imaging were obtained. The results of these tests were normal, including levels of troponin, brain natriuretic peptide, and immunoglobulin E and white blood cell and eosinophil counts, making the diagnosis of myocarditis questionable. The risks and benefits of clozapine retrial were discussed with the patient and his family, and the dosage of clozapine was increased to 550 mg daily, with a serum level of 250 ng/ml. There were no adverse effects, and the patient's psychosis improved.

The risk of restarting clozapine after myocarditis is high (2), and evidence is insufficient to support a universal clinical guideline. Retrial may be reasonable in cases with severe psychiatric decompensation and absence of serious physical compromise during the initial episode of myocarditis or when the diagnosis of myocarditis is unlikely, such as in the present case. Retrial should involve slow inpatient titration of clozapine, with close monitoring (3). More research is needed on the utility of diagnostic tests in the risk-benefit analysis of restarting clozapine after concern for myocarditis.

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Remission of Drug-Induced Hepatitis After Switching from Risperidone to Paliperidone

To the Editor: Risperidone and clozapine are known to potentially cause drug-induced hepatitis in 0.01%–0.1% of patients (1–3). Paliperidone, which is pharmacologically identical to 9-hydroxyrisperidone, exhibits high affinities for dopamine type 2 (D_2) and serotonin 5-HT_2 receptors but does not undergo significant hepatic metabolism (4). The drug is well tolerated in patients with poor hepatic function and seems unlikely to be susceptible to metabolic drug interactions. We report a case of risperidone-induced hepatitis, which remitted after switching from treatment with risperidone to treatment with paliperidone, in a patient receiving dual antipsychotics.

"Mrs. J" was a 43-year-old female patient suffering from schizophrenia. She was being treated with risperidone, 6 mg per day, and clozapine, 600 mg per day, when she was admitted to the Department of Internal Medicine because of drug-induced hepatitis. Clinical and laboratory tests revealed an icterus; beer-brown urine; and highly elevated liver enzymes, with a maximum of 1.159 U/l for gamma glutamyltransferase (normal range: 6–42 U/l), 206 U/l for alkaline phosphatase (normal range: 10–35 U/l), and 75 U/l for alanine transaminase (normal range: 10–35 U/l). Serum levels for risperidone active moiety were within the therapeutic range of 20–60 ng/ml (risperidone: 26 ng/ml; 9-hydroxyrisperidone: 30 ng/ml). Clozapine serum levels were also within the therapeutic range (508 ng/ml; reference range: 350–600 mg/ml), with 609 ng/ml for norclozapine (metabolite).

Risperidone treatment was discontinued, and paliperidone, 9 mg per day, was started. Clozapine doses were slightly reduced to 575 mg in the third week as a result of increasing plasma levels. The patient's psychopathology remained stable throughout clinical treatment. Liver enzymes as well as serum levels for paliperidone and clozapine were measured weekly. Aspartate transaminase levels returned to normal within 1 week, and alanine transaminase levels returned to normal after 16 days. After 4 weeks, gamma glutamyltransferase levels reached the lowest measured value, at 112 U/l, representing a 90% reduction of the initial value. Serum levels at that time were 34 ng/ml for paliperidone, 536 ng/ml for clozapine, and 483 ng/ml for norclozapine. Analyses of clozapine and norclozapine serum levels revealed that in a state of high levels of hepatotoxicity, serum levels for the metabolite were considerably higher than those for the parent drug, whereas the ratio of serum levels between the parent drug and its metabolite was higher for the parent drug after liver enzymes approximated normal ranges.

Our case shows that, first, hepatitis that was most likely induced by risperidone completely remitted after switching to paliperidone. Since treatment with clozapine remained almost unchanged, it seems plausible that risperidone rather than clozapine induced hepatotoxicity, not disregarding that clozapine itself or the combination of both drugs could have been the cause of the hepatitis. Risperidone is metabolized to 9-hydroxyrisperidone via cytochrome P450 (CYP) 2D6, while paliperidone does not undergo significant hepatic metabolism. Therefore, it can be recommended that in cases of hepatotoxicity, paliperidone is a well-tolerated alternative to treatment with risperidone.

Second, declining signs of hepatotoxicity led to an inversion of the clozapine/norclozapine ratio. As seen in Figure 1, serum levels for the metabolite were initially higher than those for the parent drug (ratio <1), but the reverse was observed with normalization of liver function (ratio >1). A possible explanation may be that in the state of acute inflammation, different metabolizing enzymatic pathways are activated on the one hand, while other metabolic pathways are likely working insufficiently as a result of the acute hepatitis. Consequently, there is a shift among the levels of the different metabolites of clozapine (e.g., norclozapine, clozapine-N-oxide) in acute hepatitis, and the ratio returns to its "normal value" after normalization of liver function.

