PSYCHEDELIC
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A CLINICAL PRIMER FOR PRACTITIONERS

# From SSRIs to Psychedelic Medicine

What every practitioner should understand before a client asks for help coming off their antidepressant: the interaction risk almost nobody explains properly, the four-phase transition sequence, and a printable readiness checklist.

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BEFORE YOU READ ON

# What this is, and what it isn't

A client has been on an antidepressant for years. They don't think it's working anymore, they've read about psilocybin or ketamine, and they're asking *you* how to come off. You are the person they trust most with that question, and most practitioners are improvising.

> **THIS PRIMER DOES NOT QUALIFY YOU TO TAPER ANYONE**
>
> Decisions to start, change, or stop a psychiatric medication belong to a licensed prescriber, full stop. Nothing here is medical advice, and nothing here should be used to encourage a client to alter their medication independently of the clinician who prescribed it. What this primer *does* do is make you competent to recognize what's happening, ask better questions, spot danger early, know where your scope ends, and collaborate credibly with the prescriber who holds the decision. Almost nobody is filling that role well.

### Why this is landing on your desk now

**68%** of Americans taking antidepressants have been on them for two years or more, roughly **one in four** for a decade or more.[1] The prescription renews. Nobody owns the exit.

That began to change in May 2026. HHS launched an action plan on psychiatric overprescribing that explicitly supports tapering for patients not experiencing clinical benefit, CMS clarified Medicare payment for deprescribing care, and a technical expert panel convened in July 2026 to develop federal guidance on tapering protocols.[2] The number of people who raise this with you is about to rise sharply, and the standards are still being written.

SECTION ONE

# What the medication is actually doing

### The window, not the mood

The most useful frame we know comes from Dr. Dave Rabin's clinical practice: an SSRI works by **narrowing the emotional window of awareness**, reducing the intensity of what a person feels at both ends. The floor comes up. That is the point, and it is often life-saving. The ceiling comes down. That is not the point, and it is rarely discussed at prescribing.

That single mechanism accounts for most of what clients report: flatness, watching life through glass, difficulty crying, lost intensity in relationships, and the sexual side effects. Orgasm, as Rabin puts it, is a peak joy state, and among the first things a narrowed window takes.

It also predicts the hardest part of coming off. As the window widens, **feeling returns at both ends simultaneously**. Joy comes back and so does grief, and a nervous system that has not processed anything at full intensity for years can read that as danger: racing heart, elevated blood pressure, sweating, racing thoughts. A client who does not know this is coming will read normal re-sensitization as relapse.

### What the imaging shows

In the head-to-head trial of psilocybin therapy against escitalopram,[3] follow-up analysis found the SSRI group showed **generalized blunting of responsiveness to emotional faces**.[4] Psilocybin therapy was instead followed by increased global integration across brain networks, tracking symptom improvement.[5] As Prof. Robin Carhart-Harris, who led that work, frames it: the SSRI **blunts**; the psychedelic **releases**. A client moving between them is changing the strategy, not the brand.

> WHERE THE HONEST LIMITS OF THE EVIDENCE ARE
>
> Carhart-Harris is explicit that there is **no clear and compelling evidence for psychedelic-induced neuroplasticity in humans** as yet. The striking findings are rodent and cell work on dendritic spine growth, not new neurons. Repeating "regrowing the brain" claims sets a client up to expect a biological miracle, the expectation that makes a merely good experience feel like a failure.

SECTION TWO

# Five things most practitioners get wrong

**1 · "Coming off is just a washout period."**

The largest analysis to date covered 79 studies and over 21,000 patients. About one in three people stopping an antidepressant reported at least one discontinuation symptom, roughly **one in six** had symptoms attributable directly to stopping rather than to expectation, and about **one in 35** experienced severe symptoms.[6] A separate 2024 meta-analysis put pooled incidence higher: **45.6%** for SSRIs, rising to **51.4%** past 24 weeks of treatment.[7] The literature disagrees about magnitude, not direction. The longer someone has been medicated, the higher the risk.

**2 · "If symptoms come back, the medication was working."**

The single most consequential error in the process. Discontinuation symptoms mimic the original condition: anxiety, insomnia, low mood, irritability, emotional volatility. A client four days into a reduction who feels awful will conclude, reasonably, that they need the drug. So might you. Sometimes that's right. Often it isn't. The differential is in Section Four.

