

pharmacOLOGIC

The logic behind using drugs...



DEPARTMENT OF PHARMACOLOGY

NEWS LETTER



PATRON



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e-mail:

aimspharmac@gmail.com

From the Editor's Desk

Obesity is a modern day problem. It is considered a risk factor for cardiovascular diseases. The incidence of metabolic syndrome is on the rise. Obesity is considered a part of the metabolic syndrome. In our newsletter, we have an article dedicated to the recent advances in the pharmacotherapy of obesity. The treatment of tuberculosis poses a challenge in the form of multi-drug resistant tuberculosis and extensively drug resistant tuberculosis. We study some newer drugs and targets for tuberculosis. A comprehensive review on probiotics provides some interesting details.



RECENT ADVANCES IN THE PHARMACOTHERAPY OF OBESITY

DR MANU G, ASSISTANT PROFESSOR

INTRODUCTION:

Obesity is a complex metabolic disorder and chronic non-communicable disease resulting from the abnormality between energy intake and energy expenditure. Generally this imbalance is because of life style and behavioral origin. It is also associated with insulin resistance, dyslipidemia and cardiovascular disease. In USA, 1.5 billion people are obese. 30,000 deaths were related to obesity or indwelling obesity. World over obesity totally amounts to 250 million.

ASSESSMENT OF OBESITY:

BMI = Weight in kilograms / (Height in meter)²
Significant obesity of males > 30 and females > 28.6

WHO CLASSIFICATION:

BMI (kg/m ²)	Class
< 18.5	Underweight
18.5-24.9	Acceptable or 'normal' weight
25.0-29.9	Grade 1 overweight
30.0 and 39.9	Grade 2 overweight or Obese
> 40	Grade 3 overweight or Morbidly obese

THERAPIES FOR THE MANAGEMENT OF OBESITY:

A. NON PHARMACOLOGICAL MEASURES:

- 1. Life style changes:** Analyzing food intake, calorie counting i.e. intake + expenditure, change of attitude, eat only when hungry, water, vegetables, fresh fruits in daily diet, regular exercise.
- 2. Psychological therapy:** Set goals, yes to healthy foods, no to unhealthy foods.
- 3. Dietary therapy:** Diet plan for promoting sustained weight loss remains a controversial issue however four types of diets are recommended for weight loss.
These are
 - ⊙ Atkins (very low carbohydrate)
 - ⊙ Traditional (lifestyle, exercise, attitudes, relationships, nutrition)

- ⊙ Ornish (very high carbohydrate)
- ⊙ Zone (low carbohydrate)
- 4. **Physical activity:** warm up exercises, high energy impact activities for calorie expenditure, stretches, yoga, abdominal workouts, cycling, skipping, brisk walking.
- 5. **Behavior therapy:** improving self esteem, enhance self confidence, changing to healthy food stuff, recording daily diet & weight, avoiding crash diet.

B. SURGERY:

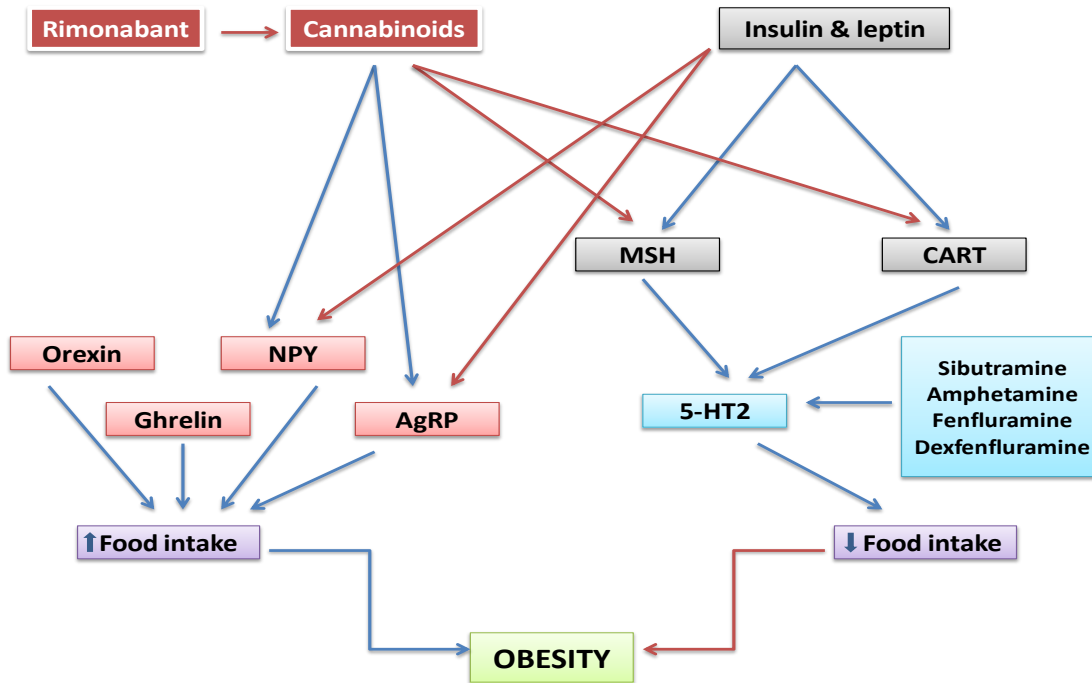
1. Weight loss surgery – Gastric bypass surgery, Banding surgery
2. Wiring of teeth
3. Cosmetic surgery – Abdominoplasty or Apronectomy.

