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Liver Illness and Psychiatric Patients

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Abstract

Patients with psychiatric disorders are usually more exposed to multiple somatic illnesses, including liver diseases. Specific links are established between psychiatric disorders and alcohol hepatitis, hepatitis B, and hepatitis C in the population as a whole, and specifically in drug abusers. Metabolic syndrome criteria, and associated steatosis or non-alcoholic steato-hepatitis (NASH) are frequent in patients with chronic psychiatric disorders under psychotropic drugs, and should be screened. Some psychiatric medications, such as neuroleptics, mood stabilizers, and a few antidepressants, are often associated with drug-induced liver injury (DILI). In patients with advanced chronic liver diseases, the prescription of some specific psychiatric treatments should be avoided. Psychiatric disorders can be a limiting factor in the decision-making and following up for liver transplantation.

Keywords: Viral Hepatitis, Non-Alcoholic Fatty Liver Disease, Mental Disorders, Hepatotoxicity

1. Context

1.1. Introduction

The prevalence of liver disease in patients with psychiatric illness, particularly those receiving a long-term psychotropic treatment is not known. Severe psychiatric disorders (schizophrenia and related disorders, bipolar disorder, depressive disorder, etc.) are associated with metabolic syndromes and the afflicted patients are at high cardiovascular risk (1, 2). Repeated and long-term exposure to toxic substances (alcohol, tobacco, etc.), chronic viral hepatitis and use of psychotropic drugs and polypharmacy, can strain the detoxification functions of the body. All these have their own hepatic toxicity in addition to metabolic effects and may be responsible for liver damages (3).

1.2. Epidemiology

Serious mental illness concerns 240 million people worldwide (4). The definition of serious mental illness covers schizophrenia and schizoaffective disorders, psychosis, and mood disorders that require specific psychotropic treatments. The prevalence of serious mental illness is 4 - 6 cases per 1000 individuals, and 4% - 6% of the general population experience a serious mental illness at least one time in their life (4).

In patients with severe psychiatric diseases, mortality is two to three times higher than in the general population. Life expectancy is reduced due to somatic, particularly, cardiovascular diseases (2). This population is also exposed to metabolic syndrome and obesity.

Furthermore, screening, prevention, and follow-up may be difficult because of poor access to care, sometimes marginalization, and insufficient compliance with health programs.

2. Evidence Acquisition

To find relevant articles, a comprehensive search was performed on Scopus, PubMed, and Google Scholar and those papers with appropriate combinations of following keywords were considered: viral hepatitis, non-alcoholic fatty liver disease, mental disorders, hepatotoxicity, mental health, psychiatric treatments, addictions, and drug toxicity.

Recent articles were in priority. Primary sources were systematic reviews and original articles with the highest possible level of evidence.

3. Results

3.1. Psychiatric Patients and Viral Hepatitis

Historical papers demonstrated the propagation of Australia Antigen in institutionalized patients with mental

disorders living in promiscuity and unhealthy conditions (5).

More recently, it has been shown that hepatitis B and C prevalence is higher in psychiatric patients than the general population, probably because of frequent drug abuse (6).

In 2016, a meta-analysis showed that, in patients with severe psychiatric illness, pooled prevalence of hepatitis C was 17.4% (95% CI: 13.2 - 22.2) in North America, 4.9% (95% CI: 3.0 - 7.9) in Europe, 3.0% (95% CI: 1.8 - 5.0) in Central and South America, 4.4% (95% CI: 2.8 - 6.9) in Asia, and 3% (95% CI: 1.0 - 9.3) in Oceania (6).

The same meta-analysis described a hepatitis B prevalence of 2.2% (95% CI: 0.5 - 9.9) in North America, 2.7% (95% CI: 1.8 - 3.9) in Europe, 9.7% (95% CI: 0.6 - 15.3) in Asia, and 2.6% (95% CI: 1.0 - 6.1) in central and South America (6).

Hepatitis C occurrence is more frequent in patients with psychosis, but independent of the duration of hospitalization (7). New reports of hepatitis C transmission in psychiatric institutions are rare (8).

