Advanced Biomarkers of Hepatotoxicity in Psychiatry

Subjects: Substance Abuse

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One of the factors that increase the effectiveness of the pharmacotherapy used in patients abusing various types of new psychoactive substances (NPSs) is the proper functioning of the liver. To review three advanced markers of hepatotoxicity in psychiatry, namely, osteopontin (OPN), high-mobility group box 1 protein (HMGB1) and glutathione dehydrogenase (GDH, GLDH), and, on this basis, to identify recommendations that should be included in future studies in patients abusing NPSs. This will make it possible to determine whether NPSs do indeed have a hepatotoxic effect or whether other factors, such as additional substances taken or hepatitis C virus (HCV) infection, are responsible. NPS abusers are at particular risk of HCV infection, and for this reason, it is all the more important to determine what factors actually show a hepatotoxic effect in them.

hepatotoxicity biomarkers psychiatry

1. Introduction

Year after year, there is an increasing number of hospitalisations of patients for the abuse of new psychoactive substances (NPSs), commonly referred to as ‘legal highs’. In 2019, in Lancet, some authors indicated that NPSs could be defined as a diverse group of substances that emerged rapidly from the early to mid-2000s. The emergence of newer and newer NPSs in a short space of time and their unknown effect profiles pose a major threat to public health [1]. In 2019–2022, articles were published in an attempt to optimise the pharmacotherapy used in a group of patients abusing mephedrone. One of the main factors increasing the risk of subsequent hospitalisation in patients is liver malfunction. In groups of mephedrone abusers with other psychoactive substances, the highest liver enzyme levels were found in patients with co-occurring HCV infection [2]. Patients participating in a methadone programme, due to mephedrone abuse with heroin, were also re-hospitalised with hepatitis C virus (HCV) co-infection [3]. Among patients with multiple hospital admissions, the number of psychoactive substances taken with mephedrone was greater than one [4]. This is supported by results published in 2020 indicating that supplementation with liver regeneration products may contribute to a reduced risk of subsequent hospitalisation in the same individuals [5]. It should also be borne in mind that due to the abuse of mephedrone with other psychoactive substances, polypharmacotherapy may be one of the factors negatively affecting liver function [6]. For this reason, it seems advisable to carry out research on the relationship between liver function and quality of life in patients abusing various types of NPSs.

The liver parameters studied so far in a larger group of patients, which are simple liver enzymes, are non-specific biomarkers as they are found in many cell types and their increase has been recorded alongside damage to almost

every organ. The parameters mentioned include simple liver enzymes such as gamma-glutyltransferase (GGT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In order to thoroughly investigate the problem of hepatotoxicity associated with NPS intake, advanced markers of hepatotoxicity, namely, osteopontin (OPN), HMGB1 protein (HMG-1; amphoterin) and glutamate dehydrogenase (GDH, GLDH), should be investigated. This choice of biomarkers was made because of an article published in 2020 in Frontiers in Pharmacology, in which the authors describe these biomarkers of hepatotoxicity, the challenges involved and future prospects [7]. OPN levels can predict liver fibrosis and also correlate with the degree of fibrosis, liver failure, portal hypertension and the presence of hepatocellular carcinoma [8]. GLDH is also a useful biomarker of hepatotoxicity, the determination of which can improve the diagnosis of hepatic cell injury [9]. Recent studies have also shown that HGMB1 is a key protein involved in the pathogenesis of acute liver injury and chronic liver disease [10].

2. Recommendations for Hepatotoxicity Testing of New Psychoactive Substances

The first recommendation concerns other substances taken with NPSs. The studies conducted to date on the effects of taking different types of NPSs are mainly based on single preclinical studies or on the examination of non-specific parameters such as AST, ALT and GGT. For this reason, it seems advisable to investigate the advanced markers of hepatotoxicity described in this research in patients abusing NPSs with other drugs or alcohol. In a study by Kravos et al., it was shown that GDH is a sensitive biomarker of alcoholism, the level of which decreases following the cessation of alcohol consumption [11]. Worner et al. showed that GDH levels showed an association with liver histology in patients who subsequently underwent diagnostic liver biopsy [12]. A 2021 review of OPN found that serum and liver levels of this biomarker are elevated in patients with alcoholic liver disease [13]. The same is true for HMGB1 expression levels correlated with alcohol consumption [14]. One of the main substances taken with NPSs, such as mephedrone, is alcohol [15]. Investigating the GDH levels in patients abusing NPSs with alcohol in relation to alcohol-only patients would help answer the question of whether it is the new psychoactive substance that has a hepatotoxic effect or whether it is, conversely, the alcohol consumed that has a greater negative impact on liver function. One of the most commonly taken substances along with NPSs is heroin. Addiction to this psychoactive substance is strongly associated with GDH type-1 polymorphisms. The dose of mephedrone used in the treatment of heroin addiction shows a relationship with the patient's respective GDH genotype [16]. In the studies to date on patients participating in a methadone programme due to heroin mephedrone abuse, it has been shown that one of the main factors increasing the risk of subsequent hospitalisation is HCV infection [3]. However, only simple liver enzymes were studied in that article. For this reason, GDH levels would need to be investigated in addition to relevant reference groups, including patients with HCV infection only. Among other things, this would make it possible to check whether or not liver function deteriorates with an increase in the dose of methadone taken.

