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Review

Potential Drug-Drug Interactions and Adverse Drug Reactions associated with Azithromycin used in the treatment of COVID-19 Infected Patients: A Drug Information Resources-Based Review

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Abstract

The end of 2019 became the most remarkable one in human history with the start of an epidemic in Wuhan city of China. The severe respiratory syndrome caused by COVID-19 (named as SARS-CoV-2) created a crisis for public well-being internationally, and the WHO had to declare it a pandemic by March 12, 2020. Many trials are being carried out to check the efficiency and safety of the drugs and treatments. Some of the commonly used drugs are Lopinavir-Ritonavir, Tocilizumab, azithromycin, Hydroxychloroquine, and Convalescent plasma. The drug Hydroxychloroquine, which gave good results earlier, now has restricted use due to a lack of usefulness, but the usage of azithromycin is continued. Micromedex® drug Interaction tool analysis to evaluate and identify Azithromycin-related possible Drug-Drug interactions. Azithromycin tablet highlights the warnings of possible health hazards associated with the administration of Azithromycin along with Precautions in certain co-morbidities and contraindicated patients. The complications with the use of Azithromycin are mostly associated with cardiac functioning; therefore, while selecting of drug, patient ECG should be ruled out before initiation of therapy. A major proportion of patients are asymptomatic; therefore, blind use of Azithromycin should be prohibited. Considering DDIs and ADRs associated with Azithromycin use, it should be used under clinical care with emphasizing proper screening in cardiovascular comorbid patients and those with liver dysfunction.

Keywords: COVID 19**,** Micromedex®**,** Azithromycin**,** Drug-Drug interactions**,** Cardiac function.

Introduction

The end of 2019 became the most remarkable one in human history with the start of an epidemic in Wuhan city of China. The severe acute respiratory syndrome instigated by a novel coronavirus (named as SARS-CoV-2 afterwards)

created a worldwide public health emergency, and the WHO had to declare it a pandemic by 12 March 2020 [1, 2]. It rapidly spread and to date has taken lives of 501,884 persons with more than 10,111,259 cases of infection, 4,125,461 being the active cases across 213 countries around the globe [3] According to New York city health latest report, even though most of the patients are with minor symptoms and the overall casualty rate is less, then also it's 6.5% in patients between the ages 65 - 74 years and to 14.3% in patients 75 years of age and above [4]. Thus, there is an urgent and critical necessity for a powerful treatment option to treat infected patients, but also to shorten the period of virus presence and to restrict community spread.

A variety of probable cures have been recommended for COVID-19, but there is uncertainty which one of these drugs will be more effective in successful persistence than the typical care patients receive while admitted to hospitals. Many trials are being carried out to check the efficiency and safety of the drugs and treatments. Some of the commonly used drugs are Lopinavir-Ritonavir, Tocilizumab, and Convalescent plasma. Other treatments include Dexamethasone; a kind of steroid medicine with small-dose, which generally has been used to lower inflammation, has been proven by a 28-day clinical trial that it lessens death by up to 17% which is almost 1/3 in admitted patients who showed Severe Respiratory Complications as a result of virus infection [5].

Amongst the potential drugs to treat novel coronavirus, repositioning or repurposing known drugs like antibiotics for use as an antiviral medicine is a remarkable approach, due to sufficient knowledge about these drugs, their precautionary details, side-effects, and their interactions with other drugs is already available [6,7]. Azithromycin an azalide, of antibiotics subclass named macrolide, which is used to treat or prevent certain bacterial infections, most often those causing strep throat, middle ear infections, typhoid, pneumonia, sinusitis and bronchitis, is one of such repositioned drug which has been experimented in several types of diseases [8] Azithromycin was shown to be effective in treatment against Ebola viruses [9] Furthermore, azithromycin is thought to prospective drug in restricting acute respiratory infections among pre-school youngsters when it is given to patients having viral infection [10] According to one of the topical study, Azithromycin -a commonly used antibiotic (first day 500 mg, with continuation of 250 mg for 2–5 days) was shown as remarkable support to the effectiveness of Hydroxychloroquine given 3 times every day with 200 mg for 10 days) in the treatment of twenty patients who were put on trial with the drug, six of them received azithromycin for 5 days to prevent bacterial super-infection and all of them were treated successfully, compared to the left over 14 infected ones [11].The drug Hydroxychloroquine, which gave good results earlier has now been restricted due to deficiency of usefulness [6] but still the usage of azithromycin is continued.