**3 · "Halve the dose, then halve it again."**

Receptor occupancy does not fall proportionally with dose. The relationship is closer to hyperbolic, so the final small reductions produce far larger changes in occupancy than the early large ones. This is why clients sail through the first two cuts, then hit a wall at the lowest dose, and why the last step needs the most time and smallest increments. Tapering strategy is the prescriber's decision. Understanding *why* a client stalls is yours.

**4 · "Once they're off, psychedelics will work normally."**

Not immediately, and not always. Sustained serotonergic exposure alters 5-HT2A receptor availability, and response can remain blunted after the medication has cleared. In the psilocybin trials, participants who *came off* antidepressants to enter the study did not, on average, do as well as those medication-free all along. Nobody yet knows whether that reflects receptor changes, the harder clinical history those patients carry, or expectation.

The failure mode: a client tapers, waits what feels like long enough, has a session, feels little, and concludes the medicine doesn't work for them. Set the expectation in advance and it costs them nothing.

**5 · "The risk is the psychedelic."**

Almost never. The danger sits in the **overlap**: the period when both are on board. That is a timing question, and timing is what you can actually help get right.

SECTION THREE

# The four phases of a safe transition

Most transitions that go badly skipped a phase, usually the second.

01

### Assess

Is this client someone you can support at all? Look at medication history and duration, prior discontinuation attempts, current stability, severe episodes or suicidality, substance use, comorbidities, and the support around them. Bipolar I, active psychosis, and significant personality-disorder presentations are where this work stops rather than slows. The phase ends in one of three answers: support, support with medical co-management, or decline. Declining well is a clinical skill.

02

### Coordinate

The phase most practitioners skip, and the one that determines whether this is safe. The prescriber must be in the loop before any reduction begins. Arrive as a competent collaborator who is monitoring and reporting, not as someone working around them. A client who refuses to involve their prescriber is itself a finding, and usually a reason to pause.

03

### Taper

The prescriber sets the schedule. In Rabin's practice a full taper typically runs **four to twelve weeks**, and slower than expected is normal. You hold the process: tracking symptoms against expected timelines, supporting sleep and nervous-system regulation, distinguishing withdrawal from relapse in real time, escalating fast when something looks wrong. Pausing is not a failure. Reinstating is not a failure either.

04

### Sequence

Only now does serotonergic psychedelic work enter the conversation, and only when the client is stable off medication, not merely finished tapering. Those are different conditions, often months apart. Readiness is nervous-system regulation, sleep, support structure, and clarity of intention, not just the drug having cleared. What most reliably flattens a psychedelic experience is not years of prior medication but **unmanaged generalized anxiety**.

SECTION FOUR

# Withdrawal or relapse? A working differential

No single marker is decisive. The pattern across all six rows is what tells you. When it's genuinely ambiguous, bring the prescriber in rather than decide alone.

| SIGNAL | POINTS TOWARD WITHDRAWAL | POINTS TOWARD RELAPSE |
|---|---|---|
| **Onset** | Within days of a reduction, often 1–4, tracking half-life | Weeks to months later, no tight link to the reduction |
| **Course** | Rises, peaks, then eases over days to a few weeks | Builds gradually, persists or worsens |
| **Physical signs** | Dizziness, "brain zaps," nausea, flu-like feeling, sweating, vivid dreams. Somatic features absent from the original presentation | Largely absent. Affective and cognitive, not somatic |
| **Character** | Novel or unfamiliar: "this isn't what my depression felt like" | Recognizable. The client's original pattern returning |
| **Response to reinstatement** | Rapid, often within days | Slow, over weeks, as when first treated |
| **Timing vs. dose** | Follows each reduction step, worst after the smallest final cuts | No clear link to dose changes |

### A THIRD POSSIBILITY, EASILY MISSED

Neither withdrawal nor relapse: the return of ordinary feeling in someone who has not felt at full range for years. Sadness proportionate to a real loss. Anxiety proportionate to a real situation. The one presentation that needs no intervention, only naming.

### ESCALATE IMMEDIATELY, REGARDLESS OF WHICH SIDE IT LOOKS LIKE

Any emergence of suicidal ideation, self-harm, psychotic features, mania or hypomania, severe agitation, or an inability to function safely at work or at home. These are not for you to hold or to interpret. Contact the prescriber the same day, and know your local emergency escalation route before you need it.

