The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Pharmacological management of neuropsychiatric symptoms in patients with major neurocognitive disorders

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A 73-year-old woman with hypertension, mild cognitive impairment and recurrent falls was brought by police to the emergency department after she threatened her neighbour with a knife for "breaking into her apartment to steal her jewelry." Her family doctor initiated citalopram (10 mg/d) 2 months previously for anxiety and insomnia, but there was not much improvement as she was still "paranoid" according to her daughter. The physical examination and medical workup were remarkable for bilateral hand tremors, a Mini Mental State Examination (MMSE) score of 24/30, and chronic microvascular changes (a non-specific term that included white matter hyperintensities and other vascular pathology) on brain imaging. Risperidone was initiated and gradually increased to 0.5 mg over 2 weeks with fair response. The patient was later discharged to a long-term care facility, given her persistent fear of being robbed.

Major neurocognitive disorders (NCD), also known as dementias, are increasingly prevalent worldwide.[1] Comorbid neuropsychiatric symptoms (NPS), such as depression, anxiety, apathy, sleep disturbance, agitation, hallucinations and delusions, are extremely common (> 90%) in patients with all NCD subtypes and are usually more prominent in those in advanced stages.[2,3] An underlying medical condition, unmet needs and environmental factors often contribute to the emergence of NPS, which underlines the importance of ruling them out first.[4] Nonpharmacological interventions remain the mainstay of treatment for nonurgent NPS, and guidelines suggest limiting pharmacological interventions to severe, dangerous, or highly distressing symptoms.[5–7] When medication is required, clinicians are encouraged to follow the "3T" approach: 1) target specific symptoms, 2) titrate dosage upon clinical response and tolerability and 3) time-limit medication use to avoid unnecessary treatment.

Selective serotonin reuptake inhibitors (SSRIs; e.g., citalopram), serotonin–norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine), mirtazapine and bupropion are recommended as first-line agents for severe anxiety and depression in patients with NCD.[8] Emerging evidence also suggests that citalopram could be effective for NCD-associated agitation.[9] Although SSRIs are relatively safe in older adults, they can increase the risk of falls, fractures, hyponatremia and QTc prolongation (with citalopram/escitalopram), and clinicians should prescribe them cautiously.[10,11] The second-generation antipsychotics risperidone, aripiprazole, and olanzapine have the best evidence for NCD-associated agitation and psychosis,[12] but concerns about adverse effects (cardio- and cerebrovascular, metabolic, extrapyramidal) and modest efficacy limit their use.[13–17] The small (2.0%–3.7%) yet significant increase in the absolute risk of all-cause mortality associated with their use can be worrisome for patients and caregivers,[18,19] which underlines the importance of having an open discussion about the potential risks and benefits of antipsychotics before their initiation.[5] Their clinical relevance should be reevaluated every 3–4 months, and the lowest effective dose should be kept if symptoms recur.[5] Current evidence is controversial regarding the efficacy of quetiapine for NCD-associated agitation and psychosis;[20] however, guidelines still recommend its use for psychotic symptoms in patients with Parkinson disease along with clozapine.[21,22] Other second- and third-generation antipsychotics (e.g., ziprasidone, lurasidone, brexpiprazole) have limited evidence.[23,24] Pimavanserin, a selective 5-HT_{2A} inverse agonist recently approved for Parkinson psychosis, seems promising, but is available only in the United States.[25] Cholinesterase inhibitors should be favoured over antipsychotics in patients with NCD with Lewy bodies, as psychotic symptoms result from cholinergic neurodegeneration, not hyperdopaminergic activity.[26] Otherwise, evidence is lacking to recommend for or against the use of cholinesterase inhibitors and memantine for the prevention and treatment of NPS.[5,7] Robust findings are also lacking to support the use of mood stabilizers[27] as opposed to methylphenidate and trazodone, which can be modestly effective.[28,29] Benzodiazepines should be avoided given their adverse effect profile.[30] Overall, more psychopharmacology trials in aging patients with NCD are needed to support clinical treatment best practices.

In this clinical vignette, our patient most likely presented with NCD of mixed etiology, but a parkinsonian disorder had to be ruled out given the presence of tremors and recurrent falls. This diagnosis was excluded by neurology, and delirium also seemed unlikely. Citalopram was thus tapered down over 2 weeks and switched to risperidone, a commonly used antipsychotic in patients with NCD, after a discussion with the daughter, as the patient's anxiety seemed paranoia-related. Given a partial response to risperidone 0.5 mg, the dose should have been further increased while periodically reassessing efficacy and tolerability. This might have delayed the patient's placement into a long-term care facility.

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