

Schizophrenia: New Hope From an Old Drug

Clozapine, a medication first synthesized in 1960 but not available for prescription use in the United States, appears to be an effective treatment for a substantial number of schizophrenics who do not respond to other drugs, according to a study presented last week in Chicago at the annual meeting of the American Psychiatric Association.

Clozapine rarely causes the movement disorders associated with other antipsychotic drugs, also known as neuroleptics, say the researchers. Weekly blood tests are necessary, however, to check for a potentially fatal weakening of the immune system in response to the drug.

"This is the first time that a rigorously controlled study of schizophrenics has demonstrated superior efficacy for one neuroleptic over the others," says psychiatrist Herbert Y. Meltzer of Case Western Reserve University in Cleveland. The study, conducted at 16 hospitals nationwide, was directed by Meltzer and psychiatrist John M. Kane of Long Island Jewish Medical Center in Glen Oaks, N.Y.

The ongoing project is being funded by Sandoz Pharmaceuticals Corp. in East Hanover, N.J., which will submit the data to the Food and Drug Administration later this year in an effort to gain approval of clozapine as a prescription drug. Sandoz will have a five-year patent on the drug if it gets the go-ahead from the FDA, says Meltzer.

The more than 300 schizophrenic patients in the study, who ranged from 18 to 60 years old, were among the most severe cases. They had shown no improvement for at least 2 1/2 years and no response to at least three neuroleptics. All subjects were first given haloperidol, a standard antipsychotic drug, for six weeks. Only about 2 percent improved. Most of the remaining patients were randomly assigned to treatment with clozapine or chlorpromazine, another standard neuroleptic, combined with a drug used to combat neurological side effects.

After six weeks of treatment, 30 percent of 125 patients on clozapine markedly improved, compared with 4 percent of 134 patients receiving chlorpromazine. Although standard neuroleptics usually take several weeks to become effective, some clozapine patients clearly improved in the first week of treatment. Ratings of patients' symptoms on three clinical scales were made by ward psychiatrists, psychologists and nurses.

Among patients who improved, says Meltzer, clozapine not only eased schizophrenic symptoms that respond to other neuroleptics, such as hallucinations, delusions and disordered thinking, but also lessened the social withdrawal and lack

of interest and motivation that do not usually improve with typical antipsychotic drugs.

Schizophrenia affects about 1 percent of the world's population, and approximately 300,000 people in the United States with some form of this disorder are not helped by available neuroleptics, says Meltzer. The fact that many treatment-resistant patients respond to clozapine suggests, contrary to the opinion of some psychiatrists, that such previous nonresponders do not have extensive brain damage, adds Meltzer. Clozapine does not "cure" schizophrenia, he notes, but it improves symptoms enough so that patients can function in the community and benefit from rehabilitation services.

But clozapine is not risk-free. Previous experience, both in Europe and with several hundred U.S. patients treated experimentally at several hospitals, suggests that about 1 percent of those given the drug will develop agranulocytosis, a reduction in certain types of white blood cells critical in fighting infection. Several deaths from this reaction have been reported in Europe, but none in the

United States.

Weekly monitoring of white cell counts, with discontinuation of clozapine if cell counts fall, usually reverses agranulocytosis, says Kane. No cases of agranulocytosis occurred in the new study.

"Clozapine should be available [through prescription], but it's not an unmixed blessing," says psychiatrist Jonathan O. Cole of McLean Hospital in Belmont, Mass., where about 40 schizophrenics have been treated experimentally with clozapine over the past 10 years. "There will be deaths from agranulocytosis when the drug is used in the community, because some schizophrenics will be hard to keep track of and monitor regularly," Meltzer adds that some psychiatric facilities may not have the resources to monitor white blood cell counts.

Clozapine's advantage, he says, is that unlike typical neuroleptics it rarely causes tremors, muscle rigidity, restlessness or the severe movement disorder known as tardive dyskinesia (SN: 7/20/85, p.45). Says Meltzer, "We need to understand why this drug is different from other neuroleptics." — B. Bower

Advances reported in predicting violence

When the courts recently decided that presidential assailant John Hinckley Jr. should not be allowed to leave a psychiatric hospital to visit his family, the key piece of evidence was that Hinckley had written letters to convicted serial murderer Theodore Bundy. The question remains: If Hinckley had not written those letters, would he have been considered less dangerous to the community? Perhaps, but the fact that psychiatrists can only guess at such things points up how little is known, even among "experts"

"Psychiatrists should get out of the legal prediction system," says psychiatrist Antonio Convit of New York University (NYU) Medical Center in New York City. Perhaps because of the great fear of turning loose someone who will go on to assault or kill, behavioral scientists historically have erred on the side of "false positives" — predicting someone will become violent who, in actuality, does not. This has been a primary failing of hospital- and community-based predictive studies in recent years, according to Convit and others.

But Convit and his NYU colleagues now report violence-prediction results that he says are among the "strongest" to date. Convit is quick to point out that the studies were done in a closed psychiatric ward, where there is little contact with

outside society. Nevertheless, if this type of predictive model could be adapted to include the "risks" of the outside world, such as drugs, social stresses and homelessness, it might conceivably be applied to neighborhoods or communities, Convit suggested last week in Chicago at the annual meeting of the American Psychiatric Association.

In a three-pronged study, Convit and his colleagues first evaluated 69 patients on the "violent ward" at NYU's Manhattan Psychiatric Center and compared them with 40 nonviolent controls elsewhere in the hospital. This yielded four key "risk factors": conviction for violent crime; history of violent suicide attempt; a measurable (although not necessarily dramatic) neurologic abnormality; a "deviant" family environment, including a broken home, child abuse or a parent's substance abuse.

Then, in a preliminary predictive test, the researchers devised a scale of such factors and applied it retrospectively to 51 violent and nonviolent patients. They identified 35 of the patients correctly, Convit reports, with only eight false positives.

Finally, the researchers applied the test *prospectively* to 79 male schizophrenic patients admitted to the hospital. In a three-month follow-up of these patients