

## Surrogate outcomes in neurology, psychiatry, and psychopharmacology

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*A surrogate outcome can be defined as an outcome that can be observed sooner, at lower cost, or less invasively than the true outcome, and that enables valid inferences about the effect of intervention on the true outcome. There is increasing interest in the use of surrogate outcomes of treatment efficacy measurement in investigational drug trials. However, the significance of surrogate markers of treatment outcome in neurology and psychiatry has not yet been sufficiently demonstrated. Few such markers have been adequately "validated," that is, shown to predict the effect of the treatment on the clinical outcome of interest. In this article, evidence that would support the validation of such markers is discussed. Biomarkers used during early clinical development programs of new psychotropic compounds are considered in the contexts of Parkinson's disease, affective disorder, and schizophrenia. The particular case of neuroprotective trials is exemplified by Parkinson's disease, where a biomarker substituting for a clinical measure of progression could be considered as a surrogate treatment outcome.*

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Clinicians making treatment decisions generally refer to methodologically strong clinical trials examining the impact of therapy on patient-important outcomes such as morbid end points, ie, stroke, myocardial infarction, and death, or health-related quality of life end points. These trials require such a large sample size or long patient follow-up that researchers have proposed the alternative of substituting surrogate outcomes or end points for the target event, allowing shorter and smaller trials to be conducted. This offers an apparently simpler solution to the difficulty of conducting large or long-term trials.

A surrogate outcome can be defined as an outcome that can be observed sooner, at lower cost, or less invasively than the true outcome, and that enables valid inferences about the effect of intervention on the true outcome. Surrogate outcomes or end points (also known as surrogate markers) have to be distinguished from biomarkers, although the two concepts are related. According to the Biomarker Definitions Working Group,<sup>1</sup> a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic process, or pharmacologic responses to a therapeutic intervention." According to the US Food and Drug Administration (FDA)<sup>2</sup> a "valid biomarker" is one "that is measured in an analytical test system with well-established performance characteristics and for which there is an established framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic or clinical significance of the test result." Thus, in the drug development process, biomarkers can be useful tools from the discovery stage, where they are used to investigate pathophysiologic mechanisms related to

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## Selected abbreviations and acronyms

<b>FDA</b>	<i>Food and Drug Administration</i>
<b>fMRI</b>	<i>functional magnetic resonance imaging</i>
<b>PET</b>	<i>positron emission tomography</i>
<b>PSA</b>	<i>prostate-specific antigen</i>
<b>REM</b>	<i>rapid eye movement</i>
<b>SPECT</b>	<i>single photon-emission computed tomography</i>

either diagnosis or prognosis of a disease, through the later stages of clinical development. Biomarkers can be used in preclinical studies to confirm in vivo activity as well as to investigate dose-response relationships. During early clinical development programs (phase 1 and 2a), biomarkers are used to evaluate activity and to develop pharmacokinetic-pharmacodynamic relationships. In phase 3 and 4 studies, biomarkers are useful tools for stratifying study populations.

Surrogate outcomes are biomarkers that fit the following definition: “a biomarker that is intended to substitute for a clinical end point. A surrogate end point is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.”<sup>1</sup> This definition of a surrogate outcome illustrates the key difference versus the role of the biomarker. A biomarker can be used as a surrogate outcome if it can reasonably predict a clinical benefit. Thus, although a surrogate outcome is by definition a biomarker, in fact, a very small minority of biomarkers meet the standard of a surrogate outcome. Before 1991, regulatory agencies such as the FDA used surrogate treatment outcomes in limited settings, mainly in the cardiovascular area. For example, antihypertensive drugs have been approved for marketing based on their effectiveness in lowering blood pressure, and cholesterol-lowering agents have been approved based on their ability to decrease serum cholesterol, not on the direct evidence that they decrease mortality from cardiovascular diseases. In 1991, during the acquired immune deficiency syndrome (AIDS) epidemic, surrogate outcomes were utilized for the first time as a viable path toward regulatory approval. Indeed, an important milestone was the use of CD4 cell count as a surrogate marker, because of its predictive value for outcome. This led to the approval of didanosine for the treatment of HIV. In 1992, the FDA formulated a new regulatory process, often referred to as “accelerated approval,” under which marketing approval can be provided for interventions that have been shown to have compelling effects on a validated surrogate treatment outcome.

