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Targeting the problem of treatment non-adherence among mentally ill patients: The impact of loss, grief and stigma

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ABSTRACT

The present study examined the factor structure of the Hungarian version of the Medication Adherence Rating Scale (MARS) and analyzed its association with socio-demographics, insight, internalized stigma, and the experience of loss and grief as a result of the mental illness diagnosis, using confirmatory factor analysis (CFA) with a series of one covariates at a time. Mentally ill patients (N = 200) completed self-report questionnaires. CFA supported the original three-factor structure although one item was moved from its original factor to another. Lower insight, higher internalized stigma, loss, and grief were significant predictors of lower treatment adherence. Lower adherence was found to be significantly associated with lower quality of life. No difference in adherence was found between different diagnostic groups, which stresses the need to examine non-adherence in the wider spectrum of mental diagnosis. The study also stresses the importance of patients' subjective experience in promoting better adherence, and raises the need to address the experience of stigma but also of less studied experiences, such as patients' feelings of loss and grief. Integrating these experiences in intervention programs might have meaningful implications for the improvement of treatment adherence and patients' quality of life.

1. Introduction

Psychiatric medications are often the first line of treatment offered to mentally ill patients (Gilbert et al., 1995) due to their fundamental contribution to symptom relief and to patients' rehabilitation (Corrigan, 2004; Tsang et al., 2006). However, despite its advantages, non-adherence is highly prevalent among mentally ill patients. In fact, compared to patients who are receiving treatment for physical conditions, mental patients are the least likely to adhere their medication regimen (Fenton et al., 1997; Keck et al., 1996; McDonald et al., 2002; Scott and Pope, 2002).

Adherence is "the extent to which a person's behavior-taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care professional" (p.3, World Health Organization, 2003). Additionally, adherence should be regarded as a range of behaviors from complete adherence to medication, through partial adherence, to complete non-adherence (Fialko et al., 2008). Non-adherence to psychiatric medications is known to have detrimental consequences for both patients and society, including increased symptom severity, relapses, re-hospitalizations, suicides, and reduced quality of life (Ernst and Goldberg, 2004; Perkins, 2002; Puschner et al., 2009; Sajatovic et al., 2004; Svarstad et al., 2001; Weiden and Olfson, 1995). Its consequences for society is mainly through the loss of income of patients and the high costs of healthcare (Weiden and Olfson, 1995).

In order to assess medication non-adherence, a variety of methods have been utilized. Among them are "subjective methods" such as patient and clinician reports, and "objective methods" such as pill counts, electronic monitoring, and serum level measures (Velligan et al., 2006). However, it appears that there is no clear consensus regarding which method is preferable because each of them has its' particular shortcomings (Velligan et al., 2006). Patients' self-reports have been criticized for being influenced by memory deficits and social desirability bias (Sajatovic et al., 2010; Yang et al., 2012). However, patient self-reports are considered to be the most efficient due to (i) their non-intrusive and easy to administer nature, (ii) the low investment in terms

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of cost which is required to use them, and (iii) them being considered highly informative regarding individual adherence problems (Fialko et al., 2008).

The Medication Adherence Rating Scale (MARS) (Thompson et al., 2000) is a useful self-report scale that was developed to assess adherence among psychiatric populations. With the goal of developing more reliable, valid, and comprehensive tool for assessing adherence, including behavior and attitudes, Thompson et al. (2000) used two well-established self-report scales, the 30-item Drug Attitudes Inventory (DAI) (Hogan et al., 1983) and the four-item Medication Adherence Questionnaire (MAQ) (Morisky et al., 1986), to construct the MARS. The scale score ranges from 0 (*low likelihood of medication adherence*) to 10 (*high likelihood of medication adherence*) reflecting the continuous nature of adherence (Fialko et al., 2008). Previous exploratory factor analysis suggested a three-factor structure: (i) medication adherence in terms of behavior, (ii) medication adherence as reflected from ones attitudes, and (iii) individuals' attitudes towards psychiatric medications and their negative side-effects (Thompson et al., 2000). This structure was also supported by an additional validation study (Fialko et al., 2008).

