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Functional outcome and service engagement in major depressive disorder with psychotic features: comparisons with schizophrenia, schizoaffective disorder and bipolar disorder in a 6-year follow-up of the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS)

Running title: 6-year follow-up of psychotic depression

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Abstract

Objective: While long-term outcome following a first psychotic episode is well studied in schizophrenia (SZ), schizoaffective disorder (SA) and bipolar disorder (BD), major depressive disorder with psychotic features (MDDP) has received less investigation. This study compares MDDP with SZ, SA and BD at 6-year follow-up.

Methods: At six years after a first psychotic episode, follow-up data on psychopathology, functioning, quality of life and service engagement were obtained for 27 cases of MDDP in comparison to 60 SZ, 27 SA, and 35 BD.

Results: Positive psychotic symptoms were less prominent in MDDP and BD than in SZ and SA. Negative symptoms, impaired functioning and reduction in objectively determined quality of life were less prominent in MDDP and BD, intermediate in SA and most prominent in SZ. However, subjectively determined quality of life was indistinguishable across diagnoses. Service engagement was highest for MDDP, intermediate for SA and BD, and lowest for SZ.

Conclusions: At 6-year follow-up, these diagnoses are characterised by quantitative rather than qualitative differences in psychopathology, functionality, quality of life and service engagement, with considerable overlap between them. These findings suggest that MDDP should join SZ, SA and BD in a milieu of psychosis that transcends arbitrary boundaries.

KEYWORDS

Major depressive disorder with psychotic features, 6-year follow-up, functional outcome, quality of life, service engagement

1 INTRODUCTION

Functionality and quality of life are well recognised as critical indices of outcome in all medical conditions and have been widely studied in relation to psychotic illness. However, this literature derives primarily from studies on the diagnostic category of schizophrenia (SZ), while contemporary research is increasingly involving broader, dimensional concepts of psychosis¹⁻⁴. To the forefront of such research is the nosological, clinical and biological relationship between SZ and bipolar I disorder (BD)^{1,4-6}, with the long-standing conundrum of schizoaffective disorder (SA) continuing to receive consideration in this context^{7,8}. However, the most common psychotic diagnosis other than SZ and BD is major depressive disorder with psychotic features (MDDP). Though it constitutes the archetype for confluence between psychotic and affective dimensions of psychopathology⁹, MDDP [also known as psychotic depression¹⁰], has received less attention in this context. Psychotic features occur in only a minority of patients with major depressive disorder¹¹⁻¹⁴. While some contemporary evidence suggests that MDDP is not related simply to severity of depressive illness and may be better conceptualised as a distinct diagnostic category^{12,14,15}, this remains a subject of debate.

Functionality is a key measure of outcome for reasons relating to the individual/service user, service providers and broader socioeconomic concerns; this includes areas such as self-care, relationships, occupation and community and social life. Quality of life (QoL) is perhaps the most important outcome measure from an individual's perspective. Study of outcome, and long-term predictors thereof, is therefore fundamental to resource allocation in efforts to mitigate functional decline. It is well recognised that SZ can be characterised by pervasive disability over

multiple dimensions of functioning^{1,16,17}, with BD also characterised by considerable functional impairment, albeit perhaps to a somewhat lesser extent than for SZ^{5,18}. SA has commonly been included with SZ, such that fewer studies have addressed SA as a distinct category^{7,8,19}. In contrast, MDDP has received less attention, there being few long-term follow-up studies to date²⁰⁻²².

On the presumption that mental health and associated services can provide beneficial interventions, engagement with such services is an essential element in optimising outcome. Service engagement has no agreed definition, but infers acceptance of treatment, therapeutic rapport and collaboration in a shared goal of clinical and functional recovery²³. Good service engagement has been found to predict better outcome in SZ^{24,25} but has received less independent, comparative study in SA, BD and, particularly, MDDP²⁶.

