



Association of prominent positive and prominent negative symptoms and functional health, well-being, healthcare-related quality of life and family burden: A CATIE analysis

Jonathan Rabinowitz^{a,*}, Carmen Galani Berardo^b, Dragana Bugarski-Kirola^b, Stephen Marder^c

^a Bar-Ilan University, Ramat Gan, Israel

^b F. Hoffmann-La Roche Ltd, Basel, Switzerland

^c Desert Pacific Mental Illness Research, Education, and Clinical Center, Semel Institute for Neuroscience and Human Behavior at UCLA, Los Angeles, CA, USA

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ABSTRACT

Background: There is an increased interest in evaluating the impact of core symptoms of schizophrenia, both positive and negative, on functioning and burden of disease.

Objective: To examine the extent to which prominent positive and prominent negative symptoms impact functional health, well-being, health-related quality of life (HRQoL), and family burden.

Methods: Data on symptomatology, HRQoL, and resource use from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) were analyzed ($n = 1447$). Patients were divided into four groups based on the Positive and Negative Syndrome Scale (PANSS) using published criteria as having (a) *neither* prominent positive nor prominent negative symptoms ($n = 575$; 39.7%); (b) only prominent *negative* symptoms ($n = 274$; 18.9%); (c) only prominent *positive* symptoms ($n = 295$; 20.4%); or (d) *both* prominent positive and negative symptoms ($n = 303$; 20.9%). Differences were examined for overall significance between the groups and for a linear trend.

Results: There was a significant linear decline in the outcome measures with each subsequent symptom group, with the combination of prominent positive and negative symptoms incrementing the decline further on quality-adjusted life-years derived from the PANSS, Short-Form-12, Index of Functioning, HRQoL measures, and number of workdays missed by caregiver during the month prior to CATIE (all $p < 0.001$).

Conclusions: Both prominent positive and prominent negative symptoms of schizophrenia are independently associated with significant decline in functionality, HRQoL, and caregiver lost workdays. An increased burden is observed in patients with highest symptomatology. Further research is needed to determine predictors of poor outcomes and burden of schizophrenia.

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1. Introduction

There is an increased interest in the impact of core symptoms of schizophrenia, both positive and negative, on health-related quality of life (HRQoL), patient functioning, and burden of disease on the affected individual and his or her family. Although the introduction of second-generation antipsychotics was expected to lead to a breakthrough in the treatment of negative symptoms, evidence suggests that these treatments primarily treat the positive symptoms of schizophrenia and have only a modest impact on negative symptoms. The severity of negative symptoms is a predictor of poor patient

functioning. Negative symptoms affect the patient's ability to live independently, to perform activities of daily living, to be socially active and maintain personal relationships, and to work and study (Alonso et al., 2009; Harvey et al., 2012; Rabinowitz et al., 2012). Understanding the relationship between domains of psychopathology and clinical outcomes is important because interventions that focus on psychotic symptoms often fail to improve functioning and HRQoL. Long-term treatment goals for patients with schizophrenia include improving the management of negative symptoms and suboptimally controlled positive symptoms and enabling better functioning (Kane, 2006; Kirkpatrick et al., 2006; Bobes et al., 2010). We examined the extent to which prominent positive and prominent negative symptoms are associated with functional health, patient well-being, HRQoL, and family burden.

2. Methods

Data on baseline symptomatology, HRQoL, and resource use from the National Institute of Mental Health Clinical Antipsychotic Trials

* Corresponding author.

E-mail addresses: jonathan.rabinowitz@biu.ac.il (J. Rabinowitz), carmen.berardo@roche.com (C.G. Berardo), dragana.bugarski-kirola@roche.com (D. Bugarski-Kirola), marder@ucla.edu (S. Marder).

of Intervention Effectiveness (CATIE) were analyzed ($n = 1447$). CATIE was a randomized controlled trial that compared a first-generation antipsychotic, perphenazine, with four second generation antipsychotics (olanzapine, quetiapine, risperidone and ziprasidone) for up to 18 months in a double-blind study. Patients with schizophrenia were recruited at 57 U.S. sites. The primary aim was to delineate differences in the overall effectiveness of these five treatments. Broad inclusion and minimal exclusion criteria were used to allow enrollment of patients with coexisting conditions and those who were taking other medications. The study was conducted in a variety of clinical settings in which people with schizophrenia are treated with 76% of patients entering study as outpatients (Lieberman et al., 2005).