Further studies are required to try different combination of azithromycin with other potential drugs to treat COVID-19; there is huge possibility of getting it proved to be one of the most effective supportive treatment options.

Importance of Drug-Drug Interactions

Drug-Drug Interactions also termed as DDIs are reflected as escapable medication-related problems. Interactions among drugs occur when single or several drugs (Active pharmaceutical ingredients) reacts together leading to alteration in efficacy or toxicity of the drugs involved. Chances of DDIs are proportionate to the total of drugs prescribed.

Drug-Drug Interactions results in harmful outcomes to the patients either by increasing the drug toxicity or by reducing its therapeutic efficacy. An analysis of multiple studies in over 370,000 patients demonstrated that 2.2%–70.3% of patients are subjected to potential Drug-Drug Interactions. A study by Nolan and O'Malley demonstrated that the patients who took multiple medications (ten or more) were exposed to over a 90% probability of experiencing single or multiple clinically relevant Drug Interactions. Such Interactions are often related with either prolonged hospitalizations or readmissions [12, 13].

The change in the pharmacological action or therapeutic response caused by a drug due to concomitant administration of another drug is termed as drug-drug Interaction [14]. Majority of this type of interactions arises due to pharmacokinetics incompatibility of two drugs/ molecules.

Drug-drug interactions lead to medication error [15]. On the basis of therapeutic response, DDIs could be categorized in to two types:

1. Synergistic DDIs: Drug synergy is an outcome of di or multi interacting drugs which (due to similar) leads to mutual enhancement of drug effectiveness. Drug Synergy is an objective of combined drug therapy but

sometimes it has toxic effects too [16]. Synergistic drug interactions generally considered to be therapeutically effective in combination drug therapies [17].

2. Antagonistic DDIs: Drug antagonism is an outcome of di or multi interacting drugs which (due to opposite action) leads to an undesirable, reduced efficacy [18].

Adverse Drug-Reaction Consideration: An ADR is an undesirable, unwanted response of a drug. ADRs affects not only treatment efficacy but also patient's quality of life, often causing sickness and death as a result of which patients loses confidence in or have adverse sentiments toward doctors. There are many contributing factors linked to the ADRs such as increase in the quantity of drugs in the market, an aging population, and an upward trend in polypharmacy, Drug Interactions etc. [19].

Method

We have performed Analysis of Azithromycin drug interactions on Micromedex®. Micromedex® is a database available online and that contains a referenced information about the drugs based on evidences. The gathered evidences are further processed for statistical interpretation through MS Excel. Also we have systematically reviewed literature of Azithromycin pharmacokinetic properties, ADRs & Toxicities associated with the introduction of Azithromycin drug on PubMed, Google Scholar, CDC database etc. shown in table 1.

Table 1: Globally used Clinical Drug Databases.

S. No	Drug Information resources	Access	Developer	Country
1.	DrugDex® System	Subscription	Thomson Reuters MICROMEDEX® 2.0	USA
2.	Martindale		Pharmaceutical Press	UK
3.	Lexi-Drugs®		Lexi-Comp, Inc.	USA
4.	Drug Facts and Comparisons®		Wolters Kluwer Health— Facts & Comparisons™	USA
5.	Epocrates® Online	Free	Epocrates, Inc. www.epocrates.com	USA
6.	A-Z Drug Facts™		Wolters Kluwer™ Health www.drugs.com	USA

Result & Discussion

Micromedex® Drug Interaction Tool Analysis:

Micromedex® drug Interaction tool analysis to evaluate and identify Azithromycin-related possible Drug-Drug interactions results are summarized in Table 2 and Figure 1.

Figure 1 Azithromycin Drug- Drug Interactions Severity analysis chart (Micromedex®).

