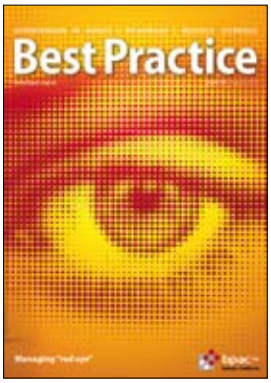

Choice of medicines for hypertension

Dear Editor

There were a few problems with the article: "Hypertension in adults: the silent killer", BPJ 54 (Aug, 2013). I usually find the bpac[nz] *resources well written and evidence based. In this review there were a number of key errors:*

1. ***Start with an ACE inhibitor or calcium channel blocker.*** *Ironically there is data that neither of these medications are more effective than chlorthalidone – a thiazide-like diuretic: see ALLHAT study, JAMA 2002;288:2981-97, which found, albeit for the secondary but important outcome of combined cardiovascular disease, that chlorthalidone was more effective than lisinopril and amlodipine. However, it was pleasing to see that chlorthalidone and indapamide were mentioned in your article as they are the probably the best diuretics in New Zealand. Now that PHARMAC has driven down the price of ACEs, chlorthalidone is slightly more expensive than lisinopril but your article did not seem too focused on cost.*

2. ***The NICE guidelines suggest that those aged < 55 years should start with ACEs and those older start on a calcium channel blocker.*** *This does not make sense given the ALLHAT results. Also I did check the NICE guidelines in their earlier version (no references on the latest one) and the ABCD model of treating blood pressure was based on blood pressure lowering rather than hard outcomes.*

3. ***Don't give ACEs and ARBs together without the recommendation of a nephrologist or diabetologist.*** *I was bewildered by this statement. I am not sure what they would say beyond monitor the potassium and creatinine. Where does this notion come from?*

Professor Bruce Arroll*, General Practitioner*
Professor of General Practice and Primary Health Care, University of Auckland

Hypertension guidelines versus individual studies: Should we hang our hat on ALLHAT?

Recommendations in Best Practice Journal are tailored to the needs of primary care health professionals by incorporating information from guidelines, and where necessary, adapting this to a New Zealand context. Naturally, this guidance will sometimes differ from conclusions that are based on individual studies. "Hypertension in Adults: The silent killer", BPJ 54 (Aug, 2013) was largely based on the United Kingdom National Institute of Health and Care Excellence (NICE) guidelines for the clinical management of primary hypertension in adults (2011).[1] The discrepancies highlighted between the recommendations in the Best Practice Journal article and the results of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) represent differences in clinical/expert opinion rather than "key errors".

1. We agree that the ALLHAT trial published in 2002 did not show evidence of superiority for thiazide-like diuretics over ACE inhibitors or calcium channel blockers. ALLHAT reported that all three medicines were equally effective in terms of primary outcomes.[2] However, ALLHAT has previously been criticised for not reflecting "real world practice".[3] Upon entering the trial, patients had all previous anti-hypertensive medicines withdrawn (including diuretics). Patients who were randomised to ACE inhibitor or calcium channel blocker treatment were then prevented by the protocol from receiving diuretic treatment, unless it was indicated by a definitive diagnosis of heart failure. Patients in the diuretic groups had no similar therapeutic restriction. The principle advantage of diuretics in treating hypertension, as reported from the ALLHAT study, was in reducing the risk of heart failure.[2] This is unsurprising given the design of the trial. Furthermore, the ALLHAT data showed a significant increase in adverse metabolic effects associated with the use of diuretics.[2] Therefore ALLHAT did not provide convincing evidence that diuretics should be used first-line in patients with diabetes, dyslipidaemia or gout, even if the metabolic adverse effects did not translate into an increased number of cardiovascular events. Also, one of the key considerations for ALLHAT investigators in recommending diuretics was their lower cost in comparison to other antihypertensive medicines; this is no longer the case.