The most effective method of addressing these issues is one that introduces the least bias into initial case identification and then proceeds in a prospective manner. The Cavan-Monaghan First Episode Psychosis Study (CAMFEPS) incepts cases of first episode psychosis ascertained on an epidemiological basis across the whole adult lifespan and via all routes to care, in the absence of *a priori* diagnostic restriction. Application of contemporary diagnostic algorithms as *post hoc* assessment, rather than as a criterion for inclusion/exclusion, then resolves all twelve DSM-IV psychotic diagnoses and allows systematic comparisons between selected diagnostic categories across several levels of enquiry²⁷. We have previously described systematic comparisons between psychotic diagnoses at first presentation in terms of epidemiology, psychopathology, neurology and QoL²⁸ and diagnostic trajectory over six-year follow-up²⁹, with a particular focus on comparing MDDP with the most populous diagnoses of SZ, SA and BD. Here, we

systematically compare functional outcome, QoL and service engagement in MDDP with SZ, SA and BD during a 6-year follow-up of the CAMFEPS cohort.

2 MATERIALS AND METHODS

2.1 Study Setting

CAMFEPS is a prospective study, operating since 1995, that seeks to identify ‘all’ incident cases presenting with a first episode of any of the twelve DSM-IV psychotic disorders in two rural counties in Ireland, Cavan and Monaghan, as described previously in detail^{27,28,30,31}. Study protocols were approved by the Research Ethics Committees of the North Eastern Health Board [and, following restructuring, of the Health Service Executive Dublin North East Area], St. Patrick’s Hospital, Dublin, St. John of God Hospital, Co. Dublin and the Central Mental Hospital, Dublin, to include subjects giving written, informed consent to follow-up assessments after these had been fully explained.

Cavan and Monaghan are two contiguous rural counties with a population of 109,139 [55,821 males and 53,318 females] at the 2002 census, the census most proximal to the middle year over which this follow-up study was conducted; the region consists of towns, villages and remote areas, in the absence of any major urban areas, and is of substantial ethnic and social homogeneity, with the great majority of the population being white Irish (32 Central Statistics Office, 2003). CAMFEPS is based within Cavan-Monaghan Mental Health Service, which operates a community-based service with a focus on home treatment, general practice liaison and services based in small local clinics. It involves two community mental health teams, a specialist service for the elderly and a community rehabilitation team; central to the delivery of health services in this model is the use of home-based treatment as an alternative to hospital

admission³³. All cases from this catchment area who present to services in other parts of the country are returned to Cavan-Monaghan Mental Health Service as soon as is practicable.

2.2 Assessment

The present study relates to findings at 6-year follow-up among the 202 cases of first episode psychosis having any one of the 12 DSM-IV psychotic diagnoses following presentation over the first eight years of CAMFEPS. Details on case ascertainment and assessment at the first psychotic episode and follow-up have been described previously in detail²⁷⁻²⁹. At follow-up, assessment included the following instruments:

2.2.1 Diagnosis

Structured Clinical Interview for DSM-IV³⁴.

2.2.2 Psychopathology

Positive and Negative Syndrome Scale (PANSS)³⁵.

2.2.3 Functioning

Global Assessment of Functioning³⁶; Health of the Nation Outcome Scale (HoNOS)³⁷; Strauss-Carpenter Scale³⁸; Specific Level of Functioning (SLOF)³⁹.

2.2.4 Quality of life

Quality of Life Scale (QLS)⁴⁰; World Health Organisation QOL-BREF Scale (WHOQOL-BREF)⁴¹.

2.2.5 Service engagement

Service Engagement Scale (SES)⁴².

2.3 Statistical analysis

Categorical data were analysed using χ^2 tests. Other data were expressed as means with standard deviations (SD) and analysed using analysis of variance (ANOVA) followed by Student's t-tests (two-tailed). A probability value of $P < .05$ was considered significant. Following these analyses, which indicated that differences in psychopathology, functionality, quality of life and service engagement across diagnoses were quantitative rather than qualitative, with considerable overlap between them (see **3 RESULTS**), diagnoses were removed to give a diagnostic composite; then, principal component analysis (PCA) was performed to establish the extent to which the four scales accessing domains of function map onto a common principal component (PC); finally, an exploratory multiple regression model was applied to identify independent predictors of the primary PC of function in psychotic illness across diagnoses. These analyses were performed using SPSS Version 21.