When examining non-adherence, understanding its underlying factors is vital in order to properly address it. Among the leading factors concerning non-adherence are poor insight, shorter illness duration, negative attitudes toward medication, lack of social support, and medication side-effects (Diaz et al., 2004; El-Mallakh, 2007; Lacro et al., 2002; Olfson et al., 2006). Internalized stigma – the adoption of stereotypes by mental patients themselves (Corrigan et al., 2009) – is another well-studied factor compromising adherence (Hajda et al., 2016; Livingston and Boyd, 2010; Yılmaz and Okanlı, 2015) because it makes patients ashamed and individuals would rather not take their medication than being labeled as "mentally ill" (Corrigan, 2004).

Grief (which although being commonplace among patients) and its impact on adherence, has never been previously examined. Grief can be experienced as a result of the mental illness due to many different types of loss (e.g., loss of functioning, relationships, sense of self, and dreams for the future) (Appelo et al., 1993; Lewis, 2004; Mauritz and van Meijel, 2009; Stein, 2005; Stein et al., 2005; Wittmann and Keshavan, 2007). Examining grief as a consequence of mental illness is meaningful especially as grief is known to be related to reduced psychological wellbeing, physical health, and suicidality (Miles, 1985; Moore et al., 1988; Porritt and Bartrop, 1985; Szanto et al., 2006) and was recently found to be associated with loneliness and lower quality of life, specifically among mentally ill patients (Buchman-Wildbaum et al., 2020). Most importantly, grief which is known to include behavioral avoidance, negative cognitions, and emotional reactions to loss (Horowitz et al., 1981), is thought to negatively affect adherence. For example, previous research involving individuals with schizophrenia reported difficulties in accepting the diagnosis and the need for treatment, avoidant behaviors, and distress (Mauritz and van Meijel, 2009). Therefore, the possibility that it impacts and hinders patients' medication-taking, requires further research.

The first main goal of the present study was to further examine the factor structure of the MARS among a non-English speaking psychiatric population. Although non-adherence is prevalent in the wider spectrum of mental diagnosis (Colom et al., 2005; Gilmer et al., 2004; Lingam and Scott, 2002; Melfi et al., 1998), previous studies using the MARS have mostly been conducted among schizophrenia patients (Fialko et al., 2008; Jaeger et al., 2012; Thompson et al., 2000). Therefore, examining its measurement model among patients with other psychiatric diagnoses is needed.

The second main goal was to examine the possible predictors of non-adherence in order to gain a better insight regarding the different ways by which it can be reduced or avoided. More specifically, the present study focused mainly on insight, internalized stigma, loss, and grief. It was expected that lower insight, increased internalized stigma, loss, and grief would all be significant predictors of non-adherence. The impact of non-adherence on patients' lives was also examined, and it was expected that lower adherence would be associated with lower quality of life.

2. Methods

2.1. Participants

The present study's sample comprised 200 individuals with a diagnosis of psychiatric disorder who were receiving routine mental care in an outpatient division of a mental health center in Budapest, Hungary. The inclusion criteria were: (i) having a mental health diagnosis according to the ICD-10 (World Health Organization, 1992), (ii) being consumers of psychiatric medications, (iii) being inpatients or outpatients in any form of psychiatric care, (iv) being patients who had not been abusing illicit substances and alcohol for a period of at least two weeks at the time of evaluation, (v) being in the age range 18 to 65 years, and (vi) having (based on their psychiatrist's view) the capability to answer the questionnaire. The exclusion criteria were (i) being at a severe (i.e., acute) phase of the illness, (ii) being diagnosed with an organic brain disorder, dementia, and/or mental retardation, and (iii) not having the mental capability and/or capacity to answer the self-report questionnaire or provide informed consent.

2.2. Procedure

The psychiatrists at the mental health center contacted and invited eligible patients to participate in the study. They supplied important information about the study, including the study's goals which were communicated both verbally and in writing. Patients who agreed to participate in the study were asked to sign an informed consent sheet and then to complete a self-report questionnaire. The study questionnaires were all translated from English to Hungarian and back translated from Hungarian to English. Any possible inconsistencies between the original and back-translated version were addressed and solved. The present study was given ethical approval by the ethical board of the regional hospital accountable for the patients' welfare.

