METHODS

**Design:** Randomised controlled trial.

**Allocation:** Unclear.

**Blinding:** Double blind.

**Follow up period:** 12 week acute phase followed by a 92 week continuation phase (total 2 years).

**Setting:** Fourteen academic medical centres in North America and Western Europe (part of a larger trial comparing olanzapine v haloperidol).

**Patients:** 262 people aged 16–40 years, with schizophrenia, schizoaffective disorder (DSM-IV), presenting with first episode psychosis. Participants scored >4 on the Positive and Negative Syndrome Scale (PANSS) and had a Clinical Global Impression (CGI) severity score ≥ 4. Exclusions: substance use in previous month, received antipsychotic drugs for more than 16 weeks, unstable medical illness, or high risk of suicide.

**Intervention:** Olanzapine (5–20 mg/day) or haloperidol (2–20 mg/day), titrated over 12 weeks. Chloral hydrate or diazepam for a maximum of 21 days was permitted. Antiparkinsonian drugs were allowed as necessary. Participants included are likely to have had less severe forms of addiction pathology. Perhaps the alleged advantages of novel antipsychotics become more evident in the chronic stages, when the cumulative effects of progressive deterioration and neuroleptic side effects are more of a factor. This short trial has nonetheless shown, once more, that atypicals enhance psychotic symptom scores in patients without a history of SUD. Olanzapine when SUD were concurrently present in people with psychosis, it did confirm the often reported finding that a history of substance misuse is a significant predictor of poorer therapeutic response. Differences in response were not significant for people with or without SUD or cannabis use disorders (see http://www.ebmentalhealth.com/supplemental for table). People with AUD were less likely to respond to olanzapine compared with haloperidol

**Outcomes:** Psychopathology assessed using established scales (PANSS, MADRS, CGI severity item) measured weekly from weeks 0–6 and then biweekly for weeks 7–12. Substance use assessed with SCID.

**Patient follow up:** Substance use assessment 100%; 12 week acute phase 60%; analysis: last observation carried forward.

**MAIN RESULTS**
Prevalence of SUD: 37% had a lifetime SUD diagnosis, most commonly with cannabis (38%), then alcohol (21%), cocaine (6%), hallucinogens/PCP (5%), and opioids (1%). People with SUD were more likely to be male and have had longer periods of untreated psychosis than their non-SUD counterparts. Response to antipsychotics: people with alcohol use disorder (AUD) were significantly less likely to respond compared with people without AUD; differences in response were not significant for people with or without SUD or cannabis use disorders (see http://www.ebmentalhealth.com/supplemental for table). People with AUD were less likely to respond to olanzapine compared with haloperidol (9% vs 27%; p<0.02).

For correspondence: Alan I Green, Dartmouth Medical School, One Medical Center Drive, Lebanon, NH, USA; Alan.I.Green@Dartmouth.edu

Sources of funding: USPHS grants and by Lilly Research Laboratories.

CONCLUSIONS
A history of substance use disorder is likely in people presenting with first episode psychosis. This may reduce their response to antipsychotic medication.

**Commentary**

A history of substance use disorder is likely in people presenting with first episode psychosis. This may reduce their response to antipsychotic medication.