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# Effects of risperidone, quetiapine and ziprasidone on ethanol withdrawal syndrome in rats

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ABSTRACT

Comorbid substance use in schizophrenic patients is common, and substance dependence is a predictive factor for psychosis. The present study was designed to investigate the effects of risperidone, quetiapine and ziprasidone, atypical antipsychotic drugs, on ethanol withdrawal syndrome (EWS) in rats. Adult male Wistar rats were used in the study. Ethanol (7.2%, v/v) was given to rats via a liquid diet for 21 days. An isocaloric liquid diet without ethanol was given to control rats. Risperidone (1 and 2 mg/kg), quetiapine (8 and 16 mg/kg), ziprasidone (0.5 and 1 mg/kg) and vehicle were injected into rats intraperitoneally at 1.5 and 5.5 h of ethanol withdrawal. At the 2nd, 4th and 6th hours of ethanol withdrawal, rats were observed for 5 min, and withdrawal signs that included locomotor hyperactivity, stereotyped behaviors, abnormal gait and posture, tail stiffness and agitation were recorded or rated. Following the observations at the 6th hour, the rats were tested for audiogenic seizures. All three drugs had some significant inhibitory effects on EWS-induced behavioral signs beginning at the 2nd hour of withdrawal. The drugs also significantly reduced the incidence of audiogenic seizures. Overall, risperidone and quetiapine seemed to be more effective than ziprasidone in ameliorating the withdrawal signs. Doses of the drugs used in the present study did not produce any significant changes in locomotor activities of naïve rats. Our results suggest that risperidone, quetiapine and ziprasidone had beneficial effects on EWS in rats. Thus, these drugs may be helpful for controlling withdrawal signs in ethanol-dependent patients.



## 1. Introduction

Epidemiologic studies and clinical assessment of schizophrenic populations indicate that there is a marked relationship between schizophrenia and addictive behaviors. Observations of the general population have recognized a high risk of alcohol dependence or substance abuse in subjects presenting with criteria for schizophrenia (Regier et al., 1990; Batel, 2000). It has also been shown that schizophrenia is four times more frequent among alcoholic than non-alcoholic subjects (Helzer and Pryzbeck, 1988). Thus, comorbid substance use in schizophrenic patients is common, and substance abuse may be acceptable as a predictive factor for psychosis (Hambrecht and Hafner, 1996).

Ethanol abuse and dependence is one of the most important worldwide public health problems. The discontinuation of chronic administration of ethanol is associated with excitatory withdrawal signs called ethanol withdrawal syndrome (EWS). EWS is the most important evidence indicating the development of physical dependence on ethanol (Jaffe, 1990). Although attenuating the severity of EWS is very important, current treatment choices are very limited except for the use of benzodiazepines. Acamprosate (a glutamate antagonist), naltrexone (an opioid antagonist) and disulfiram (an aldehyde dehydrogenase blocker) are approved for the treatment of ethanol dependence, but these medications are effective in attenuating ethanol cravings and consumption rather than treatment of EWS (Heilig and Egli, 2006). New approaches and new drug choices are necessary for treatment of EWS.

A strong body of evidence indicates that ethanol activates dopamine release from the nucleus accumbens and extended amygdala (Di Chiara, 1995; Heimer et al., 1997). The action of ethanol on the mesolimbic pathway is considered to be strongly associated with susceptibility to alcoholism (Noble, 1996) and the development of craving and loss of control (Robinson and Berridge, 1993). Neurochemical findings from clinical (Roy et al., 1987; Le Marquand et al., 1994) and experimental (Murphy et al., 1987; Uzbay et al., 1998, 2000a,b; Uzbay, 2008) studies have also suggested that significant

*Abbreviations:* 5-HT, 5-hydroxytryptamine; ANOVA, Analysis of variance; dB, Decibel; EWS, Ethanol withdrawal syndrome; Qtp, Quetiapine; Risp, Risperidone; S.E.M., The standard error of the mean; TUBITAK, Scientific and Technological Research Council of Turkey; Zip, Ziprasidone.

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changes in central serotonergic neurotransmission occur during ethanol consumption and/or withdrawal. Substantial experimental evidence indicates that serotonin has a critical role in impulsivity and craving, which are frequently seen in alcoholics (Ciccocioppo, 1999), and serotonin is at least partly responsible for alcohol dependence (Myers and Martin, 1973; Schuckit, 1996). As a result, dopaminergic and serotonergic systems play an important role in the development of ethanol dependence. Thus, drugs that affect the central dopaminergic and serotonergic systems may be helpful for controlling ethanol abuse and dependence.

Atypical antipsychotic drugs are widely used in patients with schizophrenia. In contrast to classical (or typical) antipsychotics, these drugs have substantially lower risks of extrapyramidal symptoms, including tardive dyskinesia. They also modulate serotonergic and dopaminergic receptors (Schatzberg et al., 2003). Although several reports investigating the effects of new atypical antipsychotics, such as clozapine, risperidone, quetiapine and aripiprazole, on ethanol abuse and dependence have been published, many of them examined ethanol consumption, preference or craving (Drake et al., 2000; Ingman et al., 2003; Potvin et al., 2003; Martinotti et al., 2008; Vergne and Anton, 2010). These observations imply that new atypical antipsychotic drugs could be effective in the treatment of ethanol dependence, but there are limited reports investigating the effects of these drugs on EWS. In our previous studies, we tested the effects of clozapine and olanzapine, atypical antipsychotic drugs, on EWS in rats. We observed some beneficial effects of clozapine on EWS (Kayir and Uzbay, 2008). On the other hand, while olanzapine inhibited the intensity of some symptoms such as stereotyped behavior and wet dog shakes, it had some adverse effects on other signs such as abnormal gait and posture (Unsalan et al., 2008). Effects of risperidone, quetiapine and ziprasidone, relatively new and effective atypical drugs, on EWS have not been subjected to clinical or experimental studies yet.

