▶ A randomized trial of clozapine versus other antipsychotics for cannabis use disorder in patients with schizophrenia.

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Heavy cannabis use is particularly troubling in patients already struggling with schizophrenia. This study provides the first evidence from a randomised controlled trial that switching such patients to the antipsychotic clozapine may help reduce their cannabis use, but is this worth the extra risk of clozapine compared to the alternatives?

Summary Studies have found that 13% to 42% of people with schizophrenia have at some time also been dependent on or abused cannabis, many more than in the general population. Cannabis use disorder has been associated with clinical exacerbations, non-compliance with treatment, poor global functioning, and increased relapse and rehospitalisation rates.

While the older 'typical' antipsychotic medications do not appear to curb substance use in patients with schizophrenia, preliminary findings, and a theoretical rationale based on the drug's effects on the brain, suggest that the atypical antipsychotic clozapine may help both with psychotic symptoms and cannabis and other substance abuse.

The authors tested this by recruiting 31 adult schizophrenic outpatients; generally their symptoms were not severe and had responded to treatment. Usually they had been referred to the study by clinicians at two US clinics. Typically patients were employed single white men in their 30s. All were also diagnosed with a cannabis use disorder and had used the drug at least five days out of the past 21. In practice the average was nearly five days and about a dozen joints a week, and about 8 in 10 were diagnosed as dependent on the drug. Half also were problem drinkers.

All the patients were being prescribed antipsychotics other than clozapine. A randomly selected 15 were transitioned over four weeks to clozapine instead. Over 12 weeks in total, the study's interviewers assessed the patients' use of cannabis, alcohol, and other substances, psychiatric symptoms, and experience of medication side effects, to test whether the switch to clozapine had led to improvements.

Main findings

Taking in to account differences in pre-study cannabis use, patients switched to clozapine on average smoked 4–5 joints of cannabis less per week, a medium effect size of 0.6, though with the small samples the difference was not statistically significant. Psychiatric symptoms improved in both sets of patients to roughly the same degree, and once a single 'outlier' heavy drinker had been eliminated from the analysis, excessive drinking rates too were similar. Some side effects were more common among patients switched to clozapine. Two patients in each group stopped taking their medications before the study ended. All the patients taking clozapine diligently took their medication as did all but three left on their existing medications.

The authors' conclusions

Clozapine may curb cannabis use more than continued treatment with other antipsychotics in patients with schizophrenia and co-occurring cannabis use disorders. Clozapine's lack of impact on psychiatric symptoms may reflect the overall moderate levels of psychiatric symptoms in this group of patients without treatment-refractory psychosis. The magnitude of the effect of clozapine suggests a clinically meaningful role for this medication, but the small size of the study sample limits the conclusions that can be drawn. Once an outlier had been removed, drinking was not affected. Changes in drinking were unrelated to changes in cannabis use, suggesting decreased cannabis use was not at the expense of increased drinking.

Although effective treatments for cannabis use disorder in schizophrenia are badly needed, clozapine's side-effect profile severely restricts its use. If it can definitively be shown to decrease cannabis use in patients with schizophrenia, it may be appropriate to expand the routine use of clozapine beyond treatment-refractory psychosis to stable outpatients with a co-occurring cannabis use disorder.

FINDINGS The question posed by this study was whether it is worth switching schizophrenic patients to clozapine to curb their excessive cannabis use, when their psychiatric symptoms are already relatively well controlled by their current antipsychotics. If they prove valid in replications and larger trials, the results leave patients and their doctors to make a judgement call between what may be a quite substantial reduction in cannabis use (in the study, by over a third) at the cost of more undesirable side effects (though not so troubling in this study as to lead to early termination or refusal to take the pills) and the risk of very serious and potentially fatal reactions (▶ below). Tipping the balance against taking these risks is the fact that in the featured study the fall in cannabis use and/or clozapine itself could not be shown to have improved patients' psychiatric health.

Britain's national formulary says that though an effective antipsychotic, clozapine should be reserved for schizophrenia patients unresponsive to, or intolerant of, conventional antipsychotic drugs. One of the reasons is the serious risk of a potentially fatal blood disorder, which demands regular monitoring of white blood cell and neutrophil counts – in the UK, weekly for the first 18 weeks and then continuing less frequently. Other serious side effects and withdrawal psychosis rebound are also concerns. Given these risks, in the UK clozapine patients must be registered with a clozapine patient monitoring service.

Unfortunately, while we know that in the featured study clozapine was compared to other antipsychotics, we do not know which ones. Neither do we know whether any impact on cannabis use was a short-lived 'halo effect' of trying a new drug, or would persist through to routine use over many months and years. The authors comment on the difficulty of recruiting such patients to clinical trials, a difficulty which in turn raises questions over how typical the patients were of all schizophrenic patients who frequently use cannabis. The extra reduction in cannabis use, though substantial, was not statistically significant, meaning there is an appreciable risk that it was due to chance differences between the patients.

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