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PHARMA INFO-LINE

[\(Allopurinol for refractory schizophrenia\)
new rational use for an old drug](#)

Allopurinol is a xanthine oxidase inhibitor that inhibits xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine then to uric acid. Allopurinol is metabolized to oxypurinol which is also an inhibitor of xanthine oxidase. Allopurinol acts on purine catabolism, reducing the production of uric acid without disrupting the biosynthesis of vital purines. It is currently available in Egypt under the brand name **No-Uric**® that is produced by **EPICO**. It is indicated for the prevention of attack of gouty arthritis and nephropathy, treatment of secondary hyperuricemia which may occur during chemotherapy treatment of tumors or leukemia and also for the prevention of recurrent

calcium oxalate calculi. [1]

In a recent review this question was addressed "**Is allopurinol a rational option for use in patients with poorly responsive or treatment refractory schizophrenia?**" in order to answer this question the authors reviewed all articles, case reports or clinical trials that was identified from MEDLINE, the Cochrane Library, and *International Pharmaceutical Abstracts* using the terms allopurinol and schizophrenia. [2]

The rationale behind the use of allopurinol, is the new evidence that supports a purinergic hypothesis for schizophrenia. Previously the well studied dopamine hypothesis could not alone explain refrac-

tory disease while using powerful dopamine antagonists, therefore other pathways had been proposed too for the pathophysiology of schizophrenia such as; Glutamatergic, gamma-aminobutyric acid-ergic (GABAergic), serotonergic, and cholinergic pathways. [3, 4, 5]

Furthermore adenosine agonists have been shown to have properties similar to those of dopamine antagonists, which thought to be done by reducing the affinity of dopamine agonists for dopamine receptors or by modulating glutamatergic transmission. Therefore; reduced adenosinergic neurotransmission due to purinergic dysfunction could potentiate psychosis by creating a hyperdopaminergic state. Allopurinol by preventing purine degradation to uric acid will promote adenosine accumulation therefore provide the antipsychotic and anxiolytic effects. [5] After analyzing 2 clinical trials and 2 other case reports [6, 7, 8] the authors of the review concluded that adjuvant allopurinol in

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Article summary

- ❑ Adenosine agonists have similar properties of dopamine antagonists in schizophrenia.
- ❑ Adenosine production is regulated by purine.
- ❑ Allopurinol by preventing purine degradation to uric acid may play an important role in the pathophysiology of refractory schizophrenia.
- ❑ Some clinical studies have addressed Allopurinol as one of the options for refractory schizophrenia.
- ❑ Allopurinol in doses of 300mg once or twice may help patients with poor responses to other medications.

doses of 300mg once or twice may provide benefit to patients who are poorly responsive to current treatments for schizophrenia. [2]

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World Health Organization Demands for male circumcision

In a press conference at December 13, 2006, the National Institute for Health (**NIH**) presented data from two studies — conducted in Kenya and Uganda — on adult male circumcision for the prevention of HIV infection. In both trials, healthy HIV-negative men were randomized to receive circumcision immediately or to wait 2 years. All men received HIV prevention counseling, and follow-up was extensive. Both trials met enrollment targets by September 2005 and were supposed to continue through mid-2007. However, the results of an interim analysis by the Data and Safety Monitoring Board on December 12, 2006, were impressive enough to prompt early termination, and all men in the control groups are now being offered immediate circumcision. Among nearly 2800 volunteers in the Kenyan trial, HIV incidence was 53% lower in those who received circumcision than in controls. Similarly among nearly 5000 volunteers in the Ugandan trial, HIV incidence was 48% lower in those who received circumcision. [1]

The final results for these two randomized trials can be found in **The Lancet's** 24 **February 2007** [2, 3]

In addition; an article by the title "*Demand for male circumcision rises in a bid to prevent HIV*" (by Jacqui Wise) appears in the Bulletin of the World Health Organization, July 2006; in which the editor raised the same issue, however she emphasized on the experts' concern for the risk of circumcision being performed in non-sterile conditions that can lead to infection, bleeding and permanent injury, or HIV infection from non-sterilized instruments and possible death if appropriate treatment is not provided. Every year the authorities in the Eastern Cape of South Africa report deaths and serious complications from botched circumcisions of young boys carried out by traditional healers. [4]

Earlier to this announcement, the debate con-

tinued whether or not circumcision should be performed as a preventative measure, although associations between lack of circumcision and HIV-1 acquisition have been reported in more than 40 observational epidemiologic studies. [5-8]

Furthermore, a 25-year longitudinal study of a birth cohort was done in New Zealand [9] in which information were obtained on 3 stages:

1. The circumcision status of males in the cohort before 15 years old
2. Measures of self-reported sexually transmitted infection from ages 18 to 25 years, and
3. Childhood, family, and related covariate factors.

The authors found that uncircumcised male had a statistically significant bivariate association with self-reported sexually transmitted infection. After adjustment for confounding factors, including number of sexual partners and unprotected sex, as well as background and family factors related to circumcision the results still show significant association between no circumcision and reports of sexually transmitted infection. Estimates of the population-attributable risk suggested that universal neonatal circumcision would have reduced rates of sexually transmitted infection in this cohort by 48.2%.

