APORIA · ISSUE ONE

01

Two Roads, One Circuit.

Bipolar mania and substance-induced mania reach the same clinical state through different doors. The differential decides whether the patient gets a decade of mood-stabiliser exposure they did not need, or a lifetime of unprotected episodes they did.

CLINICAL DILEMMAS IN PSYCHIATRY

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01 / STAKE

The decade-of-stabiliser problem

A young man arrives in a manic state. He has been smoking ganja daily for six months. Speech is pressured and grandiose, sleep is gone, family is exhausted. The decision the on-call resident makes in the next hour will follow this patient for the next ten years. Call it primary bipolar I, and a lithium prescription begins a relationship that may not end. Call it cannabis-induced, and the patient is sent home with a syndrome that converts to schizophrenia or bipolar disorder in nearly half of all cases. Both are wrong some of the time. Knowing which one is wrong this time is the work of this issue.

Residents are trained to recognise mania as a phenotype, an emergent set of signs the brain produces when something pushes it past a threshold. What we are less often taught is that the threshold can be crossed by very different forces, and that the forces matter at least as much as the threshold. A primary bipolar episode and a cannabis-precipitated one can look identical at the bedside on the day of admission. They diverge sharply on day thirty, on month six, on year five. The differential we are asked to make is therefore not a description of the present. It is a prediction about the future. The literature tells us we are not very good at it, and that the consequences of being wrong are large.

The headline number

The most quoted sentence in this entire literature is that bipolar disorder confers a roughly two- to threefold increased risk of violent crime, and the most-quoted clinical lore that follows is that manic patients are dangerous. Both turn out to be mostly wrong, in a specific and useful way.

Fazel and colleagues followed 3,743 patients with bipolar disorder in the Swedish national registers against 37,429 general-population controls and 4,059 unaffected siblings of bipolar patients. The unadjusted odds ratio for violent crime was 2.3, the figure that powers the lore. When the analysis adjusted for substance use comorbidity and used unaffected siblings as controls, the odds ratio fell to 1.1, with a confidence interval of 0.7 to 1.6 that crosses unity, meaning the result is statistically indistinguishable from no excess risk at all. The risk that survived the adjustment was concentrated in patients with a comorbid substance use disorder, where the odds ratio was 6.4. [2]

> A NOTE ON ODDS RATIOS
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> An odds ratio (OR) of 1.0 means no difference between groups. An OR of 2.3 means 2.3 times the odds; an OR of 6.4 means more than six times. An *adjusted* OR (aOR) controls for confounders, so the comparison is between groups matched on those variables. A confidence interval that crosses 1.0 means the difference cannot be reliably distinguished from zero. The Fazel finding therefore says: bipolar disorder without substance use is not meaningfully more violent than the population average; bipolar disorder with substance use is six times more violent.

A later quantitative-genetic analysis of 1.8 million Swedish twins and siblings put the bipolar-violence correlation at r = 0.23 and traced about 79% of it to liability shared with substance misuse, leaving only about 21% to genetic influences specific to bipolar disorder. [42] In plain language, four-fifths of the violence we see in bipolar disorder

runs through substance use, not through bipolar disorder itself. The dangerous patient is the bipolar patient with active substance use. Bipolar disorder, alone, is not.

The other headline number

If the violence finding makes us more relaxed about most manic patients, the conversion data should make us more careful with the substance-induced ones. Starzer and colleagues at the University of Copenhagen followed 6,788 Danish patients diagnosed with substance-induced psychosis between 1994 and 2014, with up to twenty years of follow-up.[1] Of these, 32.2% converted to schizophrenia or bipolar disorder over the follow-up period. Cannabis-induced psychosis converted at 47.4%, the highest rate of any substance class. Half of all bipolar conversions occurred within 4.4 years of the index episode.

Read this finding carefully. It does not say cannabis caused 47.4% of these patients to become bipolar or schizophrenic. It says that almost half of patients we labelled with cannabis-induced psychosis at the index admission turned out, with twenty years of patient follow-up, to have an underlying schizophrenic or bipolar illness that the cannabis was unmasking, accelerating, or precipitating. The label was provisional. Most of those reclassifications happened in the first five years.

> THE CLINICAL STAKE
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> A misread differential is not a minor error. It assigns the patient to one of two illness models, two pharmacological commitments, and two trajectories of relapse risk. The Danish data say nearly half of cannabis-precipitated psychotic illnesses are bipolar or schizophrenic illnesses unmasked. The Swedish data say the violence risk in bipolar disorder, with substance use removed, is close to baseline. The differential is therefore not academic. It is the lever that decides what kind of illness the patient is treated for, what kind of life the patient is asked to plan, and what kind of vigilance the family is asked to maintain.

What this issue covers

The remainder of Aporia 01 works seven questions a thoughtful resident would ask before committing to one side of that lever. We will take up the natural course of bipolar disorder against the very different course of substance-induced mood states. We will look at the shared neural circuit both routes converge on, with the receptor mechanisms that distinguish the substances along the way. We will work through the bedside signs that separate primary mania from substance-induced mania more reliably than the symptom checklist does. We will cover the depressive prodrome, the self-medication question, the lifetime mortality gap, the cultural and religious content of mania in Indian samples, the aggression and intimate-partner-violence literature, and the practical pharmacology of treatment when substance use is comorbid. The final section is a synthesis: a two-by-two matrix and the five questions to ask on the inpatient call.

The framing that emerges is the title of this issue. The clinical syndrome we call mania is a state the brain enters by more than one entrance. Knowing which entrance the patient came through is the difference between treating an autonomous illness and treating a pharmacological injury. Both deserve treatment. They are not the same treatment.

02 / COURSE

Two natural histories

The most useful single distinction in this differential is not in the present-state examination but in the predicted course. Primary bipolar disorder behaves one way over years; substance-induced mania behaves another. If you understand how each behaves over time, you understand most of what the differential is asking you to assess.

What classical bipolar disorder does on its own

The textbook by Goodwin and Jamison remains the canonical reference for the natural course of bipolar disorder. Its picture, drawn from decades of long-term follow-up cohorts, is consistent enough that residents should commit it to memory. The mean age at first manic episode falls in the late teens to early twenties. Untreated episodes last about three to six months. The recurrence rate after a single manic episode, untreated, is above ninety percent, with most recurrences happening within two years. Twin studies estimate the heritability of bipolar I disorder somewhere between 0.75 and 0.85, which puts it among the most heritable conditions in psychiatry, alongside schizophrenia and autism.

The word that matters most in this list is autonomous. Bipolar episodes recur without requiring an external trigger. They can be precipitated by stress, sleep loss, drugs, antidepressants, postpartum hormone shifts, or seasonal change, but the recurrence is not *dependent* on those triggers. Once the illness is established, it has its own clock. This is what we mean when we say bipolar disorder has a course of its own, modifiable but not abolished by treatment, and what distinguishes it from a state-dependent mood syndrome that resolves cleanly when the precipitant stops.

> KINDLING, IN PLAIN TERMS
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> Robert Post proposed in 1992 that early bipolar episodes are typically precipitated by recognisable stressors, while later episodes become increasingly autonomous. The metaphor he borrowed, kindling, comes from the epilepsy literature: repeated subthreshold electrical stimulation of certain brain regions eventually produces seizures from stimuli that previously did nothing. Post argued that mood episodes do something similar, lowering the threshold for the next episode and shortening the inter-episode interval over time. The strict version of the kindling hypothesis is contested. The clinical implication that informs prophylaxis, that early treatment may protect against later autonomy, is consistent with most modern naturalistic data even where the mechanism remains debated.

