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BULLETIN ON ADVERSE DRUG REACTIONS

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INDEX

From the Editor's Desk

Dear Friends and Colleagues,

It gives me great pleasure to present to you yet another issue of Bulletin on Adverse Drug Reactions.

In continuation of the article in the previous issue of adverse drug reactions due to antiretroviral therapy, the first article deals with the management of the adverse reactions due to these drugs.

The second article deals with the topic of occulotoxicity. We have enlisted few ocular conditions and the drugs causing the same. As it is not possible to cover all the eye conditions, we have made a note of important and relatively commoner conditions.

Other features in the bulletin include a case report on drug induced seizure, analysis of ADRs from our institute, news related to the drug regulatory update and crosswords and puzzle.

I hope the readers find this issue of bulletin as an interesting and useful.

Finally, I would like to thank all the clinical departments from our institution for their valued contribution to Pharmacovigilance, to all the authors for contributing in the bulletin and to all the members of the Department of Pharmacology for their efforts in bringing out the current issue of this bulletin.

Thank you.

Dr. Sudhir Pawar

MANAGEMENT OF ADVERSE EFFECTS DUE TO ANTIRETROVIRAL THERAPY

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Introduction

There are currently several million people taking combination antiretroviral therapy (cART) as it prolongs life and prevent progression of disease caused by HIV infection. This condition needs lifelong treatment of combination therapy to control virus replication and to prevent emergence of resistance. Prolonged exposure to drugs as well as combination therapy increase the risk of adverse effects and drug-drug interactions which can affect quality of life in these patients.[1] Treating clinician should have knowledge of potential adverse effects of ART, how to prevent and manage them in order to give better patient care and improve quality of life. The clinician must consider the toxicity potential of an ART regimen, as well as the individual patient's underlying conditions, concomitant medications, and prior history of drug intolerances. In addition, it should be appreciated that, in general, the overall benefits of ART outweigh its risks and that some conditions (e.g., anemia, cardiovascular disease, renal impairment), may be more likely in the absence of ART. [2] This article illustrates significant adverse drug reactions due to ART and their management.

Antiretroviral regimens[3]

According to National AIDS Control Organisation(NACO) the first line regimens for untreated patients universally include 2 NRTIs + 1 NNRTI.

First line Antiretroviral regimens

Preferred regimen

- Lamivudine + Zidovudine + Nevirapine

Alternative regimens

- Lamivudine + Zidovudine + Efavirenz
- Lamivudine + Stavudine + Efavirenz
- Lamivudine + Stavudine + Nevirapine

Other options

- Lamivudine + Tenofovir + Nevirapine
- Lamivudine + Tenofovir + Efavirenz
- Lamivudine + Zidovudine + Tenofovir

Principles of ART by NACO

- All regimens should have 2 NRTIs + 1 NNRTIs.
- Include lamivudine in all regimens.
- The other NRTI can be zidovudine or stavudine.
- Choose one NNRTI from nevirapne or efavirenz.
- Choose efavirenz in patients with hepatic dysfunction and in those concurrently receiving rifampin.
- Do not use efavirenz in pregnant woman or those likely to get pregnant.

Monitoring of patients who are receiving ART[4]

Safety monitoring is required for early detection of ADRs, as any condition can be managed easily and effectively if diagnosed at early stage and will limit the severity. Routine laboratory monitoring should be done approximately every 3 months to determine whether the patient has any asymptomatic abnormalities. The laboratory tests for monitoring include complete and differential blood counts and measurement of electrolyte, creatinine, liver transaminase, bilirubin and amylase levels. Patients should also be monitored at regular intervals (approximately every 3 months) for dyslipidemia, diabetes, and lipoaccumulation or lipoatrophy. Patients should be asked about and examined for changes in fat distribution. Imaging tests, such as abdominal CT to detect visceral fat, are not recommended for routine monitoring.[4]

Clinical significance and management of ADRs due to ART

Clinical assessment of adverse effects due to ART is very important as it is deciding factor for changes of drug or drugs in the ART regimen or switching of ART regimen. These adverse effects could be minor, transient, treatment limiting or life threatening. After assessment of ADRs, switching from an effective ART regimen to a new regimen or change of drug in the regimen must be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment. Other important factor is to assess whether these changes in the ART will affect treatment adherence as any new changes are not accepted easily.[2,3,4,]

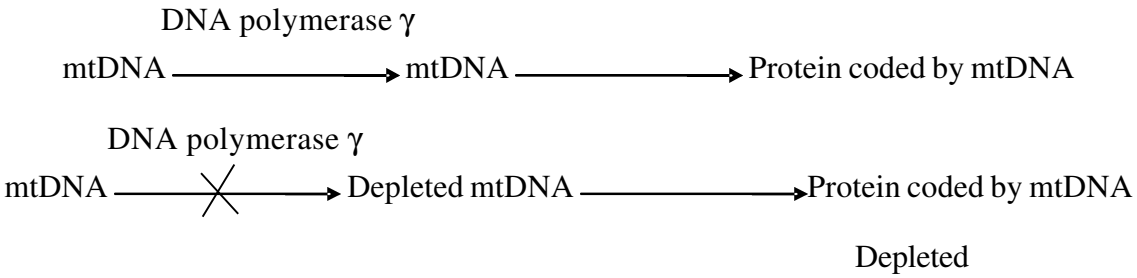
- If drug toxicity develops, either entire regimen should be interrupted or the offending drug should be changed, no dose reduction should be tried.
- Acute life-threatening events [e.g., acute hypersensitivity reaction due to abacavir, lactic acidosis due to stavudine (d4T) and didanosine (ddI), liver and/or severe cutaneous toxicities due to nevirapine (NVP)] usually require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity.
- Non-life threatening toxicities (e.g., urolithiasis with atazanavir [ATV], renal tubulopathy with tenofovir [TDF]) can usually be handled by substituting another ART agent for the presumed causative agent without interruption of ART.
- Other, more chronic, non-life threatening adverse events (e.g., dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the adverse event with additional pharmacological or non- pharmacological interventions.
- Management strategies must be individualized for each patient.[2]

One of the aim of treatment should be to prevent adverse drug reactions. During initiation of ART, safe and effective alternative drugs for the regimen should be selected. As lipodystrophy due PIs can be prevented by selecting PI sparing regimen and stavudine should be avoided as it is strongly related to lipodystrophy.[1,4,5]

Management
- Prevention
- Safety monitoring
- Adjustment in ART
- Specific Treatment

Sometimes adjustment in drugs of ART is required to reduce the chance of ADR e.g. if patient is already anaemic before initiation of ART, stavudine should be substituted for zidovudine.[3,6]

Mitochondrial toxicity[7] : Many ADRs of ART[nucleoside reverse transcriptase inhibitors (NRTIs)] are due to mitochondrial toxicity and mechanism of mitochondrial toxicity is as follows



Many of the adverse effects due to ART are associated with mitochondrial toxicity and are difficult to distinguish from effects associated with HIV infection itself.

Management of individual ADR due to ART

Management of dyslipidemia and body fat distribution

Between 33% and 75% of patients with HIV infection receiving cART develop a syndrome often referred to as lipodystrophy. Many of the patients have been noted to have a characteristic set of body habitus changes associated with fat redistribution, consisting of truncal obesity coupled with peripheral wasting. These changes may develop at any time ranging from 6 weeks to several years following the initiation of cART. The lipodystrophy syndrome has been reported in association with of protease inhibitor therapy, it appears that similar changes can also be induced by potent protease-sparing regimens. It has been suggested that the lipoatrophy changes are particularly severe in patients receiving the thymidine analogues stavudine and zidovudine. [8]

Management[5]

Prevention through initiation of regimens less likely to cause such changes.

Lifestyle modifications, such as reducing calorie intake and increasing aerobic exercise.

Switching PIs to either NNRTI or atazanavir.

For those with severe peripheral lipoatrophy switch away from stavudine to abacavir or tenofovir.

Metformin reduce central fat accumulation.

Reconstructive surgeries in severe and resistant cases.

Atorvastatin for ART associated hyperlipidemia.

In case of ART induced hyperlipidemia, switching away from Protease Inhibitors (PIs) to either Non-nucleoside reverse transcriptase inhibitors (NNRTIs) or atazanavir lead to lipid improvement, but pharmacological interventions are often required. Low dose (10mg) atorvastatin is recommended for ART associated LDLC elevations. Fibrate, niacin and fish oil is recommended for isolated hypertriglyceridemia. However serious concern exist regarding drug-drug interactions between PIs and statins.[5]

Bone marrow toxicity

Bone marrow toxicity[4,8,9]

- Clinically detectable & reversible
- Safety monitoring:

Routine monitoring of Hb at baseline & at 4 & 12 weeks.

