Duloxetine effective in the treatment of diabetic peripheral neuropathic pain

Neuropathic pain is often associated with diabetic peripheral neuropathy and is defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system. In a recent cross-sectional study in the UK, the overall prevalence of chronic (> 1 year) painful peripheral neuropathy was estimated to be 16.2% among patients with diabetes compared with 4.9% among matched controls. The rising prevalence of type 2 diabetes is likely to increase the burden of diabetic peripheral neuropathic pain (DPNP).

The main symptoms of DPNP are burning or shooting pain in the lower limbs and feet, usually occurring for more than three months. Currently, there are no approved treatments that restore nerve function. A major goal of pharmacological treatment in DPNP is therefore to control pain. Simple analgesics may provide partial, short-term relief, but, more specifically, targeted drugs are normally required for sustained control of pain of neuropathic origin.

Amitriptyline, a tricyclic antidepressant (TCA) first marketed in the 1960s, is not licensed for treatment of DPNP. However, along with another TCA (nortriptyline), it is recommended in the British National Formulary as a drug of choice for treating DPNP.

More recently, the use of anticonvulsants has been proposed for the treatment of neuropathic pain. Gabapentin is licensed for the treatment of neuropathic pain in Europe and for the treatment of post-herpetic neuralgia, a specific type of neuropathic pain, in the US. Pregabalin was approved in 2004 for the treatment of peripheral neuropathic pain in Europe, and in 2005 for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgia (PHN) in the US.

Duloxetine is a relatively balanced and potent reuptake inhibitor of serotonin and noradrenaline, approved in Europe and the US for the treatment of DPNP. It was first approved as an antidepressant for the treatment of major depressive disorder (MDD).

Study aim
Researchers conducted an indirect meta-analysis with two aims in mind. The first was to summarise the efficacy and tolerability of drug treatments licensed or recommended for DPNP by statistically pooling the available data from randomised, placebo-controlled trials. The second aim was to compare the efficacy and tolerability of duloxetine with pregabalin, gabapentin and amitriptyline. As most of the controlled clinical trials of these drugs are comparisons with placebo and very few head-to-head comparisons exist, an indirect approach was chosen using placebo as a common comparator.

Method
The researchers searched PubMed, EMBASE, CENTRAL databases and regulatory websites for randomised, double-blind, placebo-controlled, parallel group or crossover clinical trials (RCTs) assessing DLX, PGB, GBP and AMT in DPNP. Study arms using approved dosages with assessments after 5–13 weeks were eligible. Efficacy criteria were: reduction in 24-hour pain severity (24h PS) for all three drugs, and response rate (> 50% pain reduction) and Patient Global Impression of Improvement/Change (PGI-I/C) for DLX and PGB only. Tolerability criteria included: discontinuation, diarrhoea, dizziness, headache, nausea and somnolence. Direct comparisons vs placebo were conducted with pooled fixed- and random-effects analyses on endpoints reported in at least two studies of each drug. Indirect comparisons were performed between DLX and each of PGB and GBP using Bayesian simulation.

Results
Three studies of DLX, six of PGB, two of GBP and none of AMT met the inclusion criteria. In random-effects and fixed-effects analyses of DLX, PGB and GBP, all were superior to placebo for all efficacy parameters, with some tolerability trade-offs.

Indirect comparison of DLX with PGB found no differences in 24-hour PS, but significant differences in PGI-I/C, favouring PGB, and in dizziness, favouring DLX were apparent. Comparing DLX and GBP, there were no statistically significant differences.

Conclusion
Based on the pooling of common outcomes measured in randomised, controlled trials, the researchers concluded that duloxetine is comparably effective and tolerable in the treatment of diabetic peripheral neuropathic pain to two anticonvulsants, gabapentin and pregabalin, which are pharmacologically unrelated to duloxetine.

The summary reporting of trial results tends to conceal that response and tolerability to the various types of pharmacological treatment may be highly individual. In neuropathic pain, the empirical approach to treatment and the common use of off-label treatments attests to the clinical need for a wide range of drug choices. This study suggests that duloxetine may offer a valuable, additional option for this disabling condition.

Prevention of Neural Tube Defects (NTDs) with folic acid: What is the optimal dose?

A woman's risk of having a foetus or infant with a neural-tube defect can be reduced by the consumption of a multivitamin containing folic acid during the periconception period. The first results of a clinical trial showing that folic acid can prevent the risk of getting a baby with neural tube defect was published in 1980. Since then several other epidemiologic and clinical trials have been performed confirming that an adequate folate supply during early pregnancy can reduce the incidence of neural tube defects by 70 to 75 percent. Terminations of pregnancies following prenatal diagnosis of these congenital malformations could be reduced to a similar degree. Importantly, the neural tube closes within 28 days of conception and the NTD malformations may have occurred before a woman even knows that she is pregnant. Official bodies worldwide therefore recommend that women take an additional 400 micrograms per day folate/folic acid from before conception up to at least the 12th week after conception.

