Should We Consider Mood Disturbance in Schizophrenia as an Important Determinant of Quality of Life?

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Background: The main objective in the treatment of schizophrenia should be to optimize individual patient functioning and quality of life. Little is known about the possible relationship of concurrent mood symptoms and quality of life. We hypothesized that the quality of life for people with schizophrenia would be inversely related to the severity of concurrent mood disruption. ***Method:*** We conducted a post hoc analysis of an international, multicenter, double-blind, 28-week study of 339 patients who met DSM-IV criteria for schizophrenia, schizophreniform, or schizoaffective disorder and were randomized to treatment with either olanzapine or risperidone. Quality of life data were collected at baseline, 8, 16, 24, and 28 weeks or at early discontinuation; Positive and Negative Syndrome Scale (PANSS) data were collected at each visit (weekly to week 8 and monthly thereafter). Correlations were calculated between changes in quality of life (quality of life scale [QLS] total and subscales) and PANSS mood score. Regression models were used to determine the proportion of variability in the QLS total and subscores accounted for by changes in PANSS positive, PANSS negative, and PANSS mood scores. Finally, path analysis was performed to determine the mechanisms used by the PANSS mood scores to affect the QLS total and subscores. ***Results:*** Olanzapine demonstrated a significantly greater therapeutic effect on the PANSS mood item than risperidone did. However, mood improvements with either therapy demonstrated correlations of PANSS mood on the QLS total and subscores which were statistically significant, with the strongest correlation against the interpersonal relations (QLS-IPR) subscore. The path analysis results indicate that the PANSS mood item's most significant path in affecting the QLS total and QLS-IPR is direct. ***Conclusion:*** Changes in the quality of life of schizophrenic patients is inversely related to changes in the concurrent mood disruption. Early therapeutic interventions directed at a broader constellation of schizophrenic symptomatology, including mood, may be helpful in improving an individual patient's quality of life. The possible relative advantages of introducing novel antipsychotic agents earlier in the course of illness for restoration of individual quality of life merit further investigation. *(J Clin Psychiatry 1999;60[suppl 5]:23–29)*

A fundamental objective in the pharmacotherapy of schizophrenia should be to optimize individual patient functioning and quality of life. In order to approach this level of treatment effectiveness, improvement across the widest spectrum of schizophrenic symptomatology should be sought. That spectrum includes "nontraditional" schizophrenia-associated symptoms, i.e., symptoms other than delusions and hallucinations (Table 1). An example would be depressive symptoms. Such factors could be expected to influence a patient's perception of his or her quality of life.

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On first reaction, we might think of a mood disturbance as nosologically distinct from psychosis.[1] However, depressive features characterize a wide range of nonprimary mood disorders. In exploring the clinical relevance of mood disturbance in schizophrenia and, in turn, its potential relationship to quality of life, there are several questions to consider.

First, how often are depressive symptoms actually seen in schizophrenia? Siris[2(p129)] reviewed over 30 studies, concluding "that no matter what the definitions or conditions, all the studies found at least some meaningful rate of depression in the course of schizophrenia." Overall, the modal prevalence rate approached 25%. In the largest prospective clinical trial analysis to date, Tollefson and colleagues[3] reported that, at baseline, 53% of 1948 patients with schizophrenia or a closely related disorder scored at least 16 points on the Montgomery-Asberg Depression Rating Scale (MADRS),[4] consistent with at least a moderate severity of depression. From a longitudinal perspective, Martin et al.[5] found that nearly 60% of schizophrenic patients had a history of at least one depressive episode.

Thus, the prevalence of depressive symptoms in schizophrenia has been established. However, one might inquire whether or not these symptoms are clinically relevant, i.e., do they complicate the course or management of the disease? Outcomes appear to be less favorable among schizophrenic patients who manifest concurrent depressive features. Such individuals exhibit higher rates of morbidity and mortality than their minimally or nondepressed counterparts.[6] Of significant clinical relevance is a heightened risk of suicide.[7] Moreover, depressive symptoms in schizophrenia have also been associated with an increased risk of psychotic relapse[8] and rehospitalization.[9] Johnson[10] reported that depressive features may represent a prodromal phase to an acute psychotic exacerbation.

