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Rationale for the study of early intervention

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Abstract

Consistent but relatively weak evidence exists that treating patients with schizophrenia early in the course of their illness can decrease long-term morbidity. Relatedly, it is possible that treating individuals even earlier might produce better results. The findings presented set the stage for early and even earlier formal intervention studies, where the potential benefits are thought to outweigh the potential risks.

Keywords

Schizophrenia; Early intervention; Duration of untreated psychosis

1. Introduction

Until recently, the prevailing view of schizophrenia was that its course was preordained, that pharmacological treatments only decrease its devastation for the duration of their administration, and perhaps that ‘spontaneous improvement’ occurs after a lengthy period of illness (Harding, 1988; Harding et al., 1992; Nasar, 1998). Starting in the 1980s (Davis, 1985; May et al., 1981; Miller, 1989), there began to be some interest in the concept that intervening early in the course of schizophrenia might decrease long-term morbidity. Although this idea was not new, previous notions about early intervention had been very short lived (Cameron, 1938). In the last decade, however, a number of reviews concluded that early intervention in schizophrenia might produce long-term benefits in some patients (Bromet and Fennig, 1999; Lieberman, 1999a,b; McGlashan, 1996, 1998, 1999; McGlashan et al., 1996; Waddington, 1997; Wyatt, 1991, 1995a,b; Wyatt et al., 1996, 1997; Wyatt and Henter, 1998).

The term ‘early intervention’ itself is one that is used to encompass several distinct efforts, including (1) early intervention primarily with antipsychotic medications, but also with psychosocial methods, for individuals experiencing their first episode of schizophrenia; (2) community-based efforts at detection of high-risk individuals or those experiencing prodromal symptoms (in a sense, earlier intervention or intervention in the prodrome); and (3) efforts to identify and prevent causal factors of schizophrenia. The first effort is aimed at reducing morbidity, the second at decreasing the morbidity and perhaps incidence of new

cases of schizophrenia, and the third at preventing the occurrence of new cases of schizophrenia. The third type of effort is not the subject of this paper.

2. Studies of early intervention

The concept of early intervention in schizophrenia has, for the most part, focused on early treatment with antipsychotic medications. Four categories of studies address the potential long-term benefits accruing from early treatment of schizophrenia, each with their own advantages and limitations. Evidence from all of these — epidemiological studies, mirror-image studies, delayed-intervention studies, and contemporaneous control studies — when taken together, support the notion that early intervention with antipsychotic medications may help reduce long-term morbidity associated with schizophrenia.

2.1. Epidemiological studies

Epidemiological studies examine the incidence and severity of schizophrenia over the time of interest (reviewed by Warner and de Girolamo, 1995, p. 139). Generally, this time has been the mid-1930s, just before the introduction of convulsive therapies, to slightly after the mid-1950s, just after antipsychotic medications first became available. Evidence from these studies suggests that the incidence of schizophrenia has decreased over the last 50–60 years (Waddington and Youssef, 1994), although many investigators have rightly emphasized that it is difficult to accurately make such estimates. For instance, the way schizophrenia is diagnosed has changed significantly over the past few decades, especially in the United States (Hegarty et al., 1994). In the United States, the diagnosis of schizophrenia became much more exclusionary; that is, a number of diseases once thought to be among the schizophrenic disorders are now considered distinct. One instance of this is bipolar disorder with psychosis. For example, when diagnostic criteria for bipolar disorder were refined in the United States, it appeared that the incidence of schizophrenia declined when, in reality, it was the diagnostic criteria that had changed (Gurland et al., 1969). Because a distinction between schizophrenia and affective disorders similar to the one made in the United States today had been consistently made in much of Europe, data from there are not as contaminated with as many diagnostic alterations over time. And, although one might expect the incidence of schizophrenia to have remained relatively stable in countries where diagnostic criteria have always been narrow, it is likely that, even in those countries, small shifts in diagnosis occurred because of the introduction of mood stabilizers to treat bipolar disorder.

Despite the diagnostic considerations, most (Balestrieri et al., 1997; Der et al., 1990; Eagles et al., 1988; Eagles and Whalley, 1985; Geddes et al., 1993; Joyce, 1987; Munk-Jorgensen, 1986; Munk-Jorgensen and Jorgensen, 1986; Munk-Jorgensen and Mortensen, 1992; Parker et al., 1985; Suvisaari et al., 1999; Takei et al., 1996; Waddington and Youssef, 1994) but not all (Castle et al., 1991; Folnegovic et al., 1990; Folnegovic-Smalc et al., 1990; Häfner and Gattaz, 1991; Harrison et al., 1991; Oldehinkel and Giel, 1995) carefully performed studies have found a decline in the first-admission rates for schizophrenia over the last half century. In addition to this decline in first-admissions, population studies have also demonstrated a fall in incidence (Balestrieri et al., 1997; Brewin et al., 1997; Waddington and Youssef, 1994) and prevalence, at least in females (Stromgren, 1987).

