

# EXPERT OPINION

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## Propylthiouracil, and methimazole, and carbimazole-related hepatotoxicity

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**Introduction:** Propylthiouracil (PTU) has been used for the treatment of hyperthyroidism since the 1940s, but over the years reports of significant hepatotoxicity have come forth, particularly in children. This led to a black box warning being issued by the US FDA in 2009, followed by a similar warning by the European Medicines Agency and the United Kingdom Medicines and Healthcare Regulatory Agency later that year.

**Areas covered:** This article provides a concise review of the data on hepatotoxicity associated with the currently available antithyroid drugs: PTU, methimazole (MMI) and carbimazole. The differences in mechanism are examined in detail, as well as clinical presentation, management and monitoring. Use in special populations and trends in use of antithyroid medication are also discussed.

**Expert opinion:** PTU is known to cause severe hepatic failure, particularly in children. Its use in children should be avoided. In adults, it is beneficial to use in the first trimester of pregnancy and thyroid storm. In the rest of the adult population, it should be used with caution. Carbimazole and MMI are associated with less severe hepatic injury and should be preferred when choosing thionamides as a treatment option.

**Keywords:** carbimazole, hepatotoxicity, methimazole, propylthiouracil

*Expert Opin. Drug Saf. [Early Online]*

### 1. Introduction

The antithyroid thionamide drugs, propylthiouracil (PTU), methimazole (MMI) and carbimazole (CBZ), remain one of the mainstays of treatment for Graves' disease worldwide and can also be used for the treatment of other causes of hyperthyroidism, such as toxic nodular goiter. The overall incidence of hepatotoxicity with any antithyroid medication is < 0.5%, but published evidence now shows an increased risk of serious liver injury associated with one of the thionamides, PTU, with a higher prevalence in the pediatric population [1]. Because of this, CBZ and its active metabolite, MMI, are now the preferred antithyroid drugs except in select circumstances. In the following sections, we will review the literature that has emerged regarding the prevalence, mechanism and clinical presentation of thionamide-induced hepatotoxicity, as well as the limited data available to guide monitoring and management.

### 2. Methods

Literature search was conducted in the Medline database using the keywords 'propylthiouracil', 'methimazole,' 'carbimazole' and 'hepatotoxicity'. Additional searches were also conducted in particular with prior keywords in addition to specifics including 'mechanisms,' 'monitoring' and 'management' of hepatotoxicity. Once these data were collected, searches using the keywords and special populations

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**Article highlights.**

- Comparison of hepatotoxicity caused by propylthiouracil (PTU) and methimazole (MMI) with emphasis on mechanism, presentation and management.
- PTU is associated with more severe hepatotoxicity and worse outcomes in children compared with adults. The use in children is not recommended.
- Drug regulatory agencies issued warnings in 2009 about hepatotoxicity with PTU and recommendations to limit its use.
- PTU remains the preferred treatment in the first trimester of pregnancy as MMI causes more significant embryopathy.

This box summarizes key points contained in the article.

(children, pregnant females, breastfeeding population and during thyroid storm) were conducted.

Use of papers was limited to those that were published in the English language. Preference was given to more recent data. Cohort studies and cross-sectional studies received precedence over case reports. The US FDA website was also used to follow the sequence of events and the date the black box warning was issued.

### 3. PTU and hepatotoxicity

Over the years the most serious side effect that has been linked to PTU is hepatotoxicity. After PTU was in use for six decades, the FDA issued a black box warning about hepatotoxicity on the PTU drug insert.

It is estimated that 1 in 10,000 adult patients prescribed with PTU will develop hepatotoxicity [2]. In children, the incidence of severe hepatotoxicity is higher, with an estimated 1 in 2000 children developing liver dysfunction.

In a case series of 35 patients, 8 deaths were linked to hepatotoxicity from PTU. The average age was 28 years and no dose-dependent relationship was found [3].