At the present time, there are well-defined procedures in the FDA in which such approvals are routinely examined<sup>2</sup>; for example, some anticancer treatments have been approved under the accelerated approval regulations.<sup>3</sup> In these cases, drugs tested in patients refractory to available treatments are approved on the basis of their effects on tumor size, as assessed by imaging. The labeling adopted at the time of the approval indicates that the approval was based on the effects of the treatment on tumor size, without evidence of an effect on other clinical variables. It is only when subsequent studies demonstrate an effect on clinical outcome that the labeling is changed to include a description of the documented effect on survival.

In the field of drugs acting on the central nervous system (CNS), no treatments for neurologic or psychiatric diseases have been approved to date on the basis of an effect on a surrogate outcome. One obvious reason for this is the fact that no surrogate outcomes have been validated until now; this will be discussed in the next section.

## Surrogate outcome validation

The presence of a correlation does not suffice to justify the replacement of a true clinical outcome by a surrogate marker of this outcome. Indeed, a surrogate outcome might not involve the same pathophysiologic process that results in the true clinical outcome. In oncology, an elevated level of a tumor marker such as prostate-specific antigen (PSA) in prostate cancer is the indication of an advanced tumor stage, and is clearly correlated with morbidity/mortality risks. However, PSA is not the mechanism through which the disease process influences the clinical outcome. It is thus questionable whether treatment-induced changes in this marker accurately predict treatment-induced effects on the clinical end points.<sup>4,5</sup> General guidelines for the interpretation of clinical trials using surrogate outcomes have been proposed.<sup>6</sup> In a recent paper, Fleming<sup>7</sup> suggested a four-level hierarchy for outcome measures.

*Level 1* is a true clinical efficacy measure, and includes those outcomes that directly reflect real benefits for the patient; for example, reducing the risk of stroke could be a surrogate for reducing the risk of death.

*Level 2* is a validated surrogate outcome for a specific disease setting and class of intervention. This outcome, while not directly representing tangible clinical benefits, can be used to reliably predict the level of such benefits.

An example is blood pressure reduction as a surrogate risk for stroke, for a well-studied class of antihypertensive agents.

*Level 3* is a nonvalidated surrogate outcome, yet one established to be reasonably likely to predict clinical benefit for a specific disease setting and class of intervention. “Reasonably likely” implicates considerable clinical evidence that the effect of the intervention on the surrogate outcome measure (i) will accurately represent the effect of the intervention on what is thought to be the predominant mechanism through which the disease process induces tangible events; (ii) does not have important adverse effects on the clinical efficacy end point that would not be detected by the outcome measure; (iii) is consistent with the effects on the true clinical outcome; and (iv) is sufficiently strong and durable that it is reasonably likely to product meaningful clinical benefits on clinical efficacy measures. Illustrations of this level 3 of outcome measures would be a reduction in viral load to an undetectable level for 6 months in patients with advanced HIV infection.

*Level 4* is a correlate outcome that is a measure of biological activity, but that has not been established to be at a higher level in this four-level hierarchy for outcome measures; biological markers, such as PSA, that almost certainly do not represent the biological mechanism through which the disease process induces clinically tangible events, would tend to be at level 4.

Marketing approval under the accelerated approval process can be provided for interventions having compelling effects on biological markers that are at least at level 3 in the hierarchy. In the field of drugs acting on the CNS, to date no compounds have been approved with the accelerated approval procedure on the basis of an effect on a surrogate outcome. This highlights the lack of strongly validated (ie, level 1, 2, or 3) surrogate outcomes in the field of neurology and psychiatry. The following sections will focus on definitions, applications, successes, and failures of biomarkers in Parkinson’s disease, affective disorder, and schizophrenia, although similar examples could be found for many other neurological or psychiatric disorders.

