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Hunt on to explain antidepressant risk

Early studies investigating potential triggers of suicidal risk are beginning to uncover important clues.

Simon Frantz

An FDA advisory committee has ended months of speculation by recommending that antidepressant drug labels carry a warning of the risk of causing suicidal thought and behaviour among paediatric patients.

The decision is based on an independent assessment of all published and unpublished trials on selective serotonin-reuptake inhibitors (SSRIs), which shows that children and teenagers who take SSRIs are twice as likely as those given placebos to show suicidal behaviour.

But the increased suicide risk is still low — around 2–3%. With the need to treat depression, which itself can lead to suicidal behaviour, the perplexing situation is that not enough is known about SSRIs and paediatric depression to identify those who will respond adversely to treatment.

One unsolved issue is whether the action of antidepressants differs between children and adults. Depression in children could be a different phenomenon, because the brain is rapidly developing into the late teens.

“There is surprisingly little research, clinical or experimental, done on this issue,” says Eero Castren, Sigrid Jusélius Professor of Neuroscience at the University of Helsinki, Finland. “The current assumption seems to be that there are no fundamental differences and the only thing that you need to worry about is the appropriate dose.”

Even if such differences were identified, the story wouldn’t end there. “The question which next arises is

who is a child and who is adult, and where is the line,” says Castren.

Triggers for suicidal behaviour in depressed patients include a combination of factors, such as childhood experiences, and familial or genetic factors.

Most neurochemical evidence suggests that at least part of the predisposition to suicide in depressed patients and suicide victims involves a deficiency in the neurotransmitter serotonin in a brain region called the ventral prefrontal cortex, which governs functions such as how we act on impulse. But because SSRIs work by maintaining serotonin in the synapses between neurons for longer than normal so that it can continue to exert its effect, they would be expected to decrease, not increase, the suicide risk.

“[SSRIs] enhance serotonin function to a progressively greater degree over several weeks according to animal studies, and this lag in efficacy may leave patients vulnerable to acting on their suicidal feelings,” says John Mann, Professor of Psychiatry and Radiology at the New York State Psychiatric Institute. “It does not mean the drugs are responsible.”

Other neurobiological differences could reveal further clues. For example, a group led by Ghanshyam Pandey, Professor of Pharmacology in Psychiatry at the University of Illinois at Chicago, found that levels of guanine-nucleotide-binding proteins (G proteins) differ between adults and teenage suicides (Dwivedi, Y. *et al. Neuropsychopharmacology* 27, 499–517 (2002)). Around 80% of receptors for neurotransmitters, including serotonin and neuromodulators, elicit their



Missing link: how can SSRIs increase the risk of suicidal behaviour?

responses through G proteins. “Whether these differences in the neurobiological abnormalities between adult and adolescent suicide explain the SSRI-induced suicidality is not clear,” says Pandey.

The search for the genetic triggers of suicidal behaviour has met with mixed success, but earlier this year researchers identified six chromosomal regions that seem to harbour genes influencing suicidal behaviour in families with depression (Zubenko, G. S. *et al. Am. J. Med. Genet.* 129B, 47–54 (2004)).

These studies could help to identify high-risk individuals, for whom early intervention could save lives, and help optimize existing treatment administration, says George Zubenko, Professor of Psychiatry at the University of Pittsburgh School of Medicine, and lead researcher of this study. But there’s one problem: “The current rate-limiting step is raising the funds to support these initiatives,” he says.

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