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Food and Drug Administration Perspective on Negative Symptoms in Schizophrenia as a Target for a Drug Treatment Claim

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Negative symptoms of schizophrenia are not adequately addressed by available treatments for schizophrenia. Thus, it is reasonable to consider them as a target for a drug claim. This article describes the thought process that the Food and Drug Administration (FDA) will undertake in considering negative symptoms of schizophrenia as a novel and distinct drug target. Beyond this basic question, this article identifies a number of design issues that the FDA needs to consider regarding how best to conduct studies to support claims for this target. These design issues include (1) what population to study, (2) what phase of illness to target, (3) whether to focus on the negative symptom domain overall or on some specific aspect of negative symptoms, (4) the role of functional measures in negative symptom trials, and (5) optimal designs for targeting drugs for add-on therapy or broad-spectrum agents.

Key words: schizophrenia/negative symptoms/drug development

Negative symptoms are widely recognized as a feature of schizophrenia and in fact are listed among the 5 characteristic symptoms of this disorder in DSM-IV.[1] Furthermore, currently available drug treatments for schizophrenia have not been found satisfactory for negative symptoms. Thus, there is a compelling case for considering negative symptoms of schizophrenia as a possibly distinct target for drug development. The Food and Drug Administration (FDA) often faces the challenge of considering new clinical targets for drug development, and the purpose of this article is to elaborate on the thought process that the FDA will undertake in considering negative symptoms of schizophrenia as a novel and distinct drug target. This article is not intended as a review of the evidence for or against any particular viewpoint on the relevant issues in developing drugs for treating negative symptoms; rather, its purpose is to identify those issues and provide a perspective on how the FDA would approach them.

Most approved drugs, including almost all psychiatric drugs, have claims for recognized specific diseases or syndromes, for example, multiple antipsychotic drugs are approved for the treatment of schizophrenia. These claims are focused on the disease entity, rather than on specific aspects of the entity. In 3 recent approvals, however, the FDA has granted claims for certain distinct aspects of recognized psychiatric diseases. Intramuscular ziprasidone is approved for the treatment of "agitation" in schizophrenia, and intramuscular olanzapine is approved for the treatment of "agitation" in schizophrenia and bipolar disorder. Clozapine is approved for the treatment of suicidality in schizophrenia. In addition, the FDA has in principle endorsed the view that cognitive impairment in schizophrenia[2] and the psychosis of Alzheimer's disease[3] are legitimate targets for drug development. A third type of claim that the FDA will consider is for a nonspecific symptom, that is, one that is not limited to a single disease entity. The nonspecific symptoms pain and fever are examples of this third type of claim.

In order to carve out negative symptoms of schizophrenia as a specific feature of this illness to pursue in drug development, the first challenge is to establish such symptoms as sufficiently distinct from other aspects of the illness to justify a claim that is focused only on this part of the illness. In the absence of an argument supported by data to make the case for such a narrow focus, the FDA would consider such a narrow claim "pseudospecific."[4] Such narrow claims, if not supported by data, serve only promotional purposes and are potentially misleading, in the sense that they imply advantages over other drugs in the class. In order to evaluate such a claim with regard to the question of pseudospecificity, the FDA asks a series of questions. First, are negative symptoms phenomenologically distinct from other symptoms of schizophrenia, and do they have a course that is distinct from other symptoms? Since the FDA has already endorsed cognitive impairment in schizophrenia as a legitimate drug target, a related challenge is to show that negative symptoms are distinct from cognitive impairment in

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schizophrenia. If these 2 constructs are overlapping, it weakens the case for separate claims. The FDA also considers the views of experts in the field, that is, Do schizophrenia experts consider negative symptoms a distinct aspect of this illness, and is this distinctness reflected in the diagnostic nomenclature? Although DSM-IV does not include a separate negative symptom subtype of schizophrenia, it does include "with prominent negative symptoms" as a course specifier to refer to the prominence of such symptoms during the residual phase of the illness. A critical third question is whether or not there is evidence for the differential responsiveness of different schizophrenic symptoms, that is, Do negative symptoms respond differently to drug treatment than other schizophrenic symptoms? As noted, it is a widely held view that negative symptoms do not respond well to available antipsychotic drugs, leaving many patients with residual negative symptoms after their positive symptoms have been controlled. Finally, there is the question of mechanism. If the pathophysiology of negative symptoms were understood and could be shown to be different from the physiological basis for other schizophrenic symptoms, then that would be a strong argument for the specific targeting of negative symptoms. Of course, there is not as yet an understanding of schizophrenic symptoms at a biological level, but this is also not a necessary condition to justify targeting negative symptoms in drug development.

Beyond these basic issues of defining negative symptoms and ensuring that they represent a distinct aspect of the illness, there is a host of practical issues that the FDA needs to consider in evaluating proposed development programs targeting negative symptoms. One question is what population to target. Do all schizophrenic patients need treatment for negative symptoms or only a subgroup? How are negative symptoms distributed in the schizophrenic population? Is there a continuum, or are there distinct subgroups that can be characterized as having prominent negative symptoms? In recruiting patients for a trial, how should patients be selected with regard to negative symptoms?

