DSH PSYCHOTROPIC MEDICATION Operational Procedures

APPENDIX -- HYPERPROLACTINEMIA:

NOTE: Directive statements and procedures described in this chapter are informational and advisory in nature.

I. Hyperprolactinemia (HPRL):

The most common cause of nontumoral HPRL is medications. Hyperprolactinemia is a common side effect of neuroleptic antipsychotic treatment due to interference at the pituitary gland, with a prevalence of about 70% in patients with psychotic illnesses requiring chronic antipsychotic treatment. Interference is caused by neuroleptic antagonism of pituitary dopamine-D2 receptors on lactotroph cells in the anterior pituitary because dopamine is a tonic inhibitor of prolactin release.

Prolactin secretion is also stimulated by serotonin and decreased by serotonin antagonists due to serotonin's capacity to decrease dopamine release by dopamine neurons expressing 5HT-2A receptors.

A. Medications which can cause hyperprolactinemia:

- Dopamine Receptor Antagonists
- Monoamine Oxidase Inhibitors
- Tricyclic Antidepressants
- Amoxapine
- Reserpine
- Methyldopa
- Ca++ Channel Blockers
- Estrogen
- H2 Receptor antagonists
- Cocaine
- Selective Serotonin Receptor Inhibitors

B. Risperidone and its metabolite paliperidone (or 9-hydroxy-risperidone, sold as Invega®, Invega Sustenna®, Invega Trinza®, Erzofri®, and Invega Hafyera®) are particularly prone to causing prolactin elevation, as both are actively effluxed at the blood-brain barrier making the concentration at the pituitary higher than that in the CNS.

C. Asenapine, Iloperidone, lurasidone, ziprasidone and first-generation antipsychotics tend to elevate prolactin levels more robustly—but usually not to the extent seen with risperidone or paliperidone.

D. Lumateperone and olanzapine tend to elevate prolactin levels moderately at most.

E. Clozapine, quetiapine, and pimavanserin do not typically elevate prolactin levels significantly, unlike conventional antipsychotics.

F. Aripiprazole, brexpiprazole, and cariprazine, being partial dopamine agonists, typically cause a decline in prolactin secretion, but in combination with D2 antagonist antipsychotics can lead to destabilization and increased psychosis.

II. Sequelae of HPRL:

A. Galactorrhea and amenorrhea or menstrual cycle changes in women

B. Erectile dysfunction in men

C. Hirsutism also may occur, as may gynecomastia

Guidelines have not been clearly developed regarding monitoring of bone density or the effectiveness of interventions such as calcium supplementation, vitamin D supplementation, or bisphosphonate treatment.

Prolactin-related adverse effects become increasingly likely at serum concentrations exceeding 50 ng/mL.

III. Potential long-term risks of HPRL:

A. Hypogonadism, due to loss of anabolic effects of sex steroids.

B. Osteoporosis/osteopenia, due to loss of bone calcium as a result of altered mineral metabolism. [NOTE: The magnitude of this risk has not been well characterized.]

IV. Other causes of hyperprolactinemia

A. Physiological causes: pregnancy, nipple stimulation and lactation, exercise, stress, seizures, sleep, sexual intercourse

B. Pituitary disease: prolactinoma, acromegaly, Cushing disease, macroadenoma, plurihormonal adenoma, lymphocytic hypophysitis, parasellar mass, macroprolactinemia

1. Prolactinoma is a benign tumor of lactotrophs account for up to 40% of pituitary adenomas.

C. Hypothalamic disease-stalk damage: tumors, granulomas, infiltrative disease (histiocytosis disease), Rathke's cyst, pituitary stalk transection, cranial irradiation

D. Systemic disorder: primary hypothyroidism, chronic renal failure, polycystic ovarian disease, liver cirrhosis, pseudocyesis

V. The diagnostic approach to HPRL is as follows:

A. Identify symptomatic patients (i.e., women exhibiting amenorrhea or galactorrhea and men exhibiting erectile dysfunction or gynecomastia)

B. Additionally, measure serum prolactin concentrations as indicated by antipsychotic protocols included in this policy.

1. In drug-induced HPRL, prolactin levels are typically <100 ng/mL. Levels >200 ng/ml have been reported with risperidone,

paliperidone, and phenothiazines.