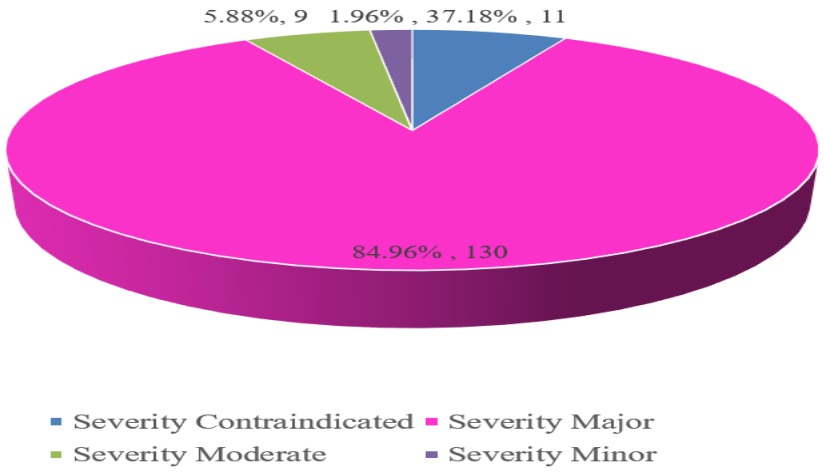


Table 2: Azithromycin Drug- Drug Interactions with Severity levels (Micromedex®).

Drugs with contraindicated severity to Azithromycin							
ERGOT DERIVATIVES	ZIPRASIDONE	SAQUINAVIR	BEPRIDIL	SPARFLOXACIN	THIORIDAZIN	PIPERAQUINE	PIMOZIDE
DRONEDARONE	CISAPRIDE	TERFENADINE					
Drugs with major severity to Azithromycin							
WARFARIN	LOFEXIDINE	DONEPEZIL	DIGOXIN	HYDROXYCHLOROQUINE	DISOPYRAMIDE	SIMVASTATIN	LOPINAVIR/RITONAVIR
APOMORPHINE	VARDENAFIL	CLOZAPINE	RANOLAZINE	ARTEMETHER/LUMEFANTRINE	VEMURAFENIB	AMOXAPINE	MIFEPRISTONE
GRANISETRON	SUNITINIB	MORPHINE	GATIFLOXACIN	PROMETHAZINE	CITALOPRAM	NILOTINIB	PALIPERIDONE
FLUOXETINE	PROCAINAMIDE	SOLIFENACIN	IMIPRAMINE	ALFUZOSIN	MOXIFLOXACIN	OSILODROSTAT	METHADONE
RIBOCICLIB	ENTRECTINIB	IVOSIDENIB	ENCORAFENIB	ARIPIPRAZOLE	CIPROFLOXACIN	PROTRIPTYLINE	LEVOFLOXACIN
TELITHROMYCIN	PANOBINOSTAT	SORAFENIB	DEUTETRABENAZINE	QUETIAPINE	SERTRALINE	CHLOROQUINE	HALOPERIDOL
PROPAFENONE	EDOXABAN	SEVOFLURANE	ERYTHROMYCIN	NORFLOXACIN	ASTEMIZOLE	SULPIRIDE	NORTRIPTYLINE
HALOFANTRINE	DASATINIB	GEMIFLOXACIN	ILOPERIDONE	ESCITALOPRAM	ASENAPINE	IVABRADINE	ARSENIC TRIOXIDE
DROPERIDOL	VINFLUNINE	EFAVIRENZ	ZUCLOPENTHIXOL	ARIPIPRAZOLE LAUROXIL	VINCRISTINE	CHOLERA VACCINE	DABRAFENIB
TRICLABENDAZOLE	QUINIDINE	OSIMERTINIB	ONDANSETRON	GONADOTROPIN RELEASING HORMONE AGONISTS	DESIPRAMINE	OXALIPLATIN	CLARITHROMYCIN
CLOFAZIMINE	FINGOLIMOD	GLASDEGIB	AMITRIPTYLINE	CLASS III ANTIARRHYTHMIC AGENTS	TRIFLUOPERAZINE	DELAMANI	INOTUZUMAB OZOGAMICIN
OFLOXACIN	LEFAMULIN	FLUCONAZOLE	VORICONAZOLE	CRIZOTINIB	SIPONIMOD	PITOLISANT	PIMAVANSERIN
TETRABENAZINE	PASIREOTIDE	ANAGRELIDE	LAPATINIB	FOSCARNET	TOREMIFENE	TACROLIMUS	METRONIDAZOLE
FLECAINIDE	CLOMIPRAMINE	TRAZODONE	BUPRENORPHINE	VANDETANIB	QUININE	TRIMIPRAMINE	PROCHLORPERAZIN
LENVATINIB	KETOCONAZOLE	MACIMORELIN	OCTREOTIDE	CHLORPROMAZINE	DOXORUBICIN	AMISULPRIDE	POSACONAZOLE
HYDROXYZINE	OZANIMOD	PIXANTRONE	MEFLOQUINE	PENTAMIDINE	PAZOPANIB	PAZOPANIB	SODIUM PHOSPHATE
DOMPERIDONE	DOLASETRON						
Drugs with moderate severity to Azithromycin							
NELFINAVIR	LOVASTATIN	RIFABUTIN	THEOPHYLLINE	ATORVASTATIN	PHENYTOIN	VISMODEGIB	HEXOBARBITAL
CYCLOSPORINE							
Drugs with minor severity to Azithromycin							
TRIAZOLAM	LUMINUM- OR MAGNESIUM-CONTAINING PRODUCTS			CARBAMAZEPINE			

