Drug & Poison Information Center Bulletin
Faculty of Pharmacy - Tanta University

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Inside this issue:

Immunotherapy for allergic rhinitis and asthma

Allergen immunotherapy (AIT) for allergic rhinitis and asthma is effective long-term, according to a literature review of real-world evidence by researchers in Germany and Poland. AIT is the only treatment that targets the underlying pathophysiology of allergy with disease-modifying effects. To investigate the long-term effectiveness and medication adherence of immunotherapy in allergic rhinitis and asthma, the authors searched PubMed for retrospective cohort assessments of prescription databases in Europe as of March 31, 2022.

The 13 publications that met their search criteria involved studies of people allergic to grass pollen, tree pollen, or house dust mites, as well as studies not differentiating between allergens. Three reports focused on medication adherence. Some analyses were funded by allergen immunotherapy manufacturers. All 13 studies collected and analyzed data of retrospective cohorts from national prescription databases of patients in Germany, France, and the Netherlands. The researchers summarized and evaluated data on long-term effectiveness of the AIT shots, tablets and drops for four endpoints:

Allergic rhinitis, allergic asthma, time to onset of asthma, and medication adherence.

A. For allergic rhinitis progression, they compared the number of prescriptions for symptomatic treatment of allergic rhinitis with or without allergic conjunctivitis during follow-up vs pre-index (before AIT application) compared to a non-AIT group receiving only symptomatic treatment.

B. AIT reduced allergic rhinitis progression more effectively than a non-AIT control group receiving only symptomatic allergic rhinitis treatment for up to 6 years.

C. For asthma development in patients without pre-index asthma, they compared prescriptions for anti-asthma medication with those in the non-AIT control group. For asthma progression in patients with pre-index asthma, they compared the number of prescriptions for asthma medication in AIT-treated vs non-AIT control patients.

D. Asthma development and progression were hampered for most endpoints in patients treated with most preparations, compared with the non-AIT group receiving only anti-asthma medication.

E. Results for time from beginning AIT to asthma onset were inconsistent.

F. In adherence to AIT medication, although AIT decreased during the recommended 3-year treatment period, most studies showed higher adherence to subcutaneous than to sublingual AIT.

Findings confirm what allergists see in clinic:

- Samuel Friedlander, MD, clinical assistant professor at Case Western Reserve University School of Medicine in Cleveland, Ohio, told Medscape Medical News that this study supports what allergists see in the clinical practice.
- "Allergy immunotherapy (allergy shots) improves nasal and eye allergies as well as asthma, and this immune system improvement prevents the development of asthma in real-world settings. In the United States, allergy shots are the dominant method for treating patients with immunotherapy, but in this European study, under-the-tongue tablets also successfully treated allergies," said Friedlander, who was not involved in the study.

Asthma and allergic rhinitis rates rising worldwide:

Patricia Lugar, associate professor at Duke University School of Medicine, cautioned that: global rates of asthma and allergic rhinitis are rising, with many factors contributing to the rise in allergic diseases including climate change and decreasing air quality due to pollution. This trend is not expected to slow down but rather to continue to rise globally. To control disease states and worsening of disease states, AIT can provide long-lasting symptom management, and for many patients, can be curative.

References:

- Immunotherapy for Allergic Rhinitis and Asthma Has Lasting Effects. Available at: https://www.medscape.com/viewarticle/982447?src=#vp_2. Accessed in October, 2022.
- Shamji MH, Sharif H, Layhadi JA, Zhu R, Kishore U, Renz H. Diverse immune mechanisms of allergen immunotherapy for allergic rhinitis with and without asthma. J Allergy Clin Immunol. 2022;149(3):791-801.

By: Marwa Elsayed, PGCPD.

The use of anti-depressants for the treatment of fibromyalgia

- **What is fibromyalgia?**

Fibromyalgia is a chronic, widespread, non-inflammatory musculoskeletal pain syndrome with multisystem manifestations that include widespread pain, stiffness, fatigue, disrupted and unrefreshing sleep, and cognitive difficulties. It typically presents in young or middle-aged women, but it can affect patients of either sex and at any age.

Although some physicians still do not accept fibromyalgia as a discrete illness, basic and clinical investigations have clarified the neurophysiologic bases for fibromyalgia and led to its current classification as a central sensitivity syndrome (CSS).

- **Pathophysiology:**

Fibromyalgia is currently understood to be a disorder of central pain processing (central sensitization) or a syndrome of central sensitivity with afferent augmentation of peripheral nociceptive stimuli. Inflammation is not a feature of fibromyalgia.

Pain in patients with fibromyalgia derives also partly from a generalized decrease in the pain perception threshold, with reduced discrimination of nociceptive sensations from non-nociceptive sensations (e.g., touch, warmth, cold).

Research has provided evidence for altered functional connectivity and chemistry in the pain-processing system of the brain. A number of abnormalities in pain processing have been demonstrated in fibromyalgia which include:

- Excess excitatory (pronociceptive) neurotransmitters.
- Low levels of inhibitory neurotransmitters (e.g., serotonin and norepinephrine) in descending anti-nociceptive pathways in the spinal cord.
- Altered endogenous opioid analgesic activity in several brain regions known to play a role in pain modulation.
- Dopamine dysregulation.

