P.2.d.013
Evaluating depressive symptoms in mania: a naturalistic study using a structured diagnostic tool, the DSM-5 'With Mixed Features' specifier M.I.N.I. module

Allan H. Young[1], Jonas Eberhard[1,2]

[1]King's College London, UK; [2]Corporate Medical Affairs, H. Lundbeck A/S, Copenhagen, Denmark

Introduction

- Bipolar disorder is a chronic disease that has a lifetime prevalence of approximately 2%, and which is characterised by periods of mania, depression or combinations of both (mixed states).[1]

- Manic episodes with depressive symptoms are generally more severe, and are associated with a poorer prognosis, than pure manic episodes.[2,3] Although these types of episodes are common, they are not easily identified by clinicians.[2,3] Reaching a correct diagnosis by systematically searching for depressive symptoms during a manic episode is important for optimising patient outcomes.[2]

- Recently, the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) provided a new 'With Mixed Features' specifier for hypomanic, manic or depressive episodes.[4] For hypomanic and manic episodes, at least three of six depressive symptoms must be present to allocate the specifier.[4] To complement this, a new Mini-International Neuropsychiatric Interview (M.I.N.I.) module has also been developed to enable patient self-evaluation for the DSM-5 specifier.

- The objectives of this research were to assess:
  - The number of patients presenting with depressive symptoms during a manic episode according to the DSM-5 'With Mixed Features' specifier
  - The association between the presence of depressive symptoms during a manic episode and:
    - specific mixed symptoms (anxiety, irritability and agitation)
    - suicidality
    - physician satisfaction with treatment
    - depressive symptoms included in the M.I.N.I. module.

Methods

- Study conduct
  - This prospective, real-world research, involving psychiatrists and patients with bipolar I disorder (BD1), was conducted in Australia, Brazil, Canada, Germany, Italy, Spain, Turkey and the UK. The study began in October 2013 with final data collected on 31st March 2014.
  - Patient data were anonymised, and stored and processed in agreement with the requirements of the EU Data Protection Directive 95/46/EC.
  - The study was conducted in compliance with the relevant codes of conduct (EphMRA; ABPI).

- Study population
  - Physician population: psychiatrists who were actively managing pharmacological treatment for adult patients with BD1; had 3–30 years' experience of treating patients with BD1; had a patient caseload comprising ≥20 patients with BD1 per month; and who were representative of the in-/out-patient setting for each country, were invited to take part in the study.
  - Patient population: patients aged ≥18 years; diagnosed with BD1; had onset of a manic episode within the last 3 months; and whose clinical condition was compatible with completing a short questionnaire, were included in the study.

- Questionnaires
  - Using an online survey, each psychiatrist assessed six consecutively consulted patients with BD1 who were currently receiving treatment for a manic episode. Assessments included: DSM-5 criteria for depressive symptoms (Table 1), a global assessment of symptoms (anxiety, irritability, and agitation [absent–very severe]), frequency of suicide attempts, and treatment response satisfaction (highly dissatisfied–highly satisfied).
  - Each psychiatrist also invited their patients to complete the M.I.N.I. module questionnaire, which comprises nine questions assessing the presence or absence of depressive features (six symptoms) according to DSM-5 criteria (Table 1).

- Data analyses
  - Only matched data (i.e., patients with both physician and M.I.N.I. assessments) were included for analysis.
  - Patients were stratified based upon whether they met the criteria for the 'With Mixed Features' specifier of DSM-5:
    - 0–2 depressive symptoms (did not meet the criteria)
    - ≥3 depressive symptoms (met the criteria).
  - Data were analysed using a two-sided t-test using Confirmit v17.5. Values of p<0.05 were considered statistically significant.

