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DRUG-INDUCED LIVER INJURY (P HAYASHI, SECTION EDITOR)

Spectrum of Drug Induced Liver Injury Caused by Anabolic Androgenic Steroids Abuse

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Abstract

Purpose of Review Potent anabolic androgenic steroids (AAS) are often illegally present in commercially available body building supplements (BBS) and may cause drug induced liver injury (DILI) with different phenotypes.

Recent Findings AAS induced DILI typically presents with a prolonged cholestatic liver injury with pruritus and a typical enzyme pattern of elevated transaminases that rapidly fall as alkaline phosphatase slowly increases. Liver biopsy reveals bland cholestasis that usually does not have chronic sequalae. Pathophysiology is unknown and genetic variants in genes associated with cholestatic syndromes were observed in a minority of patients. Chemical analysis of BBS have identified controlled AAS, which were not documented on the label.

Summary More frequent use of BBS in males to enhance physical performance is predicted to increase the incidence of cholestatic DILI. The typical presentation of AAS induced liver injury in an at risk populations should prompt careful assessment of BBS exposure.

Keywords Herbal · Dietary · Supplement · Bodybuilding · Hepatotoxicity · Jaundice

Abbreviations

AAS	Anabolic Androgenic Steroids
AKP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BBS	Body building supplements
DEA	Drug Enforcement Agency
DILI	Drug induced liver injury
DILIN	Drug induced liver injury network
FDA	Food and Drug Administration
GGT	gamma glutamyl transpeptidase
HDS	Herbal and Dietary supplements
NIH	National Institutes of Health
NRH	Nodular regenerative hyperplasia
RUCAM	Roussel Uclaf Causality Assessment Method
T Bili	Total Bilirubin
ULN	Upper limit of normal

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Introduction

The increased reports of liver injury due androgenic anabolic steroids (AAS) parallels the growing use of herbal and dietary supplements (HDS) overall. Indeed, AAS and bodybuilding supplements (BBS) make up the lion's share of reported HDS related liver injuries in the US. This increase use can be partly explained in the United States by the Dietary Supplement Health and Education Act of 1994, in which herbal and dietary supplements were deemed to be foods and did not require FDA approval for marketing. Thereafter sales of HDS agents flourished in a mostly unregulated and financially lucrative market. HDS sales nearly quadrupled from $9.6 billion in 1994 to $36.7 billion in 2014 [1•]. In addition, AAS were generated with minor modification in their structure to circumvent the DEA regulation of controlled substances. Sources of AAS are readily available for purchase from online providers, which may include AAS intended for veterinary use.

This rise in AAS sales is being particularly fueled by the increasingly recognized body-image distortion among males, particularly young men and adolescents [2]. A 2014 survey study suggested that 6.5% of 16–18 year old boys had body image concerns and used BBS or AAS to address perceived deficiencies [3]. This figure rose to over 8% for 19–22 year olds. Therefore, both adult and pediatric clinicians should be familiar with liver injury from AAS.

Overview of Androgenic Anabolic Steroids

History

Testosterone was initially isolated in 1935 and soon thereafter methods for its synthesis were established by Butenandt and Ruzicka [4]. The initial medical uses of anabolic androgenic steroids (AAS) in the 1940s focused on their endocrine properties for treatment of delayed puberty, hypogonadism and erectile dysfunction [5•]. Given their properties of bone marrow stimulation, AAS are still routinely used for the treatment of hypoplastic anemias [6]. In addition, their anabolic properties have been used for the treatment of chronic wasting conditions including late stage AIDS [7].

Anabolic androgenic steroids (AAS) were initially introduced for muscle building during the early 1950s when the Soviet weightlifting team began using them to enhance individual performances [8]. Over the next decade, AAS supplementation moved onto other sports that required increased muscle strength with a well described systematic program of anabolic steroid doping used by the German Democratic Republic in the 1960s. Ultimately, in 1967, the use of AAS supplementation was banned by the Olympics and other athletic associations leading to the current age of its clandestine use with several high-profile doping scandals such as sprinter Ben Johnson in the 1988 Olympics to more recently the renowned road racing cyclist, Lance Armstrong in 2013.

Physiologic Effects

AAS have both anabolic effects and androgenic effects. Anabolic effects include increase in skeletal muscle growth, body weight and fat-free mass. Supraphysiologic doses of testosterone can increase skeletal muscle strength, fat-free mass, and overall body weight [9]. Androgenic effects include development of male sexual characteristics including deepened voice, increased hair and virilization of genitalia [10].

