DSH PSYCHOTROPIC MEDICATION Operational Procedures

APPENDIX -- TARDIVE DYSKINESIA:

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

I. RISK FACTORS AND PREVALENCE IN TARDIVE DYSKINESIA:

A. Risk Factors Tardive Dyskinesia is a neurological disorder brought on by exposure to dopamine-blocking or -reducing drugs, primarily neuroleptic antipsychotics.

1. Exposure to such agents puts an individual at risk of developing tardive dyskinesia.

2. Mood disordered individuals**,** older persons, and women seem to be more at risk. Factors which may put such persons at greater risk for this disorder are:

a. increasing age of the patient

b. sex [NOTE: Geriatric females appear to be more susceptible to progressive severe tardive dyskinesia although some data are conflicted in this area. Women may be at a greater risk of developing more severe and more progressive dyskinesia than their male counterparts.]

c. dose of the neuroleptic

d. total time on the drug

e. acute neurological symptoms early in the course of treatment

f. a history of drug holidays

g. presence of brain damage

h. diagnosis (especially the presence of mood disorder).

B. The American Psychiatric Association estimates that among individuals receiving chronic first-generation (conventional) antipsychotic treatment, 15 – 20% will have some evidence of this condition after 3 months of treatment.

1. Rates are estimated to be less with second-generation antipsychotics (5.5% per year of exposure versus 3.8% per year of exposure).

2. Prevalence rates seem to correlate with time of exposure to the

causative agent. Kane and Smith found a 12% prevalence after 4 years of treatment.

3. The majority of cases are mild and not necessarily progressive (approximately 94%) even with continued neuroleptic exposure.

4. All individuals who take neuroleptic antipsychotic drugs are at risk for developing tardive dyskinesia.

- The prevention of tardive dyskinesia should be based upon the same principles as the practice of all good medicine:
    - Always weigh risks against benefits.
    - Use antipsychotic and other drugs only when needed, at the lowest effective dose, for the shortest possible time.

II. DIAGNOSIS OF TARDIVE DYSKINESIA:

A. Physical Indicators of Tardive Dyskinesia:

1. Face:

a. Blepharospasm (spasm of the eyelids, eyelid fluttering)

b. Rabbit syndrome (5-Hz vertical dystonic tremor of upper lips)

c. Pouting

d. Puckering

e. Smacking of lips

f. Chewing movements

g. Sucking movements

h. Bon-bon sign (buccal pressing of tongue)

i. Fly-catching syndrome (tongue protrusion)

2. Neck:

a. Retrocollis (head arches backward)

b. Spasmodic torticollis (head and neck twist to right or left)

3. Trunk:

    a. Axial hyperkinesia (rocking; pelvic thrusting; copulation movements)

    b. Torsion or athetoid movements (twisting or writhing)

4. Extremities:

    a. Ballistic movements (flinging or flailing)

    b. Chorea of hands or toes (quick, dance-like movements)

    c. Athetosis (worm-like, writhing movements)

    d. Rotation and/or flexion of ankles

5. Other:

    a. Grunting vocalizations (diaphragmatic dyskinesia)

    b. Asynchronous breathing (respiratory dyskinesia)

    c. Tardive dyskinesia may present as isolated dysphagia, especially among intellectually disabled individuals.

        i. A broader screening for tardive dyskinesia should be pursued among individuals presenting with isolated difficulty swallowing who are taking neuroleptic medications.

B. Diagnostic Indicators of Tardive Dyskinesia:

1. **Nature of Subjective Distress:** Movements in tardive dyskinesia are usually not subjectively distressing and awareness is often denied.

    a. In younger patients, an awareness of socially embarrassing abnormal involuntary movements may result in distress.

    b. It is important to distinguish whether the patient is moving due to restlessness (akathisia) or moving and therefore restless (tardive dyskinesia).

2. **Voluntary/Involuntary Nature of Movements:** Tardive dyskinesia movements are characteristically involuntary.

    a. During assessment, covert involuntary movements can be

uncovered by diverting attention to other parts of the body (activation).

b. These movements can also be suppressed temporarily through voluntary control.

3. **Time of Disorder Onset:** Tardive dyskinesia typically occurs late (> 30 days of neuroleptic exposure) during the course of neuroleptic therapy.

a. Although symptoms are generally not evident until after prolonged neuroleptic therapy, they can occur within weeks after drug treatment is initiated.

4. **Sign and Symptom Location:** All body areas can be involved; however, the buccolingual-masticatory areas are most often affected.

a. Younger patients are especially prone to extremity and trunk involvement.

