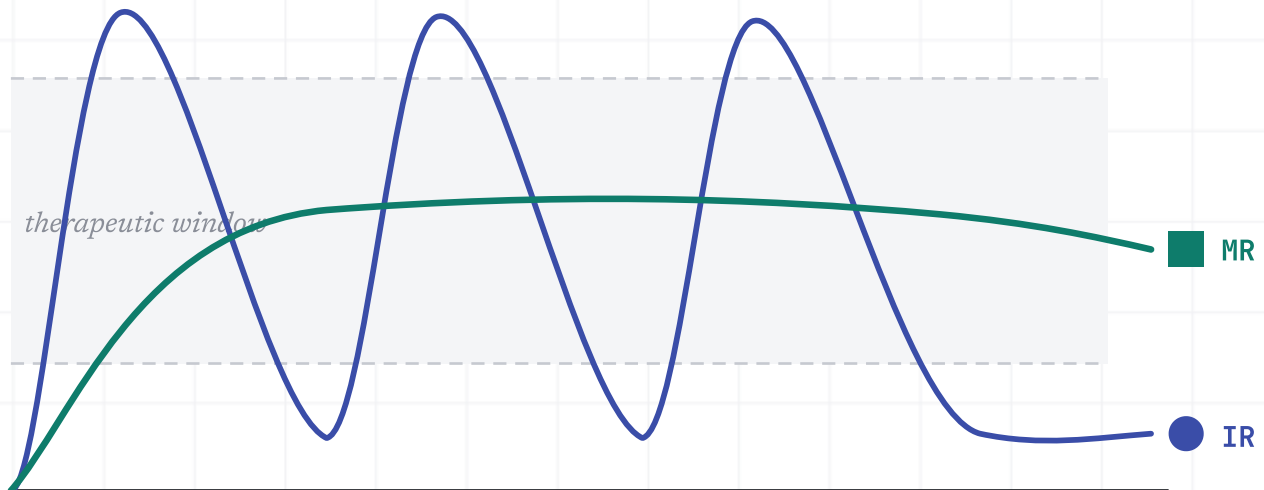




The Shape of the Dose.

The same molecule, at the same daily dose, can reach the blood as a spike or as a steady line. Immediate-release, modified-release, orodispersible, transdermal, long-acting injectable. *The dilemma is rarely which drug. It is which form, and whether you can get it in India.*

Two prescriptions can carry the same molecule, the same milligrams, the same total daily dose, and behave like two different drugs. One is immediate-release: the tablet dissolves, the drug floods in, the plasma level spikes and then falls away before the next dose. The other is modified-release: the same dose, metered out over hours, so the level climbs gently and holds. The choice between them is not cosmetic. It decides peak-related side effects, trough-related relapses, how many times a day the patient has to remember, and sometimes whether the drug works at all.

02 What a formulation does to a drug

Every drug has a therapeutic window: a band of plasma concentration high enough to act, low enough to spare the patient dose-related harm. Above the band the patient meets the side effects that track peak concentration; below it the drug is simply absent. The whole craft of a formulation is to keep the patient inside that band for as much of the day as possible, with as little effort from the patient as possible.

This issue follows the dose through five shapes it can take, and asks two questions of each. What does the formulation do to the drug? And what can you actually prescribe in an Indian clinic? The four families below recur throughout, each fixed to one colour and one shape so they survive a photocopy.

14% The number the non-oral routes escape. Atorvastatin is completely absorbed from the gut, yet only about 14 percent reaches the blood. First-pass metabolism in the gut wall and liver, not the dose on the box, is what a patch or an injection bypasses.⁵

THE FOUR FAMILIES



IR immediate-release



MR modified-release



NO non-oral (patch, spray)