Chemical Modifications of Testosterone

As orally administered testosterone is rapidly metabolized by the liver, chemical modifications were generated to increase its bioavailability and potency such as esterification of injectable testosterone to allow for delayed release or C-17 alpha alkylation or alkylation of the A, B or C steroid rings to permit effective oral administration of androgens [11]. These differences in the chemical structure also altered the relative potency of their anabolic or androgenic effectiveness, which can be assayed by the relative increase in levator ani muscle weight as compared to the ventral prostate weight in rats treated by these AAS [12, 13]. Thus, unique AAS could then be used for treatment of specific medical conditions based on their relative potency of their anabolic or androgenic effects.

Prevalence of AAS Use

The prevalence of AAS use in the non-prescription market is difficult to assess. While most AAS are banned from over-the-counter use, they are easily obtained in body building supplements (BBS) either online or at nutritional supplements stores. Overall, roughly 1% of the US population is estimated to have used these substances suggesting 2.9–4.0 million users [14, 15] with the highest prevalence observed in 12th graders [16]. There is a significant male predominance with male/female ratios of 8:1 to 50:1 reported in some studies [17]. These studies also noted that younger users often use other illicit substances prior to AAS and suffer from poor body image. The older users are typically highly educated, professional males who are motivated by the desire to increase skeletal muscle mass for physical attraction [18].

Non-hepatic Adverse Effects of AAS

Besides their direct hepatic effects, AAS also have a broad spectrum of adverse effects that should lead the clinician to consider AAS use [10]. Such knowledge of this clinical spectrum may be particular useful when assessing a liver injury but the patient is reluctant to divulge their AAS use. Several common side effects are directly related to their androgenic potency. In women and children, AAS can lead to masculinization including increased hair growth and baldness. In contrast, in men they can lead to testicular atrophy, potency problems and gynecomastia in part due to aromatization of testosterone to estradiol. Cardiac adverse effects, much of which appear irreversible, occur with long term use of AAS. Myocardial remodeling, coagulation abnormalities and atherogenic lipoprotein profiles increase the risk of cardiac arrhythmias, infarctions and early cardiac deaths [19, 20].

There are also significant neuropsychiatric effects of AAS that can vary with dosage used. At low doses, the spectrum of behavior varies from mild irritability to hypomanic [21]. At higher doses, AAS users can meet criteria for major mood disorders (bipolar and major depressive disorder) [22]. Muscle dysmorphia, a subclassification of body dysmorphic disorder, is frequent among AAS abusers [23]. Finally, the

psychoactive effects of AAS have been shown to build dependence leading to other long term adverse effects [24].

Anabolic Androgen Steroid Associated DILI

Epidemiology

The true prevalence of DILI due to AAS is difficult to ascertain as patients may not be candid to disclose use of such products to physicians or the physicians may fail to ascertain their use. Further, increased prevalence of concurrent substance use particularly alcohol and other high-risk behaviors in this population (predominately young men) along with inaccurate description or labeling of the AAS species can makes it difficult to make a diagnosis of DILI and identify the offending agent.

Despite these diagnostic challenges, liver injury due to herbal and dietary supplements (HDS) is common in prospective studies with their prevalence increasing. The only national estimate is a population-based survey from Iceland in 2012 with 16% of DILI due to HDS [25]. This estimate is similar to that observed in the NIH-funded Drug Induced Liver Injury Network (DILIN), in which 130 (16%) of 839 DILI cases were related to HDS with the proportion increasing from 9% to 19% between 2004 and 2005 and 2010–2012 [26]. Among the 130 HDS cases, 45 (35%) were attributed to body building supplements BBS, making them the largest class within the HDS category of agents.

Patterns of DILI

DILI with AAS

AAS related DILI in most cases is idiosyncratic and may depend on its chemical structure, mode of administration, dosage and duration of use. Features of DILI due to AAS are summarized in Table 1**.** To evaluate abnormal liver chemistries in DILI, upper limit of normal (ULN) for alanine aminotransferase (ALT) is defined as 33 IU/L for males and 25 IU/L for females and ULN for alkaline phosphatase (AKP) is defined as 128 U/L in males and 104 U/L in females [27•].