2. ALLHAT excluded patients aged under 55 years and is therefore of limited use in helping to guide treatment decisions for hypertension in this patient group.[2] The recommendation to use calcium channel blockers to treat hypertension in patients aged over 55 years was based on the NICE guideline.[1] However, this "cut-off" should not replace clinical judgement and in some patients, e.g. in people with heart failure, treatment options include diuretics, ACE inhibitors and beta blockers. Furthermore, a "cut-off" approach to treatment was not central to the Best Practice Journal article recommendations. Instead, the article discussed the importance of hypertension alone, but also as part of the overall cardiovascular risk and the need for multiple medicines to achieve blood pressure targets. By highlighting a combination approach to treatment, the importance of which class of medicine to initiate first is reduced. This approach is strongly supported by recent European guidelines.[4] We acknowledge the important role that thiazide-like diuretics will continue to play in the reduction of cardiovascular risk and agree that chlortalidone (chlorthalidone) has a strong evidence-base for its effectiveness.

3. The recommendations in the Best Practice Journal concerning the combined use of ACE inhibitors and angiotensin II receptor blockers (ARBs) may require further clarification. A number of guidelines recommend against combining these two medicines for the treatment of hypertension due to an increased risk of complications, including patients developing end-stage renal disease.[1, 4, 5, 6] General Practitioners are therefore not recommended to combine ACE inhibitors and ARBs unless this has been recommended by a Nephrologist or Diabetologist, e.g. to reduce protein loss in patients with diabetic nephropathy. However, this indication is controversial. New Zealand Guidelines and Best Practice Journal recommendations acknowledge that this combination of medicines will rarely be initiated.[7] New Zealand guidelines also note that combination treatment with an ACE inhibitor and an ARB in people with chronic kidney disease is not currently supported by outcome evidence.[7]

We thank the correspondent for feedback on these points and acknowledge that the management of hypertension is a controversial area, and not all experts will agree with the recommendations. The goal of Best Practice Journal is to present clear, evidence-based and above all, practical, guidance for primary care clinicians to apply to their patient populations. As with all recommendations, management of individual patients may differ and clinical judgement must always be applied.

References

1. National Institute for Health and Clinical Excellence (NICE). Hypertension: clinical management of primary hypertension in adults. London: NICE; 2011. Available from: www.nice.org.uk (Accessed Oct, 2013).
2. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288(23):2981–97.
3. Wehling M. Yet another commentary on the ALLHAT-study. BMJ. 2003. Available from: www.bmj.com (Accessed Nov, 2013).
4. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. J Hypertens. 2013;(7):1281–357.
5. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358(15):1547–59.
6. Group Health Cooperative. Cardiovascular disease (ASCVD) prevention, screening and treatment guideline. 2012. Available from: www.ghc.org/all-sites/guidelines/ascvd.pdf (Accessed, Oct 2013).
7. New Zealand Gudelines Group. New Zealand primary care handbook 2012. 3rd ed. Wellington: New Zealand Guidelines Group; 2012.

Use of dopamine agonists in restless legs syndrome

Dear Editor,

I am a consistent "user" of the Best Practice Journal and New Zealand Formulary. I have used the material on restless legs syndrome (BPJ 49, Dec, 2012) and found it to be excellent for creating discussion within GP peer groups. Two consistent queries have come out of the discussion across the nine groups we have. The first is around schedules for tapering dopamine-like treatments and the second is around "intermittent" medicines use.

1. Tapering - it is clear that there is an increased risk of neuroleptic malignant syndrome (and rhabdomyolysis in the case of L-dopa) and that ropinirole, pramipexole and levodopa/carbidopa or

levodopa/benserazide should not be stopped abruptly. The BPJ article suggests tapering over one month but the GPs find that unhelpful unless there is a dosing schedule available (a table within the document would have been helpful). I have checked the data sheets for all of these products and only pramipexole provides a down titration schedule of any use. The New Zealand Formulary states abrupt cessation should not occur but again offers no recommendation of what a "down titration" schedule might look like for these products.

2. Linked to the above query, GPs were interested in the statement that intermittent use is possible. They were talking of PRN use and applying treatment in that fashion - as you would paracetamol for pain! I am sure that this is not what the authors are meaning; just that over time the severity of the RLS may change and so over a longer period of time use can fluctuate. Is this the case?