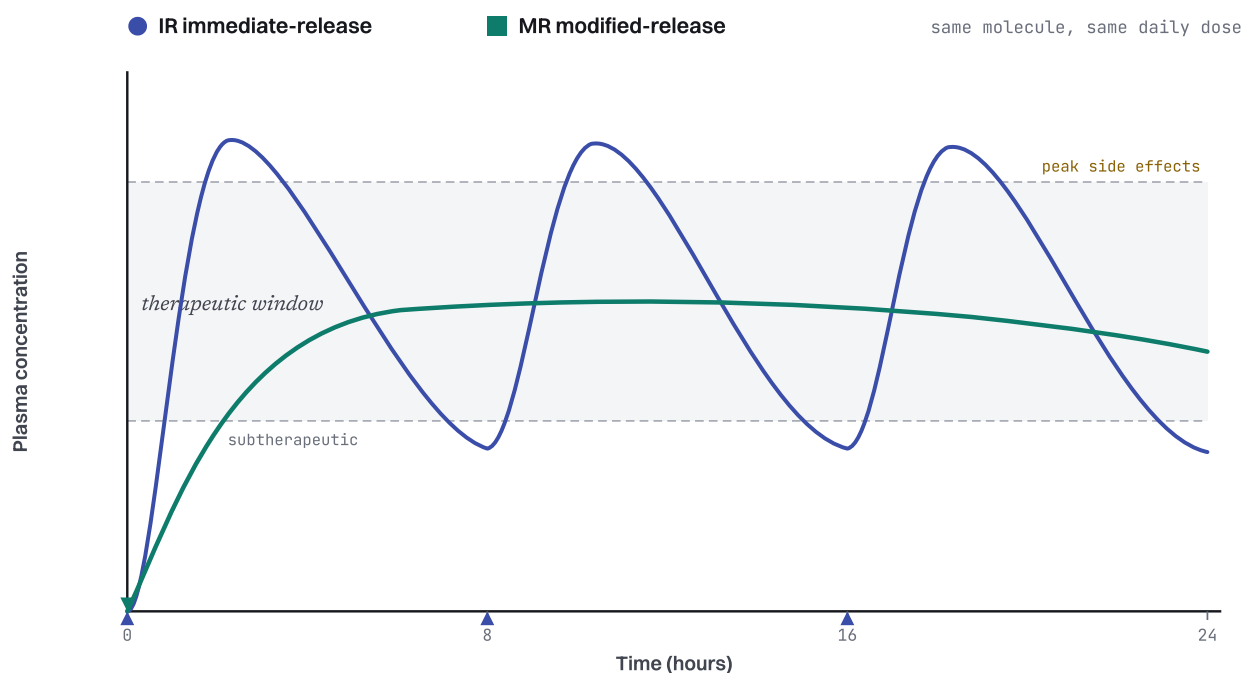
LAI long-acting injectable

QUICK CHECK

A tablet relabelled SR carries the same milligrams as the plain one. Is the patient getting more drug, or the same drug spread out?

- A The same total dose, metered over hours: a lower peak and a higher trough, not a larger amount. A modified-release form changes the shape of the dose, not how much of it the patient receives.^{1,2}

The figure on the next page is the whole argument in one image: the same daily dose, drawn as immediate-release against modified-release.



The area under each curve (total exposure) is comparable.
Modified-release changes the *shape* of the dose, not the amount.
 IR dosed 3x/day (peaks + troughs) - MR dosed 1x/day (steady)

HOW TO READ THIS Follow either line across the 24 hours. The area under both is the same daily dose; the blue immediate-release curve spikes above the peak-side-effects line and then falls below the window between doses, while the teal modified-release holds one steady band inside it.

The two curves carry the **same molecule at the same daily dose**. Everything that differs follows from the shape, not the amount.