Table 1. Questions specified in the DSM-5 criteria and the M.I.N.I. module for the presence of depressive symptoms
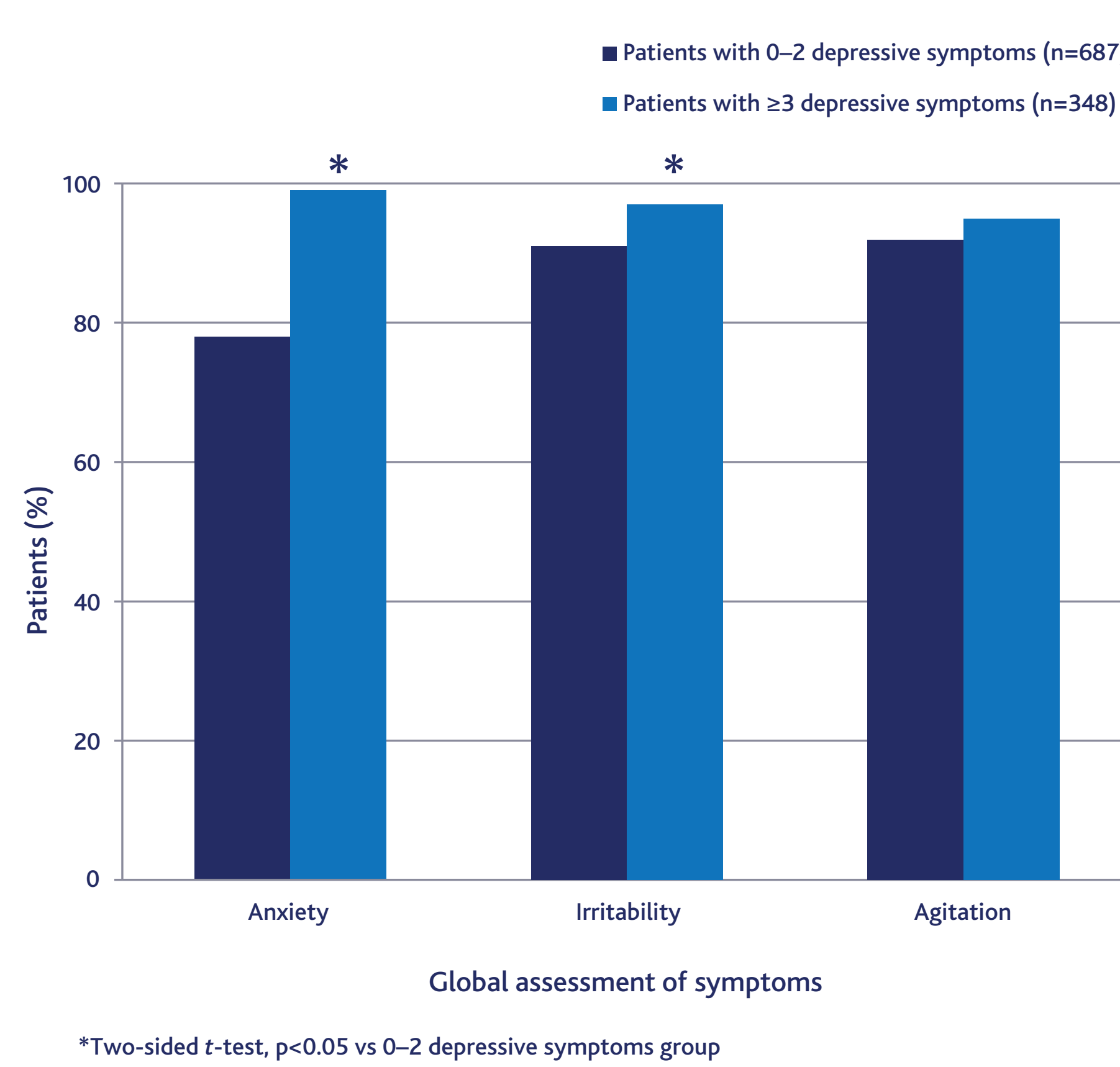
DSM-5 criteria for depressive symptoms*	Depressive symptoms according to the M.I.N.I. module DSM-5 criteria*
1. Prominent dysphoria or depressed mood as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)	1. You felt sad, empty, tearful, down or depressed?
2. Diminished interest or pleasure in all, or almost all, activities (as indicated by either subjective account or observation made by others)	2a. You were less interested in most activities?
	2b. You had less pleasure doing the activities you used to enjoy?
3. Psychomotor retardation nearly every day (observable by others, not merely subjective feelings of being slowed down)	3. You were slowed down in your speech, thoughts or movements?
4. Fatigue or loss of energy	4a. You had fatigue?
	4b. You felt without energy?
5. Feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick)	5a. You had feelings of worthlessness?
	5b. You felt excessively guilty?
6. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	6. You wished you were dead, considered hurting yourself, made plans to commit suicide or attempted suicide?

*To be present almost every day during the current manic episode

Results

- In total, 1,035 patients (184 physicians) were included in the study (mean age: 40 years). The majority were female (52%); 44% were in employment.

- According to physicians, during the most recent manic episode:
  - 69% (n=715) of patients experienced ≥1 depressive symptom
  - 34% (n=348) experienced ≥3 depressive symptoms and thus met the criteria for the DSM-5 'With Mixed Features' specifier.

- Compared to patients with 0–2 depressive symptoms, a statistically significantly higher proportion of patients with ≥3 depressive symptoms presented with anxiety (78% vs 99%, p<0.05), or irritability (91% vs 97%, p<0.05) during their most recent manic episode (Figure 1).

Figure 1. Proportion of patients with 0–2 or ≥3 depressive symptoms who presented with some degree of anxiety, irritability or agitation during their most recent manic episode

Patients with 0–2 depressive symptoms (n=687)
Patients with ≥3 depressive symptoms (n=348)

Patients (%) / Global assessment of symptoms

*Two-sided t-test, p<0.05 vs 0–2 depressive symptoms group

- Compared to patients with 0–2 depressive symptoms, patients with ≥3 depressive symptoms were characterised by statistically significantly more severe anxiety, irritability or agitation (average severity score of 3.4 vs 4.1; p<0.05; Figure 2).

- In addition, compared to patients with 0–2 depressive symptoms, patients with ≥3 depressive symptoms were statistically significantly more likely to have made ≥1 suicide attempt during their lifetime (26% vs 54%; p<0.05) and during their most recent (current) manic episode (9% vs 38%; p<0.05; Figure 3).

Figure 2. Composite score of anxiety, irritability, and agitation for patients with 0–2 or ≥3 depressive symptoms