What substance-induced mania does on its own

Substance-induced mania has a different natural history, and the contrast with primary bipolar disorder is what makes the diagnostic test possible. The DSM-5-TR definition is operational rather than mechanistic. A substance- or medication-induced bipolar and related disorder requires a mood episode arising during, or within one month of, intoxication or withdrawal from a substance capable of producing the syndrome, where the episode does not persist substantially beyond the expected physiological effect of that substance. ICD-11 holds a parallel category under disorders due to substance use.

The operational meaning of the one-month rule is the simplest and most useful clinical principle in this entire differential: watch what happens with sustained abstinence. If the manic syndrome resolves and does not recur off the substance, the substance was the cause and the diagnosis is substance-induced. If the syndrome

persists past one month off the substance, or recurs in the absence of any further use, the diagnosis is reclassified as primary bipolar disorder unmasked by the substance. This is a clinical experiment conducted in time. It is not a finding on a single examination.

The reason this rule is so useful is that the bedside picture of an acute primary manic episode and an acute substance-induced one can be indistinguishable. Both can present with elated mood, decreased sleep, pressured speech, grandiose delusions, hyperactivity, and disinhibition. The label we apply on day one is provisional. The label we apply at week six is informed. The Danish cohort is the cleanest demonstration that we should not be confident on day one. [1]

The grey zone, in numbers

Starzer and colleagues' Danish national cohort followed every patient diagnosed with a substance-induced psychosis in Denmark over a twenty-year window. Of 6,788 such patients, 32.2% converted to either schizophrenia or bipolar disorder before the end of follow-up. Cannabinoids and amphetamines were the leading conversion-risk substances. Cannabis-induced psychosis converted at the highest rate, 47.4%. Half of all bipolar conversions occurred within 4.4 years of the index episode, and half of schizophrenia conversions occurred within 3.1 years. [1] A Spanish retrospective cohort reproduced the pattern with a shorter follow-up window.

An Indian follow-up adds a useful subgroup distinction. Shah and colleagues at NIMHANS followed 35 patients with cannabis-induced psychosis for a mean of 5.75 years. [57] Patients were grouped into two clinical subtypes: those whose index psychosis was predominantly affective (manic or depressive in colour) and those whose index psychosis was predominantly non-affective (paranoid, disorganised, schizophrenia-like). Half of the non-affective patients went on to develop independent psychiatric illness over the follow-up period. Only 7.7% of the affective patients did. Sustained early abstinence was the single biggest determinant of recovery in both subgroups. The clinical reading: a cannabis-induced psychosis with an affective colour and good early abstinence is not a benign syndrome, but it carries a much better prognosis than a cannabis-induced psychosis with a non-affective presentation. The texture of the index episode predicts what happens next.

The methamphetamine picture is sharper still

Stimulant-induced psychosis is sometimes presented in textbooks as a transient, self-limiting syndrome that clears with abstinence and a brief antipsychotic course. The longitudinal data say otherwise. Hajebi and colleagues followed three matched groups of 55 patients each in Tehran: methamphetamine-induced psychosis, primary affective psychosis, and primary non-affective psychosis. By twelve-month follow-up, the methamphetamine group's outcomes converged on those of the primary psychotic disorders. [16] Stimulant-induced psychosis is not transient. A subset of these patients develops a chronic psychotic illness; the rest follow a relapsing-remitting course tied to ongoing stimulant exposure that does not respect the one-month rule.

What the Indian numbers tell us

The Bipolar Disorder Course and Outcome in India study, BiD-CoIN, followed 773 patients across fourteen tertiary centres including PGI Chandigarh and AIIMS New Delhi. About a quarter of Indian bipolar patients had a comorbid substance use disorder. Alcohol and tobacco dominated. Cannabis dependence was present in only 1.7% of the sample, far below Western estimates where cannabis use disorder is much more common in bipolar populations. An Indian-led meta-analysis pooled five prospective cohorts (n = 13,624) and estimated cannabis use raises bipolar incidence with an effect size of 2.63 (95% CI 1.95 to 3.53). [58] The Indian profile of substance

comorbidity in bipolar disorder is therefore alcohol-and-tobacco-heavy, with cannabis as a relatively smaller share than the Western literature would suggest, but with the same direction and magnitude of cannabis-mania risk where cannabis is involved.

> **THE DIAGNOSTIC TEST IS TIME**
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> The one-month rule is the operationalisation of a clinical experiment. It is not a property of the symptom checklist. A primary bipolar episode unmasked by cannabis will recur after the cannabis stops. A cannabis-induced episode in a patient without primary bipolar substrate will not. The test costs nothing except patience and structured follow-up. The alternative costs a decade of unnecessary mood-stabiliser exposure or a lifetime of unprotected relapse.

03 / MECHANISM

One circuit, two roads

If the natural histories of primary mania and substance-induced mania differ so sharply, why do the syndromes look so similar at the bedside? The answer lies in a shared neural circuit that both routes converge on, with different doors opening into the same room.

The dopaminergic spine of mania

The cardinal phenotype of mania, hyperreligiosity, grandiosity, racing thoughts, decreased need for sleep, and sexual disinhibition, has a candidate neural substrate. Previc reviewed the neuropsychology of religious activity in normal and clinical populations and concluded that ventromedial dopaminergic activation of what he called the action-extrapersonal brain system carries the phenomenology. The same circuit is activated, in different ways, in temporal-lobe epilepsy, obsessive-compulsive disorder, schizophrenia, and mania. The unifying claim is dopaminergic. The clinical syndromes diverge in what activates the system.[34]

> A FOUR-LINE TOUR OF THE CIRCUIT
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> The mesolimbic dopamine pathway runs from the **ventral tegmental area** (VTA) in the midbrain forward to the **nucleus accumbens** (NAc) in the ventral striatum, and onward to the prefrontal cortex. Dopamine released in the NAc is the brain's reward and salience signal. When this pathway is over-active, ordinary stimuli feel charged with meaning, behaviour becomes goal-directed and impulsive at the same time, and sleep need drops. When it is under-active, the same stimuli feel flat. Mania, in shorthand, is sustained over-activity of this pathway. Different substances produce that over-activity through different molecular doors.

How primary bipolar disorder activates the circuit

Primary bipolar disorder reaches the manic state through autonomous mood-network dysregulation. The mechanisms are not fully mapped, but the contributing factors are reasonably clear. Genetic loading raises baseline vulnerability. Recent genome-wide association data place the heritability of bipolar disorder at around 0.75 to 0.85, with dozens of risk loci of small individual effect. Circadian-system fragility, demonstrated by the high rate of seasonal recurrence and by the manic switches that follow trans-meridian travel, makes the system vulnerable to phase shifts. Episode kindling, in the version of the hypothesis that has held up best, makes successive episodes easier to trigger and harder to terminate. The triggers themselves vary, sleep loss, stress, postpartum hormonal change, antidepressant exposure, or substance use, but the threshold-crossing happens in a system that is already predisposed.

How substances activate the same circuit

Substance-induced mania reaches the same end state by direct pharmacological assault on dopaminergic and glutamatergic neurotransmission. The mechanisms are substance-specific, and understanding them at receptor level is the difference between memorising a list of drugs and reasoning about new ones the resident has not seen before.

Stimulants (amphetamines, methamphetamine, cocaine) are the cleanest pharmacological model of mania. Amphetamines enter the dopaminergic terminal through the dopamine transporter (DAT). Once inside the terminal, they disrupt the vesicular monoamine transporter VMAT2, the protein that loads dopamine into synaptic vesicles. The vesicular pH gradient collapses, vesicular dopamine spills into the cytosol, and the high

cytosolic dopamine concentration drives DAT to reverse direction, expelling dopamine into the synaptic cleft. [17] The synapse floods. Cocaine takes a different route to the same outcome: it blocks DAT directly, preventing the reuptake of synaptic dopamine and letting it accumulate. Both produce sustained, high-amplitude mesolimbic dopamine elevation, the cleanest pharmacological recipe for mania available.