2.3. Measures

2.3.1. Socio-demographic questions

In the present study, different factors were evaluated such as the participant's gender, age, education (finished/did not finish high school), employment status (employed/unemployed), psychiatric diagnosis, marital status (married/divorced/widowed/single) and history of former hospitalizations (yes/no). Patients were allocated into six diagnostic groups based on their diagnosis and following the ICD-10 codes classification (World Health Organization, 1992): (i) schizophrenia spectrum disorders (e.g., schizophrenia, schizotypal and delusional disorder), (ii) mood disorders (e.g., major depressive disorder, bipolar and manic disorder), (iii) stress-related disorders (e.g., phobic anxiety disorders, obsessive- compulsive disorders, somatoform disorders), (iv) behavioral syndromes associated with physiological disturbances (e.g., eating disorders), (v) personality disorders (e.g., borderline personality disorder, avoidant personality disorder), and (vi) disorders due to psychoactive substance use.

2.3.2. Adherence

The Medication Adherence Rating Scale (MARS) (Thompson et al., 2000) is a 10-item scale that encompasses three adherence elements; (i) adherence in terms of behavior (Items 1-4), (ii) adherence in terms of attitudes (Items 5-8), and (iii) attitudes towards psychiatric medications and their negative side-effects (Items 9 and 10). The scale includes ten yes/no items, and the scoring depends on whether the individual indicates adherence or non-adherence; those responses implying adherence are coded as 1, while those responses implying non-adherence

are coded as 0. The scores of the ten items are summed up to produce total score which ranges from 0 (low likelihood of medication adherence) to 10 (high likelihood of medication adherence) (Fialko et al., 2008). In the present study the scale found to have adequate internal consistency (Cronbach α = 0.61).

2.3.3. Insight

The Birchwood Insight Scale (BIS) (Birchwood et al., 1994) is a brief eight-item self-report measure which assesses three dimensions of insight into mental illness: illness awareness (Items 2 and 7), need for treatment (Items 3,4,5 and 6), and re-labelling of symptoms (Items 1 and 8). Each item contains a statement with three response options (i.e., agree, unsure or disagree). Participants' responses on each item is scored depending on the insight level it indicates, where responses indicating good insight (agree/disagree) are scored as 2, unsure responses are scored 1, and responses which indicate poor insight are scored as 0. In the present study two changes were made. First, because the study participants were not hospitalized, a minor modification was made in the item presuming hospitalization (Item 4) ("My stay in the hospital is necessary" was amended to "The treatment in the institution is necessary"). Second, in light of findings in a previous validation study from Hungary reporting on two-factor structure ('illness awareness' and 'need for treatment') (reference blinded for peer review purposes) the present study only examined these factors. The BIS in the current sample found to have moderate internal consistency (Cronbach $\alpha = 0.69$; illness awareness: Cronbach $\alpha = 0.54$; need for treatment: Cronbach $\alpha = 0.64$).

2.3.4. Internalized stigma

The Self Stigma of Mental Illness Scale (SSMIS) (Corrigan et al., 2006), assesses the four stages process of stigma internalization suggested by Corrigan et al. (2006), and included them as subscales: (i) individual's awareness of stigma concerning mental illness held by the society, (ii) individual's agreement with these stigmatic beliefs, (iii) individual's adoption of these beliefs into their own personal identity, and (iv) resultant decrease in an individual's self-esteem. Participants rate their agreement with 10 statements included in each one of the four subscales on a nine-point Likert scale ranging from 1 (*strongly disagree*) to 9 (*strongly agree*). Each subscale includes a total score ranging between 10-90, and higher scores indicates greater acceptance of stigma as indicated by the specific subscale. The scale was found to have good internal consistency in the present study (stigma awareness: Cronbach α = 0.92; stigma agreement: Cronbach α = 0.90; stigma internalization: Cronbach α = 0.83; self-esteem reduction: Cronbach α = 0.84)

2.3.5. Grief

Grief was assessed using the Mental Illness Version of the Texas Inventory of Grief (MIV-TIG) (Miller et al., 1990). The MIV-TIG is an adapted version of Texas Revised Inventory of Grief (TRIG) (Faschingbauer et al., 1977) which is used to assess grief reaction to the death of a loved one. The MIV-TIG was modified to assess grief as a result of a relative's mental illness and the loss of that individual as s/he was before the development of mental illness (Miller et al., 1990). The scale includes the different known expressions of grief such as persistent emotional distress, being constantly occupied with the lost person, and difficulties and unwillingness to acknowledge and accept the reality of the loss. The MIV-TIG comprises eight items evaluating initial grief and 16 items evaluating current grief (i.e., 24 items in total). The present study only utilized the 16 items focusing on current grief. Furthermore, as the present study assessed grief of mental patients themselves and not of their relatives, a minor adjustment of the items was made, manifested in first account statements (e.g., *"I am preoccupied with the thoughts of how I could have been if not for the illness"*) similar to previous modifications (Patterson et al., 2005). Participants were asked to respond to the items based on a five-point Likert scale ranging from 'completely true' to 'completely false'. Item scores are summed up into a total score, where higher scores reflect higher grieving (Miller et al., 1990). Excellent internal consistency was found in the present study (Cronbach $\alpha = 0.95$).

