AUTONOMIC NEUROPATHY IN DIABETES

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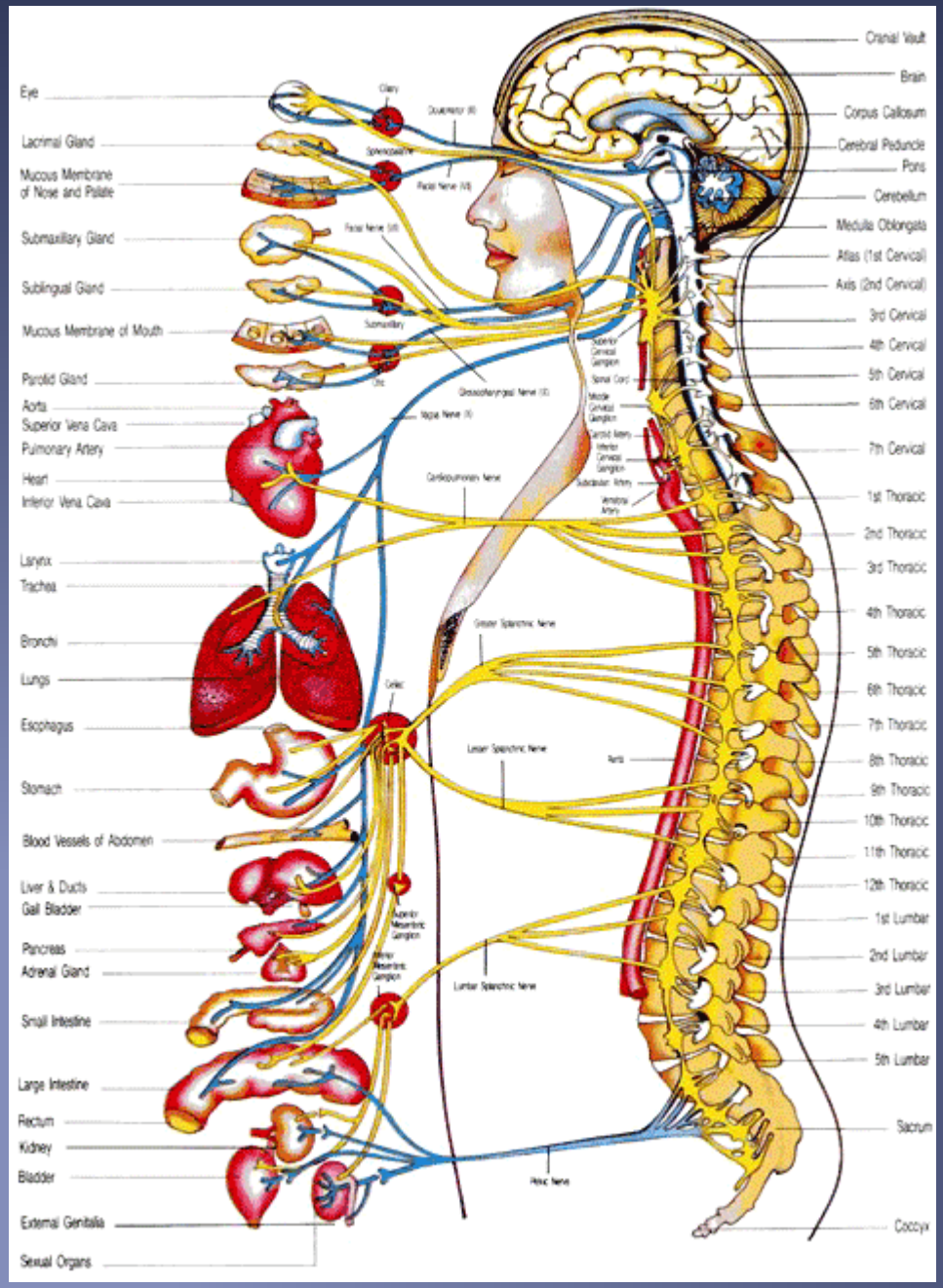
Plan of presentation

- Introduction
- Epidemiology
- Pathogenesis
- Systems involved in DAN
  - Clinical manifestations
  - Evaluation
  - Management
- Summary

