

# U.S. "WAY BEHIND" ON CLOZAPINE'S BENEFITS

*Knowledge Network says more clozapine use will reduce schizophrenia-related suicidality*

BY WILLIAM M. GLAZER, MD

In 2002, Bauer reported a 13 to 17 year delay in the clinical adaptation of behavioral health research findings, and in 2006 the Institute of Medicine estimated that this delay results in a 70 to 80 percent chance of patients *not receiving* the best practice available.<sup>1</sup>

One prominent example of behavioral health care providers' difficulty in translating research findings into practice involves the generic antipsychotic medication clozapine.

## Clozapine's effectiveness in schizophrenia treatment

Clozapine, the first "atypical" antipsychotic agent to appear in the United States, represented the first major advance in the treatment of schizophrenia since the advent of antipsychotics in the 1950s. The FDA has approved clozapine for use in treatment-resistant schizophrenia, which, depending on how one defines it, can apply to a large number of patients.

But clozapine's use in practice has been greatly limited because of its risk of agranulocytosis (lowered white blood cell count) and the necessity for frequent blood tests to appropriately monitor this risk. Experts feel that this risk has been overestimated and the importance of making the effort to monitor the white blood count underappreciated.

According to Herbert Y. Meltzer, MD, Professor of Psychiatry at the Vander-

bilt University School of Medicine, "leading economists have cited underuse of clozapine for treatment resistance and suicide as one of the two greatest failures of mental health providers to practice evidence based medicine."<sup>2</sup> Meltzer led the pivotal, blinded, randomized, olanzapine-controlled study that established clozapine's remarkable suicide prevention potential.<sup>3</sup> This study led the FDA to assign an indication for clozapine for reduction of the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.

Five percent of patients with schizophrenia commit suicide, and 25 to 50 percent make at least one suicide attempt during their lifetime.<sup>4</sup> "The risk of suicide, or the aftermath of a suicide attempt, is one of the most common reasons for hospitalization of patients with schizophrenia," says Meltzer, adding, "It's among the most likely reasons for an emergency evaluation by a mobile crisis team or an emergency room visit."

Despite these statistics, clozapine is prescribed to just three percent of schizophrenia patients in the U.S. "The U.S. is way behind China and the Scandinavian countries which have upwards of 20 percent of patients receiving clozapine," says Meltzer.

"The fear of agranulocytosis is grossly exaggerated," Meltzer asserts. "The risk of its occurrence is way under one percent and the risk of death

from agranulocytosis, with monitoring and treatment, is less than one percent of that." When monitored correctly, the frequency of agranulocytosis with clozapine has been estimated to be as low as 0.38 percent.

He adds that fears of medical liability are also exaggerated. "No one has ever been sued for clozapine-induced agranulocytosis. Meanwhile, thousands of patients with schizophrenia in the U.S. are dying needlessly from suicide each year. Everyone with schizophrenia who survives a serious suicide attempt should be considered for treatment with clozapine."

## Provider efforts to promote evidence-based practice

In September 2009, the Centerstone Research Institute (CRI, Bloomington, Ind.) convened a "Knowledge Network Summit" to advance adoption of evidence-based practices in behavioral healthcare. CRI is the research affiliate of Centerstone, the largest community-based provider of behavioral health services in the U.S. CRI conducts

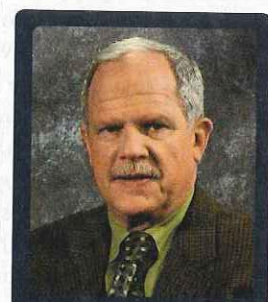
services research as well as clinical studies, partnering with leading research institutions including Vanderbilt University to advance knowledge of mental health and addiction disorders and discover innovative treatments.

"When Dr. Meltzer presented facts about clozapine at the Knowledge Network Summit, it was clear to us that clozapine serves as a case study of the failure of the diffusion of research findings in psychiatry," says Dennis Morrison, PhD, the CEO of CRI. Morrison's

organization formed the Knowledge Network (KN), a grassroots partnership with seven large CMHCs, policymakers, and industry partners to help close the 17-year "science to service" gap.

## A top-down strategy is indicated

Attending the Knowledge Network Summit were over 50 providers, researchers, and advocates from CMHCs around the country, national policymakers from the Substance Abuse and Mental Health Services Administration (SAMHSA),



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and partners including the Mental Health Corporations of America (MHCA) and the National Council.

According to Morrison, "CRI and the Knowledge Network, working in partnership with experts in research, policy, and technology, are positioned as national leaders to close the gap that currently exists between research and practice in behavioral health." With the help of Knowledge Network partners, findings from this research will be readily disseminated to impact practice across the field of behavioral healthcare.

The Knowledge Network

participants' focus has been to increase the use of clozapine for individuals with schizophrenia who are treatment refractory or at risk for suicide. "Our first step was to determine baseline prescription rates of clozapine for the 13,000 patients involved," says April Bragg, PhD, CRI's Research Communications Manager. "We were not surprised to find a range of use from zero to nine percent, well below the optimal rate supported by research." Meltzer indicates "a realistic goal is to raise the bar to 15 percent of antipsychotic prescriptions."

### Changing the clinical culture

Bragg says that "the Knowledge Network will promote the attainment of Dr. Meltzer's goal by promoting and supporting the use of thought leaders, external change leaders, social networks, user-friendly technological reporting tools, educational interventions, and infrastructural changes" among the seven participating CMHCs. She expects that "organizational culture and readiness, fidelity to the implementation model, and provider knowledge and attitudes will mediate the extent to which clozapine prescribing increases at each site."

The Knowledge Network centers are still in the early phases of employing tactics to increase clozapine use. Currently, they are collecting data for a data warehouse that will allow better tracking of suicidality and treatment resistance in their patient population. The data warehouse will aggregate anonymous data on client-level demographic and diagnostic characteristics, service utilization, and prescription patterns. It also will serve as a shared platform for staff reporting and track the rate of clozapine prescriptions. Behavioral Pathway Systems, a company of CRI, will track additional organizational benchmarking indicators.

"The establishment of a national mental health data warehouse will enable future research opportunities that will allow tracking of research dissemination and health services research in field settings," says Morrison.

"We are finalizing a survey for centers to provide

information on processes at their center that will promote greater use of clozapine," says Bragg. The Knowledge Network's Web site, [www.knproject.org](http://www.knproject.org), will house this survey. "We hope that as the centers implement strategies with their staff to increase clozapine use, they can look at the survey data to see if there is a correlation between frequency of trainings, for example, and reduction of suicidality as reflected by the data in the warehouse."

Meltzer says "a clear directive from the Medical Director of the clinic to use clozapine for its main indications will increase clozapine utilization." He is willing to share his thinking on tactical interventions with anyone who is interested.

"CRI wants to change the way healthcare is delivered," says Morrison. "Advances in our knowledge change mental health practice rapidly. The clozapine project will demonstrate the potential to keep clinicians current with best practices." ■

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