

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.

Treatment-resistant depression in later life

Heba El Bayoumi, BSc (pharm); Zahinoor Ismail, MD

A 66-year-old woman was referred for management of treatment-resistant depression (TRD). She had previously undergone a 12-week trial of sertraline up to 150 mg and then another 12-week trial of venlafaxine up to 225 mg. She initially presented with low mood and anhedonia and no longer enjoyed spending time with her grandson. In addition, she experienced fatigue, weight loss, appetite reduction, insomnia, cognitive impairment and suicidal ideation without plan or intent. Her daughter stated that this was a change from her premorbid level of functioning. She had experienced 1 previous depressive episode at the age of 51 after the death of her husband in a motor vehicle accident. She was treated to remission with sertraline (50 mg) and stayed on that medication for 2 years. She had a family history of major depressive disorder in her mother and a remote history of alcohol misuse. Her Patient Health Questionnaire (PHQ)-9 score was 16 and her Generalized Anxiety Disorder (GAD)-7 score was 11 at presentation, and these were modestly improved from the scores documented by the referring source. Augmentation with lithium was discussed, but the patient was concerned about the risk of lithium toxicity owing to her regular use of ibuprofen for osteoarthritis. Thus, she was augmented with aripiprazole (2 mg/d) after initial assessment; 2 weeks later she was increased to 5 mg. Shortly thereafter, the patient presented with bronchitis and was started on clarithromycin. Within 2 days, she became extremely agitated, anxious and suicidal and presented to the emergency department. She was subsequently admitted to the psychiatry department. In hospital, aripipra-

zole was held until the completion of her antibiotic course and then restarted at 1 mg/d. The patient was discharged from hospital and titrated up to 2.5 mg/d 2 weeks later, with remission of mood symptoms 4 weeks thereafter; her PHQ-9 score was 4 and her GAD-7 score was 3.

Depression is common in elderly patients, with a prevalence of up to 42.0% in adults aged 65 years or older.¹ While there is no consensus definition of TRD, the one most commonly used is therapeutic failure following trials of 2 or more antidepressants at adequate doses and duration.² The occurrence of TRD is relatively common in clinical practice, with up to 60% of patients not achieving adequate response following antidepressant treatment.³ While there are TRD algorithms in the general adult population, there are fewer for geriatric depression, with the Canadian Expert Consensus Algorithm for Geriatric Depression being the most recent.⁴ Initial steps in managing TRD include confirming the diagnosis, ruling out medical causes (especially important in older adults), ensuring medication compliance⁵ and incorporating family history^{6,7} and substance abuse into treatment decisions.⁸ Treatment options for TRD include adding evidence-based psychotherapy,⁹ continuing with pharmacological strategies and switching to a neurostimulation treatment, such as electroconvulsive therapy or transcranial magnetic stimulation.¹⁰ Pharmacological strategies include switching to a different antidepressant monotherapy or adding another agent to the first antidepressant.² For patients who have experienced a partial response to a first-line or second-line antidepressant (typically a selective serotonin reuptake inhibitor or a serotonin–norepinephrine reuptake inhibitor), augmenting the antidepressant with lithium or an atypical antipsychotic may be the next step.⁴ Where the physician in this case augmented with aripiprazole, clinicians

need to remain mindful of the uncontrollable increased risk of death associated with atypical antipsychotics in dementia and factor this into the risk–benefit analysis and informed consent discussion.¹¹ Hospitalization in this case was required owing to a pharmacokinetic drug interaction between aripiprazole and clarithromycin. Clarithromycin is an inhibitor of cytochrome P450 3A4, and aripiprazole is a substrate for the same isoenzyme. Co-administration produced an increased blood level of aripiprazole, with an exacerbation of dose-dependent side effects (in this case akathisia and/or activation).¹² Thus, a high index of suspicion is recommended for identifying pharmacokinetic drug interactions, particularly in elderly patients. Finally, depression and cognition are intimately connected in older adults with late-onset depressive episodes, increasing the risk for dementia.¹³ In this case, cognition should be monitored over time with a low threshold for workup of neurodegenerative/vascular disease.

Affiliations: From the Department of Community Health Sciences, University of Calgary (El Bayoumi); and the Mathison Centre for Mental Health Research & Education, Hotchkiss Brain Institute, University of Calgary (Ismail), Calgary, Alta.

Competing interests: None declared for H. El Bayoumi. Z. Ismail has acted as a consultant and advisory board member for BMS/Otsuka, Lundbeck, Janssen and Pfizer.

DOI: 10.1503/150114

References

1. Ismail Z, Fischer CE, McCall WV. What characterizes late life depression? *Psychiatr Clin N Am* 2013;4:483-96.
2. Lam RW, Kennedy SH, Grigoriadis S, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults: III. Pharmacotherapy. *J Affect Disord* 2009;117:S26-43.
3. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry* 2003;53:649-59.

4. Mulsant BH, Blumberger DM, Ismail Z, et al. A systematic approach to pharmacotherapy for geriatric major depression. *Clin Geriatr Med* 2014;30:517-34.
5. Little A. Treatment-resistant depression. *Am Fam Physician* 2009;80:167-72.
6. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am* 1996;19:179-200.
7. Akiskal HS, King D, Rosenthal TL, et al. Chronic depressions: Part 1. Clinical and familial characteristics in 137 probands. *J Affect Disord* 1981;3:297-315.
8. MacEwan GW, Remick RA. *Treatment resistant depression: a clinical perspective*. 1988, Canadian Psychiatric Association: Ottawa, Ont. p. 788-792.
9. Parikh SV, Segal ZV, Grigoriadis S, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. II. Psychotherapy alone or in combination with antidepressant medication. *J Affect Disord* 2009;117:S15-25.
10. Kennedy SH, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults.: IV. Neurostimulation therapies. *J Affect Disord* 2009;117:S44-53.
11. Drye LT, Ismail Z, Porsteinsson AP, et al. Citalopram for agitation in Alzheimer's disease: design and methods. *Alzheimers Dement* 2012;8:121-30.
12. Ismail Z, Pollock BG. General Principles of Pharmacologic Therapy. *Psychiatry*. 3rd ed. 2008:2097-2111.
13. Ismail, Z, Malick A, Smith EE, et al. Depression versus dementia: Is this construct still relevant? *Neurodegener Dis Manag* 2014;4:119-126.