These findings made the author to suggest that uncircumcised males are at greater risk of acquiring sexually transmitted infection than circumcised males. Male circumcision may reduce the risk of sexually transmitted infection acquisition and transmission by up to one half, suggesting substantial benefits gained from routine neonatal circumcision.

The most likely mechanism by which circumcision can protect against catching the virus was studied by [Donoval BA](#) and colleagues (2006). It



seems to be related to the Langerhans cells, which are receptor cells for HIV. These cells are found in large numbers on the inner surface of the foreskin but are less common elsewhere on the surface of the penis. An intact foreskin may also be more susceptible to small tears or abrasions during sex. The rest of the male penis is heavily keratinized and, therefore, provides a less likely route of entry for HIV. [10]

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Cough and common cold, what the pharmacist should know?

Common cold is the most common cause of acute cough. Triggered by the viral infection the inflammatory response previously recognized as post-nasal discharge PND may cause chronic cough which becomes self-perpetuating unless interrupted with active treatment. This explains the persistence of cough after the viral infection has been cleared. [1]

According to the latest clinical practice guidelines of the **American Chest Physician**, the management would include; combination of an older, first-generation antihistamine such as **brompheniramine** with decongestant such as **sustained-release pseudoephedrine**. [1]

However, the guidelines stated that the newer generation non-sedating antihistamines such as terfenadine and loratadine are ineffective in the treatment of the common cold (this is based on many studies). [2- 4]

The nonsteroidal antiinflammatory drug (NSAID); **naproxen** decreased cough (as well as headache, malaise, and myalgia) in one randomized controlled trial; by reducing inflammation, therefore it can be also used. [5]

Cough suppressants (such as dextromethorphan), cough expectorants (e.g. guaifenesin), and zinc are not proven to relieve cold-related coughs, therefore they are not recommended by the guidelines. [1] The use of cough and cold medications in infants and children younger than 15 years of age is inadvisable because of the lack of efficacy data. In addition, these products can increase morbidity (through adverse effects) and even mortality. In a very recent report of the CDC; three infant deaths during 2005, that were interpreted by medical examiners to have been caused by cough and cold medications. The infants were all younger than 6 months and had received varying combinations of prescription and over-the-counter (OTC) medications containing pseudoephedrine, carbinoxamine (an antihistamine), acetaminophen, and dextromethorphan. At autopsy, all three infants had blood levels of pseudoephedrine that were 9 to 14 times higher than levels expected in children aged 2 to 12 years who receive appropriate doses. [6, 7] Furthermore **The American Academy of Pediatrics** advises against use of codeine and dextromethorphan for treating any type of cough, and studies of various antihistamines, decongestants, and dextromethorphan have shown little or no benefit associated with their use in acute, nocturnal, or whooping cough. [8]

conclusion

Adult cough caused by common cold can be treated according to the American Chest Physician guidelines (if not contraindicated) with; combination of a first generation antihistamine such as (diphenhydramine, chlorpheniramine, or brompheniramine) and a decongestant such as pseudoephedrine. Based on the available evidence; the NSAID naproxen can be also used. However infants and children (aged < 15 years) with cough, management should be according to infant / child-specific guidelines, which differ from those for adults, as the etiologic factors and treatments for children are sometimes different from those for adults. Cough in children should be treated based on etiology, and there is no evidence for using medications for the symptomatic relief of cough. If



medications are prescribed by the physician (as they should never be prescribed by the pharmacist as an OTC for this age group), it is advisable to stop the medications if there is no effect on the cough within an expected time frame.

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Maternal seafood consumption in pregnancy can prevent suboptimal neurodevelopment in children

In a recent observational cohort study; researchers had found that mothers who eat seafood during pregnancy of less than 340 g per week was associated with increased risk of their children being in the lowest quartile for verbal intelligence quotient (IQ), compared with mothers who consumed more than 340 g per week.

In addition; low maternal seafood intake was also associated with increased risk of suboptimum outcomes for pro-social behavior, fine motor, communication, and social development scores. For each of these outcomes the researchers found that the lower the intake of seafood during pregnancy, the higher the risk of suboptimum developmental outcome [1]

This study suggesting that the previous advice by the **American Heart Association** and the Food and Drug Administration **FDA**[2, 3] to limit seafood consumption in children, pregnant and nursing women could in fact be detrimental and that risks from the loss of nutrients that are available in seafood were greater than the risks of harm from exposure to trace contaminants in seafood such as (mercury, polychlorinated biphenyls PCBs, dioxins). Seafood is a major source of omega-3 essential fatty acids such as docosahexaenoic acid (DHA), and eicosapentaenoic acid, (EPA), these fatty acids are very important for optimum fetal neurodevelopment. Deficiency may lead to reduced dendritic arborisation [4] and impaired gene expression for regulation of neurogenesis, neurotransmission, and connectivity[5]. In severe conditions of DHA deprivation, such as in Zellweger disease which is a genetic disorder characterized by absence of peroxisomes which are important organelles involved in aspects of the metabolism of many molecules, including fatty acids and other lipids. The disease is apparent at birth and is characterized by profound neurologic impairment, mental retardation is common, yet restoration of dietary DHA intake improves clinical outcomes and neuronal myelination. [6-8]

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