The commonly recognized and distinct pattern of injury with AAS induced DILI is a severe cholestasis syndrome with almost all presenting with jaundice and most with pruritus. The largest prospective evaluations of well characterized BBS associated DILI patients are from the Spanish and Latin American DILI and US DILIN registries. In the combined Spanish and Latin American DILI study, 25 males with a mean age of 32 were described and AAS were used to increase muscle mass and to improve physical appearance with approximately 75% of AAS being orally administered [28]. Based on initial ALT, patients were defined as either hepatocellular or cholestatic. All cholestatic patients (mean ALT 3.9 x ULN) had jaundice at presentation with a mean total bilirubin (T Bili) of 17.3 x ULN, while 87% of those categorized as hepatocellular injury (mean ALT of 19.1 x ULN) had jaundice at presentation with a mean T Bili of 8.7 x ULN. Mean AKP in both groups was only 1.2 ULN (range 0.5 to 3.1). There was no significant difference in mean time of onset of those presenting with hepatocellular injury (84 days) as compared to those with cholestatic injury (54 days) and resolution of injury took an average of 150 days. All patients consumed AAS with stanazolol being the most common.

The NIH DILIN experience with 44 patients was similar in latency, amount of jaundice, and gender, but differed in presenting enzyme elevations [29•]. The DILIN also reported more details on the course of enzyme elevations and provided genetic analysis and detailed chemical analysis of available BBS taken. All patients were male and the median latency to onset was similar at approximately 77 days with all patients presenting with profound jaundice (median serum T Bili of 9.8 mg/dL). The clinical course was typically prolonged with sustained pruritic jaundice for up to 12 weeks after onset. Only 40% of patients presented with hepatocellular injury compared to 60% in the Spanish and Latin American cohort. Liver enzymes were not significantly elevated with ALT highest at presentation at up to 5–8 x ULN that rapidly fell over the first two weeks while the AKP was usually normal at presentation and then rose to 3–4 x ULN, peaking over the first 6 weeks as shown in Fig. 1a. Thus, the DILIN study documented a transition from hepatocellular injury pattern early on to a more cholestatic pattern. As with the Spanish study, 70% of subjects in the DILIN study were hospitalized. There were no episodes of hepatic failure similar to the Spanish report and only six of the patient had an INR elevation greater than 1.5 without evidence of hepatic decompensation during the course of injury. In point of fact, persistently elevated INR or hepatic decompensation justifies workup for concomitant causes of other liver disease. Surprisingly, the gamma glutamyl transferase (GGT) when tested in the DILIN cohort were typically normal, which is unusual in typical cholestatic disorders.

The chemical analysis of the 33 recovered BBS taken by 14 subjects revealed significant inaccuracy in the chemical composition. At least one anabolic steroid was identified in 14 BBS provided by nine of the 14 patients but not in 19 supplements from the remaining five. The labels often did not accurately reflect the chemical structure of the components as 17 of the 21 BBS contained anabolic steroids that were different from those listed on the label, and 12 of the steroids listed on the labels were not identified by chemical analysis. Such discrepancies have been previously reported [30].

Lastly, Anabolic androgenic steroids injury can also present with an asymptomatic transient hepatocellular enzyme

Table 1 Drug induced liver injury (DILI) and other manifestations due to Androgenic Anabolic Steroids (AAS)

DILI by AAS indication/use	Latency	Liver Enzyme Pattern	Complications	Course/Prognosis
Treatment for Aplastic anemia	~ 12 weeks	↑ALT, ↑AST, normal AKP	none	Resolution in a few weeks with no dosage adjustments needed
Appearance and Performance Enhancment	~12 weeks	Early: ↑↑ T Bili, ↑↑ALT with nl ALP, Peak: ↑↑↑ T Bili, nl ALT with ↑ ALP	none	Resolution in 3–6 months of onset, concomitant renal dysfunction has been described
Other Hepatic Manifestations	Latency	Liver Enzymes	Complications	Course/Progosis
Peliosis Hepatis	Months to Years	usually normal	Hepatic rupture	Some regression with stopping AAS
Adenomas	Years	usually normal	Tumor rupture	Some regression with stopping AAS
Hepatocellular Carcinoma	Years	usually normal	Metastasis	Cancer progression and behavioral dependency issues

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline Phosphatase

elevation, which can routinely develop during androgen therapy for hematologic disorders such as danazol for treatment of aplastic anemia [31]. Patients may present with variable transaminase elevation, and the clinical course is usually self-limiting with neither significant hepatic dysfunction nor the need for dose adjustment. (Table 1).

