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MeReC Publications

Glucosamine▼ and chondroitin in osteoarthritis: still no good evidence of clinical effectiveness

A network meta-analysis has concluded that glucosamine▼ and chondroitin, given either separately or together, do not affect pain intensity in osteoarthritis (OA) to a clinically meaningful extent compared with placebo.[1] This supports existing NICE guidance that the use of glucosamine or chondroitin products is not recommended for the treatment of OA.

Action

Health professionals should continue to follow NICE guidance and not prescribe glucosamine or chondroitin products for the treatment of OA. However, if patients want to trial over-the-counter glucosamine, they should be advised that the only potential benefits so far identified relate just to a reduction of pain (in some people, and to only a mild or modest degree) with glucosamine **sulphate** 1500mg/day. Health professionals should also advise patients on how to perform their own trial of therapy, that is, to evaluate their pain before starting glucosamine and ensure they review the benefits of glucosamine after 3 months. In addition, they should note that the MHRA has warned against its use by people who have seafood allergies or those who are taking warfarin.

What does this study claim?

Neither glucosamine nor chondroitin, separately or in combination, produced a clinically meaningful improvement in pain score compared to placebo at conventional levels of statistical significance. This was based on improvement in pain score being greater than 0.9cm on a 10cm visual analogue scale to be clinically meaningful. There were also no statistically significant effects on radiographic joint space, withdrawals due to adverse events or rates of adverse events.

See *MeReC Rapid Review Blog No. 1929* for further details. More information on OA can be found on the musculoskeletal pain floor of NPCi .

References

1. Wandel S et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ 2010;341:c4675

Reboxetine — a striking example of publication bias

A meta-analysis of published and unpublished data on reboxetine for the acute treatment of major depression found it to be an ineffective and potentially harmful antidepressant.[1] The published evidence overestimated the benefits of reboxetine while underestimating its harms. This study raises important questions about access to, and publication of, clinical trial data.

Action

Health professionals should consider the implications of these new data, both in terms of reboxetine prescribing, and the potential impact of publication bias in clinical trials. They should follow the NICE clinical guideline on the management of depression / depression with chronic physical health problems, as appropriate. **When it is appropriate for an antidepressant to be prescribed**, NICE recommends that it should normally be a selective serotonin reuptake inhibitor (SSRI) in a generic form. The choice of agent largely depends on its safety and tolerability profile and its propensity to cause discontinuation symptoms as well as cost. Patient preference and previous experience of treatments is also important. Patients taking reboxetine for the treatment of depression should be identified and reviewed, and clinicians should carefully weigh the balance of risks and benefits on an individual patient basis.

What does this study claim?

The study was conducted by IQWIG, the German equivalent of NICE. Their preliminary health technology assessment (HTA) suggested that reboxetine had been tested in about 4,600 patients. However, Pfizer, the manufacturer of reboxetine, did not provide a complete list of unpublished trials as requested and data on almost **two-thirds** of patients were not accessible.

All information was correct at the time of publication (December 2010)

A meaningful assessment of reboxetine was not initially considered possible due to a high risk of publication bias. The manufacturer provided the missing data after publication of the preliminary HTA report.

Data on **74% of patients analysed in the study were previously unpublished**. For **benefit outcomes** (remission rates; 50% response rates), published data showed that reboxetine was superior to placebo. However, when the unpublished data were added, the full dataset showed no significant difference. Also, whereas the published data showed no significant difference between reboxetine and SSRIs, the full data set showed that reboxetine was significantly inferior to SSRIs. A similar picture emerged for **harm outcomes** (adverse events [AEs]; withdrawal due to AEs): published data showed no significant difference between reboxetine and placebo but when the unpublished data were added, the full dataset showed that reboxetine caused an increase in harms compared with placebo.

See *MeReC Rapid Review Blog No. 1977* for further details. More information on depression can be found on the depression floor of NPCi.

References
1. Eyding D, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ 2010;341:c4737

Does intensive blood glucose control reduce microvascular outcomes in type 2 diabetes? — results from ACCORD

An analysis of the ACCORD study has found that intensive blood glucose control did not reduce composite advanced microvascular outcomes (renal complications, eye complications or peripheral neuropathy) compared with standard blood glucose control.[1] These results add to similar negative findings from the original publication of ACCORD, in which the primary endpoint of myocardial infarction, stroke, or cardiovascular (CV) death was not reduced with intensive blood glucose control. The intensive blood glucose lowering arm of ACCORD was stopped early, after a median of 3.7 years, because of associated higher all-cause mortality.

Action

Healthcare professionals should continue to follow NICE guidance on type 2 diabetes and agree individual HbA1c targets taking into account patient preference, and the balance of likely benefits and burden of treatment. A "keep it simple and safe" approach seems appropriate for the initial management of blood glucose in people with type 2 diabetes, whether aiming for macrovascular or microvascular protection. Reducing blood glucose to HbA1c levels of about 7.5% by diet, other lifestyle measures or using metformin (and/or a sulphonylurea) would seem optimal based on current evidence. Uncertainty remains about the benefits of reducing HbA1c from around 9.0% to 7.5% using other glucose lowering interventions when other major CV risk factors (such as smoking, blood pressure, cholesterol) are also being managed actively. Pursuing HbA1c levels below a level of 7.5% by adding insulin or another third-line drug may not confer any benefit, adds to the risks, and requires caution.

What does this study claim?

When the intensive blood glucose control arm (aiming for HbA1c of below 6.0%) of the study was stopped after a median of 3.7 years, median HbA1c was 6.3% in this arm and 7.6% in the standard control arm (which aimed at an HbA1c of 7.0-7.9%). At this point, the first composite outcome of advanced renal or eye complications (dialysis or renal transplantation, high serum creatinine, retinal photocoagulation or vitrectomy) did not differ between groups (8.7% both groups; hazard ratio [HR] 1.00, 95% confidence interval [CI] 0.88 to 1.14). The second composite outcome, which added peripheral neuropathy, did not differ significantly either (31.2% and 32.5%, respectively; HR 0.96, 95%CI 0.89 to 1.02). Intensive blood glucose control did reduce some individual disease-oriented microvascular endpoints, such as micro- and macroalbuminuria, but others, such as doubling of serum creatinine, were not affected. Three-line worsened visual acuity, arguably a patient-oriented outcome was improved.

See *MeReC Rapid Review No. 1956* for further details. More information on the management of type 2 diabetes can be found on the type 2 diabetes floor of NPCi.

References
1. Ismail-Beigi F, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–30

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