- Management

  Patient education

  Dosage reduction or drug discontinuation

  Stop CTX or other BM suppres sant drugs

  Therapy with erythropoietin or CSF

  Transfusion for severe cases

Bone marrow (BM) toxicity occurs in up to 30% of patients taking zidovudine. Caution should be exercised when zidovudine is administered to patients with pre-existing anemia or neutropenia and to those with advanced cases of AIDS. Zidovudine should be used cautiously with any other agent that causes bone marrow suppression, such as interferon, cotrimoxazole (CTX), dapsone, foscarnet, flucytosine, ganciclovir, and valganciclovir. Hematological abnormalities can necessitate a dosage reduction, drug discontinuation, or therapy with erythropoietin (100-300 units/kg, given subcutaneously three times a week.) or colony-stimulating factors (CSF, 125-500 g/m^2 per day, slowly intravenously or s.c.).

Among the specific reversible causes of anemia in the setting of HIV infection are drug toxicity, systemic fungal and mycobacterial infections, nutritional deficiencies, and parvovirus B19 infections. Erythropoietin levels in patients with HIV infection and anemia are generally lower than expected given the degree of anemia. An exception to this is a subset of patients with zidovudine-associated anemia in whom erythropoietin levels may be quite high. [1,8,9]

Management [3,4]

The antiretroviral therapy should be discontinued immediately

Treatment of NRTI-associated lactic acidosis is supportive.

Supplementation with essential cofactors (e.g. thiamine and riboflavin) for severely ill patient.

Expert consultation whenever possible.

Administration of vitamin B complex (100 mcg i.m./s.c. daily for 1 week, weekly for 1 month) as well as coenzyme Q10 (100-600 mg/d) and L-carnitine.

Lactic acidosis

Lactic acidosis has been associated with AZT, ddI and d4T therapy. Incidence of NRTI-associated lactic acidosis was 1.3 per 1000 person-years. The clinical course is characterized by often vague complaints of malaise, nausea and vomiting, fatigue and tachypnea followed by liver failure, cardiac dysrhythmias and

death. In addition to this serious but rare syndrome, there is evidence of a persistent mild to moderate elevation of venous lactic acid (hyperlactatemia) in 10% to 20% of patients undergoing long-term treatment with NRTI containing regimens. Risk factors may include older age, obesity, HIV infection itself and nutritional depletion of cofactors and vitamins required for normal mitochondrial function, such as thiamine and riboflavin. [4]

Peripheral neuropathy

HIV-associated distal sensory polyneuropathy is similar to the peripheral neuropathy associated with stavudine, zalcitabine and to a lesser extent, didanosine. This condition may be a direct consequence of HIV infection or a side effect of dideoxynucleoside therapy. It is more common in taller and older individuals and those with lower CD4 counts. Two-thirds of patients with AIDS on electrophysiologic studies show to have some evidence of peripheral nerve disease. Presenting symptoms are usually painful burning sensations in the feet and lower extremities. Findings on examination include a stocking-type sensory loss to pinprick, temperature, and touch sensation and a loss of ankle reflexes. Motor changes are mild and are usually limited to weakness of the intrinsic foot muscles. Other entities in the differential diagnosis of peripheral neuropathy include diabetes mellitus, vitamin B12 deficiency, and side effects from metronidazole or dapsone. For distal symmetric polyneuropathy that fails to resolve following the discontinuation of dideoxynucleosides, therapy is symptomatic; gabapentin, carbamazepine, tricyclics, or analgesics may be effective for dysesthesias. Vitamin B-complex can be given prophylactically in dose of 3-10 mcg/day, orally stavudine should be given according to the weight of the patient to minimize toxicity, especially in malnourished patients.[6,8]

Hepatotoxicity

Hepatotoxicity is a serious complication in patients taking ART and 14-20% of them will experience elevations of liver enzymes, while 2-10% will need to interrupt ART due to severe hepatic injury and marked elevations in liver enzymes. High risk for hepatotoxicity includes coinfection with chronic viral hepatitis B and C, previous hepatotoxicity, cirrhosis, obesity and female gender. Hepatotoxicity and raised transaminase levels are associated with most of the antiretroviral agents, although initially most concern focused on the PIs. Drug-induced hepatitis and hepatic decompensation have been reported with all PIs. The frequency of hepatic events is higher with Tipranavir than with other PIs. Tipranavir is contraindicated in patients with moderate to severe hepatic insufficiency. Increases in unconjugated bilirubin are commonly seen with ATV and generally do not require modification of therapy unless jaundice/icterus is distressing to the patient. The NNRTIs are also associated with transaminitis and hepatotoxicity. Severe hepatotoxicity with NVP is often associated with skin rash or symptoms of hypersensitivity. NRTIs are associated with risk of mitochondrial toxicity and hepatic steatosis.

Baseline transaminases should be checked before beginning ART and all patients should be screened for pre-existing liver disease, most probably hepatitis B and C infections. In patients with normal liver

functions, transamiase may be checked monthly for first 3 months. If stable this can be broadened to 3 months interval. In patients with pre-existing liver disease monitoring should be performed more frequently (every 2 weeks) when initiating therapy. Once stable liver enzymes should be checked monthly. The less hepatotoxic drugs such as lamivudine and abacavir should be preferred in patients at high risk for hepatotoxicity. The onset of clinical symptoms, elevated serum lactate or evidence of severe hepatic dysfunction is suggestive of severe toxicity and ART should be withheld first. Hypersensitivity reactions may be treated with corticosteroids. NRTI induced mitochondrial damage may improve with riboflavin or thiamine therapy.[4, 10]

Pancreatitis

There are a number of factors predisposing to risk of pancreatitis in HIV-infected patients, including some opportunistic infections (eg, cytomegalovirus infection, Mycobacterium avium complex infection, and tuberculosis), malignancies, hypertriglyceridemia, high alcohol intake, and use of pentamidine. Antiretrovirals associated with risk are the NRTIs (didanosine and stavudine), with risk increasing when either is used in combination with hydroxyurea. Some cases of pancreatitis in HIV-infected patients receiving NRTIs have been associated with lactic acidosis. Didanosine's toxicity extends to other exocrine glands, eg, the salivary glands, with elevated levels of salivary amylase and the sicca syndrome. Didanosine should not be combined with zalcitabine as it precipitates pancreatitis. Abdominal pain associated with high pancreatic enzymes (amylase and lipase) three times above the upper normal limit abnormalities observed on ultrasound and/or CT scan should be considered for pancreatitis. Hospitalisation often required and ART should be discontinued. [7]

Hypersensitivity, rash and Stevens – Johnson Syndrome (SJS)

Hypersensitivity reaction (HSR) other than rash and SJS are seen along with use of abacavir (ABC), NNRTIs, raltegravir and maraviroc. ABC induced hypersensitivity is seen in patients with HLA-B*5701. Median onset of reactions is 9 days; approximately 90% of reactions occur within the first 6 weeks of treatment. Symptoms worsen with continuation of ABC. Symptoms of HSR are fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms. Symptoms are resolved after discontinuation of ABC Patients, regardless of HLA-B*5701 status, should not be re-challenged with ABC if hypersensitivity is suspected. TDF can be substituted for ABC.[2,6] HSR is reported when raltegravir given in combination with other drugs known to cause HSR. All ARVs should be stopped if hypersensitivity occurs. The effectiveness of supportive measures such as antipyretics and antipruritic agent is unproven, but such agents are commonly used. Glucocorticoids are ineffective for prevention of nevirapine hypersensitivity.

Rash is a common adverse effect of the NNRTIs, particularly NVP. Approximately 16% of patients taking this agent experience a mild to moderate maculopapular rash, with or without pruritus, on the trunk, face and extremities, within the first 6 weeks on therapy. In ARV-naive patients, risk is greater

for women with pre-NVP CD4 count >250 cells/ mm^3 and men with pre-NVP CD4 count >400 cells/ mm^3. Overall, risk is higher for women than men. Risk can be reduced by gradual escalation of dose over two weeks. SJS/TEN is seen with NVP > DLV, EFV, ETR. Efavirenz can be substituted for NVP or NNTRIs can be replaced with Non-NNRTI ART.[2,6,11]

Gastrointestinal (GI) toxicity[2]

Gastrointestinal effects such as bloating, nausea, vomiting and diarrhea are common, which may be transient or may persist throughout therapy and occur early in most antiretroviral regimens. GI intolerance is relatively common with boosted PIs and is linked to the total dose of ritonavir. Low doses of ritonavir (100 or 200 mg once or twice daily) are just as effective at inhibiting CYP3A4 and are much better tolerated than the 600 mg twice-daily treatment dose. More GI toxicity is seen with lopinavir than with atazanavir or darunavir. Indinavir is associated with oesophageal reflux, but should not be given with antacids, because the salts in antacids can bind to indinavir and prevents its absorption. H2 blockers and proton pump inhibitors can be used to treat oesophageal reflux. These drugs should be taken with food GI effects are often transient in nature, and do not warrant switching therapy. If GI adverse effects are persistent or intolerable, consider drug substitution.

