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Has Research Informed Us on the Practical Drug Treatment of Schizophrenia?

John M. Davis[1–3] and Stefan Leucht[4]

[2]Psychiatric Institute, Department of Psychiatry, University of Illinois at Chicago, 1601 W. Taylor Street, Room 508, Chicago, IL 60612; [3]University of Maryland Psychiatric Research Center, Baltimore, MD; [4]Klinik für Psychiatrie und Psychotherapie der TU-München, Ismaningerstr. 22, 81675 München, Germany

Has the randomized controlled trial (RCT) research over the last 56 years (since antipsychotics were discovered) informed us of the central practical questions the clinician must face on how to medicate persons with schizophrenia? In this editorial, we will consider the degree to which RCT support practice in the following areas.

1. Choice of drug and indication
2. Dose
3. Emergency treatment
4. Monitoring treatment
5. When to change drug or augment
6. Depot medication
7. Long-term changes and cost
8. Progression
9. Other considerations

Choice of Drugs and Indication

We do not know the indication (which patient for which drug) for one antipsychotic versus another or even that one may be uniquely better for an individual patient. We have some information on overall efficacy and safety, which is a different question. Some who believed second-generation antipsychotics (SGAs) as a group were more efficacious than first-generation antipsychotic (FGA) drugs were surprised when Clinical Antipsychotic Trials in Intervention Effectiveness and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study[1,2] found most were not. But this was not surprising. The results of these studies are generally consistent with both the registrational and postmarketing studies,[3–5] which have failed to demonstrate superiority for most SGAs, but agree that a few, such as clozapine and perhaps olanzapine, are more efficacious.

Dose

There is no evidence as to the correct mean dose of almost all the market of FGA drugs, but there is some evidence for SGAs.[6] Unfortunately, guidelines often ignore the evidence. There is no information about when to escalate or reduce dose. There is a limited evidence study that shows first-episode patients require less medication.[7] Many do use lower doses, but there are virtually no RCTs of first-episode patients randomized to several doses. RCTs have not established whether the sicker, the very chronic, or the treatment-resistant patients require higher dose. It is reasonable to expect that fast metabolizers, with lower plasma levels, require higher doses, but this has also been difficult to establish.

There is no evidence that a lower dose is required for maintenance than for the acute episode. For many years, guidelines recommended the progressive reduction of maintenance dose. We do have some evidence on maintenance dose for some depot drugs, suggesting more relapses with lower dose but little on the optimal oral dose for either phase.

Emergency Treatment

There is some recent evidence about how to treat a psychotic episode of severe agitation in the first day.[8] But we do not know for sure whether benzodiazepines alone, or when combined with antipsychotics, are as effective as antipsychotics only alone for days or even a week.

Monitoring Treatment

In internal medicine, the internist may adjust the dose or change drug based on monitoring clinical (eg, blood pressure) or a laboratory measure of a disease-related outcome. We do not have anything analogous in psychiatry. The hopes for biomarkers of therapeutic response

[1]To whom correspondence should be addressed; tel: 312-413-4570, fax: 312-996-7658, e-mail: jdavis@psych.uic.edu

have not yet materialized. In theory, standard rating scales such as the Positive and Negative Syndrome Scale could be administered, but this takes too much time for routine use in practice. A simple rating scale would be helpful, if well standardized. It would be particularly helpful to have RCT to show that it actually improved outcome.

When to Change Drug or Augment?

We do not know how to define treatment failure. It is possible that some seemingly responsive patient would do still better on a different dose, another drug, or augmentation.

It is possible that certain patients may do better on one antipsychotic than another. In whom, with what drug and when, should we change drugs? There is some evidence from an RCT that patients who do not tolerate a given antipsychotic will dislike the same drug when readministered.[9]

We have only limited and often contradictory evidence to guide augmentation strategies. RCTs have not informed us as to when, with what drug, and in which patient augmentation is useful. This said that there is some evidence to indicate that patients who seem to have depressive disorders superimposed on schizophrenia may respond to augmentation with an antidepressant or, if recurrent, need prophylactic antidepressants.

Depot Medication

Randomized studies of depot versus oral may not yield meaningful data because patients who do not take their medication may not volunteer for a demanding RCT.

Long-Term Changes and Cost

If a better drug was more efficacious than another drug in one or another domain, it may take a month (or even years) for this to translate into a measurable decrease in real-world outcomes such as in rehospitalizations, ability to live in a less restricted setting, getting a job, quality of life, changing medical costs, etc. We do not have a valid methodology to address most of these questions. We do have methods for determining prevention of relapse using survival methodologies, but this does not help with assessment of functional outcomes. As each patient relapses, the once initially randomized samples become no longer randomized. Consequently, the groups become progressively different on the variable of interest. This confounds the findings of long-term studies. Let me illustrate with an exaggerated example as a thought experiment: suppose a treatment for a given cancer that cured 90% and a 10-year follow-up was done on drug and placebo, 10% of the placebo-treated patients experienced spontaneous remission of the cancer but 90% rapidly died; however, 90% of the drug-treated patients recovered and 10% died. The 90% on drug and 10% remitted on placebo would be doing equally well for most of the 10 years. The cost of the placebo-treated group would be low because 90% died. Nothing saves medical costs like death. Outcome assessment would be meaningless because the groups are now nonrandom for most of the trial. This is a systematic error.

Progression

There is evidence to suggest that schizophrenia progresses after the first episode to worsen over several years. Can all drugs reduce progression? Are some better than others at this? There is insufficient evidence from RCTs to determine whether progression can be prevented and, if so, which is the best choice of drug.

Other Considerations

One of the functions of evidence-based medicine is to remind us of the absence of evidence. Some of the areas of ignorance can be answered by traditional randomized studies; others require different methodologies. Some writers claim that their recommendations are evidence based but actually state their opinion in the absence of evidence or the presence of evidence contradicting their conclusions. ''Not studied'' does not indicate ''disproved.'' Indeed, everyday issues addressed in clinical practice require integration of general knowledge rather than specifically relevant evidence for RCTs. The clinician's expertise is based on general knowledge and experience. The art of medicine is essential even in the day of evidenced-based practice.

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