SECTION FIVE

# The overlap: the one place this work is genuinely dangerous

If you take one thing from this document, take this section.

### What happens when both are on board

Three things stack. An SSRI blocks serotonin reuptake, so serotonin accumulates in the synapse. A serotonergic psychedelic increases serotonin release and binds the 5-HT2A receptor directly. And here is the piece most practitioners have never heard, emerging from work at Franz Vollenweider's laboratory over the past decade. Psilocybin and LSD also bind an **allosteric** site on that receptor, changing its shape so that it holds serotonin more tightly and for longer than it otherwise would.

Serotonin already elevated, plus more released, plus a receptor configured to hold onto it, is the setup for a chain reaction: **serotonin syndrome**. It ranges from agitation, tremor, sweating and rapid heart rate through to hyperthermia, seizure and death.

> *The number of people needed to kill with psilocybin alone is not a number that exists. With an SSRI on board it stops being zero, and a fifteen-minute screening conversation removes the risk entirely. That is the whole argument for tapering first.*
>
> — DR. DAVE RABIN, M.D., PH.D., PARAPHRASED FROM CLINICAL TEACHING

Rabin's clinical estimate of the risk is on the order of **one to two in a hundred**, dose-dependent, and he has seen it at a microdose. That is a practitioner's estimate from clinical experience, not a published incidence rate. No such rate has been established. Treat it as what it is: a clinician who has managed these cases telling you the risk is real and not vanishingly rare.

### Why you will hear the opposite

Respected voices say combination is fine. Some of that comes from researchers with no stake. Some comes from studies funded by companies whose commercial model is materially larger if patients do not have to come off their medication first. Carhart-Harris, who has no product in that market, is skeptical of the stay-on-your-SSRI position, and says researchers with fewer conflicts tend to conclude patients do better if they discontinue.

The upside of combining is convenience. The downside is a rare but potentially fatal event, and a single screening conversation removes it entirely.

# The classes, and what each changes

| CLASS | COMMON EXAMPLES | WHAT IT CHANGES FOR YOU |
|---|---|---|
| **SSRIs** | fluoxetine, sertraline, escitalopram, citalopram, paroxetine | **Not a safe overlap.** Difficulty varies enormously *within* the class: paroxetine and other short-half-life agents are hardest to come off; fluoxetine's long-lived metabolite makes it among the gentlest but slowest to clear. |
| **SNRIs** | venlafaxine, duloxetine, desvenlafaxine | Serotonergic, so the same rule applies. Venlafaxine is associated with pronounced discontinuation effects. Expect a longer, more carefully staged process. |
| **Tricyclics** | amitriptyline, nortriptyline, imipramine | Also serotonergic, also not to be combined. Anticholinergic rebound adds symptoms unfamiliar to practitioners used to SSRIs. Firmly prescriber-led. |
| **MAOIs** | phenelzine, tranylcypromine, selegiline, moclobemide | **The highest-risk combination of all.** Washout requirements are long and drug-specific. A medical question, not a timing question you help optimize. It stops with the prescriber. |
| **Atypicals** | bupropion, mirtazapine, trazodone, vortioxetine | Mechanisms and interaction profiles differ substantially. Bupropion, stimulants and antipsychotics tend to *reduce* psychedelic effect rather than amplify risk: a different problem, but one that still wastes a client's medicine and morale. |

### THE THREE QUESTIONS TO ASK IN THE FIRST SESSION

1. Exactly which medication, what dose, and for how long?
2. Have you tried to come off before, and what happened?
3. Does your prescriber know you're considering this?

The third answer tells you more about how this will go than the first two combined.

SECTION SIX

# How long to wait, and what ketamine changes

### The waiting period

There is no formally published universal interval, and any practitioner who quotes one as settled fact is overstating the evidence. What exists is convergent practice. Rabin's position is that roughly **four weeks clear of an SSRI** puts most people in a safe and responsive place, and MDMA-assisted therapy trials have long required a comparable medication-free interval before dosing. Longer-half-life agents such as fluoxetine need more. The prescriber sets the number.

Tell a client two things. The window widens gradually rather than switching back on, so the weeks after the last dose are their own process, not waiting. And duration matters less than they fear: Rabin reports no meaningful difference in responsiveness between clients on an SSRI for ten years and thirty.

