Comparison of Fesoterodine, Tolterodine, Oxybutynin and Solifenacin in patients with overactive bladder

A systematic review

Introduction
In the Netherlands, five antimuscarinic drugs can be prescribed for the treatment of overactive bladder (OAB): tolterodine, solifenacin, fesoterodine, oxybutynin and darifenacin [1]. This drugs work by blocking the M3 muscarinic acetylcholine receptor, which is responsible for bladder muscle contraction.

Overactive bladder is an idiopathic symptom complex suggestive of detrusor overactivity. OAB is characterized by urge urinary incontinence (UUI), usually with urinary frequency and nocturia [2,3]. The prevalence of OAB among adults in the USA and Europe has recently been estimated at 16-17% [4], which means that as many as 34 million people are affected in the USA alone [5]. OAB with urge incontinence is more likely to occur in women than in men (9.3 and 2.6% respectively) and it increases with age in both sexes [4].

OAB is under-treated by clinicians, despite clear evidence that antimuscarinics reduce OAB symptoms [3]. By blocking the muscarinic receptors, antimuscarinic agents inhibit the abnormal bladder contractions (detrusor overactivity) and reduce OAB symptoms. However, they also act on muscarinic receptors in other parts of the body, causing adverse effects such as dry mouth and constipation, which limits their use [6].

In recent decades, several new compounds have been developed that have fewer adverse effects than the oldest of the currently available antimuscarinic drugs, oxybutynin. Tolterodine was the first agent introduced for this purpose. This medicine is bladder-selective and has been shown in animal studies to have a greater affinity for the bladder than for other organs [7]. Clinically, tolterodine has been shown to have fewer side effects than other antimuscarinic agents [8].

Another antimuscarinic agent is solifenacin, which has also proven to be bladder-selective. Clinical trials demonstrated that solifenacin is effective in the treatment of OAB and is generally well tolerated [9].

Fesoterodine is a more recently introduced antimuscarinic agent. It acts functionally as a prodrug and is rapidly and extensively converted by nonspecific esterases to its primary active metabolite, 5-hydroxymethyl tolterodine (5-HMT). Fesoterodine is not detectable in plasma after oral dosing. 5-HMT is also the major active metabolite of tolterodine, but is formed from tolterodine via cytochrome P450 2D6-mediated oxidation in the liver [10].

Oxybutynin is another antimuscarinic treatment; it relaxes the smooth muscle of the bladder.

Darifenacin is the fifth antimuscarinic agent addressed in the present study. Similar to the other antimuscarinic agents, it works by blocking the M3 muscarinic acetylcholine receptor.

Although several studies compared two of these medications, to the best of our knowledge no comparison of all five of these medications has been reported. The aim of our study was to determine the best medication for patients with overactive bladder. In this systematic review, we addressed the following research questions. (1) Which medication shows the best decrease in UUI episodes, total voids, nocturnal voids urgency episodes and the best increase in MVV/void? (2) Which medication has the fewest adverse effects? (3) Which medication is associated with the best patient perception of bladder condition and has the highest score on the OAB questionnaire? The answers to these three questions will be used to recommend a therapy for OAB.
Methods

We searched the National Library of Medicine’s PubMed database
on January 11th, 2011. The MeSH terms used were oxybutynin [Substance] or darifenacin [Substance] or quinuclidin-3'-yl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate [Substance] (solifenacin) or fesoterodine [Substance] or tolterodine [Substance] and urinary bladder, overactive/drug therapy [Major Heading]. Our limits were humans, randomized controlled trial and English as language.

Our inclusion criterion was that the article compared at least two drugs. Exclusion criteria were: neurogenic overactivity, cost-utility analysis, studies in which one group used two different antimuscarinics, pharmacokinetic profile and the involvement of non-antimuscarinic drugs. We applied these criteria to the titles of the articles. The primary efficacy parameters we used in this study were: urge urinary incontinence (UUI), total voids, nocturnal voids, urgency episodes and the maximum voided volume (MVV). The primary tolerability parameters we used in this study were PPBC (patient perception of bladder condition) and adverse effects.

