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Drug discovery in autism: the need for a developmental context

In a recent issue of *Drug Discovery Today*, Gerlai and Gerlai [1] provided an excellent review on the advances made in autism research. These authors expressed the hope and expectation that this research will lead to a breakthrough in pharmacotherapy for autism in the near future.

Thus far, the effects of drug intervention on the core social and communicative deficits of autism have been modest, if any at all [2]. This cannot be attributed to a lack of trying because a wide range of conventional and new psychotropic medications have been tested in people with autism. These numerous trials suggest that none of the main neurotransmitter systems are directly driving the expression of the core symptoms of autism. Even medical interventions in the endogenous opioid system, which were prompted by animal models on the involvement of this system in social behaviour, had disappointing results [3,4].

Why have drug treatments been so disappointing? Our current knowledge of the etiology of autism suggests that it is foremost a disorder of brain development that presents early in life, typically during fetal phases of development or shortly after birth. It could be imagined that neurochemical systems that are involved in the early programing of the brain are only sensitive to pharmacological manipulations during those early phases of brain development. Therefore, commencing drug therapies at preschool age and thereafter could be outside the crucial time window [5]. This calls for research aimed at lowering the diagnostic threshold of autism combined with research into the early development of the brain and the effects of medication at different ages.

Gerlai and Gerlai [1] suggest that the identification of the common genes underlying autism and the elucidation of their function might be possible, and that these findings should significantly advance the development of pharmacological intervention for a range of autistic patients. We share the view that the genes for autism will probably be identified within the next decade. In addition, there is reason to believe that the genes underlying autism will be shown to be susceptibility genes [6,7]. Susceptibility genes increase the risk of developing a disease or syndrome. However, an individual susceptibility gene is neither necessary nor sufficient for the development of the disorder. Given the possibility of multiple, varying etiologies [8] and the number of possible combinations of susceptibility genes, even with the identification of autism-susceptibility genes, the development of an effective medical intervention might still be a distant target.

There is a clear role for pharmacology in the treatment of autism. Improvements in non-core symptoms, including hyperactivity, aggression, self-injurious behavior, rigidity, anxiety and irritability, demonstrate that medical interventions in autism have considerable secondary gains. However, the drug response in individuals with autism is variable. It has proven difficult to predict which drugs would be most effective in which child. This inconsistency in drug response between individuals might reflect some sort of genetic variability. Perhaps the differential responses to drug interventions, with respect to effectiveness and side effects, should be used to form subgroups of individuals for genetic analyses.

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Sophie H.N. Willemsen-Swinkels*
Jan K. Buitelaar
Department of Psychiatry and Academic Center for Child and Adolescent Psychiatry
University Medical Center St. Radboud (333)
P.O. Box 9101
6500 HB Nijmegen
The Netherlands
**e-mail: s.willemsen-swinkels@psy.umcn.nl*

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