Hepatic Manifestations of Long Term AAS Use

The long-term use of AAS can cause three distinct patterns of liver injury: 1) vascular changes known as peliosis hepatis, 2) liver tumors (both benign and malignant) and 3) rarely nodular regenerative hyperplasia (NRH). In contrast to acute DILI which more commonly occur with oral intake, these effects can occur with any route of administration.

Peliosis hepatis is a rare complication of blood-filled sinusoids and cysts in the liver [32]. It is most commonly found as an incidental finding on hepatic imaging and can be accompanied with peliosis of the spleen. Peliosis hepatis usually develops only after long term medical AAS use or in professional bodybuilders, who present with right upper quadrant pain due to hepatomegaly. The greatest concern is hemorrhagic shock due hepatic rupture with hemoperitoneum [33]. Symptoms and the degree of peliosis can be improved with cessation of AAS use [34].

Hepatic tumors are the most serious consequences of prolonged AAS use. Hepatic tumors can include adenoma, hepatocellular carcinoma and rarely cholangiocarcinoma or angiosarcoma [35]. Most reports are in patients with Fanconi's anemia or other causes of aplastic anemia in which other risk factors for liver injury are present including multiple transfusions that may have exposed patients to viral hepatitis or iron overload. However, there are several reports of HCC and large hepatic adenomas developing in body builders [36–38]. These patients typically present with right upper quadrant discomfort and the alpha-fetoprotein is usually normal. Similar to peliosis hepatis, cessation of AAS use can lead to some regression in adenomas [39–41]. NRH is a rare long-term complication of AAS use and has not been shown to progress to clinically significant non-cirrhotic portal hypertension [42].

Other Complications of DILI with AAS

Renal dysfunction, defined by a serum creatinine >1.5 mg/dL, has been described in AAS DILI presenting with a cholestatic pattern. The underlying mechanism has not fully been elucidated and this injury is also idiosyncratic. The implicated mechanism may be directly related to the chemical compound consumed [43] or possibly due to direct nephrotoxicity of bile acids [44•, 45]. Another potential complication can be ischemic hepatitis related to AAS cardiomyopathy that can be treated by stabilizing the underlying heart failure [46].

Mechanism of DILI with AAS

AAS predominately activate the intracellular androgen steroid receptor that then binds to nuclear hormone responsive genomic elements and influence transcriptional activity of androgen stimulated genes for cell growth and other pathways [47]. For some AAS, 5α-reductase can convert testosterone to dihydrotestosterone causing increased androgenic potency. This mechanism may potentially explain the risk of hepatic tumors and nodular regeneration in those taking testosterone preparation. The pathophysiology responsible for cholestatic jaundice associated with AAS is unknown. As these patients in the DILIN experience presented with profound cholestasis with often normal GGT and a bland cholestasis on liver biopsy, a concerted effort was made to identify genetic variants in *PFIC 1*, *2* and *3* genes, which are responsible for these genetic cholestatic disorders [48]. Despite using both whole genome sequencing and chip based discovery of known variants in these genes, there was no significant enrichment of any pathological variants identified in this patient population [29•].