### Where ketamine fits

Ketamine works primarily through glutamate rather than serotonin. It therefore does *not* carry the serotonin-syndrome interaction, and can be used **while a client is still on their SSRI**, which makes it the one tool available during the taper rather than only after it. Rabin uses it to support and accelerate discontinuation, often in the range of three to six sessions across three to six weeks, against a taper that would otherwise run considerably longer. The two are not interchangeable: the signature of psilocybin is insight, of ketamine dissociation.

> SCOPE, PLAINLY
>
> Ketamine is a controlled prescription medication. Nothing above is a protocol, a dose, or a recommendation you can act on. It is context, so you understand what a prescriber may be proposing. If you are not a prescriber, your role in ketamine-assisted work is preparation, presence, and integration. That is substantial enough without borrowing one that isn't yours.

THE CHECKLIST · PRINT THIS ONE

# Pre-Transition Readiness Checklist

If you cannot tick every box in sections A and B, you are not ready to proceed. Saying so is the correct clinical action.

## A · Clinical picture

- ☐ **Medication documented:** name, dose, formulation, duration, drug class.
- ☐ **Serotonergic status established across the full medication list,** including supplements. SSRI, SNRI, tricyclic and MAOI all rule out concurrent serotonergic psychedelic use, not MAOIs alone.
- ☐ **Prior discontinuation attempts explored:** what was tried, what happened, how long.
- ☐ **Psychiatric history reviewed:** episode severity, hospitalizations, suicidality, mania or hypomania, psychosis.
- ☐ **Absolute contraindications screened:** bipolar I, active or historical psychosis, significant personality-disorder presentation.
- ☐ **Current stability genuinely adequate to begin,** and substance use including alcohol screened.
- ☐ **Life stability considered.** Not mid-divorce, job loss, or bereavement.

## B · Coordination & consent

- ☐ **The prescriber knows and is engaged,** not "the client says they'll mention it," and the schedule comes from them in writing.
- ☐ **My role is written down** and the client has read it: what I do, and what I do not.
- ☐ **Informed consent covers discontinuation risk:** symptoms may be significant, the process may run long.
- ☐ **Interaction risk explained in plain language.** "Just a microdose" is not an exception.
- ☐ **Escalation route agreed and emergency contact on file.**

## C · Support structure

- ☐ **Monitoring cadence set,** increasing around each reduction, with symptom tracking the client will use.
- ☐ **Sleep support addressed** before the first reduction.
- ☐ **Nervous-system regulation practices established** and already habitual.
- ☐ **The client has been told feeling returns at both ends,** and a surge of emotion is expected, not failure.
- ☐ **At least one person in their life knows,** and pausing is pre-agreed as normal.

# Before any psychedelic work

A separate gate entirely. Section D opens only once the taper is finished and settled.

### D · Before any psychedelic work

- ☐ **Fully discontinued and clearance interval passed,** both prescriber-confirmed, with extra time for long-half-life agents.
- ☐ **Stable off medication for a sustained period,** not merely finished tapering.
- ☐ **Discontinuation symptoms resolved,** not simply tolerated.
- ☐ **Interaction risk reviewed** against every current medication and supplement.
- ☐ **Generalized anxiety addressed, and blunted-response expectation set.**
- ☐ **Intention is forward-looking,** and integration support arranged in advance.

> **IF YOU CANNOT TICK A BOX**
>
> An unticked box in section A or B is a stop, not a caution. The most common serious error in this work is not a bad taper. It is agreeing to support a client you should have declined, or declined *for now*.

SECTION SEVEN

# Where to go from here

This primer gives you the map, not the protocol: the assessment instruments, the timelines by drug, the sequencing criteria, and the judgment that comes only from working real cases alongside someone who has done this for twenty years. That is what the training is for.

## SSRI Deprescribing & Psychedelic Readiness Certification

Six live sessions with David Rabin, M.D., Ph.D., plus 6 facilitated labs where you bring your own cases · begins Wednesday, September 16 · three months · capped cohort · pre-publication access to his clinical deprescribing manual · 7.5 CE credits

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8. Clinical positions attributed to Dr. David Rabin, M.D., Ph.D. are drawn from his teaching and practice and are identified as such throughout. They represent clinical experience rather than established published incidence. Positions attributed to Prof. Robin Carhart-Harris are drawn from his published work and public commentary. Full citations, including the receptor pharmacology underlying the interaction risk, are provided in the training.