

HHS Public Access

Early Interv Psychiatry. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

Author manuscript

Early Interv Psychiatry. 2017 October ; 11(5): 375-382. doi:10.1111/eip.12256.

Associations between duration of untreated psychosis and domains of positive and negative symptoms

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Abstract

Aim—The duration of untreated psychosis (DUP) has been established as an independent and significant predictor of negative outcomes in first-episode psychosis samples. Whereas literature has supported the association between DUP and severity of positive and negative symptoms, surprisingly little research to date has explored specifically what types of positive and negative symptoms are most associated with DUP.

Methods—DUP, Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) data were collected in 247 first-episode psychosis participants (mean age: 23.9 ± 4.8) between August 2008 and June 2013.

Results—DUP was significantly but modestly associated with the severity of hallucinations ($\rho = 0.222$; P = 0.001), delusions (r = 0.202; P = 0.003) and formal thought disorder ($\rho = 0.138$; P = 0.043) but was not associated with bizarre behaviour. DUP was significantly but modestly associated with SANS avolition-apathy ($\rho = 0.164$; P = 0.016) and anhedonia-asociality (r = 0.321; P < 0.001) subscales but was not associated with affective flattening or blunting, alogia or attention.

Conclusions—DUP is a complex and multifaceted phenomenon that is associated with earlycourse illness development. In efforts to improve early intervention services, prognoses and outcomes, it is vital to understand both the factors that contribute to lengthy untreated psychosis as well as the illness characteristics that are impacted by untreated psychosis.

Keywords

duration of untreated psychosis (DUP); early intervention; Scale for the Assessment of Negative Symptoms (SANS); Scale for the Assessment of Positive Symptoms (SAPS)

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INTRODUCTION

The duration of untreated psychosis (DUP) has been established as an independent and significant predictor of negative outcome in first-episode psychosis samples. Often defined as the length of time between the onset of positive psychotic symptoms and receiving appropriate care (typically antipsychotics), DUP can be lengthy and destructive.¹ Psychotic symptoms typically emerge during formative years of adolescence and young adult development and interfere with the establishment of healthy educational, vocational and social foundations.^{2–4} Despite international efforts to reduce the DUP, in the recent National Institute of Mental Health (NIMH)-funded RAISE (Recovery After the Initial Schizophrenia Episode) project involving 404 first-episode psychosis patients treated at 34 clinics across the USA, the median DUP was 84.6 weeks.⁵ As psychosis persists and disability accumulates without intervention, adolescents and young adults in the early stages of illness are potentially missing a critical window of opportunity to benefit from services available at early intervention programmes.

Previous reports have focused on the complex and multifaceted factors that may contribute to lengthy untreated psychosis. Determinants that appear to be associated with duration of treatment delay include: (i) demographic characteristics such as age, sex, race, income and health insurance status; (ii) systemic factors such as ill-defined pathways to care and faulty referral processes; (iii) illness-related factors such as speed of symptom onset; and (iv) environmental factors such as perceived stigma and level of mental health education/ awareness within the family and community.⁶

In addition to exploring determinants of DUP, previous reports have attempted to elucidate the aspects of early-course illness that are predicted by longer untreated psychosis. These include poorer response to treatment; worse global, vocational, social and cognitive functioning; higher risk of relapse; and lower quality of life.^{1,7}

Extensive literature has additionally suggested that DUP is significantly associated with the severity of positive and negative symptoms at the time of presentation. Whereas limited previous reports have supported a link between DUP and grandiosity, bizarreness,^{8,9} unusual or dangerous behaviour,^{10,11} and avolition and poor social integration,¹² surprisingly little research to date has explored specifically what types of positive and negative symptoms are most associated with the length of untreated psychosis.

Understanding the nature of the association between untreated psychosis and specific domains of positive and negative symptoms is critical to better inform outreach and engagement efforts as well as improve our ability to develop successful early intervention services providing stage-specific, targeted care. Given a prominent dearth of research examining associations between DUP and specific domains of positive and negative symptoms, we conducted an exploratory analysis using a relatively large dataset involving first-episode patients to determine if there are any differential associations, which, if understood, might inform early intervention efforts.

