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INVESTIGATION

How the FDA approved an antipsychotic that failed to show a meaningful benefit but raised the risk of death

In trials, brexpiprazole failed to provide a clinically meaningful benefit and it increased mortality, but the FDA fast tracked its approval and the sponsor predicts $1bn in annual sales. Robert Whitaker investigates the first licensed antipsychotic for treating agitation in elderly patients with dementia

Robert Whitaker *investigative journalist*

For years, health officials have tried to rein in the prescribing of atypical antipsychotics to elderly patients with dementia. The practice has been entirely "off label" yet widespread. The US Food and Drug Administration reports that around 60% of patients with Alzheimer's dementia in residential care have received an off-label prescription for an antipsychotic, benzodiazepine, antidepressant, or anti-epileptic drug. After a 2005 FDA warning that cited a 60-70% increased risk of death associated with antipsychotic drug use, the US Centers for Medicare and Medicaid Services established the National Partnership to Improve Dementia Care in Nursing Homes, a public-private collaboration that sought to "reduce the use of antipsychotics" and "enhance the use of non-pharmacological approaches."[1]

But a May 2023 FDA approval of the antipsychotic brexpiprazole for agitation in patients with Alzheimer's dementia may reverse all of this. At a cost of around $1400 (£1102; €1280) a month, the manufacturers Otsuka and Lundbeck, which jointly brought the "first in class" approval to market, are forecasting an additional $1bn in annual sales of Rexulti.[2]

Serious questions remain, however, about the harm-benefit balance of Otsuka and Lundbeck's drug. The drug carries a "boxed warning"—the FDA's most serious type of warning, informing prescribers of increased mortality. And among four efficacy evaluations across the three prelicensure clinical trials, the highest efficacy observed was a 5.3 point improvement over placebo on a 174 point scale. In the two trials that assessed quality of life, no benefit for either the patient or the caregiver was demonstrated.

"The small benefits do not outweigh serious safety concerns," said Nina Zeldes, health researcher at the consumer advocacy organisation Public Citizen, addressing the FDA's advisory committee at its 14 April meeting before the approval.[3] "Like other antipsychotics, this is a drug that can kill patients without providing a meaningful benefit."[4]

Efficacy and safety data

Trials measuring the efficacy of drugs for treating agitation in people with Alzheimer's dementia make use of the Cohen-Mansfield Agitation Inventory (CMAI). Caregivers assess the weekly frequency of 29 behaviours, each on a score of 1 to 7, resulting in a total score of 29 to 203. In 2021 an international group of researchers reported that the "minimal clinically important difference" at 12 weeks on the CMAI scale was 17 points.[5]

The FDA found Otsuka's first two placebo controlled clinical trials unconvincing. Study 284 evaluated a flexible dosing schedule of brexpiprazole, from 0.5 mg to 2 mg a day, but results were not statistically significant. A second study, Study 283, considered two fixed doses, 1 mg and 2 mg daily. The 1 mg dose failed, while the 2 mg dose produced a 3.8 point reduction in symptoms when compared with placebo. Despite this being statistically significant the FDA informed the drug's sponsors at a 2017 meeting that it did not consider the 3.8 point difference "statistically persuasive" and recommended that the sponsor conduct a third study.[6]

Results from the third study (Study 213) found brexpiprazole, when compared with placebo after 12 weeks, to provide a 5.3 point reduction in symptoms on the CMAI scale, again far short of the 17 point minimal clinically important difference.

As for the mortality data, the risk of death was four times higher in the patients taking brexpiprazole when compared with placebo over a 16 week period. After considering various confounding factors the FDA concluded that the risk of death with brexpiprazole "appears to be consistent with the known risks with other antipsychotics in elderly patients with dementia," and it kept the prominent boxed warning regarding mortality risk on the newly approved product label. Other safety concerns included the risk of urinary tract infections, somnolence, insomnia, and cardiovascular events.[6]

Lowering of standards?

Given that the FDA fast tracked the approval of brexpiprazole, the public could be expected to assume that this drug is superior, in terms of its harm-benefit profile, to that of other antipsychotics that are being prescribed off label. However, Lon Schneider, professor of psychiatry, neurology, and gerontology at the Keck School of Medicine at the University of Southern California, noted that, in fact, the brexpiprazole outcomes mirrored the results from earlier trials of antipsychotics in patients with Alzheimer's. "There are the same small points of difference on the [CMAI scale] that you see with every other drug," he said. "With brexpiprazole you get the

same level of side effects, the same black box warning, the same concern about a whole range of adverse effects."[7 8]

Trials of other atypical antipsychotics including risperidone, olanzapine, quetiapine, and aripiprazole were conducted more than two decades ago but, unlike brexpiprazole, none of these was approved for treating behavioural symptoms in elderly patients with dementia.

Schneider added that there was something "unusual" about the results from Study 213: brexpiprazole produced no benefit at US sites, which enrolled 44% of the patients. The reported 5.3 point benefit was the result of a nine point drug-placebo difference in 125 patients treated with brexpiprazole across five eastern European countries and Spain.[6] The nine point difference at the European sites, he said, was "implausible" in the context of "no effect whatsoever" at the US sites. While the FDA expects sponsors to include US residents in clinical studies, in this instance no benefit was seen at the US sites in the one study that provided the primary evidence for approval.

The nine point placebo-drug difference recorded at the European sites was also an outlier from the results in the other two phase 3 trials of brexpiprazole and the earlier trials of other atypical antipsychotics. A meta-analysis cowritten by Schneider found five randomised controlled trials of risperidone and aripiprazole conducted before 2005 that used the CMAI scale to measure symptoms, and the drug-placebo differences in the five trials ranged from 2.3 points to 4.4 points.[8]

The FDA has a "lower standard of approval" today than it did 20 years ago, said Schneider. "We are seeing that for a wide range of drugs," he said. "We see it with other drugs for dementia," such as aducanumab and lecanemab. "This is an example of that."