2. In the absence of renal failure or late pregnancy, levels >250-300 ng/mL are almost diagnostic of prolactinoma.

C. Obtain a morning fasting prolactin level as well as a pregnancy test, TSH, LH, and FSH. Renal function tests may be indicated. Peak levels of prolactin usually occur between 4 AM and 7 AM. Food has a minimal effect on the serum concentration of prolactin so fasting is not always essential unless there is mild elevation on the initial value. Prolactin inhibits GnRH leading to inhibition of LH and FSH secretion.

1. If HPRL is due to hypothyroidism, then levothyroxine is the treatment of choice. Confirm the normalization of prolactin after treatment.

D. MRI with contrast and focus on the sella turcica if measured prolactin concentrations >100-150 ng/mL, especially if use of a less provocative medication or use of a dopamine agonist does not result in a prolactin decline to <100 ng/mL.

VI. In some individuals elevated prolactin levels can be due to macroprolactin, large circulating aggregates of prolactin and antibodies. Macroprolactin is detectable in prolactin test assays but biologically inactive. Misdiagnosis can be evaluated by precipitating macroprolactin with polyethylene glycol prior to measuring prolactin levels. Macroprolactinemia does not require treatment. Prolactin levels greater than 500 ug/L is diagnostic.

VII. Treatment of HPRL:

A. If symptomatic medication-induced HPRL, the treatment of choice would be a safe alternative medication or dose reduction.

B. <u>Dopamine agonists:</u> Bromocriptine, pramipexole and cabergoline are dopamine agonists that bind to pituitary dopamine receptors inhibiting prolactin secretion.

1. These agents can normalize serum prolactin in up to 95%; however, this is dose dependent and psychotic symptoms may emerge with higher doses of dopamine agonists.

2. Shrinkage of a pituitary adenoma occurs early, but maximum effect may take up to six months.

3. Low dose aripiprazole or other D2 dopamine partial agonists (e.g., aripiprazole, brexpiprazole, and cariprazine) are <u>*NOT* recommended</u> for lowering prolactin levels. These medications have the highest risk for causing destabilization in patients receiving dopamine D2 antagonist antipsychotics when compared with dopamine agonists.

- **Bromocriptine** is started at 1.25mg daily after dinner. It can be increased to 1.25mg twice daily after meals in 7 days. It can be increased weekly by 1.25mg BID if symptomatic. Serum prolactin should be remeasured in one to two months and the dose can be increased until an optimal therapeutic response is achieved. The therapeutic doses studied ranged from 2.5 to 15mg/day.

  Bromocriptine side effects may include nausea, vomiting, nasal stuffiness, digital vasospasm, depression and postural hypotension. Contraindications are uncontrolled hypertension, hypersensitivity to bromocriptine or ergot alkaloids, history of cardiac valvular disorders or pulmonary, pericardial, or retroperitoneal fibrotic disorders.

- **Pramipexole** is a non-ergot dopamine agonist with negligible in vitro activity at the 5HT2B receptor (see cabergoline below). Data from a large population-based cohort of treated Parkinson's patients did not identify an increased risk of valvular regurgitation in patients treated with non-ergoline dopamine agonists. It has been less well supported by research but is also effective in normalizing prolactin levels, but possibly less so when compared with bromocriptine and cabergoline. The recommended starting dose is 0.125mg po qhs. If symptomatic increase by 0.125mg once per week up to 2mg po qhs. If asymptomatic, hold titration until remeasuring serum prolactin in one to two months.

  Pramipexole side effects may include sedation, nausea, dizziness and vomiting.

- **Cabergoline** is preferred by endocrinologists due to higher efficacy in normalizing prolactin levels (and tumor shrinkage) and decreased side effects due to its longer duration of action with need to administer only once or twice a week. However, cabergoline should be reserved for those who have failed trials of alternative dopamine agonists due to the risk of heart valve regurgitation mitogenesis and possible proliferation of fibroblasts via affinity to 5HT2B receptors expressed in heart valves (higher risk vs. bromocriptine).