In South Africa, the RDA (recommended daily allowance*) of 800 micrograms of folic acid for pregnant women has remained unchanged since 1985. This is despite the fact that since 2003, all maize and wheat bread flour has been fortified with a legislated fortification premix in accordance with the Food Fortification Programme and thus contributes to the optimum levels of folic acid required.

In Europe there is still reluctance to mandatory food fortification because of safety concerns regarding chronic exposure to folic acid. However other countries have identified the need and have reacted. In the US and in Canada fortification of cereal grains has substantially increased folate status and in October 2003 South Africa embarked on a programme of folic acid fortification of staple foods. They measured the change in prevalence of Neural Tube Defects before and after fortification and assessed the cost benefit of this primary health care intervention conducted among 12 public hospitals in four provinces of South Africa. The study showed a significant decline in the prevalence of NTDs following folic acid fortification in South Africa and declines of up to 30.5% were observed. The decrease in NTD rates post-fortification is consistent with decreases observed in other countries that have fortified their food supplies, yet the legislation in South Africa regarding RDA's remains unchanged, while in other countries it is regularly reassessed and adjusted accordingly. Science supports 400 mcg Folic Acid plus additional food folate from your diet for the prevention of Neural Tube Defects. Taking into account the Fortification Pro-gramme, the South African RDA of 800 mcg Folic Acid may result in total consumption levels higher than recommended, with potential negative effects.

The Department of Health (2003) has set the level of fortification for folic acid in wheat flour at 1.5 mg/kg and in maize meal at 2.21 mg/kg and it is well known that maize meal and bread are among the most widely consumed staple foods in South Africa, especially in the lower income groups. Experience from the US demonstrates that folic acid fortification could consist of about 180 – 200 micrograms of folic acid to the food. In higher income groups where the consumption of staple foods is less, naturally occurring folic acid is consumed via foods such as dark green leafy vegetables, broccoli, beans, peanuts, strawberries, kiwi fruit and orange juice and in most western countries the usual intake of folate is about 250 micrograms per day.

An application of additional 400 micrograms of folic acid provided by a multivitamin offers therefore the possibility to be at the optimal, recommended level for folate intake for pregnant women. Higher amounts, e.g. 800 micrograms (the current RDA in South Africa), are not needed, especially considering the safety concerns to the application of higher dosages. The issue of folate and safety of higher dosages has received recent public health and scientific attention as a result of the publication of a randomised controlled trial. This trial provided preliminary evidence that exposure to high dose folic acid (1 mg) could promote colorectal tumorgenesis. This could not be confirmed in other trials and even the opposite has been shown, but the scientific discussion is on-going that long-term exposure to higher dosages of folic acid might be harmful to certain patients. The timing and particularly the dose of folic acid and duration of the supplementation seem to be relevant.

Taking into account this newly emerging science, the introduction of food fortification in South Africa and the restriction of supplementation of folic acid to the time of pregnancy, it seems to be highly reasonable to select 400 micrograms/day of folic acid as optimal dose for supplementation.

Wyeth Consumer Healthcare have recently launched Centrum Materna in South Africa, a single multivitamin for the three stages of pregnancy: preconception, pregnancy and during breast-feeding. Centrum Materna is a cost effective nutritional insurance for both mother and baby, safeguarding both their bodies and helping to facilitate that the progression of the pregnancy will not be threatened by either too little or too much of any of the vital nutrients. From before conception through the nine months of pregnancy and even during the tasking months of breast-feeding, Centrum Materna offers nutritional reinforcements, without over-loading the body with potentially toxic levels of any one substance. Centrum is concerned with constantly reevaluating RDA levels in light of developments such as food fortification and other environmental changes, and therefore looks to global developments to ensure their formulas represent the latest findings in the healthy use of supplements.

The supplementation of a healthy diet with a prenatal multivitamin while planning pregnancy, during pregnancy and breast-feeding offers many other benefits for mother and baby, but recent evidence suggests that health professionals should question the dietary habits of their patients to determine the possible folic acid intake and suggest the supplementation accordingly.
Christo Rademan, Managing Director of pharmaceutical benefit management company, Mediscor PBM today said that medicine expenditure in the South African private healthcare industry had increased by 26% between 2006 and 2008.

Commenting on the findings of the annual Mediscor Medicines Review, which was released at the beginning of July, Rademan said this sharp rise in medicine expenditure added further impetus to the now well-established notion that medicines remain one of the largest factors influencing healthcare costs in the medical schemes environment.

