Why can't we use quinine for night cramps?

Dear Editor,
As a continuing prescriber of quinine for leg cramps, I wonder if the Medsafe guideline should really still be regarded as the last word on it for leg cramps in New Zealand. The Medsafe advice on prescribing comes over as an all or nothing risk, when the reality is that it is about estimated risks versus benefit to the patient. Responsible, informed prescribing should address these.

The Cochrane systematic review describes this quite succinctly: "There is moderate quality evidence that there is a significant increase in minor adverse events with quinine compared to placebo but not in major adverse events. Overdosage, however, is well documented to cause serious harm including death."

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In the article "Nocturnal leg cramps", BPJ 49 (Dec, 2012), we agree that quinine is an effective treatment for reducing the frequency and severity of cramps, however, the unpredictable and serious nature of its potential adverse effects mean that it is no longer recommended for this indication. After reviewing the safety of quinine, Medsafe informed prescribers in 2007 that muscle cramps had been removed as an approved indication,[1] with a reminder again in 2010.[2] Many other international medicine regulatory agencies, e.g. the United States Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA), have issued similar statements.[3, 4] We acknowledge the correspondent's point of view, but believe that the risk of prescribing quinine outweighs the benefit gained, for a condition, which although unpleasant, is not life-threatening.

The adverse effects associated with quinine can be grouped into three categories:[5]

1. Dose-dependent reactions (occur with normal therapeutic use, but more common with higher doses): gastrointestinal disturbance, tinnitus, vertigo, visual disturbance
2. Overdose reactions (occur at doses higher than therapeutic level): cardiac arrhythmias, blindness, seizures
3. Hypersensitivity reactions (occur at any time, and with any dose): thrombocytopenia, disseminated intravascular coagulation, acute renal failure, haemolytic uraemic syndrome

Other risk factors for using quinine, particularly in elderly people, include renal impairment, medicine interactions (e.g. digoxin, anticoagulants, phenothiazines) and memory loss which increases the potential for medicine administration errors and overdose.[5]

The Cochrane review in 2010 included 23 trials with 1586 participants (of which 58% were from five unpublished studies). It was concluded that compared to placebo, quinine reduced the number of muscle cramps over two weeks by 28%, reduced intensity by 10% and reduced the days on which cramp occurred by 20%. Cramp duration was not significantly reduced.[5] The review also found that although more minor adverse effects occurred with quinine compared to placebo, there was no significant difference in risk of major adverse reactions between quinine and placebo.[5] However, the occurrence of major, life-threatening adverse effects with quinine is rare – one patient had an event (thrombocytopenia) out of the 1103 participants for which data was available.[5] Had there been more participants able to be studied, and the power of the study greater, a different conclusion may have been reached.

The authors of the Cochrane review summed this up with the following: *"On the basis of these* [number of adverse events]*, quinine appears to be reasonably safe, but it is not possible to accurately calculate the true incidence of serious or life-threatening side effects which are rare…It is however on the basis of these serious adverse effects that the FDA has banned the marketing of quinine for muscle cramps and that the American Academy of Neurology has recommended in their report that it only be used as a last resort in intractable cramps and with close monitoring…Major adverse events are rare but can be serious or fatal so that in some countries prescription of quinine is severely restricted."*[5]

The main problem when weighing up the risks and benefits of using quinine is that the most serious adverse effects are due to hypersensitivity reactions, which are not dose-dependent, and may occur rapidly, after taking quinine for the first time, or after years of use. There is no current evidence which enables clinicians to predict which patients will experience serious adverse effects.[5]

Since January, 2008 (i.e. after the Medsafe warning), the Centre for Adverse Reactions Monitoring (CARM) in New Zealand has received 12 reports on quinine, six of which were for patients who had developed thrombocytopenia. Two of these patients experienced life-threatening effects, and in one, haemorrhage occurred within 12 hours of their first dose of quinine. The indication for prescribing quinine in all six reports was for muscle cramp.

