

Marijuana Users Aren't at Increased Kidney Disease Risk

Current or past use of marijuana does not appear to affect the risk of developing kidney disease or decreased renal function, reports a study in *The American Journal of Medicine*.

The cross-sectional study included data from 13,995 respondents, aged 15 to 59, to the National Health and Nutrition Examination Survey from 2007 to 2014. Self-reported marijuana use, recent or past, was analyzed for association with renal outcomes: serum creatinine concentration, estimated glomerular filtration rate, and

chronic kidney disease (stage 2 or higher).

In the nationally representative survey, 46.3% of respondents said they had never used marijuana, 39.3% were past users, and 14.4% were current users. Current marijuana users were more likely to be male, younger, and current alcohol and tobacco users. Unadjusted data suggested higher mean serum creatinine and lower mean eGFR in past and current marijuana users.

However, on adjusted analysis, none of the three renal outcomes was associated with marijuana use. Serum creatinine and

eGFR showed an increasing trend in past and current marijuana users versus never-users, but these were not statistically significant. Sensitivity analysis limited to respondents free of cardiovascular disease also found no significant associations.

As more states legalize medical and recreational marijuana, use of this drug in the population is likely to increase. As for other acute and chronic health effects, little is known about how marijuana affects renal function.

This study—the largest of its kind—

finds no clinically significant effect of past or current marijuana use on serum creatinine, eGFR, microalbuminuria, or stage 2 or higher CKD. While characterizing the results as “somewhat reassuring,” the authors note that their study provides no information on the renal safety of marijuana in heavy users, older adults, or patients with pre-existing CKD [Lu C, et al. Marijuana use and renal function among US adults. *Am J Med* 2018; 131:408–414]. ■

Auryxia® (ferric citrate) tablets

AURYXIA® (ferric citrate) tablets for oral use containing 210 mg of ferric iron equivalent to 1 g AURYXIA for oral use.

INDICATION AND USAGE

AURYXIA is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis.

CONTRAINDICATIONS

AURYXIA is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).

WARNINGS AND PRECAUTIONS

Iron Overload: Iron absorption from AURYXIA may lead to excessive elevations in iron stores. Increases in serum ferritin and transferrin saturation (TSAT) levels were observed in clinical trials. In a 56-week safety and efficacy trial evaluating the control of serum phosphate levels in patients with chronic kidney disease on dialysis in which concomitant use of intravenous iron was permitted, 55 (19%) of patients treated with AURYXIA had a ferritin level >1500 ng/mL as compared with 13 (9%) of patients treated with active control.

Assess iron parameters (e.g., serum ferritin and TSAT) prior to initiating AURYXIA and monitor iron parameters while on therapy. Patients receiving intravenous iron may require a reduction in dose or discontinuation of intravenous iron therapy.

Risk of Overdosage in Children Due to Accidental Ingestion: Accidental ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Advise patients of the risks to children and to keep AURYXIA out of the reach of children.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to adverse reaction rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Iron Deficiency Anemia in Chronic Kidney Disease Not on Dialysis

Across two trials, 190 unique patients with CKD-NDD were treated with AURYXIA. This included a study of 117 patients treated with AURYXIA and 116 patients treated with placebo in a 16-week, randomized, double-blind period and a study of 75 patients treated with AURYXIA and 73 treated with placebo in a 12-week randomized double-blind period. Dosage regimens in these trials ranged from 210 mg to 2,520 mg of ferric iron per day, equivalent to 1 to 12 tablets of AURYXIA.

Adverse reactions reported in at least 5% of patients treated with AURYXIA in these trials are listed in Table 1.

Table 1: Adverse Reactions Reported in Two Clinical Trials in at least 5% of patients receiving AURYXIA

Body System Adverse Reaction	AURYXIA % (N=190)	Placebo % (N=188)
Any Adverse Reaction	75	62
Metabolism and Nutrition Disorders		
Hyperkalemia	5	3
Gastrointestinal Disorders		
Discolored feces	22	0
Diarrhea	21	12
Constipation	18	10
Nausea	10	4
Abdominal Pain	5	2

During the 16-week, placebo-control trial, 12 patients (10%) on AURYXIA discontinued study drug because of an adverse reaction, as compared to 10 patients (9%) in the placebo control arm. Diarrhea was the most common adverse reaction leading to discontinuation of AURYXIA (2.6%).

DRUG INTERACTIONS

Orally administered doxycycline has to be taken at least 1 hour before AURYXIA. Orally administered ciprofloxacin should be taken at least 2 hours before or after AURYXIA. Oral drugs that can be administered concomitantly with AURYXIA are: amlodipine, aspirin, atorvastatin, calcitriol, clopidogrel, digoxin, diltiazem, doxercalciferol, enalapril, fluvastatin, glimepiride, levofloxacin, losartan, metoprolol, pravastatin, propranolol, sitagliptin, and warfarin.