Cannabis works indirectly. Delta-9-THC is a partial agonist at CB1 cannabinoid receptors. CB1 sits on presynaptic GABAergic interneurons in the VTA. When CB1 is activated, GABA release falls, and dopaminergic VTA neurons that were under tonic GABAergic inhibition fire more, releasing more dopamine into the NAc. The result is a milder, less direct version of the stimulant effect. **Synthetic cannabinoids**, the so-called spice or K2 compounds, are full CB1 agonists rather than partial agonists. They produce maximal CB1 activation, and the psychiatric and physical toxicity profile reflects that potency. Indian residents seeing campus presentations of severe agitation, seizures, and frank psychosis after smoking what looks like cannabis but is not detected on standard urine cannabinoid screens are typically dealing with these compounds. [15]

Anabolic-androgenic steroids reach the circuit by a different route altogether. They cross the blood-brain barrier and bind androgen receptors in limbic structures, including the amygdala and hypothalamus. Beyond the slow genomic effect, they exert rapid non-genomic membrane effects that alter the subunit composition of GABA-A receptors, particularly the delta subunits that mediate tonic inhibition. The net effect is reduced limbic inhibition, with secondary disinhibition of dopaminergic activity. The Pope, Kouri and Hudson randomised crossover trial, the only experimental demonstration of steroid-induced mania at human doses, gave 56 healthy men 600 mg per week of testosterone cypionate for six weeks. Twelve percent became mildly hypomanic, 4% became markedly hypomanic, and aggression scores rose significantly above placebo. [12] Indian metropolitan gym culture has produced a population at non-trivial risk that residents in OPD do not always think to screen for.

Ketamine and other dissociatives open the circuit through a paradox. They are NMDA receptor antagonists. NMDA antagonism preferentially silences inhibitory parvalbumin-positive GABAergic interneurons in the cortex, which then disinhibits the cortical pyramidal cells those interneurons normally constrain. The result is a glutamate surge in the prefrontal cortex, with secondary AMPA receptor potentiation. The same mechanism that produces ketamine's rapid antidepressant effect can produce a manic switch in vulnerable patients. Liu and colleagues' 2025 retrospective cohort of 2,126 bipolar-depressed patients on esketamine is the first adequately-powered safety analysis and quantifies the manic-switch and suicidal-outcome risks at clinically meaningful magnitudes. [13] As ketamine clinics expand through Indian metros, this is data residents need.

Sleep is the final common pathway

Wehr, Sack and Rosenthal proposed in 1987 that sleep deprivation is the final common pathway in the genesis of mania, and that the various psychological, interpersonal, environmental, and pharmacological factors that trigger episodes act, at least in part, through their capacity to reduce sleep. [20] The model has held up over four decades. Leibenluft and colleagues showed that in rapid-cycling bipolar patients, decreased sleep duration was the best predictor of mania or hypomania the following day, better than any psychological or environmental variable. [18] Bunney and Bunney later mapped the underlying clock-gene machinery, the BMAL1, CLOCK and NPAS2 transcription factors that drive E-box-controlled period gene expression, that links sleep loss to mood-state switching at the molecular level. [19]

For residents, the clinical implication is direct and useful. Any factor that disrupts sleep architecture or shortens sleep can precipitate a manic switch in a vulnerable patient. This is true whether the precipitant is a long-haul flight, a manic prodrome that bleeds back into deepening sleep loss, the wakefulness-promoting properties of

stimulants, or the sleep-fragmenting effects of chronic cannabis or alcohol use. Watching the sleep is watching the mania, and protecting the sleep is one of the few non-pharmacological interventions with a strong mechanistic basis.

Genetic moderation, briefly

The cannabis-bipolar relationship is no longer dismissable as confounding. A Lancet Psychiatry analysis of GWAS summary statistics put the genetic correlation between cannabis use disorder and bipolar disorder at approximately 0.30, with overlapping risk loci. [6] A bidirectional two-sample Mendelian randomisation, which uses genetic variants as natural experiments to test causal direction with summary data, found that genetic liability for cannabis use causally raises bipolar risk and that bipolar liability causally raises cannabis use. [7] The relationship is bidirectional and partly causal in both directions. Bartoli and colleagues applied Bradford Hill criteria to the adolescent cannabis and bipolar onset literature in 2025 and concluded that biological gradient and consistency are met, the strongest causal-inference standard such observational data can pass. [8]

> *The differential is not "mania versus not-mania." It is how did this circuit get activated, and will it reactivate spontaneously.*
>
> APORIA 01

04 / BEDSIDE

The factor structure of mania

If the present-state examination cannot reliably separate primary mania from substance-induced mania on day one, what tools do we have at the bedside? The most useful single instrument is the factor structure of mania, the empirical observation that mania presents in clinically distinct flavours that map onto different aetiologies with non-trivial accuracy.

Cassidy's two faces of mania

Cassidy, Forest, Murry and Carroll factor-analysed the signs and symptoms of 237 manic patients and recovered five factors. Two carry most of the diagnostic information.[3] The first is an elated-grandiose dimension, characterised by expansive mood, jovial pressured speech, classical religious or grandiose delusions, and sleep loss without distress. The second is a dysphoric-irritable-paranoid dimension, characterised by irritability building toward belligerence, persecutory ideation, sexual disinhibition without euphoria, and sleep loss with hostile arousal.

> WHAT FACTOR ANALYSIS MEANS HERE
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> Factor analysis is a statistical technique that identifies which symptoms tend to cluster together in real patients. If two symptoms always co-occur, they probably load on the same underlying factor. The two manic dimensions Cassidy recovered are not opposite ends of one axis. They are partially independent, which is the technical meaning of partly orthogonal in this literature. A patient can score high on both, producing a mixed picture; a patient can score high on one and low on the other, producing a relatively pure presentation. The two factors recovered the empirical fact that experienced clinicians had been describing for a century: mania has at least two faces.

Which face goes with which aetiology

Primary bipolar I mania, particularly in a first episode, skews to the elated-grandiose pole. The patient is euphoric or expansive, often with religious or grandiose delusional content. Speech is pressured and jovial. The reduction in sleep need is experienced as energising rather than distressing. The patient is often unaware that anything is wrong, and family members describe the change as a personality shift rather than as suffering.

Substance-induced mania skews to the dysphoric-irritable-paranoid pole. Methamphetamine and cocaine binges produce the cleanest dysphoric pictures: persecutory ideation, formication or other tactile hallucinations, hostile arousal, and a quality of irritability that escalates rather than fluctuates. Alcohol-withdrawal mania, when it occurs, sits in the same neighbourhood. Cannabis-precipitated mania can present at either pole and is the hardest single substance to read on factor structure alone, which is part of what makes the cannabis differential so difficult.

This single heuristic, elated-grandiose suggests primary, dysphoric-irritable-paranoid suggests substance-induced or mixed, is the most clinically useful bedside tool in this differential. It is not perfect. Patients exist at every point on both axes. But used in combination with the temporal relationship to substance use, the family history, and the temperamental substrate, it gets you closer than any other single sign on examination.

