

## Publication

### Efficacy of drugs against clonorchiasis and opisthorchiasis: a systematic review and network meta-analysis

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**BACKGROUND:** Clonorchis sinensis, Opisthorchis viverrini, and Opisthorchis felinus are the three most important human liver fluke species in the Opisthorchiidae family, infecting approximately 25 million people worldwide. Drug treatment is needed to control morbidity and is also useful in lowering transmission. Several drugs used in various regimens are available to treat these infections, but their comparative efficacy is uncertain. We aimed to compare the efficacy in terms of cure rate and egg reduction rate of currently registered drugs against human liver fluke infection. **METHODS:** We conducted a systematic review using readily available electronic databases (MEDLINE, Embase, Cochrane Central Register of Controlled Trials, KoreaMed, China National Knowledge Infrastructure, and Wanfang Data) without language restrictions from inception until June 29, 2021. Clinical trials with pairwise comparison of drugs (praziquantel, albendazole, mebendazole, tribendimidine, or combinations of these drugs) against C sinensis, O viverrini, and O felinus were eligible, including trials comparing these drugs or their combinations with placebo. We compared efficacy in terms of cure rate by network meta-analysis. We conducted mixed binomial regression analyses for each species to derive predicted median cure rates for each drug regimen. The models included treatment and infection intensity as fixed factors, year of publication as covariate, and random effects of the different studies assumed to be normally distributed. We also assessed the quality of the included studies. This study was registered with PROSPERO (CRD42018109232). **FINDINGS:** Overall, 26 trials from 25 studies were included, of which 18 involved C sinensis, seven studied O viverrini, and one focused on O felinus. These trials included a total of 3340 participants. The two long-term treatment courses against C sinensis infection using 400 mg of albendazole (400 mg twice a day for 5 days and 400 mg twice a day for 7 days) resulted in cure rates of 100%, while two other multiple-dose regimens of albendazole resulted in high predicted cure rates: 300 mg twice a day for 5 days (93.9% [95% CI 49.6-99.6]) and 400 mg twice a day for 3 days (91.0% [50.9-99.0]). The WHO-recommended praziquantel regimen (25 mg/kg three times a day for 2 days) also showed a high predicted cure rate (98.5% [85.4-99.9]) in C sinensis infection, and predicted cure rates were above 90% for several other multiple-dose praziquantel regimens, including 20 mg/kg three times a day for 3 days (97.6% [74.7-99.8]), 14 mg/kg three times a day for 5 days (93.9% [44.8-

99.7%]), and 20 mg/kg twice a day for 3 days (91.0% [50.9-99.0]). In *O. viverrini* infection, the regimen of 50 mg/kg and 25 mg/kg of praziquantel given in a single day showed the highest predicted cure rate (93.8% [85.7-97.5]), while a single dose of 50 mg/kg praziquantel also resulted in a high predicted cure rate (92.1% [64.9-98.6]). The single dose of 400 mg tribendimidine showed a high predicted cure rate of 89.8% (77.5-95.8). A low quality of evidence was demonstrated in most studies, especially those published before 2000. Selection bias due to poor random sequence generation and allocation concealment was high, and performance and detection biases were frequently unreported. **INTERPRETATION:** Praziquantel shows high efficacy against clonorchiasis and opisthorchiasis. Tribendimidine might serve as a treatment alternative and warrants further investigation. Although albendazole is efficacious when long treatment schedules (5 days or 7 days) are applied, limited size of studies and high risk of bias affect the interpretation of results. More high-quality studies are needed to promote the establishment of treatment guidelines for human liver fluke infection. **FUNDING:** Fourth Round of Three-Year Public Health Action Plan (2015-2017; Shanghai, China) and Swiss National Science Foundation.

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