### Neurology: Parkinson’s disease

Parkinson’s disease is a progressive neurodegenerative disorder characterized by rigidity, bradykinesia, postural instability, and tremor. Clinical decline reflects the ongoing

degeneration of dopaminergic neurons. Development of specific biomarkers for Parkinson’s disease may be useful at the onset of neurodegeneration, the onset of disease, and/or to mark disease progression. At present, the most mature surrogate measures for Parkinson’s disease are based on the functional imaging of dopaminergic neurons with dopamine transporter ligands on the measures of dopamine metabolism with fluorodopa.<sup>8,9</sup> 2- $\beta$ -Carbomethoxy-3- $\beta$ -(4-[<sup>125</sup>I]iodophenyl)tropane (<sup>125</sup>I-b-CIT), a single photon-emission computed tomography (SPECT) radioligand that binds to the dopamine transporter on the presynaptic dopamine terminal,<sup>10</sup> has been most extensively evaluated as a potential surrogate outcome in Parkinson’s disease. It has been reliably shown to distinguish healthy control subjects from parkinsonian patients.<sup>11</sup> Moreover, longitudinal studies reveal an annual 6% to 10% reduction in striatal dopamine transporter as measured by <sup>125</sup>I-b-CIT uptake in early Parkinson’s disease, with a slower decline in more advanced disease.<sup>9,12</sup> However, the results of CALM-PD trial and the ELLDOPA trial contradicted these results. In the CALM-PD trial, subjects with early Parkinson’s disease requiring dopaminergic therapy were randomized to either initial pramipexole or initial levodopa.<sup>13</sup> A subgroup of patients (n=28) were studied in terms of rate of striatal dopamine transporter loss as measured by SPECT <sup>125</sup>I-b-CIT uptake.<sup>14</sup> Results show that, over the course of 46 months, the pramipexole-treated patients showed a 16% decline in striatal uptake compared with 25% in the levodopa group. The biomarker advantage of pramipexole, however, did not translate into a clear, clinically meaningful advantage. Indeed, although patients on pramipexole had a lower incidence of complications, patients randomized to initial levodopa had an early and sustained improvement in function, and less somnolence and edema. In the ELLDOPA trial<sup>15</sup> during which three increasing doses of levodopa were compared with placebo in patients with early Parkinson’s disease not requiring dopaminergic therapy, discordant results were noted between the clinical outcomes and the neuroimaging end point. Analysis of the <sup>125</sup>I-b-CIT outcome suggested a trend toward a more rapid decline in striatal dopamine transporter in individuals on the highest doses of levodopa, but the largest clinical improvement was observed in the levodopa group, in the direction opposite to what would be predicted on the basis of the imaging marker. These results corroborate those of the CALM-PD trial, and indicate that the SPECT <sup>125</sup>I-b-CIT

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biomarker advantage did not translate into a clinically meaningful advantage.

Studies using  $^{18}\text{F}$ -fluoro-L-dopa (F-dopa) positron emission tomography (PET) as a surrogate outcome of Parkinson's disease treatment show similar negative results. The accumulation of these radioactive dopamine metabolites within the striatum, and evidence correlating their reduction with clinical and pathologic measures,<sup>16-18</sup> make F-dopa PET a potential surrogate outcome for treatment assessment. In the REAL PET trial, 2 years after starting treatment, a 13% decline in F-dopa uptake was seen in the ropinirole group compared with a 20% decline in the levodopa group.<sup>19</sup> However, patients treated with levodopa had significantly greater functional improvement and fewer side effects (excepting dyskinesia), suggesting that F-dopa PET did not meet criteria for a surrogate outcome of treatment efficacy. Additional concerns regarding the ability to utilize PET as a marker of therapeutic efficacy come from studies evaluating the safety and efficacy of fetal tissue transplantation.<sup>20-22</sup> In these studies, a significant increase in F-dopa uptake was demonstrated in patients receiving fetal tissue transplantation. Regrettably, functional improvement was not clearly established, and a significant proportion of treated subjects in both studies developed disabling dyskinesias. This is a clear example of a case where unexpected consequences of an intervention, not detected by a potential surrogate outcome, resulted in patient harm.