Although not all authors agree (Warner and de Girolamo, 1995), there is considerable consent that schizophrenia has become less severe over the last 50–60 years (Hare, 1983). It is unlikely that changes in severity can be attributed solely to changes in diagnostic methods. For example, around 1940, when convulsive therapies were introduced, the percentage of first-episode patients with schizophrenia who were discharged from hospitals increased. This increased discharge rate was associated with a decrease in the number of patients with schizophrenia who had a sudden onset and severe deterioration or ‘catastrophic schizophrenia’ (Bleuler, 1972, 1978).

2.2. Mirror-image studies

Mirror-image studies compare similar patients before and after the introduction of antipsychotic medications. In previous reviews, we found nine studies that could be used to examine these effects (Wyatt, 1995a,b, 1991). Seven of the nine suggest that there was improvement in the long-term course of schizophrenia after antipsychotic medications were introduced in the mid-1950s. Not included in our previous reviews was a study by Opjordsmoen (1991). He reported on patients with schizophrenia and schizophreniform disorder admitted to the University of Oslo between 1946 and 1948. Half of these patients received ECT at first admission, but had to wait for antipsychotic medications until they became available 5–9 years later. These patients had a worse long-term outcome than similar patients admitted between 1958 and 1961, most of who received antipsychotic medications at first admission.

Matching patients in before and after groups is, at best, a rough approximation, and this may confound these findings. Furthermore, other advances in patient care had already begun by the mid-1950s. For example, even during the mid-1950s, there were efforts to make the large institutions where most patients with schizophrenia were treated more therapeutic, and patients who had been previously warehoused were starting to be discharged to what were, at times, more humane settings (Issac and Armat, 1990; Opjordsmoen, 1991).

2.3. Delayed-intervention studies

Delayed-intervention studies compare first-episode schizophrenic patients who received early intervention with antipsychotic medications with patients for whom the intervention was delayed. Nine fairly well-controlled studies of this nature were identified by 1996 (Astrup et al., 1962; Astrup and Noreik, 1966; Loebel et al., 1992; McEvoy et al., 1991; Szymanski et al., 1995, 1996; Waddington et al., 1995; Wyatt, 1991), and all but one of these indicates that delayed intervention leads to poorer long-term outcome. A more complete analysis (Robinson et al., 1999) of the study originally conducted by Loebel et al. (1992) added more subjects and found a relationship ($p < 0.03$) between delayed intervention and treatment response. Nevertheless, because of the number of variables tested in the paper by Robinson et al (1999), the p value could no longer be considered statistically significant. Studies that were not as well controlled have also found a connection between delaying initial treatment and treatment response (Angrist and Schulz, 1990; Wyatt, 1995a,b).

Because there has been an international effort to examine the issue of early intervention on long-term morbidity, more data are becoming available. In 1996, McGorry and colleagues (Yung et al., 1996) published findings from Melbourne, Australia showing that first-episode patients who had been psychotic for less than 28 days when treatment began had more complete recoveries at the end of 12 months of treatment than patients whose psychosis had been present for more than 28 days before treatment began.

In the last year, there have been reports from several delayed intervention studies, not all of which support the hypothesis that delayed treatment has long-term adverse effects. Johnstone et al. (1999) performed a 2.5-year follow-up of a group of patients with functional psychosis. The group consisted of some patients with a first psychotic episode and others who had had more than one previous episode. In the experimental part of the study, patients were randomly assigned to an antipsychotic medication (pimozide), pimozide plus lithium, lithium, or a placebo treatment phase. As might be expected, the patients initially treated with pimozide had a more profound improvement during the 28-day experimental period than patients given other treatments. Despite using a number of evaluation techniques, at 2.5 years there were no differences in the outcomes between the groups. Nevertheless, because this study was not limited to first-episode patients, and because there is evidence that patients may become less responsive to treatment after each psychotic episode, it is not clear that these results speak directly to the issue of delays in treating first-episode patients. Also, a placebo period lasting only one month, the time used here, particularly in patients who have been ill for some time, may not be long enough to produce long-term deficits (Wyatt et al., 1999).

Ho et al. (2000) examined the quality of life of 74 first-episode patients with schizophrenia six months after their initial admission to the hospital. They found no relationship between the length of untreated psychosis and 11 measures of quality of life after correcting for the number of statistical tests performed (prior to the correction, impaired relations with family members correlated with length of untreated psychosis, $p < 0.02$). In a stepwise discriminate analysis, quality of relations with family members also discriminated between those subjects with the longest and shortest duration of untreated initial psychosis when patients were divided into first and fourth quartiles, defined as the median time from full psychotic syndrome to first treatment.

