When and how to use anticholinergic compounds?

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Indications

- MNE that is refractory to max dose desmopressin alone (Neveus 1999, Austin 2008, Montaldo, 2012)
- Restricted bladder capacity because of detrusor overactivity at night (Austin 2008)
- Non-MNE
  - LUT symptoms (urgency/frequency, or other signs of bladder instability)
  - Overactive bladder
• Only anticholinergic approved by the U.S. FDA;
• The recommended maximal dosage is 0.4 mg/kg;
• Immediate release (IR), extended release (ER) and transdermal forms of the drug are available.
**Oxybutynin**

- **Anticholinergic**
  - Decreases uninhibited bladder contractions

- **Unselective antimuscarinic**
  - Antagonizes M1, M2, M3 muscarinic acetylcholine receptor: relaxation of detrusor muscle
  - Salivary glands, bowel

- **Spasmolytic**
  - Direct effect on bladder smooth muscle
Oxybutynin Efficacy in the Treatment of Primary Enuresis (Lovering et al., Pediatrics 1988)

- 30 children with primary nocturnal enuresis (NNE)
- One double-blinded study: oxybutynin vs placebo for treatment of NE
- 30 children with primary MNE
- 10 mg of oxybutynin for 4 weeks
- All: 4 weeks of placebo before or after the drug Tx period and the placebo period
Comparison of effects of treatment of primary nocturnal enuresis with oxybutynin plus desmopressin, desmopressin alone or imipramine alone: a randomized controlled clinical trial, Lee et al, 2005

- N=145 (100 M, mean age 7.8 +/- 2.5 years) followed for 6 mths

- Randomly assigned to 1 of 3 groups and Tx with DDAVP (N=49), imipramine (N=48), or DDAVP+Oxy (N=48)

- Efficacy: measured at 1, 3 and 6 months in terms of average enuretic frequency

- 68 patients (47%) had MNE and 77 (53%) had non-MNE

- Combo Tx produced the best and most rapid results regardless of whether the children had MNE or non MNE
Combination Therapy With Desmopressin and an Anticholinergic Medication for Nonresponders to Desmopressin for Monosymptomatic Nocturnal Enuresis: A Randomized, Double-Blind, Placebo-Controlled Trial-Austin P et al, 2008

- Monosymptomatic PNE
  - Desmopressin
    - Nonresponders 0%-49% reduction
    - Partial responders 50%-89% reduction
      - Randomization (double-blinded)
        - Includes stratification of nonresponders and partial responders
          - Desmopressin + Tolterodine LA
            - 0.6 mg
            - N=18 (12 M)
          - Desmopressin + placebo
            - 4 mg
            - N=16 (12 M)
Sign. 66% decrease in the risk of a wet episode vs placebo

LA tolterodine+DDAVP had a higher rate of full and partial responses (44% success) compared with the placebo group (31%)
Combo Tx

- Retrospective review, N=28 (20 M, 9-18 yo) with NE who failed single agent (Cendron and Klauber, 1998)
- Combo intranasal desmopressin and hyoscyamine-complete dryness 57% of the patients within 6 months
- Desmopressin+Oxybutynin in treating DDAVP-resistant mono PNE (Neveus et al, 1999)
- 71% of 28 patients who were nonresponsive to DDAVP alone had 50% reduction in the number of wet nights on 5 mg of oxybutynin + desmopressin
Desmopressin and oxybutynin in monosymptomatic nocturnal enuresis: a randomized, double-blind, placebo-controlled trial and an assessment of predictive factors, Montaldo P. et al, 2012

No sign. diff. 120 µg vs 240 µg in terms of response

The oxybutynin group showed a higher rate of full and partial responses (45% success) compared with the placebo group (17% success), $P < 0.01$

The responders to combined oxybutynin+DDAVP had significantly lower bladder volume and wall thickness index (BVWI, %) vs other patients

BVWI (%) = maximum measured bladder volume divided by measured mean BW thickness

BVWI as a predictive factor for treatment response to combo: BVWI< 70 small bladder capacity with a thick BW
• A combo of oxybutynin + imipramine was more effective in terms of number of wet nights when compared to imipramine alone

• Oxybutynin alone was less effective than combination therapy of oxybutynin and imipramine

• A combination of imipramine and oxybutynin was also more effective than monotherapy with either drug in terms of the number of children failing to achieve 14 dry nights

• The rate of failure or relapse during follow up was also lower with the combination of imipramine and oxybutynin than monotherapy with either drug

• Oxybutynin did not appear to enhance the effect of desmopressin
Evaluating use of higher dose oxybutynin in combination with desmopressin for refractory nocturnal enuresis, Berkenwald, 2016

Figure 1  Nocturnal enuresis treatment flow diagram.
Propiverine

- Antimuscarinic with additional calcium channel modulating properties
- Suggested pediatric dosage is 0.8 mg/kg/24 h
- Marschall-Kehrel et al. confirmed the efficacy of this drug compared to placebo

Multicenter cohort study: the efficacy of propiverine and oxybutynin was similar, but the former was associated with significantly fewer side-effects, such as dizziness, nausea, and hot flashes
Tolterodine

