See article by Fu et al

# Does Indication Drive Use, or Does Use Drive Indication?

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In this issue of *The Journal of Clinical Psychiatry*, Fu et al[1] report on the results of a study of paliperidone palmitate once-monthly in patients diagnosed with schizoaffective disorder. In this well-designed and well-executed trial, paliperidone monthly was used either as monotherapy or as an adjunct to mood stabilizers or antidepressants. The subjects were randomized to continue paliperidone monthly or switch to placebo after a 12-week fixed-dose stabilization phase. The groups were stratified on the basis of use of mood stabilizers or antidepressants (monotherapy vs adjunctive arms). In both groups, paliperidone monthly significantly reduced relapse compared to placebo, with placebo having a 2.5 times greater risk of relapse overall. As one might expect, the relapse risk was a bit more pronounced in the monotherapy arm compared to the augmentation arm (3.3 times vs 2.0 times). The effectiveness of paliperidone monthly was not particularly surprising, as oral paliperidone has been US Food and Drug Administration (FDA)–approved for treatment of schizoaffective disorder since July 2009. The positive results of this clinical trial led to the approval of paliperidone monthly by the FDA for the treatment of schizoaffective disorder as a monotherapy or an adjunct to mood stabilizers or antidepressants on November 13, 2014.

For any medication, FDA approval for additional indications has significant effects. It allows the medication to be marketed by the pharmaceutical company for that use, when prior to the indication this was expressly forbidden. In addition, it can remove potential roadblocks by insurers hesitant to approve a medication for non–FDA-approved indications. In some cases, a new indication dramatically broadens a medication's use, an example being antipsychotics for antidepressant augmentation. In some cases, formerly generic medications are "repackaged" as proprietary medications for novel usage. Balancing the benefits of expanded use is the possibility that a larger number of patients will be exposed to the risks of these potent compounds. A concern that is not often fully appreciated by clinicians and patients is the potential for the long-term risks of antipsychotics (eg, tardive dyskinesia). Whether these risks are equal, lesser, or even greater in illnesses other than schizophrenia has not been extensively studied.[2]

The use of paliperidone monthly for schizoaffective disorder is an important development, but it raises the following question: Were patients with schizoaffective disorder not receiving paliperidone monthly before the FDA approval? We would venture the opinion that many patients with schizoaffective disorder were prescribed and received paliperidone monthly as well as other nonindicated long-acting antipsychotics. How is that possible? First, the diagnosis of schizoaffective disorder is subject to some degree of interpretation. *DSM-IV-TR* criterion C for schizoaffective disorder states that the "symptoms that meet criteria for a mood episode are present for a *substantial* portion of the total duration of the active and residual periods of the illness."[3(p323)] What *substantial* means was left nonspecific, and one can imagine that a clinician might opt to diagnose a patient in need of a long-acting antipsychotic as having schizophrenia on the basis of a lack of substantial duration of the mood episodes. *DSM-5* schizoaffective disorder criterion C makes a deliberate change by stating, "Symptoms that meet criteria for a major mood disorder are present for the *majority* of the total duration of the active and residual portions of the illness."[4(p105)] Replacing the term *substantial* with the term *majority* denotes that the mood episode must be present for greater than 50% of the total illness duration. Likewise, using *DSM-5* criteria, clinicians might consciously or unconsciously decide that the duration of the mood episodes is a minority of the illness duration, allowing the use of a long-acting agent.

Another practice that could account for historical use of long-acting antipsychotics in schizoaffective disorder is the clinician's prerogative to use a medication for a nonindicated use. This right is based on the legal standing that, while the FDA can approve indications for medications, it does not practice medicine. This allowance leaves room for the use of medications for "off-label" conditions. In some cases, clinical off-label practice has actually driven formal investigation. A prime example is the acknowledgment that valproate/valproic acid could be used as a mood stabilizer, which was followed by formal trials of divalproate (a mixture of valproic acid and sodium valproate) confirming its efficacy in bipolar disorder, which led to its official FDA approval.[5] Off-label use potentially benefits patients who could respond to the treatment, but the trials have not been done (eg, some use of adult-indicated medications in children). However, it can lead to the prescribing of medication without a full understanding of the efficacy and, importantly, the safety in the expanded population. Increasing indications, therefore, while time consuming and expensive, establishes efficacy and ideally safety.

One of the interesting elements of Fu and colleagues' study[1] is the separation of the subjects into a group that could be treated with paliperidone monthly alone and a group who were already established prestudy on mood stabilizers and antidepressants and were allowed to remain on them. The investigators understood that schizoaffective disorder

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is often treated with multiple drugs. In our experience, treatment nearly always includes an antipsychotic with or without a medication for mood.

The FDA approval of paliperidone monthly as monotherapy and as an adjunct to mood stabilizers and antidepressants is technically correct but possibly a bit misleading. In our practice, we would more likely describe the treatment of schizoaffective disorder as antipsychotic monotherapy or with "adjunctive mood stabilizers and antidepressants." Why so particular about the wording? Understanding the diagnosis and prognosis in schizoaffective disorder leads us to this specificity. In *DSM-IV-TR* and *DSM-5,* criterion B mandates at least 2 weeks of delusions or hallucinations during which there is no mood aberration. In other words, the psychotic component must have a driver independent of the mood disorder. This independent psychotic component requires an antipsychotic, usually on a continual basis, with or without mood disorder medications. In long-term studies of individuals with schizoaffective disorder, their outcomes more closely resemble those of individuals with schizophrenia and not major depression or bipolar disorder.[6] In our clinical practice, if we were starting de novo with a patient, we would begin with an antipsychotic (and often a long-acting one if there are issues of nonadherence or partial adherence). We would add a mood stabilizer or antidepressant if continued symptoms warranted. It is significant that monotherapy with paliperidone monthly was effective in many of the patients. The study was not designed to look at whether this monotherapy could have been effective in patients who entered the study already on mood stabilizers or antidepressants. We would encourage such a study, since it could greatly simplify treatment, reduce potential additive side effects, and more accurately monitor adherence to treatment.

The results of Fu and colleagues' study are a welcome addition to the field's understanding of appropriate treatment for schizoaffective disorder. It is especially noteworthy in that the investigators took on a complex, not always agreed upon, diagnosis. Having a long-acting antipsychotic approved by the FDA has advantages for the pharmaceutical company, the clinician, and most importantly the patient. These benefits are particularly relevant in this case, as the oral formulation of the medication has been FDA approved for many years, and poor adherence is a significant hurdle in the treatment of patients with schizoaffective disorder, as noted by the authors. We would encourage other makers of long-acting antipsychotics to expand their indications and in particular study whether long-acting monotherapy might replace multiple medication use.

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