A Nursing Perspective:
Best practices for pubertal suppression for individuals with central precocious puberty and transgender

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Introduction

Active members of the Canadian pediatric endocrine nurses (**CPEN**) group frequently put out questions to the group via email around testing, treatment and management of side effects in pediatric endocrine disorders. Recently these questions were around the use of GnRH analogs like Depot Lupron (DL) injections for Central Precocious Puberty (CPP) and Transgender (TG) youth and side effects.

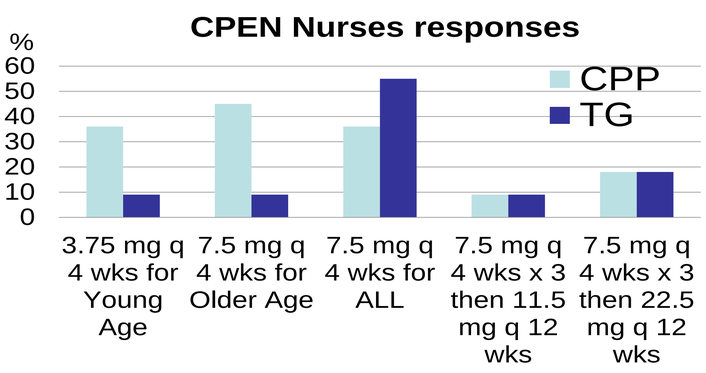
•**CPEN nurses answered** a recent survey to identify their perspective of current practices for the use of GnRH analogs.

Goals of treatment

• Prevalence of CPP is **1:5-10,000 kids with girls > than boys** with historical treatment data of over 20 years (Silverman et al. 2015)
• Goals of treatment with GnRH analogs remain to **stop pulsatile GnRH** secretion and halt further puberty development
- ➢ CPP treatment starts prior to age 8 in girls and 9 in boys
- ➢ Leads to a **predicted adult height (PAH) gain** of up to 4.5-5 cm (Carel et al. 2009; Fuld et al. 2011; Poomthavorn et al. 2011)

• DL in **TG youth** is to halt puberty (after reaching tanner stage 2) and thus **decrease depressive symptoms, improve mental health functioning** and possibly allow for **lower doses of cross hormone therapy** (Bonifacio & Rosenthal, 2015; deVries et al., 2011; Radix & Silva, 2014; Rosenthal, 2014; Spack, 2013)

GnRH Analog doses used for new Dx.



• Doses of DL for CPP differ greatly from North America to Europe:
- ➢ In North America: **DL 0.2-0.3 mg/kg/q 4 wks. OR 11.25 mg every 12 wks**. (Carel et al. 2009)
- ➢ In Europe **DL 3.75 mg q 4 wks.** standard start dose **works 85%** of the time, with increases if needed based on findings/follow-ups. (Kendirci et al. 2015; Bertelloni & Baroncelli 2013)
- ➢ Fuld et al (2011) discussed the DL **11.25 mg q 12 wk. injection as being sufficient** in most cases.

• Doses in **TG youth vary** from DL 7.5 mg IM q 4 weeks to 11.25 mg **or** 22.5 mg IM q 12 weeks, to 40 mg IM q4 or 6 mo. as well as Histrelin SC implant of 50 mg q 12 month (Bonifacio & Rosenthal, 2015; Spack, 2013)

Patient comfort

64 % of CPEN nurses offer pain reducing strategies such as:
• EMLA numbing cream (stretch and lift dressing off), Pain Ease Spray, “Buzzy Bee” (Tactile stimulation – gate control theory of pain)
36 % of CPEN nurses offer distraction techniques:
• Deep breathing, blowing bubbles or a pinwheel,
• “Buzzy Bee”, TV/music/handheld devices
• These practices are supported by Taddio et al (2010) from a meta-analysis of literature related to intramuscular injections and pain. They also suggest the following:
- ➢ Positioning of the child: ***upright position = less distress*** than supine
- ➢ IM inj. techniques: ***a rapid injection technique without aspiration***
  - ➢ One study suggested one second per 0.5 ml volume

TIP: **Do not suggest it will not hurt.** Oral analgesics prior to the injection and the use of skin-cooling techniques such as **ice alone were not supported by evidence** according to Taddio et al. (2010).

