

EDITORIAL

Pharmacotherapy in geriatric psychiatry: what we know and what we need to know

Given the growing numbers of older people with mental illnesses, it seems obvious that more resources should be put into research on geriatric psychopharmacology. This becomes even more necessary because of the already existing wide gaps in the literature on psychopharmacology in younger versus older adults. Most randomized controlled trials (RCTs) of psychotropic medications, except for those to be used in neurocognitive disorders like Alzheimer's disease, conducted by the pharmaceutical industry for approval by the USA Food and Drug Administration (FDA), are typically restricted to adults under the age of 65 years. Yet, when a drug is approved by the FDA, it is commonly used in older adults in daily clinical practice, irrespective of the fact that such use should be considered "off-label" because of a lack of empirical evidence on its utility and dosage in that age group. Indeed, there are unique pharmacokinetic and pharmacodynamic issues suggesting that older adults have differential sensitivity and a greater risk of a number of side effects with these medications when administered at the FDA-approved standard dosages. Yet, few systematic trials are conducted in older populations to determine optimal dosages. Similarly, although many of these drugs are used clinically over a long time period, there is a dearth of prolonged longitudinal studies of these drugs in older adults. Thus, there is limited evidence-based knowledge about the efficacy and safety of many psychotropic drugs, which have not been formally assessed and approved for use in older patients.

This issue of the *International Psychogeriatrics* presents three papers on the use of specific psychotropic medications – i.e. clozapine in primary psychotic and bipolar disorders, anticonvulsants in the prevention and/or treatment of delirium, and mirtazapine for agitated behavior in patients with dementia. Two other papers focus on the impact of standardizing care for agitation in dementia using an integrated care pathway on an inpatient geriatric psychiatry unit and a qualitative study of the perspectives of residents of long-term care facilities on shared decision making in medication management.

Renzenbrink and Wand (2022) reviewed seven primarily observational studies including a total of 128 patients aged 65–86 years, treated with

clozapine. Most (87%) of these patients had schizophrenia which was either treatment refractory or treatment intolerant. The sample was predominantly male (94%) and White (87%). In view of the demographic homogeneity of the sample, the authors are cautious in their clinical recommendations for diverse groups of older patients with psychotic or bipolar disorders. While agranulocytosis was less of an issue in this population, other toxicities were of a greater concern – e.g. anticholinergic side effects, delirium, seizures, and orthostatic hypotension. As the population ages, there will be more patients with schizophrenia in the geriatric age group, and a proportion of them will be treatment refractory to first- and second-line therapy, and thus could be candidates for clozapine trials. Therefore, more detailed studies of the patient experience with clozapine in the geriatric age range are clearly warranted.

There are currently no evidence-based effective pharmacological treatments for managing delirium, particularly hyperactive delirium with psychosis and severe agitation. Anticonvulsants are used clinically to manage delirium, based on observational studies in adults across the lifespan suggesting some benefit with the use of valproic acid. However, it is necessary to examine the data specifically in older patients who are at a considerably higher risk of delirium than younger adults. Gupta *et al.* (2022) conducted a systematic review of RCTs of anticonvulsants to prevent or treat delirium in geriatric population. They identified only four RCTs, all involving gabapentinoids (pregabalin or gabapentin) in patients undergoing orthopedic or spinal surgeries. The authors conclude that there is no high-quality evidence supporting the use of anticonvulsants in preventing or treating delirium in hospitalized older adults. Fortunately, several initiatives are currently underway to standardize delirium research (Bingham and Flint, 2022). Some multicomponent prevention studies have suggested useful strategies for delirium management. Hopefully, high quality, interdisciplinary, and collaborative research will lead to development and use of better treatment options for older patients with delirium.

Severe agitation is an extremely common problem in older patients with dementia. There is an unquestionable need for safe and proven pharmacological treatments for persons who do not respond

to psychosocial or behavioral treatments. Yet, clinicians are left with unreliable clinical trial information regarding optimal pharmacologic treatment of individual patients. While antipsychotics are partially effective, their safety is generally a major concern (Tampi and Jeste, 2022). At the same time, antipsychotic withdrawal may result in worsening of the agitated behavior. Many non-antipsychotic drugs have been tried, and some including trazodone, hydroxyzine, and bupropion have reported to have mixed success. But these drugs have not been studied with RCTs, so no conclusions regarding their efficacy can be drawn (Salzman, 2022). Additionally, it is important to note that not only therapeutic but also economic benefits of medication trials should be assessed in older adults. Henderson *et al.* (2022) performed a careful economic analysis of cost-effectiveness of an RCT of mirtazapine for agitated behaviors in patients with dementia and found that the data were unconvincing. So, what should a clinician do for controlling severe agitation in an older person with dementia? Evidence-based nonpharmacological treatments such as familiar music and singing, familiar games, and physical activity should almost always be tried. Salzman (2022) suggests the use of atypical antipsychotic medications using the lowest possible effective doses and choosing drugs with a less severe side-effect profile. Clinicians should discuss with family members or guardians the pros and cons of medications and obtain and document their permission for the use of an antipsychotic.