Dr Shane Scahill, PhD
Clinical Advisory Pharmacist
Auckland

As the correspondent states, dopamine agonists should not be withdrawn abruptly due to the risk of potentially life-threatening neuroleptic malignant syndrome. This risk is higher in the context of withdrawing anti-Parkinsonian medications, particularly levodopa.[1] Recommended doses of dopamine agonists, such as pramipexole, are considerably lower for the treatment of restless legs syndrome than in Parkinson's disease. The National Prescribing Service (which publishes Australian Prescriber) suggests that at the doses typically used for restless legs syndrome, pramipexole can be stopped without tapering.[2] While at low doses (pramipexole ≤ 1 mg daily, ropinirole ≤3 mg daily) dopamine agonists can be abruptly discontinued, it is recommended that higher doses be halved and maintained for a week.[3] If this is tolerated, the medicine can be stopped. However, if withdrawal effects (anxiety, depression, irritability, orthostatic dizziness, diaphoresis) develop then the dose should be tapered gradually to zero over an extra two to three weeks.[3]

The practice of intermittent dopamine agonist use can be problematic if the patient is exposed to fluctuating dopamine levels, but it is recommended as a treatment strategy for restless legs. Pharmacological treatment options for restless legs syndrome is dominated by off-label prescribing of medicines, and treatment is driven by consensus rather than national guidelines. Again, there is clear distinction between the treatment of restless legs syndrome and Parkinson's disease. NICE specifically recommends against medication holidays in the treatment of Parkinson's disease,[4] whereas in the treatment of restless legs syndrome, they recommend that levodopa can be used intermittently when symptoms occur or in anticipation of symptoms for patients with intermittent symptoms (less than three times per week).[5] Levodopa with carbidopa has only a short duration of action of four to six hours.[6] The use of levodopa, pramipexole and ropinirole for intermittent symptoms is also supported by in North American[6] and European[7] recommendations. Therefore, to answer the second part of the correspondent's question, guidance does recommend that levodopa can be administered "as required" for restless legs syndrome.

References

1. Grosset KA, Grosset DG. Prescribed drugs and neurological complications. J Neurol Neurosurg Psychiatry. 2004;75(suppl 3):iii2-iii8.
2. National Prescribing Service. Pramipexole (Sifrol) for severe primary restless legs syndrome. Sydney: NPS MedicineWise 01 April 2009. Available from: www.nps.org.au (Accessed Sep, 2013).
3. Ahlskog JE. Parkinson's disease treatment guide for physicians. Oxford; New York: Oxford University Press; 2009.
4. National Collaborating Centre for Chronic Conditions. Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care. London: Royal College of Physicians, 2006. Available from: http://publications.nice.org.uk/parkinsons-disease-cg35/introduction (Accessed Nov, 2013).
5. National Institute for Health and Care Excellence. Clinical Knowledge Summaries: Restless legs syndrome. London: NICE 2009. Available from: http://cks.nice.org.uk (Accessed Sep, 2013).
6. Moyer DE, Zayas-Bazan J, Reese G. Restless legs syndrome: Diagnostic time-savers, Tx tips. J Fam Pract. 2009;58(8):415-23.
7. Garcia-Borreguero D, Stillman P, Benes H, et al. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC Neurol. 2011;11(1):28.

A different take on restless legs and nocturnal cramp

Dear Editor,

I found your articles on Restless Legs Syndrome and Nocturnal Leg Cramps (BPJ 49, Dec 2012) disappointing, because no clear causes were outlined and the treatment options were poor.

For the following reasons I believe the working hypothesis to use in our medical practice, as to the primary cause of both conditions, should be magnesium deficiency:

1. *No other simple explanation has been proposed*
2. *Magnesium is an essential factor for the healthy function of nerves and muscles*
3. *Widespread soil mineral deficiencies and mineral losses in food preparation combine to make the magnesium intake inadequate for many people. The requirement for magnesium is large, with the human body needing about half the mass of its sodium requirement.*
4. *The statement that: "Magnesium supplementation has no benefit in the treatment of nocturnal cramps" is an inaccurate summation of the conclusions of the research quoted in the Cochrane review. Of the four studies referenced, only two were of published studies relating to oral supplementation. These studies by Frusso et al 1999 and Roffe et al 2002, both noted a significant period effect i.e. improvement in cramp occurrence with time as magnesium treatment continued. However all six oral studies quoted, including those in pregnancy, were flawed because they used too low a dose of magnesium and/or poorly absorbed magnesium, for too short a time. Any serious attempt to treat the symptoms of magnesium deficiency with oral supplementation to raise the total body magnesium content requires months of magnesium amino acid chelate (glycinate) or perhaps magnesium of marine origin, in a dose of at least 500 mg elemental magnesium per day if tolerated.*
5. *Anecdotal accounts of benefit of magnesium supplementation for both conditions are widespread*