Looking at liver transplant data, PTU has been identified as the cause of multiple liver transplants, whereas MMI has not. In total, 51,741 cases of liver transplant were studied between the years of 1990 and 2002 [4]. Also, 270 patients were identified as having a drug-related cause of liver failure. PTU was the third most strongly linked medication to liver transplants at 9.4%. No cases involving MMI were reported in this study.

Mortality from PTU-induced hepatotoxicity is estimated to be 25% [3].

#### 3.1 Mechanism

The exact mechanism behind PTU-induced hepatotoxicity is not clear.

Various mechanisms have been proposed including inhibition of glucuronyl transferase, reduced bile acid synthesis and increased oxygen consumption by hepatocytes [5-7]. Liver biopsy and postmortem examinations have revealed various

degrees of inflammation and liver necrosis. Histological findings of plasmacytic, eosinophilic and lymphocytic infiltrates have been identified along with variable stages of necrosis [8]. The eosinophilic infiltrates are indicative of drug or autoimmune reactions [3]. Case reports with liver biopsies done during the course of liver failure where viral etiologies and other secondary causes were ruled out have demonstrated centrilobular necrosis and ceroid granules consistent with drug-related injury [9].

In studies in which lymphocyte sensitization testing was performed, patients with positive results and hepatotoxicity were thought to have an autoimmune or idiosyncratic reaction leading to liver injury [2,10-15]. These are believed to be dose-independent reactions.

In a patient who had multiple liver biopsies, one biopsy done 2 years after the onset of symptoms showed that liver architecture had returned to normal with no inflammatory activity. In this patient, biochemical markers normalized before histological evidence of inflammation resolved [16].

#### 3.2 Clinical presentation

Hepatotoxicity induced by PTU manifests with various clinical presentations.

Nakamura *et al.* described hepatotoxicity as AST/ALT elevation of > 2 times the normal limit. A small dose of PTU (300 mg daily) caused liver injury in 29.6% of patients compared with a much smaller number with MMI at 6.6 – 9% [17].

The most commonly found symptoms were nausea, vomiting, jaundice and malaise, consistent with acute hepatitis [17,18]. Laboratory data revealed elevation of liver function tests across the board with both raised transaminases and hyperbilirubinemia. Imaging revealed mild dilatation of intrahepatic ducts.

Time to presentation after initiation on therapy was variable between days to weeks [3]. The average duration of PTU treatment before the onset of hepatotoxicity is 3 months [19]. The maximum interval reported between the initiation of PTU treatment and the onset of liver disease was 4 years [16].

On commencing treatment with PTU, in the initial phases some patients can have mild elevations in their liver function tests that can resolve spontaneously [14]. Patients with continued mild elevation over a few weeks can go into liver failure without preceding transaminases trending upward [9].

A few case reports exist in the literature where PTU has caused autoimmune hepatitis leading to fulminant hepatic failure. Differentiating between autoimmune hepatitis and PTU-induced autoimmune hepatitis can be challenging and liver biopsy results may provide a clue to diagnosis, with autoimmune hepatitis demonstrating more features of chronic inflammation as opposed to PTU-induced autoimmune hepatitis with more acute features [20].

### 3.3 Monitoring

There is no consensus about the monitoring of liver function tests in patients who are on treatment with PTU.

Some authors have suggested monitoring of liver function tests monthly for 6 months after initiation [7,21].

In Japan, it is recommended to check liver function tests and blood counts for the first two months after initiating treatment. However, this has the disadvantage of a higher reported number of adverse effects that might not be significant and might lead to discontinuation of therapy [22]. Liaw *et al.* reported that 28% of patients found to have elevated liver function tests will be asymptomatic. The reporting of hepatotoxicity depends on how frequently liver function tests are being monitored and what definitions of hepatotoxicity are being used by the physician [14].

Some studies have suggested monitoring of the liver function tests should be done in the time frame of expected side effects of hepatotoxicity [23].

