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## Alcohol and cannabis use in schizophrenia: effects of clozapine vs. risperidone

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### Abstract

**Background:** Alcohol and cannabis use disorders worsen the course of schizophrenia. While the typical antipsychotics are of limited value in controlling substance use in schizophrenic patients, previous studies suggest that the novel antipsychotic clozapine (CLOZ) may decrease their substance use. We describe a retrospective study of the effects of the novel antipsychotics risperidone (RISP) and clozapine on alcohol and cannabis use in patients with schizophrenia or schizoaffective disorder and comorbid alcohol and/or cannabis use disorder. **Method:** This study involved retrospective assessment of abstinence (cessation of alcohol and cannabis use) in 41 patients treated with either risperidone ( $n = 8$ ) or clozapine ( $n = 33$ ) for at least 1 year. In 32 of these 41 patients, information was available on whether abstinence occurred during the 1-year period. **Results:** Abstinence rates were significantly higher in patients treated with clozapine than in those treated with risperidone (54% vs. 13%,  $p = 0.05$ ). The nine patients treated for at least 1 year, but excluded from the analysis because time of cessation of use was not known, had all stopped alcohol/cannabis use during clozapine treatment. **Discussion:** While the limitations of this retrospective study must be recognized, the data suggest that comorbid patients treated with clozapine are more likely to abstain from alcohol and cannabis use than are those treated with risperidone. Further prospective studies will be required to confirm these intriguing results. © 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Schizophrenia; Schizoaffective disorder; Alcohol; Cannabis; Clozapine; Risperidone

Alcohol use disorder, which is three times more common in patients with schizophrenia than in the general population, and cannabis use disorder, which is up to 10 times more common, both contribute to the

morbidity of schizophrenia, through increased relapse, noncompliance with treatment, more hospitalizations, and poorer overall functioning (Abram and Teplin, 1991; Bartels et al., 1991; Brady et al., 1990; DeQuardo et al., 1994; Drake and Mueser, 1996; Gupta et al., 1996; Knudsen and Vilmar, 1984; Linszen et al., 1994; Negrete et al., 1986; Owen et al., 1996; Peralta and Cuesta, 1992; Regier et al., 1990; Richard et al., 1985; Smith et al., 1997; Swanson et al., 1990; Treffert,

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1978). Unfortunately, the typical antipsychotic agents, the mainstay of treatment for schizophrenia for nearly 50 years, are of limited value in controlling alcohol or cannabis use in these “dual diagnosis” patients. However, case reports and preliminary data from our group and others suggest that the atypical antipsychotic drug clozapine (CLOZ) may limit alcohol, cannabis and other substance use in “dual diagnosis” patients with schizophrenia (Albanese et al., 1994; Buckley et al., 1999; Drake et al., 2000; Zimmet et al., 2000).

The basis for the effect of CLOZ in patients comorbid for substance use disorder and schizophrenia is not clear, but may relate to CLOZ's effect on negative symptoms (Khantzian, 1997), its lack of extrapyramidal system (EPS) effects (Siris, 1990), or its unique actions on the dopamine-mediated mesocorticolimbic system (Green et al., 1999). Given this, we wondered whether the post-clozapine novel antipsychotic risperidone (RISP), which has been reported to decrease negative symptoms and is associated with fewer EPS effects than typical antipsychotics (Marder and Meibach, 1994), would also share with CLOZ this beneficial effect on substance use in comorbid patients. Here, we report data from a retrospective study of alcohol and/or cannabis use in patients with schizophrenia or schizoaffective disorder treated with either RISP or CLOZ for a period of at least 1 year, and who had an active alcohol or cannabis use disorder at the time of initiation of treatment with the medication.

## 1. Methods

This retrospective study of alcohol and cannabis use was conducted in patients treated within the Massachusetts Mental Health Center (MMHC) outpatient department who were comorbid for alcohol and/or cannabis use disorder and schizophrenia or schizoaffective disorder. Patients were included in the study if: (1) they were currently being treated with or had previously been treated with risperidone (RISP) or clozapine (CLOZ); (2) they had been treated with either medication for at least 1 year; and (3) they were known to have been using substances at the initiation of treatment. The 1-year time frame was selected to ensure that patients would have a chance to demonstrate an effect of the treatment on

alcohol or cannabis use. [Our previous studies suggest that 3 months is an adequate length of treatment for the effect of CLOZ in this population (Albanese et al., 1994; Zimmet et al., 2000; Drake et al., 2000), but the length of time for RISP is unknown.] Subjects for the study were identified through the outpatient department, via chart review and clinician interview. The study was approved by the MMHC Human Studies Committee.