5. **Presence of Other Extrapyramidal Symptoms:**

a. Parkinsonism: Manifestations of Parkinsonism tend to mask the symptoms of tardive dyskinesia. Although considered to be a pathophysiologic opposite to tardive dyskinesia, Parkinsonism is reported to coexist as often as 17.4%.

b. Akathisia: A disorder that differs from tardive dyskinesia primarily by the prominent subjective complaint of restlessness centered in the lower extremities. It can also coexist with tardive dyskinesia, making differential diagnosis a formidable challenge.

c. Rabbit syndrome (5-Hz vertical tremor upper lip, tongue, and eyelid movements): A late onset neuroleptic induced disorder characterized by rhythmic tremor-like chewing movements, which is rapidly reversible when neuroleptics are discontinued.

d. This typically has a good response to anticholinergic medications.

e. Tremor: Tremor is the only hyperkinetic movement not related to tardive dyskinesia. Tremors are generally reversible and often seen in conjunction with Parkinsonism, rigidity, or bradykinesia.

6. **Response to Pharmacologic and Other Interventions:**

a. Tardive dyskinesia will typically worsen or not change with

anticholinergic medications, although certain subtypes may be responsive.

b. If neuroleptic dose is decreased, movements will initially worsen but may decrease over time in a minority of patients.

c. The majority of cases can persist indefinitely following neuroleptic discontinuation.

d. Temporary improvement in dyskinesia may occur with sedatives and benzodiazepines.

e. Amantadine (300 mg per day) and ginkgo biloba (240 mg per day of Standard Extract) have shown 15% and 22% declines in AIMS scores (items 1 – 7), respectively.

f. Reversible vesicular transporter (VMAT-2) inhibitors

    i. Tetrabenazine (a reversible vesicular transporter [VMAT-2] inhibitor), has demonstrated circa 50% improvement in abnormal movement scores. Dosing of tetrabenazine is typically 25-50 mg TID. Higher doses may produce adverse effects, including akathisia, depression, nightmares, and suicidality.

    ii. Two analog compounds, deuterium tetrabenazine (a.k.a., deutetrabenazine) and valbenazine, have shown similar efficacy in research trials.

    iii. All of these agents work by depleting presynaptic dopamine stores, thereby reducing dopamine signal transduction.

    iv. Unfortunately, tetrabenazine and its analogs are expensive and should be reserved for those with severe tardive dyskinesia (AIMS score >10 on items 1 – 7).

Many treatments have been attempted for tardive dyskinesia with limited or negative results.

The American Academy of Neurology (2013), concluded that the following could not be supported as treatments for tardive dyskinesia:

- acetazolamide, bromocriptine, baclofen, buspirone, diltiazem, galantamine, eicosapentaenoic acid, levetiracetam, vitamin E, vitamin B-6, thiamine, selegiline, melatonin, nifedipine, yi-gan

san, biperiden discontinuation, botulinum toxin type A, electroconvulsive therapy, alpha-methyldopa, reserpine, and pallidal beep brain stimulation

- Although clozapine carries a low risk of inducing tardive dyskinesia, olanzapine and clozapine have shown mixed data in reducing extant tardive dyskinesia movements.

7. **Prerequisites to Confirm Diagnosis of Tardive Dyskinesia:**

a. Exposure to neuroleptic medications including the following neuroleptic classes:

- Phenothiazines (e.g., chlorpromazine)
- Butyrophenones (e.g., haloperidol)
- Thioxanthenes (e.g., thiothixene)
- Dibenzoxazepines (e.g., loxapine)
- Dihydroindolones (e.g., molindone)
- Diphenylbutylpiperidines (e.g., penfluridol)
- Atypical antipsychotics may also induce tardive dyskinesia

b. Presence of at least "moderate" abnormal involuntary movements in 1 or more body areas OR at least "mild" movements in 2 or more body areas (face; lip; jaw; tongue; upper extremities; lower extremities; trunk).

c. Absence of other conditions that may produce abnormal involuntary movements.

d. Procedure: Determination of the movements should be made via a standard examination procedure (i.e., **AIMS** rating scale) on admission and at annual psychiatric evaluations.

1. AIMS ratings should be completed quarterly by the treating physician when the AIMS is positive until it is negative twice.
2. In individuals with symptoms consistent with tardive dyskinesia, a Medication or Therapeutic Review Committee consultation is required.