The American Thyroid Association recommends the following steps for monitoring patients who are being initiated on antithyroid drugs. Prior to initiating therapy patients should be informed of all side effects of the medication, in particular of hepatic injury and agranulocytosis. Instructions should be given to immediately contact the physician if any of these develop. Obtaining baseline laboratory data such as complete blood counts with differential and liver function tests is preferable. Patients who develop signs of hepatic injury such as jaundice, pruritis, rash, abdominal pain, nausea, vomiting, dark colored urine and light colored stool should get their liver function tested. If there is elevation of liver function tests to two to threefold the upper limit of normal, with no improvement within a week, PTU should be discontinued. Liver function tests should be monitored weekly thereafter, and if there is no apparent resolution, prompt referral to a gastroenterologist or hepatologist should be made [24].

No specific guidelines on monitoring of lab data have been published by the European Thyroid Association.

### 3.4 Management

Management is typically withdrawal of the offending agent and seeking alternate options for treatment along with supportive care.

Published case reports show that PTU was discontinued in all cases once hepatotoxicity was detected [3]. Patients were treated with radioactive iodine, surgery or MMI after discontinuation of PTU.

After discontinuation and supportive therapy alone, patients had improvement of liver function tests [10,16,25-28]. Steroids were used in some cases for the treatment of concomitant autoimmune hepatitis, rash and hypotension [18].

Liver transplantation was required for some patients with fulminant hepatic failure [3-5,29]. One pregnant patient received a successful liver transplant but had fetal death [30].

Dialysis and plasmapheresis were also used as a bridge to liver transplant in some cases [31,32].

It is advisable to stop PTU and seek other treatment options, as reintroducing PTU can lead to recurrence of hepatic injury, as demonstrated in a patient rechallenged with PTU [8]. In our research, we did not come across recurrence rates for patients who developed hepatotoxicity once PTU was restarted; only case reports have been published. Patients switched to MMI for treatment of hyperthyroidism did not subsequently develop hepatic dysfunction [8,13,30].

Features that are associated with worse outcomes are ages of < 11 or > 40, duration of jaundice of > 7 days before onset of encephalopathy, and bilirubin concentration of > 300 mmol/l. Some indications for earlier referral to a transplant center are development of a coagulation disorder, hepato-renal syndrome or encephalopathy [3].

## 4. MMI and hepatotoxicity

All antithyroid drugs are known to carry a risk of liver dysfunction. Like PTU, MMI and CBZ have also been associated with hepatic function derangement; however, the effects are less severe and seen in a different subset of the population. CBZ is metabolized to MMI and has the same side effect profile as MMI.

MMI toxicity is found more commonly in populations over 40 years of age compared with PTU, which tends to affect younger patients [33].

In a study comparing the appearance of hepatotoxicity defined as an elevation of transaminases more than threefold, it was found that MMI 30 mg per day dosing caused the earliest appearance of hepatotoxicity compared with 15 mg per day of MMI and 300 mg per day of PTU [23]. The average onset of hepatotoxicity with the higher dose of MMI was found to be about 17 days.

In a study comparing the hepatotoxicity profile of PTU and MMI in children under 17 years of age, PTU was the only antithyroid medication associated with severe hepatotoxicity; no cases were reported with MMI. When looking at mild liver dysfunction, MMI accounted for 0.02% of all cases compared with 0.08% with PTU [34].

In a study conducted in Japan, the incidence of hepatotoxicity from MMI 30 mg per day was found to be 6.6% and that with PTU 300 mg per day was found to be 26.9% [17]. Most of the adverse effects of the antithyroid drugs appear in the first 3 – 6 months (Table 1) [35-38].

No MMI-related deaths from liver failure have been reported to the FDA. On review of United Network for Organ Sharing, no liver transplants were related to MMI in the 1997 – 2007 period compared with PTU [4]. In one report, 389 patients receiving either PTU or MMI were studied. The adverse effects included five patients going on to develop hepatotoxicity. Four out these five were treated with PTU and one with low-dose MMI [39].