  The recommended starting dose is 0.125 to 0.25mg once or twice a week. The dose can be increased by 0.25mg no sooner than every 4 to 8 weeks based on monthly to bimonthly prolactin monitoring up to a maximal dose of 1mg twice weekly.

  The lowest effective dose should be used and periodic reassessment of the need for continuing therapy is recommended with echocardiogram monitoring every 6 months or as clinically indicated if there is presence of edema, new cardiac murmur, dyspnea, or congestive heart failure. Cabergoline should be discontinued if an echocardiogram reveals new valvular regurgitation, valvular restriction or valve leaflet thickening. Contraindications are uncontrolled hypertension, hypersensitivity to ergot derivatives, history of cardiac valvular disorders or pulmonary, pericardial, or retroperitoneal fibrotic disorders.

4. Shrinkage of a pituitary adenoma occurs early, but maximum effect may take up to six months.

5. In clinical studies, menses is usually reinitiated in 6 to 8 weeks though some responded in a few days up to 8 months. Galactorrhea may take longer to control depending on the degree of stimulation of the mammary tissue prior to therapy. At least a 75% reduction in secretion is usually observed after 8 to 12 weeks. Some patients may fail to respond even after 12 months of therapy.

6. Dopamine agonists are unlikely to worsen psychotic symptoms at lower doses. Proceed slowly and cautiously with upward titrations. Should psychotic symptoms emerge, reduce the dose or discontinue the dopamine agonist.

C. Because fertility is usually restored within weeks to four months, women should take oral contraceptives or use other contraceptive methods to prevent unwanted pregnancy.

D. Dopamine agonist therapy is not curative, and most individuals will experience a rebound increase in prolactin to pretreatment concentrations when treatment is discontinued. After normal serum prolactin level has been maintained for 6 months, dopamine agonists can be discontinued with periodic monitoring of serum prolactin to see if dopamine agonist therapy should be restarted.

VIII. Osteoporosis/osteopenia prevention in amenorrheic premenopausal woman with HPRL:

A. Oral calcium supplement (1.0 – 1.5 g PO QD) + Vitamin D 400 – 800 units PO daily.

B. Estrogen, plus or minus progesterone or testosterone use in patients with long term hypogonadism (hypogonadal symptoms or low bone mass) should be considered in consultation with specialists. Though this will not treat hyperprolactinemia.

IX. Osteoporosis/osteopenia in postmenopausal women

A. After menopause, women are amenorrheic and fertility is no longer a concern, and they often will not experience symptoms of hyperprolactinemia. Endocrinologists have not reached a consensus as to whether asymptomatic hyperprolactinemia in postmenopausal women requires treatment intervention.

*****Please see next page for table of interventions for prolactin.*****

Table of Prolactin Interventions:

PROLACTIN CONCENTRATION	INTERVENTION
Normal range	Monitor per relevant medication protocol
Above normal, asymptomatic	Monitor per relevant medication protocol
Above normal, symptomatic	Reduce dose of offending agent, switch to a less provocative agent, or give dopamine agonist. If intervention fails to reduce prolactin plasma concentration, then obtain a contrast MRI scan of the head with focus on the sella turcica.
Concentration > 100 ng/mL, asymptomatic	Reduce dose of offending agent, switch to a less provocative agent, or give a dopamine agonist. If intervention fails to reduce plasma prolactin concentration to <100 ng/mL, then obtain a contrast MRI scan of the head with focus on the sella turcica.
Concentration > 100 ng/mL, symptomatic	Reduce dose of offending agent, switch to a less provocative agent, or give a dopamine agonist. Obtain a contrast MRI of the head with focus on the sella turcica if either the plasma concentration fails to decline to <100 ng/mL or prolactin-related symptoms fail to resolve.
Concentration > 250 ng/mL	Switch to a less provocative agent and obtain a contrast MRI of the head with focus on the sella turcica. Also, give a dopamine agonist and/or obtain neurosurgical consultation.

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