Measures analyzed were the Positive and Negative Syndrome Scale (PANSS); Short Form Health Survey (SF-12) measure of functional health and well-being; Index of Functioning (Rabinowitz et al., 2012); and caregiver days lost from work in the past month in or out of the home (Family/Caregiver Baseline Interview).

The Index of Functioning has been previously described (Rabinowitz et al., 2012). It included items from the Heinrich and Lehman scales that conceptually did not measure negative factor symptoms. It included from the Heinrich's Carpenter the scales Instrumental role (occupational/educational), Common place objects and activities, and from the Lehman Quality of Life Scales two items that measure Leisure activities (Shopping, Go to restaurant/coffee shop, Prepare meal, Hobby) and Instrumental activities of daily living (hygiene, housecleaning, chores). Two Heinrich's subscales, measuring interpersonal relations and intrapsychic foundations were intentionally not included as they overlap with the negative symptom factor. Of the nine items from the Lehman's Quality of Life Scale included in CATIE, seven items overlapping with negative symptoms, or that had already been covered by the Heinrich's scale were not included (e.g. school and work functioning). Functioning items were converted to standardized scores (z-scores) and summed to create a total score.

2.1. Data analysis

Patients were categorized into four groups based on the PANSS, using published criteria (Kinin et al., 2006): (a) *neither* prominent positive

nor prominent negative symptoms ($n = 575$; 40.0%); (b) only prominent *negative* symptoms ($n = 274$; 18.9%); (c) only prominent *positive* symptoms ($n = 295$; 20.4%); or (d) *both* prominent positive and negative symptoms ($n = 303$; 20.9%). Prominent negative and positive symptoms were defined according to criteria as having a score ≥ 4 (moderate) on at least three, or ≥ 5 (moderately severe) on at least two subscale items in the respective subscale. For example, an individual with a score ≥ 4 on at least three PANSS positive items but not on negative items was categorized as having prominent positive symptoms. Conversely, a score ≥ 4 on at least three PANSS negative items resulted in a categorization of having prominent negative symptoms. If an individual had scores ≥ 4 on items for both positive and negative symptom items, then the individual was categorized as having both prominent positive and prominent negative symptoms. If an individual did not meet criteria for any of these groups, the individual was categorized as belonging to the None group (having neither prominent negative nor prominent positive symptoms). Groups were mutually exclusive.

Utility scores were derived from the SF-12 scores (Brazier and Roberts, 2004), using software provided by Brazier that converts SF-12 to SF-6D scores. Similarly, health burden of illness utility scores were computed, based on PANSS scores, using a method developed by Lenert et al. (Lenert et al., 2004; Lenert et al., 2005), in which PANSS scores are divided into eight groups ranging from mild (patients with a mean score on negative factor [G7, G16, N1, N2, N3, N4, N6] < 2.1 , a positive factor [G9, P1, P3, P5, P6] mean of < 2.7 , and a cognitive factor [G5, G10, G11, G12, G13, G15, P2, N5] mean of < 2.9) to extremely severe (patients with a negative factor of > 3.4 and a positive factor of > 3.9). Lenert et al. (2004) used a panel of 620 persons to rate video presentations reflecting these symptom levels. These ratings were subsequently used to assign health state classification utility weights ranging from 0.88 for mild to 0.42 for extremely severe symptoms.

Mean differences between the various symptom prominence groups (positive only, negative only, both positive and negative, or neither positive nor negative) on the PANSS, SF-12, SF-6D, caregiver lost workdays in or out of the home (Family/Caregiver Baseline Interview), and Index of Functioning (consisting of items from Lehman's and Heinrich's HRQoL scales) were examined. We examined the data using analysis of

Table 1
Association of PANSS Symptom Prominence: PANSS, SF-12 Mental Health Score, SF-6D Utility, Lost Workdays of Caregiver, and Functioning Items from the HRQoL Scale, Mean and 95% Confidence Interval.