2.3.6. Perceived loss as a result of mental illness

The Personal Loss from Mental Illness (PLMI) Scale was developed to assess individuals' perception of loss resulting from their mental illness (Stein et al., 2005). Four factors in the scale structure have been identified: 'loss of roles and routines', 'loss of former relationships', 'loss of former self' and 'loss of future' (Stein et al., 2005). The scale comprises 20 items asking about respondents' agreement with statements regarding the losses experienced by individuals with mental illness. Participants agreement levels can range from 1 (*strongly disagree*) to 5 (*strongly agree*). Item scores are summed up to generate subscale and total scores, where higher scores indicate higher perception of loss. Excellent internal consistency of the scale was found in the present study (Cronbach $\alpha = 0.90$).

2.3.7. Quality of life

The Manchester Short Assessment of Quality of Life (MANSA) (Priebe et al., 1999) is shortened version of the Lancashire Quality of Life Profile (LQLP) (Oliver et al., 1997). The MANSA comprises 16 questions, with four categorized as "objective" (asking about facts such as being accused for a crime) answered dichotomously (yes/no), and 12 categorized as "subjective" (asking about life satisfaction in general and specific different aspects of life) answered on a seven-point rating scale of satisfaction, ranging from 1 (*couldn't be worse*) to 7 (*couldn't be better*). Total scale score is the mean average of the 12 question scores, where higher scores indicate a better quality of life. The scale had very good internal consistency in the present study (Cronbach α = 0.87).

2.4. Statistical analyses

In order to assess the factor structure and item performance of the Hungarian version of the MARS in the current sample, a series of confirmatory factor analyses (CFAs) were conducted. MARS items were regarded as categorical and used the mean-adjusted and variance-adjusted weighted least squares (WLSMV) estimator. In CFA, an appropriate degree of fit means that the comparative fit index (CFI) and the Tucker-Lewis Index (TLI) should be close to 0.95, whereas model indices of <0.90 means that the model should be declined (Brown, 2006). The next fit index used was root mean squared error of approximation (RMSEA). RMSEA lower than 0.05 implies excellent fit, a value around 0.08 implies adequate fit, and a value above 0.10 implies poor fit (Browne & Cudek, 1993). After calculating the factor scores, a comparison for statistical difference in factor scores between groups with different diagnosis were conducted. Next, a series of CFAs with single covariate models were performed to examine the associations between adherence, sociodemographic factors, insight, internalized stigma, grief, and loss. This approach was chosen due to its ability to prevent the problem of multicollinearity. Finally, the association between the adherence factors and quality of life was investigated. All analyses were performed with MPLUS 8.1 (Muthén & Muthén, 1998).

3. Results

3.1. Descriptive statistics

Table 1 presents the percentages, means, and standard deviations (SDs) of the different variables used in the present study. The current sample was dominated by women and high school graduates. The predominant mental illness diagnosis was stress-related disorders, and almost half of the participants had previous hospitalizations in their history. The sample was diverse in terms of age (ranges from 32 to 56

Table 1
Descriptive statistics of the sample

Gender (female) *N* (%)	133 (66.5)
Age – mean (SD)	44.2 (11.8)
Education, graduated high school – *N* (%)	157 (78.5)
Previous hospitalizations – *N* (%)	89 (44.5)
Diagnosis	
Schizophrenia spectrum disorders – N (%)	53 (26.5)
Mood disorders – N (%)	58 (29.0)
Stress-related disorders – N (%)	89 (44.5)
Personality disorders – N (%)	10 (5.0)
Disorders due to psychoactive substance use – N (%)	2 (1.0)
Behavioral syndrome associated with physiological disturbances – N (%)	2 (1.0)
Only one diagnosis- N (%)	188 (94.0)
Two diagnoses- N (%)	10 (5.0)
Three diagnoses- N (%)	2 (1.0)

years), with a mean of 44.2 years (SD = 11.8).