He added that the average cost per beneficiary per annum, in terms of medication expenditure, had shown a sharp rise from R1 792 in 2006 to R2 258 in 2008. “The 2008 MMR saw the average gross cost per item rise by 11.5% between 2006 and 2007 and by a further 9.5% between 2007 and 2008. This increase was the driving force behind the overall increase in medicine expenditure in 2007 and 2008,” said Rademan.

According to the 2008 Mediscor Medicines Review the Single Exit Price (SEP), which increased by 8.3% between January 2006 and December 2008, was a major contributing factor in driving medicine costs. “Over the counter medicines, in particular, reflect an extremely high 13.6% increase between January 2006 and December 2008,” explains Madelein Bester, Manager : Benefit Management at Mediscor.

She adds that medicines registered with the Medicines Control Council prior to 2004 were responsible for a 9.7% increase in average gross item cost between 2006 and 2007 and again for a 7.6% increase between 2007 and 2008. New chemical entities (registered after 2003) resulted in an item cost increase of 1.8% and 1.9% for 2007 versus 2006, and 2008 versus 2007 respectively. “Although they contribute less to the total expenditure increase, new chemical entities are responsible for 4.1% of the total medicine expenditure, but represent only 1.2% of the total volume of medicines,” she explains.

“On a positive note,” adds Bester “the generic utilisation rate has shown a steady increase between 2006 and 2008, from 45.5% in 2006 to 47.4% in 2008.” She attributes this mainly to the fact that more generic alternatives are now available on the market while managed care initiatives, driving generic utilisation, are having the desired effect. “The introduction of reference pricing and formularies promoting generic utilisation, greater public awareness and mandatory generic substitution at pharmacy level are also playing a vital role in driving generic utilisation,” says Bester.

The top ten therapeutic groups for 2008 once again point an interesting picture as far as the major healthcare issues of South African private healthcare consumers are concerned. Together they represent more than 47% of the total medicine expenditure reported.

<table>
<thead>
<tr>
<th>Therapeutic group</th>
<th>Total % of</th>
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<tbody>
<tr>
<td>1. Anti-hypertensives (blood pressure lowering agents)</td>
<td>11.0</td>
</tr>
<tr>
<td>2. Hypolipidaemic agents (cholesterol lowering agents)</td>
<td>5.7</td>
</tr>
<tr>
<td>3. Cytostatics (oncology medicines)</td>
<td>5.5</td>
</tr>
<tr>
<td>4. Anti-depressants</td>
<td>5.0</td>
</tr>
<tr>
<td>5. Gastric acid reducers</td>
<td>4.4</td>
</tr>
<tr>
<td>6. Anti-diabetic agents</td>
<td>3.8</td>
</tr>
<tr>
<td>7. Beta-lactam antibiotics</td>
<td>3.1</td>
</tr>
<tr>
<td>8. Hormone replacements</td>
<td>3.0</td>
</tr>
<tr>
<td>9. Non-steroidal anti-inflammatories (including anti-arthritics)</td>
<td>2.9</td>
</tr>
<tr>
<td>10. Combination analgesics (painkillers)</td>
<td>2.8</td>
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Another interesting fact highlighted in the report is that the oncology benefit demonstrated the largest increase in contribution towards total expenditure, with an increase of 3.4% in total expenditure from 2006 to 6.4% in 2007 and 8% in 2008. “This is attributable to the significant increase in the percentage of beneficiaries claiming for oncology medicines, as well as an increase in the average cost per item claimed. Oncology prevalence increased from 0.3% in 2006 to 0.6% in 2008. Together with this, the average item cost increased from R1 445 in 2006 to R1 761 in 2007 and R1 980 in 2008, resulting in a 41% increase in cost per patient,” explains Bester.

This trend is, in part, attributed to the fact that since the introduction of SEP and professional fees, these expensive products are no longer dispensed by the treating oncologists, but dispensed by pharmacies. An increase in the prevalence of oncology in the general population and the availability of more expensive and specialised treatments for these conditions, should however not be discounted.

Mediscor PBM processes prescription claims submitted by providers from various specialities, including pharmacies (retail and courier), general practitioners, medical specialists and other disciplines.

According to the 2008 Mediscor Medicines Review the majority of claims (81.9%) were submitted by retail pharmacies while 10.2% of items were claimed by general practitioners, and a further 7.9% by courier pharmacies.

“The from 2006 to 2008 the portion of claims received from retail pharmacies increased by 6%, while claims from general practitioners and medical specialists respectively reduced by 32% and 4%. More patients were making use of retail pharmacies instead of receiving medicines from dispensing doctors,” concludes Rademan.