Management of ADHD medication adverse effects

- **Cardiovascular risk**
    - In May 2006, Health Canada issued important safety information on ADHD medications and recommended that ADHD drugs should be started at the lowest possible dose, and increased slowly, as individual patient response to these drugs is known to vary widely. The recommendation also stated that:
        - ADHD drugs should not be used if a patient has:
            - Symptomatic cardiac disease;
            - Moderate to severe hypertension;
            - Advance arteriosclerosis, coronary artery disease; or
            - Hyperthyroidism
    - Generally, ADHD drugs should not be used in patients with known structural cardiac abnormalities. Before prescribing an ADHD drug, it is important to be aware of whether the patient has:
        - a family history of sudden death, or death related to cardiac problems;
        - participates in strenuous exercise; or
        - takes other sympathomimetic drugs

      These are thought to be additional risk factors. In patients with relevant risk factors, and based on the physician's judgment, further evaluation of the cardiovascular system may be considered before starting on the drug.
    - American Heart Association recommends that before beginning therapy of stimulant medications, careful history should be obtained with special attention to symptoms, such as palpitations, syncope, or near syncope. Medications use, such as other prescribed and over-the-counter medications, should be determined. The family history should be reviewed with reference to the long QT Syndrome or other causes of sudden, unexplained death. Detection of these symptoms, or risk factors, warrants a cardiovascular evaluation by a pediatric cardiologist before initiation of therapy.
    - Patients who are considered to need long-term treatment with ADHD drugs should undergo periodic evaluation of their cardiovascular status, based on the physician's judgment.
    - Patients taking drugs for the management of ADHD should be advised not to discontinue their medications without consultation with their physician.
    - At follow-up visits, patients receiving psychotropic drug therapy should be questioned about the addition of any drugs, and the occurrence of any of the above symptoms. The physical examination should include determination of heart rate and blood pressure.
    - ECG is not routinely recommended before starting stimulant medications.
    - Risk of sudden death is found to be similar to the general population.
- **Growth and appetite suppression**

- Treatment with psychostimulant medications may result in a reduction in both height and weight. On average, the reduction in height amounts to approximately 1 centimeter per year during the first 1 to 3 years of treatment and 3 kilograms less than predicted over a year period.
- In the majority of cases, these effects are usually minor and the majority of patients fall within the 95% of the population. The small group that suffer from significant growth suppression usually show a dose dependent effect with doses over 1.5 mg per kilogram per day (given continuously) resulting in more problems; preschool children may be particularly vulnerable to growth effects.
- Reduced caloric intake and suboptimal nutrition due to appetite suppression are the more likely causes of most growth suppression. Other hypotheses considered were the dysregulation of receptors in the growth system, effect of ADHD on growth hormone, prolactin and possible increase or decrease in growth related to ADHD itself.
- Monitor growth (weight and height) closely and use the growth charts.

<u>Simple strategies that might be helpful:</u>

  - Consuming additional meals, or snacks, early in the morning or late in the evening when the stimulant effects of the drug have worn off;
  - Obtaining dietary advice *(please see the end of this chapter, after references, for nutrition information from the Scottish Guidelines*) ;
  - Consuming high calorie foods of good nutritional value;
  - Changing the timing of the dose and/or meals ;
  - Consuming high energy snacks;
  - If growth is significantly affected by drug treatment (that is, the child or young person has not met the height expected for their age), the option of a planned break in treatment over school holidays may be considered to allow "catch-up" growth to occur. Drug holidays can be planned. Current data does not support specific guidelines indicating what magnitude of height or weight gain deceleration should trigger changes in the treatment regimen.
  - If there is evidence of weight loss associated with drug treatment in adults with ADHD, clinicians should consider monitoring body mass index and changing the drug if weight loss persists.
  - In children, you can follow the medical criteria for referral to pediatric endocrinologist to consider growth hormone therapy in treatment of short stature, particularly if the height is more than 2 standard deviations below the population mean for the age, and a one year decrease of more than .5 standard deviation in height. Consideration should also be given to the mother and father's height.

- **Jaundice, signs of liver disease or biliary obstruction**

- Stop medication immediately and seek the help of a specialist.

