The "Doses" of Initial, Untreated Hallucinations and Delusions: A Proof-of-Concept Study of Enhanced Predictors of First-Episode Symptomatology and Functioning Relative to Duration of Untreated Psychosis

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ABSTRACT

Objective: A prominent limitation of literature on duration of untreated psychosis (DUP) is that researchers have studied only unidimensional duration as an early-course predictor, neglecting potential effects of frequency/severity of initial, untreated psychosis. This study demonstrates utility of the concept of "doses" of initial, untreated hallucinations and delusions—representing more complete measures of "exposure"—as enhanced predictors of symptomatology/functioning relative to DUP alone.

Method: 109 first-episode patients with a psychotic disorder based on Structured Clinical Interview for *DSM-IV* Axis I Disorders criteria were assessed at 3 public-sector psychiatric units serving an urban, socially disadvantaged, predominantly African American community between July 2004 and June 2008. Dependent variables included negative symptoms, general psychopathology, insight, and global functioning at initial hospitalization.

Results: When added to a baseline model (age, gender, and premorbid academic and social functioning), DUP predicted current negative symptoms ($P = .02$, model $R^2 = 0.20$), though dose of hallucinations and dose of delusions did not. However, regarding general psychopathology symptoms, DUP was not predictive, though dose of delusions was, when controlling for the other 5 variables ($P = .02$, model $R^2 = 0.15$). DUP was not a significant predictor of insight, though dose of hallucinations was, such that a greater dose of initial, untreated hallucinations was associated with better insight at initial hospitalization ($P < .01$, model $R^2 = 0.20$). DUP was associated with global functioning ($P = .05$), and dose of delusions added significantly to this prediction ($P = .04$; model $R^2 = 0.13$).

Conclusions: Doses of initial, untreated hallucinations and delusions add substantively, though differentially, to the prediction of early-course symptomatology and functioning. Findings suggest a need for focused research on frequency/severity of pretreatment psychotic symptoms beyond duration measures.

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Duration of untreated psychosis (DUP)—the time interval from onset of psychotic symptoms (usually hallucinations or delusions, specifically) to initiation of adequate treatment[1,2]—is generally recognized as a correlate, if not determinant, of various adverse early-course outcomes. Numerous studies, many summarized in 2 independent meta-analyses,[3,4] document associations between DUP and greater severity of negative symptoms at treatment initiation, poorer response to antipsychotic treatment, and lower quality of life. Other reports show relations of DUP with lower likelihood of antipsychotic response,[5] poorer symptomatic and functional outcomes,[6,7] and greater impairments in occupational functioning.[8] It should be noted, however, that not all reports document an independent association between DUP and early-course outcomes; for example, Singh and colleagues[9] found that the duration of the initial psychotic episode (dichotomized as < 6 months or ≥ 6 months) did not predict 3-year outcomes independently, though gender and premorbid functioning did.

Some early-psychosis researchers have suggested that associations between DUP and outcomes may be confounded by a third variable: most prominently, premorbid functioning.[10] However, not all studies find that premorbid functioning is related to DUP[11,12]; partial confounding may be a better conclusion[13–15]; and some evidence suggests that premorbid functioning may moderate the association between DUP and symptomatology.[16] It is possible that DUP is a marker or epiphenomenon of a disease type characterized by poorer outcomes[17] rather than exerting causative influences on early-course features. It is clear, however, that DUP temporally precedes measures of symptomatology at initial treatment contact and longitudinal outcomes and that DUP is statistically associated with these indicators. As such, DUP can be considered a risk factor for poorer outcomes. Given evidence from the landmark Early Treatment and Intervention for Psychosis study in Scandinavia,[18,19] DUP is likely modifiable. The burgeoning early detection and intervention paradigm for psychotic disorders is largely based on this premise.

Throughout the literature to date, DUP is a unidimensional construct, and studies have not addressed whether symptoms have been present constantly or sporadically (frequency) between onset and treatment initiation. As well, the intensity (severity) of pretreatment psychotic symptoms has not been considered.[2] That is, studies have not examined a possible "dose effect" of initial psychosis on clinical features at first hospitalization or longer-term outcomes, beyond just the duration measure, despite the fact that cumulative exposure to psychosis may be as important, if not more so, than DUP alone. As noted previously,[20] psychoses of the same general duration, yielding an equivalent measure of DUP, may vary prominently in terms of the overall "dose" of psychosis experienced before treatment initiation.

