

MARKETPLACE

Radical Study on Schizophrenia May Be Expanded

Researchers Seek to Discover Whether Antipsychotic Drugs Can Prevent the Disease

By RACHEL ZIMMERMAN

Staff Reporter of THE WALL STREET JOURNAL

Researchers and drug makers are laying the groundwork to expand a controversial experiment targeting troubled adolescents believed to be at risk of developing schizophrenia.

The study would seek out undiagnosed young people in the "prodromal," or pre-onset stages of schizophrenia, and try to determine whether antipsychotic drugs can prevent the disease, which affects 60 million people world-wide.

A group of doctors, academics and drug-industry executives are meeting this week at New York University's Medical Center to hash out the details of what could be a \$25 million multinational study that would involve 1,500 potentially schizophrenic teenagers.

The proposed study is expected to be funded primarily by makers of schizophrenia drugs. In fact, the New York meeting is being funded by Pfizer Inc., Eli Lilly & Co., Johnson & Johnson's Janssen Pharmaceutica Inc., American Home Products Corp. and France's Sanofi-Synthelabo SA. The companies covered the \$35,000 cost of the three-day event, which ends today, organizers said.

The idea is to use schizophrenia drugs "as a preventative as well as a palliative," says Tho-

mas McGlashan, a psychiatry professor at Yale University medical school who is spearheading the international effort. But he concedes that the undertaking raises some sensitive issues.

The notion of testing adolescents with powerful antipsychotic drugs—which are already approved for people with the disease—even before they exhibit definitive symptoms of schizophrenia is highly unorthodox. Symptoms of the disease can include hallucinations, delusions, hearing imaginary voices and deep withdrawal from

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society. "A big study is premature," says Rex Cowdry, medical director for the National Alliance for the Mentally Ill, citing concern that kids would get "swept up in the treatment group."

In addition, no health system in the world currently identifies adolescents in the pre-onset phase as ill. So, with this potentially vast expansion of the already lucrative \$5 billion-a-year market for antipsychotic drugs, the proposed study raises the question of whether the drug companies are mainly interested in "creating" a new illness that requires drug treatment.

"In general, if you create the drug, they will come," says David Magnus, a professor of bioethics at the University of Pennsylvania. "So it's important that the parameters of the disease get worked out before the pharmacological considerations."

Bert Spilker, senior vice president of scientific and regulatory affairs with the trade group Pharmaceutical Research Manufacturers of America, notes that it was academics who approached the drug companies to help test their theory about schizophrenia. "Given that it's a hypothesis that isn't off the wall but tenable and reasonable to check, it is not only ethical [to test the theory] but it will offer benefits to society that are astronomically large," Mr. Spilker says.

The big question, Mr. Magnus says, is how good investigators are at predicting which adolescents will ultimately develop schizophrenia. "When they say 'at risk,' what does that mean—6% or 60%?" he says. "You don't want to expose kids to risk for no reason."

The Yale researchers say they are developing more-precise diagnostic tests to identify subjects at reasonably high risk of becoming psychotic in the near term. Moreover, they add, if these potentially prepsychotic teenagers can be identified and treated early, the illness will be more widely recognized and hopefully, more manageable.

Tandy Miller, assistant clinical professor at Yale medical school and project director at the school's Prime Research Clinic—where the initial study of 31 young adults is being conducted—says that informed consent would be required in the expanded study and that it would

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include a discussion of therapy alternatives. She adds that new diagnostic instruments are being developed that appear to be reliable enough to assess patients whose symptoms are in the "absent to mild" range.

A growing body of research indicates that schizophrenia develops more gradually than previously thought, and that signs of neurobiological deterioration are already present at the time of initial onset. In addition, it's increasingly accepted that early intervention after the first schizophrenic episode may bring a better outcome than intervening later.

There are also several promising new antipsychotic medications, called "atypical neuroleptics," which can have less severe side effects than conventional antipsychotic drugs. Researchers hope the new drugs will intervene in the brain-damaging process that leads to schizophrenia, even though they don't know for sure what that process is.

The small pilot study at Yale, which has been under way for 2½ years, is testing both the ability of clinicians to determine whether patients are predisposed to schizophrenia and the effectiveness of antipsychotic drugs in delaying or preventing the onset of the illness in susceptible patients. The double-blind study, sponsored by Eli Lilly, involves giving participants either a placebo or Eli Lilly's Zyprexa (generically known as olanzapine), one of the newer antipsychotic drugs. Eli Lilly sent a representative to this week's meeting in New York, but wouldn't comment on whether it would participate in the proposed expanded study.

The expanded experiment would have the same dual goals, but would likely test a greater number of antipsychotic drugs on a much larger, international population and in-

clude funding from foundations and government agencies as well as drug companies.

Clinicians agree that despite the radical nature of the studies, the timing is right. "We wouldn't be doing this study five years ago with the old antipsychotics," says Yale's Dr. McGlashan, principal investigator of the Prime Research Clinic. "The risks of these new drugs are much, much lower."

Indeed, Yale's Dr. Miller, who has a Ph.D. in clinical psychology, compares the current research environment around schizophrenia to that of breast cancer decades ago. Back then, she says, before women were educated about breast cancer and received prescreening, the disease typically had a higher mortality rate. Now, with widespread knowledge and testing that can determine if women are predisposed to breast cancer, it can be treated much earlier and therefore managed.

Still, the details of the proposed expansion need to be worked out. The tests would require about 1,500 patients ranging in age from about 15 to 25, the period in which the disease generally strikes, says Jorge A. Costa e Silva, a New York University psychiatry professor and a former director of the World Health Organization's mental-health division who is chairman of the steering committee for the multinational study. He envisions a trial that includes six to eight countries of varying wealth and hopes to see the experiments under way by next spring.

Yves Lecroubier, a doctor with Inserm, France's national health organization, says while the study should involve many countries, basic questions about the symptoms of schizophrenia can be interpreted differently in different countries. In Arabic nations, for instance, when a young adult is asked whether he has experienced hallucinations, he might say "yes" because visions of prophets are encouraged.