Reframing memories of pain

Experience of pain can lead to avoidance of medical care as adults, can contribute to development of chronic pain (reported 18% of children having surgery develop chronic pain later), and shape reaction to subsequent painful experiences (estimated that 1 in 10 children and adults have needle phobia).

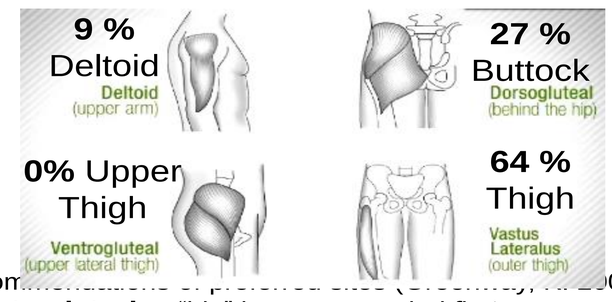
- Noel et al (2012) found that the child’s **memory** of pain intensity is a better predictor of subsequent pain perception than the actual initial reporting of the pain intensity and **fear** contributes to the memory of the event as fear is better remembered than the actual pain sensation.
- The way adults talk to children can help to reframe their memories in a positive light.
- For children age ≥ 3 yrs **talk to them** about the painful experience by focusing on what they did that was helpful such as taking deep breaths, blowing bubbles, being brave and holding still and praise them for this. *Minimize aspects that did not go well.*
- Parents have a powerful influence before, during and after the procedure and **they need to know** how and what to say to their children.
- You can use “pain denying” talk like: “You were really brave. You didn’t even cry, it was like it didn’t hurt”.

Tell children that their memory matters. Talk to them about remembering the helpful things that they were able to do and think about the positive parts. This will help them to be less afraid and make the next time go easier.

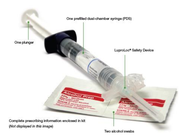
GnRH Analog (DL) injection options

CPEN nurses recommend changing a supplied 1.5 inch needle to
• 1 inch---------- (82 %)
• 5/8 inch needle and smaller syringe ---------- (27 %)
• Never change needle ---------- (9 %)

CPEN nurses most frequent recommendation for injection location:



• Recom[illegible]04) :
1. **Ventrogluteal** or “hip” is recommended first
2. **Deltoid** for 1 ml or less
3. **Vastus lateralis** (Thigh) for 1 ml or greater
4. **Dorsogluteal** “upper outer quadrant” site should be the **last** site chosen due to *risk of damaging sciatic nerve, or gluteal artery and SC admin*.



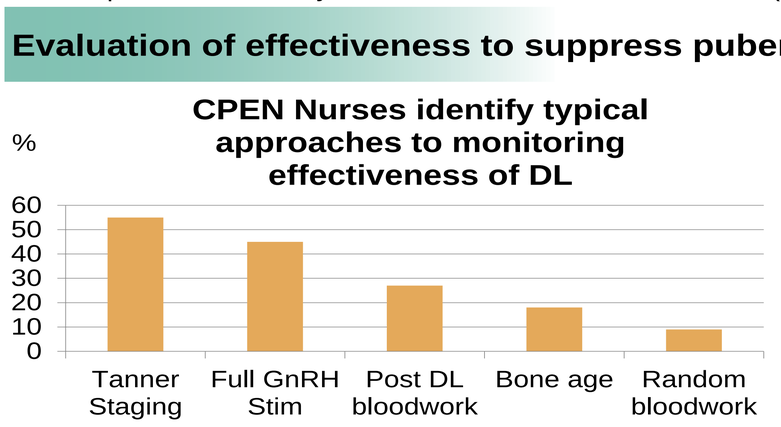
• **IM recommendation** (Koster et al. 2009):
- ➢ **5/8 inch needles for people < 60 kg**
- ➢ **1 inch for those > 60 kg**

• In insulin studies, IM depth injection was attained with **needles of 8 mm or longer at a 90 degree angle** (Hofman et al. 2007)

