Dose Response for SSRIs

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Previous research based on either individual studies or meta-analyses has been unable to demonstrate a clear dose-response relationship for selective serotonin reuptake inhibitors (SSRIs), leading to the conclusion that there is a flat dose-response curve for SSRIs. The majority of the individual studies comparing doses were not specifically designed to assess dose-response differences and included limited sample sizes. Previous meta-analyses often included dose-escalation studies or were based on a smaller number of clinical trials, making it difficult to definitively evaluate the dose-response relationship.

The article by Jakubovski et al. (1) in this issue of the *Journal* addresses this important question of whether higher doses of SSRIs can lead to better efficacy. The authors evaluated 40 randomized controlled trials that included a placebo and 49 active treatment arms. While the results are modest, they do show greater efficacy for higher doses of SSRIs in major depressive disorder. This slight benefit is coupled with a reduction in tolerability.

This study overcomes a number of shortcomings from previous work by incorporating three critical elements. First, it uses continuous outcomes to evaluate efficacy. Second, it includes studies not previously added in the meta-analyses. Third, it restricts the analysis to studies designed to evaluate multiple dose levels as opposed to flexible escalating dose trials. Using these methods, the authors demonstrate that there is a modest but clear dose-response effect for SSRIs. The study also provides an analysis of the dose-related side-effect burden. However, results point to the likelihood of important individual differences that are masked by group effects in traditional efficacy trials. Results may also argue for a need to assess specific biomarkers to carefully identify those who are likely to need higher doses to achieve the best benefit with the least side-effect burden. Whether biomarkers associated with specific side effects (e.g., CNS versus peripheral side effects) could help tailor treatment in clinical practice was not assessed.

One clear limitation of the study is the modest effect of the higher dose of SSRIs. In the absence of a clear metric that can be easily translated by clinicians to practice and the "small" incremental benefit of the higher dose in terms of efficacy, coupled with the added burden of side effects, generalizability of these results is limited. The magnitude of this effect is further compromised by the slightly higher effect of adverse events. Furthermore, the dose-response relationship within the narrower 100 mg and 250 mg equivalent doses suggests a more robust dose-response curve. Finally, this meta-analysis combines a number of SSRIs despite the fact that there are pharmacological differences among the SSRIs, which may not have identical dose-response relationships and may be masking higher effects for certain specific SSRIs at specific doses.

Future Directions

There are clear limitations to our current understanding of the dose-response relationship, with findings to date pointing to the need for studies specifically designed to address the dose-response question. Importantly, since it is clear that only a subgroup of patients benefit from the higher doses of SSRIs, biomarkers that guide the selection of the most appropriate dose early in the course of treatment will further facilitate the goal of precision medicine for depression. New approaches are needed to determine best practices to maximize the benefits of high dose and to determine exactly who is likely to benefit from these higher doses specially based on significant interindividual differences that exist in patients with major depressive disorder.

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Some of these shortcomings can be addressed by designing studies specifically to evaluate the dose-response relationship for individual SSRIs. These studies should focus on the critical dose range as opposed to too broad a range and be powered adequately. The goal of the study should thus be to evaluate a dose range that is most likely to show a difference without increasing the side-effect burden, thus better defining an optimal therapeutic range. Future studies should also be designed to allow for a better evaluation of the burden of side effect at each dose level. Evaluation of side effects should also include assessment of the type and nature of the side effects.

Despite the relative limitations of the findings from Jakubovski et al., as well as other studies, practicing physicians continue to resort to higher doses for patients who have not responded to the minimal therapeutic range for SSRIs. Practicing physicians may be determining the appropriate doses based on their assessments of the individual's clinical presentations at the current doses. These results therefore

highlight the need for measurement-based care (2) to guide appropriate use of higher doses in clinical practice. In order to maximize the benefits of measurement-based care, it is critical to measure early and often in order to adjust treatments rapidly to the individual's unique response to the current dosing level. The use of this updated measurement-based care approach may even lead us to identify the best starting dose and tailor treatment to patients best in need for higher doses through a biomarker match. Finally, in order to best match the "right dose" to the "right patient," careful assessment of associated symptoms, treatment adherence, and types of side effects are critical for the use of measurement-based care.

The ultimate goal of treatment ought to be to provide treatment that is effective for the individual (i.e., personalized care). This will require identification of specific biomarkers allowing determination of what treatments are likely to be effective with minimal side effects at what dosing levels. Pharmacodynamic and pharmacokinetic genetic markers of both efficacy and side effects are beginning to be identified. Available tests of genetic markers indicating differential metabolism of SSRIs based on genes encoding for cytochrome P450 enzymes help predict adverse effects and treatment outcomes in some but not all studies (3, 4). Other promising genetic markers for antidepressant selection include polymorphisms affecting ABCB1 gene coding for P-glycoprotein (P-gp), which influence transport across blood-brain barrier of specific SSRI medications (5). Schatzberg et al. (5) found that potentially increased expression of P-gp related to a novel single-nucleotide polymorphism (rs10245483) upstream of ABCB1 is associated with lower rates of remission and higher burden of side effects with SSRIs. Further studies are needed to test if patients with these polymorphisms get prescribed higher doses of antidepressant, which in turn lead to increased incidence of side effect and resultant dropouts from treatment.

With greater understanding of the altered gut microbiota in major depressive disorder patients (6) and its potential role in serotonin metabolism and serotonergic neurotransmission (7), there is growing appreciation of metabolic and inflammatory processes in the pathophysiology of depression. In a recent study, Mocking et al. (8) found aberrant fatty acid metabolism in depressed patients that correlated with nonresponse to paroxetine even after subsequent dose increases. Elevated markers of systemic inflammation like C-reactive protein have been associated with poorer response to SSRIs (9) and may help identify subgroups of patients who are less likely to respond to SSRI therapy and at greater risk of side effects due to sequential dose escalations or optimizations per measurement-based care protocol (2).

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REFERENCES

1. Jakubovski E, Varigonda AL, Freemantle N, et al: Systematic review and meta-analysis: dose-response relationship of selective serotonin reuptake inhibitors in major depressive disorder. Am J Psychiatry 2016; 173:174–183
2. Trivedi MH, Rush AJ, Wisniewski SR, et al: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163: 28–40
3. Hall-Flavin DK, Winner JG, Allen JD, et al: Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenet Genomics 2013; 23:535–548
4. Hodgson K, Tansey KE, Uher R, et al: Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology (Berl) 2015; 232:2609–2617
5. Schatzberg AF, DeBattista C, Lazzeroni LC, et al: ABCB1 genetic effects on antidepressant outcomes: a report from the iSPOT-D trial. Am J Psychiatry 2015; 172:751–759
6. Jiang H, Ling Z, Zhang Y, et al: Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun 2015; 48: 186–194
7. O'Mahony SM, Clarke G, Borre YE, et al: Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behav Brain Res 2015; 277:32–48
8. Mocking RJ, Verburg HF, Westerink AM, et al: Fatty acid metabolism and its longitudinal relationship with the hypothalamic-pituitary-adrenal axis in major depression: associations with prospective antidepressant response. Psychoneuroendocrinology 2015; 59:1–13
9. Uher R, Tansey KE, Dew T, et al: An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. Am J Psychiatry 2014; 171:1278–1286