A related question is what phase of the illness to focus on in treatment trials. Although acute treatment trials with antipsychotic drugs often show reductions in both positive and negative symptoms, most agree that the acute setting is not the phase of the illness in which negative symptoms are most in need of treatment. There seems to be agreement that the residual phase of the illness is the most appropriate time to target treatment trials focused on negative symptoms.[5] For completeness, it may be useful to ask the question of whether or not there is benefit in treating negative symptoms that may occur in a prodromal phase in which the psychosis has not yet emerged.

It has been long accepted that there are several distinct domains of negative symptoms.[6] A drug development question arising from this diversity of domains within this construct is whether to focus on negative symptoms as a single target or to look at effects on specific domains. Can patients be sorted into subgroups based on domain-specific impairments? Can drugs be sorted into classes based on their domain-specific effects? If so, are any of these subgroups useful from a practical standpoint? Only careful preliminary work will help to address these questions on what aspect of negative symptoms to focus on for a particular drug.

Although negative symptoms, like positive symptoms, can be considered to represent a clinically relevant aspect of schizophrenia by themselves, apart from whatever effect they have on a patient's ability to function, we think it is relevant to ask how patient functioning might be expected to improve as these symptoms are effectively treated. The studies being considered for examining negative symptoms may be long enough to permit some actual improvement in this domain, a goal that may be less reasonable for more acute studies. The FDA has for several other neuropsychiatric illnesses made it a requirement that a sponsor show a benefit both on a symptomatic measure and on a global or functional measure in order to declare a study positive, for example, treatments for the cognitive impairment and psychosis of Alzheimer's disease. We have not yet reached a judgment on this question for negative symptoms, and additional data pertinent to this question would be welcome.

Negative symptoms when present are generally persistent, and it is essential that trials for establishing drug effectiveness be long-term rather than acute. A drug development program for negative symptoms may of course have trials of shorter duration that could be helpful in the planning of phase 3 registration trials. Although the designation of trial duration for a negative symptom trial is obviously arbitrary, we would propose a 6-month trial as the standard minimum duration for a definitive trial.

The optimal study design would depend on the intended benefit of the drug of interest. Drugs that have a different pharmacology than antipsychotics and are intended to specifically treat negative symptoms would optimally be studied in an add-on design. The new drug or placebo would be added on to standard antipsychotic treatment (i.e., either typical or atypical drugs) in patients whose positive symptoms are in reasonable control and stable. The new drug could be added on to a single identified standard drug, or an "all-comers" approach could be used in which patients stabilized on 1 of several standard antipsychotics could be randomized. By current policy, the single standard drug design would require that the FDA's combination policy be met, that is, it would be necessary to show that the combination of new drug and standard is superior to each drug alone. For the "all-comers" approach the FDA would require only a 2-arm trial of new drug or placebo added on to the standard, because the alternative design

of testing all combinations against all single-dose arms would not be feasible. A 6-month trial should be ethically feasible with either design because all patients would be receiving at least standard therapy.

It is more difficult to design a trial to test the effectiveness of what might be called "broad-spectrum" agents (BSA) that would be intended to treat both positive and negative symptoms. Short-term placebo-controlled trials in acutely exacerbated patients would be needed to establish efficacy in treating positive symptoms for such drugs. Residual phase trials would be needed to establish the effectiveness of BSAs on negative symptoms. There is, however, a fundamental difficulty with such a design. Long-term placebo-controlled trials in schizophrenic patients are not ethically feasible, and the only acceptable control would be a standard agent (SA), that is, either a typical or an atypical antipsychotic. Thus, 1 approach would be to achieve stable control of positive symptoms with an SA and then randomize patients to either continuation on the SA or a switch to the new BSA. A trial of this design could be long-term, but interpretation of the results would not be straightforward. The anticipated outcome would be an improvement in negative symptoms in patients assigned to the BSA and no change in negative symptoms in patients continuing on the SA. Assuming this outcome, and also continuing stability in positive symptoms and a "fair" comparison with the SA, there would be several competing explanations: (1) the BSA improves negative symptoms, while the SA has no effect on negative symptoms; (2) the BSA has no effect on negative symptoms, however, the SA actually causes or worsens negative symptoms, so that switching to the BSA leads to apparent improvement in negative symptoms; or (3) both the BSA and the SA cause or worsen negative symptoms, however, the BSA has a lesser effect on inducing negative symptoms, so that patients appear to improve when switched to the BSA. Although a clinically relevant difference between the BSA and the SA in negative symptoms in such a study would be noteworthy and could be described in labeling, it may not be sufficient to support an efficacy claim. Rather, a benefit of this type would more likely be described in the "adverse events" section, as a relative advantage of the BSA compared to the SA on a domain that might simply reflect less adverse events for the BSA.

This preliminary discussion of possible study designs makes certain assumptions, 1 in particular being the assumption that positive symptoms can be maintained in a stable state while negative symptoms are being targeted. It would be helpful to have data to address this issue, and such data will likely need to come from preliminary attempts to utilize these proposed designs.

In summary, the FDA considers negative symptoms of schizophrenia a likely acceptable target for a drug claim. However, there are a number of design issues that need to be addressed regarding how best to conduct studies to support claims for this target. These design issues include (1) what population to study, (2) what phase of illness to target, (3) whether to focus on the negative symptom domain overall or on some specific aspect of negative symptoms, (4) the role of functional measures in negative symptom trials, and (5) optimal designs for targeting drugs for add-on therapy or broad-spectrum agents. Additional data will be needed to address some of these issues.

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