**Table 1. Comparison of propylthiouracil and methimazole hepatotoxicity in adults and children at a glance.**

	Propylthiouracil	Methimazole
Severe hepatotoxicity in adults	1 in 10,000	
Liver function elevation to twice the normal range in adults	26.9%	6.6%
Severe hepatotoxicity in children	1 in 2000	0
Mild elevation in liver function tests	0.08%	0.02%
UNOS data (1997 – 2007) for liver transplant (~ 51,000 patients)	9.4% cases	0%
Time to elevation of liver function tests	Days to months	Days to months

UNOS: United Network for Organ Sharing.

The exact mechanism of MMI-induced hepatotoxicity remains unknown. Hypersensitivity and drug reactions are the common hypotheses put forth to explain the underlying mechanism. Cell-mediated immunity may also play a role in causing cholestatic hepatitis in patients treated with MMI [40]. When lymphocytes are triggered by a particular drug, the lymphokines produced can lead to a reduction in bile flow, causing cholestasis [41].

Cholestatic patterns of liver injury are the most common type of hepatotoxicity seen with MMI use [34,42,43]. Biopsy of the liver can show expanded portal tracts with inflammatory cells. Proliferating cholangioles and bile plugs can also be seen. Diffuse swelling of hepatocytes is another feature that can be seen [23,38,44].

The length of time until presentation of symptoms can be variable, ranging from a few days to 5 months [38]. The clinical presentation of patients with MMI-induced hepatotoxicity is similar to that of PTU, with patients presenting with symptoms of jaundice, fatigue, pruritis and malaise. However, it is known that MMI causes less severe liver toxicity so the patients may not be as critically ill on presentation and may not progress to the severity of illness induced by PTU.

Management of MMI-induced liver injury is usually discontinuation of the medication and switching to other forms of therapy for Graves' disease [45,46]. A few case reports of patients being switched to PTU after MMI-induced hepatotoxicity did well with no further evidence of liver injury [40,47]. In some cases, the use of ursodeoxycholic acid therapy has been used to reverse the cholestatic drug effect. Steroids have been used in rare cases as well [48]. Our review of the literature led to just one case report of a patient requiring liver transplant after CBZ-induced hepatotoxicity [49].

## 5. Use of PTU in different subsets of the population

### 5.1 Children and PTU

Graves' disease is the most common cause of thyrotoxicosis in children, but it is still a rare entity, with an incidence of 0.1 – 3.0 per 100,000 [35]. PTU and MMI have been used over the years as a mainstay of treatment of hyperthyroidism from Graves' disease in the pediatric population [50-52].

The data collected and analyzed over the years have revealed that PTU-associated hepatotoxicity affects children more than it does adults. Rates of adverse effects were studied in a cohort of children by dividing them into groups of prepubertal, pubertal and postpubertal children. Results were consistent with the younger children being most susceptible to adverse effects of PTU. All three groups of patients were treated with weight-adjusted dosing of antithyroid medication (PTU at a mean dose of  $6.4 \pm 1.9$  mg/kg/day, MMI at a mean dose of  $0.74 \pm 0.2$  mg/kg/day). Prepubertal children had a 71% rate of side effects with one child having severe hepatotoxicity, whereas only 25% of postpubertal children showed adverse effects. The possible explanation for the higher side effects in prepubertal children was that the doses considered safe in older children may be more toxic for younger patients as they may be more sensitive to similar doses of antithyroid medication [53]. A few cases of fatal liver failure have also been reported [54].

In a study looking at 130 children with Graves' disease, neither MMI nor PTU were responsible for major side effects like liver failure. However, the rate of side effects in the MMI-treated group was lower at 25% compared with 31.9% in the PTU group. Rates of remission did not differ between the two groups [55].

Liver failure leading to liver transplantation in children occurs in 1 in 2000 – 4000 patients [56]. Among children receiving liver transplants, PTU was identified as the third most common drug leading to liver failure, accounting for ~ 10% of cases of transplant [4].

In the time frame of 1990 – 2007, PTU was associated with 10 pediatric liver transplant cases and none were associated with MMI.

PTU-associated hepatotoxicity can sometimes present as autoimmune hepatitis in children as well, as demonstrated by a case report of a 9-year-old girl on the treatment with PTU for 9 months. She was found to have elevated ANA titers and required a liver transplant. After exclusion of all other causes, PTU was felt to be the hepatotoxic agent, resulting in autoimmune hepatitis [57].