Results

Our literature search on PubMed resulted in 461 studies about overactive bladder. After applying our inclusion and exclusion criteria, six studies remained: four randomized controlled trials and two randomized post-hoc analysis studies. These six studies were used for our review.

Five of these studies were multicentric. One study was conducted in Taiwan, two in Europe and three in Canada and the USA. More than 80% of these patients were women, and the mean age was approximately 60 years.

Efficacy

In these studies, a total of four antimuscarinic agents were compared. Some studies used a placebo as well. The four agents were solifenacin, tolterodine, oxybutynin and fesoterodine. No studies on darifenacin were found. Four of these studies lasted 12 weeks, one study 8 weeks and one study 4 weeks. The data on UUI episodes, total voids, nocturnal voids, urgency episodes and MVV were collected.

Table 1 shows study details and efficacy of these agents.

Ho et al. (2010) and Chapple et al. (2007) [6,11] compared solifenacin 5 mg to tolterodine 4 mg. In both studies at week 12, the mean changes from baseline in number of micturition per 24 hours were not significantly different between the solifenacin (p = 0.58) and tolterodine groups [6,11]. In both studies, the two groups both showed significant improvements in urgency episodes per 24 hours. At the endpoint of both studies, the mean changes from baseline were not significantly different for urgency episodes between the solifenacin (p = 0.37) and tolterodine groups (p = ns) [6,11]. However, these two studies reported contradictory results in mean voided volume per micturition. In one study, mean voided volume per micturition increased significantly relative to baseline in the solifenacin group, but not in the tolterodine group [6], while the other study reported no difference between these two drugs relative to baseline (Table 1) [11].

In two other studies, Herschorn et al. (2009) and Chapple et al. (2008), fesoterodine 8 mg was compared to tolterodine 4 mg, and both drugs were compared to a placebo. In both studies fesoterodine significantly improved UUI episodes at week 12 compared with tolterodine extended release (ER) (in one study, p = 0.017 [12] and in the other, p < 0.001 [10]). In both of these studies fesoterodine was associated with significantly greater improvements in MVV than tolterodine ER (in one study, p = 0.005 and in the other p < 0.05 [10,12]). In one of these studies, tolterodine compared with placebo showed significant improvement in UUI episodes, total voids/24 h and urgency episodes/24 h, but not in MVV [12], while in the other tolterodine compared with placebo showed a significant improvement in MVV and urgency episodes, but not in UUI [10]. No significant improvement in nocturnal voids/24 h was found between fesoterodine and placebo and tolterodine and placebo (p = 0.506) (Table 1) [12].

Anderson et al. (2005) compared extended-release oxybutynin 10 mg to extended-release tolterodine 4 mg. The mean weekly UUI episodes (SD) decreased from 37.5 (14.0) recorded at baseline to 10.2 (13.7) for the ER oxybutynin treatment group, and from 36.2 (13.9) to 9.3 (13.3) for the ER tolterodine group.

Table 1 - Study details, tolerability and efficacy: summary of the clinical studies

