Peter F. Buckley, MD, is Professor and Chairman in the Department of Psychiatry and Health Behavior at the Medical College of Georgia in Augusta.

A senior clinical editor for Advanced Studies in Medicine (ASiM) interviewed Dr. Buckley to discuss choices of antipsychotic medications and their patterns of use in treating patients with schizophrenia.

ASiM: In a recent article that you wrote for Current Opinion in Psychiatry, you mention that the choices of antipsychotic medications and their patterns of use in treating patients with schizophrenia are undergoing profound and rapid change. Why are these changes taking place and how does it impact clinicians today?

Dr. Buckley: I think that this is a period of dramatic change for several reasons. In a relatively short period of time we have seen a plethora of new antipsychotic agents. Before we became comfortable with our understanding of clozapine (as a watershed new medicine between first- and second-generation antipsychotics), we had a host of other antipsychotic agents essentially become available sequentially. Because of the number of new medicines that became available in a short period of time, this is a rather rapid change for any area.

The complexity of treatment effects in terms of drug mechanisms of action is noteworthy—they are not simply "me too" agents. Each of them has different nuances to the receptor and dosing profile and mechanism of action. Therefore, this too has changed within a short period of time.

The drugs appear to have broader effects than those effects of the older antipsychotic agents. They may be doing a little more of the same, but they are also treating other aspects of the illness that earlier drugs weren't reaching in terms of improving cognitive and more of the depressive symptoms and perhaps other comorbid features.

The other area of rapid change is that the shift in practice from first- to second-generation antipsychotic agents was predicated on better efficacy and also better tolerability. The key measure of tolerability at that time was, in particular, extrapyramidal side effects and tardive dyskinesia. Now the field has changed; they are lesser considerations as we deal with issues related to weight gain, diabetes, and metabolic disturbances. Overall, over a 10-year period, all of this equates to a relatively profound change in terms of choice, complexity, efficacy, and tolerability.

ASiM: If this is change so profound and offers so dramatic an improvement in patient care, why do we find that people still use conventional agents?

Dr. Buckley: Well, the regular use of conventional agents in the United States is fairly low. Conventional agents are typically used in acute intramuscular form in the emergency room. This is a practice that is changing, but more slowly than the other areas of psychiatry, largely because emergency room doctors are perturbed by the acute effects. Also, they have been trained to use first-generation antipsychotics, and they have a high comfort level with drugs, such as haloperidol, which will certainly work in the acute emergency
situation. Emergency room physicians don’t place the same premium that psychiatrists do on extrapyramidal side effects or acute dystonia. Therefore, that is one of the main areas where there is still disproportionate prescribing of first-generation antipsychotics.

Another area, of course, is in the long-acting antipsychotic arena where there are 3 first-generation antipsychotics and only 1 second-generation antipsychotic approved by the US Food and Drug Administration (FDA). This is also changing, but slowly, and it is likely again to undergo a shift as more of the newer agents become available in long-acting formulations. Another area of disparity between American and European psychiatry is actually that of medication prescribing. In Europe, the rate and use of first-generation antipsychotics is substantially higher than in the United States. Although economic factors and access to medications may contribute to this higher use, Europeans also have a higher level of skepticism, perhaps thinking that the newer drugs are not as efficacious as the older ones. In fact, Europeans have given great credence to some of the work from the Cochran group, which has suggested that newer antipsychotics may be only just as efficacious as first-generation agents. Europeans are a little slower to adopt a practice change from first- to second-generation antipsychotics. Indeed, this may be retarded even further by concerns about weight gain and diabetes.

**ASiM:** What is meant by “risk-benefit considerations” of antipsychotic treatment, and why are they more pronounced in severely ill patients?

**Dr Buckley:** Risk-benefit considerations relate very simply to the profile of a medication with respect to what it can do for you positively and negatively. We know that the second-generation antipsychotics are efficacious for positive symptoms, general psychopathology, and negative symptoms (although that effect may not be as robust). Similarly, they have effects upon comorbid depression and may improve cognition, albeit to a fairly modest level. In an individual patient, these drugs may have a broad array of effects. The outcome overall may be less hospitalization and enhanced overall functioning. That is the positive side.

The downside is the medication risks. Some medicines cause somnolence. Many of the newer medicines, but not all, are associated with a fair degree of weight gain. We think that these medicines may cause or bring on diabetes, perhaps not to the same extent as other risk factors, but this is still a concern. Some of the medicines have side-effect profiles different from those more general profiles. Therefore, for each patient we must weigh all of those risk factors. Now when you come to more severely ill patients, that balance is a little skewed, mainly because they are not getting the full efficacy advantage. The tilt is already inherently imbalanced because their prior treatment indicates that they don’t respond as well to medicines; they may take them in the same amounts, but they do not get the same benefit, and they still have the same exposure to risk.

Therefore, these patients tend to be treated at higher doses in an effort to boost response. In general, higher doses expose people to more side effects. This is another reason that they are disproportionately disadvantaged. Patients who are more refractory tend to be on more medications that will complicate the picture and also have increased capacity or risk for additional side effects. These are some of the reasons that in more severely ill patients, the risk-benefit consideration is more complex.

