Evidence-Based Treatment for First-Episode Schizophrenia?

Evidence-based treatment is today's clarion call for psychiatry. At its best, this standard leads to rejection or acceptance of treatments on the basis of scientific documentation of efficacy. In schizophrenia, this standard has almost eliminated treatment with psychotherapy to the exclusion of pharmacotherapy, and exploratory/insight-oriented psychotherapy and treatment based on psychogenic etiology have given way to psychosocial treatments with scientific documentation of efficacy (1–3). But the evidence-based standard has not created the political clout (e.g., service system finance) or professional clout (e.g., critically informed mental health professionals) to assure broad application of proven treatments (4, 5).

Clinical trials, the primary source of data for evidence-based therapeutics, are routinely available for pharmacotherapy. Food and Drug Administration regulatory procedures assure that drugs approved for the treatment of schizophrenia have documentation of efficacy. What follows is complicated. The physician must decide which drug, at what dose, in what combination, for what period of time, for which aspects of illness, whether to use off-label, and at what risk and cost. This decision is case specific, is modified over time, and must weigh patient wishes and alternative approaches. Empirical data are inadequate.

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There is an especially large gap between clinical trial data and treatment recommendations for first-episode schizophrenia. In this issue, Gitlin et al. now add important descriptive data to the three clinical trials addressing treatment following an initial episode of psychosis (6–8). Research on medication withdrawal is crucial, for virtually all first-episode patients will have time without medication. Rates of patient nonadherence are very high, even with new-generation antipsychotic drugs, and it is unwise to base clinical care on the presumption that a young person with an initial psychotic experience will receive continuous drug therapy for the next 50 years or so. Presently there are far too few data from clinical investigations informing doctors and patients of the consequences and best management procedures for medication withdrawal. In addition to a paucity of data, another problem is that clinical trials are concerned with group effects, and what is best for the group may not be best for the individual. Clinical trials rely on narrowly defined outcome measures in selected patients, while the treating doctor must consider all aspects of each case without exclusion of complicated cases or those with uncertain diagnoses. Drug beats placebo for relapse prevention in cohorts of first-episode patients, but the physician may, for example, have a patient whose psychosis responded rapidly to treatment and who has remained clinically stable for 6 months. This patient dislikes weight gain, attributes emotional dullness to antipsychotic medication, feels depressed, and does not wish to continue taking medication. Diagnosis is difficult in single-episode cases. What is the evidence-based recommendation?

Not long ago, experts would argue along two lines. First, psychosis is devastating and may be neurotoxic, and relapse prevention trumps all other considerations. Or, second, the minority of patients who do not have a relapsing form of illness must be identified and not exposed to long-term risks of medication. The other patients will relapse sooner or later in any case, and we have better treatment for psychosis than we do for dyskine-

sia. The former position never dealt with the implication of life-long antipsychotic drug treatment for some individuals who may not have a relapsing illness, and the latter position did not deal with medication withdrawal in cases for which clinical monitoring was inadequate. Neither dealt with the fact that one patient may have insight, be cooperative, and respond quickly to drug treatment while another may have had a rapid onset, be hostile and aggressive, and resist treatment. This state of discourse led to the equivocal 1997 APA practice guideline stating that "a patient who has had only one episode of positive symptoms and has had no symptoms during the following year of maintenance therapy may be considered for a trial period without medication" (9, p. 41).

The report by Gitlin et al. advances knowledge on pharmacotherapy of first-episode patients with schizophrenia.

1. Long-term follow-up studies (10–15) previously suggested that 15%–25% of single-episode patients would not relapse within 5 years. Gitlin et al. used a sensitive indicator of exacerbation and found that all patients showed indications of recurrence. There are two profoundly important conclusions. First, of patients clearly meeting criteria for schizophrenia, there does not appear to be a substantial minority who would maintain recovery indefinitely without medication. Therefore, the benefit of continued drug treatment appears to apply to most patients. Second, mild exacerbation can be routinely detected and effectively treated, preventing severe relapse in most cases. Therefore, the risk side of medication withdrawal is substantially reduced in most cases.
2. Antipsychotic drugs are effective for psychosis but are not broadly antischizophrenic in therapeutic action. The new generation of drugs are less likely to cause negative symptoms and cognitive impairments (compared to haloperidol in most studies), but efficacy for primary negative symptoms has not been documented (16), and controlled-study evidence for pro-cognitive efficacy (rather than reduced adverse effects) is modest (17). These aspects of schizophrenia mainly account for reduced quality of life and functional outcomes. The benefit of maintenance drug treatment is relapse prevention, not comprehensive treatment of schizophrenia.
3. New-generation antipsychotic medications provide greater variation in risks and benefits, increasing the importance of individualized therapeutic recommendations. On the benefit side, the course of depression or of hostility/aggression appears more favorable with the new-generation antipsychotic medications. On the risk side of these medications, tardive dyskinesia liability is low, but weight gain and diabetic and cardiovascular risk are often greater. The doctor must tailor her or his recommendation to the very particular circumstances of each case. In the preceding example, a new-generation drug at a low dose might be selected to reduce negative subjective experience and tardive dyskinesia risk and to improve the course of depression. Given smoking and a sedate lifestyle, selecting a drug that is not likely to increase weight or diabetic and cardiovascular risk is important.
4. The risk of prolonged and serious adverse effects of psychosis per se (e.g., neurotoxicity) has not been substantiated in medication withdrawal studies (18). The study by Gitlin et al. demonstrates the effectiveness of clinical monitoring and intervention, substantiating a clinical method for minimizing risk from medication withdrawal.