This lack of consideration of dose is a prominent limitation, as theories relating DUP to outcomes—either through a neurobiological

toxicity from an "active morbid process"[21,22] or a "psychosocial toxic effect"[23,24]—ostensibly use duration as a rough, though imprecise and simple, proxy for exposure dose. In epidemiologic terms, reconstructions of "exposures" relevant to health outcomes typically consider *how long* individuals are in contact with the pathogenic factor, but also *how often* and *how much* of it they are in contact with. Yet, DUP studies have not distinguished between intermittent, mild psychotic symptoms and unrelenting, severe symptoms. Duration of untreated psychosis assumes psychosis to be persistent from onset, though this does not apply to all patients,[25] and DUP may be dominated by delusions, hallucinations, or both.[26] As noted, some conceptualizations of the mechanisms subserving DUP effects posit that stressful subjective experiences of positive psychotic symptoms entail neurotoxic processes that may contribute to brain dysfunction. Thus, the cumulative doses of hallucinations and delusions may be particularly important in determining DUP effects. However, we know of no attempts to characterize pretreatment frequency and severity of psychosis in addition to DUP or to disentangle effects of hallucinations and delusions as potentially differential determinants of specific clinical characteristics at the time of initial hospitalization or longer-term outcomes.

These critical methodological barriers are addressed in this proof-of-concept analysis using a new *dose of initial, untreated psychosis* construct (indicating frequency and severity or cumulative exposure to psychosis over the 2 years prior to first admission), as well as 2 component variables, "hallucinations dose" and "delusions dose." This analysis was conducted using data from a first-episode sample collected specifically to study predictors of DUP[27–30] and correlates of the newly proposed *dose of initial, untreated psychosis* construct. Using a series of regressions, we sought to answer whether 3 dose variables—(1) total dose of initial, untreated psychosis; (2) dose of initial, untreated hallucinations (hallucinations dose); and (3) dose of initial, untreated delusions (delusions dose)—add value to the prediction of symptoms and functioning beyond the predictive capacity of DUP in 109 newly diagnosed, first-episode patients.

METHOD

Setting, Sample, and Procedures

Participants were drawn from 3 inpatient psychiatric units that provide services for patients with no insurance or with only public-sector insurance (eg, Medicaid). The population served by these units is predominantly African American, low-income, and socially disadvantaged, as evidenced by very high rates of school dropout[31] and prior incarcerations,[32] even in a first-episode sample. A total of 281 patients were screened for participation between July 2004 and June 2008. Among these, 89 were ineligible based on the following exclusion criteria: being outside of the age range of 18–40 years, not receiving a diagnosis of a primary nonaffective psychotic disorder, having known mental retardation, having had > 3 months of prior antipsychotic treatment, or having been hospitalized > 3 months prior to index admission. Among the 192 eligible patients, 83 could not be assessed—52 (62.7%) declined participation and 31 (37.3%) were discharged before an assessment could be conducted. The 83 eligible but not enrolled patients did not differ from the 109 participants in terms of age, gender, or race/ethnicity.

Research assessments (lasting 3–4 hours) were conducted by trained and experienced master's- or doctoral-level assessors (eg, clinical psychology postdoctoral fellows) once psychotic symptoms were stabilized enough to allow for informed consent and participation in the detailed clinical research assessment (mean ± SD hospital day at the time of assessment: 9.1 ± 6.7). Assessments were preferentially conducted toward the end of the hospitalization given that better clinical stability would likely allow for more accurate reporting, and the mean ± SD length of hospital stay was 12.6 ± 7.1 days. In this setting, nearly all first-episode psychosis patients are started on an atypical antipsychotic medication upon hospital admission. Diagnoses of psychotic disorders were made using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID),[33] based on all available information gathered through a semistructured interview, review of the patient's hospital chart, discussions with treating clinicians, and collateral information from family members when available. The study was approved by all relevant institutional review boards, and participants gave written informed consent.