In the United States, preventive policies are applied on psychiatric patients who are at risk of infection. Moreover, the center for disease control and prevention (CDC) recommends HCV screening in high-prevalence population aged between 45 and 65 years ("baby boomers"), especially in the most exposed individuals, such as psychiatric patients (9). Among hepatitis C risk factors, schizophrenia, psychoactive substance abuse, injection-drug use, male gender, metropolitan area origin, age, and sexual behavior are frequently cited (10). Hepatitis B infection increases with age, high-risk sexual behavior, and urban locations, and varies in different countries (10).

Hepatitis C (11) but not hepatitis B (6) can be associated with psychiatric manifestations such as anxiety, psychosis, and mood disorders. Interferon treatment can be responsible for psychiatric disorders, which are the main cause of treatment discontinuation; hence, psychiatric disorders have to be screened before the introduction of interferon (11).

Psychiatrists are generally aware of Hepatitis C and B screening. Specific management is also well applied by nurses and doctors (12). Until recently, hepatitis C treatment in this population was difficult, due to the psychiatric side effects of interferon (13). Nevertheless, in patients with psychiatric and active drug abuse, interferon, when used with caution, demonstrated good results (11) and adherence (i.e. 87%) (14). Sparse data concerning the use of new direct antiviral agents in drug users are available: they are safe and give 93% sustained virological response, with 3, 5% relapsers and 3, 5% of reinfections. The estimated incidence of reinfection from the end of treatment to post-treatment week 12 was 10.6 (95% CI: 3.42, 24.6) per 100 person-years (15).

Nucleosidic (entecavir) or nucleotidic (tenofovir) analogues directed against Hepatitis B virus are efficient and have few side effects. Adherence has not been specifically evaluated in long-term in patients with psychiatric illness and drug abuse but it was estimated at 61% in the general population (16), enhancing the risk of drug resistance - even if the antiviral barrier of entecavir and tenofovir is high.

3.2. Psychiatric Patients and Consumption of Liver Toxic Substances

3.2.1. Alcohol Intake

Patients with chronic psychiatric disorders such as mood disorders and schizophrenia have more frequent excessive alcohol consumption than the general population (17). Alcohol is the first psychoactive substance used in patients suffering from severe mental illness (17). Disorders linked to alcohol are three times more frequent in patients with schizophrenia or bipolar trouble than the general population (17). Conversely, 50 to 70% of patients with alcohol dependence are suffering from severe mental illness (18). Alcohol is the main cause of cirrhosis in Western countries (19). Alcohol can worsen hepatic lesions from other origins and increases the incidence of hepatocellular carcinoma. Abstinence is the most efficient treatment in alcoholic cirrhosis. In Europe, 30 to 50% of liver transplantations are related to alcohol, whereas the percentage is much lower (17.2%) in the USA (19). Despite all the precautions taken, unfortunately, 18% of these patients experience severe relapse and one third of them show alcoholic cirrhosis recurrence (20). A multi-disciplinary approach to select and follow patients is crucial to reduce the risk of alcohol recurrence after liver transplantation. Patients with acute alcoholic hepatitis can be included in specific liver transplantation programs, but no recommendations are now available (20).

3.2.2. Other Drug Abuse

Cannabis, and to a lesser extent, tobacco smoke or methadone/buprenorphine use are well-known worsening factors of fibrosis in patients with hepatitis C (21). Endocannabinoids and their specific receptors, CB1 and CB2, may be involved in liver steatosis. CB1 receptor is present in the central nervous system and increases appetite, whereas CB2 is pro-inflammatory. CB1 can be overexpressed in case of obesity (22). A CB1 antagonist, named rimonabant, suppresses liver steatosis in mice (23), and decreases weight in adult patients (24). Nevertheless, due to the onset of psychiatric disorders and notably suicide ideation, rimonabant was withdrawn from the market.

Drug injection is a worldwide health problem concerning around estimated 16 million people (25) and is a main cause of hepatitis C and B transmission.

Ecstasy (MDMA: 3, 4-methylenedioxymethamphetamine) is a potential, well-known acute liver failure provider (26). Cocaine is less often associated with liver disorders (27). Even more rarely, ecstasy alone, or in association with cocaine consumption, may induce chronic hepatitis and cirrhosis (28). Heroin liver toxicity is probably linked to hypotension and/or hypoxemia induced by overdose, and may cause changes in liver sinusoids (29).