The temperamental substrate beneath

Temperament is what you find when you ask what the patient was like before the illness, in their well years. Akiskal and colleagues' TEMPS-A taxonomy identifies five affective temperaments, and one in particular, the cyclothymic temperament, is the strongest substrate for both bipolar I and bipolar II disorders.[21]

> CYCLOTHYMIC TEMPERAMENT, IN CLINICAL ENGLISH
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> The cyclothymic temperament describes a person whose emotional baseline is unstable in both directions, with frequent and unprovoked shifts between mild elation and mild dysphoria. They are described by family as moody, intense, creative, restless, and prone to falling in and out of love or interests rapidly. The shifts are not severe enough to cause functional impairment by themselves, which is what distinguishes temperament from illness. Around 50 to 60% of bipolar probands and 25 to 30% of first-degree relatives of bipolar patients have measurable cyclothymic temperament. It is the strongest temperamental marker of underlying bipolarity that we currently have.

The hyperthymic temperament, characterised by sustained energetic, optimistic and confident traits, is more equivocally associated with bipolar disorder, and has the counterintuitive property of being protective against suicide where present, even within bipolar samples. The signature of substance-induced presentations is different: high novelty seeking with low self-directedness and low cooperativeness, the character dimensions of Cloninger's psychobiological model.

A schema-therapy reading of primary mania finds a Self-Aggrandiser mode flooding over a Vulnerable Child substrate, where the manic state functions as a flight from underlying defectiveness or abandonment schemas. Substance-induced presentations more often show anti-authority and sensation-seeking content with less coherent grandiosity, fitting with the high-novelty-seeking, low-self-directedness profile.

The cluster B trap

The genuine diagnostic challenge in this whole space is not bipolar I versus substance-induced mania, where the violence and coherence of psychotic mania makes confusion with personality pathology rare. The trap is bipolar II versus borderline personality disorder. Both can present with mood instability, irritability, impulsivity, and self-harm. Both can have suicide attempts in the history. Both are common, and they overlap.

The clinical mark of borderline mood swings is that they are interpersonally triggered, usually by perceived rejection or abandonment, and that mood reverts to a chronic dysphoric baseline rather than to euthymia. Identity disturbance is sustained between episodes. The timescale of borderline mood shifts is minutes to hours. Bipolar episodes, by contrast, are autonomous (not interpersonally triggered, though triggers exist), the timescale is days to weeks, and there is return to a euthymic baseline between episodes. Family history adds force to either side: a first-degree relative with bipolar I shifts the prior toward bipolar II; a history of severe childhood adversity with attachment disruption shifts it toward borderline. Patients with both are not rare.

AXIS	PRIMARY BD-I MANIA	SUBSTANCE-INDUCED MANIA
AFFECT	Elated, expansive, grandiose	Irritable, dysphoric, paranoid
COURSE	Autonomous recurrence; family loading	Tracks substance; resolves with sustained abstinence
ONSET	Late teens to early twenties	Any age, dose-related
PREMORBID	Cyclothymic / hyperthymic temperament	Novelty seeking; low self-directedness; antisocial traits

AXIS	PRIMARY BD-I MANIA	SUBSTANCE-INDUCED MANIA
SLEEP LOSS	Without distress; energising	With hostile arousal
INSIGHT	Often absent in acute phase	Variable; sometimes preserved
TEST	Recurs without trigger	Resolves and does not return on abstinence

05 / PHARMACOLOGY

Substances and the brain

The list of substances that can produce a manic syndrome is longer than the DSM-5-TR list of substances officially recognised to cause substance-induced bipolar disorder. The Indian outpatient population sees several substances the textbooks do not adequately cover. The framework that makes this manageable is mechanism-first: which receptor system does the substance act on, how strongly does it affect mesolimbic dopamine, and through what intermediate steps?

Three principles organise the pharmacology. First, mesolimbic dopamine surge is necessary but not sufficient for mania. Substances with the strongest mania capacity all produce sustained, high-amplitude dopamine elevation in the NAc. Substances with weak mania capacity do not. Second, sleep deprivation runs in parallel as the final common pathway. A substance that elevates dopamine but fragments sleep is a stronger mania-inducer than one that does not. Third, genetic vulnerability moderates threshold. Two patients exposed to the same drug at the same dose can have very different probabilities of switching, depending on underlying bipolar liability.

SUBSTANCE	PRIMARY MECHANISM	MANIA CAPACITY	OTHER PSYCHIATRIC MORBIDITY
AMPHETAMINE, METHAMPHETAMINE	DAT/NET/VMAT2 reverse transport, monoamine release [17]	**Strong**	Stimulant-induced psychosis (often persistent), withdrawal depression, neurocognitive impairment
COCAINE	DAT/NET/SERT blockade	**Strong**	Cocaine-induced psychosis with paranoia, formication, post-binge depression
SYNTHETIC CANNABINOIDS	Full CB1 agonism (vs. THC partial agonism) [15]	**Strong**	Severe acute psychosis, agitation, seizures, persisting psychosis
SYNTHETIC CATHINONES	DAT/NET/SERT release or block	**Strong**	Excited delirium, paranoid psychosis, persisting psychosis
ANABOLIC-ANDROGENIC STEROIDS	Limbic AR plus non-genomic GABA-A modulation [12]	**Strong (dose-dependent)**	Withdrawal depression, irritable aggression, dependence, body-image disorder
CANNABIS (THC)	CB1 partial agonism, VTA disinhibition [4,5,6]	Moderate	Cannabis-induced psychosis, anxiety, amotivational syndrome, cognitive impairment
HALLUCINOGENS	5-HT2A partial agonism on layer-V pyramidals [53]	Moderate (in BD-vulnerable)	HPPD, persistent psychosis, panic, depersonalisation
DISSOCIATIVES (KETAMINE, PCP)	NMDA antagonism, AMPA potentiation [13]	Moderate	NMDA-antagonist psychosis, dissociation, cystitis, persisting cognitive deficits
MDMA	SERT-mediated 5-HT release	Moderate	Persistent depression, anxiety, panic, serotonin syndrome
TRAMADOL	mu-opioid plus SNRI activity [51]	Moderate (SNRI-mediated)	Serotonin syndrome, seizures, opioid withdrawal, depression

SUBSTANCE	PRIMARY MECHANISM	MANIA CAPACITY	OTHER PSYCHIATRIC MORBIDITY
ALCOHOL	GABA-A PAM, NMDA antagonist	Weak (depression dominates)	Major depression, anxiety, alcohol-induced psychosis, cognitive disorder
PURE MU OPIOIDS	mu agonism on VTA GABA interneurons	Weak	Opioid-induced depression, withdrawal syndrome, hyperalgesia
INHALANTS	Mixed NMDA, GABA-A, glycine	Weak	Inhalant psychosis, leukoencephalopathy, conduct disorder

Why cannabis is in the moderate column

Cannabis sits in the moderate column because the mechanism is indirect and the dose-response curve is gentle. CB1 partial agonism produces a modest VTA disinhibition rather than a direct dopamine flood. The same patient that becomes mildly euphoric on social cannabis use does not predictably switch into mania. But cumulative exposure, particularly in adolescence and particularly with high-THC strains, raises the probability of a manic switch considerably. Henquet and colleagues' three-year prospective cohort of 4,815 general-population subjects found that baseline cannabis use raised the odds of incident manic symptoms with an adjusted OR of 2.70 (95% CI 1.54 to 4.75), a finding that survived adjustment for psychotic symptoms and could not be explained by reverse causation.[4] The Marwaha-Gibbs meta-analysis pooled the prospective cohort data and confirmed the signal.[5] An Indian-led meta-analysis of five prospective cohorts pooled an effect size of 2.63.[58] Three roughly converging estimates from independent samples is unusually consistent for psychiatric epidemiology.