METHODS

Setting and sample

Data for the present analysis were collected as part of a larger study investigating the impact of premorbid cannabis use on the early course of schizophrenia and other primary psychotic disorders. Six psychiatric inpatient units in Atlanta, Georgia and Washington, DC served as recruitment sites where consecutively admitted first-episode psychosis patients were approached regarding enrolment into the cross-sectional/retrospective study. The six sites primarily serve low-income, socially disadvantaged patients with public-sector health insurance (i.e. Medicaid) or no insurance.

Patients were eligible if they met the following criteria: (i) were English speaking; (ii) were within the age range of 18–40 years; (iii) did not have known or suspected mental retardation; (iv) had a diagnosis of a primary non-affective psychotic disorder; (v) had a Mini-Mental State Examination score of 24; (vi) had not been hospitalized for psychosis >3 months prior to index admission; (vii) had not received >3 months of prior antipsychotic treatment; (viii) did not have a significant medical condition compromising ability to participate; and (ix) were able to provide informed consent.

Measures and rating scales

Diagnoses of psychotic disorders were confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)¹³ following a semi-structured interview with the study participant, a collateral interview with informants when available, and a chart review.

Data regarding psychiatric illnesses in family members of study participants were collected using an adapted version of the *Family Interview for Genetic Studies*.¹⁴ The presence of narrowly defined schizophrenia or a broadly defined psychotic disorder in a first-degree relative was determined by team consensus following a review of all information collected from the patient, informants and the medical chart.

Data regarding the onset of psychotic symptoms were collected using the *Symptom Onset in Schizophrenia* (SOS) inventory.¹⁵ Date of onset of psychosis was determined by team consensus following a thorough review of the patient's in-depth, semi-structured SOS interview, as well as informants' SOS interviews and the medical chart. DUP was operationalized as duration in weeks from the date at onset of the initial hallucinations and/or delusions to the date of first hospital admission. Mode of onset of psychotic symptoms was determined by team consensus, and was operationalized as acute with sudden onset, acute with precipitous onset, subacute, gradual and insidious, as defined for the World Health Organization International Pilot Study of Schizophrenia.¹⁶ These five levels were then trichotomized as *acute* (comprised of the sudden and precipitous categories), *subacute* and *chronic* (including gradual and insidious categories).

Following an in-depth, semi-structured interview, positive and negative symptoms were measured with the *Scale for the Assessment of Positive Symptoms* (SAPS)¹⁷ and its complement, the *Scale for the Assessment of Negative Symptoms* (SANS).¹⁸ The SAPS consists of 34 items belonging to four subscales: hallucinations, delusions, bizarre behaviour

and positive formal thought disorder. Each of the four areas includes ratings for specific symptoms (e.g. auditory hallucinations) as well as a global rating, all scored on a scale from 0 = none to 5 = severe. The SANS is structured similarly to the SAPS and is comprised of 25 items grouped into five subscales: affective flattening or blunting, alogia, avolition-apathy, anhedonia-asociality and attention. Test–retest reliability and construct validity have been demonstrated for both instruments.¹⁹

To assess the interrater reliability of the SAPS and SANS scores, intraclass correlation coefficients (ICCs) were calculated using a two-way random effects anova model with the goal of measuring consistency among the trained raters.²⁰ ICCs for the four SAPS subscale scores were as follows: hallucinations: 0.95 (95% CI: 0.90, 0.97), delusions: 0.91 (95% CI: 0.84, 0.95), bizarre behaviour: 0.73, (95% CI: 0.52, 0.85) and formal thought disorder: 0.89 (95% CI: 0.80, 0.94). ICCs for the five SANS subscale scores were as follows: affective flattening or blunting: 0.76 (95% CI: 0.58, 0.87), alogia: 0.84 (95% CI: 0.73, 0.92), avolition-apathy: 0.80 (95% CI: 0.65, 0.89), anhedonia-asociality: 0.86 (95% CI: 0.76, 0.93) and attention: 0.65 (95% CI: 0.38, 0.81).

