APPENDIX 16

MEDICATIONS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

SPECIFIC MEDICATIONS (categorized by drug class and in alphabetical order)

**Stimulants**

**Adderall XR® (mixed amphetamine salts)**
Adderall XR® is a controlled substance made up of a combination of different amphetamine salts that have effects on noradrenaline and dopamine similar to dextroamphetamine. Adderall XR® comes in an extended release capsule available in six dosage strengths (5, 10, 15, 20, 25, and 30 mg) with flat based pricing. The major strengths of Adderall XR® are that: a) the medication can give symptom control that lasts for 10–12 hours covering the major times when impairment occurs (e.g., school and homework periods); b) it is indicated for ADHD in all age categories; c) the capsules may be opened and the beads inside the capsule can be sprinkled with no loss in efficacy (particularly important to improve compliance in young children who can’t swallow pills); d) 50% of the dose is immediately available leading to a fast morning response without a need for augmentation; e) patients can be switched from immediate release dextroamphetamine very easily; f) the medication was extensively reviewed by Health Canada in 2006 and its safety has been assured; g) the abuse potential is significantly reduced due to the product formulation; h) the active ingredient dextroamphetamine has been available for more than 50 years and has a well known safety and efficacy profile; and i) it may be covered by some provincial special access programs. For dosing prepubertal children, first calculate the single dextroamphetamine dose according to the weight of the child (0.15-0.4 mg/kg/dose) and then double it for the once-daily dose of Adderall XR® (e.g., 5 mg DEX in the morning and at noon = Adderall XR® 10 mg/day). Adderall XR® has been shown to effectively reduce ADHD symptoms in adults with ADHD [86-88]. The treatment response rate and side effect profile for methylphenidate-based versus amphetamine-based products are similar [89].

**Biphentin®**
Biphentin® is a controlled release methylphenidate (MPH) product and comes in eight strengths (10, 15, 20, 30, 40, 50, 60, and 80 mg). The cost of the medication increases with dose. Biphentin® uses a multi-layer release (MLRTM)® delivery system. The efficacy of Biphentin® is that same as that for other stimulants, and its side effect profile does not differ substantially from other MPH products. The major strengths of Biphentin® include the following: a) its delivery is a 40% immediate and 60% gradual effect putting it in the middle of the other medications; b) the delivery technology has shown an effect that is sustained for 10-12 hours; c) it is available in eight doses making it easy to titrate the medication even from a much lower dose; d) the medication has been indicated in all age groups by Health Canada; d) the medication is only available in Canada and is relatively cheaper than the other long acting MPH products; e) the active ingredient is MPH which has a well known safety and efficacy profile; f) the capsules can be opened and sprinkled making it useful for children who can not swallow pills and, since the beads within each capsule are all the same, there is no concern when it is poured; g) patients can be switched from MPH very easily (5 mg t.i.d. MPH = 15 mg Biphentin®, 10 mg t.i.d. = 30 mg Biphentin®, 15 mg t.i.d. MPH = 45 mg Biphentin®) and, if necessary, can be augmented with immediate release MPH as necessary and h) it may be covered by some provincial special access programs. The major disadvantages have been: a) the occasional delay in getting the medication as it is relatively new to the market and pharmacies may need one business day to get stock and b) physician familiarity. These issues are likely to improve over time.

**Concerta®**
Concerta® is an extended release MPH using the OROS® technology and comes in four dosing options (18, 27, 36 and 54 mg capsules). The cost of the medication increases with dose. The major strengths of Concerta® are that: a) the
active ingredient has been available and actively studied for 50 years; b) there are long-term studies that are over 20 years in duration that show MPH is safe; c) it controls ADHD symptoms for approximately 10–12 hours, covering the major times that impairment occurs (e.g., school and homework periods); d) it is a 22% immediate release and 78% long acting release combination suggesting a long duration of effect; e) the non-deformable shell makes it very difficult to break, cut or crush, which virtually eliminates its abuse risk; f) patients can easily be converted from immediate release MPH to Concerta® (10 mg t.i.d. MPH = 36 mg Concerta®, 15 mg t.i.d. MPH = 54 mg Concerta®), and, if necessary, can be augmented with immediate release MPH; g) the medication has an indication in child and adolescent patients by Health Canada but the CAP-G Committee believes that it can also be used safely in adults with ADHD; and h) it may be covered by some provincial special access programs. While multiple doses can be used to create a closer titration (18 mg + 27 mg = 45 mg; 27 mg + 36 mg = 63 mg, etc), the cost of the medication may be a prohibitive.

