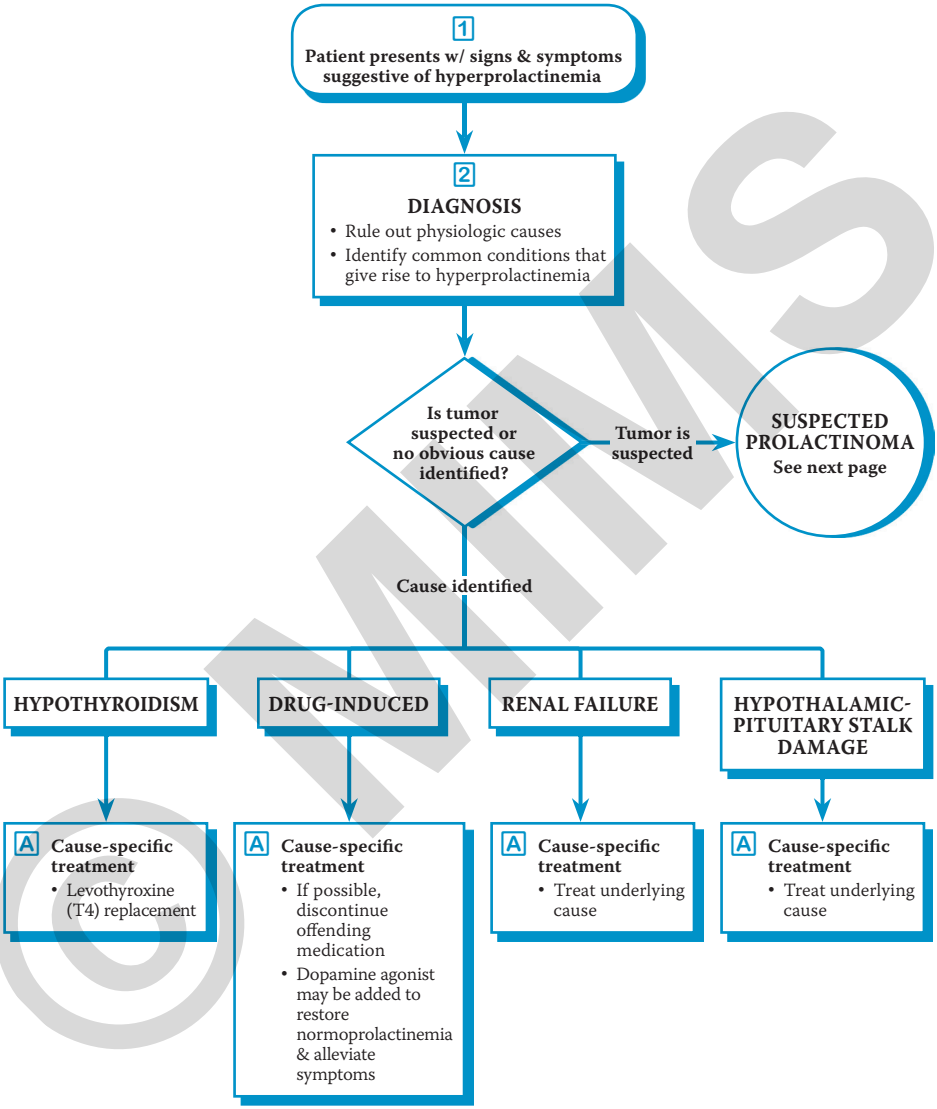