Treatment patterns of PTU-induced hepatotoxicity are also similar to those in adults, with the primary treatment being discontinuation of PTU with supportive therapy [54,58]. Steroids have been used in some cases [59]. Spontaneous recovery

was noted in some patients with discontinuation of the drug [60]. Steroids followed by liver transplantation were required in some patients [57]. Despite adequate therapy including liver transplant and close monitoring, death has been reported in children [61].

The American Association of Children's Endocrinologists strongly recommends avoiding PTU as first-line therapy [56].

### 5.2 Antithyroid drugs during pregnancy

The current recommendation is for treatment of Graves' disease, the most common cause of hyperthyroidism in pregnancy, with antithyroid drugs [62,63]. According to the current guidelines by the American Thyroid Association and American Association of Clinical Endocrinologists, during the first trimester when organogenesis is occurring, MMI should be avoided and patients should be on treatment with PTU as MMI can cause higher rates of birth defects [64].

A recently published Danish study [65] looked at a cohort of 817,093 children born to mothers who had been on antithyroid medication and compared them to women with no thyroid disease. The congenital birth defects caused by MMI/CBZ and PTU were evaluated. The prevalence of birth defects was found to be 9.1% in the MMI/CBZ group, 8% in the PTU group and 5.7% in controls. Contrary to most prior studies, both MMI and PTU were linked with birth defects.

Liver failure during pregnancy due to PTU is a rare entity [66]; however, there have been reports of serious hepatotoxicity during pregnancy [67]. A pregnant patient requiring a liver transplant has been described, which led to fetal death [29].

The first trimester of pregnancy remains one of the situations in which PTU is advocated as the treatment of choice [68]. Once organogenesis is complete in the first trimester, there is the choice of switching to MMI. Alternatively, the patient can also be given the option of continuing on PTU, given they get their hepatic function monitored every 4 weeks with thyroid function tests. It should be kept in mind that no prospective data show monitoring of liver function tests will be helpful in preventing hepatotoxicity [24].

#### 5.2.1 Antithyroid drugs and breast feeding

On review of the literature we did not find any reported cases of hepatotoxicity in breastfed infants whose mothers had been treated with antithyroid medication.

### 5.3 Thyroid storm

In thyroid storm, thionamides remain a mainstay of treatment. PTU has the added benefit over MMI of blocking T4 to T3 conversion. It has been suggested that this might enable a more rapid amelioration of symptoms in the initial hours than with MMI [69]. No case reports of hepatotoxicity from PTU while used for thyroid storm exist. Thyroid storm itself can cause derangement of liver function tests and in rare instances lead to fulminant hepatic failure [16,70]. Because of

this, it can be challenging for the managing physician to distinguish between thionamide-mediated and hyperthyroidism-mediated liver dysfunction.

## 6. Data that led to regulatory agency warnings about hepatotoxicity

PTU and MMI were introduced in the 1940s and 1950s, respectively [36]. Why then after about 60 years did the FDA put a black box warning on the label?

As Malozowski explains very well in his article, the process for having the drugs approved involved ~ 100 patients. With rare complications like PTU-related hepatotoxicity, it might not be possible to address every rare side effect and study it. To do so would require a huge study population that might not be feasible or ethical to recruit [71]. In October 2008, a conference took place to discuss the side effects of PTU in children and adolescents. The risk of PTU-related liver failure was determined to be 1 in 2000 children and adolescents [72]. This risk was estimated to be 1 in 10,000 in adults [73]. There were ~ 30 cases of liver injury associated with PTU use in the ages of 6 – 62 years. Out of these, 18 recovered without transplant, 9 deaths were reported and 3 underwent liver transplant. The pediatric population comprised about half of these 30 patients. There were 14 pediatric patients and out of the nine deaths, three were in children [34]. Additional data collected from the FDA Adverse Event Reporting System (AERS) reported 32 cases (22 adult and 10 pediatric) of serious liver injury with PTU use. Out of the 10 pediatric cases, 1 case resulted in death and 6 in liver transplant. Of the adult patients, there were 12 deaths and 5 liver transplants (Figure 1) [36,73-75]. The data in the FDA AERS are from voluntary physician reporting, so this might under-represent the true magnitude of the problem. After an evaluation of these data, the FDA placed a black box warning on PTU in August 2009.