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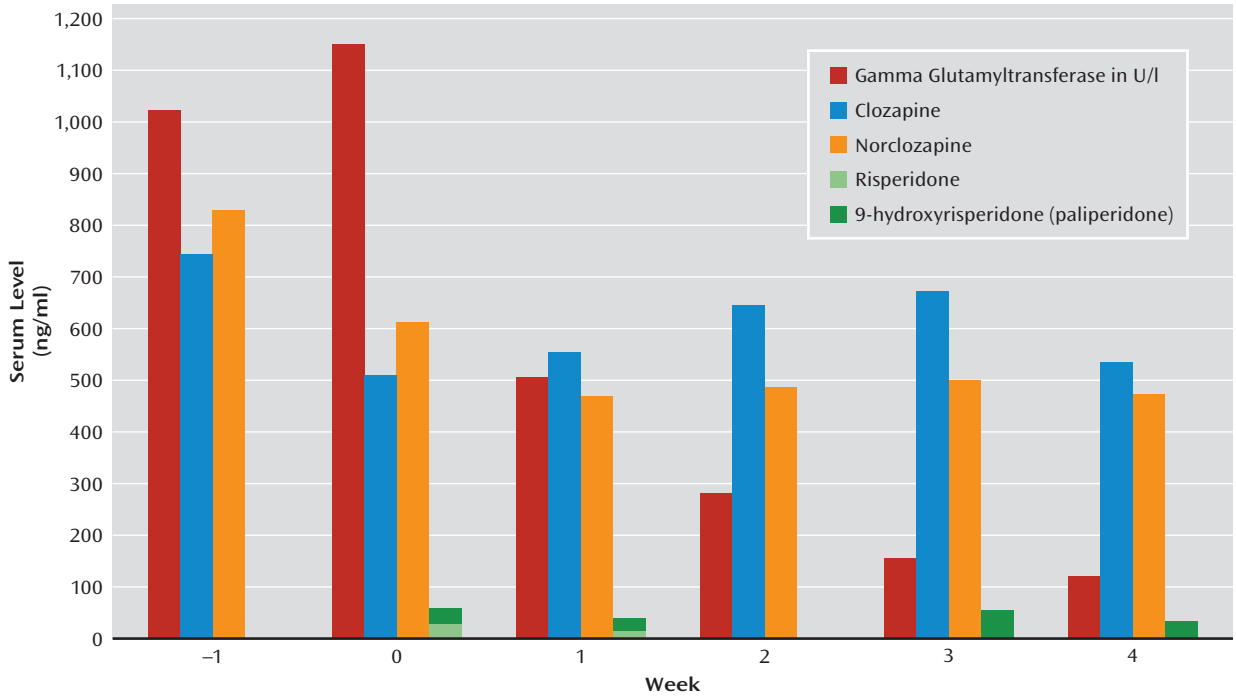
FIGURE 1. Gamma Glutamyltransferase and Plasma Levels in a Patient With Risperidone-Induced Hepatitis



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Subjective Adjustment of Individuals With Psychiatric Disorders in the Aftermath of the L'Aquila Earthquake

To the Editor: On April 6, 2009, at 3:32 a.m., an earthquake (Richter Magnitude Scale number: 6.3) struck L'Aquila, Italy, a town with a population of 72,000 residents. The L'Aquila earthquake caused the deaths of 309 people, with more than 1,000 individuals injured and 66,000 displaced. This disaster provided a unique opportunity to explore the effects of severe stress.

In the present analysis, we report the clinical evaluation of individuals examined from the third to eighth week after the earthquake (N=87; mean age: 50.37 years [SD=14.94]). Sixty-five individuals had already been engaged in a mental health program with follow-up care, and 22 were cases of new-onset illness. None had personal or familial physical injury during the disaster. All diagnoses were based on ICD-10 criteria following an interview conducted by a senior psychiatrist.

All subjects were evaluated using a visual analogue scale, with three anchor points ("better," "equal," "worse") in response to the following question: "How did you mentally feel after the earthquake?" The Clinical Global Impression (CGI), with severity of illness and global improvement (change in score from the last clinical visit prior to the earthquake), was also used to evaluate those individuals already engaged in care.

Among those who had been previously engaged in a mental health program, 25% of persons with schizophrenia (N=7/28) and 26% of individuals with affective disorders (N=5/19) reported a "worse" outcome after the disaster. The remaining patients reported "equal" (schizophrenia: N=16/28 [57.1%]; affective disorders: N=11/19 [57.9%]) or "better" (schizophrenia: N=5/28 [17.9%]; affective disorders: N=3/19 [15.8%]) outcome. Subjects with mental retardation (N=6) all reported an "equal" outcome. Individuals with anxiety disorders (N=7/12 [58.3%]) reported "worse" or "equal" (N=5/12 [41.7%]) outcome (χ^2=13.76, df= 6, p=0.03). CGI score comparison among individuals with schizophrenia, affective disorders, and anxiety disorders showed higher severity of illness for schizophrenia (Kruskal-Wallis χ^2=14.49, df=2, p=0.001), with no difference in global improvement.

Among patients with new-onset illness, one had a psychotic disorder, 18 had mood or anxiety disorders, and three had behavioral problems associated with mental retardation. Among all new-onset cases, 72.7% (N=16/22) reported a "worse" outcome and 27.3% (N=6/22) reported an "equal"