3.3. Liver and Psychiatric Disorders: Specific Situations

3.3.1. Wilson's Disease

Wilson's disease due to ATP7B mutation is characterized by copper overload, leading to acute or chronic liver disease and/or neurological or psychiatric disorders. About one third of patients present with psychiatric manifestations (30). Isolated psychiatric disorders can reveal the disease, which may remain undiagnosed (31). Liver manifestations in this situation are not symptomatic, and abnormal liver function tests or iconography may guide the diagnosis (30). If Wilson's disease is suspected in the setting of mental disorders, urine copper or blood-free copper and ceruloplasmin dosages should be performed. Relative exchangeable copper is an interesting diagnosis tool becoming available recently. In case of difficult diagnosis, liver histology is useful (30). One should evoke the diagnosis of Wilson's disease in case of concomitant abnormal liver tests and mental diseases. Specific treatment of Wilson's disease is key whether it is associated or not with psychiatric medications (30). Specific treatment (D-penicillamaine, trientine, zinc) is rarely ineffective except in case of delayed diagnosis (30). The use of neuroleptic drugs must be with caution because of the risk of potentiating extra-pyramidal symptoms. Liver transplantation improves psychiatric manifestations (32).

3.3.2. Liver Transplantation

Regardless of the indication for transplantation, the consultation with a psychiatrist is recommended in both the pre- and post-transplantation periods (33). Psychiatric complications such as mood disorders, alcohol abuse, substance intake, and social weaknesses (33) are observed in the post-liver transplantation setting. Mental disorders occur in 12 to 70% of liver transplanted patients, before and after liver transplantation (34). Presence of mental disorders alters the quality of life, treatment adherence, and survival (34). In HCV liver-transplanted patients, depression is linked to an increased mortality; but the risk of suicide remains rare (35). The psychiatrist role remains essential. Previous psychiatric disorders, alcohol or substance abuse, absence of psychosocial support, and neurocognitive side effects of immunosuppressive drugs are potential risk factors in the post-transplantation period (36). Furthermore, patients who suffer from depression before transplantation are more importantly at risk of acute rejection. The authors hypothesize that a lack of compliance with immunosuppressive medications is concerned. Access to liver transplantation may be limited for different reasons: non-adherence to ongoing treatment or to transplant medical team advices, irreversible severe cognitive impairment, primary psychotic disorders, self-destructive behaviors, and alcohol or other substances misuse (36).

In case of post-liver transplantation depression, the first classes of prescribed drugs are SSRI (selective serotonin recapture inhibitor) and SNRI (serotonin and norepinephrine reuptake inhibitor), which have a high therapeutic index and low risk of side effects (37). Interactions of the drugs with immunosuppressive agents are possible. Paroxetine and fluoxetine are CYP3A4 inhibitors that can increase calcineurin inhibitors (tacrolimus, cyclosporine) as well as m-Tor (mamellian target of rapamycin) inhibitors (everolimus) concentrations, leading to a cautious monitoring of immunosuppressant concentrations (37).

3.4. Suicidal Acute Drug Intoxication

Psychiatrists are largely involved in the management of voluntary drug intoxication with a goal of autolysis. The primary cause of these intoxications is acetaminophen (38). Liver toxicity linked to acetaminophen is dose-dependent. Acetaminophen is metabolized by the liver, and its metabolite, i.e. NPAQI (N-acetyl-p-benzoquinone imine), is toxic for the liver through depleting glutathione stores. Acetaminophen intoxication is linked to voluntary overdose in 63 to 86% of the patients (38). Another way is the regular consumption of high doses of acetaminophen in patients suffering from liver diseases (alcohol hepatitis, cirrhosis, virus, etc.) with glutathione depletion (39). The acute or chronic intoxication leads to acute liver failure and must be immediately diagnosed and treated with intravenous N-acetylcysteine, and, within the first hour, with activated charcoal (40). In case of late diagnosis and occurrence of irreversible fulminant hepatitis, liver transplantation is necessary, according to Clichy-Beaujon criteria (41) or more specifically to King's college criteria (42). Emergency liver transplantation in patients suffering from mental disorders or those with substance dependence is an ethical dilemma because it is difficult to predict post-liver transplantation compliance with specific treatments and risk of new voluntary overdose in these patients. Moreover, the time of decision making is too short.