Average score
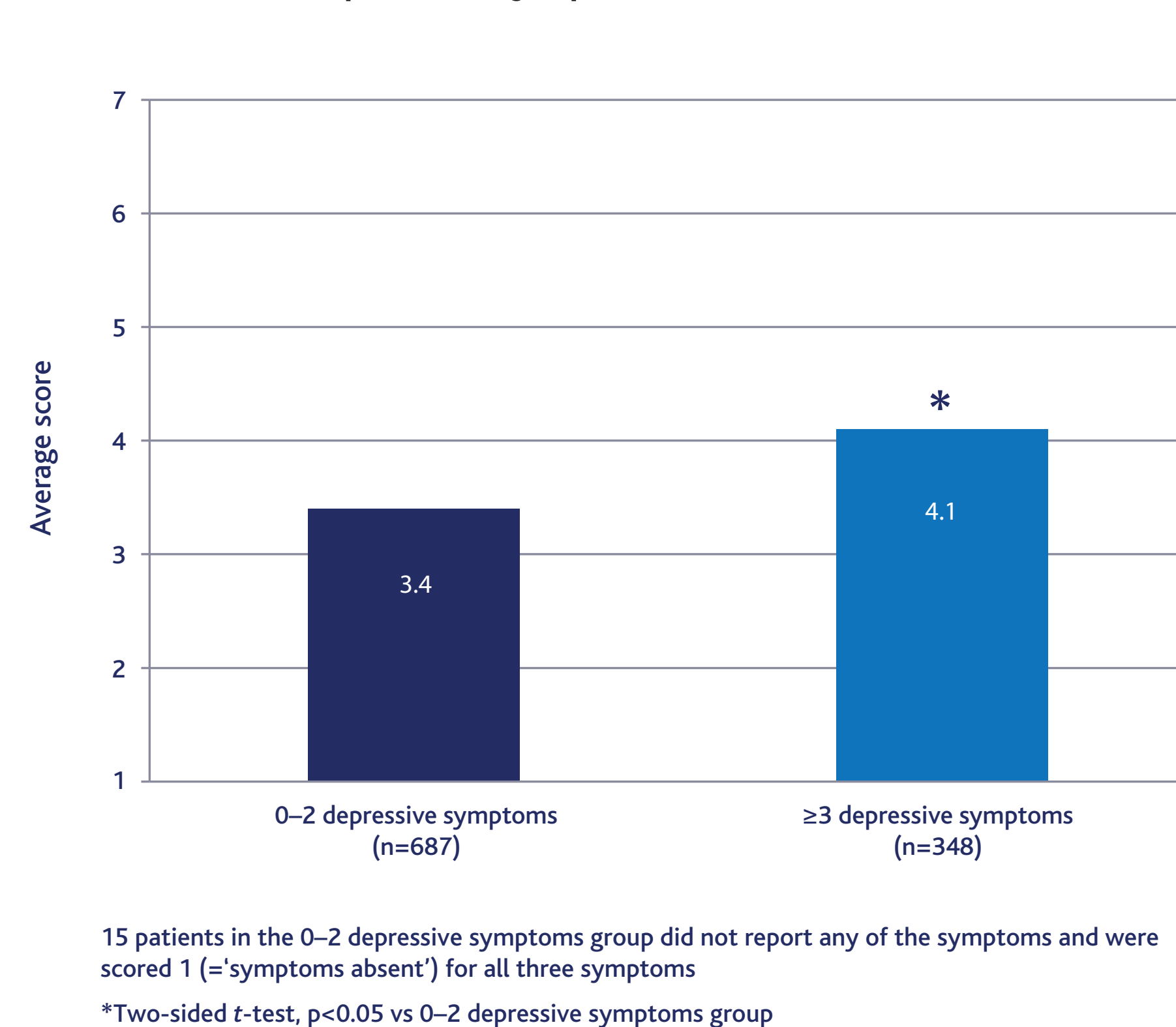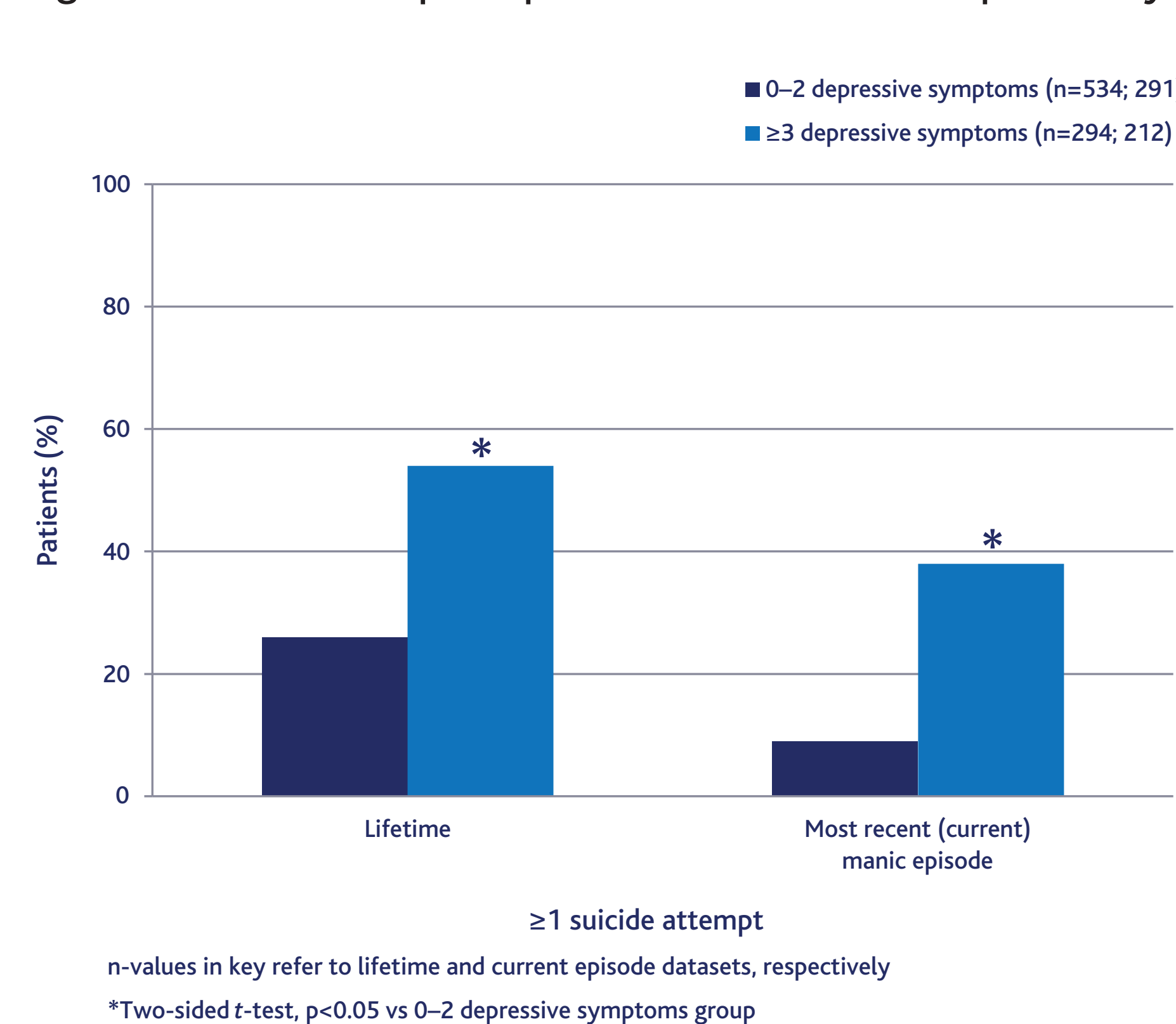