ORIGINAL RESEARCH

The Effect of Personality Dimensions on Functional Outcomes in Mood Disorders

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ABSTRACT

Introduction: Functional impairment associated with mood disorders may be related to a characteristic "profile" of normative personality dimensions.

Methods: Individuals (age ≥ 18 years) with MDD (n = 400) or BD (n = 317), as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), were enrolled in the IMDCP. Personality was evaluated with the Neuroticism−

Extraversion–Openness Five-Factor Inventory (NEO-FFI), and functionality with the Sheehan Disability Scale and Endicott Work Productivity Scale. Path analysis using linear multiple regressions was performed to identify direct and indirect effects of personality on functional impairment.

Results: Lower conscientiousness exerted a significant direct effect on global (p = 0.017) and family life dysfunction in individuals with MDD (p = 0.002), as well as lower work productivity in both MDD (p = 0.020) and BD

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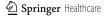
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(p=0.018). Lower extraversion exerted a significant direct effect on social impairment in individuals with BD (p=0.017). Higher neuroticism and agreeableness as well as lower extraversion exerted indirect effects on global and social dysfunction in individuals with MDD via their effects on depression severity. In BD, higher neuroticism and openness indirectly affected global dysfunction. Family dysfunction was indirectly affected by higher neuroticism and openness as well as lower extraversion in MDD and BD.

Conclusion: The results suggest that discrete personality dimensions may exert direct and indirect effects on functional outcomes in individuals with mood disorders. Personalizing disease management approaches in mood disorders with emphasis on vocational rehabilitation may benefit from measurement and intervention targeting personality.

Keywords: Bipolar disorder; Function; Major depressive disorder; Personality; Productivity; Psychiatry

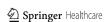
INTRODUCTION

Personality is one of the primary factors responsible for human adaptation, interaction and behavior in different environments [1]. Personality psychopathology is reflected in the current Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) Axis II classification of personality disorders, which are characterized by persistent and maladaptive traits [2–4]. However, recent evidence supports the characterization of normative personality traits in other psychiatric disorders including major depressive disorder (MDD) and bipolar disorder (BD) [5–8]. Characteristic personality traits have also been described in other medical conditions (e.g.,

obesity, metabolic syndrome) [9–11]. Despite the available evidence, assessment of normative personality traits in other non-Axis II disorders is not currently part of routine clinical assessment or diagnostic criteria.

It has been suggested that psychosocial function is influenced by one's personality characteristics [1, 12, 13]. Classically three domains of psychosocial function have been described: social life, family life and work function. Identifying normative personality traits that may be indicative of long-term functional outcomes may be useful in mood disorders. Mood disorders are highly prevalent conditions [14, 15] associated with a high rate of non-recovery, recurrence, and are a leading cause of disability in developed and developing nations [16–18]. In the United States, the estimated annual economic cost of mental illness was approximately \$100 billion of which \$51 billion was associated with work impairment [19, 20]. Similarly, the estimated losses due to lost work productivity and healthcare in Canada were \$83.1 and \$14.1 billion, respectively [21]. The work-related losses included both direct and indirect costs due to absenteeism presenteeism (low work productivity) [22]. From the economic standpoint, decreasing the human capital costs of mood disorders has been identified as a primary objective; therefore, identifying barriers or facilitators to functional recovery is a research and clinical priority.

The five-factor model (FFM) of personality organizes personality traits along five basic dimensions [1]. The five dimensions include normative personality traits and can be described as follows: neuroticism (anxious, selfconscious, vulnerable), extraversion (assertive, energetic, outgoing), openness (curious, imaginative, wide interests), agreeableness (trusting, compliant, altruistic) and conscientiousness (competent, responsible,



achievement striving). The role of maladaptive and impairing personality traits in characterizing function has been evaluated in individuals with personality disorders [23, 24]. The relationship between normative personality traits and functional outcomes in other populations has also been described [24, 25]. Using data from subjects diagnosed with a mood disorder (i.e., MDD and BD), as part of the International Mood Disorders Collaborative Project (IMDCP), this analysis explores the role of personality dimensions in characterizing global and domain-specific function in mood disorders.