In a review of my practice database covering the last 11 years and eight months, 99 current adult patients with a Read code diagnosis of cramp (N2472.00) were found. Of these, 92 had received advice on the use of magnesium supplementation, and in subsequent consultations cramp had settled in 88. In four there was a reduced amount of cramp, and of the four patients who reported ongoing cramp, two were found to have been taking no magnesium. All eight patients over the last three months have received further advice to take a higher dose of a better absorbed magnesium preparation, and will be reviewed again in due course.

In the last year only two patients have been prescribed quinine. One was a short supply for a patient with severe cramp occurring in multiple sites, to use over the time needed for a magnesium supplement to take effect. The other and only patient requiring an ongoing supply has chosen to take the advice of a specialist who initiated the prescribing of quinine.

Diuretics increase renal loss of magnesium, and appear to increase the tendency to cramp and restless legs syndrome. Therefore in this practice in order for benefit from magnesium supplementation to not be sabotaged by diuretic action, the use of frusemide, bumetanide and thiazides is minimised and where possible replaced by spironolactone.

I have made the following observations in clinical practice and have assumed they are common knowledge, but they were also omitted from the restless legs article:

1. *The sleep deprivation restless legs causes becomes in itself a major cause of the restless legs syndrome; i.e. it becomes self-perpetuating, with the increased fatigue from the inability to get to sleep increasing the restless legs condition the next night*
2. *The most effective acute management of restless legs is cooling, and in particular running cold water over the legs in the bath or shower*
3. *Much safer and cheaper medicines than those suggested in the article are effective in controlling restless legs, such as ¼ to 1 tablet of dihydrocodeine (DHC) 60 mg, each evening. Later, after magnesium supplementation takes effect, if needed restless legs may be controlled with paracetamol 500 mg plus codeine 8 mg tablets, or clonidine 25 – 50 mcg nocte.*

Observations made in my clinical practice over decades have contributed to the above hypotheses and conclusions, and there should be research to confirm them. However there is a great deal of health knowledge which has been gained in general practice

by doctors listening carefully to what patients tell us, and this huge source of information and learning should not be ignored.

Dr Ralph Brock-Smith, *General Practitioner*
Lower Hutt

Editorial comment: There are few robust studies on the use of magnesium for nocturnal cramps or restless legs syndrome. Studies include only a small number of participants and have shown limited evidence of effectiveness. Reviews of the balance of evidence have concluded that magnesium is unable to be recommended as an effective treatment for nocturnal cramps or restless legs syndrome. The data reported by the correspondent undoubtedly demonstrates an association between patients taking magnesium and experiencing an improvement in their symptoms of cramp/restless legs. However, what this data does not definitively reveal is causality. The patients' symptoms may have remitted spontaneously over time, or because of other non-pharmacological interventions the patients may have undertaken. The debate, therefore, centres on whether giving magnesium to patients with nocturnal cramps or restless legs may cause harm. Magnesium is considered safe at doses no greater than the upper recommended level of intake for supplements of 350 mg/day for adults.* Adverse effects associated with excessive use of magnesium, i.e. hypermagnesaemia, include diarrhoea, nausea, vomiting and thirst, and in more serious cases, hypotension, arrhythmias and respiratory depression. Perhaps of greater concern are the limitations on the use of diuretic medicines in these patients. In addition, although some of the medicines recommended for unremitting restless legs syndrome and nocturnal cramps are associated with adverse effects, dihydrocodeine and clonidine are not without potentially significant adverse effects also.

* Australian Government Department of Health and Ageing, National Health and Medical Research Council. Nutrient reference values for Australia and New Zealand. 2006. Available from: www.health.govt.nz (Accessed Oct, 2013).

Write to us at: Correspondence, PO Box 6032, Dunedin or email: editor@bpac.org.nz