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Common Adverse drug reactions to First line drugs in Tuberculosis care and the role of m-Health in patient self-reporting and pharmacovigilance in Nigeria: A Narrative review

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Abstract

The treatment of tuberculosis requires the use of First line drugs that often cause adverse drug reactions (ADR) in some patients and this is capable of affecting adherence to the treatment. Many patients do not report these ADRs even though technologies are available at their disposal. The objectives of this review are to assess the common adverse drug reactions reported during the care of patients on First line anti-TB drugs and the use of m-health in self-reporting the ADRs by patients receiving anti-TB care. A literature search was conducted using key words on PUBMED and GOOGLE SCHOLAR. The commonest ADRs many patients presented with were gastrointestinal symptoms and symptoms of drug induced hepatotoxicity. The use of m-Health as an intervention for reporting ADRs is poor in sub-Saharan Africa, however in spite of some challenges, it is seen as a veritable opportunity for patient reporting of ADRs and the improvement of outcomes of Directly Observed Therapy Short course, (DOTS) for tuberculosis management.

Keywords: Tuberculosis, First line drugs, Adverse drug reactions, mHealth, Patient self-reporting

Background

Tuberculosis (TB), an infectious disease, caused by *Mycobacterium tuberculosis* is still a major contributor to preventable deaths globally. It is described as the world's most deadly infectious disease.[1] TB is endemic in Nigeria and continues to generate public health concerns especially with the occurrence of multidrug-resistant TB (MDR-TB) and the fact that although incidence is decreasing, it is not decreasing fast enough. Nigeria still contributes largely to the pool of the global prevalence of tuberculosis and is one of the major countries to do so, the others being India, Indonesia, China, Philippines, Pakistan, Bangladesh and South Africa.[1] The management of tuberculosis requires the use of multiple drugs that act in synergy to reduce the chances of drug resistance and treatment failure. The First line drugs which are used for the management of TB include isoniazid, rifampicin, pyrazinamide, and ethambutol. It has been well documented that these drugs can cause adverse drug reactions in the course of use by patients either within the intensive phase of treatment (the first 2 months of treatment) or during the continuation phase. During this period, patients are expected to religiously take their drugs, as adherence is key to achieving cure. The drugs which often come in fixed dosed combinations require supervised administration in the Directly Observed Therapy short course program (DOTS).

In the course of receiving these drugs, several adverse drug reactions can occur that may affect patient's adherence to the drugs. An Adverse drug reaction (ADR) is defined as a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.[2] ADRs have now emerged as a major clinical and public health

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problem, significantly contributing to morbidity, disability and mortality.[3] In Nigeria, some studies have reported a high burden of ADRs in public health programs.[5-7] Several studies have documented poor spontaneous reporting of adverse drug reactions among health care workers.[5,7] Patients, being the end users of these drugs, need to play a more crucial role in reporting the adverse reactions that follow the use of the drugs. This will improve documentation of ADRs and increase participation in patient care.

Mobile health (m-Health) is defined as a medical and public health practice supported by mobile devices such as mobile phones, patient monitoring devices, personal digital assistant (PDA) and other wireless devices.[8] m-Health involves the utilization of features such as short messaging services (SMS), voice, as well as more complex functions and applications like the General Packet Radio Service (GPRS), Bluetooth technology, global positioning system (GPS) and third and fourth generation mobile telecom (3G and 4G) systems.[8] Mobile health has fast become a very important means for reaching large populations globally and serving as interventions for health. The utilization of m-Health for patient self-reporting of adverse drug reactions is not novel as it has been utilized in developed economies to report cases of adverse drug reactions by patients and healthcare providers.[9] With increasing utilization of mobile telecommunications in Nigeria and the provision of internet services to urban and rural communities, m-Health has become a veritable intervention for health-related challenges.

The objectives of this review are to assess the common adverse drug reactions reported during the care of patients with tuberculosis and the use of m-health in self-reporting ADRs by patients. It is important to investigate this area because more practical actions need to be taken to encourage reporting of adverse drug reactions and increase adherence to treatment.

Materials and Methods

A literature search was conducted using electronic searches from PUBMED and GOOGLE SCHOLAR. The search was done between 12th of February to the 13th of June 2020.The literature search considered the use of mobile phones either for texting or with the use of mobile applications and adverse drug reactions relating primarily to tuberculosis. Adverse drug reactions due to the first-line drugs used to treat tuberculosis were explored. The knowledge, attitude, and practice of patients to adverse drug reactions were explored. The search results were from 2000 to 2020. Selected studies which were in English Language, were appraised for quality, and analyzed descriptively. The abstracts of the studies were initially read for relevance and suitability, and thereafter the full texts (articles) of selected studies were downloaded and scrutinized. Study types that were considered for this review included randomized control trials, observational studies, prospective and retrospective reports of records, systematic reviews and meta-analysis and qualitative studies.