3.5. Non-Alcoholic Fatty Liver Disease

Prevalence of metabolic syndrome and insulin-resistance is considered as a major health problem in western countries (43). Abdominal obesity, type 2 diabetes, hypertension, hypercholesterolemia, hypertriglyceridemia, and apnea syndrome are the main consequences. Liver disease, secondary to metabolic syndrome (steatosis, nonalcoholic steatohepatitis (NASH)) and their potential consequences (severe fibrosis, cirrhosis, and hepatocellular carcinoma) are under-diagnosed. NASH is independently associated with a doubling of cardiovascular mortality and extrahepatic cancers (43).

Steatosis occurs in 20% of the general population and is associated with NASH in 10% of cases (43). Advanced fibrosis and cirrhosis are present in respectively 15-30% and 3% - 5% of NASH patients (43). The gold standard for the diagnosis of non-alcoholic fatty liver disease (NAFLD), NASH, and fibrosis remains liver biopsy but non-invasive tests can also be useful (44). Steatosis can be diagnosed with ultrasound, CT-scan, MRI, and CAP (Controlled Attenuation Parameter), which the latter estimates the attenuation coefficient of ultrasounds by fat and is linked to vibration controlled transient elastography (VTCE) (45). NASH can be assessed by specific algorithms, often based on biomarkers (45). Fibrosis, mainly assessed by biological tests and VCTE, is prognostic (46). No data evaluating these tests for the screening of NAFLD, NASH, and fibrosis in patients with mental disorders are today available and this problem has to be solved as the prevalence of NAFLD is more frequent in patients with mood disorders. On the other hand, in NAFLD patients, the prevalence of depression and sometimes its severity is higher (47) than patients with other chronic liver diseases such as hepatitis B (48), except for hepatitis C and alcoholic liver disease (49). More recently, Youssef et al. (1) in a cross-sectional study on 567 patients with a biopsy-proven NAFLD showed that ballooning was higher in patients suffering from depressive symptoms. Other histological severity criteria, such as liver fibrosis, necrosis, and inflammatory cell infiltration are also present in patients with depressive features (47).

Weight gain during neuroleptic treatment concerns half of the subjects, particularly those treated with clozapine, olanzapine, quetiapine and and to a lesser extent risperidone (2).

Antidepressants (paroxetine) as well as mood stabilizers (lithium, valproic acid) are associated with a more moderate weight gain (2). The prevalence of metabolic syndrome (abdominal obesity, dyslipidemia, glucose intolerance, and high blood pressure) in schizophrenic or bipolar patients is 22% to 42% (2).

Experience acquired in schizophrenic and bipolar populations suggests a favorable impact of psychotropic drugs on metabolic disorders, as well as liver complications of metabolic syndrome. Cannabis consumption is also associated with steatosis and fibrosis in patients with hepatitis C (50).

On a physiopathological point of view, diabetes and insulin resistance have been associated with an increased risk of depression and anxiety (51) although it remains controversial. Other metabolism disorders, such as increased cortisol or epinephrine concentrations, which are more frequent in psychiatric patients, can promote insulin-resistance (52). Pro-inflammatory cytokines like tumor necrosis factor-alpha and interleukin-6 are involved in depressive disorders and NASH process (53). Serotonin pathway may also be a good candidate for the risk of NAFLD as it is involved in mitochondrial oxidative stress and hepatic lipids metabolism (54). In case of diabetes, serotonin pathway is altered, suggesting impaired neurotransmitter function or modified hypothalamic secretion (55). 5-HT, linked to the serotonin pathway, explains some mood disorders and is a target of specific medications. 5-HT synthesis may also modulate stress-induced liver events like fibrogenesis and ductular adaptation and may explain liver pathological features observed in depressive patients (1). Monoamine oxidase-A enzyme that catalyzes monoamines may play a role in cellular oxidative stress in NAFLD pathway (55).

3.6. Psychiatric Treatments and the Liver

3.6.1. Specific Liver Side Effects of Psychiatric Treatments

Liver specific damage of all medications needs more investigations that can lead to interruption of market authorization. Danan classification of toxicity criteria, including extrinsic criteria, based on anamnesis, and intrinsic criteria, corresponding to literature report and phamarcovigilance descriptions, should be used (56). Hy's law is a potential method to conduct investigation and, overall, predict mortality (57).