Demographic and treatment information (gender, age, diagnosis, substances used, current/previous dose of RISP or CLOZ, length of time treated with RISP or CLOZ) were obtained through chart reviews. In addition, clinicians were asked: (1) to confirm that patients had been using alcohol and/or cannabis at the initiation of RISP or CLOZ; (2) to rate any change in alcohol/cannabis use achieved with RISP or CLOZ on a four-point scale (stopped use, decreased use, continued at same level of use, increased use); and (3) to rate, on a five-point scale, how soon after starting RISP/CLOZ the change in alcohol/cannabis use occurred (less than 1 month, 2–4 months, 5–11 months, 1–2 years, greater than 2 years).

For this study, we assessed the impact of treatment with either RISP or CLOZ on alcohol and cannabis use. Our outcome measure was abstinence, defined as cessation of all alcohol and cannabis use, noted by clinicians to have started during the first year of treatment with RISP or CLOZ. (Abstinence was chosen since it is an important clinical outcome and should have good reliability when assessed retrospectively, i.e., it is an all-or-nothing phenomenon that would be likely to be noticed by the clinician. In this regard, Carey (1997) has reported that retrospective assessment of abstinence from patient self-report has excellent validity in this population.) Patients treated with both RISP and CLOZ were excluded from analysis.

Data analysis included Chi-square analyses of categorical data, using the Likelihood Ratio Test when there were more than 2 *df* and small cell sizes, and the *t*-test for independent samples for continuous data.

## 2. Results

Within the clinic, we identified 8 patients meeting the inclusion criteria who had been treated with RISP,

Table 1  
Description of study subjects

Variable	Risperidone, <i>n</i> = 8	Clozapine, <i>n</i> = 33	Test
Gender	Male, <i>n</i> = 5 (63%) Female, <i>n</i> = 3 (37%)	Male, <i>n</i> = 26 (79%) Female, <i>n</i> = 7 (21%)	$\chi^2 (1) = 0.87$ $p = 0.35$
Diagnosis	Schizophrenia, <i>n</i> = 6 (75%) Schizoaffective, <i>n</i> = 2 (25%)	Schizophrenia, <i>n</i> = 24 (73%) Schizoaffective, <i>n</i> = 9 (27%)	$\chi^2 (1) = 0.02$ $p = 0.9$
Substance used	Alcohol only, <i>n</i> = 4 (50%) Cannabis only, <i>n</i> = 1 (13%) Alcohol + cannabis, <i>n</i> = 3 (37%)	Alcohol only, <i>n</i> = 16 (49%) Cannabis only, <i>n</i> = 8 (24%) Alcohol + cannabis, <i>n</i> = 9 (27%)	$\chi^2 (2) = 0.68$ $p = 0.71$
Number of substances used	One substance, <i>n</i> = 5 (63%) Two substances, <i>n</i> = 3 (37%)	One substance, <i>n</i> = 24 (73%) Two substances, <i>n</i> = 9 (27%)	$\chi^2 (1) = 0.31$ $p = 0.58$
Age	Mean = 48.7 (SD = 16.4)	Mean = 40.6 (SD = 7.7)	$T (7.8^a) = 1.3$ $p = 0.21$
Dose	Mean = 3.9 (SD = 2.4)	Mean = 439.6 (SD = 175.4)	N/a
Substance use outcome at 1 year	Did not stop, <i>n</i> = 7 (87.5%) Stopped, <i>n</i> = 1 (12.5%)	Did not stop, <i>n</i> = 11 (46%) Stopped, <i>n</i> = 13 (54%)	$\chi^2 (1) = 4.7$ $p = 0.05$

<sup>a</sup> *t*-test for unequal variance.

and 33 patients who had been treated with CLOZ. These two groups of patients are described in Table 1. Among the RISP-treated patients, 63% were male and 75% had schizophrenia (vs. schizoaffective disorder); among the CLOZ group, 79% were male and 73% had schizophrenia. The mean ages of the RISP and CLOZ groups were similar, 48.7 (SD = 16.4) and 40.6 (SD = 7.7), respectively. In the RISP group, 50% of the patients used alcohol only, 13% used cannabis only, and 37% used both alcohol and cannabis. Likewise, in the CLOZ group, 49% of the patients used alcohol only, 24% used cannabis only, and 27% used both alcohol and cannabis. Patients in both groups were taking therapeutically appropriate doses of medication: for RISP, the mean daily dose = 3.9 mg, SD = 2.4; for CLOZ, it was 439.6 mg, SD = 175.4.

