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Prodromal interventions for schizophrenia vulnerability: the risks of being "at risk"

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Abstract

Given the morbidity and difficulty of treating psychotic disorders, including schizophrenia, there has been a move toward identifying and treating adolescents and young adults who appear to be clinically at risk or "prodromal" to psychosis. The field now has greater specificity in identification, with rates of 40–50% conversion to frank psychosis within 1–2 years. There is further evidence that medications and other treatments may have some efficacy for "prodromal" patients, though with variable side effects. However, controversy remains about some of the inherent risks in prodromal research, such as medication exposure and stigma among false-positives. In this paper, we add to this discussion through an analysis of ethics in prodromal research from the more established field of predictive genetic testing. Issues are raised about the effects of information on patients, families, and institutions, as well as future insurability, the limits of confidentiality (as it relies on discretion of patients and families), the autonomy of minors with psychiatric symptoms, and even the risks for the true-positive patient.

Keywords

Prodrome; Psychosis; Ethics; Treatment; Risk; Schizophrenia

1. Introduction

Physicians studying schizophrenia have speculated for decades about the therapeutic potential of intervention prior to the onset of frank psychotic symptoms. In practice, however, diagnosis and subsequent treatment have typically followed a protracted interval of morbidity and decline. Recently, a number of researchers have turned their attention to preemptive intervention, seeking to avoid the sort of profound damage evident even in first episode schizophrenia.

One of the original rationales for preemptive intervention was the association in earlier studies of a longer duration of untreated psychosis (DUP) with worse prognosis, including more cognitive deficits, more severe negative symptoms, greater treatment resistance, poorer psychosocial functioning and increased risk of relapse (Edwards et al., 1998; Larsen et al., 1996; Haas et al., 1998; Loebel et al., 1992; Johnstone et al., 1986). It was considered that psychosis itself might damage the brain in ways that treatment after the fact cannot remedy (Lieberman, 1999). However, methodological issues in these earlier studies have been detailed (Norman and Malla, 2001), and such observational correlations cannot establish causation. Further, it may be that an association between DUP and outcome might be spurious, explained

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by the relationship of DUP to other characteristics, such as premorbid adjustment, that is itself related to outcome (Verdoux et al., 2001). In fact, the association of DUP and outcome is weakened by consideration of such confounds, though persists as a small to moderate effect (Verdoux et al., 2001; Harrigan et al., 2003; Addington et al., 2004). That is, schizophrenia with poor outcome might be characterized by a more insidious onset, or poor premorbid social adjustment, or poor insight, all factors that could lead to a delay in the treatment of psychotic symptoms (Drake et al., 2000). Definitive studies of the effect of DUP on outcome will involve the manipulation of DUP itself, which among many predictors of outcome, may be among the more malleable. Preliminary studies suggest that implementation of an early detection program leads comparatively to shorter DUP and better short-term clinical outcome (Melle et al., 2004), but longer-term assessments are needed to demonstrate whether this is a real effect on outcome and not just the result of finding patients earlier when they are less ill.

Although it is not clear whether untreated psychosis is toxic, it has been argued that prodromal symptoms carry significant risk for psychosocial morbidity. Hence, a number of the initiatives in early intervention have focused on identification and treatment of individuals at high clinical risk for psychosis. In 1996, Australian researchers Yung, McGorry and colleagues published studies describing specific criteria that predict first-episode psychosis in 40–50% of patients at 1–2 years, providing a standard for defining an at risk mental state or prodromal period that has been widely used and replicated in subsequent research (Yung et al., 1996; Miller et al., 2002). Criteria include (1) attenuated psychotic symptoms, (2) brief intermittent psychotic symptoms and (3) high genetic risk and decline in function. Though results of such studies are preliminary, many in the field are optimistic that early intervention will ultimately significantly add to our ability to treat what has remained, despite so much effort, an often devastating and intractable disease.

Inevitably, earlier intervention raises issues of potential over-treatment for the false positives in the patient population. Despite the better predictive validity of newer prodromal models, many patients will not go on to experience psychosis, at least not within the 2-year time frame that has been studied, although certainly some of these symptomatic individuals will benefit from treatment nonetheless. The risk–benefit analysis of medical treatment is more complex in the absence of a diagnosis. The personal and social ramifications of being deemed at risk for psychosis may be even harder to assess. Psychiatric treatment could conceivably affect the attitudes of insurers, employers, schools, other medical caregivers and, perhaps more subtly, friends, family and patients themselves. A full accounting of the risks of early intervention should look broadly at the potential impact on the lives of patients in order to prevent or minimize such unintended negative consequences as stigma or discrimination.

2. Defining the at-risk population

One of the ways in which treating susceptibility is more complicated than treating disease is that disease is relatively well defined and susceptibility is not. What does it mean to say that an individual is at risk for schizophrenia? Baseline population incidence is 1%; we are all born at some risk for schizophrenia. Determining who is a suitable candidate for intervention entails narrowing down what constitutes compelling vulnerability.

There are a number of variables that confer some indication of vulnerability to schizophrenia. Obviously, relevant symptoms are risk factors, such as disturbances in perception and thought (Klosterkotter et al., 2001). Suspiciousness is a sensitive risk factor and grandiosity a specific risk factor for progression to psychosis among prodromal patients (Lencz et al., 2003). Family history is another indicator of susceptibility. Other risk factors or markers under investigation include cognitive deficits in olfactory identification (Brewer et al., 2003), spatial working memory (Wood et al., 2003), and attention (Yung et al., 2004); decreased brain volumes

(Pantelis et al., 2003); and even poor functioning and high levels of depression (Yung et al., 2004). Potential environmental factors under study include traumatic brain injury and stressful life events. Given any model of susceptibility, the greater the likelihood of disease, the better the rationale for intervention.

That said, not all measures of vulnerability are created equal. An infant daughter of two parents with schizophrenia has a 50% chance of developing the disease, a statistical risk analogous to that of a 17-year-old boy who is currently experiencing attenuated psychotic symptoms. However, the teenager is at immediate risk and the infant is not. Because schizophrenia is a disease with delayed onset, there is an important difference between intervention that interrupts a presumptive premorbid period, potentially a time of relative health and normalcy, and intervention intended to address the imminent threat of disease.

Another dividing line among theoretically vulnerable individuals is the extent to which they perceive themselves to be compromised or at risk. Patients and families who are help-seeking because of symptoms or anxieties about susceptibility are already impacted; they may be struggling with the stigmatizing or alienating effects of current symptoms. A discussion of psychosis and mental illness is likely to address the current concerns of patients and their families. In contrast, patients who are healthy and who are culled from screening programs rather than help-seeking, are going to be impacted in an entirely different way by an intervention that introduces the idea of a vulnerability to mental illness.

Current and widely accepted standards for the psychosis prodrome, or what McGorry calls the At-Risk Mental State, reflect all of these parameters for narrowing the definition of at risk as it pertains to psychosis. Prodromal patients are identified as fitting into one of three categories:

1. patients with attenuated positive symptoms
2. patients with brief intermittent psychotic symptoms
3. patients with a steep decline in functioning plus a family history of schizophrenia

The three groups together are estimated by empirical studies to have about a 40% likelihood of developing psychosis by 12 months and a 50% likelihood of developing psychosis within the next 24 months (Yung et al., 1996; Miller et al., 2002).

Strictly speaking, the prodromal period can only truly be identified in retrospect. Participants in prodromal studies are a mix of true prodromals and false positives. Nonetheless, it is a well-characterized population, the risk of psychosis is both imminent and significant, and all the patients are already compromised in terms of their ability to function. These patients and their families are looking for help. Stigma and discrimination, like side effects and other medical consequences, must be considered in this group in balance with the disruption and morbidity already evident in their lives.

Research may provide answers about how and when to treat prodromal patients. Thus far, one randomized clinical trial (RCT) has demonstrated the superiority of low dose risperidone in combination with cognitive behavioral therapy over “needs-based intervention,” with a significant difference in rates of transition to psychosis (9.7% vs. 35.7%) and reported low incidence of side effects and little stigma (McGorry et al., 2002). Another RCT, which was placebo-controlled and double-blind, had differential rates of conversion to psychosis at 1 year (placebo 34.5% vs. olanzapine 16.1%) that was not statistically significant, probably due to low power (McGlashan et al., 2004); unfortunately, weight gain was also much higher in the olanzapine group (8.8 vs. 0.3 kg). Other potential alternatives to antipsychotics include medications such as antidepressant and antianxiety medications, and non-pharmaceutical therapies including stress reduction techniques and cognitive behavioral therapy.

However, it is worth noting that success in treating the prodromal population as described will not serve to clarify the issue of who to treat. If outcome can be affected by preemptive intervention, there will be a great incentive to expand the profile of eligible candidates likely to benefit from treatment. Efforts to improve the effectiveness of intervention evolve in concert with improvements in our ability to predict susceptibility; the net effect of progress in both fields will be to raise the possibility of preventing disease by treating patients who are increasingly younger or without symptoms. That eventuality requires an increasingly strict scrutiny of possible ethical issues arising from unintended consequences both for false positives, those who would not have developed the disease even without the intervention, as well as for the true positive population.

3. False Positives

There is no method of screening a population for susceptibility to schizophrenia existing or envisaged that can eliminate the issue of false positives. Although sensitivity for the present instruments is as high as 100% (indicating a very low conversion rate to psychosis in the short term for help-seeking adolescents who do not fulfill criteria for the prodome), the specificity is within the range of 71–74% (Miller et al., 2003), which reflects a substantial false positive rate. In prodromal populations as currently described the apparent false positive group also includes those for whom treatment was effective at halting the progression to illness—the “false false positives”; therefore on an individual basis no one can ever be certain that their at risk designation was actually false per se. But naturalistic studies demonstrate that, at least in the 2-year period described, a substantial number of patients will not develop psychosis. Other screening models are no more likely to provide specificity at identifying those who would progress to psychosis without treatment. For instance, concordance rates for schizophrenia are no more than 60% in monozygotic twins, so that even in the admittedly speculative event that genetic screening became a reality, there are inherent limitations to genetic predictability.

One readily apparent problem for false positives is the risk of over-treatment, and for that reason both who to treat and how to treat are subjects for debate in current prodromal research. The use of antipsychotic medication for those who have not developed psychotic symptomatology is controversial and the data are inconclusive regarding efficacy and safety. In a sample of patients with schizotypal personality disorder, a syndrome with significant overlap with prodromal symptoms (attenuated psychotic symptoms, negative symptoms), low-dose risperidone was compared to placebo (Koenigsberg et al., 2003). In this older sample of patients, who were presumed to have largely passed through the age of risk for schizophrenia (around 40 years old), risperidone was associated with a greater relative decline of attenuated psychotic symptoms. However, the dropout rate was high in the risperidone group (6/14 or 42.9%), as was the incidence of side effects (7/14 or 50%), which included galactorrhea (milk production), sedation, sexual side effects and mild dystonia. In contrast, open studies of low-dose risperidone in first-degree family members of schizophrenia patients suggest minimal side effects but improvement in negative symptoms, attention and working memory (Tsuang et al., 1999).

Some investigators believe that the newer atypical agents, such as risperidone and olanzapine (studied respectively by McGorry's and McGlashan's groups in prodromal patients) provide a safer alternative than previous neuroleptic medications, while others argue that this is questionable, particularly in this population, which are primarily young adults and teenagers. A number of studies suggest efficacy and relative safety of risperidone for a host of psychiatric problems in children and adolescents, including tic disorders (Gilbert et al., 2004; Scahill et al., 2003), the psychotic symptoms of schizophrenia (Zalsman et al., 2003), and disruptive behavior in children with low IQ (Turgay et al., 2002) or with pervasive developmental disorders, such as autism (Masi et al., 2003; McCracken et al., 2002). Similar evidence exists

for the efficacy of olanzapine in treating disorders in adolescents such as bipolar disorder (Frazier et al., 2001) and schizophrenia (Findling et al., 2003). However, each of these aforementioned studies describes significant weight gain as an observed side effect of these newer atypical agents. Weight gain of more than 10 pounds in only 3 months commonly occurs with these medications (Correll et al., 2004a), which poses a threat not only to self-image and social functioning, but also adds to serious long-term health risks of obesity and diabetes mellitus, especially as these medications have been associated with insulin resistance (Correll et al., 2004b).

The use of antipsychotic medication in childhood for a number of indications including prodromal-type symptoms has increased in clinical practice. Prescriptions for antipsychotics, mostly for these newer atypical agents, were estimated to have been written for 8 in 1000 youths as of 1996, a greater than fivefold increase from a decade earlier (Zito et al., 2003), even though as of 2004, none of these atypical antipsychotics have been approved by the Federal Drug Administration for individuals under the age of 18. These prescribing patterns likely reflect emerging findings of efficacy, as described above, for a host of disorders in childhood and adolescence, including prodromal symptoms of schizophrenia, but may also have preceded the publication of results of these clinical trials. One can speculate whether once the question of the utility of antipsychotic medications in prodromal and other patients was publicly considered by investigators, and pilot data were discussed in international meetings and described in the media, community clinicians might have been increasingly inspired to prescribe antipsychotic medications to the putatively behaviorally disturbed or “prodromal” patients in their own clinics and practices. Hence, began a race against time, as the simple construction of a research question can alter prescribing practices in the community. Prodromal and other researchers have argued that if the medications are being used in the community already, it is essential that there be controlled studies measuring efficacy. As the use of these medications becomes more commonplace, it changes the ethical considerations for those doing investigative studies. Participation in studies that include the use of antipsychotics is relatively less of an increased risk for help-seeking research subjects if the same medication might be a part of routine clinical care. On the other hand, if the use of antipsychotics continues to increase, this may prove to be a window of opportunity for naturalistic studies and clinical trials, as well as investigation of alternative therapies and pharmaceuticals.

Beyond the issue of over-treatment, it is worth considering whether there are any ethical considerations specific to the idea of participating in a program designed to study and prevent incipient psychosis. One potentiality is that the prodromal research subjects could feel themselves to be labeled as at risk for psychosis or for schizophrenia in a way that had negative implications. This does not necessarily imply that researchers would use such a label, or that the idea of being considered at risk for psychosis is inherently pejorative. If the stated goals of research include preventing psychosis in at risk candidates, would it not be possible for patients, families, insurers and other interested parties to infer that participation in such research is tantamount to acknowledging a risk for schizophrenia? If the information is available, it raises the issue of stigma and concerns about confidentiality.

4. Stigma

What does it mean to say that a patient could be stigmatized by being identified as at risk for psychosis? On a personal basis, stigma would have to affect the patient's sense of self, or relationships with friends and family. The idea of being at risk for psychosis might affect an individual's choices in terms of education, employment, or other life plans. It might impact the extent to which such plans and aspirations would be supported by other family members. Whether or not this anxiety over being at risk for psychosis is a meaningful issue needs to be looked at in the context of a given person's life. The more that symptoms are causing turmoil,

the more that the individual is currently in distress, the more that the idea of being at risk is just a footnote. Interviews with the parents of patients at prodromal clinics have shown that their concerns about stigma are strongly dependent on the behavior of the patient prior to any interaction with the clinic. Rather than increasing apprehension, treatment may offer symptomatic patients and their families a reason for new optimism that outweighs any added anxiety about being at risk.

This distinction is a good example of how the stakes change if patients are younger or less symptomatic. In a population that is not immediately at risk or impaired, the idea of being vulnerable for psychosis could leave the false positives with a lasting sense of being fragile, damaged or a little bit sick. It might alter their goals, or make them less likely to be achieved; it could be harder to find motivation for a future that threatens to be taken away by illness.

Families might well reorganize their priorities in the light of this information. In some families this could be productive, allowing them to protect the at risk individual from stress and redefining behavioral problems as illness rather than character flaws. In others, the protective impulse might mean that in effect the family ceased to encourage growth, progress or achievement. For some false positives, the same type of redefining might result in family dynamics where eccentricities or other aspects of personality were viewed as pathology.

It remains to be seen whether this potential reevaluation of an at risk individual would be more helpful or subtly discriminatory, but in either case the effects could extend beyond family dynamics. Schools and other social institutions may also be affected. Schools have reason to be increasingly leery of students whose behaviors are perceived as odd, threatening or asocial. Teachers and administrators may see any student in a different light if they are concerned about a risk of psychosis, even if that student's behavior is otherwise acceptable. They might, for instance, emphasize safer choices and fewer challenges, limiting the opportunities ultimately available to at risk individuals.

It can be difficult to appreciate the difference between a susceptibility and a disease and it is easy to envision a situation wherein a suggestion of vulnerability might be mistaken for a quasi-diagnosis. In the internet age, patients and their families have access to a great deal of information, very little of which is screened or explained. Any blurring of the distinction between being at risk and already having a disease means that their expectations could be colored by all the available information and misinformation. Thus, it is essential that family education be a part of any prodromal research program.

While families need help in navigating the subtleties of vulnerability vs. disease, third parties with financial exposure may find it simpler to dispense with the distinction altogether. Individuals should have concerns about whether intervention for susceptibility will make them uninsurable or unemployable, and whether it will constitute a diagnosis in the eyes of insurers, meaning that from this point forward they will have on record a pre-existing condition. The concern with insurability is an ongoing issue wherever medical intervention involves risk assessment, and the issue is at the heart of genetic discrimination laws that have now been passed by a majority of state legislatures.

None of these issues are unique to psychosis, and the increasing availability of information based on screening procedures or risk assessment will impact all fields of medicine. Studies of insulin treatment for children at risk of Type 1 diabetes have been similarly debated, pitting the potential of preventative therapy against the medical and social drawbacks of early intervention. It is envisioned that families of children identified as at risk for Type I diabetes mellitus must also struggle with issues of stigma, fragility and protection, the vast and conflicting information available on the Internet, and concerns regarding privacy and future insurability for their children.

Women with a family history of breast cancer who pursue genetic testing for BRCA 1 or 2 mutations have also expressed analogous concerns. Lifetime incidence of breast cancer with one of the common BRCA mutations was estimated at up to 85% (Easton et al., 1995; Ford et al., 1994, 1998), but recent research indicates that the actual rates are lower, perhaps as low as 26–46% through age 70 (Satagopan et al., 2001). Many people who are identified as being BRCA positive will never go on to develop breast cancer, whereas others will be identified well in advance of the presentation of disease. Breast cancer, like schizophrenia, presents an expense that would be significant to insurers.

Though there are no documented cases to date of discrimination secondary to BRCA test results, it is an issue that testing programs routinely cover during pretest counseling. Frequently, women opt to pay for testing out-of-pocket to avoid raising the suspicions of their insurers, present and future. Concerns with confidentiality have been so acute that the results of testing are often kept in a separate genetics file and are not included in the patients' medical records. What is relevant for those at risk for cancer is likely to be relevant for those at risk for schizophrenia, and far fewer individuals will have the option of paying out of pocket since treatment, unlike testing, is an ongoing expense.

5. Confidentiality

Confidentiality is an important tool for protecting the at-risk population from insurance discrimination and other forms of stigma, but it is not a panacea. The Health Insurance Portability and Accountability Act of 1996 (Public Law 104-191) largely addresses only the safeguarding of personal health information from unauthorized (electronic) access and it largely speaks of “code sets,” “health care clearinghouses” and “electronic exchange” (Sections 1171–1173). Likewise, a Certificate of Confidentiality, issued by the Department of Health and Human Services, also promotes privacy as it is threatened by institutions: it helps *researchers* avoid involuntary disclosure about subjects, so that the researchers “may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative or other proceedings to identify such individuals” (Section 301(d) of the Public Health Service Act 42 U.S.C. 241(3)). Neither HIPAA nor a Certificate of Confidentiality has any jurisdiction over what research subjects themselves disclose.

The concept of confidentiality therefore may extend beyond secure medical records. It includes not only who is told and what is told, but what type of language is used and what sort of messages are implied. Patrick McGorry notes that his clinic in Melbourne, Australia was given a name with deliberately neutral language that would neither frighten his at risk population of teenagers and young adults nor suggest a diagnosis of schizophrenia or psychosis to observers. He opened Personal Assessment and Crisis Evaluation (PACE) programs in a teen center in a shopping mall rather than in a hospital setting to minimize the association with mental illness (Yung et al., 1996).

Even with an approach that is consistently sensitive and thoughtful there are limitations, though, to the effectiveness of confidentiality. One problem is that it relies on the discretion of patients and their families. It is not reasonable to assume that patients and their families will keep information to themselves even if that is in their best interests. It is unrealistic to assume that patients and families will always foresee the ways in which sharing medical information may have unintended consequences. Even if they accept in theory that they should keep the information private, it imposes a burden on those involved not to be able to speak freely, particularly to those on whom they rely for emotional support. It is safest to assume that any information given to patients could become available to their community, their religious institutions, their schools, their employers and other potential third parties, by virtue of what the families choose to share.

In fact, schools, religious groups and community organizations have played a role in the networks established to refer young people exhibiting early symptoms into programs offering intervention. This is another impediment to the provider's ability to control issues of confidentiality. In addition, payment for a program of intervention can routinely require that some documentation or diagnosis be given to an insurer or HMO. While the documentation would not necessarily contain anything specific to a risk for schizophrenia or psychosis, there are many circumstances where that risk or that diagnosis might be implicit.

One suggestion that has been debated by researchers is that it might be possible to just limit the information given to patients, their families, and their insurance companies, using language that is value-neutral, and avoiding specific mention of psychosis or schizophrenia as a risk. This circumvents the problem of relying on the discretion of the patient, and it protects the patient from information that may be misunderstood. It could also eliminate what might be unnecessary stress for the patients and their families.

While there are certain benefits to a low-key or conservative approach, censoring the physician's concern about the risk for psychosis is protective in a way that poses some serious ethical complications. In general, filtering what information is available to patients even to protect them is not compatible with our understanding of patient autonomy or the requirements of informed consent. Additionally, patients and families who do not understand what is at stake may be less compliant with treatment. It is the hope and intention of researchers that intervention will improve outcome; a patient with a bad outcome who declined intervention in the absence of details on his or her risk assessment would be justifiably upset.

There is also the possibility that in tiptoeing around the word psychosis we are inadvertently contributing to the stigma associated with mental illness. Patrick McGorry has suggested that this idea of stigma is itself a by-product of the physicians' own fear of psychosis (McGorry et al., 2001). What does it convey to the at risk population if their doctor is uncomfortable with the word psychosis? Surely the patient's own fears could only be reinforced. To avoid talking about psychosis suggests that fundamentally mental illness is unlike any other illness; it is unlikely that anyone would propose avoiding full disclosure if the risk involved were for diabetes or heart disease. Deviating from the norms of medical practice serves to increase and perpetuate the stigma associated with mental illness.

6. Autonomy

Autonomy, or the right of self-rule, is a principle that is deeply imbedded in our national character and our nation's history, from the frontier values of independence to that classic of East Coast intelligentsia, Thoreau's “Self-Reliance.” Autonomy is valued as a good in and of itself because for the individual, autonomous decision-making brings meaning and dignity to life, and it is valued as a tool that serves to protect the fundamental rights of the individual vis-à-vis the interests of the majority. Protecting patient autonomy in medicine has come to be synonymous with informed consent.

There are often practical impediments to informed consent: cultural differences, language barriers, educational inadequacies, time pressure in emergencies, geographic or economic barriers to options that are available only in theory. As regards early intervention in psychosis or schizophrenia, there are a host of inherent complexities. In the prodromal period, patients are on the cusp of competence both in terms of their age and in terms of their mental status. Intervention at an earlier stage suggests that patients will be less compromised in terms of cognition or insight, but younger and less able to participate in the decision-making process. There is no easy formula for balancing the obligation of families and doctors to protect these vulnerable individuals while permitting them some latitude for self-determination.

Presumptively, parents and guardians will often be very much involved in any decision to pursue treatment. Much of the time the best interests of the child and the best interests of the family closely converge. But there are some caveats to that assumption that are unique to psychosis. As potential caregivers, family members may at times have an agenda that is at variance with the best interests of the patient. Psychosis can place an enormous burden on family members and in some cases they may feel that as regards treatment, limiting risk is more important than any other goal. If you break your leg, there is little room for debate about what comprises getting better. Stabilizing the injury, treating the pain, improving mobility—all these are positive steps toward the ultimate goal of a fully functional and intact leg. But in terms of mental illness, one person's concept of “better” may focus on the patient's feelings, the extent to which the patient feels improved or feels normal, while an alternate (and possibly contradictory) measure may be the physician's ability to control behavior that others find objectionable.

Even when all parties agree on the optimal outcome of treatment, it can be difficult to fulfill the ideal of informed consent in prodromal research and other forms of early intervention. In “Ethical issues in early-intervention clinical trials involving minors at risk for schizophrenia,” David DeGrazia counsels that the growing influence of pharmaceutical companies is a practical problem for obtaining informed consent for research subjects (DeGrazia, 2001). Inherently, pharmaceutical companies are more interested in the narrow issue of establishing a rationale for marketing their product than in assessing in a broader sense whether or not treatment has a positive or negative effect on the patient's life in sum.

All of this places a burden on the researcher or clinician to provide a relatively higher standard of informed consent. Specifically, consent should include a discussion of psychosocial as well as medical risks. The primary requirement of informed consent is the education of patients and families, but in certain circumstances physicians may be called on to take a more active role in safeguarding the well being of their patients. There are many who stand to gain from research in schizophrenia: families, particularly in light of familial predisposition; pharmaceutical companies with treatments to market; society at large in what can be learned about the disease. Nonetheless, these benefits cannot be earned at the expense of a vulnerable population.

7. Risks for true positives

It has already been pointed out that false positives may benefit from treatment, particularly false positives who are symptomatic. It should also be pointed out that the reverse is true as well; early intervention may pose some hazards even for the true positives, to be set against benefits which, though potentially very great, are as yet not well characterized. Efforts at early intervention in Type 1 diabetes mellitus may be instructive. Although the use of prophylactic insulin in normoglycemic children genetically at risk for Type 1 diabetes mellitus was inspired by both promising animal models and encouraging results from pilot studies, the ensuing large-scale screening and treatment efforts have not met expectations. In one study in which almost 90,000 first-degree relatives of IDDM patients were screened and treated, there was no evidence that type I diabetes in the at-risk group was prevented or delayed (Marks, 2002).

In efforts at prevention for both schizophrenia and diabetes, the extent to which treatment is a risk for true positives is directly related to two variables: current quality of life and the length of the interval between intervention and the onset of disease. Both medical treatment and the idea of being at risk for a serious illness are potentially detrimental to the patient's well being, though perhaps more so for the more stigmatized condition of psychosis. It is an issue to consider for prodromal patients, who by definition are currently compromised. It is that much more of an issue for any researcher undertaking to assess children for vulnerability, not to be overlooked by anyone working with a young or pre-symptomatic population. For example, in

diabetes prevention research, families reported that they had found their medical regimen “hard” or “very hard” and 40% of children, parents and spouses felt that they would have benefited from access to a mental health professional at some point during the trial (Tercyak et al., 1998).

The possibility of risk assessment therefore creates a difficult choice for affected families. Obviously any parent would be anxious to prevent onset of psychiatric disease or to mitigate its effects. But as much as early intervention looks promising, there are no guarantees that medical care is going to change the outcome for schizophrenia, as has been found for Type 1 diabetes mellitus. Given that in some instances a bad result may be inevitable, and that the problem is perhaps years down the road, would a family prefer to have prior knowledge of the event? Or would they prefer to have the intervening years of relative normalcy?

This is a complicated issue that has also been raised in the past. The classic example is Huntington disease, a fatal degenerative neurological condition with onset typically between age 30 and 45. In 1987, three centers in the Northeast began offering linkage testing for the genetic change that causes Huntington's disease. Earlier surveys of at risk individuals had shown that 60–80% of them were interested in genetic testing. Of an estimated 1500 at risk individuals in the areas served by these centers, 32 signed up for the test and 18 completed testing (Wexler, 1995).

Huntington's disease is not schizophrenia. With Huntington's disease there is a sort of certainty; if a test for Huntington's disease is positive, the risk of getting the disease is virtually 100% given that the individual lives long enough. Also, until very recently no medical intervention was possible, and anything that is available now is limited, experimental, and not widely accessible. But it is interesting to note that the at risk Huntington's disease population, given that chance to look into a crystal ball, decided more often than not that today was not a good day for knowing the future.

The limited interest in pre-symptomatic testing demonstrates that people put a high value on preserving their ability to be hopeful. A similar phenomenon has been observed with BRCA 1 and 2 testing, where preventive measures are available and the risk for developing disease is much less than 100%. The at risk population clamored for testing, but when the test was offered it was utilized by few families relative to earlier expectations. In fact, a 1997 survey of the target audience for BRCA testing suggested that a willingness to test was inversely associated with perceived hereditary vulnerability (Andrykowski et al., 1997). Those without family histories suggestive of hereditary breast cancer were interested in taking a test that would most likely only confirm their low risk status, but the high risk family members were reluctant to pursue testing. While concern with insurance discrimination has played a role in this avoidance of testing, beyond that it is incontrovertible that, when push came to shove, many people simply did not want to know their genetic risk status.

Accurate early prediction of risk factors for schizophrenia is of great value to researchers because it identifies a population of interest and adds to our basic understanding of the disease. It is possible to overestimate its value to the families and the individuals so identified. Ethically, researchers must be conservative about suggesting that individuals have early signs of a vulnerability to schizophrenia, particularly until more is known about the effectiveness of treatment options. Informed consent for any risk assessment should include a consideration of all potential psychosocial consequences for those labeled at risk.

8. Conclusions

Exploring the ethical and social implications of early intervention in schizophrenia at this stage of the game affords us a moment to consider what measures might be taken that minimize the

liabilities but do not preclude the opportunity to improve treatment. The first step in early intervention is identifying those at risk. As a result, what intervention offers patients is twofold: risk assessment and subsequent medical care. It is routine to assume that medical care can have unintended consequences; it is less frequently acknowledged that the giving out of information can also profoundly impact a patient's well-being in ways that are unintended and perhaps unforeseen.

It is important to evaluate carefully what information is available to third parties, either directly or by implication. Relevant third parties are first and foremost insurance companies, but can also include employers, schools, religious organizations and other community groups. It is not safe to assume that individuals or institutions will appreciate the difference between a risk assessment and a diagnosis. Though education can be helpful in this regard, and medical caregivers are obliged to help differentiate susceptibility from disease for patients and families, there remains the fact that patients may be at risk for discrimination as well as schizophrenia if their risk is understood or even suspected by third parties.

Confidentiality must be a part of what is offered, but it cannot be relied on as a solution. Even the certificates of confidentiality, legal documents designed to protect patient information obtained via research, include a disclaimer for information that may be disclosed by patients and their families themselves. There is a complicated balance to achieve between controlling the flow of information and respecting the imperative of patient autonomy. Informed consent for early intervention in schizophrenia should include a discussion of the potential risks for stigma and discrimination even if those issues are at present only hypothetical.

Caution is required in what is communicated to patients and their families, not only in what is said but in how it is said. In this Internet age, with its endless supply of both information and misinformation, there is a double burden on practitioners to give people enough understanding that they do not look to unvetted sources for guidance, and yet to provide this information without implying a needless or anxiety-provoking inevitability to the specter of disease.

It is incumbent on researchers and clinicians to exercise caution in defining who is a candidate for early intervention. Current prodromal populations receiving treatment are symptomatic and well defined. The potential of intervention to have a negative impact on the patient's life increases in any shift toward a target population that is younger, less symptomatic, or less strictly delineated. There is also a difference between treating a patient who is help-seeking and going out to look for patients or families based on screening criteria. Introducing the idea that an individual is at risk for psychosis or schizophrenia is a potential burden and should be undertaken with discretion.

If and when there are encouraging results from prodromal research, it can be anticipated that a number of parties will be motivated to expand the profile of who is a suitable candidate for treatment, including those researchers interested in the earliest manifestations of schizophrenia and the pharmaceutical companies whose products are potential therapeutic agents. Families that perceive themselves or their loved ones as at risk may prefer intervention to inaction on principle. Researchers from the IDDM trial DPT-1 noted that families anxious for a cure pushed practitioners to provide preemptive treatment before results from clinical trials were available (Marks, 2002). It falls to practitioners to resist these pressures unless changes in practice are justified by evidence of benefits and specificity.

Another consideration that should be taken into account in considering candidates for early intervention is the importance of protecting any period of normalcy that the at risk individual might anticipate having prior to diagnosis or, more specifically, prior to the onset of symptoms that interfere with functioning and quality of life. False positives labeled as at risk are liable to social and personal costs as well as unnecessary medical care. For the true positives identified

early the potential of effective treatment must be balanced against heightened anxiety and medicalization of their pre-symptomatic years, a period of time that could represent their best shot at normalcy in the face of what might be a lifelong struggle with mental illness.

Today, in clinical practice as well as in research programs the prodromal-like patient is increasingly likely to be offered treatment. Current circumstances encourage but do not dictate intervention; in this sense it presents a window of opportunity to investigate both the natural course of the disease and the effectiveness of medical care. A number of treatment options have been proposed, each of which needs to be evaluated, in conjunction with an ongoing effort to monitor the effect of intervention on social and personal as well as medical variables. Ethical issues about where, when and who to treat preemptively present challenges that will not be erased by the outcome of research. However, optimal decision-making is facilitated by sensitivity to all the risks involved coupled with accurate and balanced information on the potential of an array of proposed therapies that may impact the course of schizophrenia.

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