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Impact of irritability: A two year observational study of outpatients with bipolar I or schizoaffective disorder

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Abstract

Objectives: Many people experience irritability when manic, hypomanic, or depressed, yet its impact on illness severity and quality of life in bipolar and schizoaffective disorders is poorly understood. This paper aims to examine the relationship of irritability to symptom burden, functioning, quality of life, social support, suicidality and overall illness severity in a naturalistic cohort of people with bipolar I or schizoaffective disorder.

Methods: We used data from 239 adult outpatients with bipolar I or schizoaffective disorder in the Bipolar Comprehensive Outcomes Study (BCOS); a non-interventional observational study with a 2-year follow up period. Baseline demographic and clinical characteristics of participants with and without irritability were compared. A Mixed-Model Repeated Measures analysis was conducted to examine the longitudinal effect of irritability on clinical and quality of life variables over follow-up using significant baseline variables.

Results: At baseline 54% of participants were irritable. Baseline irritability was associated with illness severity, mania, depression, psychotic symptoms, suicidality, poor functioning and quality of life, but not diagnosis (schizoaffective/bipolar disorder). Participants with irritability were less likely to have a partner and perceived less adequate social support. On average, over follow-up those with irritability reported more symptoms, functional

impairment and suicidality. Furthermore, the effects of irritability could not be fully explained by illness severity.

Conclusions: Irritability was associated with more negative symptomatic, functional and quality of life outcomes and suicidality. The identification, monitoring and targeted treatment of irritability may be worth considering to enhance health and wellbeing outcomes for adults with bipolar and schizoaffective disorders.

Key words: Bipolar disorder; schizoaffective disorder; irritability, functioning, social support, suicide, quality of life, mania, depression, psychiatry.

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Introduction

Irritability has been conceptualised as being “easily annoyed and provoked to anger” (1)^{p.35} and having “a mood dominated by poor control over temper” (2, 3). It can range from subjective feelings and cognitions to overt expressions of anger (4). Irritability is part of human experience, but some people are more prone to it due to their personality, temperament, or mental health condition (5-12). Given its transdiagnostic occurrence, irritability is often considered a non-specific factor that none the less predicts worse mental health outcomes (5-12). It is also one of the possible defining criterion A symptoms of mania and hypomania, together with increased activity and energy (13) in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), and is particularly common in childhood and adolescent mania (1). Most studies of adults with bipolar disorder examine irritability together with other symptoms of mania, hypomania or mixed states, and highlight the negative effects of these symptom clusters (14-17). Even less research has been done on the significance of irritability in schizoaffective disorder, which shares some affective symptoms and treatments with bipolar disorder.

Irritability has stronger associations with dysphoric and mixed, rather than euphoric, mania and may cluster with symptoms such as paranoia and increased energy and activity in adults (16, 17). Studies point to differences in certain genetic variants between people with irritable or elated mania. Irritable mania (as opposed to elated mania) may result from a specific set of genes involving a region on chromosome 13q31 (18). Curiously, biomarkers even in treatment-naïve people with first episode mania may parse irritable from elated mania, with the latter having lower cortisol levels than controls, and the irritable group having higher cortisol levels (19). Lower levels of progesterone and polymorphisms of ARK1C4, a gene coding for steroidogenic enzymes, may also be associated with irritability in bipolar disorder (20). Although the physiological aetiology of irritability in mania is still unclear, dysphoric mania has been associated with greater suicidal ideation than elated mania (21). Furthermore, contrary to the stereotype of hypomanic mood as involving an elevated and thought enhancing factor, it can also present with an irritability-thought racing - risk taking factor (22-24) associated with increased symptoms, impaired functioning, maladaptive coping and negative consequences (25-27).

Irritability together with at least 2 to 3 other manic symptoms denoting mixed depression (28) has been associated with illness severity, worse symptomatic and functional outcomes and lower quality of life than pure depression, and with suicidality (29, 30). Given its common occurrence as a non-specific factor however, irritability in the DSM 5 is not included as a mixed specifier of major depressive episodes in adults (13). Even when conceptualised independently of other manic symptoms, irritability commonly co-occurs with episodes of bipolar depression (15, 31). In both the Systematic Treatment Enhancement Program for Bipolar Disorder study (STEP-BD) (n=1180) at baseline and the long term prospective Collaborative Depression Study (CDS) (n=142), which involved participants with bipolar depression, irritability occurred far more often than other common intra-depressive manic symptoms (14, 15). Overt expressions of irritability predicted worse illness outcomes in the CDS independently of other manic symptoms. Given that irritability is common and may affect illness outcomes, it deserves closer attention in prospective studies (14).

Despite treatment advances, many people with bipolar and schizoaffective disorder are still burdened by disruptive symptoms, impaired functioning, quality of life, social support and increased suicidality (32-37). Recognising irritability and its potential impact might help to tailor effective pharmacological and psychosocial treatments to people with mood episodes (38, 39).

In this study we prospectively examined the occurrence and effect of irritability across mood states amongst adult outpatients with bipolar disorder or schizoaffective disorder. We first characterised a profile of demographic and comorbidity issues that varied in irritable and non-irritable individuals at baseline. Based on this analysis, a set of covariates were identified and accounted for in order to investigate the longitudinal impacts of irritability on: (1) Symptom burden (2) Functioning, quality of life and social support and (3) Suicidality. Given that irritability is frequently associated with illness severity across disorders we also examined the relationship of irritability to overall illness severity (5, 6).

