Comment

A shorter course for anti-relapse therapy against vivax malaria

Although *Plasmodium falciparum* causes the greatest number of global malaria infections and deaths, the impact of infection with *Plasmodium vivax*, the dominant human malaria parasite outside of Africa, is large, with an estimated 7.4 million cases in 2017.1,2 A particular challenge with *P vivax* infection is hypnozoites: dormant liver-stage parasites that are not eliminated by standard antimalarial treatments. Hypnozoites do not cause clinical illness, but without therapy that targets them, *P vivax* infections will commonly relapse, with recurrent symptomatic blood-stage infections weeks to months after the primary infection. By enabling recurrent episodes of malaria and ongoing transmission, *P vivax* relapses contribute...
substantially to the burden of malaria and make malaria eradication more difficult.

Standard therapy to eliminate P vivax hypnozoites is primaquine administered daily for 2 weeks, beginning soon after initiation of primary therapy to eliminate asexual parasites. Primaquine is generally well tolerated, but achieving compliance with a 2-week regimen is difficult. Furthermore, primaquine has dose-dependent toxicity in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency, the most common human enzymopathy, with the potential for lethal haemolysis. Recommendations for primaquine to treat P vivax infection with or without prior G6PD testing vary around the world, but because of low expectations for full compliance, cost concerns, high risks of reinfection, and the difficulty of testing for G6PD deficiency prior to therapy, most patients presenting with P vivax infection do not receive anti-relapse therapy.

In The Lancet, Walter Taylor and colleagues present the results of a randomised, double-blind, placebo-controlled trial in four countries (Afghanistan, Ethiopia, Indonesia, and Vietnam). The trial compared a standard 14-day course of primaquine (0.5 mg/kg per day), a 7-day course of primaquine at a higher dose (1.0 mg/kg per day), and placebo, all following standard therapy for asexual infection, for the treatment of uncomplicated vivax malaria. Of the 2336 enrolled patients (62.8% men, median age 16 years [IQR 10 to 26]), 935 were randomly allocated to the 7-day primaquine regimen, 937 to the 14-day primaquine regimen, and 464 to placebo. Patients were followed up for 1 year after therapy. The incidence of recurrent malaria in the placebo group was 0.96 episodes per person-year. Both primaquine regimens were effective, with recurrent malaria subsequently causing 0.18 episodes per person-year in the 7-day primaquine group and 0.16 episodes per person-year in the 14-day treatment group. The 7-day treatment course was non-inferior to the standard 14-day regimen (absolute incidence rate difference 0.02 [95% CI –0.02 to 0.05], within the predefined non-inferiority margin of 0.07; p=0.34). This result is important. Halving the length of an anti-relapse treatment course for vivax malaria has the potential to markedly increase the number of patients who receive a full course of anti-relapse therapy, thus decreasing recurrent episodes of malaria and transmission of malaria to others.

Despite the potential benefits of 7-day primaquine therapy, two important caveats apply. First, the study excluded those with G6PD deficiency, and thus did not provide information regarding potential risks in this group. The use of primaquine is facilitated by available point-of-care tests for G6PD deficiency, but these tests might not identify all patients at risk of haemolysis, and safety concerns continue to challenge efforts to roll out anti-relapse therapy. Second, the 7-day regimen comprised a remarkably high daily dose of primaquine, four times higher than the original daily dose in a 14-day regimen, and twice the daily dose in a 14-day regimen that is recommended for areas with high rates of relapse (and was administered to the 14-day group of this trial). The higher daily dose might have been needed to yield adequate 7-day efficacy, but it would be expected to increase toxicity. In fact, although the incidence of adverse events was low, five patients, all in the 7-day arm, needed to temporarily discontinue therapy because of gastrointestinal symptoms, and three of four patients with significant haemolysis (including one patient requiring transfusion, who was G6PD-deficient but had been enrolled because of misdiagnosis as G6PD-normal) were in the 7-day group. We could reasonably ask whether, with the short-course regimen, the presumed benefit of compliance will be balanced out by missed doses due to toxic effects.

Tafenoquine became the second drug available for anti-relapse therapy in 2018. The extended half-life of tafenoquine allows single-dose anti-relapse therapy, a marked improvement over 7-day or 14-day courses.
Balancing body and mind: selecting the optimal antipsychotic

The burden of schizophrenia remains high, with one in 100 people affected globally over a lifetime.1 Symptoms are disabling, with auditory hallucinations, delusions, lack of motivation, cognitive impairment, and functional deficits. Despite advances in our understanding of the biological underpinnings of the illness, cure remains elusive. Antipsychotic medications are the mainstay of pharmacological treatment, but selecting the optimal medication for the individual patient is a delicate balance between efficacy and physical side-effects.

People with schizophrenia die up to 18 years earlier than the general population, largely due to avertable cardiometabolic diseases,2 with a standardised mortality ratio of more than 3.3 The risks are multifactorial, and include a genetic predisposition for abnormal glucose, poor diet, sedentary behaviour, and, notably, metabolic adverse reactions to antipsychotic medications.4

In The Lancet, Maximilian Huhn and colleagues5 report a network meta-analysis of antipsychotic medications for the acute management of schizophrenia that includes 402 studies of 32 different antipsychotics with data for 53,463 participants (mean age 37.40 years [SD 5.96], 29,949 [56.02%] male and 23,514 [43.98%] female, mean illness duration 11.90 years [SD 5.19]). This is the largest and most comprehensive meta-analysis of antipsychotic medication for acute psychosis to date. The use of a network meta-analysis allows comparisons between agents that might not have been directly compared in clinical trials. Other strengths include consideration of the placebo response rate, study sample size, publication year, baseline severity, sponsorship, comparability of doses, and patient demographics, using both meta-regression and sensitivity analyses of excluding poorer-quality studies. None of these factors greatly altered outcomes.

Many of the results are unsurprising. Clozapine remains the most effective antipsychotic for acute psychotic symptoms; however, it is now reserved for patients with treatment-refractory schizophrenia.6 Several commonly used second-generation antipsychotics, including...