The negative results of these trials have raised questions regarding the use of biomarkers in Parkinson's disease. How can drugs affect a biomarker that suggests a slowing of disease progression in the absence of symptomatic benefits? How should symptomatic benefits in the absence of disease-modifying effects be weighed against modest neuroprotective effects in the absence of symptomatic benefits? Are biomarkers any better than clinical measures?

Some of these questions are being addressed in neuroprotective trials for Parkinson's disease. The rationale for these trials relies on the fact that *in vitro* and *in vivo* studies have established that there is abnormal oxidative stress in Parkinson's disease.<sup>23-25</sup> The link between this particular disease mechanism and the clinical symptoms of the illness, however, is weak, and the goal of the trial is to detect no change in clinical status; even a worsening in clinical status could be considered a success if the rate of worsening is slower than expected. On the other hand, an improvement in clinical status is considered as a

potential confounding factor since it may not relate to the neuroprotective potency of the drug but, for instance, to direct effects on the synaptic transmission. This is illustrated by the DATATOP study,<sup>26</sup> a trial designed with the hypothesis that deprenyl, a monoamine oxidase B inhibitor, the antioxidant  $\alpha$ -tocopherol, and the combination of the two compounds, might slow the clinical progression of the disease. The results showed that patients on deprenyl were found to be less likely to require dopaminergic therapy over time, a finding that could be interpreted as evidence of a neuroprotective effect in cases of unaltered clinical status. However, the reason for the difference was that deprenyl produced a small but statistically significant symptomatic benefit, casting doubts about its neuroprotective effect.<sup>27</sup> Accordingly, the DATATOP study demonstrates that, in trials assessing the effects of a neuroprotective drug, clinical measures cannot be considered as a gold standard for measuring disease progression. In this particular case, a biomarker directly reflecting disease progression could be substituted for a clinical measure of progression.

## Psychiatry: affective disorder and schizophrenia

Clinical outcome measures in psychiatry provide several challenges for drug developers. Periods of several weeks or longer can be necessary to detect a response. Often, assessments are obtained from rating scales, which are based on psychometric, rather than pathophysiological, principles. Moreover, placebo response rates are high for many indications. Surrogate measures be applied to overcome these difficulties, but research in this field is still in its infancy. One may acknowledge that, compared with some neurological diseases such as Parkinson's disease, illness-specific biomarkers are more poorly defined in psychiatry. In this context, defining surrogate treatment outcomes in psychiatry is premature to say the least. At the present time, only a few biomarkers have been proposed as surrogate outcomes for screening of new drugs in early clinical phases. Accordingly, this discussion is focused on biomarkers of potential interest.

### Affective disorder

Affective disorder is characterized by episodes of depression and in some cases, of mania, that recur and remit repeatedly and cause shifts in a person's mood, energy,

and ability to function. In the most severe form of affective disorder, ie, bipolar disorder, patients experience cycling of moods that usually swing from being overly elated or irritable to sad and hopeless and then back again, with periods of normal mood in between. Unequivocally validated biomarkers for affective disorder are sparse; there are, however, studies suggesting that measurement of stress hormone regulation processes, of rapid eye movement (REM) sleep or of functional magnetic resonance imaging (fMRI) activation of limbic areas could represent valuable surrogate outcome of pharmacological antidepressant activity. Stress-related dysfunctional neuroendocrine regulation implicating the corticotropin-releasing hormone (CRH) system has been consistently demonstrated in major depression,<sup>28,29</sup> and it has been proposed that neuroendocrine dynamic challenge tests such as the combined dex/CRH test serve as a screening tool to demonstrate the antidepressive effects of new compounds in clinical drug trials.<sup>30,31</sup>

Indices of REM sleep disinhibition, such as shortened latency to REM sleep and increased density of ocular movement during REM sleep, have been proposed as a familial sleep biomarker for increased risk of developing depression.<sup>32</sup> Indeed, many studies, recently reviewed,<sup>33</sup> suggest that REM sleep disinhibition could reflect a dysfunction of the monoaminergic system involved in the pathophysiology of affective disorder. Drugs increasing noradrenergic or serotonergic functions inhibit REM sleep, a property shared by most antidepressant drugs. Consequently, REM sleep inhibition has been proposed as a potential biomarker of the antidepressant activity of a compound.<sup>34,35</sup>

Dysfunction of the prefrontal cortex, including the ventral anterior cingulate gyrus, has been implicated in anhedonia, exaggerated response to stress, abnormal response after presentation of mood-lowering stimuli, serotonergic challenges (such as tryptophan depletion paradigms), or selective serotonin reuptake inhibitor (SSRI) administration (reviewed by Hassler et al<sup>36</sup>). Changes in anterior cingulate function during affective facial processing associated with symptomatic improvement indicate that such an fMRI activation paradigm may be a useful surrogate outcome of antidepressant treatment response.<sup>37</sup> Another area of interest whose dysfunctional activation could serve as a surrogate outcome of antidepressant activity is the amygdala. Affective disorders have been characterized by an increased basal metabolism of the amygdala<sup>38</sup> that seems to relate to hypercortisolism and REM sleep abnor-

malities.<sup>37</sup> Increased amygdala reactivity in response to fearful stimuli has been observed in healthy individuals with a susceptibility to affective disorders.<sup>39-41</sup> Moreover, a recent study in healthy volunteers showed that antidepressant administration decreases amygdala responses to the presentation of fearful stimuli.<sup>42</sup> This indicates that the amygdala response to fearful stimuli, even in healthy subjects, could represent a surrogate outcome of the pharmacological effects of antidepressants.

### Schizophrenia

Schizophrenia is a chronic psychiatric illness manifested by characteristic and severe distortions of thinking and perception, and by inappropriate or blunted affect. Symptoms of schizophrenia may be divided into positive symptoms (including hallucinations, delusions, and disorganized speech and behavior), negative symptoms (including a decrease in emotional range, poverty of speech, loss of interests, and loss of drive) and cognitive symptoms (including deficits in attention and executive functions such as organizational ability and abstract thinking). The diagnosis is made from a pattern of signs and symptoms, in conjunction with impaired occupational or social functioning. As for affective disorder, there are, at the present time, no surrogate treatment outcomes for schizophrenia. Some biomarkers have been proposed as tools for the development of new antipsychotic drugs, and will be further discussed.

Abnormal evoked response electroencephalography (EEG) potentials have been shown to characterize patients with schizophrenia, and are suggested to reflect disturbances of neuropsychological functioning. In this model, it is believed that schizophrenia patients are overwhelmed by sensory input that they have trouble organizing, due to a deficit in the filtering or the gating process of extraneous sensory stimuli.<sup>43,44</sup> Among the several methods that have been used to investigate this putative deficit in inhibitory neuronal processing, we will focus on the two most widely used techniques, P50 auditory sensory gating and the prepulse inhibition of the acoustic startle response. Abnormal P50 and prepulse inhibition responses have been observed in patients with schizophrenia and in their families.<sup>44,45</sup> The P50 is a small-amplitude, positive event-related potential that occurs about 50 msec after an auditory stimulus. Repeated pairs of clicks, separated by about 500 msec, typically elicit an initial excitatory response followed by a diminished response, because the inhibitory

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mechanism activated by the first stimulus interferes with the excitatory response to the second stimulus. The percentage reduction in the amplitude of the P50 response from the first to the second click is the dependent variable labeled "P50 suppression." Significantly lower suppression is found in schizophrenia patients.<sup>44-47</sup> Interestingly, treatment with clozapine, but not with conventional antipsychotic drugs such as haloperidol, reverses this deficit.<sup>48</sup> Moreover, subsequent studies have shown that other atypical antipsychotic medication did not share this property with clozapine<sup>49</sup> and that improvement in P50 sensory gating was a predictor of clozapine response in schizophrenia patients.<sup>50</sup> These findings suggest that P50 could be a valuable biomarker for the development of new antipsychotic agents, given the fact that clozapine is clinically more effective in a significant proportion of schizophrenic patients refractory to other drug treatment.