<table>
<thead>
<tr>
<th>Variables Article</th>
<th>Duration (weeks)</th>
<th>Dose</th>
<th>No. of patients</th>
<th>Completed the study (%)</th>
<th>UUI episodes/24 h</th>
<th>Total voids/24 h</th>
<th>Nocturnal voids/24 h</th>
<th>Urgency episodes/24 h</th>
<th>MVV/void (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho et al. 2010</td>
<td>12</td>
<td>Solifenacin 5 mg</td>
<td>39</td>
<td>38 (97)</td>
<td>-2.79 ±3.31</td>
<td>-2.56</td>
<td>/</td>
<td>-1.70 ±3.07</td>
<td>27.61 ±15.74 ‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolterodine 4 mg</td>
<td>36</td>
<td>35 (97)</td>
<td>-4.67 ±4.56</td>
<td>-2.44</td>
<td>/</td>
<td>-1.15 ±2.68</td>
<td>10.60</td>
</tr>
<tr>
<td>Herschorn et al. 2009</td>
<td>12</td>
<td>Fesoterodine 8 mg</td>
<td>679</td>
<td>598 (88)</td>
<td>-1.72 * #</td>
<td>-2.2 *</td>
<td>-0.6</td>
<td>-3.5 *</td>
<td>32.9 * #</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolterodine ER 4 mg</td>
<td>684</td>
<td>629 (92)</td>
<td>-1.81 *</td>
<td>-2.1 *</td>
<td>-0.6</td>
<td>-3.1 *</td>
<td>23.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>334</td>
<td>304 (91)</td>
<td>-1.46</td>
<td>-1.5</td>
<td>-0.5</td>
<td>-2.0</td>
<td>16.8</td>
</tr>
<tr>
<td>Chapple et al. 2008</td>
<td>12</td>
<td>Fesoterodine 8 mg</td>
<td>287</td>
<td>272 (95)</td>
<td>-85% * ^</td>
<td>/</td>
<td>/</td>
<td>-20% †</td>
<td>36 † #</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolterodine 4 mg</td>
<td>290</td>
<td>281 (87)</td>
<td>-70%</td>
<td>/</td>
<td>/</td>
<td>-16% *</td>
<td>24 *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>283</td>
<td>277 (89)</td>
<td>-50%</td>
<td>/</td>
<td>/</td>
<td>-14%</td>
<td>11</td>
</tr>
<tr>
<td>Chapple et al. 2007</td>
<td>4</td>
<td>Solifenacin 5 mg</td>
<td>593</td>
<td>575 (97)</td>
<td>-1.22 ‡</td>
<td>-1.71 *</td>
<td>-0.51</td>
<td>-1.96</td>
<td>28.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolterodine 6 mg</td>
<td>607</td>
<td>590 (98)</td>
<td>-0.91 ‡</td>
<td>-1.47 *</td>
<td>-0.44</td>
<td>-1.67</td>
<td>24.29</td>
</tr>
<tr>
<td>Anderson et al. 2005</td>
<td>12</td>
<td>Oxybutynin ER 10 mg</td>
<td>381</td>
<td>52 (14)</td>
<td>-27.3 ±13.7</td>
<td>-31.7 ±22.0 #</td>
<td>/</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolterodine ER 4 mg</td>
<td>399</td>
<td>42 (11)</td>
<td>-26.9 ±13.3</td>
<td>-28.5 ±21.3</td>
<td>/</td>
<td>/</td>
<td></td>
</tr>
</tbody>
</table>

Mean change from baseline to week 12 in UUI episodes/24 h, MVV/void, total voids/24 h, nocturnal voids/24 h and urgency episodes/24 h. Data represent the full analysis set for patients reporting symptoms at baseline * p<0.05 drug vs. placebo; # p<0.05 drug 1 vs. drug 2; † p<0.001 vs. placebo; ^ p<0.001 drug 1 vs. drug 2; ‡ p<0.05 vs. baseline; OD= once daily; TD= 3 times daily; ± = standard deviation. In Anderson et al. (2005) the variables were measured weekly.

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For the ER oxybutynin group, the mean weekly micturition frequency (SD) decreased from 96.5 (27.1) voids recorded at baseline to 64.8 (22.0) at last observation, compared with a decrease from 97.9 (24.2) to 69.4 (21.3) for the ER tolterodine group. The difference between the groups was significant (p=0.035) (Table 1) [13].

Safety and tolerability
Several adverse events were associated with antimuscarinic drug use. The most common were dry mouth and constipation, but diarrhea, headache, urinary tract infection and dizziness were also frequently reported. Generally, side effects were mild and occurred only in a minority of patients. Table 1a shows an overview of the tolerability and the safety of several drugs (some compared to placebo).

Ho et al. (2010) and Chapple et al. (2007) [6,11] compared the tolerability of solifenacin 5 mg and tolterodine 4 mg. In the solifenacin group, 38.5% of patients suffered from at least one adverse effect, compared to 25.0% in the tolterodine group. However the percentages did not significantly differ between the two groups (p = 0.23) [6]. The reported adverse effects included dry mouth, constipation, hiccups, palpitations and dizziness, with the most common being dry mouth (p = 0.31) and constipation (p = 0.20) [6]. These percentages were consistent with the other study [11]. In the two groups the incidence of each adverse effect was similar (Table 1a) [11].