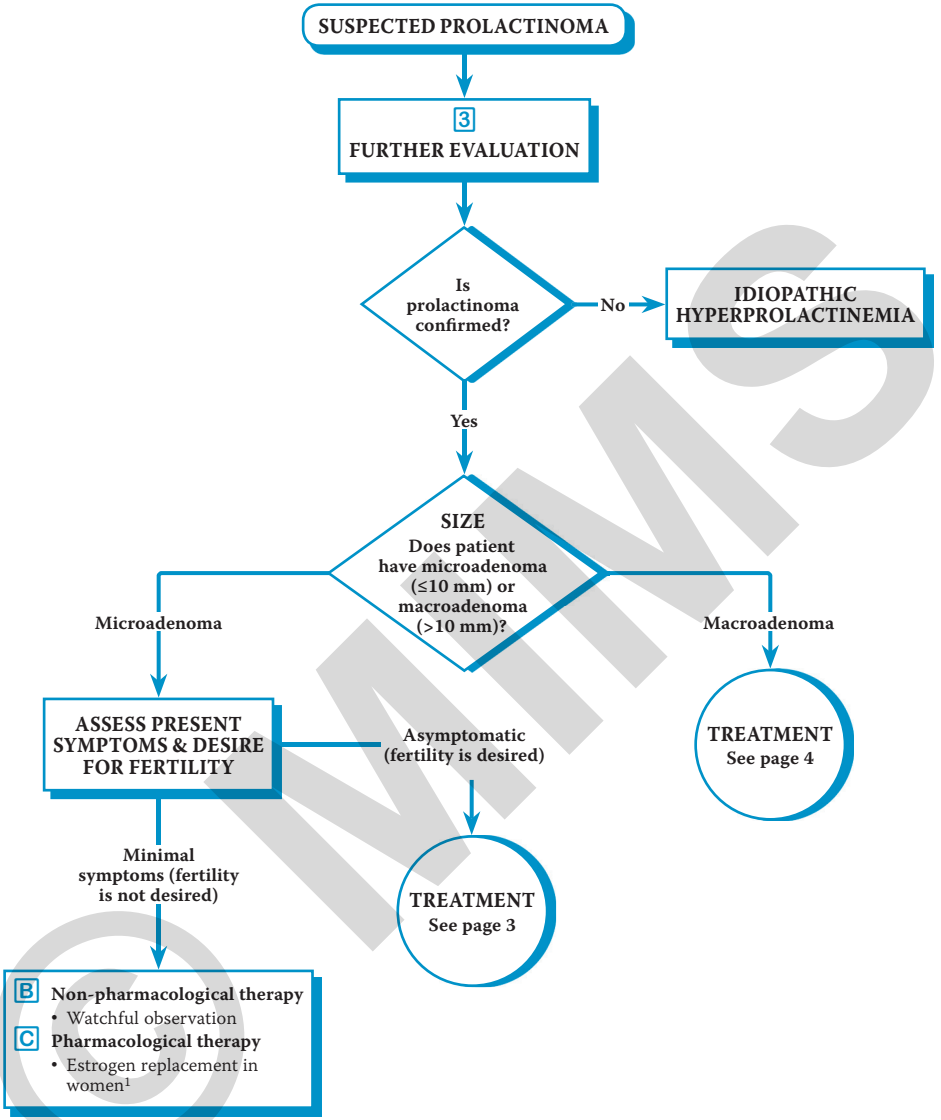
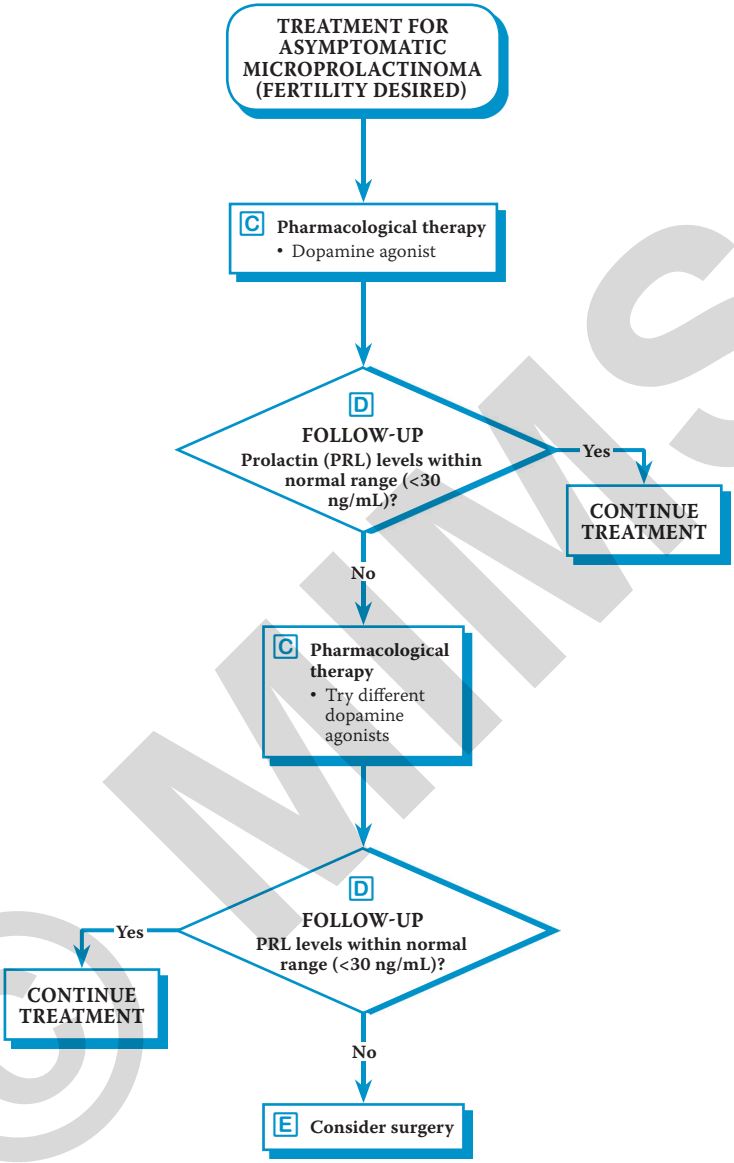
Hyperprolactinemia (1 of 9)