3 RESULTS

3.1 Demographics

Two hundred and two participants were sought for 6-year follow-up. Our procedures²⁹ allowed us to trace 196 (97%) of these individuals at a mean of 6.4 years after first presentation (SD 2.3 years; range 31 to 142 months), for which '6-year follow-up' is used hereafter as convenient shorthand. It was not possible to complete follow up for six individuals: for two, no record of the case was identifiable; for two, their records were in a private hospital and could not be accessed; two had left the country and were untraceable.

Demographics and diagnostic trajectory, interplay and convergence/divergence between first presentation and six-year follow-up have been described previously in detail²⁹ for all diagnostic categories encountered at follow-up: SZ, schizophreniform disorder, SA, brief psychotic disorder, delusional disorder, BD, bipolar II disorder, MDDP, substance-induced psychosis, psychosis due to a general medical condition, substance-induced mania, mania due to a general medical condition, psychosis not otherwise specified, Alzheimer's disease, deceased by suicide, and deceased due to natural causes or accident. The focus here is on comparisons of functional outcome and quality of life between the 149 cases [89 males, 60 females] having one of the four designated psychotic diagnoses at follow-up (MDDP, SZ, SA and BD; Table 1); the remaining 47 cases received diagnoses other than MDDP, SZ, SA and BD, as described previously²⁹. As expected, sex distribution of the 149 cases differed between these four diagnostic categories ($P < .05$): MDDP and BD were equally common in males and females; SZ was more common in males than in females; SA showed an intermediate distribution. Age differed between these four diagnoses ($P < .05$; no diagnosis \times sex interaction); patients with MDDP were older than those in each of the other three main diagnostic groupings ($P < .05$, MDDP vs each of SZ, SA and BD).

3.2 Psychopathology

PANSS assessments were available for 26 of 27 cases of MDDP, all 60 cases of SZ, all 27 cases of SA, and 33 of 35 cases of BD (Table 2). PANSS-total scores differed between the diagnoses (effect of diagnosis, $P < .001$; no effect of sex or diagnosis \times sex interaction); scores were highest for SZ, marginally lower for SA, and lower for both BD and MDDP (each $P < .001$ vs SZ). PANSS-positive scores were highest for SZ and SA and lower for both BD and MDDP (each $P < .001$ vs SZ). PANSS-negative scores were highest for SZ, lower for SA ($P < .05$ vs

SZ), and lower still for both BD and MDDP (each $P < .001$ vs SZ). PANSS-general scores were highest for SZ and SA, and lower for both BD and MDDP (each $P < .01$ vs SZ).

3.3 Functioning

GAF scores were available for all cases with each diagnosis (Table 2). GAF scores differed between the diagnoses and were lower (i.e. worse functioning) in males than in females in a manner unrelated to diagnosis (effect of diagnosis, $P < .001$; effect of sex, $P < .01$; no diagnosis \times sex interaction): scores were lowest for SZ, higher for SA ($P < .05$ vs SZ), and higher still for both BD and MDDP (each $P < 0.001$ vs SZ).

HoNOS, Strauss-Carpenter and SLOF scores were available for 26 of 27 cases of MDDP, all 60 cases of SZ, all 27 cases of SA, and 33 of 35 cases of BD. HoNOS scores differed between the diagnoses (effect of diagnosis, $P < .01$; no effect of sex or diagnosis \times sex interaction); they were highest for SZ and SA and lower (i.e. better functioning) for both BD and MDDP (each $P < .01$ vs SZ). Strauss-Carpenter scores differed between the diagnoses (effect of diagnosis, $P < .01$; no effect of sex or diagnosis \times sex interaction); they were lowest for SZ and higher (i.e. better functioning) for SA ($P < .05$ vs SZ) and higher still for both BD and MDDP (each $P < .01$ vs SZ). SLOF scores differed between the diagnoses (effect of diagnosis, $P < .01$; no effect of sex or diagnosis \times sex interaction); they were lowest for SZ and higher (i.e. better functioning) for SA ($P < .05$ vs SZ) and higher still for both BD ($P < .001$ vs SZ) and MDDP ($P < .05$ vs SZ).