METHODS

Study Design

Individuals (age \geq 18 years) with MDD and bipolar I/II disorder (BD-I and BD-II) were enrolled in the IMDCP. This is an ongoing, crosssectional, naturalistic study evaluating individuals who present for an assessment or treatment at the Mood Disorders Psychopharmacology Unit (MDPU) at the University Health Network (UHN) in Toronto, Ontario or at the Cleveland Clinic, Lutheran Hospital, Cleveland, OH, USA. The MDPU is an outpatient program while the Cleveland Clinic offers both outpatient and inpatient services. All patients enrolled between August 2005 and December 2010 with a primary working diagnosis of a mood disorder, who were willing and able to provide informed consent, were included in the current analysis. The IMDCP was approved by the UHN Research Ethics Board and the Institutional Review Board of the Cleveland Clinic Foundation.

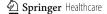
Assessments

The Mini-International Neuropsychiatric Interview (MINI Plus 5.0) [26] was used to

confirm Axis I diagnoses. Depression severity was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) [27] and the 17-item Hamilton Depression Rating scale (HAMD-17) [28]. Manic symptom severity was assessed using the Young Mania Rating Scale (YMRS) [29]. Personality was assessed using the Neuroticism-Extraversion-Openness Factor Inventory (NEO-FFI) [30]; a self-report scale that measures personality traits along five basic dimensions (extraversion, agreeableness, conscientiousness, neuroticism, and openness to experiences). The Sheehan Disability Scale (SDS) [31] and the Endicott Work Productivity Scale (EWPS) [32] were used for the assessment of psychosocial function. The SDS evaluates the degree of functional impairment over the past week in work, social, and family life. A total score reflects the degree of global functional impairment. The EWPS evaluates productivity in the workplace during the past week, with higher scores indicating greater dysfunction. All data were collected using paper versions of the scales and either manually entered or scanned using automated capture software (TeleForm, Version 8, Syscom Services, Inc., Silver Spring, MD, USA).

Statistical Analysis

Statistical analyses were conducted using Statistical Product and Service Solutions (SPSS) for Windows, Version 20.0 (SPSS Inc., Chicago, IL, USA). The Chi-square statistic was used for nominal variables and independent t tests were used for continuous dependent variables. All tests were two-tailed, with statistical significance set at p < 0.05. Path analyses using linear multiple regressions were performed to determine which personality dimensions exert a direct effect on function as the primary objective, and which dimensions exert an



indirect influence on function via depression severity as the secondary objective of the study. Age, sex, age at onset, MADRS total score, YMRS total score (for BD group only), employment status, education and presence or absence of a medical co-morbidity were included in each step-wise regression model. Separate regression analyses were performed for MDD and BD.

RESULTS

A total of 717 individuals with MDD (n = 400) and BD (BD-I, n = 208; BD-II, n = 109) were included in the analysis. There were no significant differences between individuals with MDD and BD in terms of demographic characteristics except for age (p = 0.027;Table 1). At the time of assessment, individuals with MDD were significantly older than individuals with BD [mean (SD): 40.63 (12.82) 38.52 and (12.22)vears. respectively]. Differences between sex (p = 0.079),employment (p = 0.065),marital status (p = 0.405),household annual income (p = 0.079),education (p = 0.660),race (p = 0.587)all non-significant. were Individuals with MDD had significantly greater MADRS (p = 0.002) and HAMD-17 (p = 0.011)total scores, older age at illness (p < 0.001) and depression onset (p < 0.001) as well as older age at first treatment of depression (p = 0.048)compared individuals with to BD. significantly lower lifetime number of depressive episodes (p < 0.001) as well as illness duration (p < 0.001)observed in MDD versus BD subjects (Table 2).

Using the NEO-FFI, individuals with MDD scored significantly lower on extraversion (p < 0.001), but higher on agreeableness (p = 0.004) than individuals with BD. No significant differences between the two groups

were found for any other personality factor. Greater global function (p = 0.031) and SDS-social disability (p = 0.024) were observed in MDD as compared to BD individuals. No significant differences between the two disorders were evident for the SDS-family and SDS-work domains or EWPS (Table 2).

Direct Effects of Personality on Functional Measures in Mood Disorders

After adjusting for potential confounders, lower conscientiousness was significantly predictive of a greater SDS total score in individuals with MDD (p = 0.017), but not BD (Table 3; Fig. 1). No other personality factors exerted significant direct effects on global function. Family impairment was also predicted by lower conscientiousness in MDD (p = 0.020) but not BD, while social impairment was significantly predicted by lower extraversion in (p = 0.017), but not MDD (Table 3; Fig. 1). No personality factors significantly predicted work impairment on the SDS. Lower productivity, measured with the EWPS, was predicted by lower conscientiousness in both mood disorder groups (MDD, p = 0.002; BD, p = 0.018) (Table 3; Fig. 1).