3.2. Confirmatory factor analysis of the Medication Adherence Rating Scale (MARS)

A series of confirmatory factor analysis with items as categorical indicators and WLSMV estimator were performed. The first model including only one factor yielded unacceptable degree of fit. The second model was the original three-factor model which had close to acceptable degree of fit (see Table 2 note). Inspecting the factor structure, modification indices and the content of the items, Item 5 was removed ("*I take my medication only when I am sick*") from the adherence attitude factor to the adherence behavior factor. The error covariance between Item 1 ("*Do you ever forget to take medication?*") and Item 2 ("*Are you careless at times about taking your medication?*") was allowed. The size of the correlations between the uniqueness of these two factors was large (r = 0.76). These modifications yielded excellent degree of fit in all fit indices. The factor loadings of the original (Model 2) and modified (Model 3) measurement models are presented in Table 2. The means of factor loadings of each factor in the modified model were 0.63, 0.62, and 0.87 respectively. Internal consistencies of the factors were: behavior: Cronbach α = 0.64, attitude: Cronbach α = 0.44, side-effects: Cronbach α = 0.61.

3.3. Medication adherence in different diagnostic groups

After calculation of factor scores, adherence dimensions were compared across three diagnostic groups, and no significant main effect was found (see Table 3). However, comparison between the schizophrenia spectrum disorders group and the other two groups together, showed that schizophrenia patients reported higher score of adherence behavior than the other groups together (see Table 3 note). The same analyses with the attitude and side-effects resulted in much smaller difference.

3.4. Covariates of medication adherence: Single covariate models

The predictors of the dimensions of adherence were tested in a series of CFAs with single covariate models. In these models, only one predictor was entered in each model. The standardized regression coefficients are presented in Table 4. Covariates were gender, age, insight, internalized stigma, loss, and grief. Higher insight ("need for treatment factor") predicted significantly higher adherence (adherence behavior and attitude). Higher stigma predicted significantly lower adherence. Especially adopting stigmatic views into self-identity and self-esteem reduction were associated with lower adherence behavior, attitude, and lower tolerance of side-effect. Furthermore, awareness of (and agreement with) stigmatic views were associated with lower tolerance of side-effects of the treatment. Similarly, higher loss and higher

Table 2
Confirmatory factor analyses of The Medication Adherence Rating Scale: Factor loadings of measurement models

	Original three-factor Model*			Modified three-factor model**		
	Adherence: Behavior	Adherence: Attitude	Adherence: Medications side effects	Adherence: Behavior	Adherence: Attitude	Adherence: Medications side effects
Item 1: Do you ever forget to take medication?	0.53			0.54		
Item 2: Are you careless at times about taking your medication?	0.29			0.31		
Item 3: When you feel better, do you sometimes stop taking your medication?	0.83			0.82		
Item 4: Sometimes if you feel worst when you take the medication, do you stop taking it?	0.78			0.78		
Item 5: I take my medication only when i am sick		0.99		0.72		
Item 6: It is unnatural for my mind and body to be controlled by medication.		0.46			0.53	
Item 7: My thoughts are clearer on medication.		0.38			0.76	
Item 8: By staying on medication, i can prevent getting sick.		0.33			0.56	
Item 9: I feel weird, like "zombie" on medication.			0.90			0.92
Item 10: Medication makes me feel tired and sluggish.			0.82			0.81
Factors correlations						
Adherence Behavior	-	0.62	0.58	-	0.24ns	0.53
Adherence Attitude	-	-	0.33	-	-	0.27ns

Note: Standardized factor loadings. ns = non-significant. *: Fit indices: $\chi^2 = 55.9$, df = 31, $p < .004$; CFI = 0.907, TLI = 0.866; RMSEA = 0.065 Cfit of RMSEA = 0.174. **: Fit indices: $\chi^2 = 38.6$, df = 31, $p < .1646$; CFI = 0.972, TLI = 0.959; RMSEA = 0.036 Cfit of RMSEA = 0.731.

Table 3
Comparison of adherence dimensions across diagnostic groups.