C. PHARMACOTHERAPY: ANTI-OBESITY DRUGS

1. **Orlistat** - Reacts with serine residues at the active sites of *gastric and pancreatic lipases*, irreversibly inhibiting the enzymes and thereby preventing the breakdown of dietary fat to fatty acids and glycerols.
2. **Metformin** - Activates cAMP-activated protein kinase and suppresses hepatic gluconeogenesis activity
3. **Exenatide** - GLP-1 analogue, delays gastric emptying, promotes satiety
4. **Pramlintide** - Synthetic analogue of amylin, promote Satiety, delays gastric emptying, inhibits glucagon synthesis
5. **Mazindol** – acts peripherally by increasing metabolic rate.
6. **New Hydrogel-diet Pill** – biodegradable polycellulose that imbibes water, gives feeling of satiety.
7. **RNAi Therapy (nuclear hormone co-repressor)** – silencing RIP 140 nuclear hormone co-repressor, which regulate fat accumulation.
8. **Peptide YY3-36** – suppression of pancreatic secretion, inhibition of gastric motility, appetite suppression.
9. **Sibutramine** – inhibits non selective uptake of nor adrenaline, serotonin & dopamine.
10. **Topiramate** – inactivate Na⁺ channel, potentiates GABA and some glutamate receptors.
11. **Antidepressants** (bupropion, diethylpropion), Sertraline – potentiates NA, 5HT action.
12. **Rimonabant** – CB1 receptor antagonist, acts in brain & peripheral organs
13. **Naltrexone** – opioid antagonist, reduce craving.
14. **Diazoxide** – enhances potassium release which suppresses insulin secretion.

NEW TARGETS:

- ⊙ **NPY** (Neuropeptide Y) and **AgRP** (Agouti related peptide) antagonists
- ⊙ **MSH** (Melanocyte stimulating hormone) and **CART** (Cocaine & amphetamine related transcript) agonists



Physiological and pharmacological regulation of food intake (Blue arrow indicates stimulation whereas red arrow indicates inhibition)

- ⊙ Ciliary neurotrophic factor – a glial cytokine, overcomes leptin insensitivity
- ⊙ Olestra – a polyester of sucrose used as a fat substitute which is neither digested nor absorbed & therefore has no role in production of energy
- ⊙ Atomoxetine – a central NE uptake inhibitor
- ⊙ Melanin – concentrating hormone receptors – which are G protein coupled receptors involved in regulating appetite.
- ⊙ Melanocortins – receptor 4 antagonists bring about anorectic effects by mediating its action by leptin-melanocortin pathway.
- ⊙ P57 – a steroidal glycoside, Hoodia gordonii plant extract brings about appetite suppression by increasing ATP content in hypothalamus.
- ⊙ Anti-obesity vaccine – reduce fat stores inspite of not reducing food intake
- ⊙ Anti-cellulite cream – increase the metabolism of the local area using local energy & leads to increased blood circulation, sweating that is helpful in burning & dissolving fats.