Indirect Effects of Personality on Function through Depression Severity

Path analysis revealed that the effect of personality on global functional impairment is largely indirect, occurring via effects on depression severity (Table 4; Figs. 2, 3). Global functional impairment was indirectly influenced higher by neuroticism agreeableness as well as lower extraversion in individuals with MDD, and by higher neuroticism and openness in BD (Figs. 2, 3, respectively). No significant indirect effects on

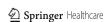


Table 1 Socio-demographic characteristics for individuals with major depressive disorder (MDD) and bipolar disorder (BD)

	MDD (n = 400) Mean (SD)	BD (n = 317) Mean (SD)	χ²	p value
Age, mean (SD), years	40.63 (12.82)	38.52 (12.22)	2.217 ^b	0.027
	n = 400	n = 317		
Sex, n (%)				
Male	136 (34)	128 (40)	3.093	0.079
Female	264 (66)	189 (60)		
	n = 286	n = 221		
Employment, n (%) ^a				
Employed	133 (46)	107 (48)	7.234	0.065
Student	39 (14)	22 (10)		
Unemployed/disability	94 (33)	86 (39)		
Homemaker/retired	20 (7)	6 (3)		
	n = 285	n = 223		
Marital status, n (%) ^a				
Single	118 (41)	99 (44)	5.087	0.405
Married	109 (38)	71 (32)		
Cohabiting	11 (4)	15 (7)		
Separated	10 (4)	9 (4)		
Divorced	34 (12)	24 (11)		
Widowed	3 (1)	5 (2)		
	n = 55	n = 55		
Annual household income,	n (%) ^a			
Less than \$19,999	13 (24)	18 (33)	9.876	0.079
\$20,000-\$39,999	9 (16)	2 (4)		
\$40,000-\$59,999	4 (7)	10 (18)		
\$60,000-\$79,999	5 (9)	8 (14)		
\$80,000-\$99,999	7 (13)	4 (7)		
More than \$100,000	17 (31)	13 (24)		
	n = 375	n = 295		
Education, n (%) ^a				
No or some high school	23 (6)	20 (7)	2.413	0.660
High school diploma	61 (16)	58 (20)		
Some college/some university	72 (19)	47 (16)		
College or undergraduate degree/ diploma	148 (40)	111 (37)		
Some or completed postgraduate degree	71 (19)	59 (20)		
	n = 263	n = 191		

Table 1 continued

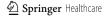
	MDD (n = 400) Mean (SD)	BD (n = 317) Mean (SD)	χ²	p value
Race, <i>n</i> (%) ^a				
Native	1 (1)	1 (1)	2.830	0.587
Asian	7 (2.5)	8 (4)		
Black/African American	8 (3)	10 (5)		
Caucasian	240 (91)	165 (86)		
Mixed/Other	7 (2.5)	7 (4)		
	n = 398	n = 314		

 $^{^{}m a}$ n determined by sex determination; sample size for each analysis varied according to available/missing data

work productivity on the EWPS through depression severity were identified. Social and work dysfunctions on the SDS were indirectly affected by higher neuroticism and agreeableness, and lower extraversion in individuals with MDD (Table 4). Higher neuroticism and openness indirectly influenced greater work and social dysfunction in BD (Table 4). In MDD, higher neuroticism and agreeableness with lower extraversion indirectly influenced greater work dysfunction (Table 4). social dysfunction in MDD was indirectly influenced by higher neuroticism, agreeableness, and lower extraversion, whereas in BD family dysfunction was indirectly influenced by higher neuroticism and openness (Table 4).