Renal Tubular Dysfunction

Renal toxicity is due to mitochondrial damage and most commonly takes the form of proximal renal tubular dysfunction or Fanconi's syndrome. Rare episodes of acute renal failure and Fanconi's syndrome have been reported with tenofovir. Tenofovir use is associated with small declines in estimated creatinine clearance after months of treatment in some patients and because the dose needs to be reduced if renal insufficiency is present, renal function (creatinine and phosphorus) should be monitored regularly in patient taking this drug. Nephrotoxicity may lead to osteomalacia and phosphate wasting as a consequence of TDF. It is often reversible on stopping TDF. Abacavir should be substituted for TDF. Nephrolithiasis is a frequent complication of indinavir and also has been observed with ATV. [2,7]

Cardiomyopathy

HIV infection is recognized as an important cause of dilated cardiomyopathy, with an estimated annual incidence of 15.9/1000 before introduction of HAART. Another important cause of cardiomyopathy is ART cardiotoxicity. Cardiomyopathy is due to mitochondrial dysfunction resulting from ART. It is seen with NRTIs (zalcitabine, didanosine, and zidovudine). Drug induced cardiomyopathy is diagnosed after exclusion of other causes and is reversible when NRTI treatment was stopped. Doxorubicin which is used to treat AIDS associated Kaposi's sarcoma can lead to dilated cardiomyopathy. In addition to conservative standard therapy (aldosterone receptor antagonists, ACE inhibitors, beta-blockers and amiodarone) implant i.e. biventricular implantable cardioverter defibrillator (bivent-AICD) can be used to improve clinical symptoms. [7,12,13]

Myopathy

Both HIV infection and zidovudine treatment have been associated with myopathy, with the respective disorders being difficult to distinguish on a clinical basis. It is also associated with zidovudine, zalcitabine and didanosine. HIV-associated myopathy may range in severity from an asymptomatic elevation in creatine kinase levels to a subacute syndrome characterized by proximal muscle weakness and myalgias. A variety of both inflammatory and noninflammatory pathologic processes have been noted in patients with more severe myopathy, including myofiber necrosis with inflammatory cells, nemaline rod bodies, cytoplasmic bodies, and mitochondrial abnormalities. Red ragged fibers are a histologic hallmark of zidovudine-induced myopathy. Profound muscle wasting, often with muscle pain, may be seen after prolonged zidovudine therapy. This toxic side effect of the drug is dose-dependent and is related to its ability to interfere with the function of mitochondrial polymerases. It is reversible following discontinuation of the drug. [8]

CNS/Neuropsychiatric Side Effects

CNS/Neuropsychiatric side effects are seen with Efavirenz and symptoms are dizziness, suicidal ideation, sleep disturbance, abnormal dreams, and depression. Risks include history of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and increased plasma EFV concentrations because of genetic factors or increased absorption with food. Bedtime dosing may reduce symptoms. In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug. Persistent or intolerable effects should prompt substitution of EFV with an alternate ARV agent. [2, 6]

Osteopenia and Osteoporosis

Decline in bone mineral density (BMD) have been observed with the start of most ART. Osteopenia and osteoporosis was associated with asymptomatic elevations in serum lactate and lower body weight prior to starting antiretroviral therapy. It has been hypothesized that osteopenia may result from mitochondrial dysfunction in bone. PIs may inhibit new bone formation by stimulating osteoclast activity or inhibiting osteoblast activity. It is evaluated by dual-energy x-ray absorptiometry (DEXA) at the spine and hip. Treatment of osteoporosis in the setting of antiretroviral therapy is evolving, and referral for specialist assessment, when possible. Standard therapy, including vitamin D (3-6 lac IU in every 2 to 6 months or 400 IU daily) and calcium supplementation (1g/day) and exercise, as well as pharmacologic measures such as hormone replacement and bisphosphonate therapy may be indicated. Modification of ART because of reduced BMD should be predicated on the clinical significance of the decline. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain. [2, 3, 4]

Conclusion:

Adverse effects have been reported with the use of all antiretroviral drugs. During initiation of ART, safe and effective alternative drugs for the regimen should be selected and patient's underlying conditions, concomitant medications, and prior history of drug intolerances should be considered. Safety monitoring is required for early recognition of these adverse events and their management, as it is important for overall patient management. Switching from an effective ART regimen to a new regimen or change of drug in the regimen must be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment.

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DRUG INDUCED OCULOTOXICITY

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Oculotoxicity is damage to eye that can be caused due to many factors including infections (viral, bacterial, fungal, protozoal), auto-immune or drug induced. When patients present with ocular conditions that have no apparent cause, it is important to consider whether it is due to medication.[1] Some of the ocular adverse drug reactions are common and well defined (Table 1) while others are rare. However the rare ADRs are equally important as they can cause permanent damage to the eye.[2] There are very few studies evaluating the frequency of ADR related to eye.[2] In the Medicines and Healthcare products Regulatory Agency's (MHRA's) Yellow Card system, 4.3 per cent of the suspected ADRs were directly referred to disorders of the eye.[3]

Table 1. Principal ocular reactions and causative agents[3]

Ocular Reactions	Causative drug
Dry eye	Anticholinergics (tricyclic anti-depressants and antispasmodics), bisphosphonates, isotretinoin
Corneal and lens deposits	Amiodarone, chloroquine, chlorpromazine, gold, hydroxychloroquine, indomethacin, tamoxifen
Cataracts	Antimitotics, glucocorticoids, isotretinoin, phenytoin
Eye accommodation	Benztropine, phenothiazines, TCAs
Raised intraocular pressure and glaucoma	Anticholinergic agents, corticosteroids
Retinal and nerve damage	Ethambutol, isoniazid, tamoxifen, vigabatrin

In this article we have compiled the more common and important adverse conditions of the eye caused by drugs.

1. Conjunctival toxicity:

Drug induced conjunctival toxicity is mainly due to drug deposition of chlorpromazine, tetracycline and Vitamin D in conjunctiva. Chlorpromazine at high dosages commonly causes abnormal pigmentation of the eyelids, inter-palpebral conjunctiva and cornea. Other prevalent ocular side-effect is anterior capsular and subcapsular lens pigmentation, followed by corneal endothelial pigmentary changes mostly isolated, brownish, dust-like specks in the anterior surface of the lens to stellate cataracts that can impair visual acuity. Treatment includes dosage reduction or therapy changed only if the patient becomes symptomatic.[4] Amongst the tetracyclines, minocycline (a second generation drug) is most often associated with the adverse effect of scleral pigmentation.[5] Minocycline can cause palpebral

conjunctival greyish deposits in which auto fluorescence can be readily demonstrated.[6] One case report mentioned occurrence of green crystals on the conjunctiva of both eyes in a patient treated for acne vulgaris with tetracycline 500 mg a day for the past 2½ years.[7]

2. Stevens – Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN):

SJS and TEN are rare but severe cutaneous drug reactions also affecting the mucous membrane including the ocular membrane. Incidence of SJS and TEN is 2.6-7.1 persons per million populations per year in US. SJS can be complicated with ocular complications in about 40% of cases comprising symblepharon, hypopyon, corneal scarring, viral or bacterial conjunctivitis, blepharitis and corneal xerosis.[8] SJS/TEN have been observed with more than 100 drugs with antimicrobials (37.27%), anti-epileptic drugs (35.73%) and NSAIDs (15.93%) more commonly associated. Carbamazepine (18.25%), phenytoin (13.37%), fluoroquinolones (8.48%) and paracetamol (6.17%) were the commoner drugs. Risk for the development of SJS/TEN with anti-epileptics is largely confined to initial 8 weeks. Early use of short term dexamethasone therapy seems beneficial. Short term dexamethasone therapy (1.5 mg/kg/day) on three consecutive days at an early stage of the reaction may reduce mortality without affecting the healing time.[8]

3. Corneal Toxicity:

The cornea may be involved alone or with the conjunctiva. Corneal toxicity is caused by chemical trauma, for which diagnosis is seldom a problem, and also by iatrogenic and factitious disease (intentional disease production by the patient), which are both often overlooked.[9] Table 2 gives a list of drugs causing corneal reactions.