PANSS Symptom Prominence Group	PANSS Total	Positive	Negative	SF-12 Mental Health	SF-6D Utility and Effect Size vs. Neither Group	Health Utility Weights of PANSS Symptom Prominence Groups	Caregiver Lost Workdays Outside or Within Household in Past Month Due to Family Member Illness	Functioning Items of HRQoL Scale*
None 39.7% ($n = 575$)	62 (61; 63)	16 (14; 16)	16 (15; 16)	43.3 (42.3; 44.2)	0.725 (0.714; 0.736)	0.732 (0.725; 0.739)	1.73 (1.21; 2.24) $n = 244$	0.99 (0.72; 1.28)
Prominent negative 18.9% ($n = 274$)†	80 (78; 81)	16 (15; 16)	26 (25; 26)	40.5 (39.6; 42.4)	0.696 (0.680; 0.711)	0.565 (0.555; 0.576)	1.81 (1.07; 2.55) $n = 119$	-0.75 (-1.13; -0.37)
Prominent positive 20.4% ($n = 295$)‡	78 (77; 79)	23 (22; 23)	17 (16; 17)	39.4 (38.0; 40.8)	0.685 (0.669; 0.698)	0.679 (0.669; 0.688)	2.17 (1.40; 2.94) $n = 108$	0.34 (-0.05; 0.74)
Both prominent negative and prominent positive 20.9% ($n = 303$)	95 (94; 97)	24 (23; 24)	26 (26; 27)	37.9 (36.5; 39.2)	0.683 (0.668; 0.699)	0.564 (0.554; 0.574)	3.28 (2.55; 3.90) $n = 143$	-1.29 (-1.67; -0.91)
Overall p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Linear p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.004	<0.001
Nonlinear p value	<0.001	<0.001	<0.001	0.83	0.16	<0.01	0.16	0.78

Abbreviations: ES, effect size; QALY, quality-adjusted life-years; HRQoL, health-related quality of life; PANSS, Positive and Negative Symptom Scale; SF, Short Form.

* Select items from Heinrich's and Lehman's HRQoL scales measuring aspects of functioning that did not overlap with negative symptoms as per Rabinowitz et al. (2012).

† Score ≥ 4 (moderate) on at least three or ≥ 5 (moderately severe) on at least two negative subscale items.

‡ Score ≥ 4 (moderate) on at least 3, or ≥ 5 (moderately severe) on at least 2 positive subscale items.

Table 2
SF-12 by Prominence of PANSS Negative and Positive Symptoms, Mean and 95% Confidence Interval.

	None (n = 575)	Negative (n = 274)	Positive (n = 295)	Negative and Positive (n = 303)	p Overall p Linear p Nonlinear
Mental (high is better)	43.26 (42.32; 44.20)	41.00 (39.63; 42.37)	39.43 (38.12; 40.74)	37.86 (36.55; 39.17)	<0.0001 <0.0001 = 0.83
Physical (high is better)	48.43 (47.60; 49.26)	47.53 (46.31; 48.74)	48.02 (46.86; 49.18)	48.63 (47.47; 49.78)	= 0.56 = 0.88 = 0.36
Items with statistically significant differences*					
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?					
1. Accomplished less than you would like (1-Yes; 2-No)	0.48 (0.43; 0.52)	0.56 (0.50; 0.62)	0.62 (0.56; 0.67)	0.60 (0.54; 0.65)	<0.001 <0.001 = 0.16
2. Didn't do work or other activities as carefully as usual (1-Yes; 2-No)	0.40 (0.36; 0.45)	0.50 (0.44; 0.56)	0.53 (0.47; 0.58)	0.54 (0.48; 0.59)	<0.001 <0.001 = 0.30
3. During the past 4 weeks how much did pain interfere with your normal work (including both work outside the home and housework)? (1-Not at all; 5-Extremely)	1.76 (1.66; 1.86)	1.90 (1.76; 2.04)	2.05 (1.92; 2.19)	1.84 (1.71; 1.98)	= 0.006 = 0.049 = 0.013
4. Have you felt calm and peaceful? (1-All of the time; 6-None of the time)	3.25 (3.13; 3.36)	3.26 (3.09; 3.42)	3.50 (3.34; 3.66)	3.53 (3.37; 3.69)	= 0.005 = 0.001 = 0.44
5. Did you have a lot of energy? (1-All of the time; 6-None of the time)	3.56 (3.44; 3.67)	3.79 (3.63; 3.96)	3.57 (3.41; 3.73)	3.95 (3.79; 4.11)	<0.001 = 0.001 = 0.009
6. Have you felt downhearted and blue? (1-All of the time; 6-None of the time)	4.44 (4.33; 4.55)	4.26 (4.10; 4.42)	4.13 (3.98; 4.29)	3.88 (3.72; 4.03)	<0.001 <0.001 = 0.77
12. During the past 4 weeks how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (1-All of the time; 5-None of the time)	3.64 (3.54; 3.75)	3.43 (3.28; 3.59)	3.21 (3.07; 3.36)	3.19 (3.04; 3.33)	<0.001 <0.001 = 0.37

* Items without statistically significant differences (1 to 5): (1) general health, (2–3) limitations in doing moderate activities and more strenuous activities (4–5), physical health limiting accomplishment or work.

variance to test for overall significance between-group differences and for the presence/absence of a linear trend to assess whether each subsequent category was associated with greater impact on functional health.

