other things, because they lead to a reduction in the number of mechanical restraints.

It has been seen that the decreased use of mechanical restraint on its own without specific training can lead to an increase in attacks against patients and staff.[8] In this regard, specific training in the different units and health centres to increase knowledge of the factors that lead to agitation, teaching the least restrictive interventions possible and learning safe reactions to patient violence are necessary for application of the technique to be effective.

It is recommended that training in behavioural emergency management and agitation, analogous to advanced training in cardiovascular life support, should be regular,[7] on an annual basis if possible. This should include not only learning in a classroom or from a book, but also putting skills into practice. In this sense, de-escalation techniques can be learned through role play or simulated encounters with patients.[7] It should be noted that all members of hospital staff, not just health workers in psychiatry, can learn de-escalation techniques and use them successfully if they are well trained and gain a certain skill set.

In conclusion, clinical staff in emergency departments and other health network facilities should be trained in de-escalation techniques, and in the prevention and management of agitated and aggressive behaviour,[7,9] therefore we recommend implementing training programmes in verbal de-escalation. We consider that this training is applicable in our environment and has the potential to improve how episodes of agitation are handled, while increasing user satisfaction with the entire therapeutic process.

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Clozapine and acute hepatitis☆

Clozapina y hepatitis aguda

Dear Editor,

Clozapine is an atypical antipsychotic introduced into clinical practice in the early 1970s and indicated in patients with schizophrenia resistant to other antipsychotics and in psychotic disorders occurring in Parkinson's disease where conventional therapy has failed.

Given the severity of the haematological (neutropenia/agranulocytosis), with incidences of 3 and .7%, respectively, and cardiovascular (pericardiomyocarditis, thromboembolic disease, arrhythmias or sudden death)side effects included in its technical data sheet,[1] its use as first line therapy is not widespread, despite its proven efficacy in resistant schizophrenia. This has probably led to less attention being paid to other side effects. This is the case with acute hepatitis, which is predominantly cytolytic and, although very rarely, can lead to fatal fulminant hepatic necrosis.

We performed a review of the medical literature (MEDLINE, PubMed; keywords: *clozapine and hepatotoxicity*

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and/or *liver enzyme elevations*) and we found several notifications of liver toxicity. Specifically, we found 2 cases in Spanish, one of which received at least 4 hepatotoxic drugs,[2] and the other based on a patient with hepatitis C virus.[3] Therefore, we believe it is of interest to present the case of a patient that we attended recently.

A 49-year-old male, with a personal history of schizophrenia who had started treatment with clozapine at a dose of 100 mg/day 45 days earlier, at the time of consultation. The patient consulted due to a mild deterioration of his general condition and nonspecific abdominal discomfort. He had also been treated, for 2 years, with metformin 850 mg/day and diazepam 5 mg/day. On physical examination the only abnormal sign was a body mass index of 33 kg/m^2. Analytically, of note was a normal blood system, prothrombin activity of 92%, aspartate aminotransferase (AST) 314IU/l (normal value [nv]: 2–38), alanine aminotransferase (ALAT) 808IU/l (nv: 2–41), gamma glutamyl transpeptidase (GGT) 104IU/l (nv: 7–50), lactate dehydrogenase (LDH) 293IU/l (nv: up to 250) and ferritin above 1000 ng/ml, with 25% saturation rate. Proteinogram, immunoglobulin G, alpha-1 antitrypsin, ceruloplasmin and serum copper were normal, and serology against hepatitis viruses A, B, C and E, HIV, cytomegalovirus, Epstein-Barr virus, herpes simplex virus I and II, *Mycoplasma pneumoniae, Chlamydia pneumoniae,* parvovirus, *Treponema* and *Coxiella burnetti* was negative. Antinuclear, anti-smooth muscle, anti-mitochondrial, anti-LKM, anti-LC and anti-SLA antibodies were also negative. Abdominal ultrasound showed only hepatic hyperechogenicity. Given the suspicion of toxic hepatitis with cytolytic predominance (ALAT/upper limit of normality[ULN]/FA/ULN > 5), clozapine was discontinued, after which liver analysis improved and normalised after 45 days. Psychopathologically, the patient remained stable after the introduction of amisulpride. The Naranjo causality scale established a probable causal attribution (6 points). The case was reported to the Regional Centre for Pharmacovigilance of Castilla y León.

Clozapine appears to frequently cause asymptomatic elevation of transaminases. Thus, Hummer et al.[4] were able to confirm it in up to 37% of their patients, of whom more than 60% had normalised in the following 3 months. This would translate as a frequent and, in most cases, transitory phenomenon. In another study, 3-fold elevations of ALAT were detected in up to 15% of treatment cycles.[5] However, and although much more rarely, liver failure and death have been described.[6,7]

Unlike the assumption of agranulocytosis, there are no clear recommendations on the follow-up of liver tests. Most authors advise discontinuing the drug when transaminase elevations are higher than 3 times normal, but they are not uniform in the frequency of their testing. In the meantime, it seems prudent to monitor liver tests initially and then weekly or depending on the clinical signs.[8]

We insist, once again, on the need to broaden the knowledge of this entity; and therefore it is very necessary to report it to the relevant pharmacovigilance centres, which implies, on the other hand, an obligation that concerns us all as professional practitioners.

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