Not all products are available or approved for above use in all countries.
Specific prescribing information may be found in the latest MIMS.



[1]Various estrogen replacement products are available. Please see the latest MIMS for specific formulations.



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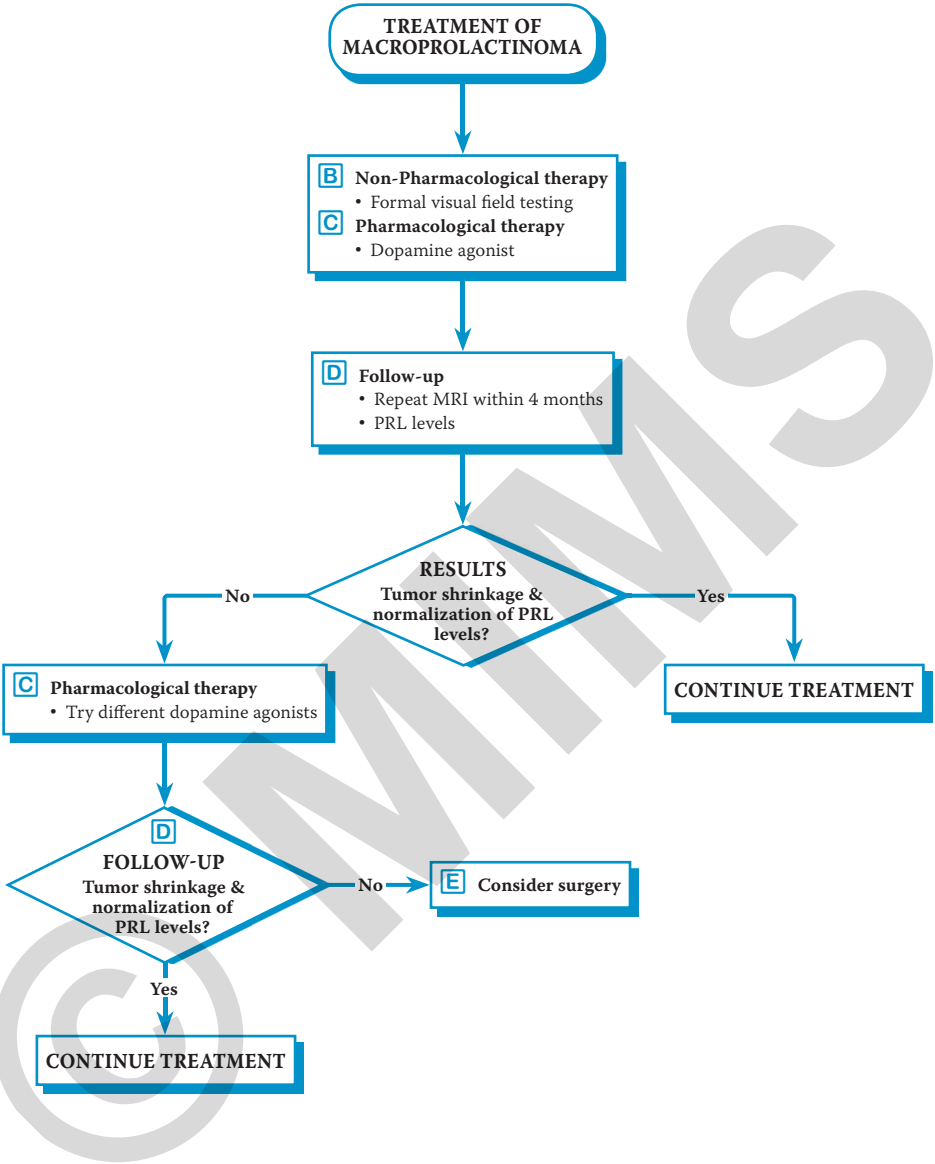

1 HYPERPROLACTINEMIA

- Hyperprolactinemia is the presence of elevated prolactin (PRL) levels

Signs & Symptoms

- For both sexes, a pituitary tumor may cause visual field defects or headache

Women

- Menstrual irregularity
- Galactorrhea
- Infertility
- Vaginal dryness
- Dyspareunia
- Loss of libido
- Reduction in vertebral bone mineral density in sustained, pronounced hyperprolactinemia

Men

- Diminished libido
- Visual loss caused by optic nerve compression
  - Extraocular muscle weakness
- Hypogonadism
- True galactorrhea is uncommon
- Gonadotropin suppression
  - Reduced testosterone
  - Impotence
  - Oligospermia
- Osteopenia, decreased muscle mass & decreased facial hair may occur in prolonged hyperprolactinemia

2 DIAGNOSIS

Etiology

Physiologic

- Pregnancy
- Lactation
- Chest wall stimulation
- Stress
- Sleep
- Coitus
- Exercise

Drug-induced

- Dopamine receptor blockers
  - Thioxanthines
  - Phenothiazines eg Chlorpromazine, Perphenazine
  - Butyrophenones eg Haloperidol
  - Metoclopramide
- Dopamine synthesis inhibitors
  - Methyldopa
- Opiates & opiate antagonists
- H_2-receptor antagonists (H_2RA) eg Cimetidine, Ranitidine
- Catecholamine depletors
  - Reserpine
- Imipramines eg Amitriptyline, Amoxapine
- Hormones eg Estrogens
- Ca antagonists
  - Verapamil
- Selective serotonin reuptake inhibitor (SSRI)
  - Fluoxetine
- Anesthetics
- Anticonvulsants eg Phenytoin

Neurogenic Disorders

- Lesions on the chest wall
- Spinal cord injury
- Stimulation of breast

Systemic Disorders

- Hypothyroidism
- Chronic renal failure (CRF)
- Cirrhosis
- Epileptic seizures
- Polycystic ovarian disease
- Pseudocyesis

