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REVIEW ARTICLE

Changing Pharmaceutical Regulation in India to Promote Rational Use of Antimicrobials

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ABSTRACT

The discovery of antimicrobials has reduced the mortality and morbidity throughout the world, but the infectious diseases continue to be the major causes of mortality and morbidity in India. The use of antimicrobials has increased over the years and study has proved that many of them have not been used inappropriately. The inappropriate use of antimicrobials increases the chance of developing resistance and treating resistant organism becomes cost prohibitive. The reported emergence of superbug, NDM-1, awakened the Government of India. The Government of India initiated regulatory measure by including new Schedule H1 covering higher antimicrobials to reduce the free sale or availability. Though the Government initially proposed a stringent rule similar to Narcotics and Psychotropic Substances, the rule has been diluted to the form of H drugs. The proposed Schedule H1 intends to prevent their selling without doctor's prescription. This raises many concerns like its impact on non-availability of these medicines in rural areas especially where physicians are not available. The lack of proper guidelines for rational use of these medicines and ineffective implementation of the rules have further raised the concern whether insertion of this new Schedule H1 would improve the use of antimicrobials and reduce or delay development of resistance.

Keywords: Antimicrobials, the super Bug, Rational use of antibiotics, drug and cosmetics act, Schedule H 1.

INTRODUCTION

During the World War II antimicrobials are one of the greatest medical discoveries which have drastically reduced the morbidity and mortality from infectious diseases caused by microorganisms worldwide. Majority of the morbidity and mortality in India are due to infectious diseases among people.[1] But, unfortunately the usage is not rational due to many reasons although it looks common and simple for a normal person, seeing this issue in a medical prospect is like an iceberg. The underlying effects of this irrational use of antibiotics is going to change the fate of the health fields throughout the world, it was nothing but the emergence of resistance.[3]

In India the antibiotics consumption has increased between 6% and 7% annually in the past 5 years (from 2005 to 2009).[2,4] In India, the prevalence of use of antimicrobial agents varies from 24 to 67%.[3] Akram Ahmad et al (2012) conducted a study at community based south India and showing 51% of antibiotics were prescribed inappropriate.[3] These findings provide compelling evidence of the need for more rational use of antimicrobial agents in India.[2,3,4]

With the event of superbug the government of India was alarmed and insisted from different sources to enact strict laws for rational use of antibiotics. Thus, came to limelight the necessity for schedule H1, even though schedule H is much similar to schedule H1 in most aspects with minor differences and discussed in the following sections. Some questions are to be answered before implementing this schedule and few recommendations are made based on the requirements.[5, 13]

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THE SUPER BUG:

The urgency in making a national drug policy on antibiotic prescriptions is initiated with the discovery of the New Delhi super bug. It was in the August 2010 a report in Lancet stated that a new microbe was discovered in India, named as New Delhi metallo-beta-lactamase-1 (NDM-1). This enzyme makes the bacteria resistant to almost all antibiotics including carbapenems which were of the last line. Even though this was found out in a Swedish patient who has undergone a surgery in New Delhi, the fault is accounted to India because subsequent studies has shown the presence of same type of microbe in people from New Delhi.[5] Besides stringent infection control in hospitals, good sanitation in the community is also needed to contain the spread of such clones, the paper concluded. The study conducted in the hospital itself found 22 patients having NDM-1 bacteria of a total of 24 carbapenem (a strong antibiotic) organisms that were collected in a period of three months. This made the hospital come up with an antibiotic policy that did not allow indiscriminate use of carbapenem's. Discovery of this super bug has thrown the future of antibiotics into question.[6, 13]

WHO IS RESPONSIBLE? DEVELOPED OR DEVELOPING:

Many argue that the problem of emergence of resistance comes with developing countries where the screening techniques are not up to mark and where the accessibility of health is not appreciable. But, this argument does not hold good in many contexts as some developing countries like Chile has initiated an antibiotic drug policy that is well framed. Even countries like America could not find a solution for this problem. The US has begun to support measures to address the issue of antimicrobial resistance: Policy Statement 9908 advocates educational programs for providers and patients on appropriate antibiotic usage as well as recommendations for increased and improved oversight. China is going to launch nationwide campaign this year to regulate the antibiotic use. It implies that the problem is not only with India but, the world wide is to face the blame for this issue. These conditions are forcing all the countries to initiate the drug policies or appropriate measures to curb the misuse of antibiotics.[4,10,13]

WHAT IS SCHEDULE H1?

In order to curb the irrational drug use, particularly the antibiotics that led to this situation, the Ministry of Health mulls for options to draft law amendments to include many antibiotics and sedatives along with some other drugs in Schedule H1 list.[7] A provision could be incorporated for spot suspensions /cancellation of the sale license for contravention of the provision of Schedule H1.[13] The proposed rule is in the final stages of drafting, and amendment of existing Drugs and Cosmetics Act 1945 and the Ministry will officially implement it soon.[13] The Law Ministry will examine the viability of the proposed draft and may provide suggestions and nod, before the amendment is passed in either houses of Parliament, said on official from Ministry of Health.