The DSM-5-TR cannabis omission

DSM-5-TR lists alcohol, phencyclidine, hallucinogens, sedatives or hypnotics, amphetamines and other stimulants, and cocaine as causes of substance- or medication-induced bipolar and related disorder. It does not list cannabis. The omission is at odds with the strongest available evidence, which residents should know about even if examiners do not raise it.

Why does it matter? Diagnostic systems shape what gets recognised, what gets coded, and what gets treated. A clinician using DSM-5-TR strictly will struggle to record a cannabis-induced manic episode using a substance-induced bipolar diagnosis, and may default to either a primary bipolar diagnosis (with all the long-term commitments that entails) or to cannabis-induced psychotic disorder (which mis-codes the affective phenotype). ICD-10 F12 and ICD-11 already classify cannabis-induced affective psychosis with manic features, and Indian residents diagnose it under that code routinely. The practical lesson: where DSM-5-TR is silent, ICD-coding is more accurate to the literature, and the resident on call should not be deterred from a substance-induced label because DSM-5-TR omits it.

India-relevant warnings

Three substances deserve specific attention in Indian practice because they are over-represented in OPD presentations relative to what the Western textbooks emphasise.

Tramadol is widely used in Indian outpatient practice both as an analgesic and as a substitution agent for opioid use disorder. Its mechanism is not a pure mu-opioid effect; it has substantial serotonin and norepinephrine reuptake inhibition activity, the SNRI effect, which is what mediates its mood-elevating and mania-precipitating

potential. Sarkar and colleagues' PGI Chandigarh series of seven tramadol-dependent patients reported euphoria in all seven. [51] Indian residents seeing a manic episode in a patient with chronic pain or with opioid use disorder on tramadol substitution should think SNRI before mu-opioid in mechanistic terms.

Anabolic-androgenic steroids are a rising and chronically under-recognised cause of mania in metropolitan Indian gym populations. The Pope, Kouri and Hudson randomised crossover trial, conducted in 56 healthy men receiving 600 mg per week of testosterone cypionate, produced mild hypomania in 12% and marked hypomania in 4%. Aggression scores rose significantly above placebo. This is the only experimental demonstration of steroid-induced mania at human doses in the literature. [12] Residents should screen for gym attendance, supplement use, and visible muscular hypertrophy in any young male presenting with first-episode mania, and should ask directly about injectable testosterone, dianabol and similar agents. The history is not always volunteered.

Methamphetamine in the form of yaba pills is rising along the north-east corridor of India, with Manipur and adjacent states the regional epicentre. **Synthetic cannabinoids** are increasingly seen on Indian campuses. A critical practical point for emergency triage: synthetic cannabinoids are not detected on standard urine cannabinoid screens. A patient presenting with severe agitation, seizures, and frank psychosis who screens negative for cannabis on a standard immunoassay panel is not necessarily drug-free.

06 / TRAJECTORY

Prodrome, self-medication, lifetime gap

Mania does not appear out of nowhere. The episode that brings the patient to a ward has typically been preceded by weeks of subtle change, often with depressive features dominant in the prodrome before the switch. Understanding the prodrome matters for two reasons: it gives the family a framework to recognise relapse early in established illness, and it raises the question of why so many patients destined for bipolar disorder spend years labelled as having unipolar depression before the first manic episode arrives.

The prodrome to a manic episode

Manic episodes have prodromes 60% to 80% of the time. Jackson, Cavanagh and Scott's systematic review identified sleep disturbance as the single most reliable prodromal signal, present in roughly three-quarters of all manic prodromes.[22] Sleep changes precede mood changes more reliably than any other variable. Decreased need for sleep, increased energy, racing thoughts, irritability, increased goal-directed activity and mild grandiosity are the next most common, in that rough order. Depressive symptoms are the second most common prodromal feature overall, particularly in bipolar I, where the manic episode often emerges out of an antecedent depressive low.

Bipolar at-risk criteria

Bechdolf and colleagues operationalised what they called the bipolar at-risk (BAR) construct, describing three high-risk groups for first-episode bipolar disorder. The first is sub-threshold mania, where the patient meets manic symptom criteria but not the duration or functional impairment threshold. The second is depression accompanied by cyclothymic features. The third is depression with a first-degree relative with bipolar disorder. Twenty-eight percent of help-seeking adolescents and young adults meeting at least one of these BAR criteria transitioned to full bipolar I over an eleven-year follow-up.[23] Most transitions occurred via a depressive episode that switched, not via a manic episode that arrived first. The depressive prodrome is therefore not a separate illness; it is the iceberg's underside.

The self-medication question

Edward Khantzian's hypothesis, that drug choice in addiction reflects the affective state being modulated, has more rhetorical force than empirical support in bipolar disorder specifically. The claim is intuitively appealing: a patient is depressed, alcohol or cannabis dulls the dysphoria, and so the substance use rises during depressive phases. Some patients describe their use this way. The literature does not bear out the simple version.

Bipolar patients use substances during both depressive and manic phases. Several studies show greater use during manic phases, when disinhibition and impulsivity rise. The cleaner formulation, supported by the genetic-correlation and Mendelian-randomisation findings cited earlier, is shared vulnerability with bidirectional escalation. Cyclothymic temperament and high novelty seeking sit upstream of both bipolar disorder and substance use. The two conditions share genetic and personality substrate. Once both are present in a single patient, each accelerates the other: substance use destabilises mood, mood instability drives further substance use, and the combination is much harder to treat than either alone.

The clinical implication is that asking a patient whether they use substances to self-medicate is a useful conversation to have, but the answer should not be taken as the mechanism. The substance is rarely doing exactly what the patient thinks it is doing.

The suicide stack

Comorbid substance use multiplies suicide risk in bipolar disorder, and the magnitudes are larger than residents typically appreciate. Carra and colleagues meta-analysed twenty-nine studies of suicide attempts in bipolar disorder with co-occurring alcohol or substance use disorders. The pooled crude odds ratios were 1.96 for combined alcohol and drug use, 1.72 for alcohol alone, and 1.77 for drug use alone, all significant at p less than 0.01.[24] Bipolar plus comorbid substance use roughly doubles the odds of a lifetime suicide attempt.

The Indian BiD-CoIN cohort adds a counterintuitive twist. In Indian bipolar patients, cannabis dependence (not alcohol) was the substance-related independent predictor of lifetime suicide attempt, despite cannabis dependence being the rarer comorbidity in the Indian sample. Hawton and colleagues' earlier systematic review identified substance abuse alongside hopelessness, prior attempt history, mixed states and rapid cycling as the robust predictors of non-fatal suicidal behaviour in bipolar disorder.[46] Of these, substance abuse and prior attempt history are the two most reliably modifiable in clinical practice.

The mortality gap

The all-cause mortality findings in bipolar disorder are sobering. Crump and colleagues followed 6,618 Swedish bipolar patients against a population control of 6.6 million. Women with bipolar disorder died on average 9.0 years earlier than the general population; men died 8.5 years earlier. Suicide-specific adjusted hazard ratios ranged between 8 and 10. Cardiovascular disease, diabetes, COPD, pneumonia, and unintentional injury all contributed substantially to the excess mortality, as did suicide itself.[44]

Hayes and colleagues' UK primary-care cohort of 2000 to 2014 showed the bipolar mortality gap widening over time, with the adjusted hazard ratio against the general population increasing by 0.14 per year from 2006 onwards.[43] Walker, McGee and Druss pooled mortality across mental disorders in a meta-analysis and estimated a relative risk of approximately 2.22 with median ten years of potential life lost.[45] Bipolar disorder, in modern healthcare systems with access to mood stabilisers, antipsychotics and primary care, still shortens life by roughly a decade.

