# A Primate Model of the Effects of Childhood Antidepressant Treatment

All pharmacological treatments for human disease carry the risk of unintended, adverse effects that may only become evident upon long-term follow-up. The concern about such long-term effects is particularly heightened when medications that affect the CNS are administered to children or adolescents. As a result of the substantial and protracted developmental changes in the molecular and structural features of the human brain, children and adolescents may be particularly susceptible to the eventual development of adverse effects of medications. However, detecting such long-term effects can be particularly problematic in human studies because patients receive the medications for illnesses that themselves may have long-term adverse effects on brain development. Other confounding factors are the long follow-up period required for children to reach adulthood, the potential for the same medication administered at different ages to have different (or no) long-term effects, and the multiple other potentially confounding factors (e.g., use of other medications, illicit substance use, exposure to environmental stress or abuse, or other illnesses) that may occur in the interim.

One strategy for addressing these challenges is conducting experimental drug administration studies in nonhuman primates. Macaque monkeys provide a particularly informative resource, as the behavioral repertoire, structure of brain circuitry, neuronal cell types, molecular features, and protracted postnatal development of the macaque brain are more similar to those of the human brain than any other available animal model. In addition, many medications can be administered to macaque monkeys in a manner that is similar to their clinical use in humans in terms of route of administration, dosing frequency, length of exposure, and serum drug levels. Moreover, studies in monkeys, as in other animal models, provide the unique ability to control for individual and environmental factors that can confound the identification of medication effects on the brain and behavior. Additionally, early life adversity leading to long-term behavioral changes, similar to those characteristic of several mental health disorders including anxiety, affective disorders, and addictive disorders, can also be modeled well in macaques. These include early separation of infant monkeys from their mothers and rearing in an unpredictable environment.

The study by Shrestha et al. (1) published concurrently with this editorial employs this approach to examine the possible long-term impact of fluoxetine treatment during adolescence. In this study, 32 male rhesus monkeys were randomly assigned to one of four conditions in a balanced two-by-two design. Half of the monkeys were separated from their mothers whereas the others were reared with their mothers, and half of each group were treated for 1 year with fluoxetine at 3 mg/kg beginning at 2 years of age (roughly equivalent to late childhood in humans), while the other half received placebo; thus each combination of rearing and treatment condition had eight primates assigned. At a minimum of 1.5 years after the end of treatment, when monkeys were fully adult, all monkeys were assessed behaviorally and underwent positron emission tomography (PET) imaging to examine serotonin

transporter (SERT) and serotonin 1A (5-$HT_{1A}$) receptor binding. After correcting for multiple comparisons, no imaging or behavioral effects of rearing condition remained, nor were there any behavioral effects of fluoxetine treatment. However, monkeys treated with fluoxetine showed increased SERT binding compared with those treated with placebo, with no treatment differences for 5-$HT_{1A}$ receptor binding.

The authors are frank about the limitations of the study. The design was underpowered to be able to detect any but the largest of effect sizes, especially interactions between treatment and rearing. No PET or behavioral data were obtained prior to treatment, so baseline differences across groups cannot be excluded. The combined level of fluoxetine and norfluoxetine was lower than in therapeutic studies in humans, and in fact, the percent binding for SERT was below the accepted therapeutic level for treatment response, which is 80% (2). Finally, fluoxetine is primarily a serotonergic agent, but norfluoxetine has strong noradrenergic properties. Therefore, it is likely that treatment affected multiple neurotransmitter systems, making it difficult to speculate about the possible implications of an increase in SERT binding in isolation from more detailed information about the status of the noradrenergic system, which was not examined in this study.

In fact, clinical studies in humans are decidedly mixed with regard to the significance of SERT binding in depression, with some studies finding decreased binding, some no change, and some finding increased binding, although the most support is for increased SERT binding associated with depression (3). Meyer (2) reported that while SERT binding per se was not associated with depression, greater binding was correlated with a measure of cognitive distortion and pessimism, which in turn could predispose to future depressive episodes. In humans, we do not know if an increase in SERT binding predicts future episodes of depression, as has been demonstrated for greater monoamine oxidase A binding (2).

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Nevertheless, the idea that a treatment for a circumscribed period of time results in long-term changes in function of the serotonin system, even without clear behavioral changes, is unsettling. This study should be replicated with behavioral and PET data in primates obtained prior to and after treatment, with a larger number of monkeys, and with measures of the noradrenergic system. In humans, follow-up studies of adolescents treated with antidepressants compared with psychotherapy should be conducted to look for any specific, enduring changes in brain function and receptor binding and whether those changes are related to changes in behavior and long-term outcome. We should also learn, in controlled studies, to what extent medication compared with psychotherapy protects against recurrent depression. In adults, some evidence indicates that depressed patients treated with cognitive-behavioral therapy (CBT) are less likely to relapse than patients treated with antidepressants (4), but the existing evidence in adolescents, at least with relatively brief interventions, does not support a similar protective effect of CBT compared with antidepressants (5, 6). The British National Institute for Health and Care Excellence guidelines, with regard to concern about suicidal events and antidepressants in adolescents, firmly recommend a trial with psychotherapy

before the use of medication. However, given the much slower response to CBT for adolescent depression than to antidepressants that was found in the Treatment of Adolescent Depression Study, American guidelines recommend antidepressants as a first-line treatment for adolescent depression (7, 8). It is also important not to paint recommendations about antidepressant use in adolescents with too broad a brush, since the risk-benefit ratio is even more favorable for the treatment of anxiety than for the treatment of depression, as a result of greater efficacy (9).

What should clinicians say to their adolescent patients and to their patients' parents in light of this study? We think the honest answer is that although these findings and some other animal studies have shown long-acting effects on the brain as a result of antidepressants, we do not know the clinical meaning of these findings. Indeed, the field waits for a convergence of findings from well-designed and controlled studies in animals and from longitudinal studies in humans in order to truly understand the impact of antidepressant treatments in adolescents, and thus inform their use.

In the meantime, although current clinical data suggest that the risk-benefit ratio for antidepressants is acceptable, and that antidepressants may work more quickly than psychotherapy, effective psychotherapeutic treatments are available for adolescent depression, namely CBT and interpersonal therapy (8, 9). Already, concern about the possible negative effects of antidepressants in adolescents has resulted in a decline in their use for the treatment of depression, without an offsetting increase in referral for psychotherapy (10). While we need more research to understand the long-term effects of antidepressants, we must also recognize that untreated depression carries substantial risk, and that beginning with one of the indicated treatments—either psychotherapy or antidepressant medication—is better than succumbing to unjustified therapeutic nihilism.

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