and, to a lesser extent, other central pain syndromes.[7 8] So why is there a discrepancy?

One key difference between the current study and studies with positive findings[5678] is that Frank and colleagues used allodynia (which signifies evoked pain) and sympathetic dysfunction as inclusion criteria. Collectively, these signs are experienced by only a small subset of patients with chronic pain. In the current era, in which treatment of pain is ideally based on mechanism(s) of pain, pharmacotherapy should preferentially target specific pain generators.[9] In multiple sclerosis, the condition with the strongest evidence for the effectiveness of cannabinoids, the most common manifestations of pain are continuous or spontaneous dysaesthesias, which are mechanistically different from allodynia.[10] In addition, the evidence to support a sympathetic component in multiple sclerosis is scant.

Another potential flaw in the current study is that it assessed outcomes after only six weeks, which is too short a time frame to detect the low but clinically significant risk of adverse psychiatric effects such as psychosis, depression, cognitive deficits, and addiction.[4] Similarly, short term reductions in pain scores do not necessarily translate into longstanding improvements in pain, functional capacity, and psychological wellbeing. Future trials evaluating treatment with cannabinoids might consider using risk assessment tools, like those used for opioids.[11]

Finally, there is the problem of the prohibition surrounding the medicinal use of cannabinoids. The therapeutic use of cannabinoids is about 50 years behind that of opioids, and the associated stigma poses a considerable barrier to research and development.[12] Yet history tells us that the line dividing what is and isn't socially acceptable behaviour is often arbitrary and inseparable from the cultural-political context. Not so long ago, blood letting and the curative use of heavy metals were considered state of the art medical care. Although many such practices have been abandoned, others remain that do more harm than good.

Strong evidence supports the use of cannabinoids for chronic pain, but more research is needed to determine which diagnoses, pain characteristics, and clinical variables are most amenable to treatment; the long term effectiveness of these drugs; optimal drug selection and dosages; the risk-benefit ratio of combining cannabinoids with other drugs; and how adverse effects can be minimised. This research can occur only in a political climate conducive to the continued use and investigation of cannabinoids to alleviate pain and suffering.

1 Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ* 2008 10.1136/bmj.39429.619653.80.
2 Benedetti F, Vighetti S, Amanzio M, Casadio C, Oliaro A, Bergamasco B, et al. Dose-response relationship of opioids in nociceptive and neuropathic postoperative pain. *Pain* 1998;74:205-11.
3 Campbell FA, Tramer MR, Carroll D, Reynolds JM, Moore A, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* 2001;323:13-6.
4 Rice AS, Lever I, Zarnegar R. Cannabinoids and analgesia, with special reference to neuropathic pain. In: McQuay HJ, Kalso E, Moore RA, eds. *Systematic reviews in pain research: methodology refined.* Seattle: IASP Press, 2007:233-46.
5 Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy. A randomized placebo-controlled trial. *Neurology* 2007;68:515-21.
6 Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, Sansom C. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 "N of 1" studies. *Anaesthesia* 2004;59:440-52.
7 Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled trial. *BMJ* 2004; 329:253.
8 Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, Thompson A; UK MS Research Group. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled study. *Lancet* 2003;362:1517-26.
9 Cohen SP, Verdolin MH, Chang AS, Kurihara C, Morlando BJ, Mao J. The IV ketamine test predicts subsequent response to an oral dextromethorphan treatment regimen in fibromyalgia patients. *J Pain* 2006;7:391-8.
10 O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple sclerosis: systematic review and proposed classification. *Pain* 2007 Online first 8 October 2007.
11 Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. *Pain Med* 2005;6:432-42.
12 Zimmerman B, Bayer R, Crumpacker N. *Is marijuana the right medicine for you? A factual guide to the medical uses of marijuana.* New Canaan, CT: Keats Publishing, 1998.

Costs of treating malaria according to test results

Improving diagnostic tests can reduce costs if adherence to results is improved

RESEARCH, p 202

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In the accompanying study, Lubell and colleagues assess the effect of clinicians' adherence to the results of a rapid diagnostic test or microscopy on the overall costs of the management of malaria in Tanzania.[1]

In recent years, most treatment policies for malaria in Africa have shifted to artemisinin combination treatments, which are highly effective but more expensive than older regimens. To avoid over prescription, current guidelines recommend that the diagnosis should be confirmed with a laboratory test before treatment. Immunochromatographic tests for malaria allow diagnosis to be made even in health settings that lack laboratory facilities. Economic models and decision making models support the use of these tests.[2-4] However, models generally assume that clinicians or nurse practitioners fully adhere to the test result when deciding how to manage the patient. But evidence proves the opposite—clinicians are likely to treat people for malaria even after negative results from rapid diagnostic tests or microscopy.[5 6] In a randomised controlled trial in Burkina Faso we recently found (data not yet published) that more than 80% of febrile patients with a negative test result were treated for malaria.[7] Economic evaluations that fail to take into account what clinicians actually do in practice are therefore merely speculative.