- **Psychotic symptoms**
  - New onset psychotic symptoms that develop during the course of treatment of ADHD should be carefully evaluated. Development of psychosis as a side effect of psychostimulant is very rare, and in most cases, the impact of psychotic adverse events is mild and mostly self-limiting. As indicated in the Australian and UK guidelines, caution would be appropriate when prescribing ADHD drugs to children and young people with a family history of psychosis, or past history of psychotic episodes. A full psychiatric assessment should be conducted to determine if the psychotic symptoms are primary or secondary. A determination of starting an antipsychotic should be made at that point.
- **Seizures**
  - Despite the thin evidence of ADHD treatment in children with seizure disorder, it is not a contraindication to treat ADHD in the presence of seizure disorder.
    New onset seizure has been observed after starting a few patients on ADHD medications, and ADHD patients have been shown to have incidence rates of unprovoked seizures and epilepsy two or three times greater than non-ADHD children. After careful evaluation, some patients who had documented seizure may start an antiepileptic medication.
  - If seizures are exacerbated in a child or young person with epilepsy, or de novo seizures emerge following introduction of stimulant or Atomoxetine, another approach is to discontinue the drug and trial a different class.
  - It is important to rule out the possibility of substance abuse inducing seizure in patients with ADHD.
  - Some studies support the lowering of seizure threshold with the use of psychostimulants but other studies found no evidence for an increase in relative risk for either MPH (.8) or Atomoxetine (1.1)
  - Fatal hepatotoxicity has been reported as an extremely rare event in young epileptic children with polypharmacy or inborn errors of metabolism, and the combination of Atomoxetine with antiepileptic agents that might increase the risk of liver toxicity. Requires close clinical monitoring.
  - ADHD symptoms in epilepsy may be improved by non-specific interventions, such as better seizure control, decreasing AED polypharmacy, reducing drug interactions, and switching to AEDs with fewer cognitive and behavioral effects epilepsy.
- **Sleep disturbance**
  - Some clinicians concluded from several studies that the effect of ADHD medication on sleep may be beneficial, at least in some patients, but further research with more subjects, and with a variety of medication, is needed. Many patients treated with psychostimulants complain of insomnia, so an approach to manage this problem is necessary. Clinicians should document sleep patterns and complaints before

treatment to help interpret problems that may arise after medication has been prescribed.

- Sleep hygiene, consisting of simple behavioral approaches that promote sound sleep (e.g., creating a restful environment and avoiding caffeine), is a primary approach for most patients with insomnia.
- It might be helpful to look into shifting the dose to an earlier time or reducing an existing evening dose.
- Mirtazapine 15 mg HS has been reported as safe and effective for adults taking psychostimulants.
- Atomoxetine may have an effect on sleep that is different from that of psychostimulants, including reduced sleep latency, but less efficiency. In a randomized, double-blinded, crossover trial, Methylphenidate treatment for children with ADHD caused more initial insomnia, but fewer awakenings compared with Atomoxetine treatment. Switching to Atomoxetine may be considered for patients who prefer it, or who do not respond to adjunctive interventions for stimulant-associated insomnia.
- Melatonin 3 to 6 mg at least half hour before sleep can be used. Other pharmacological options include: Zopiclone 7.5 mg HS, Trazodone 25 to 50 mg HS, Benzodiazepines, such as Lorazepam, (consider, though, the high addiction potential), Methotrimeprazine 10 to 15 mg HS, or Quetiapine 25 mg HS for some resistant cases.

- **Suicide**
    - First, assess the suicide as a separate issue. Determine whether the patient is expressing suicidal ideation, intent, plan or is there a history of chronic self-harm behavior as in a personality disorder. Evaluate if suicide developed after starting Atomoxetine (more risk) or psychostimulant medications. Suicide prevention should be the first priority over any other consideration. You can use a tool, such as the Nova Scotia Suicide Risk Assessment Tool, to determine the risk level and management strategy. It is important to document all your findings about suicide and communicate them to others involved in the care of the patient. Caution is required when prescribing ADHD drugs to children and young adults with a past history of serious suicide attempts or depression. Families and caregivers should be advised of the need to recognize any emergence of emotional change, or self-injurious thinking, and to communicate well with the prescriber.
    - Patients being treated with ADHD drugs should be observed for the emergence of suicide-related events. If they do emerge in treatment, consideration should be given to dose reduction and/or other changes in therapeutic regimen, including the possibility of discontinuing medication, especially if symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms.
- **Tics**

- Tic Disorder is not a contraindication for psychostimulant use; however, several patients may suffer from worsening of tics. Taking a history, and closely monitoring comorbid tics is needed. It is important to note that several literature reviews suggested that stimulants are adequately safe in patients with both ADHD and Tic Disorder since tics are naturally waxing and waning. It is often difficult to decide if worsening of tics is provoked by the ADHD medication.
- Treatment of both Tics and ADHD symptoms can be treated together by adding antipsychotic medication to the psychostimulant or Atomoxetine. The alpha-2 adrenergic agonist Clonidine and Guanfacine have been showing promise in the treatment of tics, particularly in combination with stimulant medications.

For information on Alternative Therapies that have been researched or tested, please see the end of this chapter, after references, for excerpt of information from the Scottish Guidelines.

COMMON SIDE EFFECTS AND CONTRAINDICATIONS – ATOMOXETINE

- The common adverse effects associated with ATX include decreased appetite, drowsiness, abdominal pain, nausea and vomiting, dizziness, increased heart rate and blood pressure.
- Less common side effects include dyspepsia and mood swings. There have been three published case reports of severe liver injury in children and adults using ATX. These individuals recovered when the drug was discontinued. Suicide-related behavior (suicide attempts and suicidal ideation) has been reported in patients treated with Atomoxetine.
- Atomoxetine is contraindicated for people with narrow-angle glaucoma and concurrent treatment (or treatment within 14 days) with monoamine oxidase inhibitors (MAO). It is also contraindicated in people with structural cardiac abnormalities, symptomatic cardiovascular disease, or other serious heart problems as it increases the heart rate and the blood pressure.