Having reviewed evidence that concurrent depressive symptoms are both common and clinically important, when are these symptoms typically seen during the course of schizophrenia? Early models hypothesized that depression was the reactive consequence of a chronic psychosis.[11] However, Koreen and colleagues[12] reported that depressive symptoms were also evident among first-episode schizophrenic patients. While depressive symptoms may wax and wane over time, they have been described during both acute exacerbations of psychosis[13] and as a postpsychotic event.[14] Realistically, depressive features may appear at any time during the course of schizophrenia and contribute to the devastating long-term impairment that characterizes the disorder.[15] In turn, a decrement in quality of life would appear inevitable.

For individuals maintained on antipsychotic drug therapy, as proposed by Awad and colleagues, quality of life represents the subjective perception of a therapeutic outcome.[16] This outcome further reflects the interaction of residual symptom severity, adverse events, and the level of psychosocial adaptation attained by the individual. In the literature, quality of life in schizophrenia may be adversely affected by a variety of factors, including duration of illness, cumulative hospitalization days, tardive dyskinesia, and the magnitude of negative symptoms. However, relatively little is known about the relationship of concurrent mood symptoms and patient quality of life.

In the present set of post hoc analyses, we hypothesized that the quality of life for people with schizophrenia would be inversely related to the severity of concurrent mood disruption.

METHOD

This article represents several post hoc analyses drawn from the double-blind, prospective study of olanzapine and risperidone by Tran and colleagues.[17] The study was conducted by 38 investigators in 9 countries. The study protocol was approved by each site's institutional or ethical review board, and a signed, informed consent was obtained from all eligible patients after the procedures and possible side effects were explained. Subjects were screened during a single-blind, 1-week neuroleptic-free run-in by a standard history, physical examination, and laboratory profile. Eligible participants were men or women between the ages of 18 and 65 who met DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder and exhibited a minimum score on the Brief Psychiatric Rating Scale (BPRS) extracted from the Positive and Negative Syndrome Scale (PANSS)[18] of at least 42 (items scored 1 to 7). Both inpatient and outpatient subjects were eligible. No comorbid or other recent major Axis I disorder was allowed. Pregnant or lactating women or patients with serious medical illnesses in which pharmacotherapy posed a substantial clinical risk or confounded diagnosis were excluded.

Table 1. Spectrum of Symptoms in Schizophrenia

Traditional	Nontraditional
Hallucinations	Negative symptoms
Delusions	Disorganized thoughts
	Behaviors (e.g., agitation, hostility)
	Cognitive symptoms
	Mood
	Anxiety

The trial was conducted over 28 weeks; subjects were randomly and blindly allocated to either olanzapine (10 to 20 mg/day) or risperidone (4 to 12 mg/day). Olanzapine was initiated at 15 mg/day once daily for the first 7 study days. Thereafter, investigators could adjust the daily dosage upward or downward by 5 mg every 7 days (range, 10–20 mg). Risperidone titration began at a dosage of 1 mg twice daily on day 1, 2 mg twice daily on day 2, and then 3 mg twice daily on days 3 through 7. After the first week, investigators could optimize the daily risperidone dosage upward or downward by 2 mg/day every 7 days within a range of 4 to 12 mg/day. With either drug, a wide dose range was permitted in order to maximize an individual patient's outcome. Concomitant psychotropic medications were not allowed during the study with the exception of limited benzodiazepine for agitation, chloral hydrate for insomnia, or biperiden or benztropine mesylate (up to 6 mg/day) for treatment-emergent extrapyramidal symptoms (EPS). Prophylactic use of anticholinergic medications was prohibited.

Assessment

Clinical assessments were first performed at baseline. Postrandomization follow-up assessments were conducted weekly during the first 8 weeks and thereafter every 4 weeks. The primary efficacy measure was the PANSS. Secondary analyses were performed on the PANSS subscales (positive, negative, general psychopathology) and the PANSS depression item. The Heinrichs-Carpenter Quality of Life Scale (QLS)[19] was also analyzed. Adverse events were collected by spontaneous report at each visit.

