Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Therapeutic Review
Attention Deficit Hyperactivity Disorder (ADHD)
Various Manufacturers

Description:

The purpose of the therapeutic review was to review medications for the management of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric and adult patients.

In their review, the DBC considered the following: a December 2011 Drug Class Review of Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder from Oregon Health & Science University; an October 2011 *Comparative Effectiveness Review (Number 44) of ADHD Treatment* by the Agency for Healthcare Research and Quality; a December 2015 class review of drugs used in the management of ADHD in adults by the Ontario Drug Policy Research Network; a March 2016 review by the Canadian Agency for Drugs and Technologies in Health (CADTH) of Guidelines for Pharmacologic Management of Patients with ADHD; an October 2011 review by CADTH of guidelines and recommendations for ADHD in children and adults; a March 2011 quality assessment by CADTH of the Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA) ADHD practice guidelines in adults; correspondence from physicians regarding drugs for treatment of ADHD; correspondence from the College of Physicians and Surgeons of BC; a review of Special Authority requests made to PharmaCare for drugs for treatment of ADHD; a review of the utilization and compliance of the Collaborative Prescribing Agreement for Concerta®; comments and correspondence from CADDRA; and manufacturer's comments. The DBC also considered Patient Input Questionnaire responses from 40 patients, 56 caregivers, and one Patient Group (the Centre for ADHD Awareness, Canada, or CADDAC), Clinical Practice Reviews from three general physicians, five specialists and one pharmacist; and a Budget Impact Assessment.

Dosage Forms:

- atomoxetine (Strattera® and generics) is available as 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, and 100 mg capsules;
- dextroamphetamine (Dexedrine® and generics) is available as 5 mg tablets;
- dextroamphetamine sustained-release (Dexedrine® Spansules®) is available as 10 mg and 15 mg sustained-release capsules;
- guanfacine (Intuniv XR®) is available as 1 mg, 2 mg, 3 mg and 4 mg extended-release tablets;

- lisdexamfetamine (Vyvanse®) is available as 10 mg, 20 mg, 30 mg, 40 mg, 50 mg and 60 mg capsules;
- methylphenidate controlled-release (Biphentin®) is available as 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 80 mg controlled-release capsules;
- methylphenidate extended-release (Concerta® and generics) is available as 18 mg, 27 mg, 36 mg, and 54 mg extended-release tablets;
- methylphenidate (Ritalin® and generics) is available as 5 mg, 10 mg, and 20 mg tablets;
- methylphenidate sustained-release (Ritalin® SR and generics) is available as 20 mg extended-release tablets; and
- mixed amphetamine salts (Adderall XR® and generics) is available as 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg extended-release capsules.

Recommendations:

1) **Overall Coverage Recommendation for Pediatrics:** Based on the evidence provided, is the current PharmaCare coverage provided by the British Columbia Ministry of Health (the Ministry) for the management of ADHD in pediatric patients appropriate with regard to clinical efficacy, effectiveness, safety and cost-effectiveness?

    a) The DBC recommends PharmaCare coverage of drugs for the management of ADHD in pediatric patients should be changed. The following drugs should be listed as Limited Coverage benefits for pediatric patients, with specific criteria as noted:
        i) methylphenidate extended release (Concerta® and generics) and controlled release (Biphentin®);
        ii) atomoxetine (Strattera® and generics);
        iii) dextroamphetamine-amphetamine (Adderall XR® and generics); and
        iv) lisdexamfetamine (Vyvanse®).

    b) Guanfacine (Intuniv XR®) should remain a non-benefit for pediatric patients.

    c) Biphentin® and Adderall XR® should be listed with the same Limited Coverage criteria as the existing Concerta® criteria.

    d) Atomoxetine Limited Coverage criteria:
        i) In patients where stimulants are not appropriate, not tolerated, or ineffective.

        Rationale: atomoxetine has similar efficacy to stimulants, but a higher risk of adverse events such as vomiting (approximately 3 times greater for atomoxetine than methylphenidate immediate release or mixed amphetamine salts extended-release), somnolence (approximately 3 to 4 times greater than methylphenidate osmotic release oral system [OROS] and methylphenidate extended release), nausea or anorexia (greater than methylphenidate immediate release in one trial).

e) Lisdexamfetamine Limited Coverage criteria:
   i) Only considered for use if other extended release stimulants are ineffective.

   Rationale: there is no convincing superiority data for lisdexamfetamine when compared to other, less costly stimulants.

f) **Of Note:** the DBC recommends that, if prioritization is required due to budgetary constraints, coverage for the pediatric population should be prioritized over the adult population.

2) **Overall Coverage Recommendation for Adults:** Based on the evidence provided, is the current PharmaCare coverage provided by the Ministry for the management of ADHD in adult patients appropriate with regard to clinical efficacy, effectiveness, safety and cost-effectiveness?

   a) The DBC recommends PharmaCare coverage of drugs for the management of ADHD in adult patients should be changed to list the drugs in Recommendation I.a.i-iv (above) as Limited Coverage benefits for adult patients, with the same specific criteria for atomoxetine and lisdexamphetamine as noted above. Methylphenidate controlled-release, methylphenidate extended release and dextroamphetamine-amphetamine should be listed with similar criteria as the existing methylphenidate extended release criteria for pediatrics; however, the age restriction to patients 18 years of age and under should be removed.