_Dextroamphetamine - DEX_

_Dexedrine® and Dexedrine® Spansules_

Dextroamphetamine is classified as a psychostimulant with effects due to the blockade of the reuptake of dopamine. It also increases the release of dopamine and noradrenaline from the vesicles accounting for its increased potency over MPH (i.e., half the dose is required). DEX is indicated in ADHD patients and as an adjunctive treatment of narcolepsy. It is a controlled substance. Dexedrine® and Dexedrine® Spansules are placed in the second line group as their duration is shorter than that of long-acting versions and they are therefore prone to having peak/valley effects that may be uncomfortable. Their efficacy and safety, however, are well established. The major strengths of DEX are that: a) the active ingredient has been available and actively studied for many decades; b) it may be useful in situations where a top up of the once-daily medication is required or if the patient desires more flexibility over the dosing schedule; c) a consensus of the CAP-G Committee suggests that DEX may be indicated in some adult ADHD patients who want the medication for situational versus continuous use; d) the Dexedrine® Spansules may be covered by some government special access programs; and e) the active ingredient, dextroamphetamine, has been available for more than 50 years. A weight-adjusted dose between 0.15 and 0.4 mg/kg provides a range in prepubertal children although the CAP-G Committee continues to recommend a ‘start low and go slow’ approach (see relevant tables for initiation, titration and maximum doses). Dexedrine® Spansules last about 6-8 hours.

_Methylphenidate – MPH_

_PMS®-Methylphenidate, Ratio®-Methylphenidate, Ritalin®, Ritalin® SR_

MPH is a controlled substance which seems to work by blockade of the reuptake of dopamine and is indicated in ADHD and narcolepsy. In Canada, MPH has generic brands available. Ritalin® SR has a slower uptime and may last slightly longer than regular Ritalin®. Ritalin® LA, a once-a-day extended-release MPH formulation, is currently not available in Canada. The MPH patch may be coming to Canada in the near future. The efficacy and safety of MPH is well established with significant reduction in the core ADHD symptoms. MPH short and medium-acting products are placed in the second line group as their duration is shorter than that of long-acting versions and they are therefore prone to having peak/valley effects that may be uncomfortable. The major advantages of MPH are that: a) the active ingredient has been available and actively studied for 50 years; b) there are long-term studies that are over 20 years in duration that show MPH is safe; c) they may be useful in situations where a top-up of the once-daily medication is required or if the patient desires more flexibility over the dosing schedule; d) a consensus of the CAP-G Committee suggests that MPH may be indicated in some adult ADHD patients who want the medication for situational versus continuous use; and e) they are relatively inexpensive. A weight-adjusted dose between 0.3 and 0.8 mg/kg provides a range in prepubertal children although the CAP-G Committee continues to recommend a ‘start low and go slow’ approach. A dose of 1 mg/kg/day is theorized [90] as the maximum dose in adults, although most adults respond to much smaller doses. Adolescent doses fall between the prepubertal and adult doses. All symptoms do not respond equally to each dose of medication so it is important that the target symptoms are defined before initiating medication.
**Non-stimulants**

*Atomoxetine - ATX*

**Strattera®**

Atomoxetine is a specific noradrenaline (a.k.a. norepinephrine) reuptake inhibitor and comes in five doses (10, 18, 25, 40 and 60 mg). All doses cost the same per pill. ATX is not classified amongst the psychostimulants and it is not a controlled substance. The major strengths of ATX are that: a) it provides continuous coverage including the late evening and early morning periods; b) it is indicated by Health Canada in all ADHD patients across the lifespan; c) it may be particularly useful for ADHD patients who have tic spectrum disorders or comorbid anxiety, resistance and/or side effects to stimulant medications, and there is little problems with worsening of sleep; d) at this time, there appears to be no substance abuse or diversion potential; e) samples may be available to establish efficacy before a commitment is made though it is covered by the majority of private insurance carriers; f) it may be covered by some provincial special access programs, and g) a new indication may be emerging for its use in enuresis [39, 40]. The onset of action is slower than stimulants as they act on different neurotransmitters and the maximum treatment effect may not be reached for two months. The clinical changes are gradual. It would not be suitable in cases where there is an urgency to obtain a rapid onset of action. The dose is calibrated to the weight of the patient (see relevant tables for initiation, titration and maximum doses). There appears to be no increased benefit past 1.4 mg/kg/day though there may be some improvement of ODD after 1.8 mg/kg/day [95]. The American Academy of Child and Adolescent Psychiatry has stated that the doses could go as high as 2.2 mg/kg/day but this is much higher than the Canadian standard [14]. If higher doses are contemplated, a referral to an ADHD specialist should be made. If the doses should exceed one pill a day, the cost of the medication is doubled. The capsules should never be opened as it may cause irritation of the gastric lining. The medication's safety profile has been established including the same risk factors related to cardiovascular conduction irregularity similar to those of stimulant drugs. Two cases of reversible alteration in hepatic enzyme are noted. No special monitoring protocol is required (i.e., blood tests) but patients should be advised of the clinical symptoms of hepatic dysfunction. Poor metabolizers (i.e., 7% Caucasians and 2% African-Americans) are unlikely to have toxic effects given the slow titration schedule. Measurements of blood levels are not required. There have been rare reports of increase in suicidal ideation; one suicide attempt (overdose) was identified; no completed suicides occurred [96, 97]. Clinicians need to carefully monitor suicidal ideation, especially in the early phases of treatment not unlike many antidepressant medications. The clinical efficacy was the same as stimulants in patients who were treatment naive [98, 99]. ATX can be combined with stimulants to augment the effect in the case that the clinician feels the patient has not achieved an adequate response, but in these circumstances, a referral to an ADHD specialist maybe indicated.