Table 2. Efficacy Measures at Baseline[a]

Measure/Therapy[b]	N	Mean Baseline
PANSS total score		
Olanzapine	166	96.3
Risperidone	165	95.7
PANSS positive score		
Olanzapine	166	22.6
Risperidone	165	22.5
PANSS negative score		
Olanzapine	166	26.0
Risperidone	165	25.6
PANSS general psych score		
Olanzapine	166	47.7
Risperidone	165	47.6
PANSS mood score		
Olanzapine	166	3.0
Risperidone	165	2.9
BPRS total score		
Olanzapine	166	36.7
Risperidone	165	36.2
SANS summary score[c]		
Olanzapine	157	12.2
Risperidone	151	11.6
CGI Severity score		
Olanzapine	166	4.6
Risperidone	166	4.6

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI Severity = Clinical Global Impressions-Severity of Illness, N = number of patients with baseline and postbaseline measure, PANSS = Positive and Negative Syndrome Scale, psych = psychopathology, SANS = Scale for the Assessment of Negative Symptoms.
[b]Olanzapine dosage = 5, 10, 15, or 20 mg/day; risperidone dosage = 4, 6, 8, 10, or 12 mg/day.
[c]$p < .05$.

Statistical Methods

All analyses used a last-observation-carried-forward (LOCF) algorithm; that is, the last available visit (visits 3 through 15, weeks 1 through 28) served as endpoint. Statistical Analysis Software (SAS) was used to perform all statistical analyses. Main effects were tested at a 2-sided α level of .05. For analyses of baseline efficacy and safety measures and change from baseline to endpoint, only patients with baseline and at least 1 postbaseline value were included. In the computation of total scores, if any of the individual items were missing, then the total score was treated as missing.

An analysis of variance (ANOVA) model with terms for treatment, geographic region, and treatment-by-geographic-region interaction was used to evaluate continuous data. Both original and rank-transformed data were fit to the ANOVA models evaluating LOCF change from baseline to endpoint in the efficacy and safety measures; the primary inference was taken from the analysis of the original data unless the assumptions of the ANOVA seemed to be violated. Least-squares means were used to calculate between-treatment group p values. The Wilcoxon signed rank test was used to test the hypothesis that within-treatment group change from baseline to endpoint was significant.

Correlations were calculated between changes in QLS (total and subscales) and PANSS mood scores. Regression models including terms for PANSS positive, PANSS negative, and PANSS mood scores were used to determine the proportion of variability in the QLS total and subscores accounted for by changes in these variables. Type I sums of squares were used to calculate the partial R^2 values. The terms in the regression models were entered using a stepwise, forward selection approach (resulting in the following order: PANSS negative, PANSS positive, PANSS mood).

A path analysis[20] of the PANSS mood score's effect on the QLS total and subscores was conducted in order to determine the percentages of direct effect, indirect effect via PANSS positive, and indirect effect via PANSS negative.

Table 3. Correlation Analysis Results[a]

QLS Subscore	Correlation	p Value
Total	–0.32	< .001
Common objects and activities	–0.23	< .001
Interpersonal relations	–0.31	< .001
Intrapsychic foundation	–0.26	< .001
Instrumental role categories	–0.20	= .002

[a]Abbreviation: QLS = Quality of Life Scale.

RESULTS

Patient Characteristics

A total of 339 patients (olanzapine N = 172, risperidone N = 167) were assigned to receive double-blind therapy. The treatment groups were comparable with respect to baseline demographic and illness characteristics with the exception that the olanzapine group had a higher baseline Scale for the Assessment of Negative Symptoms (SANS) summary score (Table 2).

In the acute 8-week phase of the study, the PANSS mood item (scored 1 to 7, p = .006) among olanzapine-treated patients achieved a mean improvement of 1.13 points versus 0.85 improvement among their risperidone-treated counterparts. The difference in baseline to endpoint change during the maintenance phase of the 28-week trial was also statistically significant (p = .004) in favor of olanzapine.

The correlations of PANSS mood with the QLS total and subscores were statistically significant with the most significant correlation coming from the interpersonal relations (QLS-IPR) subscore (Table 3). The results of the multiple regression analysis of the QLS total and subscores with a model of PANSS positive, PANSS negative, and PANSS mood showed that while PANSS mood did not contribute as much as PANSS positive and PANSS negative in explaining the variability in the QLS scores, it was statistically significant for the QLS total and the QLS-IPR (Table 4). The magnitude of the PANSS mood effect (as measured by the partial R^2 values) was also in the neighborhood of the magnitude of the PANSS positive effect.

Table 4. Regression Analysis Results

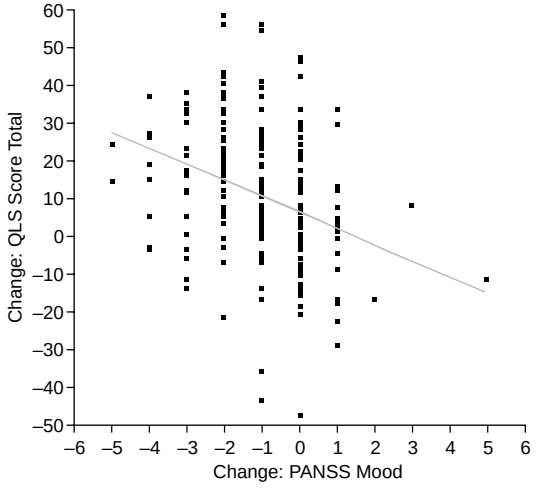
QLS Subscore	Partial R^2 PANSS Negative	PANSS Positive	PANSS Mood	p Value[a] PANSS Mood
Total	0.261	0.065	0.020	.008
Common objects and activities	0.122	0.027	0.012	.064
Interpersonal relations	0.195	0.040	0.026	.004
Intrapsychic foundation	0.259	0.059	0.007	.110
Instrumental role categories	0.089	0.038	0.009	.111

[a]Type III sums of squares from multiple regression model.

Table 5. Path Analysis Results

QLS Subscore	Indirect % PANSS Negative	PANSS Positive	Direct % PANSS Mood
Total	30.0	22.5	47.5
Common objects and activities	28.5	20.0	51.5
Interpersonal relations	26.6	17.9	55.5
Intrapsychic foundation	39.5	25.8	34.7
Instrumental role categories	20.5	27.5	52.0

Figure 1. Change in QLS Score Relative to PANSS Mood Score[a]



[a]Change in QLS total = 6.767 – 4.186 (change in PANSS mood score).

The path analysis[20] results indicated that the PANSS mood's most significant path in affecting QLS total and QLS-IPR was direct (Table 5). While a large portion of PANSS mood's effect on QLS total and QLS-IPR was indirect through PANSS negative, about half of the effect was direct. There were no significant between-treatment effects.

Figure 1 is a scatterplot of change in QLS total score relative to change on the PANSS mood item. The figure illustrates the relationship between mood and quality of life improvements during the pharmacotherapy. The correlation coefficient of –0.32 indicates a moderate, yet statistically significant, correlation. The slope estimate of –4.2 is interpreted to mean that a 1-unit improvement in PANSS mood corresponds to a 4.2 unit improvement in the QLS total score, on average. An analysis of the residuals generated from regressing change in QLS total on change in PANSS mood indicated a satisfactory model with insufficient evidence to reject the assumption of normal residuals ($p = .075$).

DISCUSSION

Our study hypothesis, that depression severity and quality of life are inversely related, was demonstrated in the present analyses. Moreover, the dynamic movement of depressive symptoms during the trial corresponded with changes in quality of life scores on the Heinrichs-Carpenter QLS. The relative impact of mood on quality of life was at least as prominent as the impact seen with positive or negative symptoms and was particularly evident in the area of interpersonal relationships. These observations underscore the impact of depressive symptoms in schizophrenia upon patient well-being. Moreover, the data demonstrated that concurrent depressive symptoms are treatment-responsive and, in turn, were associated with an improvement in quality of life during atypical antipsychotic treatment. If corroborated, these findings argue that concurrent depressive symptoms should represent an important dimension of schizophrenia and become a routine therapeutic target.

Several aspects of the above relationship merit further discussion. First, is there previous evidence in the literature supporting the relationship between mood symptoms and quality of life? Secondly, what is the experience in treating such symptoms? And thirdly, what features in the pharmacology of atypical antipsychotic drugs might differentially benefit individual mood and/or quality of life?

Browne et al.[21] interviewed 64 ambulatory schizophrenic patients actively engaged in a rehabilitation program. On average, the participants scored less than 50% of the possible total score on the quality of life scale, indicating a moderate to poor life quality. A strong inverse relationship to negative (SANS) but not positive (Scale for the Assessment of Positive Symptoms [SAPS]) symptoms was reported. Unfortunately, the authors did not address concurrent mood symptoms. However, Kemmler and colleagues[22] reported that both self-esteem and affective state were closely associated with general life satisfaction among 48 chronic schizophrenic patients evaluated with the Lancashire quality-of-life profile. A similar observation has been made by Carpiniello et al.,[23] who reported a significant correlation between self-rated depression and subjective quality of life. Using a multiple regression analysis with subjective quality of life as the outcome variable, Awad et al.[16] identified 3 significant factors accounting for nearly half of the observed variance (PANSS total score [$R^2 = .32$], Hillside akathisia scale rating [$R^2 = .11$], and

dysphoria [$R^2 = .06$]) among 62 schizophrenic patients stabilized on medication. Thus, this literature provides validation for the hypothesis that a patient's subjective mood experience during pharmacotherapy could affect quality of life. To this end, Browne et al.[24] suggested that a dysphoric response to neuroleptic agents adversely affected quality of life. In light of this apparent relationship, we hypothesize that treatment strategies that alleviate concurrent dysphoria may enable outpatients with schizophrenia to achieve greater benefit from rehabilitation efforts.

Despite the prognostic relevance, the treatment of depressive symptoms in schizophrenia has received relatively little attention in the literature. Robertson and Trimble[25] reviewed early experience with the D_2 receptor antagonists when used for depression across 34 double-blind trials. The results suggested that neuroleptics exhibited, at best, a modest antidepressant effect. Paradoxically, conventional D_2 antagonists have also been implicated in the induction of depressive and/or equivalent symptoms. Rifkin et al.[26] noted that akinesia could be easily confused with depression. Siris[27] suggested such "akinetic depressions" were benztropine-responsive. Van Putten and May[28] reported in 94 schizophrenic patients treated with conventional antipsychotic agents that some individuals, while becoming less psychotic, actually experienced an increase in their depressive symptoms. One explanation for this phenomenon may be the blockade of dopamine-rich frontal reward pathways leading to a relative state of anhedonism.[29] Thus, the well-recognized benefit of D_2 receptor blockade on positive schizophrenic symptoms does not necessarily transfer to concurrent mood symptoms.

Recently Tollefson and colleagues[30] reported in a double-blind, placebo-controlled schizophrenia trial that haloperidol (10–20 mg/day) achieved significantly better improvement on BPRS total and positive symptom change than placebo; however, it failed to separate from placebo on the BPRS anxiety/depression cluster (items 1, 2, 5, and 9). In contrast, olanzapine (10 ± 2.5 or 15 ± 2.5 mg) demonstrated superior results to placebo on all 3 BPRS measures. In a subsequent study, subjects randomized to haloperidol (dose range, 5 to 20 mg/day) achieved significantly less improvement on the MADRS than those randomized to olanzapine (5–20 mg).[3] Moreover, those receiving haloperidol demonstrated a significantly higher incidence of a treatment-associated mood worsening (i.e., ≥ 50% MADRS change) than their olanzapine-treated counterparts. Use of path analytic methods in both of the above trials highlighted that the modest evidence for a haloperidol-associated mood improvement was almost exclusively related to a primary reduction in positive psychotic symptoms. In contrast, the majority of olanzapine's treatment advantage appeared as a direct effect on subjects' mood.

Novel antipsychotic medications may bestow a superior quality of life advantage over the conventional D_2 antagonists through a greater breadth and depth of symptomatic change and/or through fewer and less severe adverse events. Franz et al.[31] followed 33 schizophrenic outpatients taking atypical antipsychotic agents and 31 matched subjects receiving conventional D_2 blockers for 4 months. Those patients receiving the atypical compounds achieved significantly higher scores in overall quality of life, including the domains of physical well-being, social life, and everyday life. In a 6-week, double-blind, multinational comparison of olanzapine (5–20 mg) with haloperidol (5–20 mg), significantly superior improvement on the Heinrichs-Carpenter Quality of Life Scale was achieved among the olanzapine-treated patients (6.5 versus 3.1; $p < .005$).[32] This treatment advantage, while evident on each of the 4 subscales, was principally driven by significant advantages in interpersonal relationships and intrapsychic foundations.