CPEN nurses description of who typically administers injections

• Family MD/pediatrician/ nurse practitioner in community ---- (82%)
• CPEN nurse---------- (36%)
• Parent ---------- (27%)
• Home care ---------- (18%)
• Youth/patient/self or Day unit RN ---------- (9 %)

Evaluation of effectiveness to suppress puberty



• Lawson & Cohen (1999) showed that a single sample SC LHRH stim. test with measurement of LH at 40 min. post injection is accurate at showing suppression AND preferred by patients
• This method was supported by the 2009 Consensus statement on the use of gonadotropin-releasing hormone analogs in children. (Carel et al.,2009) and further enforced by Chi et al (2012) and Chen & Eugster 2015) to get peak LH < 4 IU/L at 30 minutes
• Reinforces what CPEG clinics practice with suppression verified by a combination of hormone levels, physical exam, bone age and growth rate (Carel et al., 2009 & Lee et al., 2014)

CPEN nurses described that if puberty is NOT suppressed the usual approach is to:
• Change to q 3 weeks injection instead of q 4 weeks-------- (82%)
• Increase the dose per mg---------- (64%)
• Change to q 10 weeks if on q 12 weeks---------- (27%)

Side Effects

• Occasional complaints of headaches or hot flashes occur
• 10-15% of patients have local adverse events requiring a change in agent when persistent because they can cause **sterile abscess (SA) formation** (Carel et al., 2009)
• Lee et al (2014) describe **injection site pain in 26.5 %** of children receiving GnRH analog tx. with the **3 month DL formulations** (11.25 mg and 30 mg doses) versus **15 % pain in monthly DL** (7.5-15 mg doses) one month formulations
They do not comment on the use of pain reductions strategies!

• **1.5-3% of patients develop SA**, there seems to be a reaction with DL due to the **synthetic biodegradable Polymer** that entraps the Leuprolide to allow for release at a constant rate
- ➢ 1-mo. DL product polymer is polyactic/glycolic acid
- ➢ 3-mo. DL product is polyactic acid (Miller et al. 2010)

- **Former emails of CPEN nurses discussed clinic responses to reactions to be:**

➢ Change to daily SC Lupron Injections (Ø polymer, Ø sterile abscess)
➢ Change to Nafarelin Nasal Spray BID (used before lupron came out)
➢ Change to Triptorelin (Decapeptyl) injections (hexylsubstituted polyactic acid)

• S**tart on a monthly DL for a few months before moving to a q 12 week preparation** in order to monitor for SA formation/development as this does not always occur on 1st dose (Johnson et al. 2011)
• Khatchadourian et al. (2014) described one TG patient who was **changed to Triptorelin** due to SA with DL and tolerated this well
• Recent studies show **no increase in BMI** with GnRH tx. and upon discontinuation of treatment the hypothalamic-pituitary-gonadal axis is reactivated on average 1.5 +/-0.5 years (Chen and Eugster, 2015; Poomthavorn et al. 2010)
• **GnRH tx. may be a risk factor for Slipped Capital Femoral Epiphysis (SCFE)** and should be explained as a potential risk with symptoms to monitor for (Inman et al. 2013)

Resources

Key elements for training the clinician on the use of distraction for injections: www.cmag.ca/cgi/contant/full/cmaj.101720/DC1
Depot Lupron specific resources: www.abbvie.ca
Family resources: www.lupronped.com www.pubertytoosoon.com www.magicfoundation.org

Future treatment/monitoring options

• Histrelin implant (1 Year formulation, but can have SA reaction), in USA now
Chen and Eugster (2015) describe:
• Treatment with Kisspeptin agonists and antagonists by acting upstream of GnRH, animal studies are showing this to cross the blood-brain barrier
• Monitoring with Free alpha-subunit (FAS) LH levels respond quickly and is not a stimulation test

Acknowledgements

CPEN/ICEP nurses who participated in this survey and email correspondences
Carol A. Cooke, HSC Librarian / HSL Web Services Librarian Neil John Maclean Health Sciences Library, University of Manitoba. 23 Nov 2015.

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55ESPE 793--P2
Pituitary and Neuroendocrinology
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DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS