Improving outcomes for patients with schizophrenia: new hope for an old illness

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As treatments for psychiatric illnesses become more and more sophisticated, primarily because they are increasingly targeted to identifiable molecular impairments of neurotransmission or of intracellular signalling, we can begin to develop effective primary prevention programs. Any efforts in this area, such as those presented for schizophrenia by Ashok Malla and colleagues[1] (page 843), are probably still premature, but the prospects are looking decidedly more hopeful.

Schizophrenia, arguably the worst of the psychiatric illnesses, is of unknown origin, its causes as mysterious today as they ever were. Because there are no reliable biological markers for the disease, the generally accepted criteria for diagnosis depend on the endorsement by the patient of a variety of subjective symptoms, the elimination of other potential causes of the symptoms (hyperthyroidism, for instance, or alcohol withdrawal or temporal lobe epilepsy), the determination of the minimum duration of the symptoms and the documentation of progressive social disability. Thus defined, schizophrenia occurs in families with high heritability, but there is no clear mechanism of inheritance, nor are there any good clues as to what genetic material is inherited or how or why the responsible genes are activated at the time of onset, usually during late adolescence.

Views of the illness have changed radically in recent years. Not long ago, the thinking was that pubertal changes, either hormonal or immunological, occurring at adolescence and interacting with the social stressors that accompany the assumption of adulthood, nudged the schizophrenia genes, whichever they were, into expression mode, initiating a cascade of intracellular and intercellular events in the brain that ultimately produced the psychotic symptoms. It was well recognized that these symptoms (delusions, hallucinations and disorders of thinking) generally and inexplicably came and went. Those affected also experienced volitional symptoms (specifically anergia and inhibition) that tended to get steadily worse, mood symptoms (characterized as unpredictable and flattened) that endured and cognitive symptoms that progressed. The progressive deterioration of cognitive abilities led to the original term for this illness, dementia praecox.[2] The schism between what was true in one's outer world and what was true in one's inner world led to the newer term, schizophrenia.

As an aside, it should be made clear that the diagnosis of schizophrenia has never referred to the coexistence of multiple personalities, to rapid shifts of mood or behaviour, or to the holding of 2 or more irreconcilable positions, nor does it imply a tendency to unprovoked violence.

Recently, the diagnostic limits of schizophrenia have changed, as has the understanding of its pathogenesis. Researchers in a number of fields — postmortem pathology, embryology, neuroanatomy and neurochemistry, epidemiology, twin studies, longitudinal studies of children genetically at risk, longitudinal brain imaging studies and cognitive follow-up studies — have concluded that, for the most part, the responsible genes are expressed early in the development of the brain. According to current thinking, a faulty genetic signal induces subtle changes in the brain's wiring, perhaps local, perhaps widespread. The disturbance is generally not detectable until adolescence, not because it does not exist but presumably because the requisite stage of brain maturation must be attained before particular symptoms can emerge.[3,4]

Buttressing this theory is the evidence that many young people with schizophrenia show early signs of distress several years before the onset of illness.[5] In fact, one view is that subtle signs of faulty neural development are detectable from birth.[3] There is new evidence that brain impairment, as reflected by structural neuroimaging or neuropsychological assessment, is present by the time of initial diagnosis.[4] Significantly, there is cause to believe that this early brain impairment does not appreciably worsen over time. This idea is controversial, and the extent to which it holds true seems to differ among individuals, but there is hope that, as far as the brain is concerned, the worst of the damage is done by the time the illness manifests itself.

But why, then, if brain impairment does not progress, are progressive social disability and apparent cognitive de-

cline hallmarks of schizophrenia? Is it the treatment? Standard treatment since the 1950s has been a class of drugs called neuroleptics, which attach to a number of neurotransmitter receptors, notably those for dopamine, and thus control the delusions, the hallucinations and the disturbances of thinking. Taken over the long term, these drugs up-regulate their receptor targets, an effect that is held responsible for the production of a late-appearing motor syndrome, tardive dyskinesia. It is possible that volitional, emotional or cognitive pathways behave in a fashion similar to motor pathways and produce "tardive" social decline. Nonetheless, although drug effects cannot be dismissed as potential contributors to the problems that accompany long-term schizophrenia, it must be remembered that social and cognitive decline formed part of the earliest descriptions of dementia praecox, long before modern drugs were in use.

Another target of blame for the "dementia" of schizophrenia used to be long-term institutional care because, until the advent of the neuroleptic drugs, receiving treatment for schizophrenia meant living in an institution, far from family and friends, understimulated, usually undernourished and subject to monotonous routines. That is no longer the case, but the cognitive decline continues — not, of course, in every case, but in many.

Today's view of the pathogenesis of schizophrenia is that, during the years before the onset of frank symptoms, the early-established, subtly faulty wiring of specific neural networks underlies a phenomenon analogous to visual field neglect or disuse. Because the relevant neurons do not fire together, they do not wire together. They fail to communicate, a situation that may set the stage for the apathy, inertia, lethargy and amotivation that increasingly dominate the later stages of schizophrenia and give the impression, perhaps mistakenly, of cognitive decline. If this is the case, then it makes eminent good sense to try to reconnect the wires as early as possible. Hence, early identification and early treatment would seem appropriate.[5]

However, such a strategy is still premature. The evidence that shorter duration of untreated psychosis predicts fuller and quicker recovery applies, in the main, to the psychotic symptoms — the delusions, hallucinations and thinking disorders. Whereas it is unquestionably important to control these symptoms as early and as effectively as possible, and we have the means to do so with neuroleptic drugs, there is as yet no reason to believe that such treatment will stop the social and cognitive deterioration.

The availability of the second-generation antipsychotics makes early intervention safer with respect to possible neuromotor side effects, but there is no evidence yet that starting them early in the course of the illness is, in the long run, more effective than treatment with the older neuroleptics. Cognitive rehearsal and remediation, started early, could, at least theoretically, prevent the disuse phenomena mentioned above, but early intervention of whatever sort comes at a price.[6] Early medication, active stimulation and rehabilitation of lost skills, as well as stress reduction, all hold the promise of preventing social decline, especially if applied at the proper stage of illness and with the needs of the particular individual paramount.[7] But what all of these approaches can inadvertently engender is the stigma of psychiatric labelling at a vulnerable age, a stigma that still exists, even in our present-day "enlightened" era, and one that induces its own cycle of pathology.[8] In fact, the social decline and voluntary isolation of patients with schizophrenia may result, to a large extent, from their perception of being stigmatized. The challenge is to involve young people who are exhibiting prodromal or nonspecific symptoms in interventions associated in their minds with full-blown schizophrenia *without* prematurely inflicting on them and their families a label that carries with it so many dehumanizing myths.[6]

All the more disturbing is the fact that many clinicians equate early intervention solely with the prescription of drugs.[9] So many new psychiatric drugs have been marketed in recent years, and the marketing has been so skilled and successful, that the general unproven view is that newer drugs are more effective and result in fewer side effects than the older ones.

A more accurate picture of the current revolution in psychiatric medications is that newer drugs have successfully combated some of the disabling side effects of the older drugs but are not necessarily more effective for treatment and, unfortunately, have side effects of their own. That is not to say that some patients do not improve to a greater degree with the newer drugs than they did with the older ones — there have been anecdotal descriptions of miraculous recoveries. Perhaps most important, the new drugs offer new hope, which, for serious illnesses like schizophrenia, is desperately needed.

I think, however, that the real new hope lies in uncovering the mechanisms by which this illness does its damage, in developing reliable markers for diagnosis and in perfecting specific interventions that target specific known impairments. Psychiatric diseases are complex, so complete answers are not just around the corner. But this very complexity intrigues and focuses restless young researchers, lures the most gifted to this exciting field of enquiry and promises, in time, to yield its secrets to science. Therein lies the real hope.

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Sex or body size? Selection of dialysis type revisited

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In their Research Letter appearing on page 818, Christine Florakas and colleagues[1] describe a reconsideration of conclusions drawn in a previous study, which had suggested a gender bias in the selection of type of dialysis in Canada. In their earlier study,[2] published in *CMAJ* in 1994, these authors found that, for the period 1981 to 1991, women were more likely than men to undergo peritoneal dialysis. That study was based on data from the Canadian Organ Replacement Registry (CORR), for variables available at that time.

For the new analysis, the authors used data for 4467 patients who began therapy in 1993 and 1994, including variables (specifically weight, height and body surface area) that were not included in the CORR data collection before 1993. Using logistic regression analysis, they show that selection of type of dialysis in 1993 and 1994 was most likely determined by patient weight, not sex. The nephrology literature from 1993 and 1994 suggested that lower body weight was associated with better success of peritoneal dialysis.[3] Thus, given the educational material and prevailing practices at the time, it would appear that the patients who, under the guidance of their physicians, selected peritoneal dialysis did so appropriately, as they were of lower weight than those who chose hemodialysis. Interestingly, there was no association with body surface area, which is also derived from weight and height measurements. The logistic regression analysis thus isolated the independent effect of weight on type of dialysis when body surface area, sex and other variables were entered into the model.

This new analysis highlights the importance of including in such studies all of the variables that might have an impact on the outcome of interest. It also heightens our awareness that sex is often a marker for other variables (e.g., weight, height, body surface area, muscle mass and socioeconomic status). When designing statistical models, researchers must define, *before* the analysis, all of the variables that might affect the outcome of interest, so that confounding can be minimized.

The possibility of gender bias continues to be raised in the context of treatment for many diseases, so it behoves both researchers and clinicians to continually review both study results and treatment practices with respect to this determinant. For example, an analysis of data from the BC Cardiac Registry showed that women had a much higher risk of illness and death during cardiovascular surgery than men,[4] and there is substantial evidence for this type of bias with respect to outcomes of cardiovascular disease.[5–7] However, further analysis — in particular, a review of other confounders — has raised a number of issues and insights. Women are often referred later than men for invasive procedures; they often present with atypical chest discomfort, which leads to a delay in diagnosis and treatment; the instruments for angioplasty and surgical procedures are usually designed for and tested on men; and differences in vascular anatomy (e.g., vessel calibre) have been demonstrated.[6,7] Any or all of these factors might account for differences in outcome between men and women. Thus, while sex may be a marker for poorer outcomes for cardiovascular disease and related surgery, it is confounded by potentially modifiable variables (e.g.,