

## Concerns about injectable naltrexone for opioid dependence

In *The Lancet*, Evgeny Krupitsky and colleagues<sup>1</sup> report on the use of injectable naltrexone for treatment of opioid dependence. Their report comes some months after the US Food and Drug Administration (FDA) approved use of the preparation for opioid-dependent patients on the basis of the same findings. The study by Krupitsky and colleagues suggests the strong potential of a once-monthly, extended-release formulation of injectable naltrexone for opioid addiction—the median proportion of weeks of confirmed abstinence was 90.0% in the depot naltrexone group compared with 35.0% in the placebo group (treatment effect 55% [95% CI 15.9–76.1],  $p=0.0002$ ). The study is also striking, however, for the questions it raises about the FDA's approval processes and clinical trial ethics. Factors requiring scrutiny include paucity of efficacy data, adequacy of risk assessment (particularly of overdose risk in treatment dropouts), and the questionable ethics of a placebo-controlled trial when an accepted standard of treatment exists.

The FDA's assessment of depot naltrexone's efficacy was based on then-unpublished evidence from this trial in Russia, in which 250 eligible patients at 13 sites were randomly assigned to receive 380 mg depot naltrexone or placebo.<sup>2,3</sup> This single study, in which 54% of patients did not complete the protocol and just over half of those on naltrexone received the full treatment course,<sup>1,2</sup> was judged sufficient proof by the FDA.

For evidence on safety, the FDA accepted data from the Russian study and another in the USA in patients with alcohol or opioid dependence, or both.<sup>2</sup> Strikingly, neither the materials provided to the FDA advisory committee nor the *Lancet* study make clear what follow-up was done to evaluate post-treatment opioid overdose in the participants in the Russian trial. Data from the US study are similarly vague on post-treatment adverse events.

The FDA sometimes requires only a single clinical trial for new indications of an already approved drug. A single trial is not justified, however, when there are questions about the safety of the drug as it will be prescribed or recommended.<sup>4</sup> Although voluntary reporting captures only a small portion of serious adverse events that occur once a drug enters the marketplace, approval of depot naltrexone for alcoholism treatment has been followed by reports to the manufacturer of 19 fatalities, some tied to suicidal ideation or opioid overdose.<sup>2</sup> The FDA's

Adverse Event Reporting System includes 51 reports of deaths associated with depot naltrexone between 2006 and 2010.<sup>5</sup> Serious unlabelled adverse events of this magnitude have triggered black-box warnings for other drugs.<sup>6</sup> Although it is not clear whether the approximately 45 000 patients that the manufacturer reports to have received depot naltrexone were all being treated for alcoholism, prescription of the drug for opioid dependence raises the question of whether injectable naltrexone might inadvertently increase risk of fatal overdose. Detoxified opioid-dependent patients are vulnerable to overdose in the event of relapse, including relapse after treatment with naltrexone.<sup>7</sup> The need for careful scrutiny of mortality after treatment with injectable naltrexone is further underscored by the lack of deaths reported in placebo-treated patients in Krupitsky and colleagues' study, which is in stark contrast to other trials of opioid-dependent participants with placebo controls in whom multiple deaths have been reported.<sup>8,9</sup>

Experience with oral naltrexone highlights the importance of adequate investigation of overdose risk following treatment with depot naltrexone. Risk of overdose for detoxified heroin-dependent patients receiving oral naltrexone treatment is well documented.<sup>10</sup> A review of 13 trials of pharmacotherapies for opioid dependence in Australia showed that the heroin overdose rates were more than trebled (at 6.8 per 100 person-years) for patients on oral naltrexone treatment compared with those receiving opioid agonist treatment (1.9 per 100 person-years). Patients on naltrexone were as much as six times more likely to experience a heroin overdose once out of treatment than while receiving medication, and patients who stopped naltrexone were 7.6 times more likely than patients on opioid agonist to experience an overdose after treatment cessation.<sup>7</sup> Retrospective analysis based on coronial records and prescription data also found high mortality rates (22.1 per 100 person-years) for those prescribed naltrexone who subsequently stopped.<sup>11</sup>

An additional question, particularly in light of earlier research that showed oral naltrexone to be less effective in the treatment of opioid dependence than buprenorphine,<sup>12</sup> is why researchers and institutional review boards deemed it ethically acceptable to expose



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some study participants to placebo. The Declaration of Helsinki, which sets standards for all medical research on human beings, states clearly that the benefits, risks, burdens, and effectiveness of a new drug should be tested against best available treatment, and authorises a placebo group only when there is no accepted standard of care.<sup>13</sup> This is not the case for opioid dependence. The fact that Russia does not permit methadone or buprenorphine treatment does not excuse the use of placebo, but rather raises the question of why investigators chose that country to test a drug for which US approval would be sought. The testing of depot naltrexone in Russia is akin to finding a location with no access to antiretrovirals and then testing a new HIV drug against placebo.

The FDA should justify why it has lowered the scientific, regulatory, and ethical standards in approving depot naltrexone for treatment of opioid dependence. Although there is public demand and a market for new treatments for opioid dependence, approval in this instance might endanger patients, and sets a precedent that unjustifiably degrades standards for all treatment of opioid dependence.

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