3. Results

Table 1 presents the PANSS, SF-12 mental health score, SF-6D utility, lost workdays of caregiver, and functioning items from the HRQoL scale. The PANSS total score was 62 for the None (neither prominent positive nor negative symptoms) group, 95 for the both (prominent positive and negative symptoms) group, and 78 and 80 for the prominent positive and prominent negative symptom groups, respectively. In addition, the positive symptom group had a higher positive score and the negative symptom group, a higher negative score. There were no statistically significant differences (all p's > .11) between the groups on age (overall mean 40.54 SD 11.10), sex (25.8% female, 74.2% male), race (61.2% white) and marital status (59.5% never married). Patients with negative symptom prominence were least likely to have completed high school (66.1%), followed by those with prominence on both positive and negative (72.3%), those with no prominent symptoms (76.5%), and those with prominent positive symptoms (80.3%) (Chi-square = 17.65, df = 3, p = .001).

On the SF-12 and the SF-6D utility, there was a significant linear decline for each subsequent group such that the pattern of decline was significant, with the combination of prominent positive and negative symptoms further increasing the decline. Individuals with neither prominent positive nor prominent negative symptoms had the highest quality-adjusted life-years, followed by individuals with only prominent negative symptoms, only prominent positive symptoms, and both prominent positive and negative symptoms (respectively, 0.725 [95% CI, 0.714 to 0.736]; 0.697 [95% CI, 0.681 to 0.713]; 0.685 [95% CI, 0.670 to 0.701] and 0.683 [95% CI, 0.668 to 0.698]). The effect sizes versus the comparator group, the group

with neither prominent positive nor prominent symptoms on utility were 0.21, 0.30, and 0.31, respectively.

The number of workdays missed by caregivers in the month prior to CATIE had the expected linear decline across symptom groups. The functioning scale (from HRQoL scales) showed significantly greater (p < 0.001) functional impairment for the prominent negative symptom group than the prominent positive symptom group (data not presented in table), and a similar additive effect (i.e., most impairment), as with other measures in individuals with both prominent positive and negative symptoms (Table 1). Similar to the mental health score, there were also significant differences (p < 0.006) among all seven mental health items measuring work and daily activities, feeling calm, depression, energy, and social activities, which were significantly linear for five items (Table 2). There was no significant difference in physical health or among any physical health items (Table 2).

4. Discussion

Prominent positive and negative symptoms were common in a cohort, primarily of outpatients, with schizophrenia, receiving antipsychotics. Using criteria for prominent symptoms, we showed that 19% of individuals were classified as having prominent negative symptoms, 20% as having prominent positive symptoms, and 21% as having both prominent positive and prominent negative symptoms. The coexistence of prominent positive and negative symptoms was independently associated with a significant decline in functional mental health, health utility and well-being, health related quality of life, and caregiver burden. Negative symptoms were more associated with impairment, as measured by the scale of functioning, than positive symptoms.

These results suggest that outpatients with prominent positive, prominent negative, or both prominent positive and negative symptoms of schizophrenia may experience an improvement in HRQoL

by treating either domain of psychopathology. It has been previously recognized (Alonso et al., 2009) that treating positive symptoms may result in improved HRQoL; however, results of the current analysis suggest a distinct improvement in HRQoL as a consequence of treating prominent negative symptoms as well. These findings are consistent with studies that have demonstrated that negative symptoms, particularly apathy and avolition, are related to poor community outcomes such as poor social functioning, poor work functioning, and remission (Kirkpatrick and Buchanan, 1990; Fenton and McGlashan, 1991).

In this study of a broadly inclusive randomized controlled trial, we found that the presence of positive and negative symptoms was associated with increased burden, as represented by the results of the group with both prominent positive and prominent negative symptoms. Although negative symptoms are a predictor of poor patient functioning and can affect a patient's ability to live independently, perform activities of daily living, be socially active, and maintain personal relationships (Novick et al., 2009; Harvey et al., 2012; Rabinowitz et al., 2012), there have been no studies specifically designed to assess health economic aspects related to negative symptoms.