Methods

Study design and participants

We used data from Bipolar Comprehensive Outcomes Study (BCOS, study code F1D-AY-B004), a study designed to prospectively observe the clinical, functional and economic outcomes of treatment in a naturalistic setting of adult outpatients with bipolar I disorder (n=175) and schizoaffective disorder (n=64). Comprehensive details about the BCOS design and cohort are published elsewhere (40). In brief, participants over the age of 18 were required to have been prescribed a mood stabiliser (lithium carbonate, sodium valproate, or carbamazepine) or atypical antipsychotic (olanzapine) by their clinician to be included in the study. In this non-interventional study, researchers were not involved in treatment decisions and participants continued to receive treatment as usual from their existing clinician.

Generalizability was facilitated by minimal exclusion criteria, which included a diagnosis of schizophrenia, organic psychosis or dementia, or having been involved in a clinical trial 30 days before study entry or during the study. To obtain as broad a sample as possible, participants were recruited from private clinics, private hospital systems and primary care as well as from the community. The research took place between 2003-2008 at two sites in Australia: Monash Alfred Psychiatry Research Centre in Melbourne, and Barwon Health in Geelong. Ethics approval was obtained at both sites. All participants provided written informed consent for study participation, and the study was conducted in concordance with Australian privacy and ethics legislation.

Measures and definitions

Participants were assessed by trained researchers using a range of clinician and self-rated measures every three months over a 2-year follow-up period (9 study visits). The following measures from the broader study were used:

Irritability

Irritability was *a priori* defined as a dichotomous categorical variable (score of greater $\geq$ 2) on item 5 of the clinician-rated Young Mania Rating Scale (YMRS) (41), commonly used to assess manic symptoms (42). Item 5 has been used to assess irritability in other studies (43). According to this definition, irritability is operationalized as including both subjective mild, and more intense, irritability, as well as occasional and more frequent

overt expressions of irritability, anger and hostility with scoring between 1-8 and using 4 anchor points indicative of severity.

Diagnosis, comorbidity and psychotic symptoms

Bipolar I and schizoaffective diagnoses were defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) (44) and confirmed along with comorbid generalised anxiety disorder in the past 6 months or alcohol and drug dependence in the past 12 months using the Mini-International Neuropsychiatric Review Version 5 (MINI) (45). Anxiety and irritability commonly co-occur (13), and anxiety disorder comorbidity is considered to predict worse prognosis in bipolar disorder (46). Similarly, irritability is prominent in users of illicit substances such as alcohol, amphetamines and ecstasy/ designer drugs, and comorbid substance use disorders negatively affect illness outcomes (47). The Habits form (48) was used to collect information about smoking habits over the past 3 months. The presence of psychotic symptoms was also assessed on the MINI at baseline to examine whether this was associated with irritability.

Mania, depression, mixed states and illness severity

Affective symptom burden and overall illness severity were assessed at every visit using the:

- a) YMRS with syndromal mania defined by a total score of ≥ 15 , subsyndromal mania as between 5-14, and symptomatic remission as < 5 (49, 50).
- b) 21-item Hamilton Depression Rating scale (HAM-D21) (51) with syndromal depression defined as a total score of ≥ 15 , subsyndromal depression classified as between 8-14, and symptomatic remission ≤ 7 (49).
- c) Clinical Global Impressions-Bipolar Version Severity of Illness scale (CGI-BP-S) (52) used as an indication of severity of overall bipolar disorder/schizoaffective illness.

In order to examine the association between irritability and mixed states, the latter was defined subsyndromally in accordance with a previous paper using the same BCOS sample (30). According to this classification, participants meeting DSM-IV-TR criteria for a major depressive episode (MDE) with 3 or more hypomanic symptoms current with a MDE were considered to have “mixed depression” (53) (54). Mixed mania involved

having a DSM IV TR full manic episode concurrent with at least 2 out of six possible depressive symptoms; depressed mood, anhedonia, guilt, suicide, fatigue and anxiety(55).

Functioning, quality of life and social support

Self-reported functioning and quality of life were assessed at every visit using the 36-item Short-Form Health Survey (SF-36) (56), and EuroQol health-related quality of life 5-dimension questionnaire (EQ-5D) (57). The SF-36 evaluates eight dimensions including social functioning, mental health, role limitations due to emotional problems, physical functioning, role limitations due to physical problems, physical pain, vitality (energy and fatigue) and perceptions of general health. These dimensions can be divided into two summary measures, the Mental and Physical Component Summaries (MCS and PCS). The EQ-5D measures emotional and physical health related quality of life associated with the capacity for mobility, self-care, usual activities as well as the experience of pain/discomfort and anxiety and depression, and in addition respondents are asked to rate their overall health state on a score between one and 100.

We also examined the connection between irritability and perceived social support using the Social Provisions Scale (SPS) (58). This scale was added later in the study (in 2006) so data was only gathered from 109 participants who had not already completed the study. In addition, the Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation (SLICE/LIFE) (59) was used at baseline to assess whether those who were irritable were more likely to be without a partner.

Suicidality

Two proxy measures of suicide risk were included. At baseline, the suicide risk scale on the MINI was used to assess the extent of participants' suicide risk over the past month with a total score of ≥ 10 denoting high suicide risk, between 6-9 moderate suicide risk and 1-5 low risk (60). This scale includes suicidal ideation, plans and attempts over the past month and enquires about any previous suicide attempt using weighted scores. In order to examine suicide risk over time, item 3 on the HAM-D21 was used. This is a 4 point scale with 0 denoting the absence of any suicidal ideation; 1, general thoughts that life is not worth living; 2, more specific thoughts about death to the self; 3, actual suicidal ideas or gestures and 4 refers to a serious suicide attempt. Suicidal ideation is a known marker of patients who may be at risk of suicide attempts and actual suicide (61, 62).