Eligibility criteria

Eligible studies were those that reported adverse drug reactions following the treatment of pulmonary and/or extrapulmonary TB using first-line drugs. The search also included studies that showed how the adverse drug reactions were reported by the patients to their caregivers. Studies that reported on adverse reactions from multidrug-resistant tuberculosis (MDR-TB), and other co-morbidities were excluded from the review. ADRs reported by other means such as the use of social media, were also excluded.

Keywords used for search on PUBMED included 1. Mobile phones plus adverse drug reactions; 2. Adverse events plus TB drug reactions plus Nigeria; 3. Patient reporting plus Adverse drug reactions plus Nigeria; 4. Patients knowledge plus adverse drug reactions plus TB; 5. Electronic reminders plus TB care. On Google scholar, the search was done with the following keywords; 1. Patient reporting plus adverse drug reactions Plus Nigeria; 2. Patient knowledge plus adverse drug reactions plus TB; 3. Electronic reminders +TB care. Direct reporting of adverse drug reactions in patients plus TB care; Direct reporting of adverse drug reactions. A total of 22 studies were reviewed for this study.

Results

Common adverse drug reactions from First line

Tuberculosis drugs

The review showed that ADR from 1st line anti-TB drugs is scarcely reported in Nigeria, and most of the published data are from secondary sources, ie hospital records. Some studies have tried to determine how frequently adverse drug reactions occur among patients receiving First line anti-tuberculosis drugs. A study in India, reported an ADR prevalence of 8%.[10] While in Saudi Arabia, although 34.7% of 1011 patients sampled reported ADRs, only 10.09% had definite cases of ADRs.[11] In a six-year study in Western Nepal which documented adverse reactions from 326 patients, the authors observed that ADRs in patients undergoing TB treatment was common and that more than half of the reactions occurred within 20 days of the initiation of treatment.[12] In a descriptive study using population-based database from 2000 to 2005, the hospital records of 1061 patients taking anti-TB were reviewed. The authors showed that at least 318 patients had at least one major adverse drug reaction in the course of receiving treatment for primary tuberculosis.[13] According to the authors, ADRs was present more in combinations of RMP, INH and PZA at 13.6 (95% CI 13.3 TO 14.0) when compared to combinations of INH and RMP 2.4 (95% CI 2.3 to 2.6). The implication of this is that patients tend to have more adverse drug reactions in the intensive phase of drug TB treatment than in the continuation phase.

Some authors agreed that gastrointestinal symptoms were common during the treatment of tuberculosis. In a study in India, the authors identified gastrointestinal symptoms and fatigue as the commonest symptom patients complained of when receiving care.[14] In another study by Sinha et al. the authors identified gastrointestinal symptoms (53.52%), generalized body weakness (16.9%), liver dysfunction (15.49%), and neurological system disorders (2.85%) as common symptoms among a sample of 102 patients that were receiving treatment.[15] In a cross-sectional study by Gor and Desai, the authors said that most of the patients receiving treatment for tuberculosis in a rural tertiary facility had presented with gastrointestinal symptoms as an initial complaint.[16] In a longitudinal study of adverse effects of anti-tuberculosis drugs among 50 patients that accessed care for TB in Mangalore, gastrointestinal problems were also said to be the earliest and commonest ADRs out of the 9 types of ADRs that the patients complained of.[17]

Some studies have also identified drug induced hepatitis as a common presentation by many patients. In a study by Yee et al, the authors identified pyrazinamide induced hepatoxicity as the commonest adverse drug reactions patients tend to present with.[18] In a retrospective cohort study that was carried out in Nigeria, the authors said hepatoxicity was an early and common feature among patients receiving treatment for TB.[19] A study by Tanani et al reported hepatotoxicity as a common adverse drug reaction that occurred in the intensive phase of TB care.[20] A prospective population-based cohort study in China identified liver dysfunction as a common ADR many patients complained of in their TB program.[21] In Nigeria, an assessment of adverse drug reactions of TB treatment identified reddish discoloration of urine as the commonest and earliest adverse drug reaction often complained of by patients. The author agreed with other studies that the intensive phase of TB management was the time many ADRs occurred and could affect adherence to treatment.[23] A study carried out in Western Nepal documented that the most common ADRs occurred in the hepatobiliary system with an elevation of liver enzymes.[12] It is important to note that most of these studies listed gastrointestinal problems and drug induced hepatitis as common adverse drug reactions experienced by patients receiving care with First line drugs for tuberculosis. Other ADRs documented included arthralgia, allergic reactions and neurologic disorders.[15,21,23]. These reactions are capable of influencing patients' adherence to the First line drugs used for treatment of tuberculosis.[20]

Spontaneous reporting of ADRs by Patients using mHealth

Direct patient reporting is a system of reporting suspected ADRs directly to competent bodies.[7] Many developed countries have since utilized this mode of patient-centered reporting of ADRs to ensure adherence and prompt response from healthcare providers. In Nigeria, the Pharmacovigilance Rapid Alert System for Consumer Reporting (PRASCOR) is the electronic platform for which patients are expected to report