Data analyses

Basic descriptive statistics and distributional properties of all variables were examined. Correlational analyses were conducted using Pearson product–moment correlations when both variables had distributions that approximated a normal distribution (based on our review of descriptive statistics and the Kolmogorov–Smirnov test for normality), and Spearman correlations when one or both did not. After examining correlations between DUP and the four SAPS domain scores and five SANS domain scores, we then examined any potential confounding by four additional variables of interest: gender, family history, mode of onset of psychosis and age at onset of psychosis. We also examined the effects of alcohol and drug abuse/dependence based on SCID-based substance use disorder diagnoses. All analyses were conducted using IBM SPSS Statistics 19.

RESULTS

Sample characteristics and descriptive statistics

As shown in Table 1, the mean age of study participants (n = 247) was 23.9 ± 4.8 years. Their mean years of educational attainment were 11.9 ± 2.2 . The majority were male (184, 74.5%), African American (213, 86.2%), single and never married (212, 85.8%), living with family members prior to hospitalization (162, 65.6%) and unemployed (169, 68.4%). Among the 247 patients, SCID-based psychotic disorder diagnoses were as follows: schizophrenia, paranoid type (97, 39.3%); psychotic disorder, not otherwise specified (38, 15.4%); schizophrenia, undifferentiated type (33, 13.4%); schizophrenia, disorganized type (11, 4.5%); schizoaffective disorder, bipolar type (5, 2.0%); delusional disorder (4, 1.6%); brief psychotic disorder (2, 0.8%); and schizophrenia, catatonic type (2, 0.8%).

The mean DUP among those for whom DUP could be reliably ascertained (n = 214) was 135.4 \pm 222.4 weeks; the median was 40.0 weeks. In order to create a more normal

distribution, we calculated log (DUP), which had a mean of 3.4 ± 1.9 and a median of 3.7. The Kolmogorov–Smirnov test indicated that the distribution approximated normality. For ease of reading, we refer to log (DUP) simply as 'DUP' in the presentation of results.

Mean scores for the SAPS hallucinations, delusions, formal thought disorder and bizarre behaviour were 12.1 ± 7.9 , 18.1 ± 8.7 , 6.9 ± 6.5 and 6.9 ± 4.3 , respectively. Kolmogorov–Smirnov tests indicated that the SAPS hallucinations and formal thought disorder subscales were not normally distributed. Mean scores for SANS affective flattening or blunting, alogia, avolition-apathy, anhedoniaasociality and attention were 11.9 ± 8.8 , 6.8 ± 5.6 , 10.8 ± 4.1 , 14.3 ± 5.5 and 3.6 ± 3.2 , respectively. Kolmogorov–Smirnov tests indicated that SANS affective flattening or blunting, alogia, avolition-apathy and attention subscales were not normally distributed.

Intercorrelations between SAPS and SANS subscales were examined to shed light on the extent to which they are overlapping versus independent, which will aid in interpretation of the main results. In terms of intercorrelations among the four SAPS subscales, the strongest correlation was between hallucinations and delusions ($\rho = 0.472$), and the weakest was between hallucinations and bizarre behaviour ($\rho = 0.092$). The remaining inter-correlations are given in Table 2. With regard to intercorrelations among the five SANS subscales, the strongest correlation was between affective flattening or blunting and alogia ($\rho = 0.597$) and the weakest was between anhedonia-asociality and attention ($\rho = 0.313$). The remaining intercorrelations are shown in Table 3. In terms of correlations between SANS subscales and SAPS subscales, they ranged from no correlation at all to a maximum correlation of 0.29 between hallucinations and anhedonia-asociality. The mean correlation across these 20 correlations was 0.18.

Bivariate associations between DUP and positive symptom domains

DUP was significantly but modestly associated with the severity of hallucinations ($\rho = 0.222$; P = 0.001), delusions (r = 0.202; P = 0.003) and formal thought disorder ($\rho = 0.138$; P = 0.043) (Table 2). DUP was not significantly associated with the bizarre behaviour subscale (r = 0.063).

Bivariate associations between DUP and negative symptom domains

DUP was significantly but modestly associated with avolition-apathy ($\rho = 0.164$; P = 0.016) and anhedonia-asociality (r = 0.321; P < 0.001) sub-scales (Table 3). Interestingly, DUP was not significantly associated with the remaining three SANS subscales: affective flattening or blunting ($\rho = -0.037$), alogia (r = -0.045) and attention (r = 0.024). Figure 1 shows the relative magnitudes of significant correlations between DUP and symptom severity subscales.