In November 2009, the European Medicines Agency proposed a similar warning be placed on the label of PTU in Europe [76]. The United Kingdom Medicines and Healthcare Regulatory Agency has added a similar caution on the PTU drug insert, warning patients about cases of reported hepatotoxicity in adults and children. The drug insert also recommends not using PTU for children under the age of six [77].

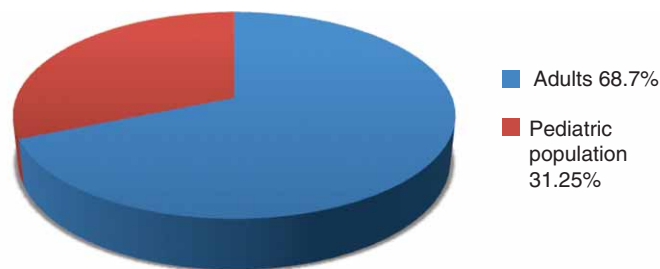
The black box warning was updated in 2010 by the FDA to limit use of PTU to only include certain populations: patients planning pregnancy or in the first trimester, and patients with no other treatment options.

The timeline of events leading to a warning being placed by regulatory agencies can be seen in Figure 2.

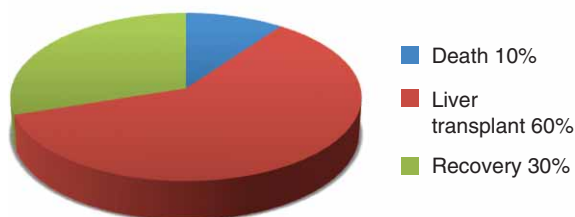
## 7. Changes in treatment trends over the last two decades

From 1996 to 2008, MMI use has increased by 800% in the US. PTU, on the other hand, increased from 348,000 to

Cases of severe liver injury reported to the FDA AERS  
(n = 32), % of cases categorized by age



Outcomes in pediatric population  
(n = 10)



Outcomes in adult population  
(n = 22)

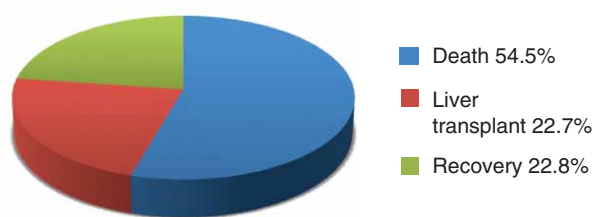


Figure 1. Cases of severe PTU-induced liver injury reported to the US FDA AERS, where 'n' is the number of cases.

AERS: Adverse Events Reporting System; PTU: Propylthiouracil.

415,000. This trend indicated an increased use of thionamides for the treatment of Graves' disease [78]. MMI was predominantly used in both sexes; however, in the 2002 – 2008 period, the use in females of ages 18 – 41 decreased compared with males. PTU use during this time decreased regardless of the gender. Children received the lowest percentage of PTU prescriptions. Factors responsible for this increased use of MMI include a lowered cost of the MMI in the 1990s and the number of serious hepatic side effects seen in patients on PTU, with the decreased use of MMI preceding the official regulatory agency warnings [79].

## 8. Conclusion

Antithyroid medications have been available since the 1940s for treatment. PTU was introduced first and was a cornerstone of treatment. When introduced initially, it was known to cause hepatotoxicity, but the severity and extent of this only became evident as years passed. Evidence is now available that shows that PTU leads to higher rates and a greater severity of hepatotoxicity than MMI.

The data are more serious in the pediatric population with the morbidity and mortality being higher compared with adults. Hepatotoxicity can appear at any time during therapy and there is no clear evidence that monitoring will diagnose hepatotoxicity early and prevent severe complications.