Another auditory electrophysiological parameter assessing sensorimotor gating is the prepulse inhibition of the acoustic startle response. It refers to the ability of a weak (prepulse) stimulus to transiently inhibit the reflex response to a closely following stronger (pulse) stimulus. Prepulse inhibition deficits have been observed in patients with schizophrenia<sup>44,45</sup> including in drug-naïve patients.<sup>51,52</sup> In rats, prepulse inhibition is disrupted by systemic administration of dopamine agonists, serotonin agonists, or glutamate antagonists, and this paradigm has been proposed as an animal model for predicting antipsychotic activity of novel compounds.<sup>53</sup> As for P50

suppression, there is preliminary evidence suggesting that, in contrast to other antipsychotic drugs including atypical antipsychotics, clozapine treatment improves the prepulse inhibition deficits of schizophrenic patients.<sup>54</sup> This indicates that indices of sensorimotor gating deficit measured by either P50 or prepulse inhibition paradigms are interesting biomarkers for the development of new clozapine-like antipsychotic drugs.

## Conclusions

At this time, the significance of surrogate markers of treatment outcome in neurology and psychiatry is not yet sufficiently understood; moreover, no surrogate markers have been validated to be used as a sole primary measure of effectiveness in trials of investigational drugs. Although unvalidated (in the sense described earlier) surrogate outcomes have been successfully used for anticancer or anti-AIDS drugs, a sponsor who wishes to obtain approval on the basis of the effect of a drug on such an unvalidated marker will need to adequately demonstrate that any such effect will be "reasonably likely" to predict the desired clinical effect. Evidence supporting this remains to be found. It may include both animal and human data, and requires further investigation into the pathophysiology of the condition under study and into the pharmacology of the drug under study. □

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### Mediciones sustitutas en neurología, psiquiatría y psicofarmacología

Una medición sustituta se puede definir como un parámetro (marcador) mensurable en forma precoz, a un menor costo y de manera menos invasora que el parámetro real; y que permite inferencias válidas acerca del efecto de la intervención en el parámetro real. Existe un creciente interés en el empleo de mediciones sustitutas de la eficacia terapéutica en investigación de ensayos de fármacos. Sin embargo, el significado de mediciones sustitutas de eficacia terapéutica en neurología y psiquiatría aun no ha sido suficientemente demostrado. De hecho, pocos de estos marcadores han sido adecuadamente "validados," es decir, que hayan mostrado su valor predictor en relación al efecto clínico de un determinado tratamiento. En este artículo se discute la evidencia que podría sustentar la validación de tales marcadores. Los biomarcadores empleados durante los programas de desarrollo iniciales de nuevos fármacos psicotrópicos son considerados en el contexto de la enfermedad de Parkinson, los trastornos afectivos y la esquizofrenia. El caso particular de los ensayos de moléculas neuroprotectoras está ejemplificado en la enfermedad de Parkinson, donde un biomarcador sustituto para la medición clínica de la progresión de la enfermedad podría considerarse como una medición sustituta de la eficacia del tratamiento.

### Marqueurs de substitution en neurologie, psychiatrie et psychopharmacologie

Un marqueur de substitution peut se définir comme un paramètre (marqueur) mesurable de façon plus précoce, ou moins invasive, ou encore pour un coût moindre que le paramètre réel, et qui permet de tirer des conclusions valides sur l'effet d'une thérapeutique sur ce paramètre réel. Un intérêt croissant se porte sur l'utilisation de tels marqueurs de substitution dans le domaine des études d'évaluation clinique des médicaments. Toutefois, la pertinence des marqueurs de substitution d'efficacité n'a pas encore été démontrée de façon satisfaisante dans les domaines de la neurologie et de la psychiatrie. En effet, peu parmi ces marqueurs ont été suffisamment « validés », c'est-à-dire, ont fait la preuve de leur valeur prédictive quant à l'effet clinique recherché du traitement. Cet article passe en revue les arguments en faveur de la validation de ce type de marqueur. Les biomarqueurs utilisés dans les programmes de développement initiaux de nouvelles molécules psychotropes sont évoqués dans le contexte de la maladie de Parkinson, des troubles affectifs et de la schizophrénie. Le cas particulier des essais cliniques de molécules à visée neuroprotectrice est illustré par la maladie de Parkinson, où un biomarqueur de la progression de la maladie pourrait être considéré comme marqueur de substitution du résultat thérapeutique.

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