Nevertheless, in our study, the response to metrics of suicide risk was limited mostly to suicidal ideation, rather than attempts and actual suicide; hence we refer to this variable as *suicidality*.

Statistical analysis

The data pertaining to demographics, depression (HAMD), mania (YMRS), quality of life (SF-36 and EUROQOL), SLICE/LIFE, MINI and Habits Form were merged into one master file and additional variables were created for analysis. Using irritability as a dichotomous variable, comparisons were made between the group with, and without irritability on socio-demographic and other patient related characteristics using appropriate parametric tests where data were normally distributed, and non-parametric statistical tests for categorical or non-normal data. The association between irritability, demographic characteristics and social relationships was based on the Chi-square test. If any association was significant, we further tested the equality of proportions using the z-test for proportions. Either the two-sample t-test or the Mann-Whitney U test was used to check for significant differences between the two groups for continuous outcome measures and tests were adjusted for all pairwise comparisons using the Bonferroni correction.

A sub-group analysis was done for the participants who completed the social provisions scale. For this sub-group analysis we took the last completed visit of these participants and made comparisons by irritability status. The associations between baseline irritability and depression, mania and suicide risk were performed using contingency tables to calculate the odds ratios (OR) and the 95% confidence interval (CI).

Mixed-Model Repeated Measures Analysis (MMRM) was used to analyse change in HAMD, YMRS, SF-36 physical and mental health scores, and suicide risk and the estimated marginal means are presented by irritability status. The MMRM model utilised data with statistically significant differences from the baseline analysis to inform on the most appropriate variables for inclusion in the MMRM model. This model was used due to the higher power with increased focus on relevant variables and reduction of error of many unnecessary analyses based on already obtained results. Statistically significant variables included in the MMRM modelling included the presence/absence of psychotic symptoms, alcohol or substance dependence over the past twelve months, generalised

anxiety disorder diagnosis over past six months and suicide risk from the MINI. It was determined that the pre-specified MMRM include an irritability*CGI Bipolar interaction term in the model. This allows for the consideration of potential influences that illness state might have on irritability and avoids ascribing changes without consideration of overall mental state. The mean difference comparing the irritability status along with the 95% confidence interval and the p-values are presented. All tests were 2-tailed and a p-value of 0.05 was used for statistical significance. All analyses were performed using SPSS (Version 21).

Results

Participant characteristics

In the full sample, 54% were irritable. A third of those in the irritable group were more overtly irritable, that is, expressed their irritability in observable behaviour (n=41; 32%), scoring 4 or above on item 5 of the YMRS. Further exploratory analysis revealed that in terms of actual aggressive or disruptive behaviour, 35 (27%) of the irritable group scored as aggressive or disruptive on item 9 of the YMRS, suggesting that the irritable group represented a range of levels of irritability, although many of the irritability group were only subjectively irritable. In terms of demographic factors, the sample included a larger proportion of females (58.2%) than males (41.8%), with an average age of 41.8 years (range: 18-79 years). Table 1 includes the key demographic and clinical characteristics of the 239 participants at study entry (baseline) comparing those with and without irritability.

Insert table 1 about here

There was no univariate association between irritability and demographic factors such as gender, age or income but those with irritability were significantly less likely to have a partner. Irritability was not significantly associated with diagnosis (bipolar or schizoaffective disorder).

The expected association between irritability and syndromal mania and depression and subsyndromal mania was evident. While irritability was reasonably prevalent in those with mixed states, the association was not significant. Irritability was however, significantly associated with suicidality measured using the suicide risk scale on the MINI, and with generalised anxiety disorder (GAD) and alcohol and drug dependence comorbidity and

with psychotic symptoms..Slightly more people with bipolar (n=28) than schizoaffective disorder (n=24) had any psychotic symptoms at baseline.

Mean baseline differences in illness burden in irritable and non-irritable groups

Table 2 compares the mean differences on affective symptoms, severity of illness, suicidality and quality of life between those who were irritable and not irritable.

Insert table 2 about here

There was a statistically significant difference in the means of the YMRS total score, HAMD₂₁ total score and the CGI-BP-S overall score, suggesting that those who were irritable had greater symptom burden and overall illness severity. The difference in the means on the SF-36 physical and mental functioning indexes and EQ-5D VAS and utility score suggested that those who were irritable also experienced more impaired functioning and quality of life. There was also a significant difference in suicidality as measured by Item 3 on the HAMD. Effect sizes with regard to clinical symptoms, suicidality and QOL were in the expected direction. The highest effect sizes were found with regard to manic/hypomanic (YMRS) and depressive symptoms (HAMD). Suicidality, illness severity and quality of life had medium effect sizes.

Perceived social support

Responses to the SPS were collected for a subsample (n=109) of BCOS participants. Average scores during the last visit are presented in table 3 by irritability status at study entry. In this sub-sample, 56% were irritable and the remaining 44% were not irritable.

Insert table 3 about here

Those reporting irritability had poorer perceptions of social support overall than those without irritability at two-year follow-up, and on the guidance, reassurance of worth, social integration and attachment scales.

Multivariate analysis - effects of irritability

Results of modelling for changes in mania, depression, SF36 - Physical and Mental health scores and suicidality (item-3 of the 21-item HAMD) by irritability status using Mixed Model Repeated Measures (MMRM) analysis are presented in Table 4. All nine visits

over 2 years were considered for analysis and the MMRM model adjusted for those comorbidity factors identified at baseline as significantly affected by irritability. These factors included alcohol and drug dependence, current psychotic symptoms, generalised anxiety disorder and suicidality.