DISCUSSION

This study identified that conscientiousness and extraversion exert direct effects on function while different combinations of personality features including neuroticism, extraversion, agreeableness and openness indirectly influence function by affecting depression severity. Lower conscientiousness directly contributes to lower work productivity in



t test

Table 2 Illness severity, function, and personality in individuals with major depressive disorder (MDD) and bipolar disorder (BD)

	MDD Mean (SD)	BD Mean (SD)	p value
Markers of illness severity			
HAMD-17	17.29 (7.79)	15.68 (8.52)	0.011
MADRS	25.27 (11.19)	22.72 (12.73)	0.002
YMRS		4.78 (4.56)	
Age at depression onset, years	23.58 (12.77)	18.09 (9.19)	<0.001
Age at first treatment of depression, years	28.03 (11.63)	25.18 (10.85)	0.048
Number of lifetime depressive episodes	12.42 (20.57)	28.64 (37.07)	<0.001
Age at hypomania/mania onset, years		22.37 (10.62)	
Age at first treatment of hypomania/mania, years		30.35 (12.11)	
Number of lifetime hypomanic/manic episodes		22.37 (32.37)	
Duration of illness, years	16.58 (13.30)	20.20 (12.26)	<0.001
Total lifetime number of suicide attempts	2.29 (2.33)	3.51 (5.25)	0.059
Age at illness onset, years	23.58 (12.77)	17.60 (9.20)	<0.001
Functional measures			
SDS-total	19.34 (8.15)	13.98 (8.38)	0.031
Work	6.42 (3.37)	6.01 (3.48)	0.126
Social	6.68 (2.94)	6.17 (3.08)	0.024
Family	6.59 (2.98)	6.25 (3.04)	0.132
EWPS	54.99 (33.91)	57.77 (31.94)	0.375
Personality (NEO-FFI)			
Neuroticism	27.87 (7.53)	27.88 (7.38)	0.974
Extraversion	22.51 (6.17)	24.58 (6.27)	<0.001
Openness	24.56 (5.44)	25.25 (6.03)	0.106
Agreeableness	29.00 (6.23)	27.68 (5.79)	0.004
Conscientiousness	27.61 (6.8)	27.05 (5.90)	0.241

Bold values are significant

EWPS Endicott Work Productivity Scale, HAMD-17 17-item Hamilton Depression Rating Scale, MADRS Montgomery-Asberg Depression Rating Scale, NEO-FFI Neuroticism–Extraversion–Openness Five-Factor Inventory, SDS Sheehan Disability Scale, YMRS Young Mania Rating Scale

MDD and BD, and global and family impairment in MDD. Lower extraversion had a direct impact on social dysfunction in individuals with BD but not MDD. Higher neuroticism and agreeableness and lower

extraversion exerted indirect effects on global and social dysfunction in MDD. In BD, higher neuroticism and openness indirectly affected global dysfunction. In MDD, family life impairment was indirectly affected by higher neuroticism and openness and lower in family extraversion while. BD. life impairment was indirectly affected by higher neuroticism and openness.

Taken together, distinct personality features may either directly or indirectly influence the global and domain-specific severity of functional impairment as well as the degree of workplace dysfunction in individuals with MDD and BD. Conscientiousness is the most consistent direct contributor to global and domain-specific (i.e. family) functioning, as well as work productivity. Conscientiousness is the personality dimension that organizes and directs behavior according to one's conscience and is characterized by motivation, selfdiscipline, achievement striving, responsibility and thoroughness [33]. As such. conscientiousness would be expected to contribute to functioning, and lower levels can be expected to negatively relate to both function and work productivity [34, 35]. Conscientiousness and extraversion have been documented to have the greatest influence of the personality factors on adaptation in interpersonal relationships [36]. Extraversion was found to exert a direct effect on social function in individuals with BD but not MDD. Those with lower levels of these traits have the tendency to withdraw and not seek interaction, contributing to social impairment with decreased levels of social activity satisfaction in social relationships [36, 37]. This is thought to lead to functional impairment in the areas of social and family life because of decreased tendencies to maintain responsibilities, be reliable, committed and

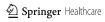


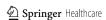
Table 3 Direct effects of personality on psychosocial function and depression severity in major depressive disorder (MDD) and bipolar disorder (BD)

	Effect on psychosocial function		Neuroticism	Extraversion	Openness	Agreeableness	Conscientiousness	MADRS
	R^2	p value	β	β	β	β	β	β
	0.472	<0.001	0.095	-0.084	-0.008	-0.028	-0.159*	0.561**
BD $(n = 115)$	0.338		0.063	-0.099	-0.051	0.059	0.003	0.473**
SDS-social								
$ MDD \\ (n = 161) $	0.476		0.097	-0.113	-0.053	-0.009	-0.111	0.536**
BD (n = 115)	0.408		0.028	-0.222*	-0.109	0.089	-0.017	0.456**
SDS-family								
$ MDD \\ (n = 161) $	0.424		0.129	-0.045	-0.040	-0.001	-0.163*	0.470**
BD (n = 115)	0.314		0.047	-0.102	-0.061	0.024	-0.148	0.357*
SDS-work								
MDD (n = 151)	0.315		0.093	-0.035	0.024	-0.098	-0.121	0.478**
BD (n = 108)	0.143		0.137	-0.012	0.032	-0.009	0.105	0.357*
Work production (EWPS total Score)	•							
$ MDD \\ (n = 110) $	0.443		0.067	-0.028	0.031	0.021	-0.263**	0.143
BD $ (n = 73)$	0.355		0.071	0.226	-0.135	0.055	-0.304*	0.221

