TECHNICAL COMMENTARY

Mania

Introduction

A manic episode is a period of at least one week when a person is high spirited or irritable in an extreme way most of the day for most days. A manic episode involves changes in normal behaviour, including showing exaggerated self-esteem or grandiosity, less need for sleep, talking more than usual, talking more loudly and quickly, being easily distracted, doing many activities at once, scheduling more events in a day than can be accomplished, embarking on risky behaviour, uncontrollable racing thoughts, and/or quickly changing ideas or topics. These changes in behaviour are significant and clear to friends and family and are severe enough to cause major dysfunction.

A hypomanic episode is similar to a manic episode but the symptoms are less severe and need only last four days in a row. Hypomanic symptoms do not lead to the major problems that mania often causes, and the person is still able to function.

The frequency and severity of manic or hypomanic symptoms vary from person to person, and may also vary according to whether the onset of bipolar disorder is in childhood, adolescence, or adulthood.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews assessing the same topic were found, only the most recent and/or comprehensive review was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2].

The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

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Results

We found seven systematic reviews that met our inclusion criteria[3-9].

- Moderate quality evidence suggests the most common mania symptoms reported in youths with bipolar disorder are (in decreasing order); increased energy, irritability, mood lability, distractibility, goal-directed activity, euphoric/elated mood, pressured speech, hyperactivity, racing thoughts, poor judgment, grandiosity, inappropriate laughter, decreased need for sleep, and flight of ideas.
- Moderate to high quality evidence suggests irritability, aggression, and low insight are more common in youths than adults with bipolar disorder. Odd appearance, grandiosity, flight of ideas, decreased sleep, and increased sexual interest are more common in adults than youths with bipolar disorder. There were no differences in rapid speech, motor features or elevated mood.
- Moderate to high quality evidence shows mania episodes are around three times less predominant than depression episodes over the course of bipolar disorder (up to 13 years). However, in studies measuring predominance retrospectively, the rates of depression and mania episodes are similar. Factors associated with mania predominance are type I bipolar disorder, a mania onset of illness, onset of illness with psychotic features, younger onset of illness, substance use.
- Moderate to high quality evidence suggests having a positive family history of any mood disorder is associated with greater likelihood of switching to mania in children with major depression. Moderate quality evidence suggests having subthreshold symptoms of mania, emotional dysregulation, or behaviour problems are also associated with greater likelihood of switching to mania in children with major depression.
- Moderate to low quality evidence shows increased prior depressive episodes was associated with increased risk of antidepressant-induced mania in people with bipolar disorder.

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Carvalho AF, McIntyre RS, Dimelis D, Gonda X, Berk M, Nunes-Neto PR, Cha DS, Hyphantis TN, Angst J, Fountoulakis KN

Predominant polarity as a course specifier for bipolar disorder: a systematic review

Journal of Affective Disorders 2014; 163: 56-64

View review abstract online

Comparison	**Factors associated with predominance of mania episodes in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (consistent, direct, large samples, unable to assess precision) suggests mania and depression predominance is similar in studies assessing symptoms retrospectively.** **Factors associated with mania predominance are type I bipolar disorder, a mania onset of illness, onset of illness with psychotic features, younger onset of illness, substance use.**

Mania episode polarity

19 studies (16 retrospective), N = 77,989

Any predominant polarity: median = 52.7%

Mania predominance: median = 26%

Depressive predominance: median = 21%

Factors associated with mania predominance;

Diagnosis of type I bipolar disorder: 4 studies, N = 1257

A mania onset of illness: 3 studies, N = 2084

Younger onset of illness: 3 studies, N = 1701

More substance use: 2 studies, N = 828

Onset of illness with psychotic features: 2 studies, N = 1532

Factors not associated with mania predominance;

Having a comorbid psychiatric illness: 7 studies, N = 3257

Rapid cycling: 5 studies, N = 3118

Factors with mixed results;

Male sex: 1 study, N = 604 found a relationship, 4 studies, N = 2056 found no relationship

More hospitalisation: 2 studies, N = 773 found a relationship, 1 study, N = 124 found no relationship

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Consistency in results	Consistent, apart from male sex and hospitalisations
Precision in results	Unable to assess; no CIs reported
Directness of results	Direct

Melhuish Beaupre LM, Tiwari AK, Goncalves VF, Lisoway AJ, Harripaul RS, Muller DJ, Zai CC, Kennedy JL

Antidepressant-Associated Mania in Bipolar Disorder: A Review and Meta-analysis of Potential Clinical and Genetic Risk Factors