As displayed in Figure 1, there are around 153 potential drug interactions possible with Azithromycin. Out of them, 11 are contraindicated at severity level, and the other 130 are of major severity and 9 of them are moderately severe, and 3 are of minor severity. Contraindicated severity signify to the drugs which are contraindicated when used together, Major severity signify to the interactions that may impose life hazard may need modification clinically so as to reduce or safeguard life threatening drug effects, whereas Moderate severity signifies the interactions that could exacerbate patient's clinically and may need any change in clinical treatment..

Figure 2 displays the documentation of these Drug interactions. Accordingly, it is good with 9.15% drugs and excellent with 0.65% drugs, and fair with the remaining 90.19% drugs. Good documentation signifies that the interaction among drugs is present, but needs to be confirmed by further studies. An excellent documentation means that confirmed interactions are being documented by controlled studies. A fair documentation signifies that the available documentation is poor; clinicians suspect that the interaction exists based on pharmacological data.

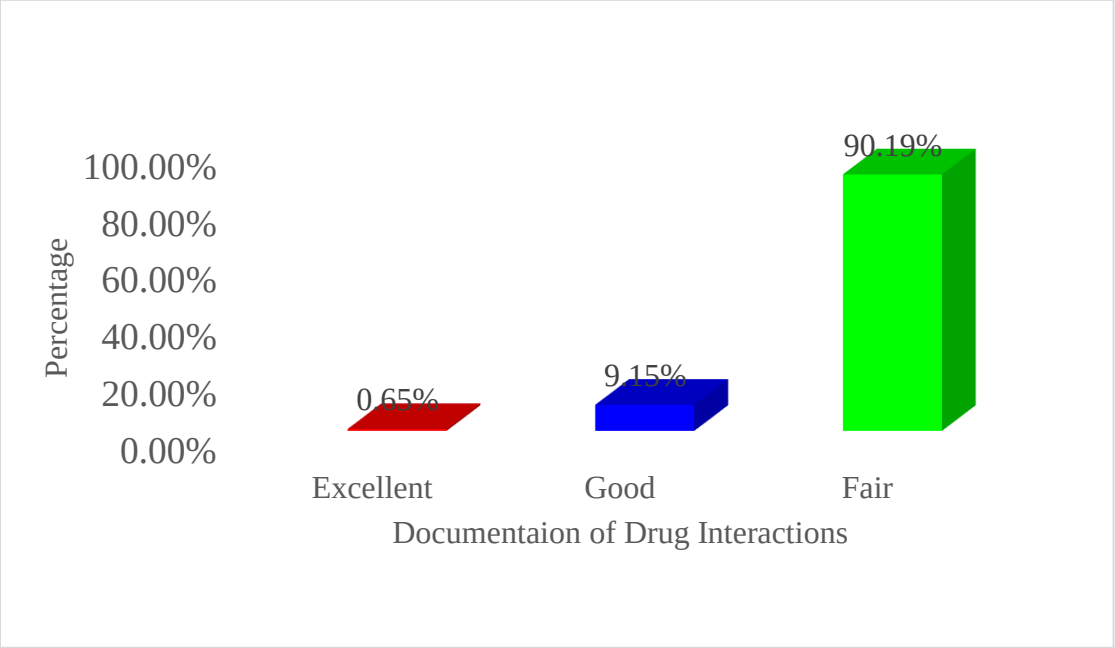


Figure 2 Azithromycin Drug- Drug Interactions Documentation analysis chart (Micromedex®).