Consideration of five additional variables

In order to assess for possible confounding of the above associations by five key variables, we explored the association of gender, family history, mode of onset of psychosis, age at onset of psychosis, and comorbid current cannabis abuse or dependence with DUP. Gender and family history were not associated with DUP. Age at onset of psychosis was negatively

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correlated with DUP ($\rho = -0.192$, P = 0.006). In order to test whether age at onset might be confounding the relationship between DUP and the various symptom domains, we assessed associations between age at onset and all symptom domains. Age at onset was only associated with affective flattening or blunting ($\rho = -0.150$, P = 0.032) and attention ($\rho = -0.193$, P = 0.005), neither of which had been associated with DUP. Age at onset was not associated with the other three SANS negative symptom domains or any of the SAPS positive symptom domains.

Mode of onset of psychosis was found to be associated with DUP. Specifically, acute onset was associated with shorter DUP (median DUP of 9.0 weeks compared to 90.5 weeks among those with a gradual mode of onset). In order to test whether mode of onset might be confounding the relationship between DUP and the various symptom domains, we tested the associations between mode of onset and those symptom domains. Mode of onset was associated only with affective flattening or blunting (Mann–Whitney *U*-test Z = 2.00; P = 0.045) and attention (Mann–Whitney *U*-test Z = 1.97; P = 0.049), which, again, had not been associated with DUP. Mode of onset was not associated with the other three SANS negative symptom domains or any of the SAPS positive symptom domains.

Current cannabis abuse or dependence was also found to be associated with DUP (although alcohol, cocaine and other drug abuse/dependence were not). Specifically, current cannabis abuse or dependence was associated with a shorter DUP (median DUP was 18.0 weeks compared to 73.0 weeks in those without cannabis abuse or dependence). Current cannabis abuse or dependence was also associated with greater symptom severity in all symptom domains except SANS anhedoniaasociality, and thus could be negatively confounding the relationship between DUP and the various symptom domains. Rerunning the correlations between DUP and symptom domains while stratifying for current cannabis abuse or dependence strengthened the association between DUP and negative symptom domains, stratified by current cannabis abuse or dependence, are shown in Table 5.

DISCUSSION

DUP is a complex and multifaceted phenomenon that is clearly associated with early-course illness development and prognosis in individuals with psychotic disorders.¹ In efforts to improve early intervention services and outcomes, it is vital to understand both the factors that contribute to lengthy untreated psychosis as well as the illness characteristics that are impacted by untreated psychosis. In light of a virtual absence of research on how specific domains of positive and negative symptoms are related to DUP, several interesting findings emerged from our analysis.

Regarding positive symptoms, longer DUP was associated with hallucinations, delusions and thought disorder, but not bizarre behaviour. One possible explanation for these findings is that as schizophrenia pathology progresses, perceptual abnormalities, unusual thought content and disorganization increase in intensity and frequency. This is in line with previous reports²¹ suggesting that the longer the illness is left untreated, the greater the severity of positive symptoms at the time of presentation. However, given the correlational nature of our

study, we cannot exclude the possibility that greater symptom severity drove DUP (i.e. greater severity of hallucinations, delusions and thought disorder led to longer treatment delays). It is conceivable that as individuals become preoccupied with increasingly severe delusions and hallucinations, they are less likely to ask for help and receive intervention. As such, the association might be mediated by impaired insight.^{10,12}

Interestingly, contrary to previous findings,⁸ bizarre behaviour was not associated with DUP in our sample. This might be because bizarreness is an objective phenomenon that can be observed by others as opposed to hallucinations and delusions, which are subjective experiences that may or may not be disclosed. Bizarre behaviour is likely perceived by friends and family who subsequently encourage (or discourage) treatment. The association between bizarre behaviour and DUP might therefore be moderated by the quality of one's environment and relationships, which can vary drastically between individuals and has been previously reported to impact DUP.²² Thus, it is possible that an association exists between bizarre behaviour and DUP, but that the effect is modified by other factors.