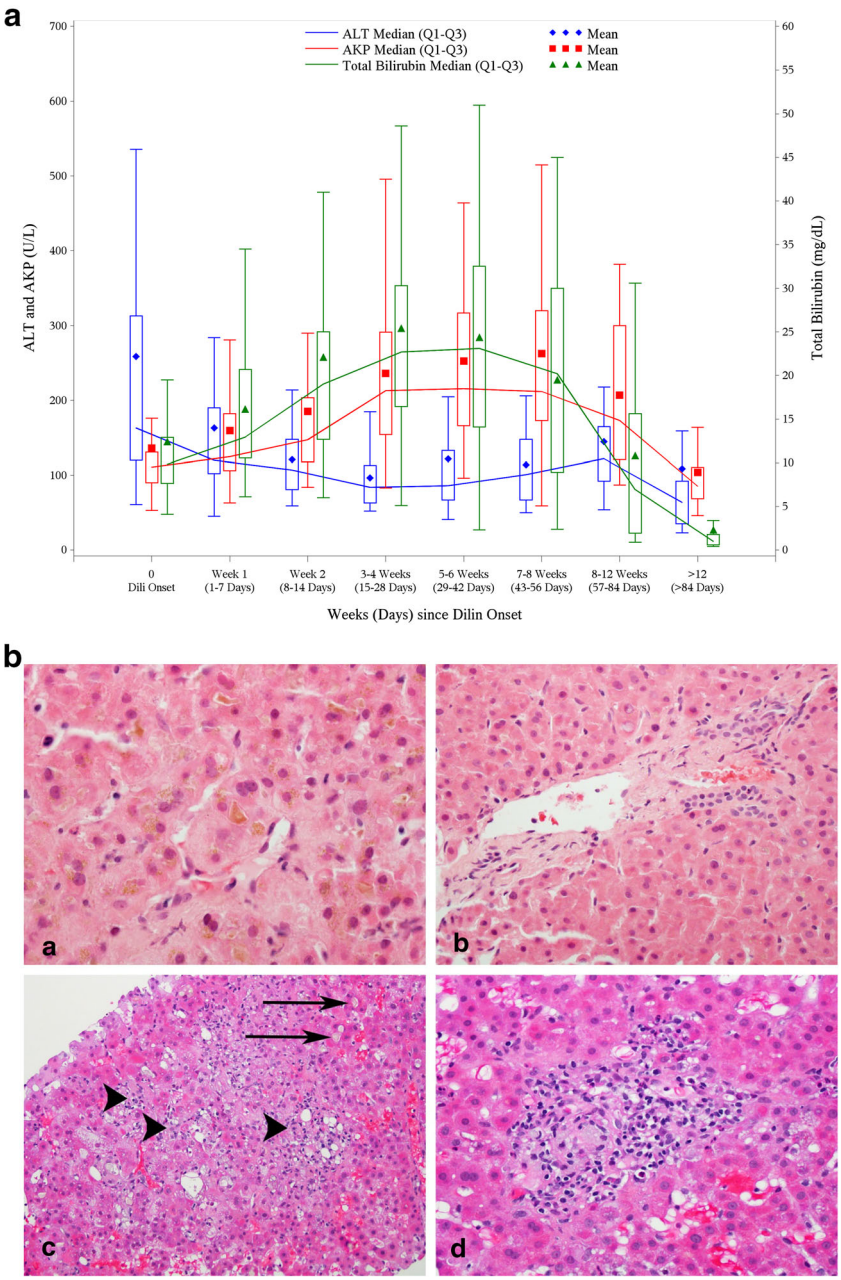

Fig. 1 **a** Median total bilirubin (mg/dL) (μmol) or Alk Phos (AKP) and ALT activity in U/L plotted over time in weeks after presentation [29]. The lines connect the median values over time for each serum test. The numbers of subjects at different time period for ALT are as follows (with about ±1 for the other serum tests): 44 at onset (day 0); 36 at week 1; 31 at week 2; 35 for week 3–4; 29 for week 5–6; 22 for week 7–8; 23 for week 8–12; 36 for >12 weeks. Mean values are depicted as symbols inside the box with the top and bottom of the box representing the 25 and 75 percentiles, respectively. **b.** Histological findings in anabolic steroid DILI. Anabolic androgenic steroid liver injury is classically associated with bland cholestasis. There is canalicular and hepatocellular cholestasis with little or no lobular inflammation (A), and portal areas have a normal appearance without inflammation (B). (H&E, 600× and 400×, respectively). Most of the cases in this report had mild inflammation [29]. Multiple small foci of lobular inflammation (arrowheads) are seen along with canalicular cholestasis (arrows) (C). The portal areas of this case also show inflammation (D)

Diagnosis of AAS DILI

Initial Diagnostic Approach

Given the different patterns of AAS DILI, an individualized approach to diagnosis should be taken. The diagnosis of DILI is considered after other more common causes of liver injury are excluded. By convention, every DILI patient should have a careful history and physical exam to evaluate for risk factors for liver disease and for any stigmata of chronic liver disease with a close attention for consumption of all medications and supplements. All patients should be evaluated for risk of concomitant alcohol, viral or autoimmune liver diseases. Additionally, patients should undergo imaging to asses for biliary obstruction given the profound cholestatic presentation or evidence of chronic liver injury. In patients with chronic use, hepatic imaging may be necessary to exclude AAS hepatic tumors. If DILI is suspected, the Roussel Uclaf Causality Assessment Method (RUCAM) scale can be useful for adjudicating causality if no other resources are available [29•, 49]. Clinicians are encouraged to access the LiverTox website (https://livertox.nlm.nih.gov/), a freely available online resource provided by the Liver Diseases Research Branch of the National Institute of Diabetes and Digestive and Kidney Diseases and the National Library of Medicine, to access

free and comprehensive reviews about specific drugs and HDS agents including AAS that are reported to cause DILI [50•].