In these two studies, there were a few patients who dropped out of the study because of adverse events. One patient in the solifenacin group dropped out because of dizziness, and another in the tolterodine group dropped out because of palpitations [6]. However, in Chapple et al. (2007) 35 patients dropped out because of adverse events. The primary reason was dry mouth, which was given as reason by 6 patients in the solifenacin group and 6 in the tolterodine group. Four patients in the solifenacin 5 mg group dropped out, giving constipation as the primary reason. The rest of the patients dropped out for several other reasons (Table 1a) [11].

Herschorn et al. (2010) compared solifenacin to oxybutynin [14]. In this study, significantly fewer patients on solifenacin reported dry mouth compared to the oxybutynin IR (immediate-release) group (95% CI 33.6–62, p <0.0001). In those reporting dry mouth, solifenacin was associated with significantly lower severity of this adverse effect than oxybutynin IR (p = 0.001) [14]. Excluding dry mouth, the overall incidence of other adverse events was 59% in the solifenacin group and 70% in the oxybutynin IR group (p = 0.17). After dry mouth, the most commonly reported adverse events in the oxybutynin IR group were nasal dryness in 14% of patients, dizziness in 9% and fatigue in 9%. In contrast, the most commonly reported adverse event in the solifenacin group was constipation in 13% of patients [14]. Oxybutynin was associated with higher rates of adverse events. Similar results were found by Anderson et al. (2005) when comparing oxybutynin to tolterodine [13]. Dry mouth was the most commonly reported adverse event in each group. Dry mouth was more common in the extended release (ER) oxybutynin group compared to the ER tolterodine-treated group (p = 0.004). The majority of dry mouth events were mild in severity [13]. While the overall dropout rate did not differ significantly between the solifenacin and oxybutynin IR groups (p = 0.081), significantly fewer solifenacin patients dropped out due to dry mouth compared to the oxybutynin IR treated group (3% vs. 19%, p = 0.003) [14]. Similar results were found in the study with oxybutynin and tolterodine. However, the overall dropout rate in this study did not differ significantly between the tolterodine and oxybutynin IR groups (Table 1a) [13].

Compared to solifenacin, tolterodine was associated with fewer adverse events [6,11]. In two studies, tolterodine 4 mg was also compared with fesoterodine 8 mg [10,12]. The most frequently reported adverse events in the fesoterodine group were dry mouth, headache and constipation. These were also the most frequently reported adverse events in the tolterodine ER group and in the placebo group. Fesoterodine was associated with more adverse events than tolterodine [12]. In another study, fesoterodine was also associated with more adverse events than tolterodine. [13]. The most common adverse events reported in this study were dry mouth and constipation (Table 1a).

In all treatment groups studied by Herschorn et al., the majority of adverse events, including dry mouth, were mild or moderate [12]. Overall, 3.2% of patients dropped out of this study because of an adverse event. The reasons included urinary retention, which occurred in 1% of patients in the fesoterodine 8 mg group, and which required catheterization in one patient. However no patients receiving tolterodine ER or placebo dropped out due to urinary retention, and none required catheterization. Only one patient (<1%) in either group dropped out because of dry mouth. One patient (0.3%) in the fesoterodine 8 mg group dropped out because of constipation; no patients in the tolterodine ER or placebo groups dropped out because of constipation (Table 1a) [10].

Patient Perception of Bladder Condition and OAB-q
Besides considering the effects on the bladder and the adverse effects, quality of life was estimated as well. The instruments for estimating quality of life differed per study. The instruments used most often were the Patient Perception of Bladder Condition (PPBC) and the OAB Questionnaire (OAB-q).

Patients completed the Patient Perception of Bladder Condition (PPBC) [6,12,14] and OAB Questionnaire (OAB-q) at baseline and at week 12 [10,12,14]. The PPBC is a validated single-item questionnaire that asks patients to rate their overall bladder condition: lower scores indicate less-severe bladder-related problems [15]. The validated OAB-q includes an eight-item single-item questionnaire that asks patients to rate their overall bladder condition; lower scores indicate less symptom bother. The categorical change in PPBC score from baseline to week 12 was significantly improved in the solifenacin and tolterodine groups. At week 12, the mean changes (SD) from baseline in PPBC