**ASiM:** You mentioned the treatment of refractory patients. Can you elaborate on that concept?

**Dr Buckley:** We used to think that at least 25% of patients were refractory to antipsychotic medications. It is somewhat more complex now in the era of second-generation antipsychotics. In the prior era of first-generation antipsychotics, 1 patient may respond to a medicine and another patient would not respond. In general, the medicines were fairly similar in mechanism of action and there wasn’t much inherent variability. Thus, we used to think that approximately 25% or more of patients were treatment refractory (ie, they didn’t respond to a trial of least 2 medications for a reasonable period of time, which we typically thought was approximately 8 weeks of treatment at standard doses). That is a little less clear now because we have a range of medications that are different among themselves. The dosing profile of each medicine is also different, thus we don’t have a true estimate of one proportion of patients that is treatment refractory within that context. We think that because these medications are a little more efficacious and hit a broader array of domains, they may be more effective for treatment-refractory patients.

When we designate a patient as treatment refractory, that has important therapeutic implications. One
ASiM: In terms of the dosage of an atypical antipsychotic, would you medicate a first-break patient differently from a patient who is chronic? On another level, would you have a different approach for a patient who is treatment refractory?

Dr Buckley: Yes, as I mentioned earlier in this interview, the dosages of newer antipsychotics is a complex issue. Because these drugs have variable mechanisms of action, it wouldn't be surprising that their dosing profiles may differ. Therefore, if we see someone in his or her first psychotic episode, we tend to use doses that are lower than the maintenance dose or those doses for treating someone with established schizophrenia. We think first-episode patients are inherently more sensitive to medications, in particular to their side effects. In the first-episode psychosis, inherently we don't know the course of the illness, thus there is a tendency to proceed carefully, gently, and slowly. You have an individual who has not had these medicines before and who will have concerns about their side effects. It is a real balance between wanting to dose appropriately, thus you get the full efficacy of these medicines, and being too aggressive, resulting in side effects that will cause patients to stop taking them. In the long run, taking medicine is the most important characteristic, thus typically we adopt the strategy for a first-episode patient that involves a lower dose.

Someone who is treatment refractory is on the other end of the spectrum. Here we try to maximize the dosing profile of each of the agents. That, in itself, is complex because it may be defined partly by the side effects and by the profile of these drugs. Thus, for instance, with risperidone we really have not moved toward using high doses for treatment of refractory schizophrenia because the extrapyramidal side-effect profile is not favorable.

However, we do use high-dose olanzapine and, in fact, are currently involved in a study looking at its efficacy and tolerability in high doses. This drug works robustly, thus the question is whether higher doses may be more efficacious. We have begun to increase the dose of quetiapine, and now some studies are looking beyond FDA-recommended doses in more refractory patients. In general, these doses appear to be better tolerated. Ziprasidone is another drug that has not been used in appropriate dosages, thus we are beginning to look at high doses (again, beyond FDA recommendations) in more refractory patients. For aripiprazole, it is a bit early and, because we are not sure yet of the dosing profile, it would be reasonable to look at higher doses. However, from what we know about this agent, there is no dosing signal that says 30 mg is better than 15 mg or that some other dose would be better than 30 mg. You can see that when we talk about the refractory patient, the picture gets a little bit more complex.

ASiM: It is often said that clinicians prescribe based on side-effect profile. Do you feel that this is the best approach to pharmacologic intervention in individuals with serious mental illness?

Dr Buckley: I think that this is a very important concept, increasingly as we enter an era in which the side effects of medicines are more complex. Weight gain, diabetes, and metabolic disturbances occur in interaction with the other risk factors that the patient may bring to the table. Although this is very important, I don't think we can get away from the overall balance viewpoint of efficacy and tolerability. Tolerability is extremely important, but so is efficacy; they are uniquely tied together. Just as the balance of efficacy and tolerability is different across each of the drugs, it may be different also with respect to dosing, thus the side-effect profile is critical to treatment choices and needs to be individualized with respect to each patient's risk-factor profile. Additionally, the clinician must accelerate the expected efficacy of that medication for the particular stage and form of illness involved.

ASiM: What does the average psychiatrist need to know about pharmacokinetics or pharmacodynamics?

Dr Buckley: You need to know enough to be careful. As each medication becomes available, it is really important to understand its pharmacokinetics with respect to drug interactions in special patient populations, such as the elderly or those patients who have hepatic or renal impairment. Pharmacogenetics is a growing research field that may be relevant to predicting treatment response and tolerability of medicines.
At the present moment, that is really not an area for clinicians to be concerned.

**AS/M: Polypharmacy has been the rule rather than the exception in the past few years. What are your thoughts on this approach and where do you think the concept is heading in the next few years?**

**Dr Buckley:** This is a very complex issue that we are certainly concerned about in the treatment of schizophrenia. Beyond psychiatry, polypharmacy is very common and perhaps practiced with a little more target. For example, with hypertension it is common to use 2 or 3 antihypertensive agents. The selection of each agent is typically driven on a different mechanism of action, thus you can synergize the effects of lowering blood pressure across many points in the pathophysiology.

We are not quite there with respect to schizophrenia. Polypharmacy tends to be the addition of one medicine that is known to work with another medicine that may be beneficial or that has a different side-effect profile, thus we are not as mechanistically driven as in other areas of medicine where this practice is high. However, polypharmacy probably has some merit in the sense that clinicians have adopted this practice because of their experiences and the benefits they have seen in their patients. It is really hard to discount that polypharmacy has a role. The dilemma for us is trying to move toward a rational practice of it. That may again be driven partly by tolerability, thus adding a medicine that may have a tolerability profile different from that of the primary drug may boost efficacy without doubling up the risk of side effects in one area. However, in terms of efficacy, you may consider adding a second drug that has a slightly different mechanism of action to boost the antipsychotic effect through 2 different mechanisms. It certainly would be nice to have some good clinical studies of polypharmacy, thus we can understand the phenomenon better. We are likely to see it move toward a refinement over the coming years in which polypharmacy is more rational and targeted.