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Strategy found for safely prescribing antidepressants to children and adolescents

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A multidisciplinary team of Johns Hopkins researchers has developed two new strategies to treat depression in young people using the selective serotonin reuptake inhibitor (SSRI) class of medications. These strategies, published May 5 in the journal *Translational Psychiatry*, incorporate a new understanding of how to mitigate the risk of suicide while on SSRI treatment.

"These medications have to be dosed in a careful way," says senior investigator Adam Kaplin, M.D., Ph.D., an assistant professor of psychiatry and neurology at the Johns Hopkins University School of Medicine. Just as with medications for high blood pressure, diabetes and anti-coagulation therapy, Kaplin says careful dosing of SSRIs is "exactly what psychiatrists have been doing for a long time in adults" to mitigate the negative effects of the medications.

For children and adolescents, however, treatment regimens have tended to be more intense in order to treat depression quickly. Kaplin says that's because "it is excruciatingly painful to wait for kids to respond when they are often already at the end of their ropes before meeting with a medical professional." Young people rarely seek treatment for depression on their own, and it may take a while before parents become aware of their child's depression, he says. Once aware, parents may try other means of treatment before seeking medical attention.

SSRI treatment, however, has proved to increase the risk of suicidal thoughts and behavior ("suicidality") in children and adolescents. In

2004, the U.S. Food and Drug Administration issued a black box warning for SSRIs—the most serious warning a prescription medicine can receive—because in a summary examination of all drug company-sponsored studies, the drugs increased suicidal thoughts and action by 2 to 4 percent, compared with a placebo during the initial weeks after starting the medications.

With over 10 percent of all children and adolescents in the U.S. suffering from major depressive disorder, however, the black box warning had an unintended effect. "The suicide rate has gone up," says Kaplin, apparently because clinicians hesitate to prescribe SSRIs even though there's greater risk of suicide from leaving major depressive disorder untreated.

In their study, Kaplin and his team asked whether these early negative effects shortly after starting SSRIs could be mitigated either by the same kind of careful dosing done in adults with anxiety disorders or by combining SSRI treatment with another medication previously shown to hasten SSRIs' therapeutic effects in adults.

The team began by analyzing the same data the FDA used in 2004 to issue its black box warning. They found that SSRIs made young patients more impulsive, particularly during the first month of treatment, but don't create suicidal thoughts where there were none before, Kaplin says.

The researchers then performed a computer simulation to find optimal dosing for the faster-acting SSRIs—paroxetine, citalopram, sertraline, venlafaxine and fluvoxamine—in kids so that these other SSRIs would act in a similar way to fluoxetine, says Kaplin. Currently, fluoxetine, the slowest-acting SSRI, is the only SSRI that is FDA-approved for children 8 to 12. It can take several weeks or months for fluoxetine to reach therapeutic levels in the blood and begin to have an effect.

When they tested their model, the researchers found that it generated the same kinds of dosing regimens psychiatrists use for dosing adults experiencing SSRIs' negative effects. Those regimens often start with half the normal initial dose and slowly increase it to achieve therapeutic levels.

The newly proposed dosing guidelines likely would improve safety, but they would also slow how long it takes before patients receive relief, even from the faster-acting SSRIs. "One of the hardest parts of our jobs is to get people through that delayed period of time when we all wish our medicines worked faster," says Kaplin. So the researchers also looked for a way to completely block SSRIs' negative effects.

Working with mice, the researchers found that adding a molecule called WAY-100635—used in adult human research studies—produced "a synergistic effect when given with an SSRI," says Kristen Rahn, Ph.D., an instructor of psychiatry and behavioral sciences and of neurology. "And it completely alleviated the anxiety the animals had."

Given by itself, though, WAY-100635 had no significant effect on anxiety levels. The compound helps the brain get serotonin, a neurotransmitter. Long-term exposure to SSRIs eventually increases serotonin levels—the goal of treatment—but the initial exposure reduces serotonin. Researchers think it's this stop-start mechanism that explains why SSRIs cause adults' anxiety and increase children's impulsivity. Coupling SSRI treatment with WAY-100635 eliminates the stop-start and creates a smoother transition.

"Now that we have uncovered this effect and worked out this mechanism," says Kaplin, "we are in the process of communicating with pharmaceutical companies to see which of them might have tested a drug similar to WAY-100635 that didn't do anything by itself and therefore was abandoned."

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