Figure 3 displays the outcome of drug interactions, and accordingly, most of the drugs like moxifloxacin, Solifenacin, Osilodrostat, Mipramine, Alfuzosin, and Ciprofloxacin are found to cause an interaction leading to QT interval prolongation, which may lead to further cardiac abnormalities. There are around ten drugs (e.g.: theophyllines) causing an increase in drug concentration when administered with azithromycin. For some statins like Simvastatin, Lovastatin, Atorvastatin, there may be rhabdomylosis and cardiac arrhythmias are shown with Pitolisant and QT-prolonging drugs. Increased risk of torsade de pointes with Donepezil, Propafenone, and Iloperidone. Synergism with triazolam, increased risk of bleeding with warfarin. Acute Ergotism with Ergot Derivatives and Digoxin. Increased risk of morphine exposure with morphine and two other drugs shows GI toxicity.

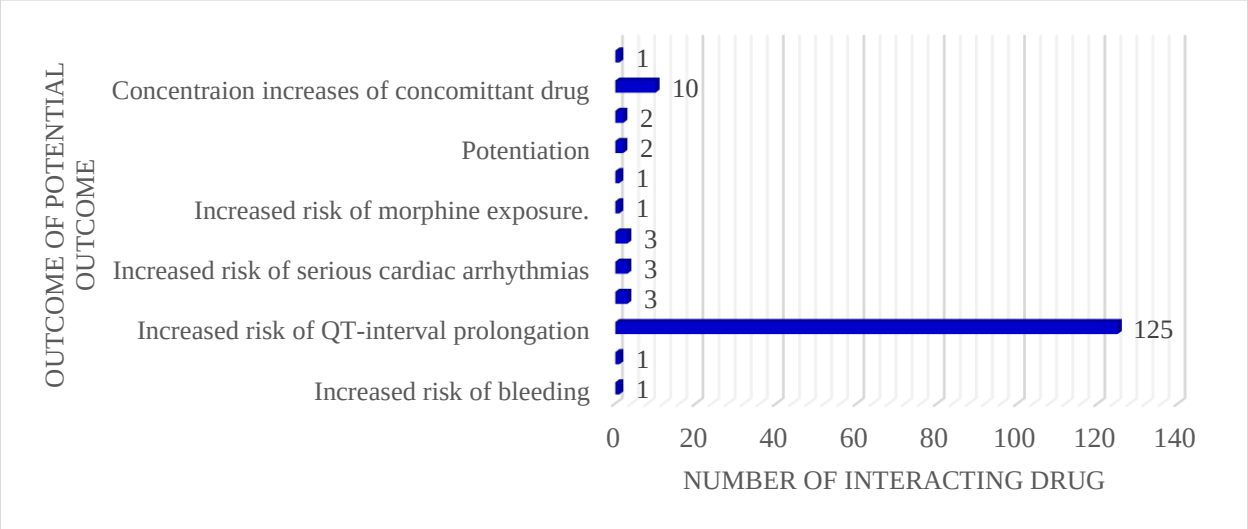


Figure 3: Azithromycin DDIs Potential Outcome analysis.

Digoxin toxicity is a problem with Macrolides like Azithromycin. This is due to P-glycoprotein. This was reported in the case where a child developed digoxin toxicity after starting Azithromycin [20]. Reports are confirming that there exists an interaction between azithromycin and warfarin that resulted in an international normalized ratio (INR) [21].

Amisulpride (Oral) may enhance the effect of QT-prolonging Agents. Azithromycin (Systemic) may enhance the myopathy (rhabdomyolysis) effect of atorvastatin; such combinations need monitoring of therapy. Antibiotics may diminish the therapeutic effect of BCG. These combinations should be avoided. QT-prolonging miscellaneous agents may aggravate the QTC-prolongation effect of Chloroquine and piperaquine. When these drugs are given in combination, look for ventricular arrhythmias and ATC interval prolongation. Patients with other risk factors that may cause extension of QTC may be at even higher risk [22].

Use of contraindicated drugs as concomitant therapy should not be done with Azithromycin to prevent further morbidity. Safer drug regimen should always be preferred under regular clinical monitoring. The complications with use of Azithromycin are mostly associated with cardiac functioning, therefore while selection of drug patient ECG should be rule out prior to initiation of therapy. Patient with history of cardiovascular disorder must be evaluated and dose calculation as per the body weight could also be considered.