The limitations of the current study include concerns regarding the representativeness of the CATIE sample. Although individuals were managed in a variety of community treatment settings, those agreeing to participate in the trial were likely to be dissatisfied with their current treatment. Individuals who declined participation may have had lower levels of positive and negative symptoms. Also the study was conducted in a single country. Our use of caregiver days lost from work is only an indirect indicator of family burden. In addition, the PANSS has relatively few items for scoring negative symptoms, particularly apathy and avolition.

In conclusion, both prominent positive and prominent negative symptoms of schizophrenia are independently associated with significant decline in functionality, HRQoL, and caregiver lost workdays. An increased burden is observed in patients with highest symptomatology.

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Contributors

Jonathan Rabinowitz drafted the manuscript and analyzed the data.

Carmen Galani Berardo, Dragana Bugarski-Kirola and Stephen Marder were involved in conceptualizing the study, developing the study plan and interpreting the results. All author's reviewed and commented on multiple versions of the manuscript and approved the final version.

Conflict of interest

Drs. Bugarski-Kirola and Berardo are employees of F. Hoffmann-La Roche. Dr. Rabinowitz has received research support, and/or consultancy fees, and/or travel

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References

- Alonso, J., Croudace, T., Brown, J., Gasquet, I., Knapp, M.R., Suarez, D., Novick, D., 2009. Health-related quality of life (HRQL) and continuous antipsychotic treatment: 3-year results from the Schizophrenia Health Outcomes (SOHO) study. *Value Health* 12 (4), 536–543.
- Bobes, J., Arango, C., Garcia-Garcia, M., Rejas, J., Group C.S.C., 2010. Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: findings from the CLAMORS study. *J. Clin. Psychiatry* 71 (3), 280–286.
- Brazier, J.E., Roberts, J., 2004. The estimation of a preference-based measure of health from the SF-12. *Med. Care* 42 (9), 851–859.
- Fenton, W.S., McGlashan, T.H., 1991. Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. *Arch. Gen. Psychiatry* 48 (11), 978–986.
- Harvey, P.D., Heaton, R.K., Carpenter Jr., W.T., Green, M.F., Gold, J.M., Schoenbaum, M., 2012. Functional impairment in people with schizophrenia: focus on employability and eligibility for disability compensation. *Schizophr. Res.* 140 (1–3), 1–8.
- Kane, J., 2006. Commentary: consensus statement on negative symptoms. *Schizophr. Bull.* 32 (2), 223–224.
- Kinon, B.J., Noordsy, D.L., Liu-Seifert, H., Gulliver, A.H., Ascher-Svanum, H., Kollack-Walker, S., 2006. Randomized, double-blind 6-month comparison of olanzapine and quetiapine in patients with schizophrenia or schizoaffective disorder with prominent negative symptoms and poor functioning. *J. Clin. Psychopharmacol.* 26 (5), 453–461.
- Kirkpatrick, B., Buchanan, R.W., 1990. Anhedonia and the deficit syndrome of schizophrenia. *Psychiatry Res.* 31, 25–30.
- Kirkpatrick, B., Fenton, W.S., Carpenter Jr., W.T., Marder, S.R., 2006. The NIMH-MATRICES consensus statement on negative symptoms. *Schizophr. Bull.* 32 (2), 214–219.
- Lenert, L.A., Sturley, A.P., Rapaport, M.H., Chavez, S., Mohr, P.E., Rupnow, M., 2004. Public preferences for health states with schizophrenia and a mapping function to estimate utilities from positive and negative symptom scale scores. *Schizophr. Res.* 71 (1), 155–165.
- Lenert, L.A., Sturley, A.E., Rapaport, M., Chavez, S., Mohr, P.E., Rupnow, M., 2005. Corrigendum to Public preferences for health states with schizophrenia and a mapping function to estimate utilities from positive and negative symptom scale scores. *Schizophr. Res.* 80, 135–136.
- Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J., Hsiao, J.K., 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N. Engl. J. Med.* 353 (12), 1209–1223.
- Novick, D., Haro, J.M., Suarez, D., Vieta, E., Naber, D., 2009. Recovery in the outpatient setting: 36-month results from the Schizophrenia Outpatients Health Outcomes (SOHO) study. *Schizophr. Res.* 108 (1–3), 223–230.
- Rabinowitz, J., Levine, S.Z., Garibaldi, G., Bugarski-Kirola, D., Berardo, C.G., Kapur, S., 2012. Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: analysis of CATIE data. *Schizophr. Res.* 137 (1–3), 147–150.