Dimensions of adherence*	Schizophrenia spectrum disorders $N=51$ Mean (SD)	Mood disorders $N=56$ Mean (SD)	Stress-related disorders $N=84$ Mean (SD)	F	p	Effect size f
Behavior	0.03 (0.31)	-0.07 (0.34)	-0.08 (0.37)	1.77	0.1737	0.08
Attitude	0.01 (0.31)	-0.03 (0.33)	-0.04 (0.34)	0.38	0.6843	0.04
Side effects	-0.06 (0.57)	-0.12 (0.54)	-0.12 (0.59)	0.21	08134	0.04

Note: *Factor scores were used in the calculation. *f:* effect size index, An f = 0.10 is a small effect and an f = 0.25 is a medium effect (Cohen, 1988). f values for group comparisons: *Behavior*: Schizophrenia versus Mood disorder: $f=0.06$; Schizophrenia versus stress-related disorder: $f=0.08$; mood disorder versus stress-related disorder $f=0.01$. *Attitude*: Schizophrenia versus Mood disorder: $f=0.03$; Schizophrenia versus stress-related disorder: $f=0.04$; mood disorder versus stress-related disorder $f=0.01$. *Side effects*: Schizophrenia versus Mood disorder: $f=0.03$; Schizophrenia versus stress-related disorder: $f=0.03$; mood disorder versus stress-related disorder $f=0.00$. Comparison between the schizophrenia spectrum disorders group and the mood and stress-related disorders together, showed that schizophrenia patients reported higher score of adherence behavior than the other groups together (t[186] = 1.93, p = 0.055, Cohen's d = 0.33). The same analyses with the attitude and side-effects resulted in much smaller effect size estimates (Cohen's d = 0.16 and 0.11 respectively).

Table 4
Covariates of medication adherence: Single covariate models[#]

	Dimensions of medication adherence		
Covariates	Behavior	Attitude	Side effect
Age	0.15	0.10	0.08
Gender	0.04	-0.05	-0.21
Grief (MIV-TIG)	-0.10	-0.01	**-0.45*****
Internalized stigma			
Awareness of the stigmatic views	-0.14	0.10	**-0.22***
Agreement with the stigmatic views	-0.09	-0.04	**-0.23***
Adopting stigmatic views into self-identity	**-0.35*****	**-0.19***	**-0.24***
Self-esteem reduction	**-0.30****	**-0.27***	**-0.21***
Personal loss (PLMI)	-0.16	-0.02	**-0.29****
Insight			
Illness awareness	-0.10	0.08	-0.12
Need for treatment	**0.30****	**0.49*****	0.09

Note: [#]: CFA with single covariate models include only one covariate, therefore each line of the table represents one model. Standardized regression coefficients. Medication adherence dimensions are used as latent variables and covariates are used as observed variables. *$p<.05$; **$p<0.01$; ***$p<.001$.

grief were associated with lower adherence in terms of lower tolerance of side-effects.

3.5. Correlations between adherence and quality of life

Adherence was expected to be associated with quality of life. Due to the medium-sized correlations among adherence factor and possible multicollinearity, instead of the traditional regression analysis to predict quality of life, the focus was only on the correlations of the construct. Increased behavior and tolerance of side-effect aspects of adherence correlated significantly with increased quality of life ($r=0.24$ $p<.01$ and $r=0.25$ $p<.01$, respectively). When the correlations between behavior and side-effect aspects of adherence ($r=0.535$) were controlled for, the remaining partial correlations were still significant ($r=0.13$, $p<.05$ and $r=$ 0.15, $p<.05$, respectively).

4. Discussion

The present study confirmed the three-factor structure of the Medication Adherence Rating Scale (MARS) (Fialko et al., 2008; Thompson et al., 2000) among non-English speaking patients with different diagnoses. However, a minor modification was required, namely Item 5 ("I take my medication only when I am sick") should be removed from the 'attitude' factor and added to the 'behavior' factor. In addition to the psychometric considerations, the content of this item also warranted this change. Similar change was proposed in a validation study of the Taiwanese version of the MARS (Kao and Liu, 2010). However, in the Taiwanese study, the MARS was found to have two factors (adherence behavior and subjective response to medications), which reinforce the need for further examination of the scale among different populations from different cultural backgrounds.

The present study also examined possible differences in adherence among different diagnoses. Participants from the three major diagnostic categories did not differ in the three adherence scores. However, based on the results, it is possible that the sample size was not large enough to allow the detection of small differences among diagnostic groups. This finding conflicts with the literature claiming that the problem of non-adherence is especially higher among those with schizophrenia (Cramer and Rosenheck, 1998; Sajatovic et al., 2010; Taj et al., 2008; Tesfay et al., 2013). However, this finding might be also the result of the inclusion of participants who were not hospitalized and in a stable state, and therefore cannot be generalized to the wider schizophrenia patient population.