Briefly, alcohol dependence over the past 12 months was associated with differences on the HAMD, HAMD item 3 (suicidality) and SF36 Mental Scales (p-values of .003, .014, .002 respectively). Drug dependence over past 12 months was associated with differences on the SF36 Physical and Mental Scales (p-values of .018 and <.001 respectively). Psychosis was associated with worse scores on the YMRS, HAMD and SF36 Physical scale (p-values of <.001, <.001 and .010 respectively). Comorbid GAD over the past six months was associated with significantly worse scores on the HAMD, HAMD item 3 and SF36 physical functioning scales (p-values <.001, .015 and .005 respectively). Finally, suicidality was associated with significantly worse scores on the SF36 Physical and Mental scales over the study duration (p-values <.000, .001 respectively). Suicidality was not assessed with regard to depression in the HAMD measure, as it is a component of the measure. The clinical global impression was introduced as the covariate to control for the impact of illness severity when considering the additive impact of irritability. The simple main effects for the CGI Bipolar total scores indicated the strong convergent validity with other scales, with a significant association between severity on this scale and all other scales (p-value <.001 for each scale).

Insert table 4 about here

As illustrated in Table 4, the direction of the main effects was as expected, with those who were irritable showing significantly more depressed (mean difference = -4.42; $p < 0.001$), manic (mean difference = -6.02; $p < 0.001$), and suicidal symptoms (mean difference = -0.13; $p = 0.004$) and having worse mental (mean difference = 4.79; $p = .017$) and physical (mean difference = 5.48; $p = .043$) functioning and quality of life on the SF 36. On average, participants who were irritable were more syndromally depressed, but those in the non-irritable group were still within the subsyndromal depression range. Although both those with irritability and those without fell, on average, within the subsyndromal range for mania, those with irritability were significantly more symptomatic. All participants, on average, had poor levels of psychosocial functioning and quality of life, although those who were irritable scored significantly lower on the SF 36. Although average suicidality

scores over two years were not high, these scores were significantly elevated in the irritable group.

Interaction between irritability and overall illness severity

In addition to measuring the simple main effects of irritability on this longitudinal sample, we included analyses of the interaction between irritability and overall illness severity in the MMRM modelling. The model revealed a statistically significant effect of this interaction in relation to YMRS ($p < .001$), HAMD ($p = .006$) and suicidality scores (.038). Figures 1-3 show the interaction between irritability and CGI Bipolar (total measure of symptomatology), and demonstrate the additive impact of irritability over and above general levels of illness state in relation to suicidality, YMRS and HAMD scores.

Insert figures 1-3 about here

Discussion

This study highlights that irritability, besides its role in manic and hypomanic episodes may be a relatively common and stable indication of emotion reactivity and dysregulation in bipolar and schizoaffective disorder. After accounting for illness severity (CGI-BP), psychotic symptoms, generalised anxiety disorder and substance use comorbidity as well as whether the individual was in a relationship, irritability significantly influenced YMRS, HAMD, SF36 mental index, physical index and suicidality over the two-year study. Far from being benign, irritability may confer increased risk of more symptom burden, functional and social impairment, worse quality of life and suicidality especially, but not only when the person is severely ill.

Irritability and symptom burden

Unlike studies that examined irritability in either mania/hypomania, mixed states or bipolar depression (14, 15, 17, 25, 29), this study examined irritability in outpatients across mood states.. Our results do however, confirm a significant association between irritability and both syndromal and subsyndromal mania, and the negative effects this is reported to have on illness outcomes (16, 17, 25, 63). Irritable hypomania, for example has been linked to higher rates of sleep disturbances, depressive symptoms, perceived stress, and somatic complaints than non-irritable hypomania (25).

Consistent with previous findings, the impact of irritability was also clear for those experiencing depression (14, 64). Overt irritability (expression of irritability, annoyance or anger) in a bipolar MDE in the Collaborative Depression Study (CDS) for example, predicted depressive episode persistence and, in conjunction with agitation, depression severity (14). The definition of irritability we used however included subjective as well as overt irritability, and less than half our sample were acutely depressed. A recent study measured irritability in a slightly different way using the STEP-BD Affective Disorders Evaluation and asked outpatients with bipolar I and II disorder about the number of days within the last 10 days that they experienced irritability. (65) The sample included both participants in a depressive episode and those who had been euthymic for at least 8 weeks. This study conducted in America reported that baseline irritability was associated with shorter time to depressive recurrence and delayed depressive recovery over two years, which is broadly consistent with the negative impact of irritability on depression in our study in Australia (65).

The lack of association between irritability and mixed states at baseline should not be confused with prevalence studies that show irritability is common in mixed states (14, 28, 31, 66). If we look at the proportion of participants who were irritable within the mixed BCOS sub-sample, a reasonably high percentage (66% $n=22$) were irritable - true for both mixed mania ($n=33$) and mixed depression ($n=33$). Notably, the number of participants with a mixed state at baseline was limited, given that entry requirements did not require participants to be in a mood episode and this may have limited statistical power.

Furthermore, Vieta and colleagues (67) reported that irritability alone was less associated with mixed mania than aggressive behavior arising from irritability. When considering overt irritability alone in a post-hoc exploratory analysis of our data, there was actually a significant univariate association between manic mixed states and irritability ($p=0.008$), but two thirds of the irritable group in our study was subjectively irritable and relatively few were manic. Furthermore, Judd et al (14) reported that having at least one manic symptom and in particular irritability and/or agitation as part of bipolar depression, may account for some of the negative consequences usually associated with mixed states.