Table 2: List of common drugs causing corneal reactions.[9]

Effects	Examples
Corneal epithelial deposits	Amiodarone, chloroquine, mepacrine
Corneal stromal deposits	Metals (copper, gold, mercury, silver) Drugs (indomethacin, chlorpromazine)
Lacrimation	Arsenic, chloral hydrate, heroin
Inflammation	Practolol, isotretinoin
Photosensitised keratitis	Methoxsalen (psoralen used for PUVA)
Corneal epithelial vacuoles	Thiacetazone (antimycobacterial)
Corneal endothelial injury	Animals only (dichloroethane in dogs)

Avoiding the use of preserved medications or those known to be toxic (i.e. aminoglycosides, some glaucoma medications, and antivirals) in high-risk cases (chronic disease, dry eyes, and patients on multiple topical therapies) is the most important preventive measure. Treatment in corneal toxicity includes identification of the culprit drug and withdrawing the medications where possible. Drug and

preservative side effects should be understood for each drug that is prescribed so that toxicity and allergies are included in the risk/benefit assessment for topical therapy.[9]

4. Dry Eye syndrome:

Keratoconjunctivitis sicca, also known as dry eye, is a growing public health concern and affects as many as 17% of women and 11.1% of men in the United States.[10] It is defined as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface which is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."[11] Systemic or topical ocular medications and preservatives used in topical ocular drugs may cause dry eye through the drug's therapeutic action, ocular surface effects, or preservatives, and the effects probably are additive. Long-term use of topical ocular medications, especially those containing preservatives such as Benzalkonium Chloride (BAK), may play an important role in this condition and the role of polypharmacy needs to be further studied. The following tables give the list of systemic and topically applied drugs implicated for causing medication-related dry eye.

Table 3: Systemic drugs probably causing or aggravating dry eyes[12]

Class	Examples
Antihypertensive agents (beta-agonists)	Acebutolol
Antihypertensive agent (alpha-agonists)	Atenolol
Antiarrhythmic and beta blockers	Carvedilol, labetalol, metoprolol, nadolol, pindolol, clonidine, prazosin, oxprenolol, propranolol
Antipsychotic agents	Chlorpromazine, fluphenazine, lithium carbonate, perphenazine, prochlorperazine, promethazine, quetiapine, thiethylperazine, thioridazine, brompheniramine, carbinoxamine, chlorphenamine, (chlorpheniramine), clemastine, cyproheptadine, dexchlorpheniramine
Bronchodilators, Antispasmodics/ antimuscarinic, Antiarrhythmic agents	Diphenhydramine, doxylamine, ipratropium, atropine, homatropine, tolterodine, hyoscine (scopolamine), hyoscine methobromide, (methscopolamine), disopyramide
Antineoplastic agents	Busulfan, cyclophosphamide, interferon (alpha, beta, gamma, or PEG), vinblastine, cetuximab, erlotinib, gefitinib,
Antihistamines	Cetirizine, desloratadine, fexofenadine, loratadine, olopatadine, tripelennamine
Antidepressants	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Antileprosy agents	Clofazimine
Antirheumatic agents/analgesics	Aspirin, ibuprofen

Class	Examples
Sedatives and hypnotics	Primidone
Drugs secreted in tears	Aspirin, chloroquine. clofazimine, docetaxel, ethyl alcohol, hydroxychloroquine, ibuprofen, Isotretinoin
Antiandrogens	Tamsulosin, terazosin, doxazosin, alfuzosin
Neurotoxins	Botulinum A or B toxin
Antimalarial agents	Chloroquine, hydroxychloroquine, retinoids, isotretinoin
Antiviral	Acyclovir
Thiazides	Bendroflumethiazide, chlorothiazide, chlorthalidone, hydro-chlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, polythiazide, trichlormethiazide
Cannabinoids	Dronabinol, hashish, marijuana
Chelating agents	Methoxsalen
Strong analgesics	Morphine, opium/opioids
Antipsychotic agents	Pimozide

Table 4: Topical ocular drugs that may cause or aggravate dry eye[12]

Class	Examples
Agents used to treat glaucoma	
Beta-blocking agents	Betaxolol, carteolol, levobunolol, metipranolol, timolol
Adrenergic agonist drugs	Apraclonidine, brimonidine
Carbonic anhydrase inhibitors	Brinzolamide, dorzolamide
Cholinergic agents	Pilocarpine
Prostaglandins	Bimatoprost, latanoprost, travoprost
Others	Dipivefrine, unoprostone, ecothiopate
Agents used to treat Allergies	Emedastine, olopatadine
Antiviral agents	Aciclovir, idoxuridine, trifluridine
Decongestants	Naphazoline, tetryzoline
Miotics	Dapiprazole
Mydriatics and cycloplegics	Cyclopentolate, tropicamide, hydroxyamphetamine
Preservatives	Benzalkonium chloride
Topical local anesthetics	Cocaine, proxymetacaine, tetracaine
Topical ocular NSAIDs	Bromfenac, diclofenac, ketorolac, nepafenac

It is widely recognized that inflammation has a significant role in the etiopathogenesis of dry eye, promoting ocular surface disruption and symptoms of irritation, a number of anti-inflammatory treatments are currently in use for its management.[13] Other options under evaluation include tear substitutes, some novel lubricating drops and tear secretagogues.[14]

5. Drugs causing Glaucoma:

Glaucoma is a form of optic neuropathy with specific visual field loss. It is usually associated with raised intraocular pressure (IOP). Several drugs have the potential to cause raised IOP; this can occur via an open-angle or angle-closure mechanism.

Open-angle: The most common drugs causing this condition are the steroids. Steroid-induced IOP elevation could be secondary to increased resistance to aqueous outflow, increased accumulation of glycosaminoglycans, increased production of trabecular meshwork-inducible glucocorticoid response (TIGR) protein, mechanically obstructing the aqueous outflow and by others mechanisms. In this case, discontinuation of corticosteroids or using a lower potency steroid medication, such as the phosphate forms of prednisolone and dexamethasone, loteprednol etabonate or fluorometholone should be considered. In those patients who must continue to be on corticosteroid medications, topical antiglaucoma medications are considered.[15,16]

Closed-angle: Medications, by stimulating sympathetic or inhibiting parasympathetic activation causing pupillary dilation which directly or indirectly can precipitate acute angle-closures in predisposed patients. These drugs include adrenergic agonists (e.g. phenylephrine), β2-specific adrenergic agonists (e.g. salbutamol), non-catecholamine adrenergic agonists (e.g. amphetamine, dextroamphetamine, methamphetamine and phendimetrazine) and anticholinergics (e.g. tropicamide). Histamine H1receptor antagonists (antihistamines) and histamine H2 receptor antagonists (e.g. cimetidine and ranitidine) have weak anticholinergic adverse effects. Antidepressants such as fluoxetine, paroxetine, fluvoxamine and venlafaxine have been associated with acute angle-closures. Sulfa-containing medications like topiramate can also result in acute angle-closures but by some different mechanism. This condition too responds to discontinuation of the offending drug however in some cases antiglaucoma medications may have to be started. Other treatments include laser trabeculoplasty, argon laser peripheral iridoplasty (ALPI), laser iridotomy or trabeculectomy can be performed.[16]

6. Drugs causing Cataract:

Cataract is considered as the most serious toxic effect that can occur on the lens, since they are irreversible and can necessitate removal. Glucocorticoids most commonly and chlorpromazine to a lesser extent are implicated in causation of cataract. Long term use of glucocorticoids is a significant risk factor for the development of posterior subcapsular cataract. Topical and systemic steroids both have propensity for cataract formation with topical steroids having increased risk. Once opacification of lens occurs it is usually progressive, and treatment includes cataract removal by surgery.[17, 18]

Certain other drugs also associated with cataract formation include lovastatin, amiodarone[19] antimitotics such as busulfan, nitrogen mustards, isotretinoin and phenytoin. Although high-dose tamoxifen (up to 180mg) has been associated with cataracts and retinopathy, standard doses (20mg) are considered to have a lower propensity to cause eye damage, have less severe effects and are reversible in nature.[3]

7. Retinopathy:

The retina is the part of the eye suffering most damage from pharmaceutical drugs.[1] Retinopathy due to drugs can be pigmentary, choroidal or crystalline in type. The main lesions occur in the macula and can include degeneration, oedema, alterations in the pigment, detachment, vascular disorders (e.g. hypertensive, diabetic, or other types of retinopathy), inflammation, haemorrhages, and deposits. Table 5 below reports the drugs mainly responsible for causing visual damage with a particular affinity for the retina.[1]

Table 5. The most noted drugs inducing damages to the retina.[1]