Previous reports have supported an association between negative symptoms and DUP.²² In our sample, longer DUP was associated with avolition-apathy and anhedonia-asociality but was not associated with affective flattening or blunting, alogia and attention. One possible interpretation of these findings is that those individuals who remain untreated longer tend to develop diminished interest in social activities, and become increasingly isolated, withdrawn and apathetic. Grooming and hygiene, work and school, recreational activities, sexual interest and intimacy may become less of a priority and increasingly challenging. Alternatively, it is possible that negative symptoms drive longer DUP. It is conceivable that those individuals who are more apathetic and asocial may be less likely to ask for help or to be noticed by others who would subsequently refer for psychiatric intervention.

Interestingly, DUP was not associated with three of the five SANS subscales (affective flattening or blunting, alogia and attention). It is again possible that the association between flat or blunted affect, alogia, and attention and DUP is moderated by the quality of one's environment and social relationships (i.e. others' capacity to identify such symptoms as pathological and necessitating psychiatric care). This can drastically vary between individuals and therefore any association between those symptom domains and DUP may be modified by those unmeasured factors.

Because the presence of current cannabis abuse and dependence was associated both with a shorter DUP and with a greater severity of symptoms in some SAPS/SANS domains, we showed that it was a negative confounder of the association between DUP and some symptom domains. When this suppression effect was addressed using stratification, the correlations between DUP and a number of the symptom domains strengthened.

There are several noteworthy limitations to our study. First, our analysis provides associations between specific positive and negative symptom domains and DUP, but it cannot determine directionality. This is nonetheless crucial information that can inform future research projects exploring which aspects of DUP (e.g. help-seeking delay, referral delay) are predicted by specific symptoms, as well as which aspects of illness are impacted

by DUP. A second limitation pertains to generalizability, as our sample consisted primarily of socially disadvantaged, African American, hospitalized patients. Nonetheless, this population is deserving of focused research as they are often underrepresented in early-psychosis samples. Finally, the retrospective nature of several variables in our data, including age at onset of psychosis and mode of onset, may have introduced recall errors. However, as described above, we rigorously assessed these variables and are confident that they are as accurate as possible.

Efforts to improve our understanding of DUP are aimed at enhancing early detection, engagement and intervention services. The more we know about determinants and predictors of outcome, the better we can tailor our programmes to meet the stage-specific needs of affected individuals. A thorough understanding of early-stage psychosis progression and its association with DUP will also assist in our advocacy and educational initiatives. Determining the specific symptoms that are less likely to receive clinical attention and therefore lengthen DUP is critical to informing campaigns designed to reach youth who would otherwise go months to years before finally receiving appropriate intervention. Future research should focus on better understanding why certain positive and negative symptom domains are differentially associated with treatment delays. This information will help mental health clinicians educate youth to identify early warning signs in peers as well as themselves. It can also serve to educate parents, teachers and others who interact with youth and young adults to better identify early warning signs and improve trajectories to appropriate early intervention and care.

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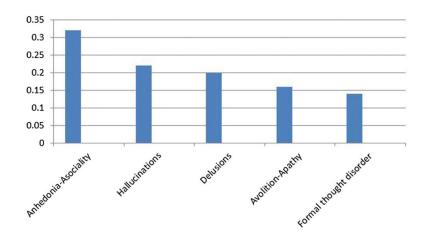


FIGURE 1.

Magnitude of correlations between domains of positive and negative symptoms and DUP, only statistically significant correlations are shown, in decreasing magnitude.