Importantly, the impact of irritability may extend beyond its occurrence in mania/hypomania, depression or mixed states (68). The link between irritability and generalised anxiety and substance use disorders in the BCOS is supported by other studies (8, 65, 69-71). The direction of these associations is however uncertain. Irritability for

example, could develop as a result of substance use or people may use substances to self-medicate and reduce irritable dysphoria. Either way, in the BCOS study irritability predicted worse illness outcomes over and above the measured comorbid disorders, and psychotic symptoms. The significant association with psychotic symptoms may however be important clinically as a risk factor for aggressive behaviour (72). A study involving inpatients with schizoaffective disorder and schizophrenia found that the co-occurrence of psychotic symptoms and irritability can increase the risk of violent behaviour (73).

Studies of unipolar depression highlight the transdiagnostic negative impact of irritability. Most cross-sectional and prospective studies connect irritability with severity, chronicity or persistence of unipolar depression, as well as comorbid anxiety and substance use disorders (4-6, 12). In the large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) for example, irritability was reported in nearly half the participants with a depressive episode and associated with depression severity and anxiety, and it is notable that the irritable group did not have more bipolar spectrum disorder signs (e.g. atypical depression or family history of bipolar disorder) than the non-irritable group (5).

Similarly, Judd et al (6) in a later 31 year prospective study involving participants with unipolar major depressive disorder found a link between overt irritability and depressive episode persistence and severity, that could not be accounted for by manic/hypomanic symptoms or other comorbidity. Whether irritability is a non-specific factor or manic/hypomanic symptom, overall, our findings suggest that irritability is linked with considerable symptom burden in a subgroup of adults with bipolar or schizoaffective disorder and should not be ignored (14, 15, 73).

Negative impact on psychosocial functioning and quality of life (QOL)

On aggregate, the level of functioning and quality of life were impaired in both the irritable and non-irritable groups, but those with irritability fared even worse in this regard. QOL relates to how a person perceives their life and is influenced by their symptoms, functional impairment, expectations, goals and values (33, 74). Irritability and lack of sleep were the manic symptoms with the most disruptive effect on quality of life in a cross-sectional study of 125 outpatients with bipolar disorder, independently of depressed mood, gender, age and income. (43). A similar negative impact on functionality was found when irritability was connected to hypomania (25), and again when considering both hostile attitudes and behavioural expressions of irritability and anger (72). A study of

emerging mania in 1755 adolescents suggested an “under control” dimension typified by symptoms of irritability, risk taking and distractibility that may predict psychosocial impairment, whereas a more energized and cheerful “exuberant” dimension is more likely to enhance functioning (27). In addition, irritability has been strongly linked to functional impairment and poor quality of life in studies of people with unipolar depression, again highlighting its more non-specific adverse effect (5, 6, 12).

Irritability at home or work can have negative consequences (75, 76). Irritability was found to impair accurate recognition of affect in others, to decrease social cognition or mentalising, as well as mutual affection in relationships, and to exacerbate interpersonal stress (77, 78). It can “spread” by a process known as “emotional-contagion” whereby non-verbal and verbal expressions of affect are shared (79). Family, friends and work colleagues commonly find it difficult to know how to respond when interacting with a person who is irritable (80). Ensuing interpersonal stress and high expressed emotion can increase the risk of affective relapse, undermine relationships and job security (75) (76, 81).

Judd et al (14) reported that overt irritability independently of other manic symptoms was associated with greater impairment in spouse/partner relationships. Although irritability in the BCOS sample was mostly subjective, those with irritability were less likely to have a partner/spouse.

Good social support has been considered vital to quality of life in bipolar disorder (35), but our prospective findings suggest that those with irritability perceived worse overall social support at follow-up, and particularly missed having a sense of belonging, emotional closeness, attachment, reassurance of their self-worth and having someone to turn to for information and guidance. This finding is clinically important considering that perceived lack of social support has been connected to both depressive and manic relapse (82). Thus, irritability may be a signal of greater symptom burden, impaired functioning and worse quality of life in areas that are meaningful to the individual. Furthermore, poor quality of life, lack of social support and feelings of disconnection and isolation may contribute to suicidality (83, 84).

Irritability and suicidality

Any potential association between irritability and suicidality is worth examining given that a third to a half of bipolar disorder patients attempt suicide at least once and 15-20% die by suicide (36, 85). When examining factors that contributed to suicide in people with schizophrenia, schizophreniform or schizoaffective disorder, meeting the criteria for a concurrent DSM IV diagnosis of mood disorder significantly increased the risk of suicide (34). Although BCOS participants were generally not very suicidal possibly because acuity was not a criterion for inclusion and there was close follow-up and support, those with irritability scored higher on measures of suicidality both at baseline and prospectively (86). It must however be noted that suicidality in our study was analysed as a general score that involved mostly suicidal ideation (as there were too few actual suicide attempts). Nevertheless, suicidal ideation is known to increase the risk of attempts and completions (61, 62, 87).

The link between irritability and suicidality is supported by most studies (34, 88, 89). For example, in the Isle of White epidemiological study that followed adolescents to midlife (n=1426), irritability in adolescence was significantly associated with adult suicidality over and above the variables of psychopathology and neuroticism (89). In addition, the presence of even a few manic symptoms in bipolar depressive episodes including irritability, has been connected with a history of suicide attempts (15, 29, 90). For example, irritability, and to a lesser extent psychomotor agitation, were the most common co-occurring intra-depressive hypomanic symptoms amongst suicide attempters (29). Furthermore, overt irritability independently of other manic symptoms, was a significant predictor of future suicide attempts (14). Baseline irritability was also associated with a lifetime suicide attempt in outpatients with bipolar disorder who had been euthymic for at least 8 weeks. (65) By contrast, however, Pawlak et al (91) found no association between irritability and previous suicide attempts in a sample that included people with unipolar and bipolar disorders. Interestingly, when it came to viewing overt irritability in people with a unipolar MDE in the Collaborative Depression Study, there was also no significant association between irritability and with suicide attempts or ideation (12). Given that irritability is potentially modifiable, more clarification is needed on the link between irritability and suicidal ideation, attempts and completion in conditions involving affective symptoms, and whether this varies between unipolar and bipolar disorder (38).

