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PSYCHOPHARMACOLOGY

Switching from Clonidine Immediate-Release to Guanfacine Extended-Release

Dean Elbe PharmD, BCPP[1,2,3]

As a clinical pharmacy specialist in child and adolescent mental health, I am frequently asked how to switch patients from clonidine immediate-release (IR) to guanfacine extended-release (XR). This therapeutic switch may be required when poor adherence to a clonidine IR regimen (typically requiring 3–4 doses daily) is identified, when clonidine dose-optimization is limited by sedation, bradycardia or hypotension, or when coverage situations change. The latter may occur if, for example, new eligibility for a government program or a third party-payer occurs.

Guanfacine XR, a selective alpha$_{2A}$ agonist, was first marketed in Canada in late 2013 for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents (Shire Pharma Canada ULC, 2019). Guanfacine IR is not marketed in Canada, but has been available in the United States since 1986 for treatment of hypertension in adults (Takeda Pharmaceutical Company Limited, 2015). Guanfacine XR has been shown in randomized controlled trials to be superior to placebo for treatment of ADHD symptoms in children and adolescents, both as monotherapy, and as adjunctive treatment to psychostimulants (Biederman et al., 2008, Sallee et al., 2009; Connor et al., 2010, Kollins et al., 2011; Wilens et al., 2012; Newcorn et al., 2013; Elbe & Reddy, 2014).

Clonidine IR, a nonselective alpha$_2$ agonist, is the only oral IR alpha$_2$ agonist available in Canada, which is approved for treatment of hypertension in adults and as a vascular stabilizer for the treatment of menopausal flushing (Boehringer Ingelheim (Canada) Ltd, 2012a, Boehringer Ingelheim (Canada) Ltd, 2012b). Clonidine has been used off-label in children for many years for treatment of insomnia, ADHD, and disruptive behaviour disorders (Hunt, Capper & O'Connell, 1990; Rubinstein; Jaselskis, Cook, Fletcher & Leventhal, 1992; Silver & Licamele, 1994; Palumbo et al., 2008; Efron, Lycett & Sciberras, 2014). A clonidine XR formulation is not available in Canada, but is available in the United States for treatment of ADHD (Concordia Pharmaceuticals, Inc. 2015).

Weight-based dosing guidelines exist for clonidine IR (0.003–0.008 mg/kg/day) and guanfacine XR (0.05–0.08 mg/kg/day) (Shire Pharma Canada ULC, 2019; Elbe et al., 2018). Based on these guidelines and other literature, guanfacine has an approximate 10-fold lower potency than clonidine (Stahl, 2013; Elbe & Reddy, 2014). Most children who take clonidine IR for ADHD typically take a dosage in the range of 0.15–0.4 mg/day (in 3–4 divided doses) while children under 12 years of age typically take a guanfacine XR daily dose in the 2-4 mg/day range (Elbe et al., 2018).

An internal review conducted at BC Children's Hospital identified a sharp uptick in clonidine IR prescriptions for children starting in 2010. The timing of this increase corresponded with the publication of randomized controlled trial data showing the benefits of XR formulations of clonidine and guanfacine for treatment of children with ADHD and the introduction of these products in the United States (Biederman et al., 2008; Sallee et al., 2009; Connor et al., 2010; Jain, Segal, Kollins & Khayrallah, 2011; Kollins et al., 2011a; Kollins et al., 2011b; Wilens et al., 2012; Newcorn

[1]Department of Pharmacy, Children's and Women's Health Centre of British Columbia, Vancouver, British Columbia
[2]Child and Adolescent Mental Health Programs, BC Children's Hospital, Vancouver, British Columbia
[3]Department of Psychiatry, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia

Corresponding E-Mail: delbe@cw.bc.ca

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et al., 2013; Elbe & Reddy, 2014). Guanfacine XR then entered the Canadian market in late 2013.