Zeldes echoed that theme in an email interview. "We are very disappointed that the FDA approved this additional label indication for brexpiprazole on such weak data," she said. "The FDA has set a dangerous precedent about the data it may require for future drug approvals for this vulnerable patient group."

The path to approval

The FDA's drug advisory committee meeting included a brief discussion of whether brexpiprazole provided a minimum clinically important difference, and Jess Fiedorowicz, a professor of psychiatry at the University of Ottawa, cited the 2021 paper[5] as a reference. "I think the minimal clinically important difference is important to consider, but I don't think it is super easy to determine," he told *The BMJ*.

Fiedorowicz, who voted for approval, turned to other data to guide his decision: the fact that there were two statistically significant results; a small effect size in Study 213; and evidence of a dose dependent response. He explained, "I tried to look at it from a couple of different angles, and from those angles there seemed to be a small effect, and whether that crossed a threshold of minimally important clinical difference, it was hard to tell. It may or may not."

In a vote, nine of the committee's 10 members indicated that they believed the sponsor had provided sufficient data to identify a population in whom benefits outweighed the drug's risks. But even among those voting yes, multiple advisers expressed concern about using the drug in patients with mild symptoms—a population the FDA did not exclude from approval. Some emphasised the need for an individualised risk-benefit evaluation in collaboration with patients' families.

"There is a lot of variability in presentation and the severity of agitation, and I think the risk-benefit equation is very difficult to make in broad strokes," said Fiedorowicz. "Ultimately, I think the risk-benefit depends on the context, the nature of the behaviours, and what sort of resources or options a person has for their ongoing care. We have some sense of what the risks are with these agents, and as long as people aren't exaggerating the potential benefit, and not continuing the [treatment] if there is no benefit, it seems potentially prudent to give clinicians a tool they can use to make that determination."

The chair of the advisory committee, Rajesh Narendran, did not respond to multiple requests for an interview to answer three questions raised by this approval: was there evidence that brexpiprazole provided a clinically meaningful benefit? Was there evidence that its risk-benefit profile was superior to antipsychotics that are prescribed off label to this population? And was the lack of an effect in Study 213 at the US sites important?

Those same questions were posed to the FDA, which in its 11 May press release stated that two phase 3 trials of brexpiprazole had shown "statistically significant and clinically meaningful improvements in total CMAI scores compared to patients in the placebo group at week 12."[9] After an exchange of emails 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. The spokesperson later said that *The BMJ* would "need to file a FOIA [Freedom of Information Act request]" to ask for records if it wanted answers to these questions.

Clinical impact

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. The Alzheimer's Association also "welcomed" the decision, which suggests that the FDA's decision, together with public sentiment, may markedly change clinical practice.

This public support is partly fuelled by commercial interests. LEAD, for instance, is a "coalition of more than 200 organisations" that includes Otsuka and other drug companies among its members. The Alliance for Aging Research, which lists 31 partners, receives funding from Otsuka and other drug companies for "non-branded health education and advocacy on neuropsychiatric symptoms of dementia."[6] The alliance's 17 member board of directors includes representatives from Otsuka and four other drug companies, from two marketing companies that help drug companies sell their products, and from two investment companies that invest in life science companies.[10] The board's chair, Jim Scott, previously worked at Hoffmann-La Roche, where he helped the company obtain Medicare and Medicaid coverage of its products. He is now chief executive of Applied Policy, which provides consulting services to help "healthcare providers and companies succeed."[11]

Erick Turner, former FDA reviewer and a professor of psychiatry at Oregon Health & Science University, said that clinicians' responses to the approval would probably vary according to their current beliefs about prescribing antipsychotics to patients with Alzheimer's. Those who are "strongly opposed" to this practice "will not be swayed by this approval," he said. However, for those "on the fence," the "FDA approval could undermine the message from the CMS [Centers for Medicare & Medicaid Services], making them more likely to prescribe antipsychotics in general and brexpiprazole in particular." Those who are "already committed" to prescribing antipsychotics may be encouraged to switch from the inexpensive

generics currently prescribed off label to the much more costly brexpiprazole.

"These clinicians will ask themselves whether brexpiprazole is superior to their go-to antipsychotic," said Turner. "To make that case, the company will want to get its KOLs [key opinion leaders] out on the trail with their slide decks, perhaps in the context of a dinner talk to more easily 'educate' the clinicians. I'm sure they've already curated a number of talking points addressing both efficacy and safety."

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. Although the fourfold higher mortality rate was actually much higher than the increased risk with other antipsychotics, the incidence of death in the patients taking brexpiprazole, as one of Otsuka's slides stated, was lower "compared to other antipsychotics in [an] elderly population with dementia."[12]

However, as the FDA noted, that favourable safety comparison was built into Otsuka's design of phase 3 trials. The mean age of enrolled patients was 74, seven years younger than the average age of patients in the earlier trials of antipsychotics. Moreover, most of the earlier trials had been conducted in nursing homes, whereas the brexpiprazole trials enrolled patients in institutional and residential settings, a combination that could be expected to produce a healthier population. Only one death in the placebo group was recorded in the brexpiprazole trials, a much lower incidence of death than in the placebo groups in the earlier trials.

That explanatory point, however, may be missing from key opinion leaders' slide decks. "On the topic of marketing, I do think it will come down to KOLs and drug reps 'educating' clinicians," said Turner.

Such marketing efforts will probably be at odds with ongoing efforts by the Centers for Medicare & Medicaid Services. A CMS spokesperson said, "Antipsychotic medications are especially dangerous among the nursing home population because of their potentially devastating side effects, including death. 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."

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