EWPS Endicott Work Productivity Scale, MADRS Montgomery-Asberg Depression Rating Scale, SDS Sheehan Disability Scale

dutiful. Moreover, conscientiousness is described as the strongest predictor of workplace performance [38]. This stems from the facets used to describe conscientious traits and behaviors which relate strongly to work

performance and motivational tendencies [39]. It is possible that these behaviors and tendencies may perpetuate greater dysfunction that can affect other domains [40]. For example, impairing facets that result in poor work



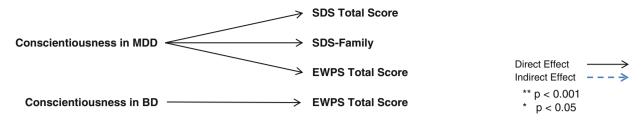


Fig. 1 Direct effect of conscientiousness on global function and work productivity in major depressive disorder and bipolar disorder



Fig. 2 Indirect effects of personality features on global function in major depressive disorder



Fig. 3 Indirect effect of personality features on global function in bipolar disorder

Table 4 The effect of Neuroticism–Extraversion–Openness Five-Factor Inventory on the Montgomery-Asberg Depression Rating Scale

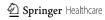
	R^2	p value	Neuroticism β	Extraversion β	Openness β	Agreeableness β	Conscientiousness β
$\overline{\mathrm{MDD}\ (n=161)}$	0.398	< 0.001	0.468**	0.228**	0.043	0.166*	0.094
BD $(n = 115)$	0.366	< 0.001	0.450**	-0.145	0.211*	-0.008	-0.067

Due to smaller sample the contribution of NEO to MADRS varies numerically for SDS-Work and EWPS total score; it did, however, alter outcomes and is not presented in the table

BD bipolar disorder, MADRS Montgomery-Asberg Depression Rating Scale, MDD major depressive disorder, SDS Sheehan Disability Scale

performance may include the inability to handle responsibilities, which may extend to family and social commitments.

Neuroticism, openness and agreeableness did not demonstrate significant direct effects on global functional impairment but did influence function through depression severity. Specifically, in BD and MDD, respectively, higher openness in conjunction with higher neuroticism, and agreeableness in conjunction with lower extraversion were found to indirectly influence function. This indirect



effect may explain the conflicting results pertaining to openness and its moderational role on function as reported by others [24, 25, 41, 42].

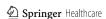
Higher conscientiousness has also been shown to be predictive in positive healthpromoting behaviors [43, 44]. Thus, enhancing conscientiousness may positively functioning not only in the affected functional domain but also health in general. Moreover, lower conscientiousness has a significant impact on mood and may be a vulnerability factor for depressed individuals that persists into remission [45]. Taken together there bidirectional association is between conscientiousness and work performance; poor performance as caused by low conscientiousness helps to form negative beliefs about one's self and abilities, which in turn further hinders performance [46].

The major limitations of our analysis were its cross-sectional assessment, retrospective post hoc design, and small number of subjects per group. Observations regarding the longitudinal stability of personality features and their predictive ability over time could not be explored. Measures of function relied on self-report, and are vulnerable to recollection bias and potential under-reporting or over-reporting of dysfunction. There was a discrepancy between the predictive personality dimensions identified by the two work function measures (SDS-work and EWPS) likely due to the related but not identical outcome measures and the sensitivity of the two self-reported scales; SDS-work assessed general functional work impairment with one item compared to the EWPS which assessed work productivity with 25-items. It is possible that the personality traits identified as predictive of dysfunction may not be unique to the mood disorder population but may extend to other conditions and the general population.