Pharmacovigilance sources are available on the web, for example on the Livertox database (http://livertox.nih.gov/). Moreover, interactions with cytochromes should be known before prescription. Particularly, carbamazepine, metabolized by CYP3A4, or valproate, metabolized by cytochromes and mitochondrial oxydase, is associated with toxicity in case of overdose.

3.6.1.1. Benzodiazepines

They are not classically responsible for liver toxicity. Cholestatic liver injuries are described but remain rare. In a Spanish multicenter recording report, liver toxicity of benzodiazepines was suspected in 20 cases, 5 with potassium clorazepate, 5 with alprazolam, 6 with lorazepam, and 4 with diazepam (58).

3.6.1.2. Antidepressants

Tricyclic antidepressants were classically used until the late 90's, and are largely replaced by new generations. Impipramine, amitriptyline, and chlorimipramine seem to be more often related to liver toxicity (59). Possible cross-toxicity between tricyclic antidepressants and phenothiazine is possible (60).

New generation antidepressants, such as SSRI and SNRI, are rarely toxic. Clinical presentation is a cytolytic hepatitis (61).

SSRIs mostly implicated in hepatitis onset are paroxetine, fluoxetine, sertraline, and citalopram (61).

SNRIs, described as hepatotoxic, are venlafaxine, desvenlafaxine, and nefazodone (62). Nefazodone market authorization has been consequently interrupted (61). Mirtazapine, monoamine oxidase inhibitors (MAOI), agometaline, a melatonergic antidepressant, and bupropion (61), a norepinephrine-dopamine reuptake inhibitor (NDRI), are rarely associated with liver injury.

3.6.1.3. Neuroleptics

Weight gain is associated with neuroleptic treatment, particularly with clozapine, olanzapine, and, to a lesser extent, quetiapine, risperidone, and aripiprazole (2). Neuroleptics are frequently associated with steatosis development (63).

Historical neuroleptics, phenothiazines - chlorpromazine - and butyrophenones - haloperidol - frequently gave elevated liver enzymes and, rarely, liver failure (64). Olanzapine and clozapine give elevated liver enzymes and rare acute cytolytic hepatitis (64). Quetiapine can be associated with cholestatic hepatitis and rare fulminant hepatitis (65).

Risperidone has been associated with non-severe elevated liver enzymes in 53% in a patient cohort of children and adolescents (mostly alkaline phosphatase) (66).

3.6.1.4. Mood Stabilizers

Valproate classically gives mitochondrial steatosis with potentially important damages, and also possible acute liver failure. Liver biological tests must be controlled carefully. Approximately, 5% of patients develop cytolysis during the follow-up (67). Rarely, Reye syndrome is described. Risk factors of liver enzymes elevation are young age, metabolic disorders, and neurological diseases (67). Hyperammonemia can also be seen in patients taking valproate, leading to hepatic encephalopathy in cirrhotic patients (68). Luef et al. (69) described a steatosis prevalence (detected by ultrasounds) of 61% in patients taking valproate. Valproate is not indicated in patients suffering from mitochondrial diseases.

Carbamazepine mostly gives cytolysis and less often cholestasis. DRESS syndrome (drug related rash with eosinophilia and systemic symptoms) and granulomatosis are less frequently reported in literature (70). Oxcarbamazepine can induce liver toxicity, generally included in systemic toxicity, like Stevens-Johnson syndrome (71).

Lamotrigine is reputed to give rare fulminant hepatitis. Follow-up of liver tests is required (72).

Other anti-epileptic drugs are safe in use and blood tests follow-up is not needed.

Lithium is not considered as hepatotoxic because of its renal elimination. Nevertheless, ascites, liver enzymes elevation, and hyperbilirubinemia are reported (61).

Other specific treatments, used in alcoholic diseases, such as nalmefene or acamprosate, even if metabolized by the liver, are not associated with liver injury. Baclofene (73) liver toxicity has been identified in only one report. Naltrexone is contra-indicated in patients with hepatic insufficiency; descriptions of mild liver enzymes elevation are also available (74).

Methadone and buprenorphine have exceptionally been implicated in liver toxicity. Interactions with other medications are potentially at-risk, because of their metabolism by CYP3A.

Inhibitors of acetylcholinesterase as well as glutamate inhibitors, which are used in patients suffering from dementia, can be rarely associated with liver toxicity (74).