> THE HONEST SUMMARY
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> Bipolar disorder shortens life by roughly a decade. Comorbid substance use raises suicide-attempt risk and is the dominant moderator of the violence signal. The mortality gap is widening rather than closing in well-resourced healthcare systems. The Indian numbers are insufficiently studied, but no theoretical mechanism predicts a smaller gap here, and the cardiometabolic and substance burden in Indian practice would suggest the same direction or worse.

07 / CULTURE

Religiosity, content, the Indian phenomenology

The content of mania varies in ways that are clinically important and that the Indian resident encounters in a more concentrated form than Western textbooks describe. Religious and sexual delusions are common in Indian manic presentations. The cultural envelope of the symptom carries diagnostic information that the symptom checklist does not.

What Sethi and Khanna found

Sethi and Khanna studied 100 consecutively hospitalised manic patients at the Central Institute of Psychiatry, Ranchi, using the Hindi Present State Examination. They documented expansive mood, subjective ideomotor pressure and grandiose delusions in nearly every patient. Religious delusions and sexual delusions were both recorded as very common. Flight of ideas, by contrast, was recorded as rare. The authors argued explicitly that the religious-delusional prominence reflected cultural factors rather than disease essentials. [10]

This paper is the load-bearing Indian phenomenology citation for residents preparing for examinations. It establishes that the mania an Indian resident sees, particularly in eastern India, is more likely to feature religious and sexual delusional content than the textbook descriptions drawn from American or European samples would suggest. The phenomenology is not different in kind. It is different in cultural envelope.

Form versus content

The diagnostic question is what the religious content tells us about the differential. Cook reviewed religious content in delusions and hallucinations across diagnostic groups and found a prevalence range of 20% to 60% across cultures. The conceptual move he insists on, and that residents should adopt, is the form-versus-content distinction. [35]

Form is the property that makes the symptom delusional: the falseness of the belief, its unshakeability in the face of contradicting evidence, its cultural incongruence even within the patient's own community of practice, the patient's distress or impaired functioning. Content is the religious frame: the patient says they are Krishna, or that Shiva has chosen them, or that they are receiving instructions from Christ. Content tells us about the cultural envelope. Form tells us about the pathology. Confusing the two is a common error in both directions: dismissing pathology because it is religious in content (in religious clinicians and families), or pathologising religious content because it is religious (in secular clinicians and families).

Cross-cultural data also refuse the lazy intuition that more religious cultures produce more religious delusions. Stompe and colleagues compared Austrian schizophrenics (Christian, secularised) with Pakistani schizophrenics (Muslim) and found Austrians scored higher on grandeur, guilt and religious delusions, against expectations. [36] Suhail and Cochrane separated environmental from ethnic origin by comparing Pakistanis in Birmingham, Pakistanis in Lahore, and British Whites; immediate cultural environment shaped delusional content more than ethnicity. [37] Mishra, Das and Goyal reported on Hindu schizophrenia patients in Ranchi: those with religious delusions scored higher on private religious practices, longer duration of untreated psychosis, and greater illness severity. Families read the early signs as spiritual progress before bringing patients to care. [11] The pattern is consistent and useful: religious content in delusions tracks the surrounding cultural environment more than the patient's underlying religiosity, and families with religious frameworks are systematically slower to seek psychiatric help when the early signs look like religious experience.

The kundalini differential

Indian residents sometimes see patients who present with symptoms framed as awakening, kundalini rising, samadhi, or other technical terms drawn from yogic and meditative traditions. The diagnostic problem is real, and the literature has begun to address it.

Sharma, Mahapatra and Gupta reviewed twenty-eight cases of meditation-induced psychiatric morbidity drawn from the world literature. Mania with psychotic symptoms accounted for three of the twenty-eight cases. The practices implicated included Transcendental Meditation, mindfulness, Buddhist meditation, Bikram yoga and pranic healing.[54] Damodaran's case from CIP Ranchi remains the most useful published Indian vignette of religiously-framed manic content: a forty-year-old Hindu man in his fourth manic episode, plucking out his hair as part of an attempt to attain divinity by discarding the impure demoniac hair.[52] The case illustrates the form-content distinction in action: the religious frame is culturally legible and locally meaningful; the behaviour itself, the unshakeability, the recurrence pattern, and the functional impairment are unambiguously pathological.

Huddar, Raja, Jain and Singh's reconstruction of Tajuddin Fakir, the late nineteenth-century inmate of the Nagpur Mental Asylum diagnosed by the British medical officers as a case of cannabis psychosis and later canonised by his community as a Sufi saint, is the cleanest historical example of the cultural pathway from psychotic illness to sanctity in Indian society.[55] The case sits in an Indian psychiatric journal and is worth reading in full for residents working in regions where saint-veneration around mentally ill historical figures remains active.

Religious coping as moderator

Religiosity is not a single variable. It splits into protective and risky components, and the distinction matters clinically.

The Stroppa group followed 168 bipolar outpatients in Brazil for two years using the standard religious-coping inventories developed by Kenneth Pargament. Positive religious coping at baseline (using prayer, religious community, and benevolent religious reappraisal as supportive resources) predicted better quality of life across all four WHOQOL domains at follow-up. Negative religious coping at baseline (the Pargament construct that includes feeling abandoned or punished by God, demonic attribution, and religious struggle) predicted manic symptom emergence at two years.[9]

The clinical-interview implication is direct and operational: ask how the patient relates to their religion, not whether they are religious. A patient with a sustained sense that their illness is divine punishment, or that demons are responsible for their state, has a poorer prognosis than a patient with the same religious framework who experiences the illness as a trial endured with divine support. The Schema Therapy correspondence is to the Punitive Parent mode, where the pathological internalisation does not subside with a change of belief content but with a change in the relationship to that content.

The Pentecostal differential

Hempel and colleagues' forensic series of glossolalia, speaking in tongues, in a maximum-security population studied 18 glossolalists against 130 controls. The glossolalist group clustered in the manic spectrum with religious and sexual delusional content prominent, and with the offences that brought them into forensic care.[39] Indian residents working in southern Pentecostal contexts, or in Goa-Mumbai charismatic Christian settings, encounter glossolalia as part of religious practice and as part of manic phenomenology, and the two are not always easily separated. The clinical lesson is to treat glossolalia as part of the affective and motor examination during a manic admission, not as a religious phenomenon outside the assessment.

08 / AGGRESSION

Violence, irritability, the Fazel reframe

The clinical lore that manic patients are dangerous is, on the available evidence, mostly wrong. The Fazel finding deserves to be quoted carefully because it changes how a resident should approach the manic patient on the inpatient call.

The Fazel finding, in detail

Fazel and colleagues used Swedish national registers to follow 3,743 patients with bipolar disorder against 37,429 general-population controls and 4,059 unaffected siblings of bipolar patients, all over a 31-year window. Violent crime, defined as conviction for homicide, assault, robbery, arson, sexual offence, or threat, was committed by 8.4% of bipolar patients and 3.5% of general-population controls. The unadjusted odds ratio was 2.3. The risk was almost entirely confined to patients with comorbid substance abuse, where the odds ratio was 6.4. Among bipolar patients without substance abuse, the odds ratio fell to 1.3, and to 1.1 against unaffected siblings, with a confidence interval of 0.7 to 1.6 that crosses unity. There were no differences in violence rates by manic versus depressive subgroup or psychotic versus non-psychotic clinical features. [2]

WHY THE SIBLING COMPARISON MATTERS

Comparing bipolar patients to the general population mixes up the effects of bipolar disorder itself with the effects of everything else that varies between bipolar patients and the general population: childhood adversity, socioeconomic status, family-of-origin disturbance, neighbourhood, schooling. Comparing bipolar patients to their unaffected siblings holds many of those other factors roughly constant, because siblings share much of the family environment. The sibling-comparison odds ratio of 1.1 is therefore the cleanest available estimate of the effect of bipolar disorder itself on violence, controlling for shared family-level confounders. It is statistically indistinguishable from no effect.