Measurement of Independent Variables

Premorbid functioning was measured with the widely used Premorbid Adjustment Scale (PAS)[34] for which reliability, validity, and predictive utility have been established previously.[34–36] Functioning was assessed in 2 domains—academic and social—across 3 age periods: childhood (≤ 11 years), early adolescence (12–15 years), and late adolescence (16–18 years), yielding 6 premorbid functioning scores. Higher scores indicate poorer premorbid functioning. To very conservatively safeguard against inadvertently assessing prodromal functioning during the rating of premorbid functioning, the PAS was not rated for any age period that would have included the year before the onset of prodromal symptoms.[37] Two overall indices of premorbid functioning, in academic and social domains, were computed by averaging childhood, early adolescence, and late adolescence scores, as applicable.

Duration of untreated psychosis was defined as the number of weeks from onset of positive psychotic symptoms to first hospital admission and measured systematically using the Symptom Onset in Schizophrenia inventory[38] and select items from the semistructured Course of Onset and Relapse Schedule/Topography of Psychotic Episode interview.[39] Date of onset of positive symptoms was operationalized as the date on which hallucinations or delusions met the threshold for a Positive and Negative Syndrome Scale (PANSS)[40] score of ≥ 3. Systematic methods were used to resolve ambiguities in obtaining exact dates for the onset of psychotic symptoms; for example, cross-referencing with milestones and memorable events was used to enhance accuracy of dating. A consensus-based, best estimate of DUP was derived

from all available information, which included 1 or 2 family member/informant in-depth interviews (conducted without the patient present) in 44 cases (40.4%). Data gathered from chart reviews, treating clinicians, and family member/informants were not used simply to check the accuracy of patients' data; rather, all available data were compiled and considered together to derive a best estimate of date of onset of positive symptoms (and thus, DUP).

The dose of initial, untreated psychosis and its 2 components—dose of initial, untreated hallucinations ("hallucinations dose") and dose of initial, untreated delusions ("delusions dose")—were assessed in a rigorous, stepwise fashion designed to facilitate retrospective recall while gathering data on frequency and severity of preadmission psychotic symptoms. First, the 24 months prior to the hospital admission date were divided into 4 quarters, representing the most recent 6-month period (fourth quarter), the 6 months prior to that (third quarter), etc. Second, a timeline was drawn to indicate these 4 quarters of the past 2 years, and the assessor worked with the patient to mark milestones and memorable anchoring events (eg, grade levels in school, employment, birthdays, holidays, family events) on the timeline. Third, through focused questioning of the patient, hallucinations were rated for each 6-month quarter using 5 items from the Psychotic Symptom Rating Scales (PSYRATS)[41]: frequency, duration, loudness, intensity of distress, and disruption of life caused by voices. Fourth, delusions were rated for each 6-month quarter using 5 PSYRATS items: amount of preoccupation with delusions (frequency of thinking about delusions), duration of preoccupation with delusions, conviction, intensity of distress, and disruption of life caused by beliefs. For each of these 10 items, ratings ranged from 0 (eg, "voices are not present" for the duration of hallucinations item) to 4 (eg, "voices last for hours at a time" for the same item).

Psychotic Symptom Rating Scales items were used because this measure has demonstrated good reliability and validity in the assessment of both chronic and recent-onset psychosis.[41,42] The PSYRATS offers a useful tool for measuring specific symptom characteristics in a detailed manner. For the present study, to compute a hallucinations dose and delusions dose, the 5 select items, each ranging 0–4, were summed across the four 6-month quarters, representing a cumulative dose (including duration, frequency, and severity); these values could range from 0 to 80. A total dose of psychosis was calculated by summing these 2 scores (possible range, 0–160).

Measurement of Dependent Variables

Positive and negative symptoms were assessed with the PANSS,[40] a 30-item, 7-point rating scale, with items grouped into 3 rationally derived categories: positive symptoms (7 items); negative symptoms (7 items); and general psychopathology symptoms, such as anxiety, depression, poor impulse control, and active social avoidance (16 items). The PANSS was rated using data gathered from a chart review and an in-depth, semistructured interview focused on the patient's symptoms during the past 1-month (rather than 1- or 2-week) period. (Thus, symptom ratings were unlikely to be influenced by acute treatment effects or clinically significant symptom improvements during hospitalization despite the delay in consent and assessment of, on average, 9 days.) The PANSS has documented criterion-related validity, predictive validity, drug sensitivity, and utility for both typological and dimensional assessment.[40] Ongoing training and interrater reliability assessments ensured a high degree of reliability across the several raters. Of note, an a priori decision was made to use the 3 traditional subscales of the PANSS—positive, negative, and general psychopathology symptoms. Yet, it must be acknowledged that results of factor analytic studies among first-episode and multiple-episode patients have varied (eg, some have shown that the traditional concept of positive symptoms includes distinct syndromes of psychotic and disorganization symptoms). The present sample was not deemed large enough for a confirmatory factor analysis. Furthermore, given the very wide use of the 3 traditional PANSS subscales, these scores were considered meaningful measures of psychopathology.