The next recommendation is to investigate the effect of psychotropic drug use on the levels of advanced markers of hepatotoxicity in patients abusing new psychoactive substances. According to data published in Pharmacological

Research, one of the main factors increasing the risk of subsequent hospitalisation for patients abusing NPSs with other substances may be the polypharmacotherapy used. The use of a range of psychotropic drugs increases the risk of associated side effects, which may consequently hinder the therapeutic effect [17]. For this reason, it is advisable to test for advanced markers of hepatotoxicity before starting treatment in a patient taking a particular NPS and then several times during the course of the treatment being administered, while being mindful of whether the drug being taken may adversely affect liver function. This would make it possible to determine whether taking psychotropic drugs has an additional hepatotoxic effect or whether, on the other hand, worsened liver function was present during the patient's admission to hospital, i.e., before the implementation of treatment. Psychotropic drugs with potential hepatotoxic effects should not be used in patients with suspected liver abnormalities [18], and such patients may be NPS abusers. The same is true for investigating the effect of liver regeneratives taken that may reduce the risk of subsequent hospitalisation of the same patients [5].

Another recommendation is to test the levels of advanced markers of hepatotoxicity in patients abusing NPSs with co-occurring depressive behaviour. Psychoactive substance use may be related to the response to different types of stressful situations [19]. In published case reports of patients abusing NPSs, depressive disorders are often described [6]. In a review on HMGB1 levels, an association with depression-like behaviours that are similar to motivational deficits was found [20]. This biomarker appears to be a promising therapeutic target for the treatment of depression [21]. For this reason, one additional recommendation is to measure HMGB1 in patients taking NPSs, as its inappropriate levels may be responsible for an increased risk of depressive disorders. The group of patients abusing various types of NPSs is mainly male. One of the studies mentioned in this research indicates that a reduction in GDH levels was observed in men suffering from depression compared with a control group [22]. It is also worth noting that impaired fear memory and social interactions and the reinforcement of depression-like behaviours were observed in GluD1 gene knockout mice [23]. A study on 3023 marginalised, nocturnal and online NPS users found that they reported, among other things, increased medium- and long-term mental and physical problems and more social problems [24]. A similar recommendation applies to schizophrenia. An example herein is the case report of a patient who took NPSs such as 'el blanco' while on leave, which consequently contributed to the onset of schizophrenia relapses [25]. Schizophrenic patients have elevated levels of HMGB1 compared with controls. This is related to the strong association of the HMGB1 protein with schizophrenic behaviour [26]. Another argument is that in schizophrenic patients, baseline GDH levels may serve as a predictor of the efficacy of antipsychotic therapy [27]. Long-term use of antipsychotics compared with short-term treatment has a significant reductive effect on OPN levels [28]. For this reason, investigating advanced markers of hepatotoxicity in patients abusing NPSs could answer the question of whether their levels show statistically significant associations with the severity of psychiatric disorders.

Summarising the recommendations indicated above, it is recommended to investigate the indicated advanced markers of hepatotoxicity in patients abusing various types of NPSs with other substances in the future for several reasons. Firstly, with the inclusion of appropriate comparison groups, it would be possible to answer the question of whether it is indeed NPSs that exhibit hepatotoxic effects or whether it is the additionally ingested substances that do so. Secondly, due to the high prevalence of HCV infection in the patient group in question, a group of people with this type of infection only, i.e., not taking any psychotropic substances, should also be included in a future

study. Thirdly, investigating the effects of the psychotropic drugs used in patients abusing NPSs would allow researchers to check whether they have additional hepatotoxic effects and are therefore increasing the risk of subsequent hospitalisations for the same patients. One more argument pointing to the necessity of testing OPN, GDH and HMGB1 levels is to relate the results obtained to the patient's mental state measured with appropriate scales and questionnaires, thus increasing the chance of obtaining a therapeutic effect, such as patients stopping taking NPSs.

The limitations of the studies carried out so far lie primarily in the investigation of simple liver enzymes in patients abusing various types of NPSs. For this reason, it is difficult to determine the effect of their intake on liver function. It is essential that future studies take into account factors such as the pharmacotherapy used, additional psychoactive substances taken with NPSs, and HCV infection. Only then will it be possible to determine whether the various types of NPSs have a hepatotoxic effect or whether another factor plays a major role. Multiple hospitalisations due to NPS abuse pose a major public health challenge, and one important predictor may be inadequate liver function. For example, one study found that predictors of thirty-day re-hospitalisation in patients with decompensated cirrhosis included elevated liver enzymes and hepatic encephalopathy [29]. Another example includes taking opioids, which can contribute to chronic liver disease (CLD) and increase the risk of subsequent hospitalisations [30]. A 2019 article published in Frontiers in Psychiatry pointed out, among other things, that the chances of hospital readmission increase when multiple substances are taken concurrently, which is characteristic of NPS use [31]. In a 2017 article published in BMC Psychiatry, the authors found that in a group of people with substance use disorders, hepatitis C was associated with an increased risk of hospital readmission [32]. The use of polypharmacotherapy alone may cause subsequent hospitalisations because of hepatotoxic effects often resulting from drug interactions. A study by Kadra et al. found that antipsychotic polypharmacy increased the risk of hospital readmission within six months compared with patients who received monotherapy [33]. The concomitant intake of a number of NPSs with other substances showing hepatotoxic effects, combined with the adverse effects of multiple psychotropic drugs, can only further increase the risk of subsequent hospital admissions. This is all the more reason why the advanced markers of hepatotoxicity discussed in this research should be investigated in order to study the real impact of taking NPSs on liver function. Measurements should be taken several times starting from the moment a patient is admitted to hospital, during hospitalisation and ending with his discharge home. It is also important to bear in mind the necessity of supplementing patients abusing NPSs with liver regeneration preparations, as the proper functioning of this organ may subsequently contribute to improving the metabolism of the drugs taken and thus reduce the risk of subsequent hospitalisation.

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