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TABLE 1

Sociodemographic characteristics of the full sample (n = 247)

Mean age	23.9 ± 4.8 (range: 18-40
Years of education	11.9 ± 2.2 (range: 5-19)
Gender	
Male	184 (74.5%)
Female	63 (25.5%)
Race	
Black/African American	213 (86.2%)
White/Caucasian	19 (7.7%)
Asian American	4 (1.6%)
African (Ethiopian, Nigerian)	3 (1.2%)
Biracial	3 (1.2%)
Other	5 (2.0%)
Relationship status ($n = 246$)	
Single and never married	212 (85.8%)
Married or living with a partner	13 (5.3%)
Separated, divorced or widowed	21 (8.5%)
Who patient lived with before hospitalization	
Parents, siblings or other family members	162 (65.6%)
Alone	16 (6.5%)
Friends or roommate	13 (5.3%)
Boyfriend, girlfriend, spouse or partner	10 (4.0%)
Homeless	24 (9.7%)
Structured living arrangement	2 (0.8%)
Other	13 (5.3%)
Employment status the month prior to hospitalizatio	
Unemployed	169 (68.4%)
Employed	78 (31.6%)
SCID diagnosis	
Schizophrenia, paranoid type	97 (39.3%)
Psychotic disorder not otherwise specified	38 (15.4%)
Schizophrenia, undifferentiated type	33 (13.4%)
Schizophreniform disorder	29 (11.7%)
Schizoaffective disorder, depressive type	26 (10.5%)
Schizophrenia, disorganized type	11 (4.5%)
Schizoaffective disorder, bipolar type	5 (2.0%)
Delusional disorder	4 (1.6%)
Schizophrenia, catatonic type	2 (0.8%)
Brief psychotic disorder	2 (0.8%)
Current alcohol abuse or dependence ($n = 234$)	
None	195 (83.3%)

Abuse	11 (4.7%)
Dependence	28 (12.0%)
Current cannabis abuse or dependence $(n = 233)$	
None	131 (56.2%)
Abuse	26 (10.5%)
Dependence	76 (30.8%)
Current cocaine abuse or dependence ($n = 236$)	
None	225 (95.3%)
Abuse	2 (0.8%)
Dependence	9 (3.8%)
Current 'other drug' abuse or dependence $(n = 238)$	
None	221 (92.9%)
Abuse	5 (2.1%)
Dependence	12 (5.0%)

Intercorrelations among the SAPS subscales, and correlations with $\mathrm{DUP}^{\acute{\tau}}$

	DUP	1	2	3
1. Hallucinations	0.222 ***			
2. Delusions	0.202 ***	0.472 ***		
3. Positive formal thought disorder	0.138*	0.134*	0.356***	
4. Bizarre behaviour	0.063	0.092	0.215 ***	0.337 ***

* P<0.05

** P 0.01

*** P 0.001.

[†]Pearson product-moment correlation coefficients or Spearman correlation coefficients given, as appropriate.

Intercorrelations among the SANS subscales, and correlations with $\mathsf{DUP}^{\acute{\tau}}$

	DUP	1	2	3	4
1. Affective flattening or blunting	-0.037				
2. Alogia	-0.045	0.597			
3. Avolition-Apathy	0.164*	0.410 ***	0.387***		
4. Anhedonia-Asociality	0.321 ***	0.408 ***	0.335	0.551 ***	
5. Attention	0.024	0.458 ***	0.575	0.341 ***	0.313 ***

* P<0.05

**** P 0.001.

 † Pearson product-moment correlation coefficients or Spearman correlation coefficients given, as appropriate.

Magnitudes of correlations between DUP and SAPS subscale scores, stratified by current cannabis abuse or dependence †

	Overall sample	Without current cannabis abuse or dependence (<i>n</i> = 131)	With current cannabis abuse or dependence $(n = 102)$
Hallucinations	0.222	0.247	0.260
Delusions	0.202	0.282	0.219
Positive formal thought disorder	0.138	0.174	0.190
Bizarre behaviour	0.063	0.023	0.161

 † Pearson product-moment correlation coefficients or Spearman correlation coefficients given, as appropriate.

Magnitudes of correlations between DUP and SANS subscale scores, stratified by current cannabis abuse or dependence †

	Overall sample	Without current cannabis abuse or dependence (<i>n</i> = 131)	With current cannabis abuse or dependence $(n = 102)$
Affective flattening or blunting	-0.037	-0.002	-0.044
Alogia	-0.045	0.014	-0.026
Avolition-Apathy	0.164	0.115	0.249
Anhedonia-Asociality	0.321	_	_
Attention	0.024	0.104	-0.063

 † Pearson product-moment correlation coefficients or Spearman correlation coefficients given, as appropriate.