The case for levetiracetam to be included in essential medicine lists

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The Intersectoral Global Action Plan for Epilepsy and Other Neurological Disorders calls for urgent action to reduce the epilepsy burden worldwide.[1] Achieving its targets crucially centres on equitable access to, continuous availability and affordability of quality-assured antiseizure medications (ASMs). Expanding the range of ASMs on essential medicine lists will improve equitable access.

The WHO released the most recent model list of essential medicines in 2021.[2] It comprises a minimum of medicines necessary for primary health care, which are safe, efficacious and cost-effective. The list is influential in shaping similar lists in low- and low-middle-income countries (LMICs), where cost, undersupply, and system failures compromise medicine access. It includes six oral ASMs, i.e., phenobarbital, phenytoin, carbamazepine, valproate, lamotrigine and ethosuximide, and six non-oral formulations. National essential medicine lists incorporate these ASMs with some omissions and additions. The 2015 version of the Indian national essential medicine list included clobazam. The version released in September 2022 also includes levetiracetam.[3]

Traditionally, pharmacological treatment of epilepsy essentially encompassed four medications: phenobarbital, phenytoin, carbamazepine and valproate. Their continued use over time has promoted prescriber confidence but, also added to complexities in their usage. These are extensively metabolised in the liver and either induce or inhibit enzymatic systems responsible for metabolising other drugs. They are bound heavily to plasma albumin, so they are subject to interactions with other medications which are similarly bound and to variations in their levels because of hypoalbuminemia, e.g., with liver disease and pregnancy. The British National Formulary lists numerous clinically significant drug–drug interactions for traditional ASMs.[4] Keeping track of these complexities during prescribing can be daunting for primary healthcare providers. Valproate, is teratogenic, with adverse neurodevelopmental outcomes and malformations in up to a third of children born to exposed mothers.[5] Lastly, compelling data suggest potentially adverse cardiovascular and musculoskeletal outcomes associated with the long-term use of some traditional ASMs.[6] This eventually translates to increased associated healthcare costs. The complexities, consequences and costs underscore the need for a relatively "easy to use" drug, sparing physicians of the need to attain requisite knowledge and skills for traditional ASM use.

Levetiracetam is one ASM that fulfils the "easy to use" criterion. It is rapidly absorbed, unaffected by food, and peak concentrations are quickly achieved.[7] It has linear kinetics, with minimal protein binding, negligible hepatic metabolism, and is renally excreted. Therefore, neither does it have the propensity to clinically relevant drug interactions, nor is its plasma concentration influenced by protein levels. Schedules for commencing treatment are straightforward in comparison to lamotrigine. One issue is that tablets are large and taste bitter in crushed form.

Levetiracetam is available in tablet, oral solution and injectable forms and, therefore, suitable for various circumstances. Recent evidence from the SANAD II trials suggests that it is neither clinically nor cost-effective compared to valproate in generalised epilepsies and lamotrigine in focal epilepsies.[8,9] Nevertheless, it is widely prescribed for various seizure types and epilepsies, except for absence seizures. There is persuasive evidence for its use as a second-line drug for convulsive status epilepticus.[10] Its efficacy in terms of seizure termination is similar to phenytoin but with a quicker onset, probably related to the speed of its intravenous administration compared to phenytoin.

When used in monotherapy, levetiracetam is less teratogenic than other ASMs, making its use appealing in women in the reproductive age group.[6] Therapeutic drug monitoring, although available, is not routinely required, apart from some situations, e.g., pregnancy, adherence check, intercurrent critical illnesses and extremes of age. Levetiracetam's adverse effect profile is limited, making it further appealing for use in primary care. Behavioural side effects, including irritability, anger and aggression, are the most common. It is prudent to screen for suicidality and psychiatric disorders at treatment initiation bearing in mind, however, that both are raised in epilepsy.

Traditional ASMs are low-priced and often the only drugs available in LMICs. These remain indispensable to practice, especially in primary care settings in LMICs.

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Their use poses challenges on account of their complexity and long-term consequences. Levetiracetam's cost remains an issue but has lessened with the availability of generics and will likely further reduce if labelled as an essential medicine. The addition of levetiracetam to the Indian list is a commendable step. Other countries should follow suit.

Contributors

GS & JWS conceived the idea behind the manuscript. GS wrote the manuscript and JWS revised and provided additional intellectual inputs.

Declaration of interests

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