Drug Class	Examples
Antimalarial	Quinine
Synthetic Antimalarials	Chloroquine sulfate, hydroxychloroquine sulphate, mefloquine
Phenothiazines	Chlorpromazine
Chelating agent	Desferrioxamine
Cardiac Glycosides	Digitoxin, digoxin
Antibiotic and Antibacterial Agents	Amikacin, ethambutol, cephalosporins, fluoroquinolones
Anticoagulants	Coumarins
Diuretics	Acetazolamide, hydrochlorothiazide
Anticancer Drugs	Mitomycin, doxorubicin, daunorubicin, cisplatin
Anti Gout	Allopurinol
NSAIDs	Indomethacin, ketoprofen, naproxen, oxyphenbutazone, piroxicam
Antiepileptics	Valproic acid, phenytoin, hydantoin
Antidepressants / MAO inhibitors	Isocarboxazid

Attention is also focused on drugs more recently suspected of adverse reactions in the retina including vigabatrin, gabapentin, sildenafil, isotretinoin, interferon, and omeprazole.[1]

8. Drugs induced optic neuropathy:

Optic neuropathy is a frequent cause of vision loss encountered by ophthalmologist. It can be caused by demyelination, inflammation, ischemia, infiltration, compression, and hereditary and toxic/nutritional

causes. Optic nerve dysfunction can be caused by various drugs, toxins, nutritional deficiencies or due to hereditary cause.[20] Toxic optic neuropathy (TON) is a group of medical disorders which can be defined by visual impairment due to optic nerve damage by a toxin.[21] The following table gives the list of drugs related to optic neuropathy.

Table 6: Toxic and drug-induced optic neuropathies [22]

Cause	Examples
Toxins	Methanol (methyl alcohol)
	Ethylene glycol
	Toluene (glue vapor)
	Other solvents (for example, styrene, perchloroethylene)
	Lead
Drugs	Ethambutol (antitubercular drug)
	Linezolid (antimicrobial drug)
	Disulfiram (treatment for alcoholism)
	Cyclosporin, tacrolimus (immunosuppressants)
	Cisplatin, carboplatin, vincristine (chemotherapeutic agents)
	Tamoxifen (nonsteroidal estrogen antagonist)
	Vigabatrin (antiepileptic drug)
	Amiodarone (anti-arrhythmic benzofuran derivative)*
	Sildenafil (cGMP-specific phosphodiesterase inhibitor)*
Vitamin deficiencies	Folate, vitamin B12 (cobalamin), vitamin B1 (thiamine) or vitamin B2 (riboflavin) deficiency

**Possible drug cause of optic neuropathy. Abbreviations: ION, ischemic optic neuropathy; NAION, nonarteritic anterior ischemic optic neuropathy.*

The first step in managing toxic optic neuropathy, as with any toxic process, is to remove the offending agent. This may cause some reversal of the process. Tobacco-alcohol amblyopia is a term used for a condition that may be due both the toxic effect of the tobacco and a nutritional deficiency state.[20] Treatment of such and other conditions includes improved nutrition and vitamin supplementation. Unless the vision loss is extensive, there is an excellent prospect for recovery or at least improvement. Patients with toxic/nutritional optic neuropathy should be observed initially every 4-6 weeks and then, depending on their recovery, every 6-12 months.[21]

9. Pathologies of eye lids and eye lashes:

The common conditions of the eye lids and eye lashes include madarosis, loss of eye lashes and excess growth of eye lashes, to name a few.

Madarosis: Madarosis is defined as hair loss of the eyebrows (superciliary madarosis) or loss of eyelashes (ciliary madarosis).[23]

Retinoids, heparin, angiotensin-converting enzyme inhibitors, and androgens can precipitate shedding of telogen hair and madarosis. Other drugs commonly attributed to causing madarosis are miotics, anticoagulants, anti-cholesterol drugs, antithyroid drugs, propranolol, valproic acid, boric acid, and bromocriptine. Anticoagulants in high doses have been found to produce loss of scalp, pubic, axillary, and facial hair with loss of eyebrows after a latent period of a few weeks of treatment with dextran and heparin. Propranolol can cause diffuse alopecia along with loss of eyebrows due to telogen effluvium, usually after three months of therapy. Loss of medial aspect of eyebrows can be seen in fetuses exposed to valproic acid. Levodopa has been noted to cause severe diffuse alopecia within three months of daily use. Hair loss can occur soon after starting topical minoxidil therapy (due to detachment of club hairs following resting hairs reentering anagen), and after cessation of therapy.[24] Reversible loss of eyebrows and lashes along with other ocular side effects, possibly due to use of niacin to treat hyperlipidemia, has been reported.[24] Identification of the cause and stopping the drug can be effective treatment. Madarosis can be camouflaged by eyeliner, artificial lashes or permanent pigment tattooing. Interlesional triamcinolone can be tried in the case while other may require surgical repair of the traumatic madarosis.[23]

Milphosis: Loss of eyelashes is also known as milphosis.[23] Loss of eyelashes may occur in numerous skin infections and other conditions, endocrinologic disorders, traumatic insults or sue to certain drugs. Drugs like miotics, anticoagulants, anticholesterol drugs, antithyroid drugs, boric acid, bromocriptine, propranolol, valproic acid have been implicated to cause this condition.[25] Intoxication with Arsenic, bismuth, thallium, gold, quinine, vitamin A is also known to cause this condition.[25] There is a significant positive association between long-term use of eye cosmetics like mascara and fall of eyelashes.[26]

Hypotrichosis of the eyelashes: Causes of eyelashes hypotrichosis are many, including hereditary, aging, chemotherapy, other medical treatment and unknown causes. Physical trauma involving the face, eye surgery and trichotillomania may also cause thin or absent lash growth.[27] Apart from the other cosmetic options, bimatoprost ophthalmic solution 0.03%, is the only FDA-approved drug for the treatment of hypotrichosis of the eyelashes. Bimatoprost results in increased eyelash growth including improvements in length, thickness, and fullness in a controlled clinical trial.[27]

Trichomegaly: Trichomegaly or hypertrichosis is defined as an increase in the length, thickness, stiffness, curling, and pigmentation of existing eyelashes beyond normal variation for a patient's ethnicity,

age, and/or gender. Eyelash dysfunction may have significant effects, ranging from ocular discomfort to visual acuity decrease.[28] Trichomegaly has been described as part of congenital syndromes, in human immunodeficiency virus 1 infection, associated with an autoimmune disease, or after certain drugs such as latanoprost, phenytoin, zidovudine, penicillamine, cyclosporine and interferon alpha. Recent communications have reported that EGFR inhibitors used in the treatment of certain malignancies can also lead to symptomatic adnexal and ocular surface changes.[29] Trimming and epilation have been found to be satisfactory and safe therapeutic options.[28]

10. Drugs causing discolouration of tears:

Rifampicin is an antibiotic used as first line drug for treatment of tuberculosis. It is also used as prophylactic for meningococcal meningitis. Rifampicin causes reddish-brown discolouration of tears. The discolouration of tears due to rifampicin is symptomless and it does not affect normal vision and rifampicin can be continued further.[30] Clofazimine which is primarily is anti-leprosy drug have also shown to cause reddish coloration of sweat, urine and tears.[31]

11. Photophobia:

Photophobia is associated with conditions like ocular inflammation (iritis, uveitis), corneal neuropathy, interstitial keratitis, retinal dystrophy, optic neuritis, papilledema, migraine, brain injury, meningeal irritation (meningitis, subarachnoid hemorrhage) and certain psychiatric conditions. Medications causing photophobia include barbiturates, benzodiazepam, chloroquine, methylphenidate, haloperidol, zoledronate, etc. Treatment includes use of darkly tinted lenses or sunglasses. However some reports have pointed out that their ineffectiveness and their habit forming tendency. Some specific optical tints have been tried successfully to combat photophobia. However caution should be exercised due to reports that red colour shades exacerbated migraine-associated photophobia. Sunglasses do make sense in the bright sunlight for patients with migraine, tension type headaches and those with light sensitivity. Other pathologies like blepharospasm, ocular inflammation, migraine, anxiety and panic disorder resulting in photophobia should be promptly treated to reduce the symptoms of photophobia.[32]

Conclusion: Ocular adverse effects due to systemic medication can range from mild to severe. Early recognition of these effects is important for prompt management to prevent and minimize serious complications. In most cases drug discontinuation is the first step of management however this may be done only when necessary. In those cases where treatment is to be continued, use of palliative therapies is warranted. In those drugs with a known propensity to affect the eye, appropriate monitoring and warning to the patients should be issued.

