Findings of the N-ICE study: a randomised controlled trial of the safety and efficacy of N-acetyl cysteine (NAC) as a pharmacotherapy for methamphetamine dependence

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Introduction and Aims: N-acetylcysteine (NAC), has been found to ameliorate glutamate dysregulation in addiction and reduce craving for methamphetamine and other drugs. We evaluated the safety and efficacy of NAC for methamphetamine dependence.

Design and Methods: A double-blind randomised placebo-controlled trial (ACTRN12618000366257). Participants were dependent on methamphetamine and were randomised to receive either 12 weeks of oral NAC (2,400 mg/day), or matched placebo, delivered as a take-home medication. The primary outcome was methamphetamine use, measured as days of use assessed using the Timeline Followback, and methamphetamine-positive oral fluid samples taken weekly. Secondary outcomes were craving, severity of dependence, withdrawal severity and psychiatric symptoms (depression, suicidality, hostility and psychotic symptoms).

Results: Participants (N = 153; 59% male, mean [SD] age 38) were randomised to placebo (n = 77) or NAC (n = 76). Both groups had a median (IQR) of 24 (15-28) days of methamphetamine use in the 4 weeks prior to baseline. Both groups significantly reduced methamphetamine use (mean [SE] reduction of 7.3 [1.2]) days for placebo, 6.8 [1.2] for NAC) but NAC did not reduce days of methamphetamine use more than placebo (group
difference of 0.5 days, 97.5% CI -3.4 – 4.3). There was no significant effect of NAC on methamphetamine-positive oral fluid samples (placebo 79%, NAC 76%; mean difference - 2.6, 97.5% CI -12.6 – 7.4). Adverse events did not differ significantly between groups.

**Discussion and Conclusions:** These findings suggest that oral NAC has no significant effect on methamphetamine use or most clinically-related outcomes amongst people who are dependent on methamphetamine.

**Implications for Practice or Policy** (optional): Our trial suggests that NAC is unlikely to be of benefit as a take-home medication for people dependent on methamphetamine who are engaged in daily or near daily methamphetamine use. Our findings do not preclude potential benefits in other settings (e.g., to reduce craving during abstinence).

**Implications for Translational Research** (optional): This is the first robust trial to evaluate the effect of NAC on methamphetamine use and related clinical outcomes. We demonstrated that NAC has no significant effect on methamphetamine use, craving, withdrawal, or severity of dependence.