Response to Letter Regarding CANMAT Recommendations for the Pharmacological Treatment of Late-life Depression

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Dear Editor:

We thank Dr. Blumberger and colleagues for their letter. They rightly note several typographical errors in Table 6 in our article,¹ which have been corrected in submitted errata and appended below (including duplication of bupropion and duloxetine, omission of paroxetine and fluoxetine, and deletion of “SSRI” to clarify that we did not recommend combining an SSRI with an SSRI/SNRI). However, they also note some issues about the recommendations and the evidence levels. This raises an important issue about evaluating evidence for subpopulations such as late-life depression (LLD), which is a broad and heterogeneous group. For example, depression treatments for a medically healthy 68-year old person would not likely differ from those recommended for younger patients. Thus, treatment recommendations for LLD are guided not only by direct evidence (e.g., randomized controlled trials [RCTs] specifically in LLD samples) but also by indirect evidence from more general samples (e.g., younger adult samples). Even for “old-old” patients, medical comorbidities and concomitant medications, which are usual exclusion criteria in RCTs with LLD, would likely have more impact in treatment selection.² Hence, many treatment algorithms for LLD, including the excellent one by several of the letter authors,³ recommend escitalopram as a first-line antidepressant even without positive RCT evidence in LLD.

Unlike other recommendation tables in the CANMAT guidelines, Table 6 represents a treatment algorithm based on both direct and indirect evidence, as well as a review of several expert consensus algorithms, including the one by Mulsant and colleagues.³ We acknowledge that it may not be clear in Table 6 whether the evidence levels were derived from adult or LLD samples. Hence, we have revised the Level of Evidence in Table 6 to indicate only direct evidence in LLD (evidence table available on request). We have also clarified that each step reflects successive failure or intolerance to one or more agents in the previous step. We generally expect that clinicians would try multiple agents at one step before moving to another.

Finally, in regard to the inclusion of amitriptyline and imipramine, meta-analyses have shown that when carefully used in LLD, tricyclic antidepressants have efficacy and safety in RCTs.⁴ However, we specifically note

Revised Table 6. Algorithmic Pharmacological Treatment of Late-life Depression (see text).

	Treatment	Level of Evidence*
First Step (use one or more agents in sequence)	Duloxetine.	Level 1
	Mirtazapine, sertraline, venlafaxine, vortioxetine.	Level 2
	Citalopram, desvenlafaxine, escitalopram.	Level 3/4
Second Step (if multiple first-step treatments are not effective or not indicated)	Switch to Nortriptyline.	Level 1
	Fluoxetine, moclobemide, paroxetine, phenelzine, quetiapine, trazodone.	Level 2
	Bupropion.	Level 3
	Or combine with Aripiprazole.	Level 1
	Methylphenidate.	Level 2
	Lithium.	Level 3
Third Step (if multiple first- and second-step treatments are not effective or not indicated)	Switch to Amitriptyline, imipramine.	Level 2
	or Combine SSRI or SNRI with bupropion.	Level 3

*Based on evidence in studies of late-life depression samples. SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

in the text that “While good clinical judgment suggests choosing antidepressants to avoid mechanisms that may be harmful in the elderly (e.g., avoiding anticholinergic antidepressants to minimize confusion and delirium risk), there is yet little evidence over the long term to support ad hoc tailoring of antidepressant choices to target symptom clusters or to leverage specific side effects for therapeutic benefit.” Hence, nortriptyline is identified as a second-step treatment, while amitriptyline and imipramine are regarded as third-step treatments because of their side-effect profile.

We agree with the sentiment previously expressed by Mulsant and colleagues³ that the evaluation of

pharmacological treatments for LLD is complex and that RCTs usually do not reflect the clinical reality of patients with medical and psychiatric comorbidity and concomitant medications. We hope that these clarifications will show that the revised Table 6 algorithm is consistent with those of other guidelines for LLD.

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Declaration of Conflicting Interests

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GMM has been on advisory boards or a speaker for Janssen, Lilly, Lundbeck, and Pfizer.

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