3. Follow up quarterly AIMS ratings, however, are to be completed by the treating physician.

8. **Differential Diagnosis of Tardive Dyskinesia:**

a. Spontaneous Movements of Psychosis: In schizophrenic patients not exposed to medication, movements not usually seen in tardive dyskinesia may occur.

i. These include repetitive, stereotyped purposeless face and body movements, a variety of tic-like disturbances and manneristic distortions of purposeful activity.

ii. However, these movements lack the rhythmic characteristics of most dyskinesia.

iii. Occasionally, relevant thought control or psychological significance is associated with the movements.

iv. Recent studies indicate that true chorea or athetosis is rare in chronic psychiatric populations when neurologic disease is absent.

b. Senile Orofacial Dyskinesia: Aged individuals are predisposed due to decreased enzymes needed for synthesis of dopamine in the basal ganglia.

i. The role of neuroleptic medication as a causative factor is unclear.

ii. Movements may be associated with neurocognitive disorders and usually demonstrate minimal extremity/trunk involvement.

c. Spontaneous Extrapyramidal Disease:

i. **Huntington's Chorea:** Often confused with tardive

dyskinesia because involuntary movements sometimes appear after the onset of behavioral disturbance.

- Usual diagnostic features include a positive family history of movement disorders, early associated neurocognitive decline and premature death.
- The following pattern exemplifies the disease:
  - Movements jerky and unpredictable

- Greater incorporation of movement into normal activity
- Less facial involvement
- Greater postural and gait disturbance
- Inability to maintain tongue protrusion.

ii. **Torsion Dystonia:** Can be mistaken for tardive dyskinesia because of similar topographical distribution according to age.

- Other than an accurate drug history, differentiation can be based on the progressive course of torsion dystonia versus the static, slow pattern of tardive dyskinesia.

iii. **Gilles de la Tourette Disease:** Facial tics, grimacing, myoclonic jerks, and minor degrees of chorea are mimicable features of tardive dyskinesia found in this disease.

- Vocalizations and frank coprolalia though are not usually found outside Tourette‘s disease.
- Childhood onset and lack of prior neuroleptic treatment are important factors in identification.

iv. **Pantothenate kinase-associated neurodegeneration:** Formally known as Hallervorden-Spatz disease is a rare autosomal recessive neurodegenerative disorder associated with iron accumulation in the brain nuclei and characterized by progressive extrapyramidal dysfunction. Usually, the onset occurs in the first decade though 25% have an ‘atypical’ presentation with onset in second or third decade. The disorder is characterized by progressive dystonia.

i. Dystonia, dysarthria, muscular rigidity, spasms, Parkinson-like symptoms, tremors, rarely bradykinesia, choreoathetosis, athetosis, significant speech disturbances, dysphagia, and akathisia

ii. Dementia in most patients, visual impairment, seizures, neuropsychiatric dysfunction

d. **Drug-Induced Extrapyramidal Dysfunction:**

i. L-Dopa: Induced oral-facial dyskinesia is common because it is used exclusively for Parkinsonism the importance in differential diagnosis is minimal.

ii. Methyldopa: Choreoathetoid movements have been reported.

iii. Amphetamines: Abuse may produce prominent chewing movements or chorea, especially if pre-existing neurological disorder is present.

- The repetitive and stereotyped nature of the movements distinguishes them from tardive dyskinesia.

iv. Anticholinergics: Acute dyskinesia is typified by dystonic and spasmodic contractions of the neck and truncal musculature.

- Milder forms may center around the face, tongue, and extremities making comparison to symptoms of tardive dyskinesia difficult to assess.

- NOTE: Tricyclic antidepressants with high anticholinergic activity can produce myoclonus at higher doses.

v. Phenytoin: Transient choreoathetotic dyskinesia can be produced.

e. **Toxic or Metabolic Causes of Extrapyramidal Dysfunction:**

i. Wilson's Disease: Hepatolenticular degeneration and basal ganglia lesions are responsible for the movement disorder.

Other factors include:

- Liver cirrhosis.

- Green deposits in the corneal limbus.

- Eighth nerve deafness.