When managing a patient with leg cramps, first rule-out underlying causes of the cramp or associated conditions such as medicine use (e.g. diuretics, naproxen, statins, long-acting beta-2 agonists), chronic dehydration, structural disorders, peripheral vascular disease, oesteoarthritis, diabetes or neurological disorder. There is limited evidence that exercise and muscle stretching is effective in reducing symptoms.[6, 7] A 2012 Cochrane review of non-pharmacological treatments for leg cramps concluded that there is an urgent need for quality data on emerging treatments.[8]

Nortriptyline, diltiazem, orphenadrine citrate, verapamil or gabapentin may be considered for patients with severe, intolerable symptoms, used at the lowest effective dose and discontinued if no benefit is observed.[9, 10] However, the treatment of leg cramps is an unapproved indication for the use of these medicines (with the exception of orphenadrine citrate), and patients should be informed of the risks and consent to treatment (see: "Use of unapproved medicines", Page 3).

For further information see: "Nocturnal leg cramps: is there any relief?" BPJ 49 (Dec, 2012).

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Metabolic monitoring with atypical antipsychotics

Dear Editor,

I have been using BPJ 40 (Nov, 2011) and BPJ 3 (Feb, 2007) articles on atypical antipsychotic use, for discussion in peer groups. As the BPJ 40 article suggests, there is significant off-label prescribing of atypical antipsychotics in non-schizophrenic or dementia patients (risperidone), and that generally patients are started on this in secondary care. The question has been raised whether non-schizophrenics and those on lower off-label doses (generally) require the same level of monitoring. Additionally, with the HbA_{1c} test for diabetes now being the standard, has this replaced glucose monitoring in this cohort?

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The short answer is yes, all people prescribed atypical antipsychotics, regardless of dose or indication, require the same level of monitoring for metabolic effects.

People with schizophrenia or bipolar disorder have an increased risk of cardiovascular morbidity and mortality compared to the general population, due to both disease and treatment factors.[1] However, it appears that the adverse metabolic effects of atypical antipsychotics occur regardless of dose of medicine or indication for treatment.[2] Although older age is a cardiovascular risk factor, young people are particularly susceptible to the cumulative effects over time of antipsychotic-induced weight gain and insulin resistance.[1] This is a growing concern in light of recent trends of increased off-label prescribing to young people for anxiety, insomnia and post-traumatic stress disorder.[2]

Adverse metabolic effects of atypical antipsychotics include:[1]

- Impaired glycaemic control, and therefore increased risk of type 2 diabetes
- Hyperlipidaemia, particularly decreased high density lipoprotein (HDL) and increased triglycerides
- High blood pressure, particularly in males

Clozapine is associated with the greatest risk of weight gain, followed by olanzapine and quetiapine, although all atypical antipsychotics are associated with metabolic adverse effects.1 Other medicines which are commonly co-prescribed with antipsychotics can contribute to weight gain, e.g. selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants, sodium valproate and lithium.[1]

Monitoring for metabolic adverse effects should occur in any patient prescribed an atypical antipsychotic medicine, regardless of dose or indication (Table 1).

Table 1: Recommended monitoring for patients taking atypical antipsychotics

Factor	Frequency of monitoring
Lifestyle interventions	Regularly encourage and support exercise, weight loss, smoking cessation, healthy eating and reduced alcohol consumption
Hyperlipidaemia	Fasting lipids test at baseline, then every three months for year one, and annually for subsequent years
Type 2 diabetes	HbA_{1c} at baseline, then every three months in year one (or fasting glucose monthly for first three months in patients at high risk)*, and annually for subsequent years
Blood pressure	Baseline, then every three months in year one, and annually for subsequent years
Weight/BMI	Baseline, then monthly. Offer dietary intervention if significant weight gain (≥ 7% of baseline weight)

* HbA_{1c} is now the preferred test for detecting diabetes, and should be used in preference to a fasting glucose test in most clinical situations. However, HbA_{1c} is not reliable when blood glucose levels rise too rapidly to affect HbA_{1c}, such as in some patients newly initiated on atypical antipsychotics. Therefore, in patients with other risk factors for diabetes, fasting blood glucose is recommended at baseline, and monthly for the first three months. HbA_{1c} can be used for long-term monitoring.

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