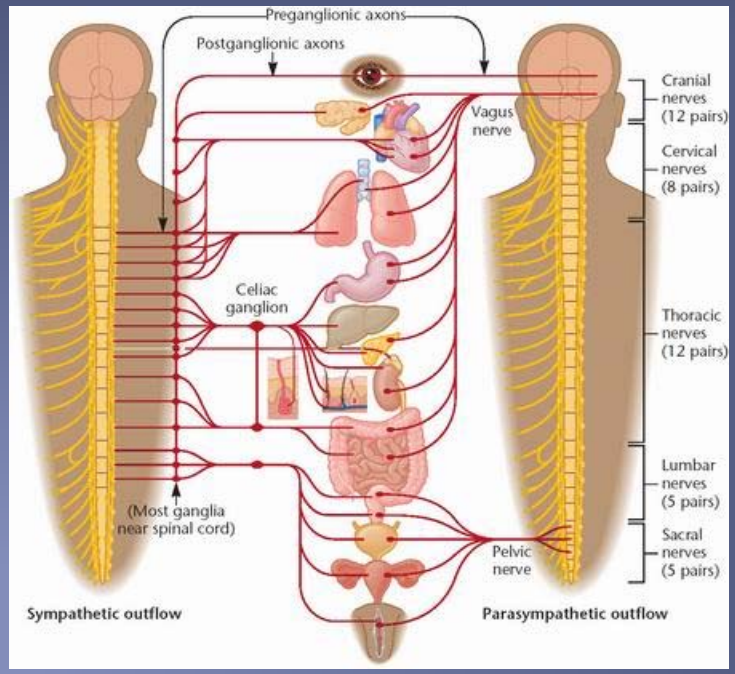
INTRODUCTION


Eye
Lacrimal Gland
Mucous Membrane of Nose and Palate
Submaxillary Gland
Sublingual Gland
Mucous Membrane of Mouth
Parotid Gland
Aorta
Superior Vena Cava
Pulmonary Artery
Heart
Inferior Vena Cava
Larynx
Trachea
Bronchi
Lungs
Esophagus
Stomach
Blood Vessels of Abdomen
Liver & Ducts
Gall Bladder
Pancreas
Adrenal Gland
Small Intestine
Large Intestine
Rectum
Kidney
Bladder
External Genitalia
Sexual Organs
Ciliary
Sphenopalatine
Facial Nerve (VII)
Submaxillary
Otic
Glossopharyngeal Nerve (IX)
Vagus Nerve (X)
Cardiopulmonary Nerve
Greater Splanchnic Nerve
Celiac
Lesser Splanchnic Nerve
Aorta
Lumbar Splanchnic Nerve
Pelvic Nerve
Cranial Vault
Brain
Corpus Callosum
Cerebral Peduncle
Pons
Cerebellum
Medulla Oblongata
Atlas (1st Cervical)
Axis (2nd Cervical)
3rd Cervical
4th Cervical
5th Cervical
6th Cervical
7th Cervical
1st Thoracic
2nd Thoracic
3rd Thoracic
4th Thoracic
5th Thoracic
6th Thoracic
7th Thoracic
8th Thoracic
9th Thoracic
10th Thoracic
11th Thoracic
12th Thoracic
1st Lumbar
2nd Lumbar
3rd Lumbar
4th Lumbar
5th Lumbar
Sacrum
Coccyx

The ANS

SNS

- activate body
- thoracolumbar (T1-L2)
- short preganglionic/long postganglionic fibers
- global responses
- postganglionic transmitter: NE (except sweat glands – ACh)



PSNS

- prepare body for rest/digest
- craniosacral (CN III, VII,IX, X & S2-4)
- long preganglionics/ short postganglionic fibers
- discrete/local responses
- postganglionic transmitter: ACh

The ANS

SNS

- "Fight -Flight" system
  - Activation
  - increases heart rate
  - increases sweating
  - dilates pupil
  - inhibits GI movement
  - closes sphincters
  - diverts blood from skin and GI tract to skeletal muscles

PSNS

- "Rest-digest" system
  - promotes digestion, GI peristalsis
  - slows heart rate
  - constricts pupil
  - empties bladder
  - relaxes sphincters
  - mediates genital erection

EPIDEMIOLOGY

Why recognise DAN?

- 25-50% die within 5-10 years of diagnosis
- 5-year mortality rate is 3-5 times higher
- Marker of adverse cardiovascular, renal and cerebrovascular outcomes

Is it common?

- Varyingly reported from 5-35%
- Symptomatic autonomic neuropathy - long after the onset of diabetes.
- Subclinical autonomic dysfunction - common

