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Expert Opinion

Standardization of Therapeutic Guidelines in Pakistan: The lack of Considerations and Input from Stakeholders

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ABSTRACT

The Standard Treatment Guidelines (STGs) are crucial to evidence-based prophylactic and therapeutic management for safe and effective patient care. To develop or review an STG, a team with all relevant stakeholders should meet regularly to put together all scientifically gathered evidence, analyse the evidence, recommend the STG, and disseminate the guidelines final among the healthcare providers. The following are the key drivers of changes for STGs personalised to local settings: emerging pharmacovigilance data, developing evidence from clinical or pharmacological studies, introducing innovative medicinal agents, etc. Due to genetic and environmental variations, the experts recommend using indigenous evidence from local populations for developing STGs. Alternatively, the international guidelines may be adapted with the necessary modifications and adjustments to cater for the specificities of the local community. Rapid dissemination and effective communication are crucial to help healthcare providers implement the latest STGs in Pakistan.

INTRODUCTION

The Standard Treatment Guidelines or the Standard Therapeutic Guidelines (STGs) are the lifeblood of evidence-based medical practice. In most developed countries, STGs are commissioned and made available for almost all medical conditions. Depending on the use, the guidelines could be of several types, such as rapid advice guidelines, standard guidelines, and full guidelines (NICE, 2014). In England, six categories of Guidelines are available from the NICE for Clinical, Public Health, Technology Appraisal, Interventional Procedures, Medical Technologies, and Social Care (NICE, 2014). Similarly, many other countries publish and update therapeutic guidelines. If all healthcare providers may not manage all disease conditions effectively, the STGs help in diagnosis, differential diagnosis, prognosis, and selecting an optimum treatment option. The STG development is an example of participatory decision-making where input comes from multiple sources, such as structurally selected research publications, pharmacovigilance data, and the insights of healthcare providers, regulators, and society representatives. In this way, the STGs provide safe, effective, and cost-effective options.

The STGs are dynamic documents and provide multiple advantages for all stakeholders, such as healthcare providers, regulators, fund providers, supply chain managers, and patients. The STGs help in evaluating the quality of the care, controlling the cost of therapy, facilitating forecasts, assuring supply accessibility, and reducing cost, to list a few. These benefits are only possible when the guidelines are accurate, comprehensive, based upon the current evidence, and developed with inputs from all the stakeholders without any prejudice and conflict of interests emerging from existing and previous affiliations with the healthcare business, pharmaceutical industry, and other agencies. For instance, the UK's National Institute of Health and Care Excellence (NICE) has a strict Conflict of Interest (COI) Disclosure policy for those engaged in clinical guidelines developments (Graham, Alderson, & Stoke, 2015).

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Another important consideration for keeping an STG relevant is a structured review process at a defined frequency or emergence of new evidence. The latter requires a robust country-wide pharmacovigilance (PV) system to capture the novelty, frequency, and severity of previously undocumented incidences related to a medicinal agent in a particular population. PV studies are crucial to improve patient safety. Moreover, it can also help to find a new therapeutic usage (repurposing) of medicines. The benefits of sharing an unusual event for a prescribed medicament with physicians and pharmacists provide the basis for expanding its use in other already approved indications, which is also known as repurposing (Krishnamurthy, Grimshaw, Axson, Choe, & Miller, 2022). The net result is the use of an already known medication other than those for the primary approved indications (Whaley, Bancsi, Ho, Burns, & Grindrod, 2021). An example could be terazosin, an alpha-blocker agent primarily studied and registered for hypertension but then approved for use in benign prostatic hyperplasia (BPH) (Kirby, 2002).