Pituitary Hypersecretion

- Acromegaly
- Prolactinoma (most common cause of prolactin levels >100 mcg/L)
- Macroprolactinemia
- Plurihormonal adenoma
- Macroadenoma (compressive)

Hypothalamic-Pituitary Stalk Damage

- Tumors (eg craniopharyngoma, germinoma, hypothalamic metastases, meningioma)
- Empty sella
- Adenoma w/ stalk compression
- Lymphocytic hypophysitis
- Rathke's cyst
- Irradiation
- Trauma (eg pituitary stalk section, suprasellar surgery)
- Granulomas
- Infiltrations

Production of Ectopic Prolactin

- Non-Hodgkin lymphoma
- Colorectal adenocarcinoma
- Renal cell carcinoma
- Ovarian teratomas
- Gonadoblastoma
- Uterine cervical carcinoma

2 DIAGNOSIS (CONT'D)

Diagnosis

Lab Tests & Physical Exam

- To establish the diagnosis of hyperprolactinemia, it is recommended to have a single measurement of serum PRL
  - A level above the upper limits confirms the diagnosis
- Careful history & physical exam including cranial nerve examination
  - Check for galactorrhea, visual field defects, signs of cirrhosis, hair growth pattern on the body, etc
  - Drug history
- Blood chemistry [blood urea nitrogen (BUN), creatinine]
- Other pituitary hormones (eg testosterone levels, cortisol, insulin growth factor-1) as necessary
- Pregnancy test
- To rule out macroprolactinemia, polyethylene glycol precipitation is recommended
- Thyroid function tests (to rule out hypothyroidism)

3 FURTHER EVALUATION

- Physiologic causes, renal failure, parasellar tumors, hypothyroidism & drug-induced hyperprolactinemia should be ruled out before extensive evaluation

Measure Fasting Prolactin (PRL) Level

- **Normal range:** <30 ng/mL normal fasting PRL level
- **Diagnostic range:** >250 ng/mL (w/ physiologic & drug-induced causes ruled out) usually indicates prolactinoma
  - A prolactinoma is less likely w/ PRL level <100 ng/mL
  - Several measurements should be made to confirm diagnosis

Radiologic Evaluation

- Should be performed if there is no obvious cause of hyperprolactinemia & if tumor is suspected
  - Physician must decide whether a radiographic study is warranted if PRL level <250 ng/mL but >100 ng/mL
- Magnetic resonance imaging (MRI) w/ gadolinium enhancement is the imaging study of choice
  - Computed tomography (CT) w/ contrast may also be used
  - Serum PRL >200 ng/mL indicates prolactinoma
    - Prolactinomas are classified as macroadenoma if the size is ≥10 mm; microadenoma if <10 mm in size
  - Serum PRL <200 ng/mL w/ large pituitary mass usually indicates hyperprolactinemia secondary to stalk compression
  - MRI & CT scan normal & no obvious cause, patient is said to have idiopathic hyperprolactinemia

A CAUSE-SPECIFIC TREATMENT (HYPERPROLACTINEMIA)

Hypothyroidism

- **Levothyroxine (T_4) Replacement**
  - Resolution of hyperprolactinemia usually occurs after adequate thyroid replacement
- *Please see Hypothyroidism disease management chart for further information*

Drug-induced Hyperprolactinemia

- If possible, discontinue offending medication for 3 days or substitute an alternative drug
  - Then, repeat measurement of serum PRL

Psychiatric patients who cannot stop medication:

- If possible, slowly decrease dose of offending antipsychotic medications or substitute an alternative drug
- Dopamine agonist may be added to restore normoprolactinemia & alleviate symptoms
  - Use w/ caution as it may worsen underlying psychiatric condition

Renal Failure

- Treat underlying cause
- Renal transplant may help to restore PRL levels to normal

Hypothalamic-Pituitary Stalk Damage

Granulomatous Infiltrates

- Glucocorticoids (rarely effective)

