **IL-6**
  - ALD518 (Phase II studies)- improved fatigue and LBM
- **TNF-α**
  - Eternacept, Infliximab, Melatonin, Thalidomid
- **Anti-IL-1a**
  - Xilonix - lesser decline in function and improved OS
- **NSAID**
  - May improve weight in cancer patients with cachexia, and some evidence of an effect on physical performance, self-reported quality of life and inflammatory parameters

preMENAC-study

- Chemotherapy vs CT and Multimodal treatment (celecoxib, EPA, exercise, ONS/nutritional advice)

- 46 patients to assess feasibility
  - Intervention group vs control group
    - Weight
    - Muscle mass
    - Physical function



(Solheim et al. in press Journal of Cachexia, Sarcopenia and Muscle)

New cachexia based mechanisms

- Drugs are mainly used for:
  - Decrease systemic inflammation
  - **Increase muscle mass**
  - Appetite stimulation

Increase muscle mass

- Growth Hormone
  - Controversial/ contraindicated in cancer
- Testosterone
  - Not compelling evidence so far, risk of side effects
- Formoterol fumarate (anabolic β2-agonist)
  - Promising, but only assessed in very small studies

Increase muscle mass

- Inhibition of myostatin/myostatin receptor
  - Awaiting results: bimagrumab, Ly2495655
- Selective androgen receptor modulator
  - SARM
- Non-selective β blocker + central 5-HT1a and partial β2 receptor agonist effects
  - espindolol

Enobosarm

- Orally active selective androgen receptor modulators (SARMs) with the potential to increase LBM
  - without side effects seen with traditional anabolic agents
- Phase II trial
  - 159 patients randomized to two different doses or placebo for 113 days
  - Significant increases in LBM
  - Improvement stair climb power test
  - No improvement grip strength, 6 min walk nor ECOG
  - Loss of fat mass

ref Dobs et al, Lancet Oncology 2013

Enobosarm

- 2 Phase III trials: unpublished
- Endpoint: maintain or increase LBM and have a 10% or greater improvement in stair climb power
- 504 study: LBM was improved, not stair climb power
- 505 study: neither LBM nor stair climb improved significantly

Espindolol

Non-selective β blocker + central 5-HT1a and partial β2 receptor agonist effects

- Eighty-seven patients were randomized placebo vs high and low dose espindolol in 4 weeks
- High-dose espindolol produced a weight gain and increase in LBM compared to placebo
- Improved hand grip strength, but not stair climbing power, and 6-min walk test

ref. Coats et al 2016

New cachexia based mechanisms

- Drugs are mainly used for:
  - Decrease systemic inflammation
  - Increase muscle mass
  - **Appetite stimulation**

Appetite stimulation

- Cannabinoids
- Zinc (taste disorder)
- Ghrelin

Anamorelin

- Ghrelin is an endogenous peptide primarily secreted by the stomach
- Upon binding to its receptor, ghrelin stimulates multiple pathways
  - metabolism, appetite, GH axis, inflammation
- Anamorelin is a selective, stable, orally active ghrelin receptor agonist

Anamorelin

- ROMANA 1 and ROMANA 2 were two international, double-blind, randomized, placebo-controlled Phase III trials
- Stage III/IV NSCLC and cachexia (≥5% weight loss within six months or BMI <20 kg/m2)
- Patients were randomized anamorelin vs placebo, given daily orally for 12 weeks
- ROMANA 1 enrolled 484 patients and ROMANA 2 enrolled 495 patients.

Anamorelin

- Median lean body mass versus placebo:
  - ROMANA 1: 0.99 vs -0.47 kg; p<0.001
  - ROMANA 2 :0.65 vs -0.98 kg; p<0.0001
- Body weight:
  - ROMANA 1: 2.20 vs 0.14 kg; p<0.0001
  - ROMANA 2: 0.95 vs -0.57 kg; p<0.0001.
- In both studies changes in handgrip strength were not different between patients receiving anamorelin or placebo

What is a good outcome in cachexia trials?

- The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are regulatory agencies responsible for scientific evaluation of medicines and licensing of drugs
  - Lean body mass (LBM) gain and improved muscle strength/power as co-primary endpoints
- But for rehabilitation programmes in COPD they focus on more patient centered outcomes such as physical activity level

What is a good outcome in cachexia trials?

- Must be clinically meaningful!
  - Must be associated with mortality or morbidity
- Related to the disease
- Biologically plausible
- Stopping decline, not necessarily improving

What is a good outcome in cachexia trials?

- Functional tests?
  - TUG? Shuttle walk? SPPB? Hand grip? Activity meters?
- PROMs
  - CAX-24? FAACT? EORTC QLQ-30? IADL? FRAIL?
- Muscle mass/weight
  - DEXA? CT-scan? Weight alone?
- Nutritional intake?
  - 24h recall? 3-5 days food dairy? PG-SGA?
- Performance status?
- Improved cancer therapy tolerance/survival?

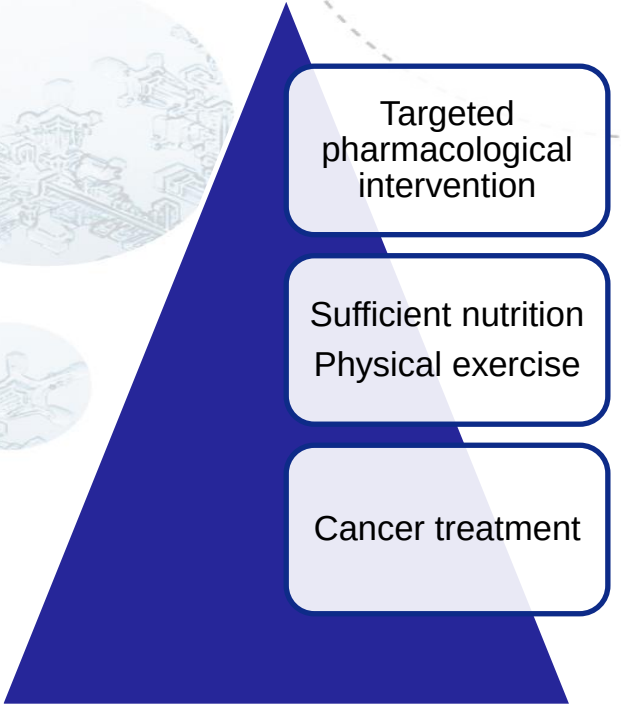
Pathophysiology

Inflammation,
Anabolism/catabolism
Appetite

Reduced food intake
Reduced physical activity

Cancer

Intervention



Drugs to treat and relief patients with cancer cachexia

- Take home message
  - Pharmacological treatment of nutritional impact symptoms is both adding the right medication – but also to discontinue the ones that are not needed
  - Corticosteroids, progestins (and prokinetics) for short time relief of appetite loss or early satiety
  - Newer drugs; still preferably include in clinical trials, what is good enough?
  - Drugs alone will perhaps not be enough

Thank you for the attention