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COMMENTARY

Treating agitated demented patients is difficult and not cheap!

In 2021, a study of mirtazapine given to elderly demented individuals in Great Britain for the treatment of agitation reported that this well-regarded antidepressant was not more effective than PBO for treating agitated behavior (Banerjee *et al.*, 2021). The present communication reports a very careful secondary examination of the cost-effectiveness of the mirtazapine treatment in this study. Henderson *et al.* (2022) of the journal present the conclusion that mirtazapine treatment was not "cost-effective." It would seem, therefore, that this was a negative study both therapeutically and economically. But very important issues, both clinical and economic, were raised and discussed in both reports making important reading.

Anyone who has tried to treat an elderly patient with severe agitation can understand the need for better treatments. Those that are available are less than reliably therapeutic. For example, serotonergic antidepressants, anticonvulsants and mood stabilizers as well as sedative-hypnotics individually and in combination fail to reliably reduce dementia-related agitation. And the mirtazapine data presented in this cost-effectiveness paper probably apply clinically and economically to many other ineffective treatments. As a practical matter, this leaves the ongoing use of antipsychotic drugs as the only pharmacological approach is currently available. Clinical experience and numerous clinical reports testify to their benefit (Salzman, 1994). But the elderly may be more sensitive to side effects such as sedation, orthostatic hypotension, anticholinergic cognitive and somatic suppression, and possible increased risk of stroke and premature death. In the US, the FDA issued a "black box warning" regarding the potential danger of antipsychotic drugs, thus making their routine use problematical or forbidden in many residential and hospital facilities.

Distraught family members search for answers to the behavioral and cognitive problems of their agitated elderly family members, sometimes choosing unproved treatments and potentially dangerous agents obtained from non-medical sources. Management of residential facilities sometimes ejects these patients because of the tumult and potential danger and discomfort of other residents. Hospitals cannot manage these patients on a long-term basis This is not just an academic problem, it is a rapidly growing issue for society in all countries, not just the US or Great Britain.

What is a clinician to do when asked to treat a demented elderly patient? It would appear that no medication is reliably effective although many have been tried, and some drugs such as trazodone, hydroxyzine, bupropion have been used with mixed success. But these drugs have not been studied with RCTs so no conclusions regarding their efficacy can be drawn. Patients whose antipsychotics have been withdrawn often become unmanageable and are forced to leave their residence, which only inflames the agitated behavior. Hallucinations and delusions as well as behavioral agitation often warrant pharmacologic treatment to maintain safety of both the individual patient and the milieu in which they life (Khanna *et al.*, 2022).

What are we to do? As the number of older individuals who suffer from dementia and potential agitation and psychosis increases, the present studies suggest an emergency crisis regarding the increasing need for safe and proven pharmacological treatments for those who cannot and do not respond non-drug treatments. In a conference that I held with colleagues regarding this dilemma 2 decades ago, the FDA opined that absent a DSM diagnosis of dementia-related agitation, they would not accept research findings of drug efficacy since the subject population from whom the data were derived was not homogenous and not screened for medications or substances that might confuse the outcome of a study. Thus, clinicians have been left with unreliable clinical trial information regarding appropriate pharmacologic treatment of the demented elderly individual.

Not all is lost or hopeless! Henderson *et al.* (2022) and Banerjee *et al.* (2021) are to be congratulated for performing an extremely thorough and careful clinical trial and an important economic analysis. Their results demand increased society support for research in the agitated demented elderly including the economic benefits or losses to society if these problems are not better addressed. At this moment, however, effectively caring for the demented elderly at home, residences or institutions requires thoughtful use of available drugs. I would suggest the use of second-generation antipsychotic medications using the

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lowest possible effective doses and choosing the drugs with a less severe side effect profile. I recommend that clinicians speak with family members or responsible adults to obtain their permission prior to using an antipsychotic medication and document their approval in the patient's medical record. I would then start treatment following the geriatric maxim: "start low, go slow" using very low starting dose (liquid preparations if necessary) and follow the patient closely for emerging side effects. When possible, medications should be administered in socially calm and quiet settings, along with non-pharmacological approaches such as familiar music and singing, simple games and physical exercise and activity when possible.

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