As an answer to controversies raised by British Medical Journal commenting India to bear the responsibility of existence of 'super-bug' or MRSA that coincided with the concerns voiced by public and private healthcare providers about the untreatable antibiotic resistance in Indian patients. In the backdrop, Government of India formed a Task Force to assess the situation and to recommend remedial and preventive measures against antibiotic resistance, MDR-TB and to curb discriminate use of antibiotics.[8]

After assessment and situational review, based on track and trace system the Task Force recommended a series of steps to prevent indiscriminate use of antibiotics and prevention of antibiotic resistance problems. The committee recommended a separate Schedule and Part as amendment under Drugs and Cosmetics Act 1945 to include many antibiotics and the new rule can prohibit the over-the-counter sale of certain antibiotics and commonly abused drugs such as sedatives and implementation of boxed and colored warnings in the drug labels. However, the rule is not applicable to hospital supply drugs. The recommendation mandated culture and antibiotic sensitivity assay for any suspected infections and provided technical, regulatory operating procedures to clinicians, for any infection diagnosis and treatments.[13]

According to Health Ministry reports, the new amendments excluded a number of drugs from Schedule H and included the same in newly created Schedule H1 list that mandated a labeled warning with Rx, highlighted in bright red color are also to be included in that class of drugs, and are exempted from retail selling without the physician prescriptions. These draft rules were first announced in March 2012 without consultation with DTAB which was eventually referred to and their nod was obtained.[9]

The proposed rules included many drugs from the Schedule H, in the Schedule H1 list. The antibiotics excluding topical preparations but including ophthalmic and ENT preparations such as carbenicillin, amoxillin, ampicillin, balofloxacin, amikacin, third and fourth generation cephalosporins, cefazolin, chloramphenicol, clarithromycin, cloxacillin, colistin, dextropropoxyphene, sparfloxacin, vancomycin, tetracycline, pyrazinamide, nitrofurantoin, trimethoprim, sulfamethoxazole, diphenoxylate salts, tobramycin, vancomycin, nalidixate, ethambutol, INH, polymyxin B, pefloxacin, minocycline,

clindamycin, kanamycin, linezolid, gatifloxacin, cotrimoxazole, gentamicin, noxifloxacin, ethambutol, streptomycin, synthetic penicillins, nalidixic acid and sedatives such as alprazolam, nitrazepam, zolpidem, codeine, diazepam, tramadol and midazolam.[9,10]

WHAT IS SCHEDULE H?

Schedule H of the act consist a list of about 536 drugs which are required to be dispensed on prescription of Registered Medical Practitioners (RMP). The third and fourth generation antibiotics will remain untouched by effective implementation of national policy for containment of antimicrobial resistance which discusses new policy and prevents these antibiotics from being misused. **Schedule H** of rules provides a list of drugs to be sold on prescription of RMP. The container of medicine for internal use shall-

a. If it contains substance specified in Schedule H be labeled with a symbol Rx & conspicuously displayed on the left top corner of label & be also labeled with following words: 'Schedule H Drug - **Warning**: 'To be sold by retail on the prescription of a Registered Medical Practitioner only'.
b. If it contains a substance specified in schedule H and comes within the purview of the Narcotic Drugs & Psychotropic Substances act, 1985 be labeled with the symbol NRx which shall be in red & conspicuously displayed on the left top corner of label & be also labeled with following words: 'Schedule H Drug - **Warning**: To be sold by retail on the prescription of a Registered Medical Practitioner only'.
c. Container of an embrocation, liniment, lotion, ointment, antiseptic cream, liquid antiseptic or other liquid medicine for external application shall be labeled with the words in capital 'For External Use Only'.

The schedule states that - the salt, ester, derivatives and preparation of substance in schedule H excluding those intended for topical or external use (except ophthalmic and ear/ nose preparation containing antibiotics and/ or steroids) are also covered by this schedule. The inclusion of a substance in schedule H does not imply or convey that the substance is exempted from the provisions of rule 122A/ 122B under Drugs and Cosmetics Act and Rules, 1945. The rule 122A and 122B states the application for permission to import new drug and application for approval to manufacture new drug other than the drugs classified under schedule C and C18. The same will be applied to Schedule HX. The only change will be in the rule 97 under Drugs and Cosmetics Act and Rules, 1945 which states about the labeling requirement of medicine mentioned therein.[11,13]

DIFFERENCES BETWEEN SCHEDULES H AND H 1:

Even though both of these schedules are mainly concerned with controlling the sale and use of antibiotics there are minor differences regarding the labeling requirements and roles of pharmacist and RMPs. These basic differences are given below:

S.NO	SCHEDULE H 1	SCHEDULE H
1	Contains of about 91 drugs including antibiotics, habit forming drugs and few anti TB drugs which were abused under schedule H1, with regulation on its sale and additional warning to patient.	Contains of about 536 medicines including antibiotics.
2	**Labeling requirement:** **Schedule H1 drug – Warning:** 1. It is dangerous to take this preparation except in accordance with the medical advice 2. Not to be sold by retail without the prescription of a Registered Medical Practitioner 3. Rx symbol highlighted in bright red colour in left top corner.	**Labeling requirement:** 1. **Schedule H drug – Warning**: 1. To be sold by retail on the prescription of a Registered Medical Practitioner only. 2. Rx symbol on left top corner of the label.
3	**Role of Pharmacist and RMP:** 1. Pharmacist has to dispense drugs under this schedule only when prescribed by a RMP. 2. Medical practitioners have to follow the guidelines that will be issued by the ministry in order to diagnose and to prescribe the above stated drugs along with mandated culture sensitivity tests for diagnosing suspected infections.	**Role of Pharmacist and RMP:** 1. Antibiotics are to be sold only on prescription of a RMP. 2. No such responsibility of RMP.
4	**Role of Drug Inspector and CDSCO:** 1. No such procedures were mentioned in draft amendments.[9,10,13]	**Role of Drug Inspector and CDSCO:** 1. Particularly for Schedule H no such procedures are mentioned in rules.[11,13]

After seeing the differences between these schedules it implies that government is planning to combine the H and X schedules thereby increasing the vigilance on antibiotics that are specified in the H1. These differences can be attributed to superiority of schedule H1 over schedule H and in some instances there are some obligations and some changes to be made for the effective implementation of the Schedule H1. The following are some obligations and proposals that are to be considered for its implementation.

DRAW BACKS:

There are certain backdrops that are to be addressed before going to evaluate the advantages and disadvantages of the proposed schedule H1.

1) The contribution to resistance by ophthalmic and ENT preparations of drugs which are specified in the schedule is almost negligible. So, there is no need to restrict the use of these types of formulations.
2) The guidelines for prescribing the drugs specified in the schedule are not clearly mentioned.
3) Lifesaving antibiotics may no longer available as OTC products which may cause deaths in emergencies.
4) Many key factors that are leading to resistance are not given importance like improper implementation of laws, patient compliance issues.
5) The schedule didn't provide any exemptions for remote areas where access to hospitals is not possible.
6) The guidelines for prescribing and refilling process are not specified.
7) Inspectors or officials who are going to audit the hospitals and pharmacies are not clearly mentioned.[12]

SUGGESTIONS:

1) Storage of duplicated prescription for every dispensing of stated drugs for a limited period and mandate number of inspections may increase the vigilance.
2) Standard treatment guidelines are to be revised and there is a need to come up with an official STG with subsequent wide distribution among the RMPs.
3) Educational campaigns are to be conducted among the public and also health care teams to create awareness among them and to seek some support from them.
4) Along with implementation of new regulations old ones are to be revised.
5) Proper prescription guidelines are to be given regarding when to prescribe certain classes of drugs with some principle guidelines developed by the health ministry.
6) Increasing the sensitivity of public in this issue by conducting campaigns.
7) Some exemptions are to be made for remote areas where the access to health care is under developed.
8) Proper packaging and labeling requirements are to be specified as there is a chance of misleading the patient.
9) Interference from the political side can lead to complete loss of control so, it should be minimized.
10) Maximum number of units to be prescribed per prescription is to be prescribed.
11) Direct supervision of pharmacist is must while dispensing the antibiotics and rules regarding this aspect are to be laid down.
12) RMPs shall not receive any physicians sample as it may lead to misuse the drugs.
13) Stocks are to be audited as black market may rise.
14) Some more drugs can be added in the lists which are at a chance of misuse like anti fungals, anti protozoals etc.
15) Patterns of self medication emerging from various sources are to be identified and controlled.
16) Frequent inspections are to be conducted and reports are to be submitted to the respective branch which is specially designated to ensure appropriate use of antibiotics.
17) Sale of newer antibiotics is to be allowed in other health care settings for the benefits of patients only after providing the health professional adequate training in rational use of antibiotics.

CONCLUSION:

Along with inappropriate dispensing government has to focus on some more important issues which include:

1. Lack of screening facilities for proper diagnosis of infections.
2. Lack of proper implementation of laws.
3. Loop holes in existing laws like allowing non pharmacist personnel to have partnership in establishing a pharmacy.
4. Self medication issues.
5. Lack of knowledge in public and health care team.

Before implementing the laws which are throwing the public health into risk government has to remember that "Rome is not built in a day" similarly, forcing to implement laws is not the solution for the issue which is due to many reasons. So, government has to focus on the reasons that led to this situation and then frame laws accordingly. Even though it is a good move, in the present context it is not possible to implement the new schedule as such. This is to be solved making adequate changes to the proposed schedule and then come up with a modified one that is accepted by all. So, there is a need for the government to consider these recommendations and make required changes in the proposed schedule.

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