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ANALYSIS OF ADVERSE DRUG REACTION REPORTED

(July 2014 - October 2014)

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Total Case Reports: 147

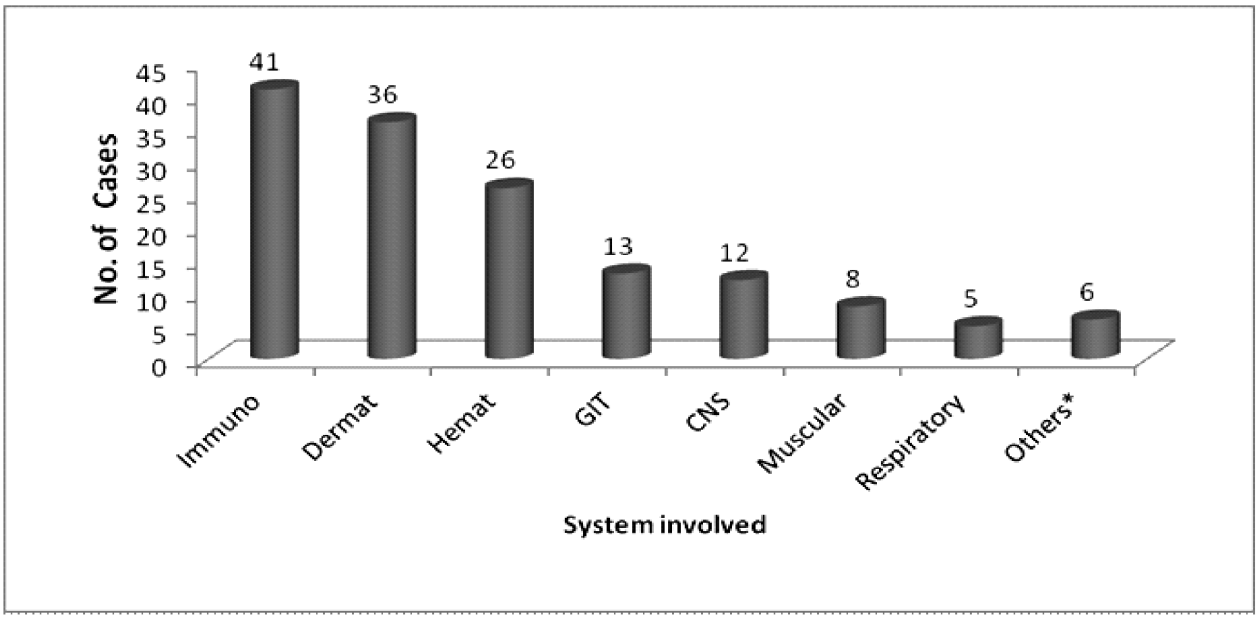
I. Age and Gender distribution:

Age groups	Number of patient	Males	Females
<3yrs	22	13	9
3-17yrs	28	18	10
18-44yrs	68	27	41
45-60yrs	15	6	9
>60yrs	14	7	7
Total	147	71	76

II. Seriousness of reactions reported:

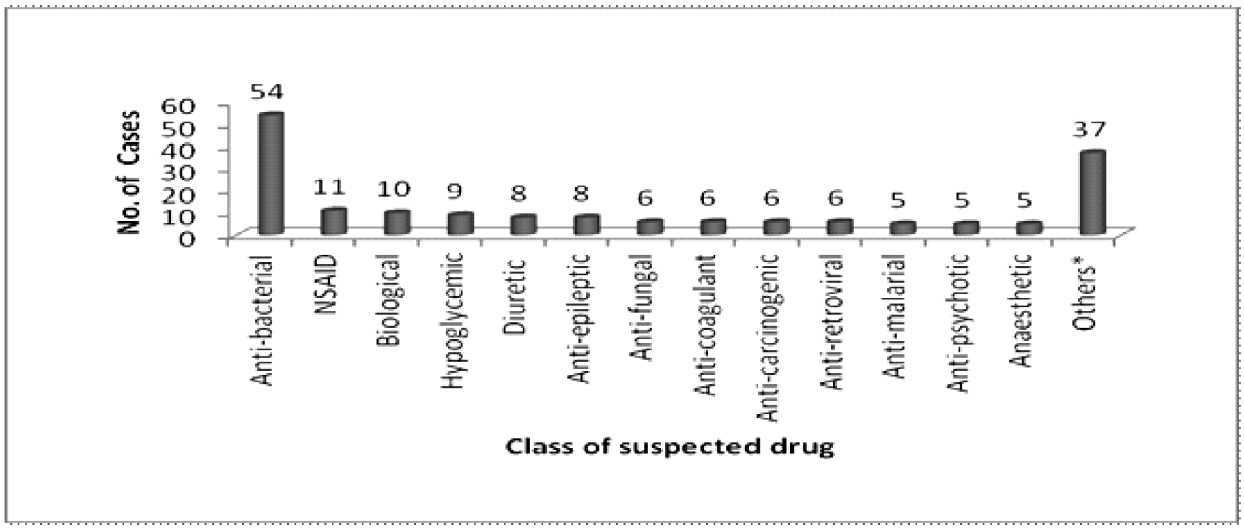
Seriousness of reactions reported	Number of cases (n=147)
Yes	135
No	12

III. System of distribution of the adverse drug reaction: (n=147)



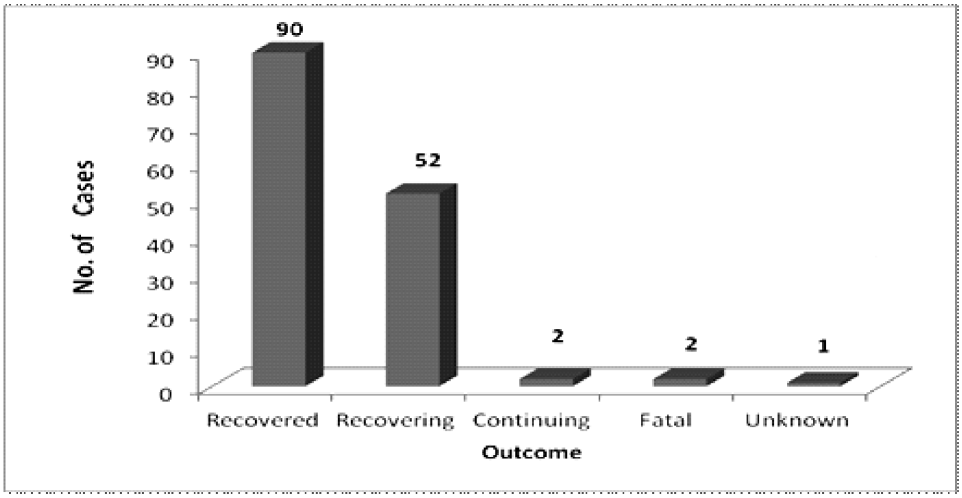
* Others include cases involving renal, ophthalmic and cardiovascular system.

IV. Class of Suspected Drugs:

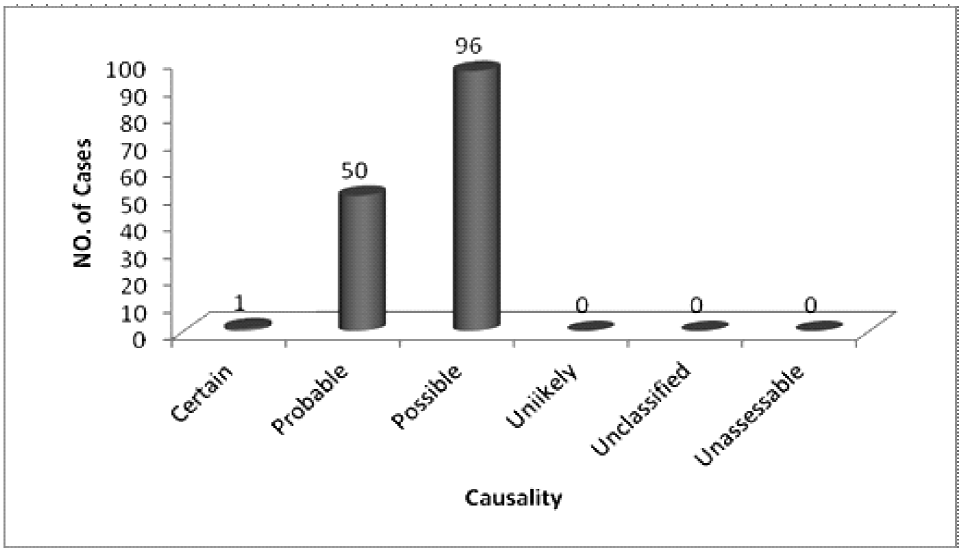


*Others include hypolipidemic, corticosteroid, immunosuppressant, mood stabilizer, antidote, CNS Stimulant, antiemetic, antacid, hematinic, antihypertensive, antihistaminic and intravenous fluids.