The findings of the present study also provide important new knowledge about the less frequently studied predictors of adherence. The present study is the first to find that patients' experience of loss and grief significantly (negatively) influenced their adherence to treatment. Although loss and grief were reported as the main experiences of patients by mental health professionals over the years (Appelo et al., 1993; Lewis, 2004; Wittmann and Keshavan, 2007; Young et al., 2004), this body of research was neglected and instead research interest was devoted mainly to the loss and grief experienced by family members of individuals with mental disorders (e.g., Davis and Schultz, 1998; Miller et al., 1990; Ozgul, 2004). Only recently was this important topic revived with the development of the Personal Loss from Mental Illness Scale (PLMIS) (Stein et al., 2005) and novel findings associating the experience of loss with higher loneliness, lower recovery rates, and lower quality of life (Buchman-Wildbaum et al., 2020; Potokar, 2008; Stein et al., 2005).

A recent study also confirmed the association between loss and higher grief among patients with mental disorders (Buchman-Wildbaum et al., 2020). That study was also the first to examine grief among patients themselves, and the first to report that it is associated with higher loneliness and lower quality of life. Grief might interfere with medication-taking due to its nature, including emotional distress regarding the loss, behavioral avoidance, and denial of the new reality and the adjustments that need to be taken (Horowitz et al., 1981). Furthermore, a previous study reported that among schizophrenia patients, grief manifested in difficulties in accepting the existence of the diagnosis and need for treatment and in withdrawal and avoidance (Mauritz and van Meijel, 2009). The taking of medication might be a painful and troublesome daily reminder of their status of "mentally ill", the losses they experienced, who they used to be before the illness, and all their previous dreams for the future. Under the influence of grief and the strong difficulty to accept the fact that they have an illness, acceptance of the need to take medications might be comprised. It is interesting to note that in the present study, both loss and grief were specifically related to the adherence aspect affected by negative

attitudes regarding the side-effects of medications. While it is possible that more significant results regarding adherence aspects might be more likely to have found among a larger sample, this finding is highly informative. Out of the adherence aspects, this aspect of the influence of medications might be the most concrete and vivid reminder for their illness and therefore it is specifically and strongly associated with grief. Previous studies have already reported that side-effects of medications negatively influencing individuals' adherence behavior (Perkins, 2002; Perlick, 2004; Robinson et al., 2002; Sajatovic et al., 2011). Furthermore, Mauritz and van Meijel (2009) found that the negative influence of medications was related to feelings of loss and grief in schizophrenia.

The findings of the present study may contribute to the extant literature by implying that it is not necessarily the actual side-effects of medications but the grief and the difficulty to accept their illness and the need in medications, which is associated with higher tendency to perceive medications as having negative influence, irrespective of medications having more or less side-effects. This in turn might reduce their probability of adherence. However, due to the preliminary nature of the present study, more research is needed on the topic of loss and grief in mental health and its influence.

The present study also found that insight into mental illness is a significant predictor of better adherence, in line with previous literature (e.g., Beck et al., 2011; David et al., 1992; Kao and Liu, 2010) and with the proposition that better insight leads to better understanding of the need for treatment and to better adherence (Beck et al., 2011; Droulout et al., 2003; Kozuki and Froelicher, 2003; Lysaker et al., 2018; Misdrahi et al., 2012; Mohamed et al., 2009; Yen et al., 2005). The present study found that only the insight aspect of 'awareness of the need for treatment' was significantly associated with adherence (as manifested in patients' behavior and their attitudes) while 'awareness of the illness' aspect did not predict any dimensions of adherence. This is in line with studies reporting that awareness of the need for medication leads to better adherence (Kao and Liu, 2010; Misdrahi et al., 2012; Mutsatsa et al., 2003; Rocca et al., 2008) but in contrast with previous findings reporting positive associations between illness awareness and adherence (Misdrahi et al., 2012; Mutsatsa et al., 2003; Rocca et al., 2008). Interestingly none of the insight aspects predicted adherence in terms of negative attitudes and medications side-effects. This finding was also found by others (e.g., Misdrahi et al., 2012; Mutsatsa et al., 2003) and might mean that for patients with insight, possible side-effects will not play significant role in adherence because they understand and prioritize the positive consequences that treatment has.