Association with peripheral neuropathy

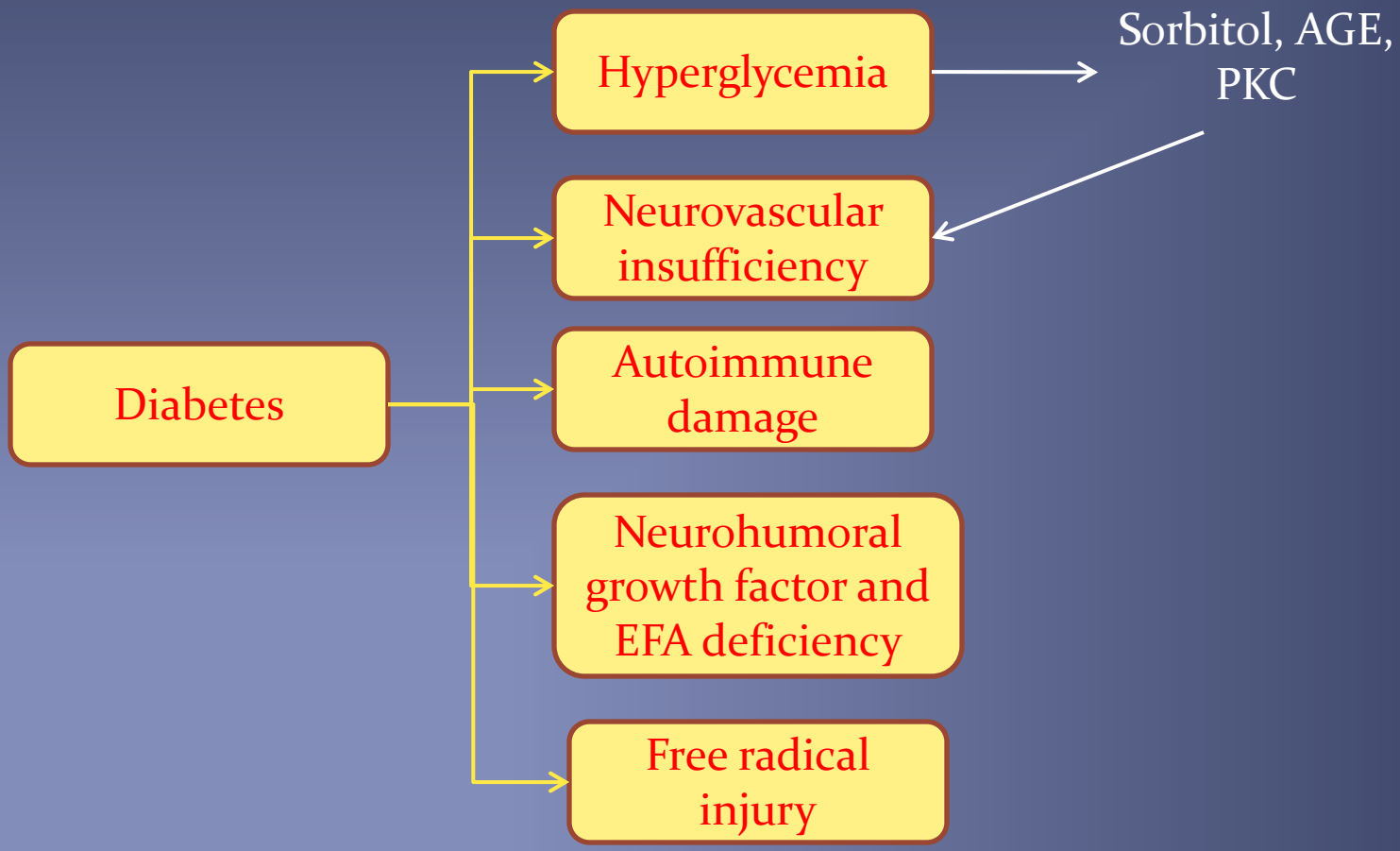
- tthough there is an association parasympathetic dysfunction may appear independant
- Hence, tests for sensory and motor nerve functions (eg. monofilament, quantitative sensory testing, nerve conduction studies, muscle strength testing) may not be effective in detecting DAN that cardiovascular autonomic function testing can detect at early stage of emergence.
- Thus, tests for other forms of diabetic peripheral nerve dysfunction should not substitute for the tests for cardiovascular autonomic dysfunction.

Epidemiology

- Risk factors
  - poor glycemic control
  - long duration of diabetes
  - increasing age
  - female sex
  - higher body mass index
  - ? smoking and elevated triglycerides

PATHOGENESIS

Pathogenesis



SYSTEMS INVOLVED IN DAN

Systems involved in DAN

- Vagus nerve (~75% of all parasympathetic activity), earliest nerve
- Effects are widespread but symptoms may be related to single system
- Systems
  - Cardiovascular
  - Gastrointestinal
  - Genitourinary
  - Adrenomedullary
  - Peripheral vasomotor & sudomotor
  - Pupillary

CARDIOVASCULAR AUTONOMIC NEUROPATHY

Clinical manifestations

- Heart Rate changes
  - Impaired Heart rate variability
  - Resting tachycardia and fixed HR
- BP changes
  - Nocturnal hypertension
  - Orthostatic hypotension
  - postprandial hypotension
- Limited exercise tolerance

Other clinical implications

- QT prolongation, altered repolarisation, nocturnal arrhytmogenesis and death
- Silent myocardial ischemia
- Diabetic cardiomyopathy
- Intraoperative cardiovascular liability (vasopressor support, severe intraop hypothermia)
- Stroke

Evaluation

- No single approach
- For parasympathetic HR responses to
  - Breathing
  - Standing
  - Valsalva
- For sympathetic BP responses to
  - Standing
  - Isometric exercise

Evaluation

Test	Technique	Interpretation
HR reponse to deep breathing	Patient lies quietly and breathes deeply at a rate of six breaths per minute and ECG is recorded. The difference between the maximum and minimum heart rate and Expiration to Inspiration (E:I) R-R interval ratio are calculated.	A difference in HR of < 10 bpm and E:I ratio is >1.17 are abnormal.
HR response to standing	ECG is recorded in lying followed by full upright position. The R-R interval is measured at beats 15 and 30 after the patient stands.	A 30:15 ratio of < 1.03 is abnormal.
HR response to Valsalva	The patient forcibly exhales into the mouthpiece of a manometer, exerting a pressure of 40 mm Hg for 15 seconds. There are 4 phases during this maneuver. The longest and shortest R-R intervals are measured. The ratio is called valsalva ratio	Valsalva ratio of < 1.2 is abnormal.