Journal of Clinical Psychopharmacology 2020; 40: 180-5

View review abstract online

Comparison	**Clinical factors associated with the emergence of mania in people with bipolar disorder who are taking antidepressants.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, mostly consistent, unclear precision, direct) shows increased prior depressive episodes was associated with increased risk of antidepressant-induced mania.**

Mania episodes

Increased prior depressive episodes was associated with increased risk of antidepressant-induced mania;

Number of prior depressive episodes: 5 studies, I^2 = 0%, MD = 1.42 95%CI 0.54 to 2.3, p = 0.0016

There were no significant associations with;

Sex: 12 studies, I^2 = 35.3%, OR = 1.22, 95%CI 1.00 to 1.48, p = 0.05

Age of onset of mania: 9 studies, I^2 = 0%, MD = -0.41, 95%CI -1.31 to 0.48, p = 0.37

Bipolar I vs. bipolar II: 7 studies, I^2 = 39.3%, OR = 0.94, 95%CI 0.70 to 1.25, p = 0.66

Number of prior mania episodes: 5 studies, I^2 = 80.9%, MD = -0.24, 95%CI -1.78 to 1.3, p = 0.76

Consistency in results	Consistent, apart from prior mania episodes.
Precision in results	Precise for ORs, unable to assess MD (not standardised).
Directness of results	Direct

Miller S, Dell'Osso B, Ketter TA

The prevalence and burden of bipolar depression

Journal of Affective Disorders 2014; 169 Suppl 1: S3-11

View review abstract online

Comparison	**Predominance of mania vs. depression episodes in people with bipolar disorder from prospective studies.**
Summary of evidence	**Moderate to high quality evidence (consistent, direct, large sample, unable to assess precision) shows mania episodes were less prevalent than depression episodes over the course of bipolar disorder (1-13 years).**
Mania episodes	
Mania/mixed episodes were more prevalent than depressive episodes over time; 5 prospective studies, N = 1,071, follow-up 1 to 13 years Mania/mixed symptoms: average = 12.3% of the time Depression symptoms: average = 34.1% of the time	
Consistency in results	Authors report data are consistent regardless of study location or methodology
Precision in results	Unable to assess; confidence intervals were not reported
Directness of results	Direct

Ryles F, Meyer TD, Adan-Manes J, MacMillan I, Scott J

A systematic review of the frequency and severity of manic symptoms reported in studies that compare phenomenology across children, adolescents and adults with bipolar disorders

International Journal of Bipolar Disorders 2017; 5: 4

View review abstract online

Comparison	**Frequency of mania episodes across different age groups in people with bipolar disorder.**
Summary of evidence	**Low quality evidence (inconsistent, small samples, unable to**

	assess precision, direct) is unable to determine any consistent differences in mania symptoms between children, adolescents and adults with bipolar disorder. **However, authors conclude that irritability is a key feature of childhood-onset, activity of adolescent-onset and pressure of speech of adult-onset bipolar disorder.**
Mania symptom frequency	
<u>In childhood-onset</u> 1 study (N = 83, age 7-17yrs) of children with bipolar disorder type I found irritability 83% of the time, easily distracted 49% of the time, euphoria 42% of the time, decreased sleep 31% of the time, grandiose 27% of the time, hyperactive 26% of the time. 1 study (N = 56, age 5-11yrs) of children with bipolar disorder type I found poor judgement 91% of the time, racing thoughts 88% of the time, bizarre/grandiose thoughts 86% of the time, talkative 84% of the time, easily distracted 82% of the time. 1 study (N = 14, age <13yrs) of children with bipolar disorder type I, II or not otherwise specified found irritability, aggression and anger out-burst 64% of the time, psychotic episodes 7% of the time, euphoria 0% of the time. 1 study (N = 16, age not reported) of children with bipolar disorder type I, II or not otherwise specified, found irritability and aggression 63% of the time, depression 19% of the time, euphoria 13% of the time, mood swings 6% of the time. 1 study (N = 9, age 7-12yrs) of children with bipolar disorder type I, II or not otherwise specified, found elevated mood 89% of the time, decreased concentration 44% of the time, restlessness 33% of the time, decreased sleep 33% of the time, impulsiveness 27% of the time, hyperactive 22% of the time. <u>In adolescent-onset</u> 1 study (N = 9, age <21yrs) of adolescents with bipolar disorder type I found grandiosity 78% of the time, decreased sleep 67% of the time, pressured speech 67% of the time, belligerence 67% of the time, flight of ideas 44% of the time, hypersexuality 44% of the time, reckless spending 44% of the time. 1 study (N = 34, age 12-17yrs) of adolescents with bipolar disorder type I found goal directed/aggressive behaviour 88% of the time, racing thoughts 88% of the time, distractibility 88% of the time, bizarre/grandiose thoughts 79% of the time, talkative 77% of the time. 1 study (N = 29, age >13yrs) of adolescents with bipolar disorder type I, II or not otherwise specified, found euphoria 35% of the time, psychotic episodes 7% of the time, aggression, and anger out-bursts 3% of the time. 1 study (N = 37, age not reported) of adolescents with bipolar disorder type I, II or not otherwise specified, found depression 49% of the time, irritability, and aggression 24% of the time, euphoria 16% of the time, mood swings 11% of the time. 1 study (N = 26, age 13-18yrs) of adolescents with bipolar disorder type I, II or not otherwise specified, found elevated mood 73% of the time, decreased sleep 62% of the time, decreased concentration 46% of the time, impulsiveness 39% of the time, restlessness 39% of the time,	