- Mental retardation.

ii. Manganese Poisoning (Chronic): Usually accompanied by dementia if extrapyramidal symptoms occur.

iii. Hyperthyroidism: Chorea may be present.

iv. Hypothyroidism: Basal ganglia calcification can lead to chorea-like movements.

v. Kernicterus

vi. CNS Vasculitis

vii. Hypoglycemia

f. **Infectious or Post Infectious Extrapyramidal Dysfunction:**

i. Post Encephalitic Syndromes.

ii. Syndeham's Chorea (Rheumatic Fever).

g. **Chorea Gravidorum.**

9. **Objective Evaluation of Dyskinesia:** Objective evaluation of suspected dyskinesia not due to neuroleptic medication should include the following:

a. Neurology consult.

b. Chemistry profile.

c. Thyroid function.

d. Liver function.

e. Serum copper and ceruloplasmin.

f. Dental Examination.

g. Slit lamp examination to rule out Wilson's disease.

h. Electroencephalogram.

i. CT scan or MRI.

10. **Methods of Assessment:**

a. Abnormal Involuntary Movement Scale (AIMS).

b. Rockland-Simpson Dyskinesia Rating Scale:

i. Abbreviated version.

ii. Long form version.

TARDIVE DYSKINESIA CONTROL AND MANAGEMENT:

A. Best practices to monitor for and minimize the risk of developing tardive dyskinesia:

1. Use conservative but effective dosage regimens of neuroleptics on clear cut indications (continuing objective evidence of manifestations of chronic psychosis and their responsiveness to treatment).

2. Documentation of continued indications and effectiveness of neuroleptics should be reviewed periodically and documented in the patient's chart at least every month as part of the monthly medication review with regular reconsideration of benefits and risk for development of tardive dyskinesia.

   At those times, the person's neurological and psychological status should be recorded.

B. Management Approach to Tardive Dyskinesia:

- Once a patient develops symptoms of tardive dyskinesia, there are three goals associated with treatment: Elimination of unnecessary antipsychotic agents, mitigating risk of tardive dyskinesia progression, and reducing the severity of dyskinetic movements.

- It should be recognized that elimination of unnecessary agents, and risk mitigation generally involve eliminating medications, reducing doses of medication, and/or switching to lower risk agents. These steps can unmask dyskinetic movements suppressed by neuroleptic agents and increase the severity of adventitious movements.

- Available data suggest that tardive dyskinesia may be reversible early in its course (less than five years), although it may take months to improve.

Step 1: Ensure that chronic antipsychotic use is indicated, and eliminate unnecessary antipsychotics:

- Neuroleptic drugs are to be avoided in patients who do not clearly need them or when they are not required or effective. Seek alternative therapies in anxiety, mood, and personality disorders.

- In general, maintenance treatment with neuroleptics is supported by scientifically sound data only for schizophrenia and schizoaffective

disorders.

- Before maintenance therapy is recommended for a schizophrenic patient, there should be reasonable evidence that neuroleptic antipsychotic drugs help improve the individual's symptoms and social adjustment.

a. Step 2: Minimize risk associated with antipsychotic medications moving forward:

- At the earliest sign of tardive dyskinesia, lower the dose by 30 to 50%, or change to a less potent neuroleptic. Theoretically, stopping treatment is the ideal step, but this may not be feasible due to risk of destabilizing the patient.

- Await remission of tardive dyskinesia as long as psychiatric status permits.

- If the individual's psychosis exacerbates after neuroleptic is reduced or discontinued and tardive dyskinesia is also present, the risk/benefit ratio must be considered.

- If neuroleptics must be continued, use the lowest effective dose and avoid concurrent anticholinergics.

- Switch to an atypical antipsychotic, especially clozapine or olanzapine.

b. Step 3: Commence treatment to reduce severity of dyskinetic movements:

If clinical data supports the presence of moderate to severe tardive dyskinesia, or there is evidence that tardive dyskinesia is causing significant impairment, it is appropriate to commence treatment to reduce dyskinetic movement symptoms.

1. Available data is most robust in support of using VMAT2 inhibitors such as valbenazine, tetrabenazine, or deutetrabenazine for initial treatment of tardive dyskinesia.

2. Clonazepam and gingko biloba are the next appropriate treatment steps based upon available data; however, security related risks including the risk of diversion, as well as increased risk of dementia associated with long term use of clonazepam reduce the practical utility of clonazepam in the setting of care of DSH. The therapeutic use of gingko biloba is complicated by the lack of FDA regulation of dietary supplements.

3. Amantadine is the final medication step in the treatment algorithm for tardive dyskinesia.

C. **THERAPEUTIC or MEDICATION REVIEW COMMITTEE (TRC / MRC) PROTOCOL FOR PATIENTS WITH SUSPECTED TARDIVE DYSKINESIA:**

Initial consults must have an AIMS form attached that can be completed by either the requesting physician or a pharmacist.

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