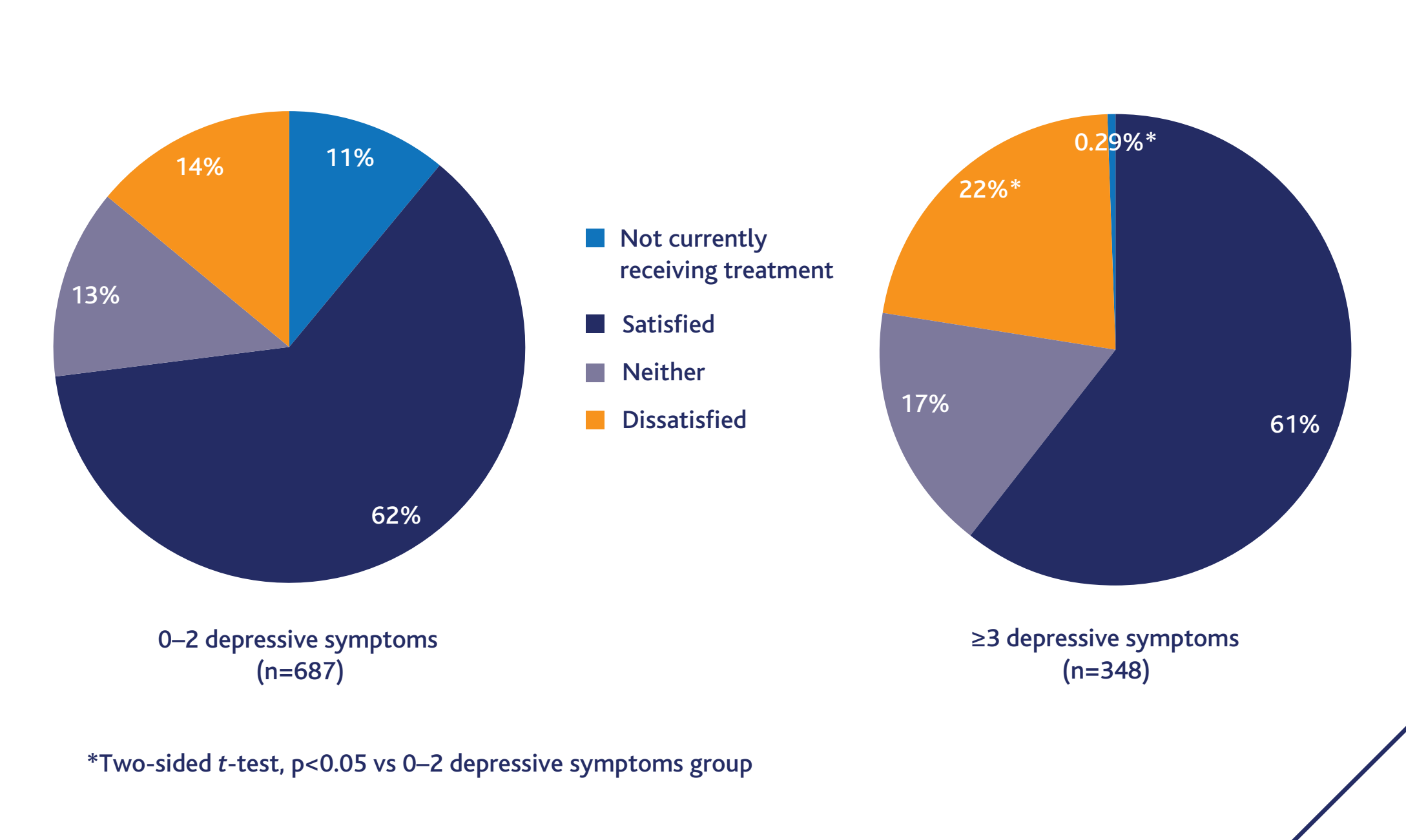
0–2 depressive symptoms (n=687): 3.4
≥3 depressive symptoms (n=348): 4.1