3) **Recommendation on Expansion to Regular Benefits:** Based on the evidence provided, should PharmaCare coverage for drugs for the treatment of ADHD be expanded to Regular Benefit for all or most drugs?

   a) The DBC did not recommend expanding coverage for drugs for the treatment of ADHD to Regular Benefits. If PharmaCare were to list all ADHD medications as Regular Benefits, the estimated total budget impact would be approximately $122.5 million over three years.

4) **Recommendation on Stimulant Drugs as Compared to Non-Stimulant Drugs:** Based on the evidence provided, are there significant differences in therapeutic benefit (clinical efficacy, effectiveness or safety) between stimulant drugs (e.g., formulations of amphetamine, methylphenidate) as compared to non-stimulant drugs (e.g., atomoxetine, guanfacine) for the treatment of ADHD?

   a) The DBC recommends non-stimulant drugs should be used where stimulants are not appropriate, tolerated, or ineffective.

      Rationale: the data supporting use of non-stimulant drugs is of lower quality. The majority of the efficacy data is found in trials for stimulants, with the majority of that data being for methylphenidate.

b) Subgroups or clinical considerations in which atomoxetine may be appropriate include in patients experiencing seizures or tics with stimulants; where there is a history of or risk of diversion; or where there is a history of or risk of illicit drug use by the patient or family.

c) There is insufficient evidence to support guanfacine (Intuniv XR®) for either first-line or second-line use.

5) **Recommendation on Immediate-Release Drugs as Compared to Extended-Release Drugs:** Based on the evidence provided, are there significant differences in therapeutic benefit (clinical efficacy, effectiveness or safety) between immediate-release (IR) formulations as compared to extended-release (ER) formulations of drugs for the treatment of ADHD?

a) The DBC noted there is similar evidence of efficacy and safety between IR and ER formulations. Studies of methylphenidate IR vs. ER formulations in children generally were unable to identify significant differences in symptom improvement. Studies of methylphenidate IR and methylphenidate OROS were conflicting; double-blind studies did not find a difference while open-label studies indicated greater improvement with methylphenidate OROS on some measures.

b) Evidence-based clinical practice guidelines recommend that selection of treatment with an IR or ER stimulant should be based on individual patient characteristics.

c) Dosage of ER drugs may be too high to be used as starting doses (IR is appropriate, as smaller doses are available for titration when initiating therapy).

d) The DBC acknowledged that efficacy data shows few differences between IR and ER drugs; however, there may be anecdotal, qualitative, or observational differences between IR and ER drugs with regards to stigma, adherence to therapy, and other factors.

6) **Recommendation on the Extended-Release Stimulants:** Based on the evidence provided, are there significant differences in therapeutic benefit (clinical efficacy, effectiveness or safety) among the extended-release stimulant drugs (e.g., formulations of dextroamphetamine, lisdexamfetamine, methylphenidate, mixed amphetamine salts) for the treatment of ADHD in pediatric and adult patients?

a) The DBC noted clinical trial evidence for lisdexafetamine was weaker relative to other stimulants. Based on clinical evidence, there are no significant differences between the extended-release stimulants; however, the DBC acknowledged there may be some benefits for the different extended-release formulations (e.g., the ability to sprinkle or dissolve some formulations, or possible misuse or diversion potential).

7) **Drug Specific Coverage Recommendation:** Based on the evidence provided, does one or more drug(s) demonstrate greater therapeutic benefit with regard to clinical efficacy, effectiveness or safety relative to other drugs for the treatment of ADHD that have not been addressed in the previous questions?

   a) The DBC noted drug-specific recommendations have been addressed in the previous questions.

8) **Recommendation on Reference Drug Pricing for the Extended-Release Stimulants:** Based on the evidence provided, are the extended-release stimulants for the treatment of ADHD appropriate for inclusion in a new Reference Drug Pricing (RDP) category? Are there significant therapeutic differences among the extended-release stimulants that would warrant inclusion of more than one drug as reference drugs?

   a) The DBC recommends extended-release stimulants for the treatment of ADHD as not appropriate for inclusion in a new RDP category. The DBC noted the RDP is not appropriate for mental health conditions, as drugs for ADHD need to be individualized.

Of Note:

- The DBC considered Patient Input Questionnaire responses from 40 patients, 56 caregivers, and one Patient Group. All patients had tried at least one ADHD drug. Patients and caregivers for school-age children described the effects of ADHD, including difficulty focusing on tasks, problems at work and school, poor academic and work performance, time management issues, difficulty in relationships, anxiety, depression, difficulty regulating emotions, sleep problems, the need for constant caregiver supervision, and the prohibitive cost of ADHD treatments. Patient experiences with ADHD drugs varied greatly, as a drug may work well for one patient, but be ineffective or have too many side-effects for another. Many patients reported the slow-release ADHD drugs made it easier to schedule their medications.
- Clinical Practice Reviews were provided by three general physicians, five specialists, and one pharmacist. All reviewers emphasized there is significant morbidity and mortality associated with untreated ADHD. Reviewers noted wide variations in effectiveness and tolerability of ADHD medications in individual patients. Reviewers also reported observing differences between stimulant and non-stimulant medications in individual patients. Reviewers noted the convenience advantage of once-daily dosing may improve compliance in adults and children and reduce the stigma of taking medication in school-age children. Most reviewers commented that abuse and diversion may be less likely with the long-acting medications.