Irritability and illness severity

A possible explanation for the seemingly transdiagnostic association of irritability with worse current and future illness outcomes may be that it is simply an artefact of more severe illness. Our results however suggest that illness severity cannot fully explain the longitudinal negative effects of irritability. The figures of the suicidality, depression and mania scores for irritable and non-irritable participants demonstrate the consistently higher scores for the irritability group across severity and these states. This suggests that rather than just being one element of more severe illness, irritability is associated with risk of future mania, depression and suicidality irrespective of how severely ill the person is, although when irritability is accompanied by illness severity, future outcomes may be worse. Clinicians may need to address irritability regardless of the person's overall illness severity to elicit symptomatic, functional and personal recovery, and be even more vigilant when it goes hand in hand with more overall illness severity.

Limitations and future directions

The findings need to be viewed in the context of study limitations including the following:

Generalizability

Participants in our study were adult outpatients, mostly with bipolar I disorder and relatively few were in a severe manic episode or very suicidal or psychotic, which may limit generalizability of the results. Nevertheless, the irritable group were not distinguished by diagnosis (bipolar vs. schizoaffective disorder) and this study involved a naturalistic cohort with a 93% retention rate.

Irritability and its measurement

Even using only a single scale item to measure irritability, our results highlight the importance of irritability as a broad and influential factor in a subgroup of adults with bipolar or schizoaffective disorder. Although use of a single scale item to measure irritability is not unique (65, 76), future studies could develop and use more comprehensive measures of adult irritability that assess levels of intensity, frequency and the chronicity of irritability and tease out the relationship between chronic and more episodic irritability, and how this differs from occasional irritability that is part of usual experience. Recently, the Affective Reactivity Index (3) demonstrated encouraging psychometric properties in measuring chronic irritability in adults (92) and the Sheehan Irritability Scale was validated for use in Major Depressive Disorder (93).

Furthermore, perhaps there is a “tipping point” beyond which irritability has a progressively destructive impact on symptomatic and functional outcomes (94). To better understand the dimensionality and severity of irritability, it may help to consider it as an ordinal variable in future studies, rather than dichotomously as we have done in this study.

Comorbidity

Although a strength of our study was its consideration of certain comorbidities commonly associated with irritability, future studies may usefully consider others including personality disorders such as borderline personality, bipolar temperaments, and impulse control disorders that may both involve irritability and predict worse illness outcomes (7, 12, 95-97). Data from population- based studies suggest that conduct problems (especially but not exclusively more persistent conduct problems) may infer risk of depression accompanied by irritability and disruptive behaviour in young adults (98, 99). The BCOS study did not involve reports of early conduct disorder, depression or irritability, nor did it investigate the link between depression accompanied by irritability and disruptive behavior in adulthood. Furthermore, there was little evidence of antisocial personality in our adult sample (measured using the MINI).

Factors such as trait or state dependent low frustration tolerance, hostility, aggressiveness, impulsivity or theory of mind deficits may connect irritability with more negative outcomes such as relationship problems, poor quality of life and suicidality (76, 96, 100, 101). Some people with mood disorders for example, may be at an increased risk of harm to themselves or others when they experience increased irritability together with impulsivity and/or psychosis and this deserves more thorough study (34, 73, 88).

Treatment

In naturalistic observational studies like the BCOS study, polypharmacy is often the rule (86) and treatments are frequently changed, making it difficult to examine effects of any particular medication or treatment on outcomes or their confounding influence on our results. Treatments such as lithium may help to prevent suicide, self-harm and impulsive aggression (102, 103). Antidepressants however, may drive irritable dysphoria in patients prone to hypomania/mania whereas certain antipsychotics may have a role in reducing irritability (38, 104, 105). This also speaks to the need to further clarify the connection

between irritability and mixed states, and the extent to which treatment indications currently overlap (65, 106).

Furthermore, besides being amenable to pharmacological treatment, irritability could also be a target of adjunctive psychosocial treatments (e.g. psychoeducation about irritability, ways to deal with goal-frustration and emotion dysregulation that may evoke irritability, and to reduce irritability in social/ work/family contexts or as a warning sign of illness) (11, 39, 107, 108). A closer examination of inadequate perceived support and high expressed emotion as variables linking irritability with worse illness course may provide more insight into psychosocial treatment targets. Studies of larger samples of people with bipolar disorder and schizoaffective disorder in various mood states, with and without mixed features, in euthymia, and especially where pharmacological and psychological treatment are actively monitored and controlled are needed to confirm these findings.

Conclusion

Our study supports the importance of considering irritability, not only as a diagnostic criterion of mania/hypomania, but also as an independent and clinically powerful factor, deserving of increased research and clinical attention. Irritability may have wide ranging impacts on symptomatic, functional and social elements of a person's life. Comorbidities and severity do not uniquely account for this important role, although the role of temperament and personality needs further study. Irritability appeared to predict depression, mania and suicidal ideation over follow-up irrespective of illness severity, but this association was more pronounced in those with more overall illness severity. More studies are needed to corroborate these findings and to enhance the identification, monitoring and treatment of irritability, and help patients improve their quality of life across the spectrum of symptoms to interpersonal relationships.