> *The clinical lore that "manic patients are dangerous" is wrong about most manic patients. The dangerous patient is the bipolar patient with active substance use, not bipolar disorder per se.*
>
> AFTER FAZEL ET AL. 2010

What the broader literature confirms

Witt, van Dorn and Fazel's meta-regression of 110 studies of violence in psychosis (n = 45,533) identified hostile behaviour, recent drug misuse, recent alcohol misuse, poor impulse control and non-adherence as the strongest dynamic risk factors. Static factors were dominated by criminal history. [41] The dynamic factors are what the resident on the inpatient call can act on; the static factors are what the resident notes for risk stratification.

Sariaslan, Larsson and Fazel's multivariate quantitative-genetic analysis of 1.8 million Swedish twins and siblings put the bipolar-violence phenotypic correlation at r = 0.23 and traced about 79% of it to genetic and environmental liability shared with substance misuse, leaving only about 21% to genetic factors unrelated to substance use. [42] The genetic architecture of the bipolar-violence link is largely the genetic architecture of the bipolar-substance use link. This is mechanism-level confirmation of the Fazel finding.

The substance hierarchy

If substance use is the master variable, which substances drive most of the violence?

McKetin and colleagues' within-subject analysis of 278 dependent methamphetamine users, none of whom had a lifetime history of schizophrenia or mania, found that 1 to 15 days of recent methamphetamine use raised the odds of violence 2.8-fold; 16 days or more raised them 9.5-fold (95% CI 4.8 to 19.1). Critically, psychotic symptoms accounted for only 22% to 30% of the methamphetamine-related violence; most of the violence was dose-related and independent of psychosis. [40] Stimulant violence is not primarily a psychotic phenomenon; it is a dopaminergic state effect.

Alnıak, Erkıran and Mutlu studied 100 male bipolar I inpatients in Turkey and found that current substance use carried a threefold violence risk, with previous violence the single strongest predictor and cannabis plus alcohol the commonest substances involved. [31] Ballester and colleagues found that bipolar disorder carries both state and trait aggression, with the state component largely accounted for by active substance use and the trait component persisting at lower magnitude outside acute episodes. [32]

The mixed and dysphoric phenotype is the highest-risk presentation

The highest-risk acute manic presentation is not the elated grandiose mania but the mixed-features irritable-disruptive picture. This matters for triage: the patient who is euphoric, jovially pressured and grandiose is annoying to manage but rarely dangerous. The patient who is irritable, paranoid, dysphoric and physically restless is the one who hurts staff, family and themselves.

Aggression in primary mania resolves with mood stabilisation. Methamphetamine-induced aggression decays within days of the drug clearing. Alcohol-precipitated mania is rare; alcohol-related aggression in patients with bipolar disorder is not. The triple stack of premorbid antisocial traits with bipolar disorder and active substance use predicts the worst aggression trajectories, and these are the patients for whom early aggressive pharmacological control, structured supervision, and engagement of the addiction services matter most.

Intimate partner violence

Reingle and colleagues used NESARC Wave II data, a nationally representative US sample of 25,778 adults, to estimate the relative risks of psychiatric disorders for intimate partner violence perpetration. Mania carried an odds ratio of 2.32 for IPV perpetration, comparable to the 2.53 for antisocial personality disorder. About 35% of IPV episodes co-occurred with alcohol use. [14] The clinical implication for residents is to ask about partner violence specifically when seeing a manic patient, especially one with substance comorbidity, and to recognise that the family conversation about safety includes both family of origin and partner.

Postpartum mania and infanticide risk

Bergink, Rasgon and Wisner reviewed postpartum psychosis as an entity with an incidence of 0.25 to 0.6 per 1,000 births, a 31% relapse risk in the next pregnancy, and an illness predominantly bipolar-spectrum in nature. The condition carries non-trivial suicide and infanticide risks, and the indications for prophylactic mood stabilisation in any subsequent pregnancy in a patient with a postpartum-psychosis history are unambiguous. [33] Indian residents working in obstetric and post-natal psychiatry should treat a history of postpartum psychosis as a near-mandatory indication for both peripartum lithium or olanzapine prophylaxis and structured postpartum mental-state monitoring.

09 / TREATMENT

Pharmacology, ethics, the Indian scaffolding

The honest evidence picture for treating bipolar disorder with comorbid substance use disorder is austere. Brady and Sonne flagged the gap in 1995. Three decades on, it remains. No adequately-powered head-to-head randomised controlled trial of lithium versus valproate in bipolar disorder with alcohol use disorder has ever been published. No placebo-controlled pharmacotherapy RCT in bipolar disorder with cannabis use disorder. No RCT in bipolar disorder with stimulant use disorder. Most of what residents are taught in this space is extrapolation from a thin and partial evidence base, and it is worth knowing where the evidence is solid and where it is not.

What we have

The single positive moderately-powered trial in this space is Salloum and colleagues' 2005 randomised controlled trial of valproate in 59 patients with bipolar I disorder and alcohol dependence. All patients received lithium as treatment-as-usual. They were randomised to add-on valproate or placebo for 24 weeks. The valproate group had significantly fewer heavy drinking days and fewer drinks per heavy drinking day. Mood symptoms improved in both arms, consistent with the lithium effect. [48] This is the keystone reference for the recommendation that patients with bipolar disorder and alcohol use disorder should usually have valproate added to their regimen.

Two adequately-sized quetiapine RCTs in bipolar disorder with alcohol dependence found no reduction in heavy drinking days versus placebo, despite some mood-symptom benefit. The absence of an alcohol-outcome signal for quetiapine pushes back hard against the widespread off-label use of quetiapine as a substance-mood agent. Quetiapine is fine for mood stabilisation in this population. It is not a treatment for the alcohol problem.

The Indian operational position

Murthy, Mahadevan and Chand's NIMHANS synthesis is the most operationally useful Indian-authored statement on this question and the one residents should commit to memory. Their position: valproate is the mood stabiliser of choice in bipolar disorder with substance use disorder; lithium and quetiapine "may not be effective in this population"; naltrexone is the most effective anti-craving agent in severe mental illness with alcohol use disorder. [47]

Kapur and colleagues' NIMHANS lithium-response cohort of 210 bipolar I patients found 62.86% good responders to lithium, a higher response rate than Western literature would predict, with severity of course (more episodes, more hospitalisations) the only independent predictor of poor response. [56] Indian patients respond to lithium better than the Western literature suggests on average, which moderates the Murthy position somewhat: lithium is not abandoned in Indian bipolar patients; it is moved off first-line in those with substance comorbidity.

What ECT contributes to this differential

ECT response rates in mania exceed 80% in older series, with no pharmacological interaction with substance use. Comorbid substance use lowers, not raises, the threshold for considering ECT in mania. Catatonic mania, severe mixed states, lithium non-responders, suicidal mania, and pregnant patients with mania remain ECT's

anchored indications, and the Indian regulatory framework under MHCA 2017 has clarified the legal procedure for delivering ECT with the requisite safeguards (muscle relaxants, anaesthesia, informed consent or substituted decision-making through nominated representatives).

