Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

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Stress Urinary Incontinence: Meta-analysis of clinical study reports questions use of duloxetine

The authors of a meta-analysis, which included individual patient data from clinical study reports, have questioned the rational for the use of duloxetine in the treatment of stress urinary incontinence (SUI). This was based on a comparison of potential benefits versus risk of harms. Their findings are summarised below. A reminder of NICE and MHRA guidance on duloxetine is also provided.

Reference: Maund E, Schow Guski L and Gøtzsche PC. Considering benefits and harms of duloxetine for treatment of stress urinary incontinence: a meta-analysis of clinical study reports *CMAJ. 14 Nov 2016.* doi:10.1503/cmaj.151104

What do we know already?

- The serotonin-noradrenaline reuptake inhibitor duloxetine, at doses of 20 mg and 40 mg twice daily, is licensed in Europe for the treatment of SUI. Duloxetine is not licensed for this indication in the USA or Canada. The FDA has previously advised that a higher than expected rate of suicide attempts was observed in the open-label extensions of studies of duloxetine for SUI.
- The 2013 NICE guideline on UI (*currently being updated*) gives duloxetine a limited place tin therapy. Instead, pelvic floor training is recommended as first-line treatment for SUI, as it is more effective and less costly (*ref: full NICE guideline*). The guideline also discusses lifestyle interventions (caffeine reduction; modification of fluid intake; weight loss.) Surgery was also considered to be more cost-effective than duloxetine, although generic duloxetine is now available, which may alter cost-effectiveness assessments. The 2013 NICE guidance recommends that:
  - duloxetine should not be used as a 1st-line treatment for women with predominant SUI
  - it should not be routinely offered as a 2nd-line treatment for women with SUI
  - it may be offered as a 2nd-line therapy where a woman prefers pharmacological to surgical treatment or is not suitable for surgical treatment
- If duloxetine is prescribed, NICE recommends that women should be informed about its adverse effects. A 2007 MHRA Drug Safety Update advised that patients should be assessed regularly due to reported cases of suicidal ideation and suicidal behaviour during treatment with duloxetine or shortly after stopping treatment.
- Meta-analyses of individual patient data, although resource intensive, can improve quality of data and the type of analyses that can be done, and are considered to be the 'gold standard' of systematic reviews (*ref: Cochrane*).

What does this publication add?

- This new analysis uses some different outcomes and studies from systematic reviews previously published by Cochrane and the US Agency for Healthcare Research and Quality. Findings on treatment-emergent adverse events (AEs) and discontinuations due to AEs were broadly in line with these earlier reviews. However, the clinical study reports of the four 12-week placebo controlled studies submitted to the European Medicines Agency (EMA) provided the authors with more information on harms, including some individual patient data. This allowed the authors to review 'narratives' describing serious AEs or treatment discontinuations due to AEs. This led to reclassification of some AEs.
- A statistically significant difference between duloxetine and placebo was found for reductions in frequency of incontinence episodes and quality of life scores, but effect sizes were small (*see overleaf for details*).
- The authors were also able to carry out meta-analyses of harms that consisted of multiple symptoms. Their focus was on events of suicidality and violence and their potential precursor events, for example psychotic behaviour and 'activation' (*a group of stimulating events, including anxiety and agitation*). The authors' assertion that "*the harms of duloxetine outweigh the benefits*" stems from the number needed to treat (NNT) of 8 calculated for duloxetine for a Patient Global Impression of Improvement rating of "*much better or very much better*". This exceeded the number needed to harm (NNH) calculated for discontinuation due to an AE, or for experiencing a core or potential activation event* (both NNHs were 7). *Note* – there were no actual reports of suicidality or violent event in the studies. Also, the inclusion of some AEs as precursors to suicidality and violence, and the categorisation of some events as 'activation' events, are open to debate and need to be considered when interpreting these findings. The paper, however, presents an opportunity to remind prescribers of MHRA safety advice that the benefit of duloxetine for patients with SUI should be assessed regularly, and that patients and caregivers should be advised to monitor and report any distressing thoughts or feelings.

Study details

Participants:

- The meta-analysis included data from the clinical study reports of 4 key trials that were submitted to the EMA to support the licensing of duloxetine for SUI. The trials included 1913 women; 958 received duloxetine.
- Use of antidepressants within 14 days of the study start or during the study was not permitted, and arms in individual trials were comparable for baseline characteristics of psychiatric symptoms and disorders, except for 1 study where the placebo arm had more women with pre-existing depression.