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Table 1: Participant characteristics at study entry (baseline)

Baseline Characteristics		Irritability				Total		Sig.
		Absent		Present				
		(n=110)		(n=129)		(n=239)		
		n	%	n	%	n	%	p
Demographics								
Sex	Male	52	47.3	48	37.2	100	41.8	0.116
	Female	58	52.7	81	62.8	139	58.2	
Age (years)	Less than 30	17	15.9	28	21.7	45	19.1	0.724
	30 - 39.9	33	30.8	38	29.5	71	30.1	
	40 - 49.9	30	28.0	34	26.4	64	27.1	
	50 or above	27	25.2	29	22.5	56	23.7	
Partner status	No	56	51.4	82	64.1	138	58.2	0.048
	Yes	53	48.6	46	35.9	99	41.8	
Income	<=\$199/week*	8	7.3	14	10.9	22	9.2	0.383
	\$200-\$499/week	74	67.3	93	72.1	167	69.9	
	>=\$500/week	27	24.5	21	16.3	48	20.1	
Diagnosis	Bipolar I	80	74.1	94	72.9	174	73.4	0.894
	Schizoaffective	28	25.9	35	27.1	63	26.6	

Symptom burden								
Mania ¹	Symptomatic	78	70.9	30	23.3	108	45.2	<0.001
	remission*							
	Subsyndromal mania*	27	24.5	59	45.7	86	36.0	
	Syndromal mania*	5	4.5	40	31.0	45	18.8	
Depression ²	Symptomatic	47	43.1	19	14.7	66	27.7	<0.001
	remission*							
	Subsyndromal depression	32	29.4	34	26.4	66	27.7	
	Syndromal depression*	30	27.5	76	58.9	106	44.5	
Mixed depression	Yes (53, 54) ^a	11	10.0	22	17.1	33	13.8	0.115
	No ³	99	90.0	107	82.9	203	86.2	
Mixed mania	Yes (55) ^b	11	10.0	22	17.1	33	13.8	0.115
	No ⁴	99	90.0	107	82.9	203	86.2	
Comorbidity and psychotic symptoms								
Psychotic Symptoms	No	92	85.2	93	72.1	185	78.1	0.015
	Yes	16	14.8	36	27.9	52	21.9	
Anxiety Disorder ^c	Yes	14	13.0	44	34.4	58	24.6	<.001
	No	94	87.0	84	65.6	178	75.4	
Alcohol dependence	Yes	13	88.0	28	78.3	41	82.7	0.050
	No	95	12.0	10	21.7	196	17.3	
Drug dependence				1				0.009
	Yes	10	90.7	28	78.3	38	84.0	
	No	98	9.3	10	21.7	199	16.0	
				1				0.272
Smoking ⁶	Never	31	28.7	23	18.1	54	23.0	

Suicidality ⁷	Occasionally	4	3.7	7	5.5	11	4.7	
	Daily	52	48.1	68	53.5	120	51.1	
	Not anymore	21	19.4	29	22.8	50	21.3	
	No Risk	48	44.4	42	32.6	90	38.0	0.011
	Low Risk	39	36.1	37	28.7	76	32.1	
	Moderate Risk	7	6.5	12	9.3	19	8.0	
	High Risk*	14	13.0	38	29.5	52	21.9	

¹ Mania is classified based on the YMRS total score: 0-4 Normal; 5-14 Subsyndromal mania; ≥ 15 Syndromal mania

² Depression is classified based on the HAMD₂₁ total score: 0-7 Normal; 8-14 Subsyndromal depression; ≥ 15 syndromal depression.

³ No mixed depression involves DSM IV MDE but not ≥ 3 hypomanic symptoms, and those without MDE

⁴ No mixed mania involves DSM IV Manic episode (ME) without depressive symptoms required for mixed mania, and those without ME

⁵ Alcohol and drug dependence over past 12 months based on MINI

⁶ Smoking based on Habits scale for smoking patterns over past 3 months

⁷ MINI defines current high suicide risk ≥ 10 , moderate risk 6-9, and low risk 1-5

^a Concurrent hypomanic symptoms (53, 54)

^b Concurrent depressive symptoms (55)

^c Diagnosed generalised anxiety disorder in past six months according to MINI

*Indicates statistically significant difference ($p < 0.05$)

Table 2: Clinical characteristics and quality of life (at baseline)

Other characteristics	Irritability				Total (n=239)		Effect size ^d	p- value ^e
	Absent (n=110)		Present (n=129)					
	Mean	SD	Mean	SD	Mean	SD		
<u>Symptom burden</u>								
YMRS total score	3.7	4.8	12.0	9.1	8.2	8.5	-1.14	<.001
HAMD ₂₁ total score	10.1	7.6	16.3	8.3	13.4	8.5	-0.77	<.001
CGI-BP-S overall score	3.5	1.4	4.1	1.2	3.8	1.3	-0.46	0.003
<u>QOL/ functioning</u>								
<i>SF-36^a</i>								
Physical Functioning Index	78.36	21.61	70.19	27.18	73.95	25.06	0.30	0.012
Mental Health Index	62.8	21.26	55.64	22.34	58.93	22.25	0.	0.013
<u>EQ-5D</u>								
VAS ^b	69.5	18.6	63.8	21.0	66.4	20.1	0.28	0.038

Utility score ^c	0.8	0.2	0.7	0.3	0.7	0.3	0.39	0.001
Suicidality (HAMD ₂₁)	0.18	0.62	0.53	0.95	0.37	0.82	-0.43	0.000

YMRS, Young Mania Rating Scale; HAMD₂₁, Hamilton Depression Rating Scale; CGI-BP-S, Clinical Global Impression Scale.