A COMPREHENSIVE REVIEW ON PROBIOTICS

DR PADMANABHA TS, ASSISTANT PROFESSOR



The word "probiotic" was derived from the Greek word which means "on behalf of". The concept was introduced by Lilly & Stillwell and was intended to stimulate substances produced by one microorganism to enhance the growth of another. Probiotic therefore is the exact opposite of antibiotic. Probiotic was used later to refer to animal feed supplement, which beneficially affects the host animal by improving its intestinal microbial balance. According to the currently adopted definition by WHO, Probiotics are: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host". Lactic acid bacteria (LAB) and Bifidobacteria are the most common types of microbes used as probiotics, but certain yeasts and bacilli may also be used.

Probiotics are commonly consumed as part of fermented foods with specially added active live cultures; such as in yogurt, soy yogurt, or as dietary supplements. The health and nutritional benefits ascribed to probiotics can be generalized under the following categories: maintenance of normal intestinal, maturation of the immune system and development of normal intestinal morphology, micro flora balance in infant and old age, improvement of lactose tolerance and digestibility of the milk products, antitumorogenic activity, reduction of serum cholesterol levels, synthesis of B-complex vitamins, and absorption of calcium. It also shows inhibitory action towards the production of inhibitory compounds such as hydrogen peroxide, Reuterin/Bacteriocins, alteration of pH values by the production of organic acids. There are various other significance on human health based on newly developed scientific data that reveals reduction of diseases risk and promises to cure various diseases such as Lactose intolerance, Bacterial Vaginosis, Colon cancer, Heart strokes, Cholesterol abnormalities, Chronic disorders. Example of most common probiotic bacteria are such as *Lactobacillus acidophilus*, *Bifidobacteria*, *Lactobacillus plantarum*, *Lactobacillus spentosus*, *Lactococcus lactis*, *Lactobacillus scasei*, *Bifidobacterium breve*, *Bifidobacterium longum*.

Commercially used probiotic species:

- **Lactobacillus species** - *L. acidophilus*, *L. casei*, *L. fermentum*, *L. gasseri*, *L. johnsonii*, *L. lactis*, *L. paracasei*, *L. plantarum*, *L. reuteri*, *L. rhamnosus*, *L. salivarius*.
- **Bifidobacterium species** - *B. bifidum*, *B. breve*, *B. lactis*, *B. longum*.
- **Streptococcus species** - *S. thermophilus*

The probiotics that are marketed as nutritional supplements and in functional foods, such as yogurts, are principally the Bifidobacterium species and the Lactobacillus species

Various genera of lactic acid bacteria that can be used as probiotics:

- Bifidobacterium
- Lactobacillus, Lactococcus and Streptococcus thermophilus
- Enterococcus

Use of lactic acid bacteria in various diseases conditions:

- Lactose intolerance
- Hypertension
- Antibiotic therapy diseases
- Vaginosis
- Constipation
- Small bowel bacterial overgrowth
- Elevated blood cholesterol

NEWER DRUGS AND TARGETS FOR TUBERCULOSIS

DR K M NARASIMHAMURTHY, POSTGRADUATE

UNITE TO → END TB

FDA approved (2012) - BEDAQUILINE

- First anti-TB drug to interfere with bacterial energy metabolism
- Novel mechanism of action to the treatment of pulmonary MDR-TB
- Specifically inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*.
- Diarylquinoline class
- 2 month treatment in newly diagnosed MDR-TB : rapid sputum culture conversion

- 400mg daily for 2 weeks, then 200mg 3 times a week for 22 weeks ; added to MDR-TB regimen
- CYP3A4 interaction

Drugs under Clinical Trials

- **Delamanid** - nitroimidazole class Inhibits mycolic acid synthesis
- **Pretomanid** - Bicyclic nitroimidazole like molecule, Active against both replicating and hypoxic, non-replicating *Mycobacterium tuberculosis*
- **Sutezolid**- Like linezolid belongs to oxazolidinone class, Prevents the initiation of protein synthesis by binding to 23s RNA in the 50S ribosomal subunit of bacteria , 600mg once daily or 1200mg once daily
- **SQ 109** - 1,2-ethylenediamine analogue of ethambutol, Target the MmpL3 gene in M. tuberculosis

Discovery portfolio

LEADS	HITS
SPR113	ATP synthesis inhibitors
DprE inhibitors	RNA polymerase inhibitors
Cyclopeptides	Energy metabolism inhibitors
Ruthenium phosphine/picolinate complexes	Menaquinone inhibitors
Leucyl-t-RNA inhibitors	Malate synthase inhibitors

1. SPR 113

- Excellent anti-mycobacterial activity
- Concentration in macrophages
- MDR and XDR tuberculosis strains affected
- No CYP or HERG activity