Intervention and comparison:

- All studies were placebo-controlled and had a 2-week base-line assessment period (no treatment), a 2-week placebo lead-in period before randomisation, and 12 weeks of treatment with duloxetine 80 mg daily or placebo. One study initiated treatment at 40 mg duloxetine, before upwards titration.
- Authors used data in the summary tables and listings provided in the clinical study reports, which categorised harms using preferred MedDRA terms. They also analysed the notations containing investigator-reported 'verbatim' terms that were available for patients who had a serious AE or who had discontinued due to an AE.

Outcomes and results:

Efficacy:

- The authors used the protocol-specified primary outcomes of % change from baseline in frequency of incontinence episodes and change from baseline in Incontinence Quality of Life score (0 [worst] to 100 [best]).
- The weighted mean baseline value for weekly frequency of incontinence episodes was 16.8.
- Duloxetine was significantly better than placebo for % change from baseline in weekly incontinence episodes (mean difference –13.56%, 95% Confidence Interval [CI] –21.59% to –5.53%), and change in weekly incontinence episodes (mean difference –2.85, 95% CI –3.91 to –1.78). Minimum clinically important differences (MCIDs) for this outcome could not be identified from published literature.
- Effect sizes were small for both of these outcomes (standardised mean differences [SMDs] of –0.13, 95% CI –0.22 to –0.04 and –0.26, 95% CI –0.35 to –0.16, respectively). *N.b. 'effect size', in this case, is a measure used in meta-analyses to quantify differences between groups, with contributing studies weighted based on sample size. An SMD of 0.2 was considered a 'small' effect, 0.5 a moderate effect and 0.8 a large effect.*
- The weighted mean baseline value for Incontinence Quality of Life total score was 64.0. Mean changes (improvements) in this score were greater for duloxetine than placebo (mean difference 3.24, 95% CI 2.00 to 4.48). The MCID is 2.5 for this scale. As the lower 95% CI was below this, the authors question whether the difference is clinically important. Effect size for this outcome was also small (SMD 0.24, 95% CI 0.15 to 0.33).
- The Patient Global Impression of Improvement rating is a validated measure of improvement as perceived by a patient since starting treatment. Responses of "*much better or very much better*" were considered to represent a response to treatment. When all 4 trials were included in a meta-analysis for this outcome, there was considerable heterogeneity (i.e. *too great a variation between trails*). To reduce heterogeneity, 1 trial was removed from the analysis, which resulted in a risk ratio (RR) of 1.51, 95% CI 1.29 to 1.77, with an NNT of 8.

Harms:

- Cross-referencing summary tables, listings and narratives led the authors to reclassify or exclude some AEs from their analyses. Several AEs were also only identifiable from narratives.
- 727 patients receiving duloxetine and 548 receiving placebo experienced at least 1 AE (RR 1.32, 1.24 to 1.41; NNH 6). 20% of patients receiving duloxetine and 3.4% of patients receiving placebo discontinued study participation due to an AE. The risk of discontinuing due to an AE was >5 times higher with duloxetine (RR 5.73, 4.00 to 8.20; NNH 7). The risk of experiencing a serious AE was higher with duloxetine but was not statistically significant (RR 1.77, 95% CI 0.79 to 3.98).
- No events of violence, suicidality or akathisia were reported. Core or potential activation events* were experienced by 187 patients in the duloxetine group and 42 patients in the placebo group, with 41 in the duloxetine group and 5 in the placebo group experiencing more than 1 event. The risk of experiencing a core or potential activation event was >4 times higher in the duloxetine group than in the placebo group (RR 4.45, 95% CI 3.22 to 6.14; NNH 7). The risk of experiencing a core activation event was >3 times greater with duloxetine (RR 3.59, 95%CI 2.04 to 6.32, NNH 25)
- 18 patients in the duloxetine group and 3 in the placebo group experienced at least 1 event of emotional disturbance** (RR 4.73, 95% CI 1.62 to 13.85; NNH 65). 21 in the duloxetine group and 9 in the placebo group experienced a core or potential psychotic behaviour event*** (RR 2.25, 95% CI 1.06 to 4.81; NNH 80. Depression-related events were similar between groups.

Level of evidence: Level 1 (good quality patient-oriented evidence) according to the SORT criteria.

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terms for 'core' activation events were agitation (aggression, hostility), akathisia, anxiety, increased energy (euphoria, irritability, jitteriness, mania), restlessness (hyperactivity), shakiness. 'Potential' activation events included the terms insomnia, panic, tension, and tremor. * emotional disturbance: included the terms anhedonia, apathy, depersonalization, derealisation, disinhibition, emotional detachment, emotional lability, flat affect, impulsivity, lack of empathy *****terms for 'core' psychotic behaviour events were abnormal thinking (intrusive thoughts, unusual thoughts),confusion (disorientation, incoherent thoughts), delirium, delusions, hallucinations, hysteria, manic reaction, paranoia, psychosis. Terms for 'potential' psychotic events were abnormal dreams, and nightmares.