The present study also found that internalized stigma predicted lower adherence in accordance with previous findings (Hajda et al., 2016; Livingston and Boyd, 2010; Yılmaz and Okanlı, 2015). This is especially important considering the high rates of individuals with mental illness that experience internalized stigma (Brohan et al., 2010). Interestingly, adherence was also found to be negatively affected even if patients do not necessarily internalize the stigma. However, even the simple recognition of the existence of negative stereotypes in the society towards mental illness or the agreement with these stereotypes predicted lower adherence. More specifically, they were both predictors of the adherence aspects related to negative attitudes regarding medication side-effects. This might be the reflection of the high stigma exists towards psychiatric medications and their impact, perceiving them as unnatural with harmful impact irrespective of its accuracy (Angermeyer et al., 1993; Croghan et al., 2003; Horne, 1999; Mojtabai, 2009). The importance in examining adherence was also validated in the present study because non-adherence was found to be significantly associated with lower quality of life, which also supported by previous findings (Hayhurst et al., 2014; Puschner et al., 2009).

The present study might have some important clinical implications. Perhaps the most significant one is the need in understanding that patients' subjective experience such as of stigma, loss, and grief while coping with any mental illness is important, if not crucial in targeting treatment adherence. As such, there is a need for an intervention plan which will address such painful experiences. An example of an intervention which has been found to increase insight (Yanos et al., 2012), reduce internalized stigma, and improve patients quality of life (Hansson et al., 2017; Roe et al., 2010) is Narrative Enhancement and Cognitive Therapy (NECT) (Yanos et al., 2011). As the first step in coping with grief is to accept the existence of loss (Worden, 1982), acknowledging patients' experience and defining it as a normal reaction of grief, can facilitate patients' acknowledgment and acceptance of their experiences, illness, and perhaps also the need in treatment routine (Young et al., 2004). Finding new meaning to life can also have healing impact and reduce grief (Young et al., 2004). Another important implication is that the study of grief might shed insight concerning another critical and common problem in the psychiatry field – the lack of insight (Pini et al., 2001). It is possible that what appears in many instances as lack of insight might be a clear manifestation of grief (Appelo et al., 1993; Mauritz and van Meijel, 2009; Young et al., 2004), which has important implications for the treatment offered. Furthermore, the present study provided support for the application of the MARS to the broader spectrum of mental diagnoses, and the need for examining treatment adherence in diagnoses other than schizophrenia. However, it might also raise the need to develop an illness-specific adherence scale, especially because different diagnoses may carries specific barriers to adherence (Velligan et al., 2010, 2009).

Importantly, the study findings are limited here in several aspects. First, because the sample of the present study was diverse in terms of diagnoses, patients were divided and grouped into main diagnostic groups. Therefore, the detection of differences which might exist between diagnoses in the same groups was not possible. Moreover, this specific grouping might compromise the generalization of the results to these diagnostic groups. This should be addressed in future studies by examining adherence in more specific and larger diagnostic groups. Another factor which might limit the generalization of the study results is the convenience sample utilized and the inclusion of a relatively stable and functioning sample. Second, as the present study was cross-sectional, cause and effect patterns between variables cannot be verified, and the impact of third variables cannot be excluded. Finally, adherence was assessed by patients' self-report, which is known for inaccuracies (Sajatovic et al., 2010). However, other measurements are also known for their inaccuracies (Velligan et al., 2006), and focusing on patients' perspectives was preferable for the present study in examining patients' subjective experience.

In spite of the limitations presented, the present study offers valuable insights to the study of medication adherence. These mainly include the importance of examining non-adherence in a broader range of diagnoses and of focusing on patients' grief and loss while tackling adherence problems. This might be especially important in order to help patients come to terms with their illness, the need for treatment, and in finding new meaning and goals for life, which will facilitate adherence, healing, and a better quality of life.

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CRediT authorship contribution statement

Tzipi Buchman-Wildbaum: Conceptualization, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Project administration. **Enikő Váradi:** Resources. **Ágoston Schmelowszky:** Supervision. **Mark.D. Griffiths:** Writing - review & editing, Supervision. **Zsolt Demetrovics:** Conceptualization, Resources, Supervision, Writing - original draft, Writing - review & editing. **Róbert Urbán:** Conceptualization, Data curation, Formal analysis, Supervision, Writing - original draft, Writing - review &

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Declarations of interest

None

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