hyperactive 23% of the time. In adult-onset 1 study (N = 12, age >30yrs) of adults with bipolar disorder type I found pressured speech 100% of the time, decreased sleep 100% of the time, hyperactive 92% of the time, euphoria 75% of the time, belligerence 75% of the time, flight of ideas 67% of the time. 1 study (N = 184, age 18-59yrs) of adults with bipolar disorder type I found irritability 74% of the time, racing thoughts 55% of the time, distractibility 46% of the time, talking fast 45% of the time, not sleeping 38% of the time, grandiose 27% of the time. Authors report that assessment procedures varied in quality, most studies originated in the USA, and there was a failure to consider the impact of psychiatric comorbidities.

Consistency in results	Appears inconsistent
Precision in results	Unable to assess; no CIs reported
Directness of results	Direct

Safer DJ, Zito JM, Safer AM

Age-grouped differences in bipolar mania

Comprehensive Psychiatry 2012; 53: 1110-7

View review abstract online

Comparison	**Mania symptoms in youth vs. adults with bipolar disorder type I.**
Summary of evidence	**Moderate to high quality evidence (precise, direct, large sample, unable to assess consistency) suggests irritability, aggression, and low insight is more common in youths than adults with bipolar disorder. Odd appearance, grandiosity, flight of ideas, decreased sleep, and increased sexual interest are more common in adults than youths with bipolar disorder.**

Mania symptoms

4 studies, N = 457 youth (mean age 14yrs), N = 649 adults (mean age 39yrs)

The following symptoms were significantly more common in youth than adults with bipolar disorder;

Irritability: 16.7%, 95%CI 16.3% to 17.2% vs. 13.9%, 95%CI 13.5% to 14.3%

Aggression: 15.0%, 95%CI 14.5% to 15.5% vs. 8.7%, 95%CI 8.3% to 9.2%

Low insight: 4.7%, 95%CI 4.3% to 5.1% vs. 2.7%, 95%CI 2.4% to 3.0%

The following symptoms were significantly more common in adults than youth with bipolar disorder;

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Odd appearance: 3.4%, 95%CI 3.1% to 3.7% vs. 4.1%, 95%CI 3.8% to 4.3% Grandiosity: 10.3%, 95%CI 9.7% to 10.9% vs. 15.8%, 95%CI 15.2% to 16.4% Flight of ideas: 7.0%, 95%CI 6.8% to 7.2% vs. 7.8%, 95%CI 7.5% to 8.0% Decreased sleep: 5.8%, 95%CI 5.5% to 6.1% vs. 7.8%, 95%CI 7.5% to 8.1% Increased sexual interest: 3.5%, 95%CI 3.1% to 3.8% vs. 5.3%, 95%CI 5.0% to 5.6% There were no significant differences between youth and adults in rapid speech, increased motor or elevated mood. Authors report similar findings for studies with mixed bipolar disorder diagnoses (I, II, and not otherwise specified).	
Consistency in results	Unable to assess; no measure of heterogeneity is reported
Precision in results	Appears precise
Directness of results	Direct

Uchida M, Serra G, Zayas L, Kenworthy T, Hughes B, Koster A, Faraone SV, Biederman J

Can manic switches be predicted in pediatric major depression? A systematic literature review

