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Commentary

Impact of age on optimal dose of antidepressants

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Major depressive disorder (MDD) is the leading cause of disability worldwide. It is the most common mood disorder characterized by a persistent feeling of sadness or a lack of interest in outside stimuli. Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors, have been widely used to treat depression. Optimizing the dose of antidepressants is important to reduce the burden of depression.

Furukawa et al. [1] investigated fixed doses of five SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline), venlafaxine, or mirtazapine in the acute treatment of adults with MDD. For SSRIs, the dose–efficacy curve showed a gradual increase up to doses between 20 mg and 40 mg fluoxetine equivalents. The relationship between the dose and dropouts for any reason showed optimal acceptability for the SSRIs in the lower licensed range, i.e., between 20 mg and 40 mg fluoxetine equivalents. Venlafaxine exhibited an increasing dose–efficacy relationship up to approximately 70–150 mg, whereas efficacy for mirtazapine increased up to 30 mg. For the most commonly used antidepressants, the lower range of the licensed dose shows optimal balance among efficacy, tolerability, and acceptability in the acute treatment of MDD [1].

Although age is another important demographical covariate in treatment with antidepressants, the meta-analysis by Furukawa et al. [1] did not adjust dosing for age. The use of antidepressants among the elderly is associated with an increased risk of potentially significant clinical adverse events, such as the cardiovascular, metabolic, and the central nervous system events, osteoporosis, falls, and fractures [2–5]. In addition, the use of antidepressants is also associated with suicidal risk in the elderly [6]. Collectively, it is likely that age is an important factor when assessing risk versus benefit of the antidepressant use.

Using the same dataset (21 antidepressants based on 522 randomized controlled trials), in this issue Holper investigated the role of age using a Bayesian network meta-analysis [7]. The combined covariance action of dose and age reduced between-trial heterogeneity by 29% (efficacy), 51% (acceptability), and 59% (tolerability). Agomelatine and escitalopram have been suggested to be the best balanced antidepressants in terms of efficacy and tolerability. The dose of bupropion, citalopram, desvenlafaxine, duloxetine, fluoxetine, milnacipran, and vortioxetine may be increased until the 40 mg/day fluoxetine equivalent. In contrast, amitryptiline, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine may not be given in doses greater than the 20 mg/day fluoxetine equivalent because of the risk of adverse events. All antidepressants may require dose reductions both in patients aged <35 years and >65 years. None of the antidepressants were observed to provide balanced benefits in patients aged >70 years because of adverse events exceeding efficacy. The present analysis using a Bayesian network meta-analysis provided a new next step in optimizing the doses for antidepressant use. It is time to reconsider the nonlinearity of dose-age dependencies when recommending antidepressant doses in adult patients with MDD [7].

Although the aforementioned antidepressants have been widely used in the treatment of depression worldwide, there is a significant time lag of weeks to months in achieving antidepressant efficacy. Importantly, approximately one-third of the patients with MDD are treatment-resistant to these antidepressants. In contrast, off-label use of the *N*-methyl-D-aspartate receptor (NMDAR) antagonist (*R,S*)-ketamine in treatment-resistant patients with depression is common in the United States (US) because ketamine has rapid-acting and sustained antidepressant effects in treatment-resistant patients with MDD or bipolar disorder. On March 5, 2019, the US Food Drug Administration (FDA) approved the use of (*S*)-ketamine (or esketamine) nasal spray for treatment-resistant depression in conjunction with an oral antidepressant [8]. This is the first NMDAR antagonist to receive FDA approval for treatment-resistant depression. However, this is available only through certified physicians' offices or clinics under a Risk Evaluation and Mitigation Strategy program because of the risk of serious adverse events. In addition, Turner pointed seven concerns about efficacy and FDA approval [8]. Importantly, (*R*)-ketamine (or arketamine) has greater and longer-lasting antidepressant effects in rodents than esketamine, and the side effects of arketamine are lower than those of esketamine [9,10]. A clinical trial on arketamine in humans is currently underway. In the near future, it will be of interest to optimize the dose and treatment duration of ketamine enantiomers in young and elderly patients with MDD.

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Declaration of competing interest

Dr. Hashimoto is the inventor of filed patent applications on "The use of *R*-ketamine in the treatment of psychiatric diseases" and "(*S*)-norketamine and salt thereof as pharmaceutical" by the Chiba University. Dr. Hashimoto has received research support and consultant from Dainippon Sumitomo, Otsuka, and Taisho.

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