**Off Label Medications**

*Bupropion HCl - BUP*

**Wellbutrin® SR, Wellbutrin®XL**

Bupropion hydrochloride is indicated as an antidepressant with effects that appear to be mediated by the reuptake blockade of mainly noradrenaline and also dopamine. It is not a controlled substance. Wellbutrin® XL, a newer once-daily extended release version, is also currently available in Canada. The therapeutic dose of Wellbutrin®XL is 300 mg though in clinical trials it has been tested up to 450 mg [100]. There is no specific indication for patients with ADHD but off label use is common given its pharmacological and safety profile. The major strengths of BUP are that: a) it may be useful in adult ADHD patients with comorbid depression and/or nicotine use; b) BUP does not cause sexual dysfunction like serotonin-based antidepressants [101]; c) it carries no risk of substance abuse or diversion; and d) it is relatively cheap as the proprietary compound, Wellbutrin® SR, is now generic in Canada. There is a slight increased risk of seizures (0.4%) with those with a prior history of seizures or those with eating disorders. Limited clinical studies in ADHD children and adults show BUP to have efficacy in improving the core symptoms of ADHD [102, 103]. BUP is slower acting and its lag to response is much like traditional antidepressants. The safety in combination with other ADHD medications has not been established and, if this is contemplated, a referral to an ADHD specialist is warranted.
Imipramine - IMI
Apo®-Imipramine
Imipramine is a tricyclic-based antidepressant that has mixed effects due to its reuptake blockade of noradrenaline and serotonin. The metabolite, desipramine (DES), is active and purely noradrenergic. The brand Tofranil® affords no additional advantage over the generic and is not recommended. While not specifically indicated in ADHD, there have been many studies that have looked at the efficacy and safety of this medication in children, adolescents and adults [94, 95]. There seems to be evidence of sustained efficacy in both short-term and long-term studies for up to two years. The difficulty with IMI has been the anticholinergic and antihistaminic side effects that can make the patient uncomfortable. However, in some patients these effects may be a benefit. For example, a child who has concurrent enuresis, ADHD and sleep problems may benefit from IMI. It may also prove helpful in patients with a concurrent tic disorder, anxiety or depression. The dosing schedule is reported in the medication tables. Blood levels and ECGs are not necessary, although the patient should have a cardiovascular exam to ensure their status is within normal limits. Combination strategies with other ADHD medications can be made but referral to an ADHD specialist is advised.

Modafinil
Alertec®
Modafinil is defined as a CNS stimulant. It is primarily indicated for narcolepsy, sleep apnea and shift work sleep disorders. However, it has been used off label (i.e. does not have a Health Canada indication) for ADHD patients [91-94]. It comes in a 100 mg tablet with start doses of 200 mg for adults in divided doses twice a day. The dose is to be raised by 100 mg to a maximum of 400 mg. The advantages of modafinil include: a) it is a non-controlled substance although there is a recognized, albeit mild, abuse potential; b) samples are available and c) anecdotally, it has a much weaker stimulant effect which has a commensurate lower side effect profile (e.g., most common side effects were headache, nausea, rhinitis and anxiety). However, the medication has not been rigorously studied in ADHD, it has some minor problems when combined with psychostimulants (e.g., an increase in blood pressure), the efficacy has not been established in ADHD patients and it only has one dosage strength.

* Insurance coverage may be different from one Canadian province to another and is subject to change. For example, in Quebec all long acting medications (Adderall XR®, Biphentin®, Concerta®, and Strattera®) may be reimbursed under certain conditions (‘medications d’exception’ and ‘patients d’exception’ programs). In Ontario, reimbursement may occur for treatment of children and adolescents suffering from ADHD in whom a) a trial of immediate release MPH, Ritalin®SR, and/or Dexedrine® did not show efficacy, b) the long-acting agent has been tried showing efficacy (often requiring the use of ‘coupons’ to access the medication), and c) there is a demonstrated financial need.

Table 5. Long-Acting Medication Comparison Profiles

<table>
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<th>Adderall XR®</th>
<th>Biphentin®</th>
<th>Concerta®</th>
<th>Strattera®</th>
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