Journal of Affective Disorders 2015; 172: 300-6

View review abstract online

Comparison	**Features associated with manic switches in children and youth with major depression disorder followed for 1-11yrs.**
Summary of evidence	**Moderate to high quality evidence (direct, large sample, consistent, unable to assess precision) suggests a positive family history of any mood disorder is associated with greater likelihood of switching to mania in children with major depression.** **Moderate quality evidence (direct, large sample, inconsistent, unable to assess precision) suggests subthreshold symptoms of mania, emotional dysregulation, and behaviour problems are associated with greater likelihood of switching to mania in children with major depression.**
Manic switches	

7 studies, N = 985 children and youth (aged 6-18 yrs) The average rate of manic switching was 28.3% *Factors associated with manic switches include;* 4/4 studies reported a positive family history of a mood disorder 2/4 studies reported subthreshold symptoms of mania 2/4 studies reported emotional dysregulation 2/4 studies reported behaviour problems 2/4 studies reported psychotic symptoms Authors report course of illness, severity of depression, and comorbid conduct disorder provided inconsistent results.

Consistency in results	Consistent for subthreshold symptoms of mania only
Precision in results	Unable to assess; no CIs are reported
Directness of results	Direct

Van Meter AR, Burke C, Kowatch RA, Findling RL, Youngstrom EA

Ten-year updated meta-analysis of the clinical characteristics of pediatric mania and hypomania

Bipolar Disorders 2016; 18: 19-32

View review abstract online

Comparison	**Prevalence of mania symptoms in children and youth with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (direct, large sample, inconsistent, unable to assess precision) suggests the most common mania symptoms reported in youths with bipolar disorder are (in decreasing order) increased energy, irritability, mood lability, distractibility, goal-directed activity, euphoric/elated mood, pressured speech, hyperactivity, racing thoughts, poor judgment, grandiosity, inappropriate laughter, decreased need for sleep, and flight of ideas.**
Mania symptoms	

20 studies, N = 2,226 youths Increased energy: 8 studies, prevalence = 79%, 95%CI 61% to 93%, I^2 = 98% Irritability: 19 studies, prevalence = 77%, 95%CI 64% to 88%, I^2 = 97 Mood lability: 6 studies, prevalence = 76%, 95%CI 55% to 92%, I^2 = 98 Distractibility: 17 studies, prevalence = 74%, 95%CI 61% to 85%, I^2 = 97 Goal-directed activity: 9 studies, prevalence = 72%, 95%CI 56% to 86%, I^2 = 97 Euphoric/elated mood: 19 studies, prevalence = 64%, 95%CI 53% to 75%, I^2 = 96% Pressured speech: 18 studies, prevalence = 63%, 95%CI 49% to 77%, I^2 = 97% Hyperactive: 8 studies, prevalence = 62%, 95%CI 40% to 81%, I^2 = 98 Racing thoughts: 15 studies, prevalence = 61%, 95%CI 49% to 72%, I^2 = 97 Poor judgment: 17 studies, prevalence = 61%, 95%CI 45% to 76%, I^2 = 98 Grandiosity: 19 studies, prevalence = 57%, 95%CI 44–69%, I^2 = 97 Inappropriate laughter: 6 studies, prevalence = 57%, 95%CI 33% to 79%, I^2 = 97 Decreased need for sleep: 19 studies, prevalence = 56%, 95%CI 46% to 67%, I^2 = 95 Flight of ideas: 12 studies, prevalence = 54%, 95%CI 42% to 66%, I^2 = 95 Increased productivity: 4 studies, prevalence = 47%, 95%CI 33% to 63%, I^2 = 91 Increased creativity: 3 studies, prevalence = 41%, 95%CI 23% to 62%, I^2 = 95 Uninhibited people-seeking: 7 studies, prevalence = 41%, 95%CI 27% to 56%, I^2 = 96 Hypersexuality: 12 studies, prevalence = 32%, 95%CI 23% to 42%, I^2 = 94 Hallucinations: 10 studies, prevalence = 31%, 95%CI 17% to 46%, I^2 = 96 Delusions: 5 studies, prevalence =24%, 95%CI 1% to 62%, I^2 = 98 *Significant predictors of mania symptoms;* Male gender predicted increased energy, pressured speech, hyperactivity, grandiosity, and uninhibited people-seeking. Increased age was associated goal-directed activity. Increased year of data collection was associated with hyperactivity. Increased study quality predicted distractibility, uninhibited people seeking, and hyperactivity.

Consistency in results	Authors report results were inconsistent.
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials tath are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[10].

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† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[10].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[11]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Correlation coefficients (eg, r) indicate the strength of association or relationship

between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[10];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[12].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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