WHAT THE CURVE SHOWS

- 1 Same area, same exposure.** Modified-release does not deliver more drug. The area under the curve, the total the patient actually receives, is identical; only its distribution across the day changes. Modified-release tacrolimus once daily matches the twice-daily immediate-release form on total exposure and trough, at a lower peak.¹
- 2 Lower peak, fewer side effects.** Flatten the peak and you lose the dose-related side effects that ride it. The patient meets a gentler maximum for the same therapeutic work.²
- 3 Higher trough, no gaps.** Raise the trough and the level stops dropping out of the window between doses, where partial response and breakthrough symptoms live.²
- 4 Fewer doses, real adherence.** Once daily instead of three times is a regimen the patient can keep, which for many drugs matters more than any pharmacological nicety.²

A drug with a longer effective half-life takes longer to reach steady state, but once there it fluctuates less across the dosing interval.⁷

Slowing the release. Modified-release is built three main ways. The names on the box (SR, CR, XR, ER) are marketing letters, not a standard grammar; only the product information tells you which mechanism is inside.²

THREE WAYS TO SLOW A TABLET

- 1 **Osmotic pump (OROS).** Water is drawn in and drug is extruded through a laser-drilled orifice at a near-constant rate, giving the flattest once-daily curve.³
- 2 **Matrix erosion.** The drug is held in a polymer that swells or erodes slowly, so it diffuses out over hours.²
- 3 **Coated multiparticulate beads.** Hundreds of tiny coated units, a multiple-unit pellet system, release in overlapping waves.^{8,9}

Surviving the first pass. Bioavailability is the fraction of an oral dose that reaches the systemic circulation. Much can be lost to first-pass metabolism in the gut wall and the liver before the drug arrives.^{4,6} Atorvastatin is completely absorbed yet reaches the blood at only about 14 percent because of it.⁵ This is the quiet advantage of the non-oral routes: a patch or an injection bypasses the gut and the liver entirely, so the first-pass loss never happens.

Dissolving without slowing. An orodispersible tablet disintegrates on the tongue without water. It is bioequivalent to the swallowed tablet: in a controlled study the orodispersible form met the 80 to 125 percent limits for both peak and total exposure.^{10,11} The point is supervised, swallow-free convenience for a patient who cannot or will not take a tablet, not faster entry to the brain. Releasing a drug faster is not the same as releasing more of it.

AT THE BEDSIDE

A patient on plain quetiapine twice daily reports a heavy one-to-two-hour sedation peak after each dose. Three moves sit on three different axes. Switch to quetiapine SR and the slower release flattens that peak. Switch to an orodispersible tablet and you only remove the glass of water, which answers a swallowing problem, not this one. Neither changes the molecule or the total daily dose.²

HOLD THIS

Faster, slower, and more are three different things

A modified-release form does not deliver more drug; it delivers the same amount over longer. An orodispersible form does not deliver drug faster to the brain; it removes the glass of water. A non-oral route does not change the molecule; it changes where the molecule enters. Keep the three axes (how fast, how long, by what route) separate, and most formulation questions answer themselves.

Six forms, four families, one table. Read each row as a trade: every formulation buys one clinical advantage and charges one caveat for it. Onset and dosing frequency are typical, not absolute, and vary by molecule.

TABLE 1 What each formulation buys, and what it costs

Form	What it is	Onset	Doses / day	Choose when	Key caveat
● IR immediate-release	Whole dose released at once	30 to 60 min	2 to 3	First line; rapid titration; when the dose may change often	Peaks and troughs; frequent dosing leans on memory
■ MR modified-release	Same dose metered over hours	Slower, blunted	1	Peak side effects; once-daily adherence; smoother level	Do not crush or split; not interchangeable mg-for-mg with IR
● ODT orodispersible	Dissolves in the mouth, no water	As IR	As IR	Cannot swallow; covert non-adherence; supervised dosing	Convenience, not a pharmacokinetic advantage
◆ Patch transdermal	Steady delivery through skin	Hours to a day	One patch lasts 1 to 7 days	Steady levels; avoid first-pass; unreliable swallowing	Skin reactions; a skin depot lingers after removal
◆ Spray intranasal	Across nasal mucosa, fast	Minutes	Per protocol	Rapid effect needed (esketamine in resistant depression)	In-clinic monitoring; dissociation, transient pressure rise
○ LAI depot injection	Slow-release injection	Days to weeks	Every 2 to 24 weeks	Non-adherence; relapse prevention; covert default	Slow to load and to clear; cannot be withdrawn