In 2009, a black box warning was placed on PTU for causing significant hepatic injury. In 2010, this warning was further updated to limit its use to certain populations.

The use of PTU is therefore not recommended in children in most cases, and advised to be used with caution in adults as well. There remain certain situations where PTU's benefits outweigh the risks, including during the first trimester of pregnancy. Table 2 gives a brief summary of when PTU is the preferred treatment.

## 9. Expert opinion

PTU remains an effective therapy for the treatment of hyperthyroidism from Graves' disease, but MMI is of equal efficacy, and is a safer drug [17]. The only situation in which PTU is clearly the preferred treatment is the first trimester of pregnancy. In pregnancy, the risk of using MMI during the first trimester leading to a higher risk of birth defects outweighs the low risk of developing hepatotoxicity with PTU during this time period. Hence, during the first trimester of pregnancy and in the preplanning phase of pregnancy, PTU is a safer option to use. However, there are select patients in whom the transition from PTU to MMI can cause a loss of control of their hyperthyroidism due to patient confusion about medication changes, lack of ability to monitor the patient closely or other factors. In these patients,



**Figure 2.** Timeline that led to warning about hepatotoxicity being placed on propylthiouracil by regulatory agencies. UNOS: United Network for Organ Sharing.

consideration of continuing PTU throughout pregnancy can be made, given the relatively low risk of hepatotoxicity in an adult, pregnant patient.

Thyroid storm remains another situation in which PTU may be more beneficial given its inhibition of conversion of T<sub>4</sub> to T<sub>3</sub>. However, it is the experience of the authors that MMI can be very efficacious in thyroid storm as well.

In the general adult population, if the patient has been well controlled on PTU without any adverse events and treatment alternatives are not available, PTU can be continued with caution.

Given that thyrotoxicosis itself can cause abnormalities in liver function tests, we do not advocate routine testing of liver

function test during therapy with antithyroid drugs. Also important to take into consideration is the fact that a specific timeframe cannot be specified for the appearance of hepatotoxicity and the decision to check liver function tests at specific time points and for what duration would be difficult to determine.

PTU is known to cause severe hepatotoxicity, and a randomized controlled trial with a large population with patients of all ages would not be ethical. Observational studies will be the cornerstone of providing further data on this.

Over the past decade, use of PTU has declined compared with MMI. Further research to investigate prescribing trends after the black box warning was issued need to be collected

**Table 2. Propylthiouracil and methimazole comparison in different populations.**

Subset of population	Propylthiouracil	Methimazole
Pregnancy	Preferred in preplanning and first trimester* Birth defects – 8% (commonly face and neck region defects) Case reports of liver failure during pregnancy	Used for remainder of pregnancy Birth defects – 9.1% (aplasia cutis, choanal atresia, ectodermal abnormalities) No liver failure reported during pregnancy
Breastfeeding	No cases of hepatotoxicity or thyroid dysfunction in breastfed children	Preferred due to less severe side effect profile* No cases of hepatotoxicity or thyroid dysfunction in breastfed children
Thyroid storm	Preferred (inhibits conversion of T4 to T3)*	No effect on inhibiting conversion of T4 to T3

\*The preferred treatment.

to see whether this has sufficiently warned physicians against use, particularly in the pediatric population.

PTU use will continue to decline, with MMI gaining more popularity. We hope the use in the pediatric population decreases to a negligible amount, so no further cases of hepatotoxicity related to PTU come forth. With decreased use in adults, severe cases of hepatotoxicity in adults should be on the decline as well.

The mechanism of hepatotoxicity is varied and not completely understood. Further research in this avenue to determine whether there is a particular pathway ultimately responsible for hepatotoxicity would be one way to eliminate or decrease hepatotoxicity as a side effect and possibly increase use of PTU again; however, this is unlikely to happen as we

have alternative treatment options available that are equally effective.

The future of PTU seems to be one of decline, other than in particular populations, until a safer option for treatment is available for these groups.

### Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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