3.4 Quality of life

QLS scores were available for 26 of 27 cases of MDDP, all 60 cases of SZ, all 27 cases of SA, and 33 of 35 cases of BD (Table 2). Scores differed between the diagnoses and were lower (i.e.

reduced quality of life) in males than in females in a manner unrelated to diagnosis (effect of diagnosis, $P < .01$; effect of sex, $P < .05$; no diagnosis \times sex interaction); they were lowest for SZ, higher for SA ($P < .05$ vs SZ) and higher still for both BD and MDDP (each $P < .01$ vs SZ).

WHOQOL-BREF scores were available for 21 of 27 cases of MDDP, 35 of 60 cases of SZ, 16 of 27 cases of SA, and 24 of 35 cases of BD. Scores did not differ between the diagnoses or between the sexes.

3.5 Service engagement

SES scores were available for 26 of 27 cases of MDDP, all 60 cases of SZ, all 27 cases of SA, and 33 of 35 cases of BD (Table 2). Scores differed between the diagnoses and were marginally higher (i.e. worse engagement) in males than in females in a manner unrelated to diagnosis (effect of diagnosis, $P < .01$; effect of sex, $P = .07$; no diagnosis \times sex interaction); they were highest for SZ, lower for SA ($P < .05$ vs SZ) and BD ($P < .01$ vs SZ), and lower still for MDDP ($P < .001$ vs SZ).

3.6 Predictors of functioning

PCA was performed across all four diagnoses to establish the extent to which the GAF, HoNOS, Strauss-Carpenter and SLOF map onto a common principal component (PC). Table 3 shows that PCA of data from these four instruments yielded a 4-factor model, with PC1 being the key factor onto which they load, explaining 80.2% of the variance; thus, function PC1 (Function 1) can be considered a unitary index that best captures what is measured across each of these assessments and this was used in subsequent analyses for predictors of functioning. The loadings for each scale onto their corresponding factors varied little by diagnostic category or sex.

As described above (see **2.3 Statistical analysis**), an exploratory multiple regression model was then applied to identify independent predictors of Function 1 across diagnoses, using age, sex, months from first presentation to follow-up, 1st (age 4-12 years) vs 2nd (age 12-18 years) level education completed, 1st vs 3rd (university/college or other age 18+) level education completed, current marital status (ever married vs never married), current living conditions (supported vs unsupported), substance abuse (present vs absent during the clinical history) and PANSS-positive, PANSS-negative, PANSS-general and SES, each at follow-up. Poorer functioning (Function 1) was predicted independently by higher PANSS-general and PANSS-negative scores, lower service engagement, not attaining 2nd relative to 1st level education, never having married, living in unsupported rather than supported living conditions, and not attaining 3rd relative to 1st level education; age, sex, months from first presentation to follow-up, PANSS-positive score and substance abuse did not predict Function 1 (Table 4). Incorporation of interaction terms by diagnosis suggested that predictors of Function 1 were similar across the four diagnoses.

4. DISCUSSION

4.1 Main findings

The present study describes outcome measures six years after the first psychotic episode for MDDP in systematic comparison with SZ, SA and BD. At follow-up, positive psychotic symptoms and general psychopathology were most evident in and indistinguishable between SZ and SA, and less prominent in and indistinguishable between BD and MDDP. As each of SZ, BD and MDDP showed indistinguishably high levels of positive symptoms at the first psychotic episode (comparative data for SA not then being available²⁸), positive psychopathology in

MDDP may share with BD a more benign long-term course or showing more sustained responsiveness to medication relative to SZ. Negative symptoms were most evident in SZ, lower in SA, and less prominent in and indistinguishable between BD and MDDP, while general symptoms were evident similarly in SZ and SA, and less prominent in and indistinguishable between BD and MDDP.

Overall, each of the four individual assessments of function followed a profile generally similar to that for negative symptoms, i.e. impairment in functionality was most evident in SZ, lower in SA, and less prominent in and indistinguishable between BD and MDDP. While objectively determined impairment in QoL also showed a profile similar to that for negative symptoms and impairment in functionality, subjectively determined QoL was indistinguishable between SZ, SA, BD and MDDP. That objective measures estimate QoL in SZ as lower than do subjective measures⁴³⁻⁴⁵ appears to apply similarly for MDDP.