Evaluation

Test	Technique	Interpretation
BP response to standing	BP is measured when the patient is lying down and 2 minutes after the patient stands	Systolic BP fall of ≥ 20 mm Hg or diastolic BP fall of ≥ 10 mm Hg is abnormal *.
BP response to isometric exercise	The patient squeezes a handgrip dynamometer to establish his or her maximum. The patient then maintains the grip at 30% maximum for 5 minutes. BP is measured in the contralateral arm.	A diastolic BP rise of < 16 mm Hg is abnormal.

AFT LAB

Stages

- Early stage: abnormality of heart rate response during deep breathing alone
- Intermediate stage: an abnormality of Valsalva response
- Severe stage: the presence of postural hypotension

Safety

- High value-to-risk ratio.
- Some adverse effects. Valsalva maneuver - transient increase in intracranial, intrathoracic and intraabdominal pressures - theoretical possibility of intraocular hemorrhage and lens dislocation.
- Children, mentally disabled and aged – difficult to perform

Evaluation

- Newer noninvasive tests
  - Power spectral analysis
  - MIBG SPECT
  - 11-C-hydroxyephedrine scintigraphy

Treatment of impaired HRV

- Prolonged QT
  - Acute mgt. (Mg, temp pacing, isoproteronol)
  - Chronic mgt. (avoid ppt. factors, electrolytes, pem pacing.
- SCD
  - ICD

Treatment of OH

- General measures
  - Gravity suits and stockings
  - Changes in posture to be made slowly in "stages”
  - Tensing the legs, dorsiflexing the feet, or doing handgrip exercise before standing
  - High salt diet, increasing water consumption
  - Treat anemia, avoid drugs aggrevating OH
- Pharmacological measures
  - Glycemic control and multifactorial risk reduction
  - Alpha lipoic acid, ACEi

Drugs for OH

- Specific Drugs
  - Midodrine 2.5 – 10 mg tid
  - Fludrocortisone 0.05 mg hs – 0.4 mg/day
    - β blockers (pindolol) – not clear
    - Clonidine – severe side effects
    - desmopressin
  - Octreotide esp. for postprandial hypotension 25 – 200 mcg/day