Insight was measured using the Birchwood Insight Scale (BIS),[43] an 8-item, self-report questionnaire. Participants indicate whether they "agree," "disagree," or are "unsure" about each statement (eg, "My stay in the hospital is necessary"). A total score is derived by established scoring conventions, with higher scores indicating better insight (0 = markedly impaired insight, 12 = full insight). The BIS has satisfactory reliability, validity, and sensitivity for assessing insight among individuals with psychosis.[43,44] Satisfactory internal consistency ($\alpha = .75$) and test-retest reliability ($r = 0.90$) have been reported.[43] The internal consistency for the BIS in the present sample was $\alpha = .82$. Global functioning was measured with the widely used, reliable, and valid Global Assessment of Functioning (GAF) scale,[45,46] a 100-point range that indicates overall psychosocial functioning. The scale is divided into 10 equal intervals with anchoring descriptions for each.[45]

Data Analyses

Distributional properties of all key variables were examined. Model outcomes were assessed for normality using the Shapiro-Wilk statistic and histograms. Sample size was deemed sufficiently large to allow the use of linear regression methods for model building in instances in which tests of normality failed. Dependent variables in a series of regression analyses included PANSS negative symptom score, PANSS general psychopathology symptom score, BIS score, and GAF score. The PANSS positive symptoms were not examined given that this would have been tautological (pretreatment dose of hallucinations and delusions predicting the level of positive symptoms at the time of admission). Each of the 4 symptomatic and functional domains were examined using a series of 5 regressions: (1) a baseline model including age, gender, premorbid academic functioning, and premorbid social functioning; (2) the independent variables of that baseline model with the addition of DUP; (3) the baseline

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model variables, DUP, and total dose of initial, untreated psychosis; (4) the baseline model variables, DUP, and hallucinations dose; and (5) the baseline model variables, DUP, and delusions dose. This allowed for an assessment of the total dose variable (model 3), as well as the 2 component dose scores (models 4 and 5), while controlling for effects of age, gender, premorbid adjustment, and DUP. Descriptive statistics and correlation analyses were conducted using SPSS 16.0 (SPSS Inc, Chicago, Illinois), and models were constructed using the general linear models procedure (PROC GLM) in SAS 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Sample Characteristics and Basic Descriptive Statistics

Sociodemographic characteristics of the 109 hospitalized first-episode patients are shown in Table 1. The SCID-diagnosed psychotic disorders included: schizophreniform disorder (n = 22 [20.2%]), schizophrenia (n = 62 [56.9%]), schizoaffective disorder (n = 8 [7.3%]), delusional disorder (n = 1 [0.9%]), brief psychotic disorder (n = 4 [3.7%]), and psychotic disorder not otherwise specified (n = 12 [11.0%]). Some 91 participants (83.5%) were initially admitted involuntarily, and the mean ± SD length of hospital stay was 12.6 ± 7.1 days.

The median DUP was 22.3 weeks. The mean ± SD hallucinations dose and delusions dose were 13.7 ± 14.5 (median = 11.0; range, 0–68) and 21.7 ± 15.6 (median = 18.0; range, 0–76), respectively. Duration of untreated psychosis was relatively weakly correlated with hallucinations dose ($r = 0.32$, $P < .01$) and slightly more so with delusions dose ($r = 0.39$, $P < .001$). The doses of hallucinations and delusions were moderately correlated ($r = 0.62$, $P < .001$). Intercorrelations among the 4 dependent variables of interest are shown in Table 2.