^aSF-36 score of 100 = best imaginable health state.

^b Visual analog score (100 is best imaginable Health state).

^c 1 is Perfect Health.

^d The unadjusted effect size is based on Cohen's d; large effects if ≥ 0.6 and medium if between 0.3 to 0.5

^e The p-value is based on the independent samples Mann-Whitney U Test as all the variables were not normally distributed using the Shapiro-Wilk test

Table 3 Irritability (at baseline) and social support on the SPS (at last visit)

Social Provisions Scale	Irritability status (n=109)				p-value
	Absent (n=48)		Present (n=61)		
	Mean	SD	Mean	SD	
Guidance	13.7	2.7	12.8	2.8	0.046 [*]
Reassurance of Worth	12.7	2.4	11.6	2.3	0.023 [*]
Social Integration	13.3	1.9	12.2	2.2	0.011 [*]
Attachment	13.3	2.6	12.3	2.4	0.018 [*]
Nurturance	11.8	3.0	12.2	2.3	0.685
Reliable Alliance	13.8	2.3	13.4	2.4	0.293
Total social provisions	78.7	12.0	74.4	11.8	0.044 [*]

The p-value is based on the independent samples Mann-Whitney U test

The total social provision score range from 24-96

Table 4: MMRM analysis (includes all 9 visits) modelling for changes in mania, depression, SF36 and suicidality by irritability status

Characteristics	Estimated Marginal Means		Mean difference ¹	p-value	95% CI of Mean diff.	
	Irritability	Irritability			Lower	Upper
	Absent	Present				
<u>Symptom burden</u>						
<i>YMRS score</i>						
Mania ²	4.23	10.25	-6.02	<0.001	-7.47	-4.56
<i>HAMD₂₁ score</i>						
Depression ²	11.73	16.14	-4.42	<0.001	-5.97	-2.87
<u>QOL/ functioning</u>						
<i>SF-36</i>						
Physical index ²	77.22	71.74	5.48	0.043	.018	10.78
Mental health index ²	51.48	46.68	4.79	0.017	0.86	8.74
<u>Suicidality</u> ^{2,3}	0.18	0.31	-0.13	0.004	-0.22	-0.04

¹ The mean difference is between irritability absent and irritability present and is based on estimated marginal means

² The model adjusts for alcohol and drug dependence (12 months), generalised anxiety disorder (past six months), suicidality measured on the HAMD₂₁ item 3, presence of current psychotic symptoms and the CGI Bipolar total score.

Table Legends

Table 1:

¹ Mania is classified based on the YMRS total score: 0-4 Normal; 5-14 Subsyndromal mania; ≥ 15 Syndromal mania

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^a Concurrent hypomanic symptoms (53, 54)

^b Concurrent depressive symptoms (55)

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*Indicates statistically significant difference ($p < 0.05$)

Table 2

YMRS, Young Mania Rating Scale; HAMD₂₁, Hamilton Depression Rating Scale; CGI-BP-S, Clinical Global Impression Scale.

^a SF-36 score of 100 = best imaginable health state.

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^e The p-value is based on the independent samples Mann-Whitney U Test as all the variables were not normally distributed using the Shapiro-Wilk test

Table 3:

The p-value is based on the independent samples Mann-Whitney U test

The total social provision score range from 24-96

Table 4:

¹ The mean difference is between irritability absent and irritability present and is based on estimated marginal means

² The model adjusts for alcohol and drug dependence (12 months), generalised anxiety disorder (past six months), suicidality measured on the HAMD₂₁ item 3, presence of current psychotic symptoms and the CGI Bipolar total score.

Abbreviations

- Bipolar Comprehensive Outcomes Study (BCOS)
- Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)
- Systematic Treatment Enhancement Program for Bipolar Disorder study (STEP-BD)
- Young Mania Rating Scale (YMRS)
- Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR)
- Generalized anxiety disorder (GAD)
- Mini-International Neuropsychiatric Review Version 5 (MINI)
- Hamilton Depression Rating scale (HAMD21)
- Clinical Global Impressions-Bipolar Version Severity of Illness scale (CGI-BP-S)
- Major depressive episode (MDE)
- Manic episode (ME)
- Short-Form Health Survey (SF-36)
- EuroQol health-related quality of life 5-dimension questionnaire (EQ-5D)
- Mental and Physical Component Summaries (MCS and PCS)
- Social Provisions Scale (SPS)
- Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation (SLICE/LIFE)
- Odds ratios (OR)
- Confidence interval (CI).
- Mixed-Model Repeated Measures Analysis (MMRM)

- Quality of life (QOL)
- Lesley Berk (LB), Kamalesh Venugopal (KV), Andrew James Lewis (AJL), David W Austin (DWA), Jayashri Kulkarni (JK), Seetal Dodd (SD), Anthony de Castella (ADC), Paul B Fitzgerald (PBF), Michael Berk (MB)

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Figure 1. Depiction of significant interaction effect between CGI-Bipolar and irritability scores from MMRM on item 3 (suicidality) of the HAMD₂₁ (+SEM).

Figure 2. Representation of significant interaction effect between CGI-Bipolar and irritability scores from MMRM on YMRS Total Scores (+SEM)

Figure 3. Representation of significant interaction effect between CGI-Bipolar and irritability scores from MMRM on HAMD₂₁ Total Scores (+SEM).

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