The profile for service engagement across SZ, SA, BD and MDDP was distinct from the profiles for domains of psychopathology, functionality or QoL, being lowest for SZ, intermediate for SA and BD, and highest for MDDP. Some of the variables shown previously to correlate with poor service engagement in SZ/first episode psychosis include poor insight⁴⁶, fewer depressive symptoms⁴⁶, higher rates of ‘excitatory’ symptoms⁴⁷, younger age^{25,47}, younger age at onset²⁵ and male sex²⁵. Thus, further studies are necessary to disentangle the roles of such variables in relation to higher service engagement in MDDP.

In summary, on the background of an extensive literature on long-term outcome in SZ, SA and BD in terms of positive, negative and general symptoms, functionality, QoL and service engagement across various diagnostic combinations at varying stages of illness^{5,6-8,17,19}, the

present prospective findings inform on comparative long-term outcome in MDDP. Importantly, apparent differences in PANSS psychopathology, functioning, QoL and service engagement between diagnoses were quantitative rather than qualitative, with considerable overlap between them.

4.4 Strengths and limitations of the study

The strengths of the present study include a defined catchment area, case inception via all routes to care [i.e. public, private or forensic; inpatient, outpatient or home-based], full diagnostic scope [to include each of SZ, SA, BD and MDDP] and no arbitrary upper age cut-off [i.e. cases incepted throughout the adult lifespan]; high long-term follow-up was facilitated by the low geographical mobility of this rural population, together with primary care links established by the area mental health service that aims to deliver community-based treatment to patients where possible. The limitations of the study are typical of many such investigations, primarily the numbers of subjects involved, variations in treatment practice and compliance that may influence outcome, and the range of psychopathologies assessed. While well established and widely used for assessing psychosis, the PANSS may be less incisive for the assessment of affective psychopathology. Also, as expected, there were inevitably a modest number of diagnostic transitions, both from MDDP at inception to other diagnoses at 6-year follow-up (most commonly to BD and SA) and to MDDP at 6-year follow-up from other diagnoses at inception (most commonly from brief psychotic disorder), as described previously in detail²⁹. The service delivery model in which CAMFEPS is embedded, focusing on community-based care, may limit generalizability to other clinical services. Future studies should further address these issues.

4.5 Trans-diagnostic evaluation of functionality

Given the present findings of quantitative rather than qualitative differences between these psychotic diagnoses in assessments at long-term follow-up, and the considerable overlap between them, an exploratory multiple regression model across the trans-diagnostic composite suggested higher general (i.e. less diagnostically specific) psychopathology, together with higher negative but not positive psychopathology, and lower service engagement to predict poor functioning, in association with lower educational attainment, never having married and living in unsupported living conditions. These preliminary findings may be heuristic vis-à-vis evolving concepts of the trans-diagnostic nature of psychotic illness, as considered further below. While poorer QoL appeared similarly predicted by higher general psychopathology, never having married and lower service engagement, and also by age at presentation and positive psychopathology, these exploratory findings should be augmented by similar studies utilizing broader assessment of QoL.

4.6 Major depressive disorder with psychotic features within a milieu of psychosis

There is increasing opinion and evidence that diagnostic categories such as SZ, SA and BD reflect not discrete entities but, rather, domains characterised by certain psychopathological dimensions, pathobiological processes and functional characteristics, the boundaries of which are likely arbitrary and in continuity or intersection with other domains of mental illness, through to the limits of 'normal' human experience and functioning^{1-4,28,48,49}. That the long-term outcome of MDDP differed quantitatively but not qualitatively from that of SZ, SA or BD in terms of psychopathology, functionality, QoL and service engagement suggests that MDDP should join

SZ, SA, BD and likely other arbitrary diagnostic categories in what is, in reality, a milieu of psychosis.

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Disclosure

The authors declare no conflict of interest.

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TABLE 1 Subject demographics by diagnosis at 6-year follow-up

Sex	Diagnosis	n	Mean age (yr)	SD	Sex	Diagnosis	n	Mean age (yr)	SD
Males	SZ	42	36.7	14.2	Females	SZ	18	42.3	17.9
	SA	16	35.4	12.2		SA	11	37.9	14.8
	BD	18	39.4	15.8		BD	17	41.9	15.1
	MDDP	13	45.9	20.4		MDDP	14	51.0	18.9

SZ, schizophrenia; SA, schizoaffective disorder; BD, bipolar I disorder; MDDP, major depressive disorder with psychotic features; n, number of cases; SD, standard deviation.