GASTROINTESTINAL AUTONOMIC NEUROPATHY

Clinical manifestations

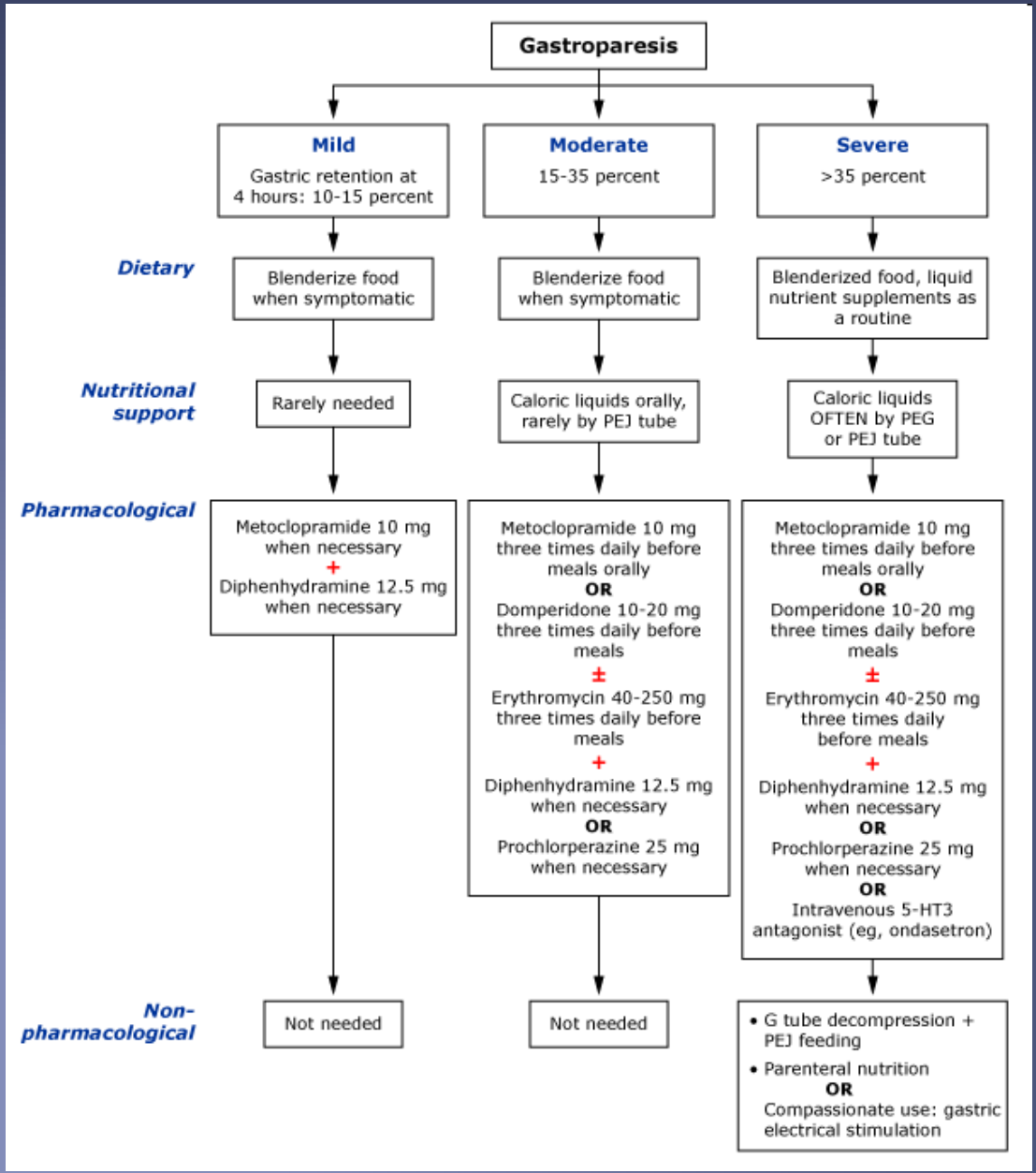
- Esophageal dysmotility
  - GERD common, dysphagia is uncommon
- Gastroparesis diabeticorum
- Enteropathy
  - Nocturnal watery painless diarrhea
- Constipation
- Fecal incontinence
- Gall bladder atony and enlargement

Gastroparesis

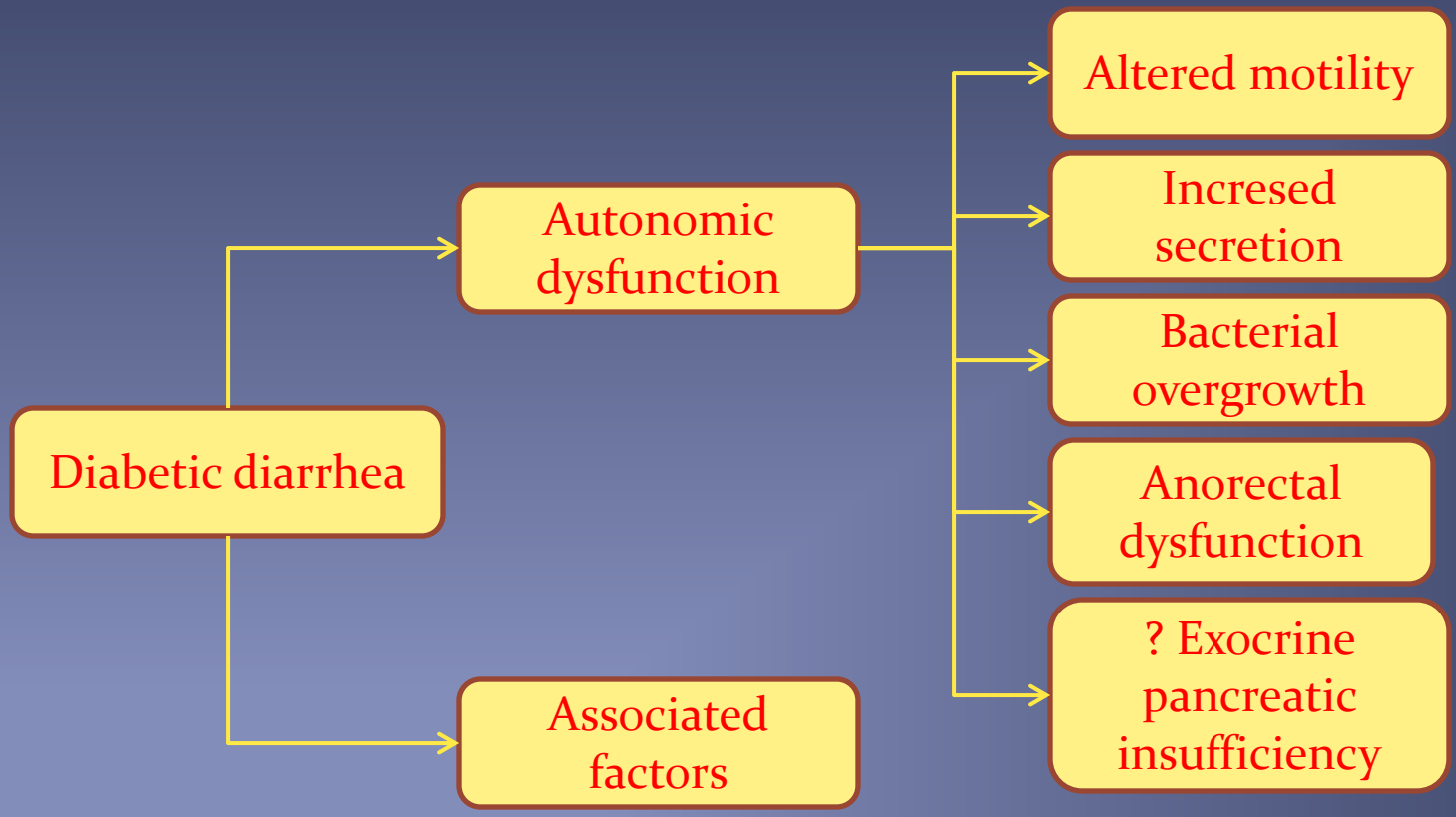
- Clinical presentation
  - Classic “bloating, early satiety and postprandial fullness”
  - Dyspepsia and “brittle diabetes”
- Clinical evaluation
  - History of drugs (opiods and TCA) and eating disorders
  - Metabolic evaluation – electrolytes, thyroid, addisons
  - Endoscopy, barium radiography,USG, MRI
  - Gastric emptying scintigraphy (low fat eggwhite meal – 0, 1, 2, 4 hrs imaging; retention of >10% at 4 hours, and >70% at 2 hours defines delayed gastric emptying)