Role of Liver Biopsy

Liver biopsy usually has a mixed pattern of hepatocellular and cholestatic injury with mild inflammation [29•]. In patient without other causes of liver injury, there is no bridging fibrosis or confluent necrosis, significant duct loss or portal fibrosis. Paralleling the elevated serum bilirubin, there is typically some degree of cholestasis. Fig. 1b illustrates common histologic findings on liver biopsy. Depending on the chronicity, NRH or peliosis may also be noted on the liver biopsy. Given the distinct clinical and laboratory pattern of liver injury in patients with BBS DILI, liver biopsy is recommended only in those patients where another competing diagnosis is being considered or to assess for underlying severity or chronicity of liver disease.

Confirmation of Diagnosis

As the diagnosis of DILI is based on exclusion of other causes of liver injury, the RUCAM scale can be used to identify a causal relationship between AAS use and liver damage in cholestatic DILI. In the DILIN experience, all cases scored definite or highly probable on the RUCAM scale [29•]. Additionally, in difficult cases where either the patient is not forthcoming, or the offending product is not obvious, further evaluation can focus on an endocrine evaluation of exogenous androgens as evidence for AAS exposure or by a chemical analysis of either supplements or biospecimens from the patient. The endocrine evidence of exogenous androgens can include measuring follicular stimulating hormone and luteinizing hormone levels that will be downregulated with exogenous AAS use [51]. Given large observed differences in urinary concentration of testosterone, a ratio of testosterone to epitestosterone glucuronides greater than 2 can also suggest exogenous use of testosterone [52]. Chemical analysis is usually performed using either gas chromatography with mass spectrometry or liquid chromatography with mass spectrometry [53]. Chromatography separates the different components based on their chemical properties and mass spectroscopy can identify specific chemicals based on their ionic mass-to-charge ratio. These analyses can be performed on suspected supplements in specialized laboratories and are routinely performed in anti-doping athletic programs on serum, urine or hair samples of athletes [54].

Management

As DILI with AAS can present with various patterns, the primary treatment is prompt identification and complete cessation of use of the offending substances. Those with pruritic cholestasis may benefit from symptomatic therapy with anion exchange resins, naltrexone or other medical therapies for pruritus. Those with prolonged cholestasis should receive fat soluble vitamin supplementation. Lastly, education and psychological care to evaluate those at risk of underlying body dysmorphic disorder should be provided to avoid recidivism.

Conclusions

The health impacts of AAS use as with other HDS is substantially underreported, on the rise and often unrecognized by health care professionals. The challenges to diagnosis AAS DILI are patient non-disclosure (willful or not) of AAS use, and the clinician's limited awareness of this common DILI, leading to failure to recognize the clinical picture and discover of AAS use. Such failure to recognize can be mitigated because this particular DILI carries signature characteristics that lend themselves to pattern recognition. Astute clinical identification coupled with a history of AAS use will often make the diagnosis and obviate the need for liver biopsy.

Thus patients, particularly young men, presenting with a profound cholestatic syndrome, jaundice and a normal GGT should routinely be asked about the use of BBS or AAS. Signs of AAS use on physical exam (e.g. increased muscle mass, testicular atrophy) should be sought. The clinician should not be distracted from the diagnosis by concurrent renal insufficiency or failure. The early recognition of this distinct pattern of AAS DILI should lead to early discontinuance of the offending agent and reduction in morbidity. While morbidity can still be significant, mortality is distinctly rare in these acute injury cases. Unusual vascular liver injuries (e.g. peliosis hepatis, rupture) and tumors should prompt consideration of chronic injury and a search for long-term use of AAS. Unfortunately, there are no characteristics to predict injury among the large number of AAS users. The idiosyncrasy of the injury remains unexplained though research into genetic markers continues. For now, we are left with early recognition, supportive care and education of the patient and public to prevent recurrences and new cases.

Compliance with Ethical Standards

Conflict of Interest Varun Takyar and Andrew Stolz each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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