Medications that reduce pain in fibromyalgia function in this regard by either increasing levels of inhibitory neurotransmitters (e.g., duloxetine) or decreasing levels of excitatory neurotransmitters (e.g. pregabalin).

- **The role of anti-depressants in the treatment of fibromyalgia:**

As no cure exists for fibromyalgia, treatment involves both non-pharmacologic and pharmacologic approaches. **Non-pharmacologic treatment** is central to successful outcomes. It includes lifestyle modifications such as regular physical activity and sleep hygiene. Proper medications can help the individual achieve significant improvement.

Currently the United States Food and Drug Administration have approved only three drugs for use in fibromyalgia. They are **duloxetine, milnacipran, and pregabalin.**

Pregabalin is used to reduce pain and improve sleep. The antidepressants duloxetine and milnacipran, which are used to relieve pain, fatigue, and sleep problems, are generally prescribed at lower doses than for treatment of depression.

Other anticonvulsants and antidepressants are often used off-label to treat fibromyalgia and there is evidence that many can decrease pain sensitivity, with tricyclic antidepressants (TCAs), in particular, have proven benefit but anticholinergic side effects often limit their use. Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine and paroxetine, improve symptoms in fibromyalgia but the high doses required often cause adverse effects that are poorly tolerated, so they have largely been replaced as a treatment for pain by dual serotonin/norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, milnacipran, or duloxetine. SNRIs can cause nausea, so they should be taken with food.

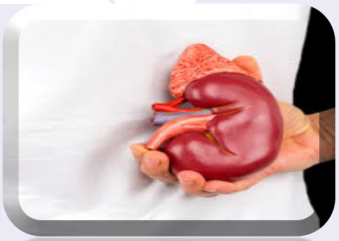
The use of two or more agents may be more effective than monotherapy. A study suggested that a useful combination is a TCA (e.g., amitriptyline or cyclobenzaprine in low dosage at bedtime) and a first-generation SSRI (e.g., fluoxetine, paroxetine), which allows for improved efficacy with lower dosing that can help prevent adverse effects. Fibromyalgia patients are frequently treated with multidrug therapy; they should be monitored for drug interactions, sedative, and anticholinergic burden. In particular, patients taking combinations of serotonin-active drugs should be closely monitored for the development of serotonin syndrome, and all patients taking antidepressants should be carefully monitored for worsening depression or the emergence of suicidal thoughts.

References:

- Fibromyalgia. Available at: https://emedicine.medscape.com/article/329838-overview#a1. Accessed in October, 2022.
- Fibromyalgia monograph at Lexicomp. Available at: https://online.lexi.com/lco/action/search?q=fibromyalgia%20treatment&t=name&acs=true&acq=fibro. Accessed in October, 2022.

By: Amr Noweir. B.Sc.

Refresh your knowledge with: "Drug induced kidney disease"



Drug induced kidney disease (DIKD) is a significant contributor of acute kidney injury (AKI) and chronic kidney disease (CKD). The incidence of drug induced nephrotoxicity is14-26% in adults and 16% in pediatric cases. Most studies have defined nephrotoxicity as 0.5mg/dl or 50% rise in serum creatinine over 24-72 hour time frame and a minimum of 24-48h drug exposure. But 50% increase in serum creatinine may not be highly specific. Nephrotoxicity caused due to administration of various drugs can be explained by their different mechanisms like:

Medications associated with pseudo-AKI and hemodynamically mediated AKI:

Medications block tubular creatinine secretion as well as hemodynamic causes of increases in serum creatinine.

Medications Associated with Pseudo-AKI by ↑ serum creatinine	Medications Associated with Hemodynamically Mediated AKI
Cimetidine - Trimethoprim - Dronedarone - Cobicistat and dolutegravir - Tyrosine kinase inhibitors - Pyrimethamine - Dexamethasone - Cefoxitin - Flucytosine - Corticosteroids - Fenofibrate - Calcitriol and alfacalcidol .	• Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). • Non-steroidal anti-inflammatory drugs (NSAIDs). • Sodium-glucose cotransporter-2 (SGLT2) inhibitors. • Calcineurin inhibitors.

Medications associated with acute tubular injury:

Antibiotics **Aminoglycosides** (gentamicin, neomycin, amikacin), **Vancomycin** (+/- piperacillin-tazobactam), **Colistin/polymyxins**	**Chemotherapeutic agents** **Cisplatin (less common with other platin analogs), Ifosfamide, Pemetrexed**
Antifungals **Amphotericin B products**	**Analgesics** **Foscarnet, NSAIDs including cyclo-oxygenase (COX)-2 inhib-itors, Acetaminophen overdose**
Antiviral agents **Cidofovir, tenofovir, adefovir**	**Calcineurin inhibitors** **Cyclosporine, tacrolimus**
Radiocontrast agents **Iodinated radiocontrast agents**	**Bisphosphonates** **Pamidronate, zolendronic acid**

Medications associated with inflammation in glomerulus, renal tubular cells, and surrounding interstitium:

Inflammatory condition due to immune mechanism, non-dose dependent idiosyncratic response, or hypersensitivity reactions are the possible ways for the following medication examples inducing these mentioned kidney damage.