2. DprE inhibitors

- Identified by high-throughput screening against mycobacterial whole cells
- DprE1 :essential mycobacterial enzyme that is involved in the synthesis mycobacterial cell wall
- DprE1 , MoeW, Molybdenum : factors responsible for cell wall synthesis

3. Cyclopeptides

- Griselimycin : a natural cyclic peptide isolated from *Streptomyces* species
- Lead optimization: CYCLOHEXYLGRISELIMYCIN
- Target: DNA polymerase sliding clamp (DnaN)
- Potent bactericidal activity in vitro and in vivo against drug resistant tuberculosis strains
- DnaN is the gene that codes for the DNA clamp (also known as β sliding clamp) of DNA polymerase III
- The β clamp physically locks Pol III onto a DNA strand during replication to help increase its processivity

4. Ruthenium II PHOSPHINE /PICOLINATE COMPLEXES

- Inorganic compounds
- Highly selective for *M.tuberculosis*
- MIC levels comparable to first line (in vitro)
- Nanotechnology : tool to improve bioavailability stability and controlled release of these compounds

5. LeuRS INHIBITORS

- Target: Leucyl-t RNA synthetase enzyme
- Cellular translation and protein synthesis
- Good in-vitro and in-vivo activity against mycobacterial tuberculosis

6. inhA inhibitors

- Isoniazid : activated within the mycobacterial cell by the KatG (catalase peroxidase)
- KatG couples isonicotinic acyl with NADH to form isonicotinic acyl-NADH complex
- Complex binds tightly to the enoyl-acyl carrier protein reductase (InhA), blocking the natural enoyl-AcpM substrate and action of fatty acid synthase
- Most isoniazid resistance : mutations in KatG leading to the inability to activate the drug
- Direct InhA inhibitors: Thiadiazole series

Drugs in preclinical phase

- a. Benzothiazinone
- b. Spectinamide
- c. Capuramycin
- d. TBI-166 (Riminophenazines antibiotic)

ACADEMIC SESSION

LIST OF PUBLICATIONS:

ORIGINAL RESEARCH ARTICLE

- ❑ **Shivamurthy S, Manchukonda R**, Ramadas D. Evaluation of learning and memory enhancing activities of protein extract of *Withania somnifera* (Ashwagandha) in Wistar albino rats. *Int J Basic Clin Pharmacol* 2016;5:453-7.
- ❑ **Shivamurthy S, Manchukonda RS, Gurappanavar D**. Evaluation of self-medication patterns among under-graduate medical students of Adichunchanagiri institute of medical sciences, Karnataka, India: a cross-sectional questionnaire based study. *Int J Basic Clin Pharmacol* 2016; 5: 965- 8.
- ❑ Ramadas Dinesha, **Ravishankar M, Shwetha S**, Leela Srinivas. The learning and memory enhancing properties of *Bacopa monnieri* plant leaves: A systematic study in Wistar Albino rats model system. *Sch. Acad. J. Biosci.*, 2016; 4(2):179-184
- ❑ Ramadas Dinesha, **Ravishankar M, Shwetha S**, Chikkanna D. Phytochemical studies and antioxidant activity of *Bacopa Monnieri* plant leaves proteins. *Indo American Journal of Pharmaceutical Research*.2016:6(01).
- ❑ Ramadas Dinesha, **Ravishankar M, Shwetha S**, Chikkanna D. Phytochemical studies and antioxidant activity of *Withania Somnifera* plant root proteins. *World Journal of Pharmaceutical and Medical Research*.2016:34-7.
- ❑ **Gangadhar M, Shivaraju P T, Thippeswamy C**, et al. A survey study on use of over-the-counter (OTC) drugs among medical students of a tertiary care centre, B.G.Nagar. *J. Evid. Based Med. Health*. 2016; 3(24): 1059-1063.
- ❑ **Padmanabha TS, Manu G, Savkar M K, Chandrakantha T, Neha K**. Student's perception towards learning medical sciences: problem based teaching versus lecture based teaching methods. *Int J Basic Clin Pharmacol* 2016; 5: 411-5
- ❑ **Gangadhar M, Shivaraju P T, Thippeswamy C**, et al. Prevalence of depression, anxiety and stress: a cross-sectional survey among 2nd year medical students in a rural tertiary care centre. *J. Evolution of Med. Dent. Sci*. 2016; 5 (30):
- ❑ **Padmanabha TS**, Bhaskara K, **Manu G, Chandrakantha T**. Post Operative Utilization Pattern Of Analgesics In Orthopedic Department Of An Indian Tertiary Care Teaching Hospital. *Current Pharmaceutical & Clinical International Journal of Research*. 2016; 6(1): 27-31.
- ❑ **Shivaraju PT, Gangadhar M, Manchukonda R, Thippeswamy C, Krishnegowda N**. Impact of educational intervention on awareness of pharmacovigilance among medical undergraduates in Karnataka, India: a cross- sectional study. *Int J Basic Clin Pharmacol* 2016;5:986-90.
- ❑ **Shivaraju PT, Gangadhar M, Thippeswamy C**, et al. Perception of pharmacology teaching methods among second year undergraduate students towards better learning. *J. Evid. Based Med. Healthc*. 2016; 3(30), 1352-1355. DOI: 10.18410/jebmh/2016/309