<table>
<thead>
<tr>
<th>Variables</th>
<th>Dry mouth (no.%)</th>
<th>Adverse effects constipation (no.%)</th>
<th>Withdrawal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho et al. 2010</td>
<td>7 (18.0)</td>
<td>5 (12.8)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Herschorn et al. 2010</td>
<td>24 (35)</td>
<td>9 (13)</td>
<td>16 (23.5)</td>
</tr>
<tr>
<td>Chapple et al. 2009</td>
<td>112 (16.4)</td>
<td>28 (4.1)</td>
<td>28 (4.1)</td>
</tr>
<tr>
<td>Chapple et al. 2008</td>
<td>48 (16.9)</td>
<td>8 (2.8)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Anderson et al. 2005</td>
<td>100 (25.2)</td>
<td>41 (10.2)</td>
<td>19 (4.8)</td>
</tr>
</tbody>
</table>
were −1.40 (1.40) in the solifenacin group and −1.40 (1.60) in the tolterodine group; the two groups did not differ significantly (p = 0.73) [6].

However, in the other study PPBC was significantly more favorable in the fesoterodine group than in patients on placebo (p < 0.001) and tolterodine ER (p < 0.001) [12]. Changes in the tolterodine ER group were also significantly more favorable than in the placebo group (p < 0.001). Consistent with this finding, the proportion of patients reporting ‘some minor problems’ or better on the PPBC at week 12 was higher in the fesoterodine group (55%) than in the tolterodine ER (45%, p < 0.001) and placebo (33%, p < 0.001) groups. The difference between the tolterodine ER and placebo groups was also statistically significant (p < 0.001) [12].

According to the OAB-q scores, fesoterodine was also more favorable compared to tolterodine and placebo. Improvements in OAB-q scores from baseline to week 12 were significantly greater in the fesoterodine than the placebo group on the Symptom Bother scale, total HRQL scale and all four HRQL domains (all p < 0.001) [12].

Discussion

Based on our findings, we recommend fesoterodine. This drug has shown the best decrease in UUI episodes, total voids, nocturnal voids urgency episodes and the best increase in MVV/void. Although oxybutynin improves the UUI episodes and total voids more than fesoterodine (Table 2), the adverse effects must be considered as well. The most prevalent adverse effects were dry mouth and constipation. Studies on oxybutynin [14] and fesoterodine [10,12] reported more cases of dry mouth than studies on the other antimuscarinics. The drug most associated with constipation was solifenacin [6,14]. The other adverse effects that were measured were reported by only a small percentage of the patients. Most adverse effects did not bother patients enough to discontinue the treatment. Dropout rate was low, except in the study comparing oxybutynin and solifenacin (Table 1a) [14]. We therefore conclude that fesoterodine is the best medication for overactive bladder. It is effective and has fewer adverse effects than oxybutynin.

This conclusion is subject to a number of limitations. First, no studies on darifenacin were found, so we cannot draw any conclusions about the advantages or disadvantages of this drug. Second the patient populations for the other four medications differed. In total, 1973 patients took tolterodine, but only 455 patients were placed in the oxybutynin group. Third, fesoterodine was compared only to tolterodine, not to any other drugs. Fourth, the patients did not live in the same area of the world. One study was done in Taiwan, while the others were done in Europe, Canada or the USA. Differences between the populations, such as lifestyle, could have affected the efficacy of the drugs.

Another limitation concerns the inclusion and exclusion criteria. The inclusion criteria were generally the same, but the exclusion criteria differed. Some studies excluded patients with specific diseases, while others did not. It is possible these diseases affected the results, but we have no evidence about this.

An evidence-based recommendation is difficult to make due to the different or unclear parameters used in the studies. For example, Herschorn et al. (2010) did not discuss the parameters used (Table 1). Those researcher primarily investigated the adverse effects, but they did state a p-value or confidence interval to support their assertion that PPBC improved significantly [14]. The parameters for the quality of life were especially different between the studies. Different quality of life questionnaires are difficult to compare. Therefore we were unable to answer the third research question. For future studies, we recommend that researchers use common parameters.