Table 1. Sociodemographic Characteristics of Hospitalized Patients With a First Episode of Nonaffective Psychosis (n = 109)

Characteristic	Value
Age, mean ± SD, y	23.1 ± 4.7
Male gender, n (%)	83 (76.1)
Race/ethnicity, n (%)	
Black/African American	98 (89.9)
White/Caucasian	7 (6.4)
Asian American	2 (1.8)
Level of educational attainment, n (%)	
Did not graduate high school	48 (44.0)
High school graduate	21 (19.3)
> 12 y	39 (35.8)
Marital status, n (%)	
Single and never married	100 (91.7)
Married or living with a partner	5 (4.6)
Separated or divorced	4 (3.7)
Who the patient lived with in the month prior to hospitalization, n (%)	
Parents, siblings, or other family members	76 (69.7)
Alone	10 (9.2)
Friends, roommates, boyfriend, girlfriend, or spouse	13 (11.9)
Other	10 (9.2)

Table 2. Intercorrelations Among the 4 Dependent Variables of Interest (*P* values shown in parentheses)

	PANSS Negative Symptoms	PANSS General Psychopathology Symptoms	BIS Score
PANSS general psychopathology symptoms	0.56 (< .001)		
BIS score	−0.19 (.06)	−0.20 (.04)	
GAF score	−0.37 (< .001)	−0.35 (< .001)	0.03 (.78)

Abbreviations: BIS = Birchwood Insight Scale, GAF = Global Assessment of Functioning, PANSS = Positive and Negative Syndrome Scale.

Models Involving Negative and General Psychopathology Symptoms

First, PANSS negative symptom scores were examined as the dependent variable. The baseline model, including age, gender, premorbid academic functioning, and premorbid social functioning, was significant (both age [$\beta = -0.32$, SE = 0.13, $P = .02$] and premorbid social functioning [$\beta = 2.02$, SE = 0.65, $P < .01$] were significant independent predictors). As shown in Table 3, when DUP was added to this model, a significant effect was observed (adjusted $F = 5.77$, $P = .02$). The R^2 value indicated that the 5 independent variables in this model accounted for 20% of the variability in PANSS negative symptom scores. Adding total dose of psychosis did not reveal a significant effect. When hallucinations dose and delusions dose were examined separately, there were no effects of these variables in predicting negative symptoms beyond the effect of DUP.

Models were then used to evaluate the prediction of PANSS general psychopathology symptom scores. The baseline model was not significant, though, within this model, premorbid social functioning was a significant predictor ($\beta = 1.78$, SE = 0.90, $P = .05$). Neither DUP nor total dose of psychosis added significantly to the prediction of general psychopathology symptoms. However, when hallucinations dose and delusions dose were examined separately, the latter was a significant predictor (adjusted $F = 5.56$, $P = .02$) when controlling for the effects of age, gender, premorbid academic functioning, premorbid social functioning, and DUP (Table 3). The R^2 value associated with this model was 0.15.

Models Involving Insight and Global Functioning

Birchwood Insight Scale scores were then assessed as the dependent variable. The baseline model, again including age, gender, premorbid academic functioning, and premorbid social functioning, was not significant, though the effect of gender approached significance ($\beta = -1.45$, SE = 0.76, $P = .06$). As shown in Table 4, when DUP was added to this model, no significant effect was observed. However, adding total dose of psychosis revealed a significant effect (adjusted $F = 5.57$, $P = .02$). Furthermore, when the 2 component doses were examined separately, hallucinations dose was a significant predictor of *better* insight (adjusted $F = 11.16$, $P < .01$) when controlling for the effects of age, gender, premorbid academic functioning, premorbid social functioning, and DUP. The R^2 value indicated that the 6 independent variables

Table 3. Effects of Duration of Untreated Psychosis (DUP) and "Doses" of Initial, Untreated Hallucinations and Delusions in Predicting Negative and General Psychopathology Symptoms at Initial Hospitalization

Dependent Variable	n[a]	F[b]	df[b]	P[b]	R^2
PANSS negative symptoms					
Baseline model					
Age, gender, premorbid academic functioning, premorbid social functioning	104	4.55	4	<.01	0.16
Baseline model + additional predictors					
+ DUP	100	5.77	1	.02	0.20
+ DUP + dose of psychosis	91	0.02	1	.90	0.24
+ DUP + hallucinations dose	92	0.01	1	.93	0.24
+ DUP + delusions dose	94	0.02	1	.88	0.24
PANSS general psychopathology symptoms					
Baseline model					
Age, gender, premorbid academic functioning, premorbid social functioning	104	1.80	4	.13	0.07
Baseline model + additional predictors					
+ DUP	100	1.97	1	.16	0.08
+ DUP + dose of psychosis	91	2.57	1	.11	0.13
+ DUP + hallucinations dose	92	0.41	1	.52	0.11
+ DUP + delusions dose	94	5.56	1	.02	0.15