TABLE 2 PANSS, function, quality of life and service engagement scale scores at 6-year follow-up

Scale	Diagnosis											
	SZ			SA			BD			MDDP		
PANSS												
PANSS-total	65.2	(20.7)	[60]	56.8	(20.7)	[27]	44.6 ^c	(11.8)	[33]	43.6 ^c	(15.1)	[26]
PANSS-positive	13.0	(5.5)	[60]	11.5	(5.5)	[27]	8.8 ^c	(3.2)	[33]	7.8 ^c	(1.8)	[26]
PANSS-negative	20.3	(8.8)	[60]	15.8 ^a	(9.3)	[27]	10.1 ^c	(4.3)	[33]	11.4 ^c	(7.3)	[26]
PANSS-general	32.9	(10.4)	[60]	30.0	(9.2)	[27]	26.2 ^b	(8.9)	[33]	24.6 ^b	(7.7)	[26]
Function												
GAF	52.5	(12.8)	[60]	59.2 ^a	(13.3)	[27]	66.7 ^c	(12.4)	[35]	68.2 ^c	(10.6)	[26]
HoNOS	10.8	(6.8)	[60]	8.1	(5.2)	[27]	6.1 ^b	(5.6)	[33]	6.0 ^b	(6.1)	[26]
Strauss-Carpenter	21.4	(7.7)	[60]	25.3 ^a	(6.1)	[27]	29.5 ^c	(6.8)	[33]	28.5 ^c	(7.0)	[26]
SLOF	186.1	(22.9)	[60]	197.7 ^a	(19.7)	[27]	205.7 ^c	(19.8)	[33]	201.1 ^a	(27.0)	[26]
QoL												
QLS	70.2	(27.1)	[60]	85.2 ^a	(24.8)	[27]	100.7 ^c	(19.5)	[33]	97.6 ^c	(24.4)	[26]
WHOQOL-BREF	94.1	(10.8)	[35]	94.8	(11.7)	[16]	98.8	(16.4)	[24]	100.4	(14.7)	[21]
SES	20.4	(12.5)	[60]	13.3 ^a	(11.6)	[27]	12.2 ^b	(12.2)	[33]	8.7 ^c	(10.1)	[26]

SZ, schizophrenia; SA, schizoaffective disorder; BD, bipolar I disorder; MDDP, major depressive disorder with psychotic features. PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; HoNOS, Health of the Nation Outcome Scale; QLS, Quality of Life Scale; WHOQOL-BREF, World Health Organisation Quality of Life-BREF; SES, Service Engagement Scale. Data are presented as means (SD) [number of cases]; SD, standard deviation. ^a $P < .05$ vs SZ, ^b $P < .01$ vs SZ, ^c $P < .001$ vs SZ.

TABLE 3 Principal component loadings among measures of functioning at 6-year follow-up

Scale	PC			
	1	2	3	4
HoNOS	-0.878	0.256	0.405	0.012
Strauss - Carpenter	0.948	0.022	0.186	-0.258
GAF	0.909	-0.260	0.266	0.189
SLOF	0.845	0.521	-0.074	0.099
% variance explained	80.2%	10.1%	6.9%	2.8%

PC, Principal component; HoNOS, Health of the Nation Outcome Scale; GAF, Global Assessment of Functioning Scale; SLOF, Specific Level of Functioning Scale.

TABLE 4 Regression model for predictors of Function 1 at 6-year follow-up

Variable	B	SEB	t	P
PANSS-general	-0.077	0.005	-14.195	0.001
PANSS-negative	-0.047	0.007	-7.114	0.001
SES	-0.019	0.005	-4.154	0.001
1 st vs 2 nd level education	0.019	0.059	3.632	0.001
Never-married	0.276	0.087	3.193	0.002
Supported vs unsupported living	-0.126	0.052	-2.397	0.018
1 st vs 3 rd level education	0.148	0.074	1.985	0.031

PANSS, Positive and Negative Syndrome Scale-general and -negative symptom subscales; SES, Service Engagement Scale. Age, sex, months from first presentation to follow-up, PANSS-positive symptom subscale and substance abuse did not predict Function 1.