A polymorphic ventricular tachycardia is the torsade de pointes whereas drug-induced long QT syndrome is symbolized by a prolonged corrected QT interval in an electrocardiogram. Although the cardiovascular risk associated with QT prolonging drugs is well established but such medications are necessary in many clinical conditions. Therefore the risks benefit ration of such drugs should be studied before using. Polypharmacy i.e., multiple QT prolonging drugs must be avoided. Various other conditions of patients that may put patient at risk, Comorbidities must be evaluated. If possible and based on availability, alternative drugs should also be considered thoroughly [23]**.** Monitor Parameters like Liver function tests, CBC with differential when administering Azithromycin in combination with other drugs [22]. Safer course of therapy should always be preferred under consistent clinical observations. QT interval is affected by drugs most often in elderly population. [24]. The patients with comorbidities should be closely observed and managed. A drug dose given should be adjusted according to the health condition and contraindications.

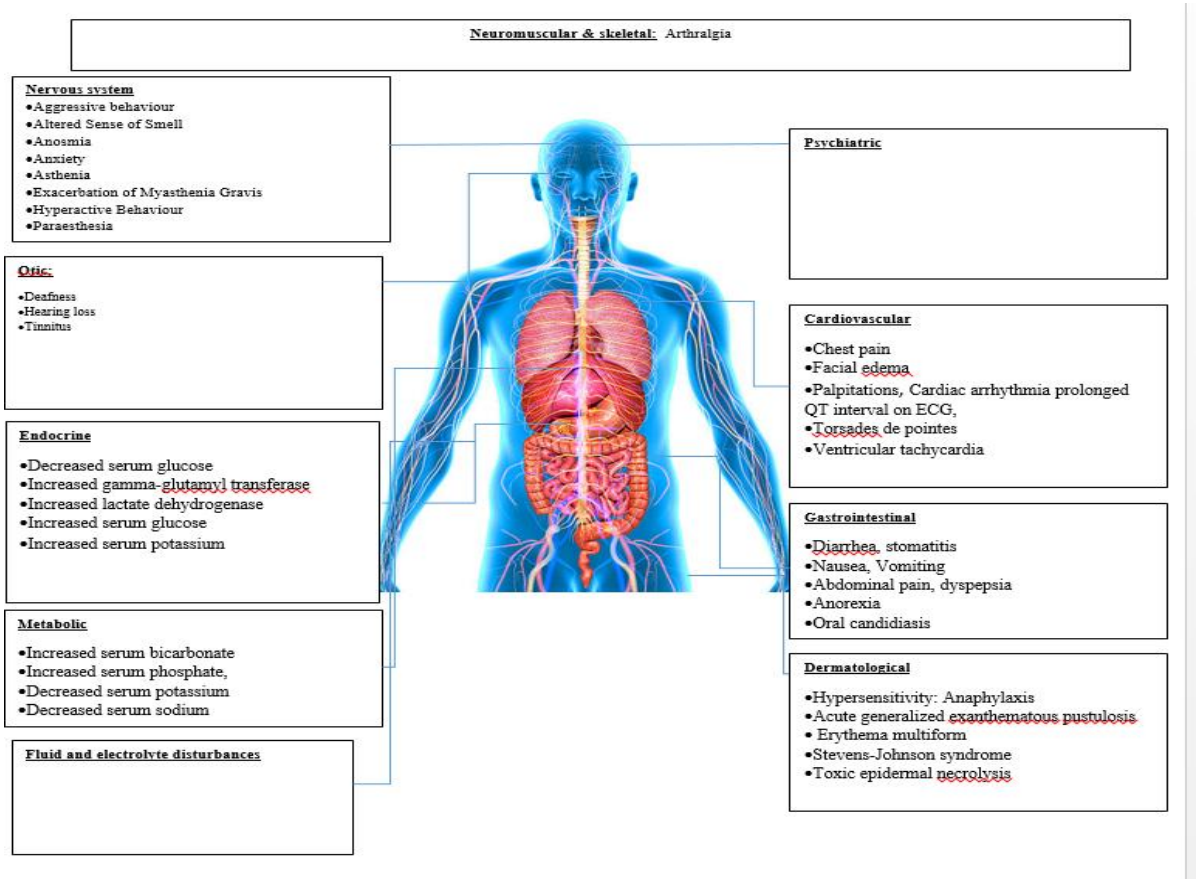
Adverse Reactions

Summary of Product Characteristics (SmPCs) of Azithromycin tablet highlights the warnings of possible health hazards associated with the administration of Azithromycin along with precautions in certain co-morbidities and contraindicated patients. Table 3 and Figure 4 represent the safety summary of the Azithromycin tablet SmPC. Patients with higher sensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic are