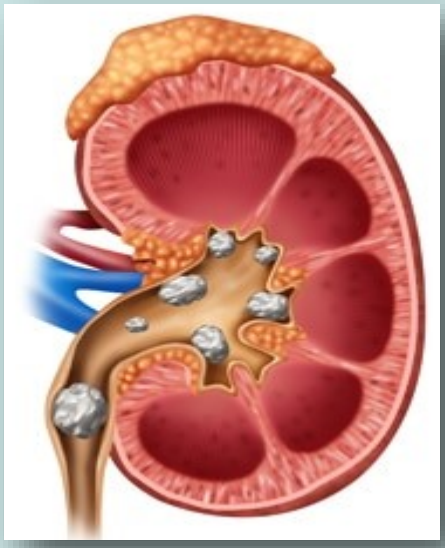
Glomerulonephritis	Acute interstitial nephritis	Chronic interstitial nephritis
• Gold • Hydralzine • Interferon alpha • Lithium • NSAIDs • Propylthiouracil • Pamidronate	• Allopurinol • Antibiotics (Beta lactam, Quinolones, Sulphonamides, and Vancomycin) • Antivirals (Acyclovir, Indinavir) • Diuretics (Loop and Thiazide) • NSAIDs • Phenytoin • Antiacid GI drugs (Omeprazole, Pantoprazole, Lansoprazole, and Ranitidine)	• Calcineurin inhibitors (Tacrolimus, Cyclosporin) • Lithium • Aspirin • Acetaminophen

Medications-induced crystalline nephropathies:

Use of drugs which produce crystals that are insoluble in urine. These crystals precipitate within the distal tubular lumen, obstructing the urine flow and eliciting the interstitial reaction.

Examples:

- Methotrexate
- Sulfadiazine and sulfamethoxazole
- Indinavir, atazanavir, and darunavir
- Acyclovir
- Ciprofloxacin and levofloxacin
- IV ascorbic acid, Orlistat (by causing enteric hyperoxaluria), and Ethylene glycol
- Sodium phosphate purgative (oral rather than enema)
- Triamterene
- Amoxicillin
- Foscarnet.



N.B. Exposure to multiple nephrotoxins and underlying comorbid medical conditions
increase the likelihood of kidney injury.

Common risk factors for drug-induced acute tubular injury	
Modifiable Risks	Non-modifiable Risks
• Volume depletion and/or hypotension • Exposure to concomitant nephrotoxins • High-level exposure to nephrotoxins (high-dose and long duration therapy • Excessive medication dose for underlying GFR	• Advanced age especially with concomitant CKD • Comorbid conditions such as liver disease, diabetes mellitus, heart failure, major surgery (especially cardiovascular • High-risk settings such as intensive care unit, burn unit, cardiovascular care unit • Shock states such as sepsis • Solid organ transplantation • Stem cell transplantation • Genetic vulnerability

Management

- ***Treatment of nephrotoxicity*** is dependent on phenotype, severity of the injury, underlying condition for which the medications were prescribed and patients risk factors. The decision to stop or reduce the dosage depends on careful observation of risk versus benefit and on the type of the adverse drug reaction.
- ***Preventive measures of DKID include:*** use of equally therapeutic effective drugs which are non nephrotoxic, correction of the risk factors for nephrotoxicity, before starting the therapy assess the baseline renal function, avoid nephrotoxic drug combinations. Adequate perfusion is important to maintain the renal perfusion and to avoid renal impairment. In patients associated with multiple risk factors, serum creatinine level has to be monitored after starting the treatment and while increasing the dosage of a drug. A systematic approach towards the electronic medical record for automated monitoring of patients at risk of nephrotoxicity is also required.

References:

- Perazella MA, Rosner MH. Drug-Induced Acute Kidney Injury. Clin J Am Soc Nephrol. 2022;17(8):1220-1233.
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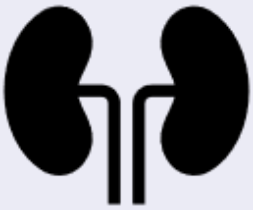

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Vision

The vision of Tanta University DPIC is to improve national healthcare service through provision of evidence-based, unbiased, patient oriented drug information services & adverse drug reporting system.

Mission

* Responding to drug inquiries related to the use of the drug and providing the health care professionals and patients with drug information related to the patient's care to achieve the optimal use of the drug in addition to the provision of other toxicological managing information.
* Educational activities to support the rational optimal use of drugs as well, supporting research activities.
* Continuous medical education and training courses in various fields of pharmacy for students, undergraduates, postgraduate students, and researchers.
* Issuing a Drug Information Bulletin periodically to take a look at medical & pharmaceutical news.
* Supporting the National Pharmaceutical Vigilance Program by following up and monitoring side effects and problems related to use of pharmaceutical preparations within regional hospitals.
* Contributing to the establishment of various treatment protocols and prescription booklet services in regional hospitals.

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