In our examination of the alcohol/cannabis use outcome, we found that nine CLOZ patients who had stopped alcohol/cannabis use were missing data on when the cessation occurred. Because we could not confirm that the cessation of alcohol and/or cannabis use was initiated within the first year of treatment, we considered the substance use outcome as missing for these patients. We do not believe that excluding these patients biases the results as this information is most likely missing for reasons that are unrelated to the alcohol/cannabis use outcome (e.g., that the information was not written in the patient's chart and/or that the clinician did not know or could not remember the time of cessation of use). Of the 24 CLOZ-treated patients with known "stop time" data, 13 stopped

alcohol/cannabis use during this period; of the 8 RISP-treated patients, only 1 stopped alcohol/cannabis use during this period (54% vs. 12.5%,  $p = 0.05$ ).

In our survey of patients treated with RISP or CLOZ for at least 1 year, we noted that there were 15 other patients in the clinic (12 treated with RISP and 3 treated with CLOZ) who met all the inclusion criteria for the study but who were excluded from the sample because they had been treated with RISP or CLOZ for less than one full year. These 15 patients did not differ from the 41 study patients on characteristics listed in Table 1, except for ages of 35.0 (SD = 10.9) vs. 42.2 years (SD = 10.2;  $t(54) = 2.0$ ,  $p = 0.05$ ), for the excluded and study patients, respectively. Ten of the RISP-treated patients and two of the CLOZ-treated patients had discontinued medication treatment prior to 1 year; the other three patients were still taking their medication at the time of the survey.

### 3. Discussion

This retrospective study suggests that treatment with CLOZ is more likely to be associated with a cessation of alcohol and/or cannabis use than is treatment with RISP. Moreover, since the nine study patients not included in the analysis due to lack of documentation about when the cessation occurred all stopped alcohol/cannabis use while on CLOZ treatment, our results, while significant, are probably conservative.

We were struck by the number of RISP-treated patients who discontinued medication treatment prior to the 1-year mark, as compared to the CLOZ-treated patients. Further studies will be required to determine the reason for the high drop-out rate in the RISP group prior to 1 year of treatment. One possibility is that comorbid patients tend to have a poor clinical response to RISP with a continued use of alcohol and/or cannabis.

The basis for the lack of beneficial effect of RISP on comorbid alcohol or cannabis use, especially in the face of the apparent beneficial effect of CLOZ, is not clear. Both CLOZ and RISP are effective antipsychotic drugs, with good profiles for extrapyramidal system effects (compared to typical agents), and both drugs have been reported to decrease negative symptoms in patients (Krystal et al., 1999; Marder and Meibach, 1994). The “self-medication” theories of substance use in patients with schizophrenia (i.e., that substance use decreases negative symptoms or EPS effects from typical agents; Khantzian, 1985, 1997; Siris, 1990) would predict that CLOZ and RISP might both be effective agents in this population. The fact that only CLOZ appears likely to limit alcohol/cannabis use suggests that the basis of this effect of CLOZ may not relate to its effects on negative symptoms or its lack of EPS potential. We have suggested elsewhere (Green et al., 1999) that clozapine’s effect on limiting substance use in patients with schizophrenia may relate to its ability to ameliorate reward system defects in the dopamine-mediated mesocorticolimbic circuits in these patients.

We expect that our data should be generalizable to other clinic samples of chronic patients. This is because we surveyed all the subjects in the clinic who met our diagnostic and treatment criteria, whether or not they were using substances at the time of initiation of treatment with the study drugs and whether or not they had been treated for the full year period. Those comorbid patients not included in this survey were being treated with antipsychotics other than those studied here or with multiple antipsychotics at the same time.

The limitations of this retrospective study must be recognized. First, the sample sizes are modest. Second, despite the lack of demographic differences in the patients treated with CLOZ compared to those treated with RISP, the groups may differ on the reason for medication choice (i.e., patients treated with

CLOZ were treatment refractory or intolerant and the RISP patients were not). However, since all patients were offered the same substance abuse services, there should be no particular bias regarding the alcohol/cannabis use outcome. Third, the greater frequency of clinic visits for the CLOZ patients (weekly visits for white blood counts) compared to those treated with RISP could itself have contributed to increased abstinence. Fourth, lack of data on how long the abstinence continued may limit the strength of our conclusions. We do know, however, that patients stopped their substance use within the first year of treatment and appeared to continue such abstinence at least until the end of that year period.

Prospective, double-blind studies, in which patients are randomised to study treatment, will be required to confirm these retrospective data. Such studies are currently underway to further assess whether RISP or other novel antipsychotics share CLOZ’s apparent ability to limit substance use in patients with schizophrenia.

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