Treatment of Gastroparesis

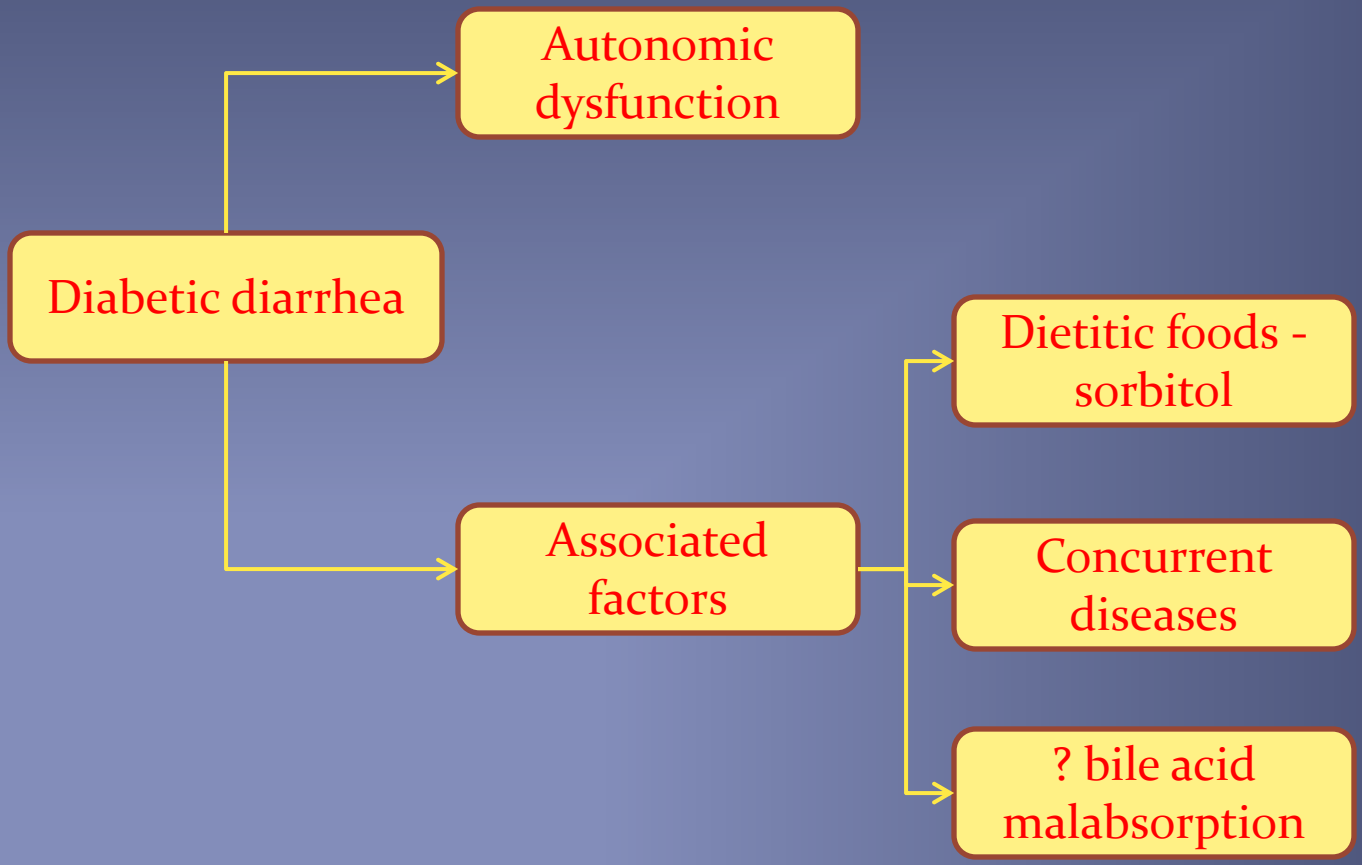
Cisapride not more than 1 mg/kg/d



Pathogenesis of diabetic diarrhea



Pathogenesis of diabetic diarrhea



Evaluation for diarrhea

Level of invesigation	Tests
First line	(a) Blood biochemistry; Stool – weight, 72 hour fecal fat, elastase, chymotrypsin, leucocytes, parasites, occult blood; Upper GI Barium studies with dedicated small bowel follow through - for gastric retention, pattern of malabsorption, small intestinal and colonic wall thickness (b) D-Xylose test for small intestinal malabsorption
Second line	(a) Upper GI endoscopy with duodenal biopsy for histology and bacteriology (b) Colonoscopy and biopsy for histology (c) Glucose hydrogen breath test for bacterial overgrowth
Third line	(a) Ambulatory small intestinal manometry for intestinal pseudoobstruction (b) Empiric cholestryamine for possible bile acid malabsorption (c) Enteroscopy with biopsy and enteroclysis (d) Secretin-pancreozymin test for pancreatic exocrine insufficiency

Treatment of diabetic diarrhea

- Initial fluid and electrolyte management
- Treat nutritional deficiencies
- Treat specifically if found (SIBO with antibiotics, celiac with gluten free diet)
- Loperamide (2-4 mg qid), diphenoxylate (5 mg qid), codiene (30 mg qid)
- Clonidine (600 mcg tid)
- Octreotide 50-75 mcg tid
- Fecal incontinence
    - Drugs to reduce stool volume (Loperamide)
    - Biofeedback exercise with toilet training