Hypothalamic or Sellar Mass Lesions

- Surgical resection may reverse hyperprolactinemia

Irreversible Hypothalamic Damage

- No treatment may be necessary

B NON-PHARMACOLOGICAL THERAPY (PROLACTINOMA)

Watchful Observation

- Appropriate in patients who present w/ microadenomas, are not concerned w/ fertility, & have minimal symptoms
- **Effects:** Studies have shown that 93% of microadenomas do not grow over a 4-6 year period
- Close observation of the adenoma is necessary to determine if it is growing
  - Serial PRL levels should be done regularly
  - MRI should be performed if a significant rise in PRL is noticed
  - Imaging studies at yearly intervals

Formal Visual Field Testing

- Performed prior to dopamine agonist treatment & every 6-12 months thereafter
- More frequent monitoring initially in those w/ visual field deficit

C PHARMACOLOGICAL THERAPY (PROLACTINOMA)

- Goal is to decrease PRL levels & to alleviate symptoms
- If possible, discontinue offending medication

Dopamine Agonists

- Titrate dose to achieve maximum PRL suppression & to restore reproductive function
- Therapy recommended to lower PRL levels, decrease tumor size & restore gonadal function in patients w/ microadenomas or macroadenomas

Bromocriptine

- Initial drug of choice
- **Actions:** Ergot alkaloid that binds to & stimulates D_2 dopamine-receptors on lactotroph cells
- **Effects:** Lowers serum PRL levels in 70-100% of patients
  - Decreases tumor size & restores gonadal function
  - Macroadenomas shrinkage of ≥50% is observed in 40% of patients
  - Headaches & visual disturbances improve rapidly within days of commencing therapy
  - Resumption of menses & ovulation in 80-90% of hyperprolactinemic women
- Discontinuation results in recurrent hyperprolactinemia & tumor regrowth along w/ the risk of visual disturbances
  - ~5% of patients do not have recurrence w/ discontinuation of Bromocriptine
- May be administered intravaginally if oral dose is not tolerated
- **Pregnancy:** Bromocriptine has been used to restore fertility in hyperprolactinemic women
  - Attempt to reduce neonatal exposure to the drug
  - Woman desiring to become pregnant should use barrier contraception & Bromocriptine until 3 regular menstrual cycles have occurred (to allow for conception timing)
  - Bromocriptine can be safely discontinued in women w/ microadenomas or intrasellar macroadenomas without significant suprasellar or parasellar extension
  - In women w/ larger macroadenomas, 2 options are recommended:
    - Discontinue Bromocriptine
    - Give Bromocriptine continuously throughout gestation, however w/ theoretical fetal risk
  - 5% of microadenomas & 15-30% of macroadenomas may grow during pregnancy
  - PRL levels rise progressively in pregnancy & monitoring of PRL levels is not useful
  - Regular visual field exam throughout pregnancy is recommended
  - Visual field testing is recommended in patients w/ macroadenomas
  - Restart Bromocriptine if tumor growth occurs & explain to patient the risks & benefits of treatment
  - Surgical decompression may be used if vision is threatened

C PHARMACOLOGICAL THERAPY (PROLACTINOMA) (CONT'D)

Cabergoline
- Useful in patients who are resistant or intolerant to Bromocriptine
  - Fewer side effects than Bromocriptine & can be given twice a week
  - Higher efficacy in normalizing PRL levels & higher frequency of pituitary tumor shrinkage
- **Actions:** Ergot derivative which is a long-acting dopamine agonist w/ high affinity for D_2 receptors on lactotroph cells
- **Effects:** Suppresses PRL secretion for >14 days after a single oral dose
  - Lowers serum PRL levels & restores gonadal function in ~80% of patients w/ microadenomas
  - Normalizes PRL & shrinks tumor in ~70% of macroadenomas

Quinagolide
- May be useful in patients who are intolerant of ergot derivatives
- **Actions:** Non-ergot Dopamine agonist
- **Effects:** ~50% of patients who are resistant to Bromocriptine respond to Quinagolide
  - Efficacy is similar to other Dopamine agonists