3.6.2 Treating Psychiatric Disorders in Patients With Liver Diseases

The majority of psychiatric drugs are metabolized by the liver. Cytochromes play a central role and interactions between drugs are expected (37). According to pharmacokinetics characteristics, half-life and elimination, treatment doses must be adjusted or interrupted in most patients.

Anti-depressants are regularly used in patients with chronic liver diseases (37). SSRI pharmacokinetics is changed in case of cirrhosis, particularly in Child Pugh B or C cirrhosis: sertraline is particularly affected, with an increased half-life and a 70% reduction of the area under the curve (AUC) in cirrhotic patients (75). Paroxetine, fluoxetine, escitalopram, and citalopram AUCs are generally doubled in case of child Pugh A cirrhosis (75). Similar modifications are seen with selective noradrenergic reuptake inhibitors such as venlafaxine and duloxetine (37), with a high clearance alteration in child Pugh C patients. Other classes of antidepressants show identical pharmacokinetics disturbances in cirrhotic patients (37). Because of their safe profile, SSRIs are the most prescribed drugs in patients with cirrhosis (76). However, caution should be taken as SSRI can increase gastric acidity and platelet dysfunction,

leading to bleeding ulcers in case of concomitant anti-platelet or non-steroid anti-inflammatory drug prescription (76). In cirrhosis, short half-life benzodiazepines such as oxazepam are privileged. Benzodiazepines prescription must be avoided in cirrhotic patients as they may trigger encephalopathy (68). Pharmacokinetics of neuroleptics is not generally changed in mild cirrhosis (77). However, metoclopramide AUC increases by 50% in cirrhosis (75). Obviously, neuroleptic agents can worsen or induce encephalopathy in patients with advanced cirrhosis or acute liver failure (78).

Pharmacokinetics of donepezil, an inhibitor of the acetylcholinesterase enzyme, is not influenced by liver cirrhosis (79).

Among anti-epileptic agents, valproate must be avoided in patients with liver lesions, especially in alcoholic disease. Carbamazepine must be used very carefully because of its liver metabolism (70).

4. Conclusions

Psychiatric disorders and liver illnesses are entangled in multiple ways. Screening for liver diseases like viral hepatitis and steatohepatitis is essential because of the availability of lifestyle and dietary rules and potential treatments, and the possible screening and prevention of liver complications. Bridges between mental disorders and specific liver diseases are possible. Psychotropic medications are potentially at liver risk particularly in cirrhotic patients and their prescription must be carefully. Drug interactions have to be evaluated since the metabolism of psychotropic drugs is mainly hepatic. Finally, these drugs may induce per se metabolic syndrome and its related liver disease, steatohepatitis.

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Footnote

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Table 1. Inspired From Selim & Kaplowitz (79), Stewart & Levenson (80)

Medications and drugs	Potential Toxicity	Type of Injury	In Hepatic Insufficiency
Benzodiazepines	Rare	Cytolytic or cholestatic	Induce or aggravate encephalopathy
Mood stabilizers			
Valprate	+	Steatosis, mitochondrial toxicity	Contra-indicated Careful prescription
Carbamazepine	Rare	Idiosyncratic	
Lithium	Rare	Hyperbilirubinemia	Can aggravate liver function
Anti-depressants			
Tricyclics	+	Idiosyncratic, more rarely hypersensitivity	Change of dose or interruption in the majority of treatments
SSRI	+	Generally cytolytic injury	
SNRI	+		
Buproprion	Rare	Essentially risk of steatosis (clozapine, olanzapine ++)	
Neuroleptics			Generally contra- indicated in patients with decompensated cirrhosis
Phenothiazines	++	More rarely, idiosyncratic or hypersensitivity	
Butyrophenones	+		
Clozapine	+		
Olanzapine	+		
Quetiapine	Rare		
Risperidone	Rare		
Others			
Naltrexone	Rare	Rarely, cytolytic injury	Generally no risk
Acamprasoate	Rare	Rarely, cytolytic injury	Generally no risk
Acetylcholinesterase	Rare	Rarely, cytolytic injury	Generally no risk
Inhibitors			
Buprenorphin/methadone	+	Cytolytic injury essentially	Possible with cautious
Ecstasy	++	Cytolytic injury essentially	To avoid
Cocaine	++	Risk of ischemia, cytolytic injury essentially	To avoid