15 patients in the 0–2 depressive symptoms group did not report any of the symptoms and were scored 1 (='symptoms absent') for all three symptoms
*Two-sided t-test, p<0.05 vs 0–2 depressive symptoms group

Figure 3. Suicide attempts in patients with 0–2 or ≥3 depressive symptoms

0–2 depressive symptoms (n=534; 291)
≥3 depressive symptoms (n=294; 212)

Patients (%)

Lifetime / Most recent (current) manic episode

≥1 suicide attempt
n-values in key refer to lifetime and current episode datasets, respectively
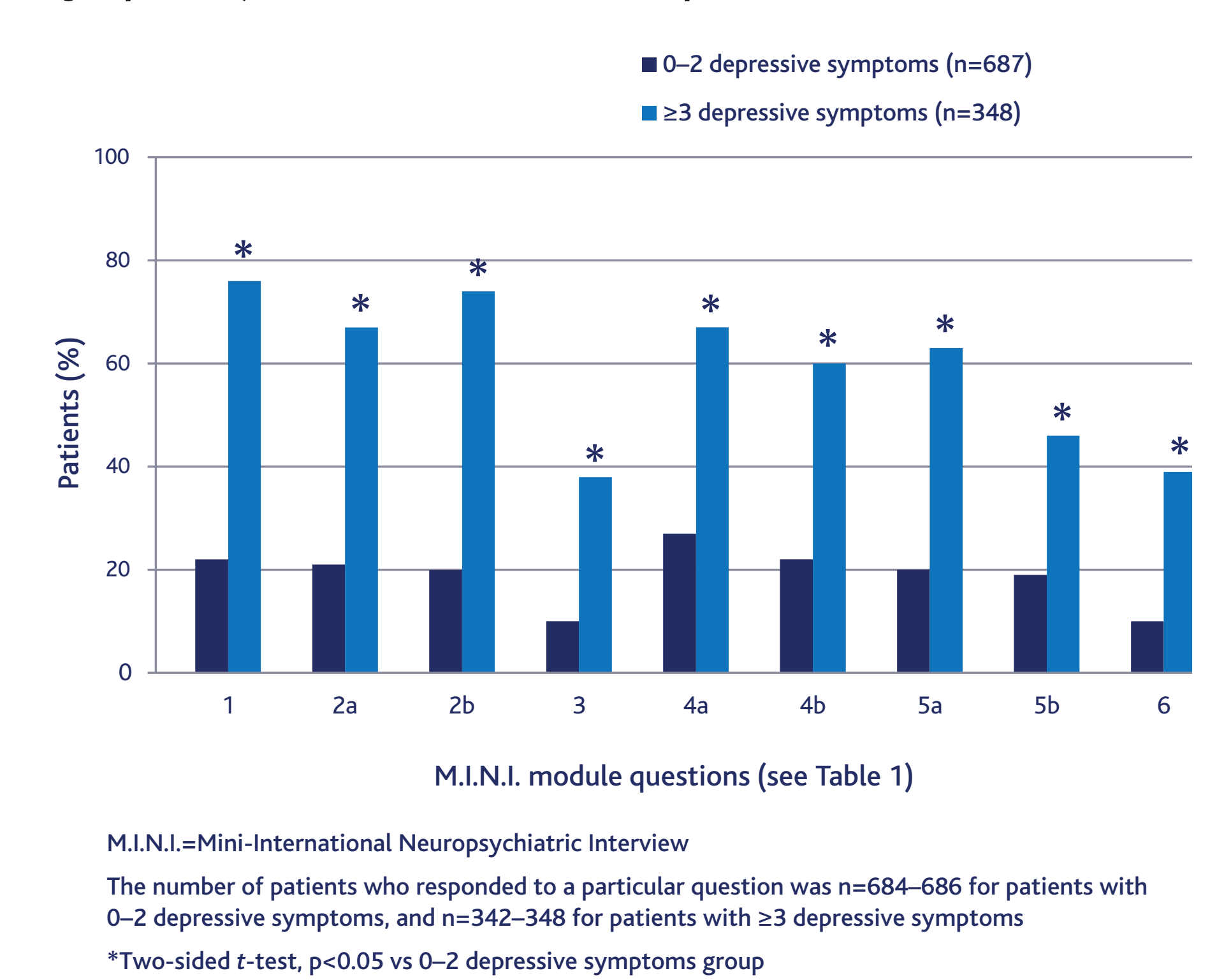*Two-sided t-test, p<0.05 vs 0–2 depressive symptoms group