Other limitations of the various studies should be mentioned. Anderson et al. (2005) distinguished between patients who used antimuscarinics prior to the study and those who did not. We used only the results from the second group, because the other studies in our review excluded patients who used antimuscarinics during a short period prior to the study.

In Chapple et al. (2007) the patients were randomized for the two drugs at baseline. After week 4 they looked at the results, and requests for increased dosage from patients in the solifenacin group were approved. However, the subsequent results showed that the number of patients in tolterodine changed as well. Because there was no explanation for that change, we used only the results after week 4.

In Chapple et al. (2008) the decrease of UUI and urgency episodes were given in percentages instead of numerical changes. Some of the studies did not discuss the results compared to baseline. Therefore we could not conclude that the drugs improved bladder condition significantly. However, we assume that all these types of antimuscarinics significantly improve the OAB symptoms, otherwise they would not be used at all.

Two major adverse effects were reported: dry mouth and constipation. One of the studies primarily investigated the adverse effects, in particular dry mouth. In that study, dry mouth was reported much more often than in the other studies. When we compared medications, we found major differences between the oxybutynin group in Herschorn et al. (2010) and the oxybutynin group in Anderson et al. We suspect that the high prevalence of dry mouth Herschorn et al. (2010) was influenced by the fact that the primary aim of this study was to determine the effect of the medications on dry mouth.

At present, we conclude that fesoterodine should be recommended as therapy for overactive bladder. However, we recommend that future studies should compare the five drugs to each other using the same parameters and equal populations of patients.

### Table 2 - Summary of the efficacy data

<table>
<thead>
<tr>
<th>Variables Medication</th>
<th>UUI episodes/ 24 h</th>
<th>Total voids/ 24 h</th>
<th>Nocturnal voids/ 24 h</th>
<th>Urgency episodes/ 24 h</th>
<th>MVV/void (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solifenacin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-1.22 to -2.79</td>
<td>-1.71 to -2.56</td>
<td>-0.51</td>
<td>-1.70 to -1.98</td>
<td>27.61 to 28.51</td>
</tr>
<tr>
<td><strong>Tolterodine</strong></td>
<td>-0.91 to -4.67</td>
<td>-1.47 to -4.01</td>
<td>-0.44 to -0.6</td>
<td>-1.15 to -3.1</td>
<td>10.60 to 24.29</td>
</tr>
<tr>
<td><strong>Oxybutynin</strong></td>
<td>-3.9</td>
<td>-4.53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fesoterodine</strong></td>
<td>-1.72 to 85%*</td>
<td>-2.2</td>
<td>-0.6</td>
<td>-3.5 to 20%*</td>
<td>32.9 to 36</td>
</tr>
</tbody>
</table>

This numbers are ranges of different drugs in different studies. * Mean percent reduction from baseline. In the article of Anderson et al. 2005 the variables were measured weekly, so the numbers in Table 1 are divided by 7.
Does pharmacologic treatment prevent children from emergence agitation after sevoflurane anesthesia?

A systematic review

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Objective: To determine whether pharmacologic treatment is likely to decrease the incidence of Emergence Agitation (EA) in children after sevoflurane anesthesia.

Methods: We performed a Medline search using the MeSH terms sevoflurane, emergence agitation, child, anesthesia and prevention. We included prospective clinical trials written in English.

Results: During anesthesia for nonsurgical diagnostic procedures, propofol, dexmedetomidine and fentanyl all caused a significant decrease in the incidence of EA. In surgical patients, ketamine (in combination with midazolam), a caudal block (in combination with midazolam), dexmedetomidine and tropisetron all significantly decreased the incidence of EA, whereas midazolam and clonidine did not.

Conclusions: For pain-free diagnostic procedures, we recommend the use of propofol to decrease the incidence of EA. In surgical patients, ketamine (with midazolam) and tropisetron may be promising options.

Introduction
Emergence agitation (EA) is very common in children who receive sevoflurane anesthesia. One out of many definitions of EA is “a disturbance in a child’s awareness of and attention to his/her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behavior in the immediate post anesthesia period (within the first 30 minutes of emergence from anesthesia)" [1].

Depending on the definition used, the age of the children and other factors, the incidence of EA can range from 10% to as high as 80% [1]. EA is a more frequent side effect in preschool children than in older children [2].