V. Outcome of the reaction: (n=147)



VI. Causality assessment (WHO causality assessment scale): (n=147)



DRUG INDUCED SEIZURE DISORDER

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Introduction: Cycloserine (CS) is a second line drug mainly used in the management of Multi Drug Resistance Tuberculosis (MDR-TB).With the increase in MDR-TB cases, the use of cycloserine has also increased. Among the second-line agents, drug associated with most adverse drug reactions (ADRs) is cycloserine;causing psychosis and seizures.[1] Seizures are infrequent but a limiting adverse reaction for its use.[2] Reports of adverse effects with Acyclovir areuncommon and occur almost always in adults, with renal dysfunction and neurotoxicity being the most frequently reported. Both oral and intravenous administration of acyclovir is associated with adverse reactions.[3] Overlapping toxicity between drugs used for HIV and TB could complicate the management of HIV/TB coinfected patients, particularly those carrying multiple opportunistic infections.[4]

Here we, report a case of drug induced seizure in an immunocompromised patient with MDR-TB exposed to CS as well as acyclovir both having a potential to cause neurotoxicity.

Case history:

A 36 year old male, known case of immunocompromised status with MDR-TB on antitubercular therapy since 5 months reported to the medicine department with complaints of generalized tonic clonic seizure on 6th of September 2013. Patient's medications for MDR-TB were Tab. Protionamide 250 mg thrice a day, Tablet Cycloserine 250 mg thrice a day and Tablet Levofloxacin 500 mg twice a day since 128 days (approx. 4 months) along with pyridoxine supplement. Patient being a diagnosed case of immunocompromised status was taking Tab. Atazanavir 300 mg twice a day, Tab. Ritonavir 100 mg twice a day and Tab. Tenofovir 200 mg twice a day. Patient also received Tablet Acyclovir 400 mg thrice a day for acute HIV syndrome since 90 days.

On examination, he was afebrile with normal vital parameters. Neurological examination revealed no sensory or motor abnormalities.The cerebrospinal fluid examination was normal. Serum electrolytes and calcium levels were normal. MRI Brain & spine were normal.

In view of this, the diagnosis of drug induced convulsion was made and cycloserine and acyclovir were withdrawn. He was started on oral valproate and diazepam. Also cotrimoxazole 1g twice a day for prophylaxis of opportunistic infections like Pneumocystis jirovecii pneumonia was given. Rest of his treatment for immunocompromised status was continued. After 3 days of monitoring patient was discharged as he recovered symptomatically.

Discussion:

Cycloserine (CS) is a broad-spectrum antibiotic that has shown moderate in vitro bactericidal and clinical activity against Mycobacterium tuberculosis since its discovery in 1955. The World Health Organization (WHO) currently classifies CS as a secondlineGroup IV oral bacteriostatic drug. CS is valuable for the treatment of drug-resistant cases, as it does not share cross-resistance with other active TB agents.[5] Neuropsychiatric symptoms are common with cycloserine therefore is notoriously called as "psych-serine".[6] The frequency of any adverse drug reaction with cycloserine was reported as 9.1%; it was 5.7%for psychiatric adverse drug reactions, and 1.1%for CNS related adverse drug reactions.[7]

The neurotoxicity may manifest as drowsiness, headache, dizziness, dysarthria, psychosis, seizure and coma. This may be dose-related and more commonly seen with daily doses greater than 500 mg. This is consistent with our case also where patient was taking 750 mg daily. Convulsions occur in about 10 percent of all patients receiving large doses of cycloserine.[7] They are frequently seen with peak serum concentrations > 30 mcg/ml of CS. Serum concentration of CS was not assessed in our case.[8] CS induced seizures can develop within two weeks to two months of therapy.[8,9] In this case patient developed seizure after 4 months of CS treatment.

The risk of cycloserine induced seizure increases with concomitant ingestion of alcohol. WHO guidelines do not recommend the use of CS if the patient has a history of seizures or epilepsy.[1] Vitamin B12 and pyridoxine deficiency may be the other associated factors in cycloserine induced seizure.[6] The patient neither had history of seizures in past nor of alcohol intake. Cycloserine is selective partial agonist of the N-methyl-D-aspartic acid (NMDA) glutamatergic receptors found in the basolateral nucleus of the amygdala.[10] Glutamate being major excitatory neurotransmitter is mainly involved in initiation and propagation of seizure disorder.[11]

Cycloserine induced seizures are mostly focal however may be generalized as seen in this case. Discontinuation of the drug and symptomatic management of seizure disorder along with pyridoxine supplementation is recommended. The reversible cytotoxic edema in the dentate nuclei may be considered as one ofthe MRI findings associated with cycloserine toxicity. Early diagnosis by using brain MRI and prompt cessation of the medication may facilitate reversibility of the brain lesions.[7]

Acyclovir is an effective antiviral drug. Its use is particularly important in proven or suspected Herpes orVaricella infections.[3] The incidence of neurotoxicity of acyclovir is increased due to the rise in number of AIDS and transplant patients. Renal dysfunction is a known risk factor for acyclovir neurotoxicity.[12] Johnson et al reported a case where an elderly woman started on acyclovir developed acute renal failure and confusion followed by seizures within two days of oral acyclovir therapy which resolved after 9 days of stopping the drug.[13] Valacyclovir a congener of acyclovir is also associated with neurotoxicity but most commonly accompanied by chronic or acute renal failure preceding it.[14]

In this case, patient developed seizures after 3months of therapy. In our patient there were no signs of alteration of renal parameters thus favoring implication of cycloserine in causing seizures. Though, a possibility that both the drugs together might have increased the liability for neurotoxicity cannot be negated.

In our case patient recovered completely in 3 days after discontinuation of CS and acyclovir. According to WHO scale of Causality assessment, the association of cycloserine and acyclovir with the ADR can be considered to be "Possible" because more than one drug can be implicated and discontinuation of both the drugs lead to complete recovery i.e. dechallenge is positive for both of them.

For patients with the most serious forms of MDR-TB, where treatment options are limited, CS is potentially life-saving, yet due to its poor perceived safety profile, CS has not been uniformly recommended for TB treatment. Adequate information should be provided to patients, their families and attending health care workers about possible toxicity due to CS.[15] Thus bearing in mind the overlapping toxicities of antitubercular and other antiviral drugs is important in curbing the adverse effects.

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PUBLISHED CASE REPORTS ON CYCLOSERINE INDUCED NEUROLOGICAL SYMPTOMS

Compiled by **Dr. Jaisen Lokhande**

Assistant Professor, Department of Pharmacology, LTMMC & GH, Sion, Mumbai-22.

Reversible magnetic resonance imaging findings in cycloserine-induced encephalopathy: A case report

Neurology Asia 2014; 19(4) : 417 - 419

Kim S, Kang M, Cho JH, Choi S

Cycloserine is a broad spectrum antibiotic used as a second drug for treatment of drug resistant tuberculosis. Inappropriate usage in excessive doses can give rise to neurological problems. We report a case who developed aphasia, anxiety and seizure during anti-tuberculosis medication. MRI of the brain showed reversible cytotoxic edema in dentate nuclei. Clinical and MRI findings were consistent with cycloserine toxicity.

A case of multi-drug resistant tuberculosis showing psychiatric adverse effect by cycloserine.

Kekkaku. 2008 Jan;83(1):21-5.

Fujita J, Sunada K, Hayashi H, Hayashihara K, Saito T.

A 45-year-old man with multi-drug resistant tuberculosis were referred to our hospital for treatment. We started chemotherapy with cycloserine (CS), ethionamide (TH), kanamycin (KM), pyrazinamide (PZA), para-aminosalicylic acid (PAS) and gatifloxacin (GFLX). Two months later, psychosis and seizure occurred and worsened day after day. We suspected that these symptoms were due to CS. After stopping CS, psychosis and seizure disappeared. After surgical operation, positive tubercle bacilli in sputum converted to negative both on smear and culture. He was successfully discharged from our hospital. We should take care of side effects with second-line drugs that are often used in treating multi-drug resistant tuberculosis.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by **Dr. Jaisen Lokhande**

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Ziprasidone causing rare but potentially fatal skin reactions: A new warning has been added to the ziprasidone drug label regarding the occurrence of a serious condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Ziprasidone is an atypical antipsychotic drug used to treat schizophrenia and bipolar I disorder. The signs and symptoms of DRESS appeared in 6 patients between 11 and 30 days after ziprasidone treatment. The US FDA has recommended that health-care professionals should immediately stop treatment with ziprasidone if DRESS is suspected.

Amoxicillin and risk of erythroderma (dermatitis exfoliative) and meningitis aseptic: The Ministry of Health Labour and Welfare (MHLW) and the Pharmaceutical and Medical Devices Agency (PMDA) announced that revision of the package insert for amoxicillin. It is recommended that the package insert should include erythroderma (dermatitis exfoliative) and aseptic meningitis in the "Clinically significant adverse reactions" section.

