Off-label Psychotropics Use: Isn't it Now an Inevitable and a "Norm" in Psychiatry?

Sir,

"Off-label use" refers to the use of a drug outside the terms of its marketing authorization. It includes prescribing for an unlicensed indication like in unapproved indication, age group, dosage, or in unapproved form of administration.[1,2] In principle, though it may not be compliant to the ethics in clinical practice, reports of off-label use of psychotropics have been widespread across clinical diagnoses and age groups.[1,3-11] Among all medications, psychotropics are one of the most commonly prescribed for off-label purpose.[5,12] A few studies from the Indian subcontinent had found that off-label use of psychotropics was seen in a significant proportion of prescriptions (up to 42%) and off-label uses were most common for indications (48.9%) followed by for dose (37.2%).[9,10] Apart from the ethical and biological concerns arising from the unexpected adverse effects, off-label use also has an economic impact. In the United States, off-label use of central nervous system drugs contributes to 25%–80% of a drug's annual sales, and off-label indications for antidepressants, anticonvulsants, and antipsychotics are expanding each year.[5] All these drew our attention to the reasons behind the off-label prescription of psychotropics.

Factors commonly taken into consideration while choosing a psychotropic are the clinical diagnosis made, clinician's own experience with the diagnosis and the index psychotropic, evidence for efficacy of the particular psychotropic for that diagnosis, physical and family factors of index patient, and the side effect profile of the psychotropic. A clinical diagnosis naturally warrants that one prescribes a medication approved for it. In a review, Devulapalli *et al*.[5] concluded that majority of psychiatric diagnoses (up to 88%) from the Diagnostic and Statistical Manual IV – Text Revision (DSM IV – TR) had no approved medication from the Food and Drug Administration (FDA). Now that researches have confirmed the efficacy of several categories of psychotropics (e.g., atypical antipsychotics, antidepressants, anxiolytics, mood stabilizers, benzodiazepines, and stimulants) for other indications apart from the ones approved by the FDA. When clinicians come across a diagnosis which has no approved medication, the next reasonable step expectedly would be to search for medications with evidence-based efficacy, albeit a weak one. It would surely not be ethical to refrain from prescribing and let patients continue suffering for the reason that there is no approved or recommended psychotropic available in any drug regulation authority or in any guidelines. Even if the clinical diagnosis being made has an approved medication, it may so happen that the patient may not show adequate response or the illness has become refractory. Eventually, the clinician will have to prescribe a medication off-label.

Furthermore, psychopharmacotherapy does not just involve choice of molecules. For most psychotropics, several issues such as minimum and maximum dosage across age groups, titration regimens, discontinuation schedules, and status in combination or adjunct therapies are rarely adequately researched and remain beyond the purview of being "on label." Often, depending on the illness profile, the clinician has to prescribe a higher dosage than recommended. Conversely, sometimes, less than the minimum dosage can evoke an adequate response and a full recovery. Likewise, often, dosage schedules other than the recommended ones are found to be efficacious or they have to be changed to optimize the response and patient satisfaction. In addition, titration schedules recommended by the FDA do not suit all patients and are required to be tailored among patients, and this too would fall under off-label use.

Beyond the above factors related to medications, there are a few other factors that make the off-label use of psychotropics almost inevitable in Psychiatry. Unlike other branches of medicine, etiology of most psychiatric disorders remains unknown or, to say the least, remains nonspecific, thereby making it difficult to specify the target for successive upcoming research molecules. For instance, in case of antipsychotics and antidepressants, most of the molecules have affinity to more than one receptor and have similar receptor profiles, only with varying amount of affinity.

Thus, when the need arises, in a range of clinical situations, the clinicians should be in-principle reasonable enough to prescribe medications even if that falls under off-label use.

Furthermore, the process of approval for a specific molecule for a specific clinical condition is always a lengthy and time-consuming one. Several phases of trials are necessary before a proposal can be submitted to the FDA or other drug regulatory agencies. As conducting large-scale trials involves huge funding, such trials are sponsored by pharmaceutical companies, rising the

concern of potential bias. It cannot be expected that trials would be conducted for every clinical condition for which there are no approved medications. In most cases, it is the sponsor's decision as to which drug is to be tested and which clinical condition is to be addressed. Thus, off-label use of psychotropics has become an important approach in clinical psychopharmacology and we believe that it will remain so in spite of several concerns.

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