Alarm as FDA fast-tracks first antipsychotic drug for agitation in dementia

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In trials, the antipsychotic drug brexpiprazole (Rexulti) failed to provide a clinically meaningful benefit and increased the risk of death. Yet the US Food and Drug Administration (FDA) has fast tracked its approval,

making Rexulti the first antipsychotic for treating agitation in elderly patients with dementia.

At a cost of around $1,400 a month Rexulti's makers, Otsuka and Lundbeck, are forecasting an additional $1 billion in annual sales, but there are serious questions about the harm-benefit balance of this drug, writes investigative journalist Robert Whitaker in *The BMJ* today.

The decision may also reverse years of effort by the US Centers for Medicare and Medicaid Services (CMS) to reduce the widespread off-label use of antipsychotics in residential care homes.

Like other antipsychotics, the drug carries a "boxed warning," FDA's most serious type of warning, informing prescribers of increased risk of death. And in the three pre-approval trials, the FDA concluded that the death rate was four times higher in those given brexpiprazole compared to those given placebo.

On efficacy, the drug showed a maximum 5.3-point improvement over placebo on a 174-point scale, far short of the 17 points considered to be clinically important.

"The small benefits do not outweigh serious safety concerns," Public Citizen health researcher Nina Zeldes told the FDA's Advisory Committee prior to the approval. "Like other antipsychotics, this is a drug that can kill patients without providing a meaningful benefit."

Professor Lon Schneider at the Keck School of Medicine of the University of Southern California noted that the brexpiprazole outcomes mirrored the results from earlier trials of antipsychotics in Alzheimer's patients, yet none of these other antipsychotics has been approved for treating behavioral symptoms in elderly patients with dementia.

Schneider says the FDA has a "lower standard of approval" today than it did 20 years ago, a theme echoed by Zeldes, who said, "We are very disappointed that the FDA approved this additional label indication for brexpiprazole on such weak data. The FDA has set a dangerous precedent about the data it may require for future drug approvals for this vulnerable patient group."

In a vote, nine of the FDA committee's 10 members believed there was sufficient data to identify a population in whom benefits outweighed the drug's risks. But even among those voting yes, several advisors expressed concern about its use in patients with mild symptoms. Some stressed the need for individualized risk-benefit evaluation in collaboration with patients' families.

The chair of the advisory committee, Rajesh Narendran, did not respond to multiple requests for an interview to answer questions raised by this approval, while a spokesperson for the FDA's Center for Drug Evaluation and Research stated that "due to conflicting schedules and competing priorities," the FDA would be unable to respond.

Whitaker notes that a number of patient advocacy groups, such as the Alliance for Aging Research, Leaders Engage on Alzheimer's Research (LEAD), and Us Against Alzheimer's, urged the FDA to approve brexpiprazole.

This public support is fueled, in part, by commercial interests, he writes.

LEAD, for instance, is a "coalition of more than 200 organizations" that includes, among its members, Otsuka and other pharmaceutical companies, while the Alliance for Aging Research, which lists 31 partners, receives funding from Otsuka and other pharmaceutical companies for "non-branded health education and advocacy on neuropsychiatric symptoms of dementia."

Erick Turner, a former FDA reviewer and professor of psychiatry at Oregon Health & Science University, said that clinicians' responses to the approval will likely vary according to their current beliefs about prescribing antipsychotics to Alzheimer's patients.

He added, "On the topic of marketing, I do think it will come down to KOLs [key opinion leaders] and drug reps 'educating' clinicians."

Whitaker writes that if Otsuka's presentation to the drug advisory committee is any guide, the talking point it will use to market brexpiprazole is that it is much safer than other antipsychotics, even though that favorable safety comparison was built into Otsuka's design of phase III trials.

Such marketing efforts will likely be at odds with ongoing efforts by the CMS. "Antipsychotic medications are especially dangerous among the nursing home population because of their potentially devastating side effects, including death," a CMS spokesperson said. "We cannot speak to the hypothetical future use of brexpiprazole; however, CMS will continue its efforts to reduce the prescribing of unnecessary antipsychotics in nursing homes."

More information: Robert Whitaker, How the FDA approved an antipsychotic that failed to show a meaningful benefit but raised the risk of death, *The BMJ* (2023). DOI: 10.1136/bmj.p1801

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