[a]Sample sizes change slightly due to missing data for some additional predictors.
[b]For the 2 baseline models, the overall F, df, and P value are given. For subsequent models, the F, df, and P values refer to the last added variable.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Table 4. Effects of Duration of Untreated Psychosis (DUP) and "Doses" of Initial, Untreated Hallucinations and Delusions in Predicting Insight and Global Functioning at Initial Hospitalization

Dependent Variable	n[a]	F[b]	df[b]	P[b]	R^2
BIS score					
Baseline model					
Age, gender, premorbid academic functioning, premorbid social functioning	104	1.91	4	.12	0.07
Baseline model + additional predictors					
+ DUP	100	0.03	1	.86	0.08
+ DUP + dose of psychosis	91	5.57	1	.02	0.14
+ DUP + hallucinations dose	92	11.16	1	<.01	0.20
+ DUP + delusions dose	94	0.61	1	.43	0.09
GAF score					
Baseline model					
Age, gender, premorbid academic functioning, premorbid social functioning	101	0.70	4	.59	0.03
Baseline model + additional predictors					
+ DUP	97	3.97	1	.05	0.08
+ DUP + dose of psychosis	89	1.94	1	.17	0.10
+ DUP + hallucinations dose	90	0.16	1	.69	0.08
+ DUP + delusions dose	92	4.55	1	.04	0.13

[a]Sample sizes change slightly due to missing data for some additional predictors.
[b]For the 2 baseline models, the overall F, df, and P value are given. For subsequent models, the F, df, and P values refer to the last added variable.
Abbreviations: BIS = Birchwood Insight Scale, GAF = Global Assessment of Functioning.

in this model accounted for 20% of the variability in insight scores. On the other hand, dose of delusions was not a significant predictor of insight scores.

Finally, models were used to evaluate the prediction of GAF scores. Although the baseline model was not significant, DUP added significantly to the prediction of global functioning (adjusted $F = 3.97$, $P = .05$). Total dose of psychosis and the component hallucinations dose were not significant predictors. However, as shown in Table 4, delusions dose was a significant predictor (adjusted $F = 4.55$, $P = .04$) above and beyond the effects of age, gender, premorbid academic functioning, premorbid social functioning, and DUP. The R^2 value associated with this model was 0.13.

DISCUSSION

Several interesting findings emerged. First, regarding first-episode negative symptoms, DUP is a significant predictor, although neither total dose of initial, untreated psychosis nor doses of hallucinations or delusions individually added significant predictive value. Second, general psychopathology symptoms were not predicted by DUP, though delusions dose (but not hallucinations dose) was a significant independent predictor. Third, DUP was not a significant predictor of insight, and neither was total dose of initial, untreated psychosis; however, hallucinations dose (but not delusions dose) was a significant predictor. Fourth, in terms of global functioning, DUP was a significant predictor, and the addition of delusions dose added further predictive value. *Dose* refers to the measurement of an exposure, and we use this term to emphasize the potential importance of overall "amount" of psychosis in addition to duration of exposure, in predicting (or serving as a marker for) key early-course features.

Duration of untreated psychosis was associated with negative symptoms at initial treatment contact, which is consistent with prior research, though the current dose measures were not associated with negative symptoms. It should be noted, however, that the assumption that duration or dose of untreated psychosis affects outcomes by the mechanism of psychosis per se (ie, through an "active morbid process" or a "psychosocial toxic effect" as mentioned previously) must be tempered by considering help seeking and pathways to care. Negative symptoms at onset—along with premorbid dysfunction and a very insidious decline—may contribute to DUP by delaying help seeking. Thus, to assume that DUP predicts negative symptoms, rather than negative symptoms contributing to DUP, would be an overly simplistic view of these constructs.

Although associated with negative symptoms, DUP was not predictive of other domains (eg, general psychopathology symptoms and insight), whereas doses of initial, untreated hallucinations or delusions added substantively to the prediction of those domains. Perhaps most interestingly, dose of initial, untreated hallucinations and dose of initial, untreated delusions had surprisingly differential effects, with the former predicting *better* insight and the latter predicting poorer clinical features in terms of general psychopathology symptoms and global functioning. Indeed, relying on a total dose of initial, untreated psychosis (hallucinations + delusions) may obfuscate important relationships, as demonstrated by the fact that total dose of initial, untreated psychosis was not associated with global functioning, but the dose of delusions was.