Levetiracetam and risk of Rhabdomyolysis: Levetiracetam is indicated as concomitant therapy with other antiepileptic drugs for partial seizures (including secondary generalized seizure) in patients who fail to show a satisfactory response to other antiepileptic drugs. The MHLW and the PMDA announced revision to the package insert for levetiracetam. It is recommended that the package insert should include "Rhabdomyolysis" "Clinically significant adverse reactions" section of the package insert. Patients should be carefully monitored. If signs or symptoms including myalgia, feeling of weakness, increased creatine kinase (creatine phosphokinase), increased blood myoglobin, and increased urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be taken

Topiramate Visual field defects: Topiramate is an anti-epileptic agent and also indicated for the prophylaxis of migraine headache in adults. It has been found in clinical trials to cause visual field defects. This visual field defects with topiramate was independent of elevated intraocular pressure. Most of these adverse events were reversible after topiramate was discontinued however, some cases were not. It is recommended that this adverse reaction should be included in the package insert health-care professionals should advise patients and caregivers of this issue and educate them regarding the signs and symptoms of visual field defects.

Adapted from: *WHO Pharmaceuticals Newsletter. http://www.who.int/medicines/publications/pharmnewsletter1-2015.pdf?ua=1 (accessed 10 March 2015).*

CROSSWORD PUZZLE

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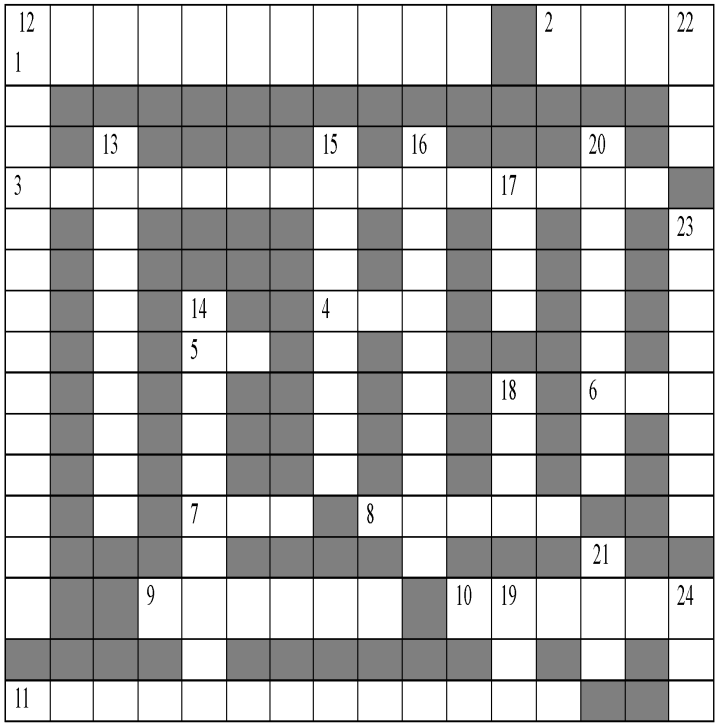

ACROSS

Q1. The newer antiepileptic drug Topiramate has a teratogenic risk of causing ----- in male infants.(11)

Q2. Lamotrigine can cause a severe reaction in the form of ----, particularly in children, requiring withdrawal. (4)

Q3. Few cases of ---- were reported with Metamizol, an NSAID and hence it is banned in USA and some European countries.(15)

Q4. Due to induction of ---- synthetase enzyme in mitochondria, barbiturates can cause adverse effect of precipitating acute porphyria.(3)

Q.5. The estrogen component of ----- has been mainly held responsible for the serious complication of venous thromboembolism.(2)

Q.6. A higher incidence of ----- burn like severe skin reaction on exposed parts in some individuals has been noted with demeclocycline & doxycycline.(3)

Q.7. Hepatotoxicity in fast acetylators and peripheral neuritis in slow acetylators can be the adverse effect of this anti-tuberculosis drug. (3)

Q.8. Adverse effects in the form of blood dyscrasias and ----- dysfunction have restricted the use of mianserin.(5)

Q.9. A reversible Fanconi syndrome like condition is produced by outdated tetracyclines which can cause ----- damage.(6)

Q 10. Triflupromazine, an antipsychotic, frequently produces the adverse effect of acute ----- dystonias in children, especially when injected.(6)

Q.11. Amoxapine used to treat psychotic depression can cause the adverse effect of ----- in males.(13)

BELOW

Q.12. The adverse effect of ----- due to Naltrexone is not seen with Nalmefene when used to treat opioid overdose .(14)

Q.13. Amitriptyline and Dosulepin are particularly dangerous in overdose as higher incidence of ----- is reported with them. (10)

Q.14. This drug used to treat gout accumulates in the intestine causing bloody diarrhea and abdominal cramps.(10)

Q.15. ----- a non-opioid antitussive can release histamine and produce the adverse effect of bronchoconstriction in asthmatics.(9)

Q.16 Clozapine has been reported to cause the adverse effect of ----- which starts like flu but may progress to death.(11)

Q.17. The adverse effect of gum hypertrophy due to phenytoin can be minimized by maintaining good --------- hygiene.(4)

Q.18. Carbamazepine produces ----- related neurotoxicity such as sedation, vertigo & ataxia.(4)

Q.19. Nitrofurantoin, a drug used for prophylaxis of lower -----, can cause adverse effect of haemolysis in G6PD deficiency.(3)

Q.20. ----- is the most common side effect (upto 25% incidence with high doses) due to probenecid.(9)

Q.21. Dry persistent cough is the most common side effect requiring discontinuation of ----- inhibitors.(3)

Q.22. ----- flushes, vomiting, vaginal bleeding & menstrual irregularities are the side effects of Tamoxifen citrate(3)

Q.23. Some cases of psychiatric disturbances and ----- have been noted with the use of Triazolam.(8)

Q.24. Risk of ----- damage limits long term use of Thioridazine.(3)

ALPHABET 'G' PUZZLE

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1. Flushing, chest tightness and palpitations are the common side effects seen after subcutaneous injection of _____ acetate in the treatment of Multiple Sclerosis.
2. Though rare, DPT vaccination has been implicated in the development of IgM autoantibody induced hemolytic anemia known as Cold _____ Disease.
3. As an alternative to Lepirudin, _____, a synthetic thrombin inhibitor, is used for treatment of Heparin induced thrombocytopenia.
4. Marked granulocytosis, with counts greater than 100,000/µl, and splenomegaly can occur in patients receiving this recombinant human G-CSF over a prolonged period of time.
5. Somnolence is a common side effect seen with this new non- ergot Dopamine receptor antagonist, used as a transdermal patch formulation, for treatment of Parkinson's disease.
6. Levamisole, originally an anthelmintic drug, is occasionally associated with fatal agranulocytosis, when used as a _____ Response Modifier in the treatment of colon cancer.
7. As compared to the transmucosal formulation (onset of action- 2-5 minutes) of Nitroglycerin, its _____ formulation (onset of action- 1-2 minutes) does not increase exercise tolerance when given to treat an attack of angina.
8. Adverse effects like hyperbilirubinemia (3.3%), nausea (2.4%), diarrhea (2.1%), leucopenia and eosinophilia has been reported with this drug which comes under the Echinocandin group of antifungals.
9. To prevent crystalluria during therapy, patients of AIDS receiving _____ for Toxoplasmosis, should drink at least 2 liters of fluid daily.
10. The alcohol dehydrogenase inhibitor Fomepizole, used for treatment of Methyl alcohol and Ethylene glycol poisoning, is approved by US-FDA in 1997 having the status of an_____.

ALPHABET 'G' PUZZLE:

1. Glatiramer 2. Agglutinin 3. Argatroban 4. Filgrastim 5. Rotigotine 6. Biological 7. Sublingual 8. Micafungin 9. Sulfa Drugs 10. Orphan Drug

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CROSSWORD ANSWERS

1) HYPOSPADIAS, 2) RASH, 3) AGRANULOCYTOSIS, 4) ALA, 5) OC, 6) SUN, 7) INH, 8) LIVER, 9) KIDNEY, 10) MUSCLE, 11) GYNAECOMASTIA, 12) HEPATOTOXICITY, 13) ARRHYTHMIA, 14) COLCHICINE, 15) NOSCAPINE, 16) MYOCARDITIS, 17) ORAL, 18) DOSE, 19) UTI, 20) DISPEPSIA, 21) ACE, 22) HOT, 23) PARANOIA, 24) EYE

We would like to request all the departments to contribute in ADR reporting.

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