Craig et al. (2000) examined the effect of untreated psychosis on 155 schizophrenic and schizoaffective patients on clinical outcome 24 months after first admission. The patients were admitted to a number of hospitals on Long Island, New York and had been treated according to the practices of the treating physicians and wishes of the patients. The median duration of untreated psychosis for patients having a complete remission was 59 days; for patients with a partial remission it was 75 days; and for patients with no remission it was 135 days. These differences, however, were not statistically significant.

An important source of potential bias in these studies is the difference between patients with an acute versus an insidious onset of illness. A number of studies (summarized by Stephens, 1970) indicate that patients with an acute onset have a better prognosis than patients with a more gradual onset. Because of the often florid nature of acute symptoms, it is likely that

such patients would receive treatment more quickly. The study by Loebel et al. (1992) attempted to control the type of onset — gradual versus sudden — and found that those patients who had been ill longer, as measured by either the time elapsed between their first prodromal or first psychotic symptoms and their first treatment, had a worse outcome. The time elapsed between the onset of prodromal and the onset of psychotic symptoms was not related to outcome. Control for premorbid functioning was also accounted for in a recent study by Larsen et al. (2000). Both poor premorbid functioning and long duration of untreated psychosis were significantly correlated with more negative symptoms and poorer global functioning at follow-up. Long duration of untreated psychosis was also significantly correlated with an increase in positive symptoms. Even after controlling for other factors, including premorbid functioning and gender, duration of untreated psychosis was a strong predictor of outcome.

Finally, one more recent delayed intervention study supports the concept that early intervention decreases long-term morbidity (Drake et al., 2000). Using a modelling technique, they found that duration of untreated psychosis has its strongest effect in the initial months of psychosis. For example, in their model, reducing the time of untreated psychosis from six months to one month produced the same effect as reducing the duration of untreated psychosis from six years to one year.

2.4. Contemporaneous control studies

Contemporaneous control studies compare patients who received treatment with antipsychotic medications with patients who received a non-somatic treatment. Although these studies should provide the best information about the role of early intervention on the long-term morbidity of schizophrenia, they are associated with their own set of confounding issues. Furthermore, because they intentionally withhold medication for some length of time, they would today be considered unethical (the withholding of medications from non-psychotic patients who are in prodromal phases of the illness is a separate issue and will be addressed elsewhere in this volume). Most of these studies were organized because the experimenters felt that their version of psychosocial treatment had an advantage over antipsychotic medications. Often, considerable attention was paid to patients receiving the psychosocial treatment, while patients receiving antipsychotic medications were given ‘usual care’, which was often wholly inadequate. Follow-up treatment, for example, was usually not equivalent for the two groups — there was much greater continuity of care, and perhaps caring, given to those patients assigned to the psychosocial treatment groups. Patients treated with antipsychotic medications were often discharged sooner and to less adequate treatment facilities than the patients who received the psychosocial treatment. It is also possible that some of the psychosocial treatments themselves might have produced benefits similar to those of antipsychotic medications.

The most important and rigorous of the contemporaneous control studies was carried out by May and colleagues (May et al., 1976a,b, 1981). A re-analysis of these data found that antipsychotic medications given to first-episode schizophrenic patients improved the long-term outcome of such patients when compared with those patients initially treated by milieu- or psychotherapy (Wyatt et al., 1997).

3. Conflicting evidence from recent studies

Most of the studies summarized before support the hypothesis that early intervention with antipsychotic medications positively affects the long-term outcome of schizophrenia. Nevertheless, few of the studies described above were specifically designed to address the issue of whether early intervention benefits first-episode patients. The issue becomes even more complicated when looking at studies where schizophrenia is well established. The effects of early intervention, at least in established schizophrenia, appear to be relatively weak. For example, in the recent community-based study by Craig et al. (2000), the results did not reach statistical significance, despite the fact that patients who had not gone into remission had a median time of untreated psychosis of 135 days, and those who had a complete remission had a median period of untreated psychosis of 59 days. The potentially statistically significant results of Ho et al. (2000) and Robinson et al. (1999) were washed out by the need to correct for the number of analyses performed in each study.

Evidence from recent studies suggests that if there is a weak effect in patients with established illness, it could indicate that there are individuals for whom early intervention is important; however, in the typical treatment setting and typical patient, a great many factors, in addition to early intervention, contribute to outcome. Some factors affecting outcome include gender, obstetric complications, having severe hallucinations and delusions, having poor attention at the time of the first admission, and the development of parkinsonism while being treated with antipsychotic medications (Robinson et al., 1999).

When treatments are not standardized, other factors could contribute to variance. For example, in community-based studies (Craig et al., 2000; Ho et al., 2000), choice of medication, medication dose, and continuity of medication use would be expected to vary considerably from patient to patient and could have major effects on outcome. Another potentially important issue is that the patients in the most recent studies — for instance, those of Ho et al. (2000) and Craig et al. (2000) — had to meet formal criteria for schizophrenia, indicating (depending upon the criteria used) that psychotic symptoms had been present for some minimum time and that the psychotic symptoms were unambiguous. Thus, if early intervention were very successful in preventing deterioration, patients would not have progressed to the point where they might meet the criteria for a diagnosis of schizophrenia.

Many of the issues discussed above can confound the investigation of early versus earliest intervention. Thus, performing studies that strive to intervene early in schizophrenia with the objective of decreasing long-term morbidity requires some degree of optimism, based in part on the results of the studies to date, but also based on the belief that the deterioration and other symptoms associated with long-term illness are not inevitable. One study found that only 6.6% of a sample of schizophrenics experiencing their first episode of illness were treatment-resistant (Edwards et al., 1998). And although some patients have slight deviations from normalcy or subtle impairment prior to any signs or symptoms of illness (Lieberman, 1999a,b; McGlashan, 1996), for most patients there is no evidence of the illness' expression until the prodromal signs and symptoms appear. Thus, some optimism seems warranted.

4. Efforts at detection: the immediate past and future

4.1. Intervention in the prodrome

Although the community mental health centres of the 1960s and 1970s were theoretically using techniques that provided early detection, there was little science to guide the professionals working in the system and, at times, the clinics seemed to operate more for the convenience of the community mental health worker than for the potential patient (Wyatt and DeRenzo, 1986). A number of studies indicate that long delays existed before individuals received treatment (Johnstone et al., 1986), and that many obstacles stood in the way of treatment (Larsen et al., 1998). For example, of 253 English patients identified with schizophrenia, 46 cases required nine or more contacts with professionals before they were admitted to the hospital. In the same study, 52 of those 253 patients had threatened the lives of others prior to their first admission (Humphreys et al., 1992). In a study from Melbourne, Australia, McGorry and colleagues (1996) found that half of patients with schizophrenia saw a general practitioner, but only 5% got to a mental health specialist because of a referral from a general practitioner.

Because of its potential importance, another aspect to early intervention includes the identification of those at risk and, because some of these individuals would not yet be identified as having schizophrenia, the use of milder forms of treatment. The first study to look at whether a proactive community-based treatment program could alter the course of schizophrenia was that of Falloon (Falloon et al., 1996; Falloon, 1992). Stress reduction and education, as well as the use of short-term, low-dose antipsychotic medications, were used for targeted dysfunctional or dysphoric prodromal symptoms such as sleep disturbances, agitation, tangled thinking, or a preoccupation with an odd idea. In this semi-systematic study, Falloon and colleagues found a significantly lower number of new cases of full-blown schizophrenia compared with historical data for the same catchment area.

McGorry and colleagues (1996) in Melbourne, Australia compared a group of first-admission patients with schizophrenia who participated in a very rich treatment program (Early Psychosis Prevention and Intervention Centre [EPPIC]) with similar patients treated just a few years earlier who had received the standard treatment at that time (pre-EPPIC patients). The treatment response and one-year outcome for the EPPIC group was better than for the pre-EPPIC patients, even though in this preliminary study there was no difference between groups in duration of untreated psychosis. In another study conducted by EPPIC, first-admission patients with psychosis were followed for three months. At the end of the three-month period, 80% had responded to medications, 63% were in remission, and most had experienced fewer and shorter hospitalizations than expected (Power et al., 1998). Furthermore, in Rogaland County, Norway a similar early detection program reduced the duration of untreated psychosis from 114 weeks to 19 weeks (McGlashan, 1999). Both programs used education and anti-stigmatizing campaigns about the signs of early psychosis targeted at health care providers, educators, and the public.

5. Conclusion

The view that early treatment benefits patients with first-episode schizophrenia has not been wholly accepted by the psychiatric community, although few would disagree that aggressive treatment of first-episode patients with antipsychotic medications, stress reduction, and education are useful in decreasing the immediate consequences of acute psychosis. Efforts at early detection stem largely from the lessons learned through what have become ‘traditional’ early intervention studies and generally presuppose that, because early intervention is helpful, earlier intervention will be even more helpful. Initial results from several international studies, presented above, support this notion. Prolonged duration of untreated psychosis has also been associated with a poorer quality of life, independent of positive and negative symptoms, at the time of first patient contact (Browne et al., 2000).

Intervening early in the course of schizophrenia is qualitatively different from preventing a future case of schizophrenia, or even from identifying the very earliest symptoms. Nevertheless, these methods may ultimately work together to prevent future cases of schizophrenia and to reduce morbidity in the ones that continue to develop. Evidence from the four types of early intervention studies described above, and from community efforts at early detection and treatment, provides tantalizing clues that early intervention in schizophrenia is both possible and beneficial.

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