contraindicated on Azithromycin administration. Most patients on Azithromycin therapy rarely develop any serious allergic reactions like Stevens-Johnson Syndrome. On reporting any such allergic reaction, the treatment should be stopped, and necessary changes should be made.

Table 4: Oral Azithromycin SmPC (Summary Product Characteristics) Safety Summary [25].

Azithromycin Tablet SmPC (Summary Product Characteristics) Safety Summary	
Contraindication	• Hypersensitivity to azithromycin or to any product component, erythromycin, or any macrolide or ketolide antibiotic.
Precautions	• Hypersensitivity • Hepatotoxicity • Ergot derivatives • electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
Warnings	• Prolongation of the QT interval • QT interval such as antiarrhythmics of classes IA and III,cisapride and terfenadine • Bradycardia, cardiac arrhythmia or severe cardiac insufficiency • Streptococcal infections • Renal impairment • Myasthenia gravis



Various Adverse Drug Reactions associated with Azithromycin (Systemic)

Figure 4 Various Adverse Drug Reactions associated with Azithromycin [23,24, 29].

Livertoxicity, liver function abnormality, hepatitis, cholestatic jaundice, and hepatic failure may develop, leading to even death in some cases. Appearance of such an ADR may lead to discontinuation of azithromycin. As azithromycin is mainly eliminated through the liver, care should be taken when azithromycin is given to patients with impaired liver function [22, 25].

Azithromycin shows the following adverse reactions:

Allergic: Arthralgia, edema, urticaria and angioedema.

Cardiovascular: Arrhythmias, ventricular tachycardia and hypotension. Rarely QT prolongation and torsades de pointes are observed.

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea and rare reports of tongue discoloration.

General: Paresthesia, fatigue.

Genitourinary: Interstitial nephritis and acute renal failure and vaginitis.

Hematopoietic: Thrombocytopenia.

Liver/Biliary: hepatic dysfunction

Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope.

Psychiatric: anxiety and aggressiveness

Skin/Appendages: Pruritus, erythema multiform, Stevens Johnson Syndrome and toxic epidermal necrolysis.

Special Senses: Hearing disturbances including hearing loss, deafness and/or tinnitus

QT prolongation and torsade de pointes may even result in death. The US FDA issued a warning in 2012 to consider the risk of fatal heart rhythms in those [24]:

- with a QT interval prolonged
- that shows a prolonged QT interval due to co-administered drugs
- With a history of torsade de pointes, arrhythmias, or uncompensated heart failure [24].

There are various factors that affect the development of ADRs, such as age, sex, drug dose, co-morbidity, etc. Careful evaluation of these factors could prevent and reduce the incidence of unwanted & undesired ADRs. Counseling, Health education & reconciliation of medications are essential duties which must be performed by HCPs. Drug Information resources and the Internet should also be utilized in evidence-based medication decision-making process, which would make HCPs aware of advancements in the medical field and basics such as drug-dosing, lethal drug interaction, and possible adverse events. As such, relevant clinical information is mandatorily required to prescribe medication for the optimum therapeutic outcome. The Benefits of medical therapy must always outweigh the risks associated with it. [26].

CONCLUSION

COVID-19 is a pandemic disaster and a health emergency of prime focus for all the world's economies. Currently, various options are available, such as Chloroquine, HCQ- HCQ-HCQ-azithromycin, Dexamethasone, Remdesivir, plasma therapy, etc., and many others in the pipeline. A major proportion of patients are asymptomatic; therefore, blind use of Azithromycin should be prohibited. Considering DDIs and ADRs associated with Azithromycin use, it should be used under clinical care with emphasizing proper screening in cardiovascular comorbid patients and those with liver dysfunction. It should be used under clinical care with emphasizing proper screening of comorbid disease and drugs.

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