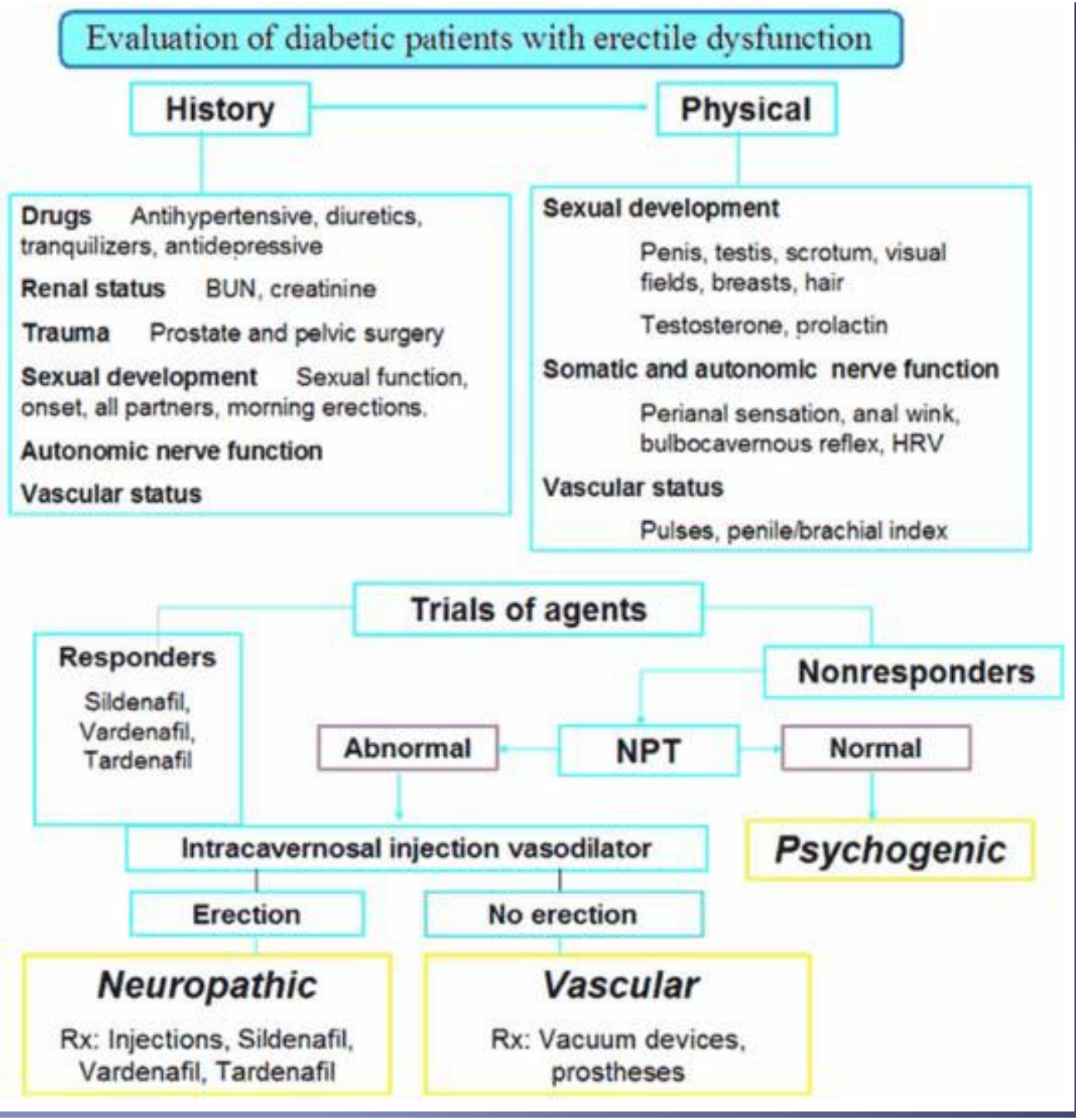
GENITOURINARY AUTONOMIC NEUROPATHY

Clinical manifestations

- Neurogenic bladder
  - Decreased bladder sensation, hesitancy, later incomplete evacuation and frequent UTI
- Erectile dysfunction
  - Neuropathy, vascular disease, metabolic control, nutrition, endocrine disorders, psychogenic factors, and anti-diabetes drugs.
- Female sexual dysfunction
  - Decreased libido and vaginal lubrication causing dypareunia

Evaluation

- Bladder
  - Urine culture, postvoidal residue, renal function tests, cystometry and voiding cystometrogram
- Erectile dysfunction
  - History, physical examination, biochemistry, hormones, penile doppler, therapeutic trial with sildanefil, intracavernosal injections of vasodilator
- Retrograde ejaculation
  - Azoospermia with spermaturia in postcoital urine specimen


Evaluation of diabetic patients with erectile dysfunction
History
Physical
Drugs Antihypertensive, diuretics, tranquilizers, antidepressive
Renal status BUN, creatinine
Trauma Prostate and pelvic surgery
Sexual development Sexual function, onset, all partners, morning erections.
Autonomic nerve function
Vascular status
Sexual development
Penis, testis, scrotum, visual fields, breasts, hair
Testosterone, prolactin
Somatic and autonomic nerve function
Perianal sensation, anal wink, bulbocavernous reflex, HRV
Vascular status
Pulses, penile/brachial index
Trials of agents
Responders
Sildenafil, Vardenafil, Tardenafil
Nonresponders
Abnormal
NPT
Normal
Intracavernosal injection vasodilator
Psychogenic
Erection
No erection
Neuropathic
Rx: Injections, Sildenafil, Vardenafil, Tardenafil
Vascular
Rx: Vacuum devices, prostheses

Treatment

- Bladder
  - CBD initially
  - later timed voiding often with Crede's maneuvre
  - bethenechol at the time of voiding
  - external sphincter relaxation with doxazosin
  - Severe cases, clean intermittent catheterisation
  - Rarely, bladder neck resection
- ED
  - 5-PDE inhibitors (> 60% patients respond)
  - Intracavernosal papaverine
  - Transurethral alprodostil

MISCELLANEOUS

Others

- Metabolic
  - Hypoglycemia unawareness
- Sudomotor
  - Peripheral dry skin and paradoxical excess sweating in trunk
  - Gustatory sweating
- Peripheral vasomotor
  - changes in the texture of skin, loss of nails, anhidrosis, callus formation and the development of fissures and cracks

- Peripheral edema and venous prominences
- The loss of sympathetic vascular innervation results in high peripheral blood flow through arteriovenous (AV) shunts and abnormal local reflex vascular control - increased osteoclastic activity resulting in reduced bone density, proneness to fractures - ?pathogenesis of Charcot's neuroarthropathy

- Pupillary involvement
  - AR pupil, diminished hippus, reduced dark adaptation

GUIDELINES FOR DIAGNOSIS

San Antonio conference, 1988

- Symptoms not to be considered as markers of its presence.
- Noninvasive validated autonomic function tests should be used taking into account confounding factors like concomitant drug use, concurrent illness, age, etc.
- Abnormality in more than one test on more than one occasion is desirable.
- Both sympathetic and parasympathetic functions should be tested independently.

San Antonio conference, 1988

- For the assessment of CAN, the panel recognized three tests of heart rate control and two tests of BP control
- These tests were judged suitable for both routine screening and monitoring the progress of autonomic neuropathy.
- No other tests including those for GI, genitourinary, sudomotor, microvascular skin blood flow and pupillary function were considered to be sufficiently well standardized for routine clinical use.

Thanks