- Bladder selective agent for OAB
- Tolterodine vs oxybutynin: similar efficacy but the former has fewer side-effects
- Initial retrospective studies in children: superiority of tolterodine over oxybutynin in terms of side-effects
- Randomized, double-blinded, clinical trials failed to show any statistical difference between tolterodine and placebo, or tolterodine and oxybutynin
- Tolterodine has not been approved for use in children to date and therefore has no recommended pediatric dosage.
- Adult dosage of 2 mg twice daily is comparable to 1 mg twice daily in children aged 5–10 years
Solifenacin

- Novel, selective antimuscarinic with moderate selectivity for M3 over M2 receptors
- Not approved for pediatric use, but studies have shown a good response and tolerance of this agent in children previously resistant to oxybutynin or tolterodine
- Retrospective study of 138 children with OAB refractory to other antimuscarinic agents, 5 mg of solifenacin was associated with an 85% response rate (full and partial) and a 6.5% dropout due to side-effects
Safety profile

Anticholinergic adverse effects

- Oral: dry mouth, dysphagia
- Visual: dry eyes, blurred vision
- GI: diarrhea, constipation, distention
- CNS: hallucinations (sensing insects or beasts crawling on the body), agitation, sedation, confusion, amnesia, cognitive impairment, and abnormal dreams (eg, nightmares)
Young children: Neurodevelopmental effects?

Neuropsychological function tests:

- 15 children with diurnal incontinence treated with oxybutynin vs 10 children receiving behavioral intervention only;
- Oxybutynin was not associated with cognitive impairment following the Treatment (Sommer et al)
- 14 children found no negative long-term effects of oxybutynin on short term memory and attention span
### Spectrum of Central Anticholinergic Adverse Effects Associated with Oxybutynin: Comparison of Pediatric and Adult Cases, Gish et al, 2016

#### Table. CNS MedDRA* Preferred Terms reported by age (n = 180)

<table>
<thead>
<tr>
<th>CNS MedDRA* Preferred Terms</th>
<th>0-5 years</th>
<th>6-16 years</th>
<th>17-59 years</th>
<th>60+ years</th>
<th>Total</th>
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<tbody>
<tr>
<td>Oxybutynin (no. of U.S. cases in parenthesis)</td>
<td>(14 (12))</td>
<td>(23 (16))</td>
<td>(46 (43))</td>
<td>(97 (88))</td>
<td>(180 (159))</td>
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<tr>
<td>Hallucination</td>
<td>4 (4)</td>
<td>6 (3)</td>
<td>5 (5)</td>
<td>24 (23)</td>
<td>39 (35)</td>
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<tr>
<td>Sedation</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>13 (13)</td>
<td>21 (20)</td>
<td>37 (36)</td>
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<tr>
<td>Confusional state</td>
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<td>2 (2)</td>
<td>4 (4)</td>
<td>29 (24)</td>
<td>37 (32)</td>
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<tr>
<td>Agitation</td>
<td>2 (2)</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>6 (5)</td>
<td>14 (9)</td>
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<tr>
<td>Anxiety</td>
<td>1 (0)</td>
<td>—</td>
<td>6 (6)</td>
<td>6 (6)</td>
<td>13 (12)</td>
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<tr>
<td>Amnesia</td>
<td>4 (2)</td>
<td>3 (3)</td>
<td>6 (6)</td>
<td>18 (11)</td>
<td>26 (24)</td>
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<td>Abnormal dreams</td>
<td>2 (2)</td>
<td>2 (1)</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>7 (7)</td>
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<tr>
<td>Thinking abnormal</td>
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<td>2 (2)</td>
<td>2 (2)</td>
<td>7 (7)</td>
<td>4 (4)</td>
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<td>Disorientation</td>
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<td>1 (0)</td>
<td>6 (4)</td>
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<tr>
<td>Convulsion</td>
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<td>5 (3)</td>
<td>3 (3)</td>
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<td>Psychotic disorder</td>
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<td>4 (4)</td>
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<td>Personality disorder</td>
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<td>2 (2)</td>
<td>3 (3)</td>
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<tr>
<td>Attention deficit/hyperactivity disorder</td>
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<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>3 (3)</td>
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<tr>
<td>Abnormal behavior</td>
<td>—</td>
<td>2 (1)</td>
<td>—</td>
<td>3 (2)</td>
<td>2 (2)</td>
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<td>Hallucination, visual</td>
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<td>2 (0)</td>
<td>—</td>
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<tr>
<td>Drug toxicity</td>
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<td>—</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>1 (1)</td>
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</tbody>
</table>


- N=20 (17 boys), mean age 9 years, who had persistent urgency and incontinence after a minimum of 1 month of therapy with an optimal dose of a well-tolerated, extended-release oxybutynin Tx

- QT interval changes significantly depending on the use of oxybutynin

- The QT changes increased cardiac arrhythmias in children

- Close monitoring for cardiac arrhythmia
Dosage

- Tolterodine 1-2 mg twice daily
- Oxybutynin 2.5-5-10 mg daily

Before starting

- Exclude or treat constipation
- Exclude or treat residual urine

Guidelines

- Regular toilet habits are important!
- Close follow-up needed (residual urine):
  - Frequency-volume chart
  - Ultrasound measurements of residual urine
- UTI risk: stop therapy and check for residual urine
Drawbacks

- No immediate effect (>6-12 months)
- Evaluate therapy after 1-2 months
- Taper gradually
- Usually needs to be combined with DDAVP
- Assure good oral hygiene (salivation inhibitor)
Thank you!

Good boy!