CONCLUSION

Identification of factors that predict functionality may facilitate long-term management strategies aimed at full functional recovery. This study suggests that personality measurement tools in combination with other factors (e.g., depression severity) may facilitate clinical care planning and management. Personality measures may also be used to monitor treatment efficacy; recent evidence supports the use of personality assessments for monitoring personality changes resulting from treatment with selective serotonin reuptake inhibitors in individuals with depression [47, 48].

Personality screening tools may also guide personalized treatment strategies targeting the dysfunctional personality facets, mitigating their effects on function. For example, occupational health services or related programs may offer counseling to employees identified as having poor work productivity and/or depression [49-51]. The potential use of interventions to targetspecific individual personality traits has previously been described. Subjective belief of performance inadequacies in depressed patients has been shown to be an accurate representation of true performance; therefore, skill(s) training that target(s) these inadequacies may improve both performance and affect [45]. Therapeutic treatments (e.g., cognitive-behavioral therapy) aimed at enhancing extraversion and reducing neuroticism have also been described [52]. As a result, by targeting personality traits the clinician may improve a patient's function across the affected domains directly, and indirectly by mitigating depressive symptoms. A "general mental illness" personality "profile" (high neuroticism, low extraversion, agreeableness and conscientiousness) [7] and a "depression profile" (high neuroticism, low extraversion) [5] have been reported. Hopwood et al. [24] explored the relation



between FFM personality dimensions and function in a sample of individuals with personality disorders and MDD. They found that functional impairment in MDD was related to high neuroticism, low extraversion, openness and conscientiousness, which is similar to the general mental illness profile [24]. In our study, conscientiousness accounted for most of the direct contribution to function, while for the other personality factors, the effect on function was mediated by depression severity.

The goal of personalized medicine is to identify more effective and better tolerated treatments which consequentially improve functional outcomes and reduce costs. Mood disorders are the most disabling and costly chronic medical disorders in the working population. The importance of the role of psychological factors, particularly personality, and the integration of this knowledge into clinical practice are emerging. Our results are some of the first to characterize the contribution of personality to function, and document the pertinence of conscientiousness to functional impairment in mood disorders.

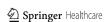
ACKNOWLEDGMENTS

The authors acknowledge the unrestricted grant provided by Pfizer, Canada Inc. Dr McIntyre is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Conflict of interest. Roger McIntyre has received grants from Stanley Medical Research Institute, the National Alliance for Research on Schizophrenia and Depression (NARSAD), Eli Lilly, Janssen-Ortho, Shire, Astra-Zeneca, Pfizer and travel funds from Bristol-Myers Squibb. He has been an advisory board member for Astra

Zeneca, Bristol-Myers Squibb, the France Foundation, GlaxoSmithKline, Janssen-Ortho, Solvay/Wyeth, Eli Lilly, Organon, Lundbeck, Biovail, Pfizer, Shire, Schering-Plough, and Merck. Dr McIntyre has also served on speaker bureaus for Janssen-Ortho, Astra-Zeneca, Eli Lilly, Lundbeck, Biovail, and Merck and has performed continuing CME activities for Astra-Zeneca, Bristol-Myers Squibb, the France Foundation, I3CME. Solvay/Wyeth, the Physicians' Postgraduate Press, CME Outfitters, Optum Health, Schering-Plough, Merck and Eli Lilly. Joanna Soczynska has received travel funds from Janssen and is a recipient of the Eli Lilly Canada Fellowship Award. Mohammad Alsuwaidan has equity ownership in Sanofi-Aventis. David Muzina has received grant/ research support from Repligen and has received honoraria from AstraZeneca, Pfizer, and Wyeth. Sideny Kennedy has been a consultant for St. Jude Medical, Bioavail, Eli GlaxoSmithKline. Ianssen-Ortho. Lundbeck and Merck Frost and has received honoraria from and served on speaker and medical advisorv boards for committees for Astra Zeneca, Bristol-Myers Squibb, the France Foundation, AstraZeneca, Bioavail, Eli Lilly, GlaxoSmithKline, Janssen-Ortho, Lundbeck, Servier, and Wyeth. Jessica Leen, Laura Ashley Gallaugher and Hanna Woldevohannes declare no conflict of interest.

Compliance with ethics guidelines. All procedures followed were in accordance with standards of the responsible the ethical committee experimentation on human (institutional and national) and with the Helsinki Declaration of 1975, as revised in and 2008. Informed consent was obtained from all patients for being included in the study. The IMDCP is approved by the UHN Ethics Board Research and the

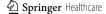


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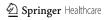
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