ADRs when they occur to a short code number, 20543 (toll-free). In a longitudinal study carried out between 2012 and 2017, the researchers opined that quantitatively, PRASCOR contributed minimally to the number of ADR reports using the spontaneous reporting system.[7] Some advanced countries have been taking patient reporting more seriously since the 1960s and this may have facilitated some of their health outcomes. According to Nwokike 2008, many Nigerians perceived ADRs as evidence of the effectiveness of the drugs. In a study carried out on 34 patients attending clinics in Abaji, Kwali, and Zaria, the author found that patients were often told what to expect as side effects following TB care. The study showed that 3 out of 4 patients reported adverse drug reactions when they occurred.[6] When asked if they wished there were other ways ADRs could be reported, a third of participants said such alternative methods would be useful. A larger sample size of this study may have produced better results. In another study to assess the patient's perspective on the self-reporting of adverse drug reactions, 15 people were purposively selected from patients already on admission in the hospital.[23] The authors reported that patients said that communication and information should have been more readily provided by the healthcare providers to them when the drugs were prescribed to ensure that they report ADRs when they occurred. Patients felt that reporting ADRs was not their responsibility. A parallel designed randomized control pilot study was done to evaluate the acceptance and feasibility of a patient-driven mobile phone intervention to support adherence to TB treatment, and 37 participants were assessed. The researchers found that the difference between the groups was not statistically significant even though the participants of the study largely accepted the intervention. The sample size may have resulted in this level of significance as only 37 of 122 persons were enrolled with 2 dropouts.[24] In a study by Liu X et al, the researchers said that frequent text messages can result in user fatigue.[25] The studies, however, agree that issues like cost of SMS, availability of mobile phones, well-powered mobile phones could be bottlenecks in the implementation of this intervention.[9]

Discussion

The literature suggests that gastrointestinal complaints and hepatotoxicity are the commonest adverse reactions patients experienced when they were taking First line TB drugs. These gastrointestinal complaints include nausea, vomiting, lack of appetite and diarrhoea, while drug induced hepatotoxicity may present as jaundice.[26] Most cases of jaundice are seen in the intensive phase of treatment,[27] and although liver injury could be asymptomatic, requiring the measurement of markers such as Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST), many patients tend to recover as treatment with the First line drugs is continued.[27] Other adverse reactions have also been documented. These reactions can affect patients' adherence to treatment and hence it is important that when the symptoms are observed by patients, they should be reported to the healthcare giver.

In Nigeria, healthcare workers are required to report suspected cases of ADRs, but unlike some developed countries, this is not made mandatory.[28] This is in spite of the fact that Nigeria is a member of the WHO International Drug Monitoring Programme, 2004.[29] The pharmacovigilance form otherwise known as the yellow form is used to report cases of ADR. The forms many times are not available in every health facility and when they are available, they are not utilized by many healthcare providers resulting in under-reporting of ADRs.[4] The Pharmacovigilance Rapid Alert System for Consumer Reporting (PRASCOR) is the electronic platform for which patients are expected to report ADRs but this also underutilized. The literature is scanty on studies encouraging patients to spontaneously report adverse drug reactions in TB care and other health challenges, especially in sub-Saharan Africa and more so with use of available interventions like m-Health. There is no doubt that integrating m-Health into the DOTs program will ensure patients spontaneously report side effects of the drugs in real time and allow the health care providers to track the adherence of patients to the drugs given. This is as seen in a study in Morocco where integration of pharmacovigilance into tuberculosis control programme improved the management of ADRs and detected new signals of the antituberculosis drugs.[20] Data generated from

the perspective of the patient can be useful in developing hypothesis about potential side effects of the drugs. Although Nigeria has a national policy on pharmacovigilance,[28] the policy does not emphasize patient utilization of m-Health to report ADRs to their care providers. Telecommunication and internet service providers can partner with the facilities offering DOTs services and the Ministry of Health to provide toll free numbers and SIM cards to health care providers. Some drawbacks in this intervention include the issue of patient's education and level expertise in the use of e-health facilities like phones and computers.[9] Also, it may be difficult to validate the symptoms patients send in as text messages but this can be overcome by calling the patients or use of other tele-consult facilities for verification.[30] There is a real risk of duplicity of reports in patients reporting and hence there is need for proper orientation of patients before starting this intervention.[9]

Conclusion

It is evident from the literature that the intensive phase of tuberculosis care is usually the phase where patients tend to have more ADRs from the anti- TB drugs. These ADRs may range from gastrointestinal disturbances to symptoms that suggest hepatoxicity. Although there are paucity studies on m-health-based reporting ADRs in Nigeria, the results of the literature agree that the use of m-health is a widely accepted intervention that can improve patients reporting of adverse drug reactions, and subsequently encourage patient's compliance to their drugs.

Recommendations

With technological advancement, DOTs services can be improved upon by integrating the use of m-Health to promote real-time monitoring of ADRs in patients receiving TB care in healthcare facilities across the country. This will improve the patient's knowledge of adverse drug reactions and their adherence to treatment. It is also expected that this will increase the documentation adverse drug reactions by healthcare workers.

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