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LETTER TO THE EDITORS

Fluoxetine and Aggression

I read with interest the review article by Ray W. Fuller* on fluoxetine and aggressive behavior (Fuller 1996). In my opinion, however, the review of the literature is incomplete and selective. The author fails to cite experimental and clinical findings that are not consistent with the antiaggressive effects of fluoxetine. Readers should be made aware that there is evidence for an association between fluoxetine treatment and increased aggression.

Mitchell and colleagues (Mitchell et al. 1991; Mitchell and Redfern 1992) employed ethological techniques to study the effects of acute and chronic fluoxetine treatments on the aggressive behavior of short-term isolated resident rats. Whereas acute treatment with fluoxetine dose-relatedly reduced aggressive behavior exhibited during social interaction, chronic treatment (14 days) markedly increased the aggressive behavior of resident rats. Troisi et al. (1995) analyzed the effects of fluoxetine on the aggressive behavior of 19 adult inpatients with mental retardation and epilepsy. The study employed an alternating control–treatment–control design in which the treatment phase lasted between 4 and 14 weeks. Aggressive behavior was measured by using the Modified Overt Aggression Scale (MOAS). There were wide individual differences in drug response. In nine patients, fluoxetine treatment was associated with a statistically significant increase in aggression ratings, and drug withdrawal led to a decrease to below-pretreatment levels.

The fact that the large majority of animal and clinical studies have demonstrated the antiaggressive effects of fluoxetine is not incompatible with the hypothesis that in a subset of vulnerable subjects fluoxetine can induce opposite effects. A number of factors may modulate the relation between fluoxetine, serotonin, and aggressive behavior, resulting in considerable interindividual differences and differences across studies. Mann and Kapur (1991) have postulated that in certain patients the initial decrease in serotonergic transmission induced by fluoxetine may continue, leading to a paradoxical worsening of aggression. On the cellular level, Yeh et al. (1996) recently reported that social experience, in the form of a dominance struggle, determined the subsequent effects of serotonin on neurons in crayfish. Serotonergic stimulation caused increased firing in neurons from the dominant crayfish, whereas the same stimulation caused decreased firing in neurons from the subordinate animal. In vervet monkeys, social status influences an animal's behavioral sensitivity to fluoxetine and other drugs that augment serotonergic function. Dominant males are substantially more responsive to fluoxetine treatment than are subordinate males (Raleigh et al. 1985).

These findings highlight a critical caveat for clinical research on the relation between fluoxetine and aggressive behavior: the differential response across individuals to ostensibly the same drug treatment cannot be understood without properly characterizing the context (biochemical, environmental, and historical) of the individuals studied.

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REFERENCES

Fuller RW (1996): The influence of fluoxetine on aggressive behavior. Neuropsychopharmacology 14:77–81

Mann JJ, Kapur S (1991): The emergence of suicidal ideation and behavior during antidepressant pharmacotherapy. Arch Gen Psychiatry 48:1027–1033

Mitchell PJ, Redfern P (1992): Acute and chronic antidepressant drug treatments induce opposite effects in the social behaviour of rats. J Psychopharmacol 6:241–257

Mitchell PJ, Fletcher A, Redfern P (1991): Is antidepressant efficacy revealed by drug-induced changes in rat behav-

*Dr. Fuller passed away on August 11, 1996.

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/97/$17.00
PII S0893-133X(96)00219-0

iour exhibited during social interaction? Neurosci Biobehav Rev 15:539–544

Raleigh MJ, Brammer GL, McGuire MT, Yuwiler A (1985): Dominant social status facilitates the behavioral effects of serotonergic agonists. Brain Res 348:274–282

Troisi A, Vicario E, Nuccetelli F, Ciani N, Pasini A (1995): Effects of fluoxetine on aggressive behavior of adult inpatients with mental retardation and epilepsy. Pharmacopsychiatry 28:73–76

Yeh SR, Fricke RA, Edwards DH (1996): The effect of social experience on serotonergic modulation of the escape circuit of crayfish. Science 271:366–369