- Twenty-two percent of physicians were dissatisfied with the treatment response in patients with ≥3 depressive symptoms, compared with 14% for patients with 0–2 depressive symptoms. This difference was statistically significant (p<0.05) (Figure 4).

Figure 4. Physician satisfaction with current treatment response for patients with 0–2 or ≥3 depressive symptoms

Not currently receiving treatment
Satisfied
Neither
Dissatisfied

0–2 depressive symptoms (n=687): 11%, 62%, 13%, 14%
≥3 depressive symptoms (n=348): 0.29%*, 61%, 17%, 22%*

*Two-sided t-test, p<0.05 vs 0–2 depressive symptoms group

- A significantly higher proportion of patients with ≥3 depressive symptoms answered 'yes' to each of the M.I.N.I. module questions during their most recent manic episode, compared with patients with 0–2 depressive symptoms; p<0.05 for all comparisons (Figure 5).

Figure 5. Percentage of patients with 0–2 or ≥3 depressive symptoms who answered 'yes' to the questions (on the presence of depressive symptoms) in the M.I.N.I. module questionnaire

0–2 depressive symptoms (n=687)
≥3 depressive symptoms (n=348)

Patients (%) / M.I.N.I. module questions (see Table 1)

M.I.N.I.=Mini-International Neuropsychiatric Interview
The number of patients who responded to a particular question was n=684–686 for patients with 0–2 depressive symptoms, and n=342–348 for patients with ≥3 depressive symptoms
*Two-sided t-test, p<0.05 vs 0–2 depressive symptoms group

Conclusion

- A third of BD1 patients presented with ≥3 depressive symptoms during their most recent manic episode, and thus met the criteria for the DSM-5 'With Mixed Features' specifier.

- These patients had a greater burden of disease; experienced more severe anxiety, irritability and agitation; and had a higher incidence of suicide attempts, both during their lifetime and during their most recent manic episode, compared to patients with 0–2 depressive symptoms.

- Physicians were more likely to be dissatisfied with the treatment response of patients reporting ≥3 depressive symptoms, compared with that of patients reporting 0–2 depressive symptoms.

- Physician and patient assessments of patients' depressive symptoms during the most recent manic episode, according to DSM-5 criteria, were in agreement with one another.

References

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3. McElroy et al. Am J Psychiatry 1992; 149: 1633–1644.
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Presented at the 27th ECNP Congress, 18–21 October 2014, Berlin, Germany

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