Despite an exacerbation/relapse rate of 96% within 2 years following medication withdrawal, Gitlin et al. do not recommend indefinite antipsychotic maintenance for all patients. Their rationale overlaps with the considerations listed here and also calls attention to social stigma, financial cost, and the patient's attitude toward the illness and drug treatment. They wisely note that clinically supervised medication withdrawal is safer than covert nonadherence, and a return of symptoms without medication may establish a stronger doctor-patient collaboration for drug treatment in the long term. The

choice is not between drug or no drug, but between continuous prophylactic and targeted, rapid-intervention drug treatment (19, 20).

The description of medication withdrawal effects by Gitlin et al. for this cohort of first-episode patients is generously informative, and their thoughts regarding the implications for clinical care are complex and wise. Clinicians make decisions for each individual patient. Group results from study cohorts are invaluable for primary treatment efficacy questions, but evidence-based therapeutics depend on knowledgeable and wise clinicians to translate data into individualized treatment.

References

1. Lehman AF, Steinwachs DM: Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. Schizophr Bull 1998; 24:1–10
2. Mojtabai R, Nicholson RA, Carpenter BN: Role of psychosocial treatments in management of schizophrenia: a meta-analytic review of controlled outcome studies. Schizophr Bull 1998; 24:569–587
3. Bellack AS: Rehabilitative treatment of schizophrenia, in Comprehensive Care of Schizophrenia: A Textbook of Clinical Management. Edited by Lieberman JA, Murray RM. London, Martin Dunitz, 2001, pp 109–120
4. Lehman AF, Steinwachs DM: Patterns of usual care for schizophrenia: initial results from the Schizophrenia Patient Outcomes Research Team (PORT) Client Survey. Schizophr Bull 1998; 24:11–20
5. Young AS, Sullivan G, Burnam MA, Brook RH: Measuring the quality of outpatient treatment for schizophrenia. Arch Gen Psychiatry 1998; 55:611–617
6. Kane J, Rifkin A, Quitkin F, Devdutt N, Ramos-Lorenzi J: Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. Arch Gen Psychiatry 1982; 39:70–73
7. Crow TJ, MacMillan JF, Johnstone EC II: A randomised controlled trial of prophylactic neuroleptic treatment. Br J Psychiatry 1986; 148:120–127
8. Robinson D, Woerner MG, Alvir JMJ, Bilder R, Goldman R, Geisler S, Koreen A, Sheitman B, Chakos MH, Mayerhoff D, Lieberman JA: Predictors of relapse following response from a first-episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999; 56:241–247
9. American Psychiatric Association: Practice Guideline for the Treatment of Patients With Schizophrenia. Am J Psychiatry 1997; 154(April suppl)
10. Johnstone EC, Crow TJ, Frith CD, Owens DGC, Done JD, Baldwin EJ, Charlette A: The Northwick Park "functional" psychosis study: diagnosis and outcome. Psychol Med 1992; 22:331–346
11. Scottish Schizophrenia Research Group: The Scottish first episode schizophrenia study, VIII: five-year follow-up: clinical and psychosocial findings. Br J Psychiatry 1992; 161:496–500
12. Vazquez-Barquero JL, Cuesta MJ, Herrera Castanedo S, Lastra I, Herran A, Dunn G: Cantabria first-episode schizophrenia study: three year follow-up. Br J Psychiatry 1999; 174:141–149
13. Schmidt M, Blanz B, Dippe A, Koppe T, Lay B: Course of patients diagnosed as having schizophrenia during first episode occurring under age 18 years. Eur Arch Psychiatry Clin Neurosci 1995; 245:93–100
14. Gupta S, Andreasen NC, Arndt S, Flaum M, Hubbard WC, Ziebell S: The Iowa Longitudinal Study of Recent Onset Psychosis: one-year follow-up of first episode patients. Schizophr Res 1997; 23:1–13
15. Linszen D, Dingemans P, Lenior M: Early intervention and a five year follow up in young adults with a short duration of untreated psychosis: ethical implications. Schizophr Res 2001; 51:55–61
16. Kirkpatrick B, Kopelowicz A, Buchanan RW, Carpenter WT: Assessing the efficacy of treatments for the deficit syndrome of schizophrenia. Neuropsychopharmacology 2000; 22:303–310
17. Keefe RSE, Silva SG, Perkins DO, Lieberman JA: The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. Schizophr Bull 1999; 25:201–222
18. Carpenter WT, Schooler NR, Kane JM: The rationale and ethics of medication-free research in schizophrenia. Arch Gen Psychiatry 1997; 54:401–407
19. Carpenter WT, Heinrichs DW: Early intervention, time-limited targeted pharmacotherapy in schizophrenia. Schizophr Bull 1983; 9:533–542
20. Buchanan RW, Carpenter WT: Targeted maintenance treatment in schizophrenia: issues and recommendations. CNS Drugs 1996; 4:240–245

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