The evidence of the disease's cause may change with time. Peptic ulcer disease (PUD) could be a good example. Perhaps until the 60s - *hurry, worry, and curry* were the causal factors (Kelly, 2021). Due to that premise, the prescribers made the patients use anxiolytics, anticholinergics, and bland foods (less spicy). Then, as gadgets with high precision became available, the evidence changed again, and the excessive generation of acid became the cause of the ulcer. To reduce acidity, healthcare providers started prescribing sodium bicarbonate, which provided immediate relief to patients. However, its frequent use resulted in problems due to acid-rebound effects. Subsequently, magnesium/aluminium-based antacids became popular. The gallons of suspensions that used to be taken monthly jeopardized the quality of life of the sufferers. Then came a great relief to the patients in the late 1970s - Histamine-2 Receptor Antagonists (H2RAs) cimetidine - a tiny tablet, revolutionized the treatment and improved the quality of life (Molindar, 1994). H2RAs were immediately pushed back by the omeprazole in 1989– a Proton Pump Inhibitors (PPI) (Strand, 2017). In 1982, the hyperacidity paradigm was changed to an infectious cause when Professor Barry J. Marshall and Dr. Robin Warren substantiated with evidence that PUD is a bacterial disease caused by *Helicobacter pylori;* for which they got the Nobel Prize in 2005 (Watt, 2005). Initially, experts, practitioners, and scientists were skeptical about his finding. However, the emerging evidence confirmed that bacterial eradication is the first port of call for the therapeutic management of peptic ulcer disease.

For STGs, another issue that needs serious consideration is genetics and inter-population variability in pharmacokinetics that leads to therapeutic and toxicological differences among populations (Johnson, 1997). Besides, immigration has led to the emergence of multi-ethnic groups worldwide that emphasize the need for factoring the practice of pharmacogenomics in mainstream therapeutics and making the situation more complex for personalized medicines (Shah & Gaedigk, 2018). The pharmacogenetic research uncovered significant differences among populations in the metabolism, clinical efficacy, and safety profiles of many clinically vital drugs. Burroughs, therefore, recommended that pharmacogenetic differences "must be considered in the design of cost management policies such as formulary implementation, therapeutic substitution, and step-care protocols. These programs should be broad and flexible enough to enable rational choices and individualized treatment for all patients, regardless of race or ethnic origin" (Burroughs, Maxy, & Levy, 2002).

With current and emerging evidence, guidelines need regular review and periodic revisions to reflect the latest evidence. Although it is evident that *Helicobacter pylori (H. pylori)*, if left untreated, could lead to malignancy (Elbehiry, Marzouk, Aldubaib, & et. al., 2023), most practitioners in Pakistan either do not use *H. pylori* eradication therapy or do not prescribe the recommended combinations, dosage, or the correct duration. Diabetes, hypertension, and migraine are other common examples in Pakistan where diagnosis and treatments are not standardized. For instance, practitioners do not involve patients suffering from migraine in treatment selection. Consequently, this does not assist a prescriber in providing migraine prophylaxis to the patients. Conversely, the STGs can help rationalize medical practice, improve the quality of care and patient outcomes, save cost, assist the regulator while approving drugs and devices, and identify opportunities for research in a socio-economical context (Klein, 2002).

In low and middle-income countries (LMIC), such as Pakistan, local guidelines for many diseases are not there, and the possibility of national STGs is a far cry soon. In the interim setup, healthcare professionals and regulators should use the internationally recognized guidelines with flexibility for adaptation in the national socio-economical context that could improve the quality of care. However, there are communication gaps and a sluggish knowledge

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transfer from healthcare experts to practitioners (Wallace, 2013). It is imperative to accelerate the speed of dissemination of evidence among healthcare providers through regular training and professional education events. On the patient's side, the lack of awareness of the disease among the laity delays the start of treatment and results in more complications with extra expenditure (Basharat, Sheikh, Rashid, & Rashid, 2019). Therefore, strategies to help improve behavioral change among the public and increase health awareness are the building blocks of improving public health.

Finally, nationally standardized treatment guidelines must be developed in LMICs considering genetic and ethnic differences of the local population juxtaposing socioeconomic context. While making the STGs, we must consider the national disease trends, pathogen surveillance, national antimicrobial resistance patterns, and availability and affordability of treatment choices.

CONCLUSIONS

This write-up underscores the significance of STGs, particularly in Low and Middle-Income Countries (LMICs), for effective, safe, and economical patient care. There is no option but to engage all stakeholders for inception or periodic review substantiated by pharmacovigilance data, emerging clinical evidence, and the entrance of innovative therapeutic agents and devices. STGs designed on the local substantiations supposedly work better. In case of no such arrangement, those developed by the NICE, WHO, or similar entities of repute must adopt necessary modifications considering genetic, environmental, or epidemiological differences. Concerted efforts are required in the LMICs to design a robust indigenous pharmacovigilance system and a structure for developing or adopting STGs as early as possible.

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