Through a cost-benefit analysis based on a decision tree model, Lubell and colleagues show that—at low

to moderate prevalence of malaria infection in febrile patients—clinician's adherence to the test result is a key factor in determining whether a diagnostic strategy is beneficial or not. This is true for rapid diagnostic tests even at higher levels of prevalence (up to 70%). For microscopy, however, they observed a paradoxical effect—because sensitivity was poor (73% *v* 93% for rapid diagnostic tests), high adherence means that more patients with malaria are not treated, which increases mortality and related costs. At very high prevalence, presumptive treatment remains the preferred option.

The novel aspect of this paper is the formal incorporation of adherence into a model that could be used for policy decisions. Both the non-adherence of patients to their prescribed drugs and the non-adherence of clinicians to guidelines have been documented, even in areas such as cardiovascular medicine where robust evidence exists.[8] Policy makers should take the importance of adherence seriously, and clinical guidelines should avoid ambiguous messages that may raise doubts about the reliability of a test,[9] such as, if the test result is negative don't treat for malaria, unless clinical suspicion is high. Clinicians should realise that if the result of a test is not going to influence their decision, then it is simply a waste of money to do the test. It would probably be more effective to help health workers understand the effect of non-adherence than it would be to monitor it. Research should focus on which training strategies are most effective for this purpose.

Research is needed in certain grey areas. Lubell and colleagues' results were most sensitive to the value attributed to life cost (the value of a year of life lost), so if mortality is underestimated or overestimated the conclusions could partly change. However, mortality from malaria could be much lower than estimated—on the basis of previous reports and expert opinion—for patients with false negative rapid diagnostic test results who are not treated. This is because false negative results tend to occur in patients who have a very low parasite density and probably a low risk of mortality.[10]

A cohort study in Uganda found almost no risk of mortality for untreated patients who had false negative results on microscopy.[11] If the same proves true for rapid diagnostic tests, this will provide more evidence to support adherence to the test result. Another grey area concerns the specificity of rapid diagnostic tests. Patients with a false positive malaria test may not be treated for the true cause of their fever. The high specificity of rapid diagnostic tests (96%) found by Lubell and colleagues makes this risk marginal. Nevertheless, in endemic areas malaria parasites in the blood may be common in the general population—malaria infection in patients with fever may not necessarily be proof of clinical malaria.[12] Some "true" positive patients (febrile patients with a positive rapid diagnostic test result confirmed by microscopy) may simply be carriers of malaria parasites, with another cause of fever. The potential harm from failure to treat, including mortality and related costs, may thus be underestimated. Future research focusing on the sensitivity and specificity of rapid diagnostic tests for clinical malaria—not just for malaria infection—would therefore be useful, although the study design may prove complex.

More data are also necessary from settings where the intensity of malaria transmission is variable over the seasons. Lubell and colleagues show that even an optimal adherence strategy based on treatment according to test results is not beneficial when transmission is high. In such circumstances it would be difficult to translate research findings into evidence based policy that is applicable throughout the year.

1 Lubell Y, Reyburn H, Mbakilwa H, Mwangi R, Chonya S, Whitty C, et al. The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis. *BMJ* 2007 doi: 10.1136/bmj.39395.696065.47.
2 WHO. *Assessing RDT cost-effectiveness*. 2007. www.wpro.who.int/sites/rdt/Assessing+RDT+Cost-Effectiveness.htm.
3 Rolland E, Checchi F, Pinoges L, Balkan S, Guthmann JP, Guerin PJ. Operational response to malaria epidemics: are rapid diagnostic tests cost-effective? *Trop Med Int Health* 2006;11:398-408.
4 Rafael ME, Taylor T, Magill A, Lim YW, Girosi F, Allan R. Reducing the burden of childhood malaria in Africa: the role of improved diagnostics. *Nature* 2006;444(suppl 1):39-48.
5 Reyburn H, Mbakilwa H, Mwangi R, Mwerinde O, Olomi R, Drakeley C, et al. Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. *BMJ* 2007;334:403.
6 Hamer DH, Ndhlovu M, Zurovac D, Fox M, Yeboah-Antwi K, Chanda P, et al. Improved diagnostic testing and malaria treatment practices in Zambia. *JAMA* 2007;297:2227-31.
7 Van den Ende J, Lodesani C, Angheben A, Halidou T, Sirima SB, Van den Ende K, et al. Does the introduction of malaria antigen tests improve clinical care? Results from a randomized study in Burkina Faso. *Trop Med Int Health* 2007;12(s1):128.
8 Bassand J-P, Priori S, Tendera M. Evidence-based vs. "impressionist" medicine: how best to implement guidelines. *Eur Heart J* 2005;26:1155-8.
9 D'Acrémont V, Lengeler C, Genton B. Stop ambiguous messages on malaria diagnosis *BMJ* 2007;334:489.
10 Hawkes M, Kain KC. Advances in malaria diagnosis. *Expert Rev Anti Infect Ther* 2007;5:485-95.
11 Njama-Meya D, Clark TD, Nzarubara B, Staedke S, Kamya MR, Dorsey G. Treatment of malaria restricted to laboratory-confirmed cases: prospective cohort study in Ugandan children. *Malar J* 2007;6:7-15.
12 Schellenberg JRM, Smith T, Alonso PL, Hayes RJ. What is clinical malaria? Finding case definitions for field research in highly endemic areas. *Parasitol Today* 1994;10:439-42.

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***Anopheles gambiae* mosquito**