Oral medications not listed above

There are no empirical data on avoiding drug interactions between AURYXIA and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration

of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

USE IN SPECIFIC POPULATIONS

Pregnancy:

Risk Summary

There are no available data on AURYXIA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies have not been conducted using AURYXIA. Skeletal and encephalic malformation was observed in neonatal mice when ferric gluconate was administered intraperitoneally to gravid dams on gestation days 7-9. However, oral administration of other ferric or ferrous compounds to gravid CD1-mice and Wistar-rats caused no fetal malformation.

An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20% respectively.

Clinical Considerations

The effect of AURYXIA on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy.

Lactation:

Risk Summary

There are no human data regarding the effect of AURYXIA in human milk, the effects on the breastfed child, or the effects on milk production. Data from rat studies have shown the transfer of iron into milk by divalent metal transporter-1 (DMT-1) and ferroportin-1 (FPN-1). Hence, there is a possibility of infant exposure when AURYXIA is administered to a nursing woman. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for AURYXIA and any potential adverse effects on the breastfed child from AURYXIA or from the underlying maternal condition.

Pediatric Use: The safety and efficacy of AURYXIA have not been established in pediatric patients.

Geriatric Use: Clinical studies of AURYXIA included 292 subjects aged 65 years and older (104 subjects aged 75 years and older). Overall, the clinical study experience has not identified any obvious differences in responses between the elderly and younger patients in the tolerability or efficacy of AURYXIA.

OVERDOSAGE

No data are available regarding overdose of AURYXIA in patients. In patients with chronic kidney disease, the maximum dose studied was 2,520 mg ferric iron (12 tablets of AURYXIA) per day. Iron absorption from AURYXIA may lead to excessive elevations in iron stores, especially when concomitant intravenous iron is used.

In clinical trials, one case of elevated iron in the liver as confirmed by biopsy was reported in a patient on dialysis administered IV iron and AURYXIA.

PATIENT COUNSELING INFORMATION

Dosing Recommendations: Instruct patients to take AURYXIA as directed with meals and adhere to their prescribed diets. Instruct patients on concomitant medications that should be dosed apart from AURYXIA. Advise patients not to chew or crush AURYXIA because tablets may cause discoloration of mouth and teeth.

Adverse Reactions: Advise patients that AURYXIA may cause discolored (dark) stools, but this staining of the stool is considered normal with oral medications containing iron.

AURYXIA may cause diarrhea, nausea, constipation, vomiting, hyperkalemia, abdominal pain, and cough. Advise patients to report severe or persistent gastrointestinal symptoms to their physician.

Accidental Ingestion: Advise patients to keep this product out of the reach of children and to seek immediate medical attention in case of accidental ingestion by a child.

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Biologic Therapies for RA Reduce Kidney Risks

In patients with rheumatoid arthritis, treatment with biologic agents is associated with a lower risk of declining renal function and chronic kidney disease (CKD), reports a study in *Kidney International*.

Using a Department of Veterans Affairs database, the researchers identified 20,757 veterans diagnosed with RA between 2004 and 2006, with follow-up to 2013. All included patients had initially normal kidney function: estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m² or higher. Treatment with biologic agents was examined for association with incident CKD, defined as eGFR less than 60 mL/min/1.73 m², with at least a 25% decrease; and change in renal function, classified as <-3, -3, <0 (reference), and ≥0 mL/min/1.73 m². Treatment and control groups were propensity-matched, based on their likelihood of initiating biologic treatment.

Overall, 22% of patients received biologic agents: most commonly etanercept, followed by adalimumab and infliximab. Patients receiving biologic therapy were younger and less likely to be male and African American. They also had higher eGFR, higher income, and less comorbidity.

Biologic therapy was associated with a lower incidence of CKD: hazard ratio 0.95 for a cutoff of under 60 mL/min/1.73 m² and 0.71 for under 45 mL/min/1.73 m². Patients receiving biologics were also less likely to have progressive eGFR decline: multinomial odds ratio 0.67 for an eGFR slope <-3 mL/min/1.73 m² and 0.76 for ≥0 mL/min/1.73 m² (relative to -3 to <0). The yearly rate of eGFR decline slowed from -1.0 mL/min/1.73 m² before to -0.4 mL/min/1.73 m² after biologics were started.

Patients with RA are at elevated risk of kidney disease, likely via chronic inflammation and/or exposure to nephrotoxic drugs. Newer biologic agents used to reduce systemic inflammation in RA have been shown to have beneficial effects in lowering cardiovascular risk.

This study suggests that biologic therapy reduces the risk of CKD and progressive decline in renal function in a nationwide cohort of veterans with RA. The associations are independent of known risk factors for CKD. [Sumida K, et al. Treatment of rheumatoid arthritis with biologic agents lowers the risk of incident chronic kidney disease. *Kidney Int* 2018. DOI: 10.1016/j.kint.2017.11.025]. ■