These significant quality of life advantages associated with atypical compounds, and specifically olanzapine, can be understood through the treatment-effectiveness model proposed by Awad and colleagues.[16] Olanzapine has been shown to be effective against a broad array of schizophrenic symptoms including positive,[33,34] negative,[35] mood,[3,30] and cognitive symptoms.[36] Moreover, the frequency of treatment discontinuations for an adverse event is similar to that seen with placebo[33,34] and significantly less than with haloperidol.[37] This latter advantage included a significantly lower incidence of extrapyramidal events including pseudoparkinsonism, dystonia, akathisia, and dyskinesia.[38] In considering the relationship of extrapyramidal adverse events to quality of life, Awad et al.[16] reported akathisia to be a principal quality of life detractor.

Beyond EPS, Baldwin and Birtwistle[39] have suggested that sexual function and satisfaction were also important quality-of-life determinants. Because conventional neuroleptic drugs may impair sexual function, leading to noncompliance, these authors advocated the use of agents with a lower risk of sexual side effects in order to enhance patient and patient partner's quality of life.

In the comparative studies, olanzapine has been associated with significantly lower treatment-emergent sexual dysfunction than either haloperidol[37] or risperidone.[18] At least 2 pharmacologic explanations merit consideration. Both haloperidol and risperidone exhibit dose-related prolactinemia (presumably related to D_2 receptor blockade), which has been related to sexual dysfunction.[40] Risperidone is also a relatively potent α-adrenergic antagonist.[41] The α-adrenoceptor participates in male erectile function.

In reviewing the above differences, a pharmacologic story does seem to unfold. Conventional D_2 antagonists exert little positive or direct effect on mood. They may actually worsen it. In parallel, their well-known EPS profile (and other prominent adverse events) would appear to suboptimize patient quality of life during pharmacotherapy. Novel agents, such as olanzapine or risperidone,

introduce a serotonergic component (e.g., 5-HT_2 receptor antagonism), which appears to benefit negative, EPS, and possibly concurrent mood symptoms. Not surprisingly, then, both agents appear to offer superior effects on quality of life.[32,42] However, olanzapine, in a head-to-head study against risperidone,[18] was associated with superior effects on negative, mood, and EPS. Bymaster et al.[43] have compared the in vitro binding of these 2 agents, and olanzapine is differentiated from risperidone by muscarinic affinities. In vivo olanzapine is active in antagonizing NMDA antagonist-induced (e.g., MK-801, PCP) behaviors.[44] Recently, via microdialysis, olanzapine was also shown to induce a dose-dependent release of both norepinephrine and dopamine in the prefrontal cortex, whereas the effects with risperidone (modest) and haloperidol (negligible) were less robust.[45] The degree to which such pharmacologic differences contribute to a differential clinical profile, and in turn, the potential to ultimately improve quality of life, represents one of the more intriguing questions in front of us.

CONCLUSION

When considering the heterogeneity of schizophrenia, the important deleterious effects of concurrent depression in schizophrenia should not be forgotten. The results of the present study highlight that early therapeutic interventions directed at a broader constellation of schizophrenic symptomatology, including mood, are beneficial for improving a patient's overall quality of life. With the introduction of novel antipsychotic agents earlier in the course of illness, these possible quality of life advantages may be even further magnified. While positive quality of life advantages were seen with both olanzapine and risperidone in this analysis, the effects on the PANSS mood item were more robust with olanzapine. The differential pharmacology among the novel antipsychotic agents is likely to bestow selective advantages on individual symptom domains. Optimal control of the broadest spectrum of schizophrenic symptoms with an agent that has a favorable safety profile should predict the greatest impact on patient quality of life. Quality of life should increasingly become an important evaluative tool in clinical psychiatric research.

Drug names: benztropine (Cogentin and others), biperiden (Akineton), chloral hydrate (Noctec), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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DISCLOSURE OF OFF-LABEL USAGE

The authors of this article have determined that, to the best of their clinical estimation, no investigational or off-label information about pharmaceutical agents has been presented that is outside Food and Drug Administration–approved labeling.