The guanfacine XR product monograph does not provide any guidance regarding how to switch from clonidine to guanfacine in children (Shire Pharma Canada ULC, 2019). The most obvious way is to taper fully off clonidine IR, and then start guanfacine XR according to the dosing instructions outlined in the guanfacine XR product monograph. Clonidine tapering is recommended to prevent rebound hypertension (Boehringer Ingelheim (Canada) Ltd, 2012a). The risk of rebound hypertension with abrupt clonidine discontinuation may be greater in hypertensive adults compared to children with normal pre-treatment blood pressure. However, gradual tapering of the clonidine dose in children is considered good practice and is still recommended (Green, 2007; Elbe, Black, McGrane & Procyshyn, 2018). A full clonidine taper may take two weeks or longer, delaying initiation of guanfacine XR and achievement of a therapeutic dose. This may result in a few weeks of relative under-treatment which may be marked by an increase in attention and behaviour difficulties impacting adversely on the child themselves, their family and classroom.

My colleagues and I have had success employing an approach in switching clonidine IR to guanfacine XR which simultaneously reduces the risk for rebound hypertension and shortens the time the child receives a subtherapeutic alpha$_2$ agonist dosage. Prescribers who are considering employing this switching method should have adequate training in the medical management of ADHD and/or seek support of experts in the field. This proposed switching method may not be appropriate for patients who were hypertensive prior to starting clonidine IR treatment.

When making the clonidine IR to guanfacine XR switch, we suggest tapering clonidine in 25% decrements twice weekly (based on the starting total daily dose, rounded to the closest available tablet strengths; the lowest tablet strength is 0.025 mg), until a total daily clonidine dose of 0.1 mg is reached. At that time, guanfacine XR 1 mg daily is started and all remaining clonidine dose(s) are simultaneously discontinued. The guanfacine XR dose is then titrated up following the product monograph dosing guidelines in 1 mg increments weekly as tolerated, to a target weight-based dosage range of 0.05–0.08 mg/kg/day (rounded to the nearest 1 mg tablet strength) (Shire Pharma Canada ULC, 2019). If a guanfacine XR dosage of 0.08 mg/kg/day is well tolerated and there are still residual ADHD symptoms, it may be increased up to 0.12 mg/kg/day, to a maximum dose of 4 mg/day in children or 7 mg/day in adolescents (when used as monotherapy) (Shire Pharma Canada ULC, 2019).

Switching from clonidine IR to guanfacine XR at these dosage levels in children who were normotensive at baseline prior to starting alpha$_2$ agonist treatment will likely be adequate to prevent rebound hypertension. For patients receiving clonidine doses at or below a total of 0.1 mg/day when a switch to guanfacine XR is contemplated, clonidine can be discontinued and guanfacine XR started at 1 mg daily, then tapered up as described above. Box 1 provides an example of dosage titration and switch from clonidine IR to guanfacine XR in a 25 kg child.

Box 1. Clonidine IR to guanfacine XR switch: Titration example

25 kg patient, taking clonidine 0.05 mg twice daily at 0800h and 1400h and 0.1 mg at bedtime (total dose of 0.2 mg/day)

- Reduce clonidine to 0.025 mg twice daily at 0800h and 1400h and keep clonidine 0.1 mg at bedtime (total dose of 0.15 mg/day).
- After three days, reduce clonidine to 0.025 mg twice daily at 0800h and 1400h, and 0.05 mg at bedtime (total dose of 0.1 mg/day).
- After three days (and on the day of switch to guanfacine XR), give the clonidine doses of 0.025 mg at 0800h and 1400h, then start guanfacine XR 1 mg at bedtime and discontinue further clonidine doses.
- After one week, increase guanfacine XR to 2 mg at bedtime (0.08 mg/kg/day [target dose]).

Time saved (compared to a full taper off clonidine before starting guanfacine XR): 7 days

Regular blood pressure and heart rate monitoring should occur during the clonidine tapering and guanfacine up-titration processes. Titration rates should be slowed if significant blood pressure or heart rate changes are detected, or the patient experiences symptoms such as dizziness, lightheadedness or excessive sedation.

Guanfacine XR can be taken once daily, either in the morning or evening without significant differences in efficacy (Newcorn et al., 2013). Many prescribers prefer evening or bedtime administration to allow the peak serum level (which occurs approximately 5 hours after the dose is taken) to occur overnight, in order to help with sleep and reduce daytime sedation (Shire Pharma Canada ULC, 2019). The manufacturer advises guanfacine XR tablets should be swallowed whole and not not be broken, chewed or crushed before swallowing as this will increase the rate of guanfacine release. (Shire Pharma Canada ULC, 2019).

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