The treatment-emergent mania trap

Antidepressant-emergent mania, the manic switch that occurs in patients with bipolar disorder treated with antidepressants, is over-represented in patients on antidepressant monotherapy: 87% of cases occur on monotherapy without concurrent mood stabiliser cover. Predictors in male patients include comorbid substance use disorder (OR 6.37) and prior suicide attempts; in female patients, thyroid disease and a bipolar I family history.[30] The clinical implication for residents: any patient with a depressive episode and any of these features should be screened for prior hypomania or mania before antidepressants are started, and where there is uncertainty, mood stabiliser cover before antidepressant exposure is the safer course.

A parallel rule applies to stimulant treatment in patients with bipolar disorder and ADHD. Methylphenidate alone increases mania risk in patients with bipolar disorder. Methylphenidate plus a concurrent mood stabiliser does not. The Viktorin Swedish national-register within-subject design supports the practical rule: stabiliser first, then stimulant, in any case where bipolar disorder and ADHD coexist.[29]

Esketamine is the new arrival. Liu and colleagues' 2025 retrospective cohort of 2,126 bipolar-depressed patients on esketamine is the first adequately-powered safety analysis. It quantifies manic-switch and suicidal-outcome risks at clinically meaningful magnitudes.[13] Indian ketamine clinics expanding through metros should heed the data; residents asked to refer or consent patients to these services should be familiar with what the published risk profile looks like.

What Indian psychiatrists do in practice

Reddy, Jhanwar and colleagues surveyed 500 IPS-member psychiatrists about their prescribing practices in bipolar disorder. The survey-derived picture: combination mood-stabiliser-plus-atypical antipsychotic is preferred over monotherapy for acute mania. Haloperidol and trifluoperazine retain a place in Indian practice for irritability, aggression and psychotic features, with explicit IPS guideline backing, even where Western guidelines have moved away from typical antipsychotics.[50] The Indian practice picture is more eclectic and more typical-antipsychotic-friendly than the Western literature suggests, and the guideline framework supports it.

The Mental Healthcare Act 2017 framework

The Indian Mental Healthcare Act 2017 reshapes the inpatient picture in ways residents cannot afford to ignore. The framework moved away from the older language of involuntary commitment toward a structure built around supported admission, advance directives, nominated representatives, Mental Health Review Boards beyond 30-day admissions, and ECT only with muscle relaxants and anaesthesia. The legal architecture matters at the bedside on the inpatient call, especially for the manic patient with poor insight.

Duffy and Kelly provide the most-cited international review of MHCA 2017.[25] Gowda and colleagues' NIMHANS study of psychiatric advance directives in 200 inpatients found 67% welcomed the instrument, with 80% following clinician advice in their drafted directives. Critically, patients lacking insight or remaining symptomatic at discharge were significantly more likely to opt against ECT, antipsychotics, or inpatient care in their psychiatric

advance directives, a foreseeable conflict for any acute manic patient with poor insight. [26] Raveesh, Gowda and Gowda's review of restraint alternatives under the Act's least-restrictive mandate is the operational counterpart for residents handling acute aggression on the inpatient unit. [27]

What this means for the resident on the inpatient call: any acute manic admission requires documentation of capacity, of the basis for supported admission if voluntary consent is not possible, of the involvement of the nominated representative, and of the specific reasons for any pharmacological or physical restraint chosen. The least-restrictive mandate is not a slogan; it is a legal standard that influences medical defensibility if questions are raised later.

10 / SYNTHESIS

The matrix and the questions

Two axes describe the patients on this differential: primary versus substance-induced; with versus without active substance comorbidity. Most of what matters clinically maps onto the resulting four cells.

PRIMARY BD WITHOUT SUD

Autonomous illness, average risk

Recurrence drives the picture. Lithium first-line. Violence risk near baseline.[2] Functional outcomes good with adherence. Indian lithium-response rate around 63%.[56] Long-term mood stabilisation reduces recurrence frequency without abolishing it.

PRIMARY BD WITH ACTIVE SUD

The dangerous quadrant

Violence aOR 6.4.[2] Suicide-attempt OR roughly doubled.[24] Mortality gap widest. Valproate over lithium.[47,48] Adherence is the master variable; integrated addiction treatment is non-negotiable. Naltrexone for the alcohol arm.

SUBSTANCE-INDUCED, NO PRIMARY

The reversible state

Resolves with sustained abstinence. The 1-month rule becomes the diagnostic test. Cannabis 47% conversion to schizophrenia or bipolar disorder over 20 years argues for vigilant follow-up rather than reassurance.[1]

SUBSTANCE UNMASKING PRIMARY

The unmasking quadrant

The episode persists past detox. Reclassify as primary bipolar disorder per DSM-5-TR. Treat as bipolar disorder with substance use disorder comorbidity. Family history and premorbid temperament call this in advance often enough to inform initial planning.

Five questions for the inpatient call

1. **What is the temporal relationship to substance use?** The three patterns to listen for: substance preceding mania, mania preceding substance, both lifelong from adolescence. The first narrows toward substance-induced or unmasking; the second toward primary bipolar disorder with secondary substance use; the third toward shared-vulnerability bidirectional escalation. The patient's own narrative is often less reliable than the family's, and the family is often less reliable than a structured timeline drawn over thirty minutes.
2. **What is the affective texture?** Elated and grandiose suggests primary bipolar I, particularly first episode. Dysphoric, irritable and paranoid suggests stimulant- or alcohol-related state, or a mixed-features primary episode.[3] Cannabis can sit at either pole and is the hardest single substance to read on factor structure alone.
3. **What does the family history say?** A first-degree relative with bipolar I disorder shifts the prior toward primary bipolar disorder substantially. Cyclothymic temperament in the patient adds force. A family history of stimulant use disorder or AAS use without bipolar disorder shifts the prior the other way.[21]
4. **What is the trajectory across one month of sustained abstinence?** Persistence of manic symptoms past one month off the substance reclassifies the diagnosis to primary bipolar disorder unmasked. Resolution of the syndrome on abstinence and absence of recurrence confirms substance-induced. The diagnostic test is time, not the symptom checklist on day one.

5. **What is the violence and suicide signal?** Active substance use raises both substantially. Mixed and dysphoric presentations are the highest-risk acute states. Treat aggressively, screen for antisocial personality features, document under the MHCA 2017 framework with clear capacity assessment and least-restrictive justification for any restraint chosen. [2,24,25]

The publishable Indian gaps

This editorial closes by naming what the Indian literature does not yet hold. There is no validated Indian TEMPS-A. There is no Indian Starzer-style longitudinal substance-induced mania conversion cohort beyond the NIMHANS cannabis-CIP follow-up. [57] There is no Indian Fazel-style quantitative analysis of mania and violence. There is no published Indian case series of tramadol-induced mania despite the clinical reality that residents see this regularly. There is no published Indian work on AAS-induced mania despite the metropolitan gym epidemic. There is no Indian PubMed-indexed quantitative study of inpatient sexual disinhibition during mania and its marriage and family consequences. There is no study of religiosity as a moderator of substance-induced mania specifically. Each of these is a thesis. Several are first-author papers waiting for residents with motivation and access to a tertiary inpatient population.

> THE CLINICAL BOTTOM LINE
>
> The state we call mania has more than one entrance. Knowing which entrance the patient came through changes everything that follows: the prophylaxis, the prognosis, the safety call, and the family conversation. The differential is not a checklist; it is the lever. Use the temporal relationship, the affective texture, the family history, and the test of time, in that order. When in doubt, the Indian guideline position holds: valproate over lithium when substance use is comorbid, naltrexone for the alcohol arm, and the abstinence trial as the quiet adjudicator.

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Educational note. This clinical-reasoning essay is for clinicians and students. It is educational, not treatment advice for any individual. Care decisions belong with the treating clinician. At Weave, care is led by Dr. Niharika Reddy, Consultant Psychiatrist.

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