THE FOUR FAMILIES BEHIND THE SIX FORMS

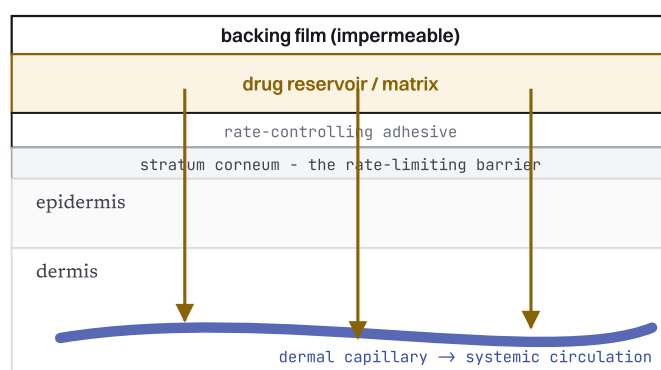
- **Immediate-release** (the circle, IR and ODT). Flexible and fast to titrate; the cost is peaks, troughs, and frequent dosing.
- **Modified-release** (the square). One smooth daily curve; never crush it, and do not assume it equals the IR dose milligram-for-milligram.
- **Non-oral** (the diamond, patch and spray). Steady levels with no first pass, or rapid onset by nose; the cost is skin care or in-clinic monitoring.
- **Long-acting injectable** (the ring). The answer to non-adherence; slow to load, slow to clear, and impossible to take back.

Orodispersible tablets sit in the immediate-release family: they change how the tablet is taken, not how the drug behaves. Patch and spray share the non-oral family; both skip the gut.

A drug delivered at a constant rate through skin reaches steady levels with far less peak-to-trough swing than intermittent tablets, and bypasses gut absorption and hepatic first-pass altogether.³⁶ The psychiatric and neurological patches make the case concrete.

THE PATCHES THAT MATTER, AND WHY

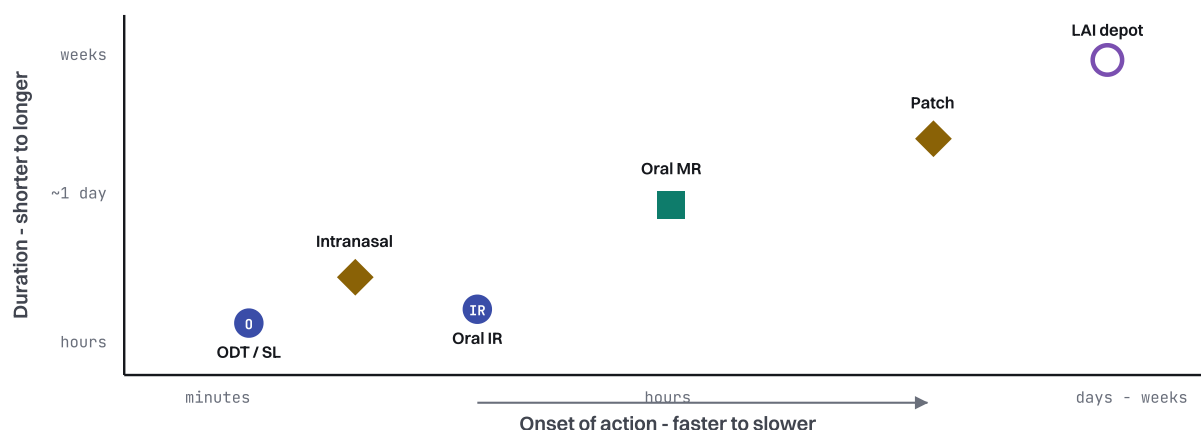
- **Rivastigmine.** Matches the exposure of the highest oral dose at roughly a third of the peak concentration (8.7 against 21.6 ng/mL), with about three times fewer reports of nausea and vomiting.^{37,38}
- **Selegiline.** Sparing the gut wall's monoamine oxidase is why a transdermal MAO inhibitor carries far less tyramine food risk, but only at the low dose: no diet restriction at 6 mg per 24 hours, restriction returning at 9 and 12 mg.^{39,40}
- **Methylphenidate and clonidine.** The methylphenidate patch delivers steadily over a nine-hour wear and can be removed to end the effect early;^{41,42} clonidine reaches steady state over days and holds it for a week.⁴³
- **Intranasal esketamine.** The outlier: the nose buys speed, a rapid antidepressant onset in resistant depression, at the cost of supervised in-clinic dosing.^{44,45}