- ❑ **Shivaraju PT, Gangadhar M, Thippeswamy C**, et al. Self-learning methods preferred by second year MBBS students in understanding pharmacology: An observational questionnaire based study. *J. Evid. Based Med. Healthc.* 2016; 3(36), 1749-1751. DOI: 10.18410/jebmh/2016/391
- ❑ **Padmanabha TS, Manu G**, Gajanan P Kulkarni, **Chandrakantha T, Neha K**. A prospective study of perceptions and preferences of medical students regarding teaching aids in teaching Pharmacology in a Medical College from India. *Sch. J. App. Med. Sci.*, 2016; 4(6C):2084-2088
- ❑ **Padmanabha TS, Manu G**, Gajanan P Kulkarni, **Chandrakantha T, Neha K**. Second year medical student's feedback and perspective on teaching methodology in Pharmacology in a tertiary care teaching hospital from India. *Sch. J. App. Med. Sci.*, 2016; 4(6C):2089-2094.

CASE REPORTS

- ❑ **Ravishankar M**, Rakshith N. Disulfiram induced hemoptysis: a case report. *Int J Basic Clin Pharmacol* 2016; 5: 220-2.
- ❑ **Manchukonda R**, Ramakrishna M. Ofloxacin/ornidazole induced fixed drug eruptions: a case report. *Int J Basic Clin Pharmacol* 2016; 5: 534-8.
- ❑ **Manchukonda RS, Thippeswamy C, Krishnegowda N, Muthahanumaiah NK**. Amoxicillin and clavulanic acid induced Stevens-Johnson syndrome: a case report. *Int J Basic Clin Pharmacol* 2016; 5: 1140-4.
- ❑ Devaraj Y, Belagola SD, Mukunda RS, **Manchukonda R**, Basavanaik P, Hasanabba AK, et al. Phenytoin induced drug rash with eosinophilia and systemic symptoms syndrome: a case report. *Int J Basic Clin Pharmacol* 2016; 5: 1148-51.

ACHIEVEMENTS

- ❑ **Dr Manu G**, Assistant Professor, presented a **paper** on "Assessment of knowledge, attitude and perception of Pharmacovigilance among nurses in a tertiary care centre" at SRIPS – 2016, held at Belagavi Institute of Medical Sciences, Belagavi.
- ❑ **Dr Manu G**, Assistant Professor, presented a **poster** on "Polypharmacy in clinical practise: Nurse's opinion, a cross sectional questionnaire study in a tertiary care centre" at SRIPS – 2016, held at Belagavi Institute of Medical Sciences, Belagavi.
- ❑ **Dr Padmanabha T S**, Assistant Professor, presented a **paper** on "Assessment of knowledge and awareness of Pharmacovigilance among MBBS students in a rural tertiary care centre" at SRIPS – 2016, held at Belagavi Institute of Medical Sciences, Belagavi.
- ❑ **Dr Padmanabha T S**, Assistant Professor, presented a **poster** on "Study of post operative utilization pattern of analgesics in orthopedics in a tertiary care teaching hospital" at SRIPS – 2016, held at Belagavi Institute of Medical Sciences, Belagavi.
- ❑ **Dr Chandrakantha T**, Postgraduate, presented a **paper** on "Perception of Interns towards teaching methods among MBBS subjects: Problem based teaching versus lecture based teaching methods" at SRIPS – 2016, held at Belagavi Institute of Medical Sciences, Belagavi.