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The observed differential effects could relate to subjective experiences and recall of hallucinations versus delusions. The ability to engage in retrospective reflection on abnormal sensory experiences may be an indirect measure of insight. The individual is "reconstructing" past abnormal sensory experiences that were intermittent. Patients who are better able to give an account of past hallucinatory experiences may therefore score higher on measures of current insight; this could account for the positive relation between past hallucinations and current insight. (However, as noted above, caution is warranted in considering insight as a dependent variable that is predicted by DUP or dose measures; insight could well be a predictor in these relationships.) In contrast, delusions are more likely to be ongoing, and retrospective recall of delusional thoughts may therefore require less capacity for reflection (ie, executive capacity). Further, patients who are currently more impaired—and more delusional—may give an account of their past delusional experiences that draws on their current delusional thoughts. This could contribute to the positive correlation between past dose of delusions and clinical severity. But it was somewhat surprising that dose of delusions was unrelated to insight, as a number of studies have documented an inverse relationship between severity of delusions and some components of insight.[47–49]

The potential importance of the present findings pertains to the possibility of expanding and refining the unidimensional DUP construct which, though controversial, is relatively weakly associated with various adverse outcomes. These findings suggest that understandings of pretreatment prognostic factors in nonaffective psychotic disorders must evolve beyond the notion of a single duration measure in predicting outcome. Further, these results clearly demonstrate that the "psychosis" of the DUP construct is multidimensional (representing both hallucinations and delusions); measures that neglect this complexity (like DUP) may obscure prognostically meaningful associations. We are unaware of prior evidence of differential associations between dose/severity of hallucinations or delusions and insight. Indeed, insight has commonly been considered vis-à-vis total positive symptom scores rather than specific positive symptoms.

Several methodological limitations must be acknowledged. First, dose measures were restricted to the 24 months prior to admission because of measurement feasibility concerns, which may also represent a limitation given that some participants had longer estimated DUP values. Additionally, the dependent measures were clinical features at the time of initial hospitalization rather than longer-term outcome measures; future research should examine the associations longitudinally. Second, future research attempting to quantify doses of initial, untreated psychotic symptoms should address reliability and validity of such measures. Although the present findings may serve as an initial validation of dose measures, reliability (eg, test-retest reliability and interrater reliability) should be examined. In the present study, PSYRATS data were obtained through an in-depth interview facilitated by a timeline, though reliability was not formally assessed. In addition to addressing reliability and validity, future studies would benefit from examining the relative effects of duration, frequency, and severity of initial, untreated symptoms. (For example, is 1 week of continuous hallucinations a greater, lesser, or equivalent dose relative to 2 weeks of less frequent hallucinations?) The present study used a straight-forward a priori approach to computing a hallucinations dose and a delusions dose by summing scores from the 5 specific PSYRATS items across the four 6-month quarters. Third, generalizability of results may be limited by virtue of the sociodemographic and clinical characteristics of the study sample. Yet, the general notions pointed out in this proof-of-concept study are unlikely to be region-, race/ethnicity-, or setting-specific. Fourth, larger sample sizes would provide enhanced power to detect small effects of some independent variables on the key dependent variables. However, the study was designed to recruit and thoroughly assess a medium to large first-episode sample (n = 100) to allow adequate testing of hypotheses and to detect clinically relevant effects.

This demonstration suggests a need for further focused research on pretreatment psychosis beyond the well-replicated findings on DUP. Although some innovation has been introduced recently in this area, including parsing DUP into help-seeking–delay and referral-delay components,[50] and new concepts, such as the duration of untreated negative symptoms,[51] we suggest that measuring frequency and severity in addition to duration (and doing so separately for hallucinations and delusions) may be beneficial. Research questions that should now be addressed include (1) In what other domains might the dose of initial, untreated psychosis construct add value beyond simpler duration measures? (2) What are the most efficient, reliable, valid, and easily disseminated methods for operationalizing and measuring doses of initial, untreated psychotic symptoms? and (3) Does the effectiveness of early intervention efforts hinge upon simply reducing the *duration* of untreated psychotic symptoms, or is the effect related more to a reduction in overall dose or cumulative exposure to psychosis? The present study challenges the prevailing paradigm in which duration alone is an adequate measure of exposure to psychosis and argues for more comprehensive measures of such exposure.

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