



## Pimavanserin for patients with Alzheimer's disease psychosis

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Pimavanserin is an atypical antipsychotic marketed in the USA for hallucinations and delusions associated with Parkinson's disease.<sup>1</sup> It acts as an inverse agonist at the 5-HT<sub>2A</sub> receptor with no effect on dopamine receptors. A boxed warning on the prescribing information approved by the US Food and Drug Administration states that pimavanserin is not approved for elderly patients with dementia-related psychosis unrelated to Parkinson's disease psychosis, and that these patients are at increased risk of death when treated with antipsychotics.<sup>1</sup> The warning applies to all other antipsychotics, and no antipsychotic is approved for agitation or psychosis associated with dementia in the USA.

The pharmacological treatment of behavioural and psychological disorders associated with late-life dementia, including agitation, aggression, and psychosis, is challenging.<sup>2</sup> Randomised clinical trials of antipsychotics for these purposes have not shown efficacy for their primary outcomes,<sup>3</sup> including the few that specifically targeted Alzheimer's disease psychosis. By comparison, structured psychotherapeutic and environmental interventions with agitated people with dementia are effective but underused.<sup>2,4</sup>

The criteria for Alzheimer's disease psychosis were published in 2000 as a clinical and labelling indication to allow for potential marketing approval of antipsychotics for Alzheimer's disease.<sup>5,6</sup> As used by Clive Ballard and colleagues<sup>7</sup> in their randomised trial of pimavanserin, reported in *The Lancet Neurology*, these criteria are hallucinations or delusions occurring after the onset of dementia, continuing for more than 4 weeks, and of such severity and frequency that antipsychotic treatment is warranted; the FDA objected at the time to indications such as agitation associated with dementia because of its vagueness and the difficulty in describing a clear indication for a potential drug.<sup>6</sup> Yet, distinction between psychosis of dementia and agitation is not clear, because delusions and agitation are particularly common and substantially overlap.<sup>8</sup>

Ballard and colleagues screened 345 patients with Alzheimer's disease psychosis residing in 133 nursing homes in the London metropolitan area, and randomly assigned 181 to placebo or 34 mg per day of pimavanserin—the dose used for Parkinson's disease psychosis<sup>9</sup>—and treated them for 12 weeks. Patients

needed minimum scores on the caregiver-rated hallucination or delusion scale of the Neuropsychiatric Inventory–Nursing Home version (NPI–NH), indicating symptoms that occur at least weekly and are distressing or disruptive, or symptoms that occur at least daily but with little or no distress. The primary outcome was the NPI–NH psychosis score (ie, the sum of the hallucinations and delusions scale scores) at 6 weeks of treatment. Outcomes on a global assessment, other NPI scales, the Cohen–Mansfield Agitation Inventory–Short Form, and a measure of daily activities at 6 weeks, and the NPI–NH psychosis scale at 12 weeks, were secondary or exploratory outcomes.

Despite a statistically significant effect for pimavanserin on the NPI–NH psychosis scale at 6 weeks, the results of this trial cannot be considered to be positive or clinically meaningful. The effect itself was small (mean change in NPI–NH psychosis score –3.76 points [SE 0.65] for pimavanserin and –1.93 points [0.63] for placebo, mean difference –1.84 [95% CI –3.64 to –0.04];  $p=0.045$ ) and no effect was evident for the NPI–NH psychosis scale at any other time during the 12-week trial. Moreover, 17 of 18 secondary and exploratory outcomes and six of seven subgroup analyses did not show evidence for efficacy. The significance of the primary outcome was driven by a worsening of the placebo-treated group at 6 weeks that was not observed at 4 weeks of treatment or at 9 and 12 weeks of treatment.

Within the subgroup with more severe symptoms (NPI–NH psychosis scores of  $\geq 12$ , who made up only a third of the study sample), there was a significant effect favouring pimavanserin (mean difference –4.43 [95% CI –7.81 to –1.04];  $p=0.011$ ), but, again, due to the unusual worsening of the placebo group at 6 weeks, and not seen before or after 6 weeks. Although this subgroup showed substantial improvement in both the placebo and pimavanserin-treated groups, patients were still very symptomatic and scores at 12 weeks remained above the eligibility threshold for study entry. Of note, virtually all patients in this more severe subgroup had hallucinations along with delusions. By comparison, the larger, less symptomatic subgroup with NPI–NH psychosis scores less than 12 had delusions but more than 75% had no hallucinations and the rest had very mild hallucinations occurring infrequently and causing little or no distress.

The designation of a primary efficacy outcome at 6 weeks while continuing double-blind treatment for 12 weeks allowed assessment for a continuing effect over 12 weeks, and is a unique feature of this trial. The absence of effect for pimavanserin both before and after 6 weeks, however, casts doubt on the clinical relevance of the score at 6 weeks. If the primary outcome had been specified for 12 weeks, typical of previous trials with antipsychotics, then pimavanserin would have been considered as not effective.

Nursing home residents are vulnerable, frail, and often are facing imminent death. Eight patients died during the 12-week trial, a 20% annualised rate, making it difficult to judge the seriousness of adverse events overall. The safety of pimavanserin is potentially concerning, in view of its association in this study not only with QT prolongation, oedema, and weight loss, but also with agitation, aggression, and anxiety, which would probably counter any therapeutic effect.

A therapeutic effect of pimavanserin might depend on underlying brain pathology, and the population of this study probably would have particularly heterogeneous proteinopathy, hippocampal sclerosis, and vascular brain injury.<sup>10</sup> For example, in view of pimavanserin's particular effects on visual hallucinations in Parkinson's disease,<sup>1,9</sup> any salutary effect it might have for people with Lewy body pathology and visual hallucinations might not be recognised in this trial.

Unfortunately, this phase 2 trial did not yield the evidence or proof of concept that would inform a subsequent phase 3 confirmatory trial. Rather, the outcomes raise questions about the indications for treatment, whether psychosis or agitation should be targeted, and the likelihood for success in a

subsequent trial in similar patients diagnosed with Alzheimer's disease. It is unfortunate that in the current environment of drug development, experimental drugs often are advanced to larger phase 3 trials without evidence from phase 2 trials.

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## DBS for Parkinson's disease with behavioural disturbances

Behavioural problems—eg, impulse control disorders, excessive and uncontrollable intake of levodopa, punding, restlessness, and disarray behaviour—are common in patients with Parkinson's disease and frequently represent a challenge for clinical management.<sup>1</sup> Behavioural complications are associated directly with medications for Parkinson's disease (particularly dopamine agonists) and typically arise after prolonged exposure to such drugs, leading to

a functional hyperdopaminergic state. Disease-related structural features of the brain (eg, the pattern of nigrostriatal dopaminergic denervation) and individual predisposing factors (eg, male sex, young age at onset) are also determinants of behavioural complications. In patients presenting with motor fluctuations and dyskinesia, neuropsychiatric disturbances are noted in a significant proportion of individuals,<sup>2</sup> and therefore these factors are especially relevant in advanced disease.



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