Pergolide
- **Effects:** Several studies have shown that Pergolide is as efficacious as Bromocriptine
  - Tolerance is similar to Bromocriptine
- Discontinued in other countries due to increased risk of valvular heart disease

Metergoline
- **Actions:** Ergot derivative which is both a dopamine agonist & a serotonin antagonist
- Indicated for use in hyperprolactinemic amenorrhea

D FOLLOW-UP

- Monitor fasting serum PRL levels
- Check tumor size w/ MRI
- Evaluate symptoms like resumption of cyclic menstruation & resolution of galactorrhea

E SURGERY

Transsphenoidal Surgery
- Preferred method
  - Craniotomy is rarely performed

Indications:
- Patients who are resistant to or exhibit non-tolerance to optimal medical therapy
- Patients w/ intrasellar tumor & long-term medical treatment is not acceptable
- Patients w/ tumors pressing on the optic chiasm
- **Effects:**
  - Microprolactinomas: Initially 70% achieve PRL normalization
  - Macroprolactinomas: Only 30% are successfully resected
  - Recurrence of microprolactinomas & macroprolactinomas occurs in 20% of patients within 1 year of surgery
  - Recurrence rates reach 50% in long-term follow-up of macroprolactinomas
- **Potential complications:** Usually infrequent when performed by experienced surgeons
  - Mortality rate: 0.3%
  - Morbidity rate: 0.4%

OTHER TREATMENT

Radiotherapy
- Recommended in patients who fail surgical treatment or who have aggressive, resistant or malignant prolactinomas
- May control tumor growth
- It may require 20 years for the maximal effect to be achieved & may never restore PRL levels to normal

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Dosage Guidelines

DOPAMINE AGONISTS		
Drug	**Dosage**	**Remarks**
Bromocriptine	**Initial dose:** 2.5 mg PO 12 hrly **or** 1.25 mg PO 8-12 hrly Gradually increase over a period of several wk to 10-20 mg PO 12 hrly **Maintenance dose:** 5-7.5 mg/day PO **Max dose:** 30 mg/day	**Adverse Reactions** • Dose-related side effects (N/V, dizziness, syncope & orthostatic hypotension); CV effects (vasospasm, prolonged hypotension, arrhythmias, erythromelalgia, pericarditis, pericardial effusions); CNS effects (headache, psychosis, hallucinations, delusions, confusion); Other effects (retroperitoneal fibrosis, pleural thickening & effusions, nasal congestion, dry mouth) • Studies have shown that Cabergoline & Quinagolide may be better tolerated than Bromocriptine **Special Instructions** • Take w/ food to minimize nausea • Use w/ caution in patients w/ CV disease, psychiatric disorders & in postpartum women w/ history of hypertensive disorders
Cabergoline	**Initial dose:** 0.5 mg/wk PO in 1-2 doses May increase dose slowly in increments of 0.5 mg/wk at mthly intervals **Maintenance dose:** 0.25-2 mg/wk	
Metergoline	**Initial dose:** 2 mg PO 8 hrly x 3-4 days then increase to **Maintenance dose:** 4 mg PO 8 hrly until menses recur & for not <90 days	
Pergolide	**Maintenance dose:** 50-150 mcg PO 24 hrly	
Quinagolide	**Initial dose:** 25 mcg PO 24 hrly x 3 days Increase dose in increments of 25 mcg at 3-day intervals **Maintenance dose:** 75-150 mcg PO 24 hrly If higher doses are needed (>300 mg/day), titrate in increments of 75-150 mcg at intervals of not <4 wk up to **Max dose:** 900 mcg/day PO	

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
Not all products are available or approved for above use in all countries.
Products listed above may not be mentioned in the disease management chart but have been placed here based on indications listed in regional manufacturers' product information.

Specific prescribing information may be found in the latest MIMS.

Please see the end of this section for the reference list.