The main objective of the present study was to investigate the effects of risperidone, quetiapine and ziprasidone on the signs of EWS in rats. Thus, the current study was focused on revealing whether these drugs are effective in attenuating ethanol withdrawal or not.

## 2. Materials and methods

### 2.1. Animals and laboratory

All procedures in this study were in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the National Institutes of Health (USA). Local ethical committee approval was also attained, numbered 08/36K-R on April 4, 2008. All efforts were made to minimize animal suffering and to reduce the number of animals used.

Adult male Wistar rats (220–320 g at the beginning of the experiments) were used ($n=8$ for each group). They were housed in a quiet and temperature- and humidity-controlled room ($22\pm3$ °C and $60\pm5$%, respectively) in which a 12-h light/dark cycle was maintained (07:00–19:00 h light). Exposure to ethanol and all behavioral experiments involved in examining EWS were carried out in other separate and isolated laboratories, which had the same environmental conditions as the colony room.

### 2.2. Chronic exposure to ethanol

For chronic ethanol exposure, the rats were housed individually and ethanol was given in the modified liquid diet as previously described (Uzbay and Kayaalp, 1995). The rats were given a modified liquid diet with or without ethanol ad libitum. No extra chow or water was supplied. The composition of the modified liquid diet with ethanol was as follows: 925–975 mL cow milk (Danone, Turkey), 25–75 mL ethanol (96.5% ethyl alcohol; Tekel, Turkish State Monopoly), 5000 IU vitamin A (Aksu Farma, Turkey) and 17 g sucrose (Uzbay and Kayaalp, 1995). This mixture supplies 1000.7 kcal/L.

At the beginning of the study, all of the rats were given the modified liquid diet without ethanol for 7 days. Then, liquid diet with 2.4% ethanol was administered for 3 days. The ethanol concentration was increased to 4.8% for the following 4 days and finally to 7.2% for 21 days. Liquid diet was freshly prepared daily and presented at the same time of the day (09:00 h). The weight of the rats was recorded every day, and daily ethanol intake was measured and expressed as g per kg per day. Control rats ($n=8$) were pair fed with an isocaloric liquid diet containing sucrose as a caloric substitute for ethanol.

### 2.3. Drug used in the study

Risperidone (Teva Ltd. API Division, Israel), quetiapine (Sanovel, Turkey) and ziprasidone (Pfizer, Turkey) were dissolved in vehicle (0.1% acetic acid). All drugs and vehicle were injected into rats intraperitoneally at a volume of 1 mL/200 g body weight. Drug solutions were prepared freshly in the morning just before administration.

### 2.4. Evaluation of EWS

At the end of the exposure to the 7.2% ethanol-containing liquid diet, diet with ethanol was withdrawn and replaced with isocaloric ethanol free diet at 09:30 h. Ethanol-dependent rats were then assigned into seven groups randomly ($n=8$ for each group). Risperidone (1 and 2 mg/kg), quetiapine (8 and 16 mg/kg), ziprasidone (0.5 and 1 mg/kg) and vehicle were injected into the rats 30 min before ethanol withdrawal evaluation. At the 2nd, 4th and 6th hours of ethanol withdrawal, rats were observed for 5 min, and withdrawal signs including locomotor hyperactivity, stereotyped behaviors, abnormal posture and gait, tail stiffness and agitation were recorded or rated as previously described (Uzbay and Kayaalp, 1995; Uzbay et al., 1997; Kayir and Uzbay, 2008).

Locomotor activities of the rats were recorded using an open-field locomotor activity test apparatus (Opto Varimex Minor, Columbus, OH, USA) as a total of horizontal, vertical and ambulatory activities and expressed as mean ± S.E.M.

Grooming, sniffing, head weaving, gnawing and chewing were observed as major stereotyped behaviors during the ethanol withdrawal in the study. The total number of stereotyped behaviors for each observation period was calculated and expressed as mean ± S.E.M. Abnormal gait and posture, agitation and tail stiffness were scored using the rating scale as previously described (Uzbay et al., 1997).

Each group received a second injection of its original drug 30 min before the 6th hour of observation. After 6 h of withdrawal testing, rats were exposed to an audiogenic stimulus (100 dB) for 60 s in a separate and soundproof place in the laboratory. The incidence and latency of the audiogenic seizures were recorded.

Control rats receiving liquid diet without ethanol were also evaluated for ethanol withdrawal signs parallel to ethanol-dependent groups.

All experiments were carried out during the light period. All ratings were scored by a naive observer who was blind to the treatments that the rats received.

### 2.5. Measurements of locomotor activity in naive control rats

The experimental drugs and vehicle were administered in seven groups of naive (not ethanol-dependent) Wistar rats. Thirty minutes after the injections, rats were put into the locomotor activity test apparatus and locomotor activities of the rats were measured for 30 min. The results of the locomotor activity tests were expressed as mean ± S.E.M.