Practicing clinicians will welcome an algorithm for treating older people with neuropsychiatric or behavioral symptoms associated with dementia. Kumar *et al.* (2022) conducted a pilot study that built on an algorithm proposed by Davies, *et al.* (2018) and implemented it as part of an Integrated Care Pathway for patients with Alzheimer's or mixed dementia, admitted to an inpatient geriatric psychiatry unit for management of agitation or aggression. The protocol starts with a thorough medical and psychiatric work-up to determine usefulness of individualized nonpharmacological and pharmacological interventions the patient is receiving, and tapering off ineffective medications that were being used for managing behavioral symptoms. Next, for patients who are still symptomatic, symptom burden is checked along with length of stay, psychotropic polypharmacy, and documented falls. The clinicians may then begin with an antipsychotic. Subsequent sequence of prescribing options should be based on decision points informed by measurement-based care. In their relatively small pilot study, the improvement in agitation and reduction of polypharmacy were promising outcomes.

There is a clear need for larger and longer RCTs of such an algorithm or a similar methodical standardized approach.

How should the clinicians involve the patients and their caregivers in making decisions about treatment? Shared decision making (SDM) involves exchange of information between healthcare professionals, patient, and significant family members with attention to values, norms, and environmental constraints. Sawan *et al.* (2022) have addressed these issues from the perspectives of frail but cognitively intact residents of long-term care (LTC) facilities of three types: low care, high care, and both. The study participants were requested to express their views and experiences. This qualitative approach to learning about SDM from residents' experiences is certainly better than presenting SDM as a value to be promoted regardless of residents' wishes. The findings include a range of experiences based on residents' beliefs and wishes regarding their ability to control decision making. Recognizing that not all residents are interested in engaging in SDM, the investigators gave them an option for not being involved in decision making regarding their medication, leaving the decision to medical staff and family members. The model presented includes several sequential steps: assessing residents' capability, beliefs, values, and preference for SDM, negotiating and deciding with the resident which SDM approach to take, providing information about the benefits and harm of medications, aligning medication decisions with resident's goals and advance directives, and implementing the decisions. At the same time, the residents could opt for declining to engage in such decisions.

Sawan *et al.*'s SDM approach applies to older adults who are physically frail but cognitively, relatively unimpaired. Many individuals with serious mental illnesses (SMI) experience limitations in their ability to make major decisions due to cognitive impairment. These individuals are then placed under legal guardianship, and substitute decision makers are appointed to make decisions on their behalf. My colleagues and I (Jeste, *et al.*, 2018) have proposed a possible alternative in some cases – use of supported decision making. This involves recruitment of trusted supports to enhance an individual's capacity in the decision-making process and enables them to retain autonomy in important life decisions. Further empirical research is obviously needed to clarify candidates for such supported decision making, decisions in need of support, selection of supporters, integration with emerging technological platforms, and outcomes of supported decision making.

In sum, policy makers at various levels must recognize the need for supporting more empirical

research focusing on pharmacological as well as non-pharmacological management of older adults with schizophrenia and other SMI as well as patients with neurocognitive or dementing disorders with common behavioral disturbances including severe agitation and aggression. This is essential for the health and well-being of millions of older patients and their caregivers.

DILIP V. JESTE

University of California, San Diego, CA, USA
Email: DilipVJeste@gmail.com

References

- Bingham, K.S. and Flint, A.J.** (2022). Management of delirium in older adults: challenges and opportunities. *International Psychogeriatrics*, 34, 861–864.
- Davies, S.J.C., Burhan, A.M., Kim, D., Gerretsen, P., Graff-Guerrero, A., Woo, V.L., Kumar, S., Colman, S., Pollock, B.G. and Mulsant, B.H.** (2018). Sequential drug treatment algorithm for agitation and aggression in Alzheimer's and mixed dementia, *Journal of Psychopharmacology*, 34, 509–523.
- Gupta, A., Joshi, P., Bhattacharya, G., Lehman, M., Funaro, M., Tampi, D. and Tampi, R.** (2022). Is there evidence for using anticonvulsants in the prevention and/or treatment of delirium among older adults? *International Psychogeriatrics*, 34, 889–903.
- Henderson, C., Knapp, M., Stirling, S., Shepstone, L., High, J., Ballard, C. et al.** (2022). Cost-effectiveness of mirtazapine for agitated behaviours in dementia: findings from a randomised controlled trial. *International Psychogeriatrics*, 34, 905–917.
- Jeste, D.V., Eglit, G.M.L., Palmer, B.W., Martinis, J.G., Blanck, P. and Saks, E.R.** (2022). Supported decision making in serious mental illness. *Psychiatry*, 81, 28–40.
- Kumar, S., Shanbhag, A., Burhan, A., Colman, S., Gerretsen, P., Graff, A. et al.** (2022). Impact of standardizing care for agitation in dementia using an integrated care pathway on an inpatient geriatric psychiatry unit. *International Psychogeriatrics*, 34, 919–928.
- Renzenbrink, M. and Wand, A.** (2022). A systematic review of Clozapine's effectiveness for primary psychotic and bipolar disorders in older adults. *International Psychogeriatrics*, 34, 875–887.
- Salzman, C.** (2022). Treating agitated demented patients is difficult and not cheap! *International Psychogeriatrics*, 34, 865–866.
- Sawan, M.J., Jeon, Y.-H., Hilmer, S.N. and Chen, T.F.** (2022). Perspectives of residents on shared decision making in medication management: a qualitative study. *International Psychogeriatrics*, 34, 929–939.
- Tampi, R. and Jeste, D.V.** (2022). Dementia is more than memory loss: neuropsychiatric symptoms of dementia and their non-pharmacological and pharmacological management. *American Journal of Psychiatry*, 179, 528–543.