Steady diffusion down a fixed gradient gives near-constant levels for 1 to 7 days, bypassing gut and liver.

removing the patch stops delivery, but a skin depot lingers

FIGURE 2 Route maps onto speed and duration

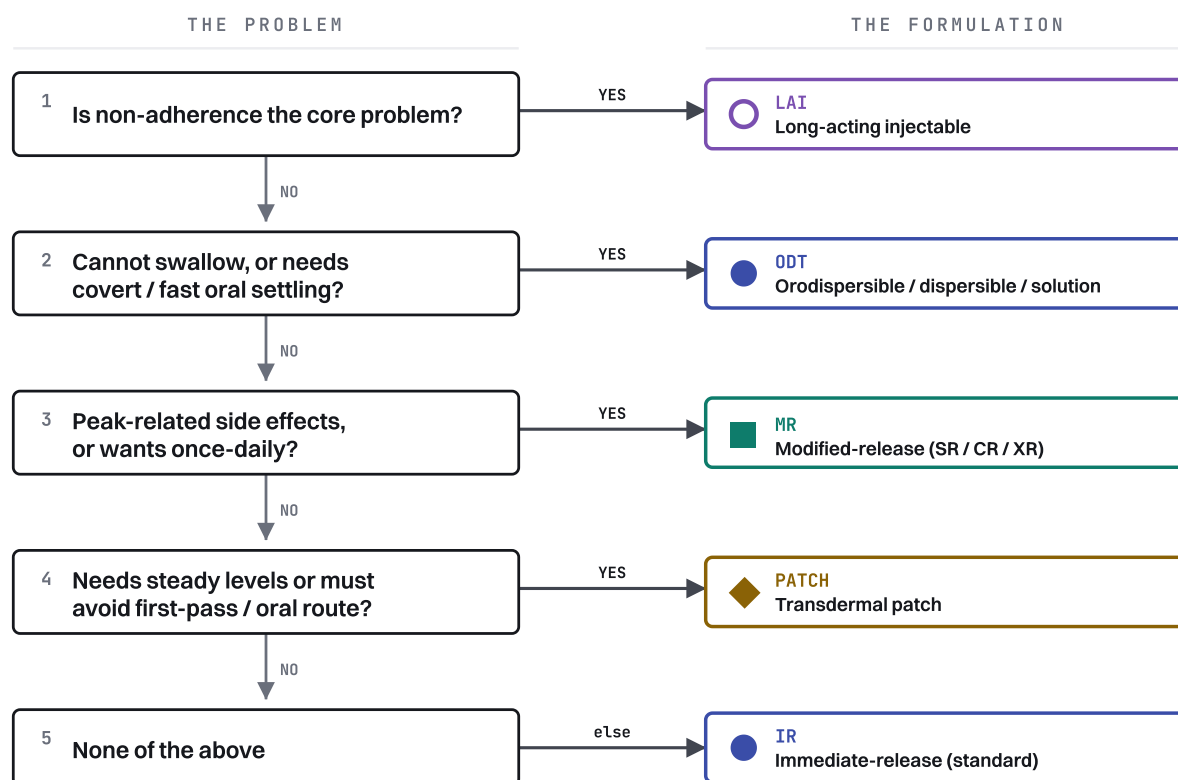


Most of the time the formulation is a convenience. Sometimes it is the treatment. The question is not which form is best in the abstract, but which clinical lever the patient in front of you most needs pulled. Each lever points to a family.

THE FOUR LEVERS

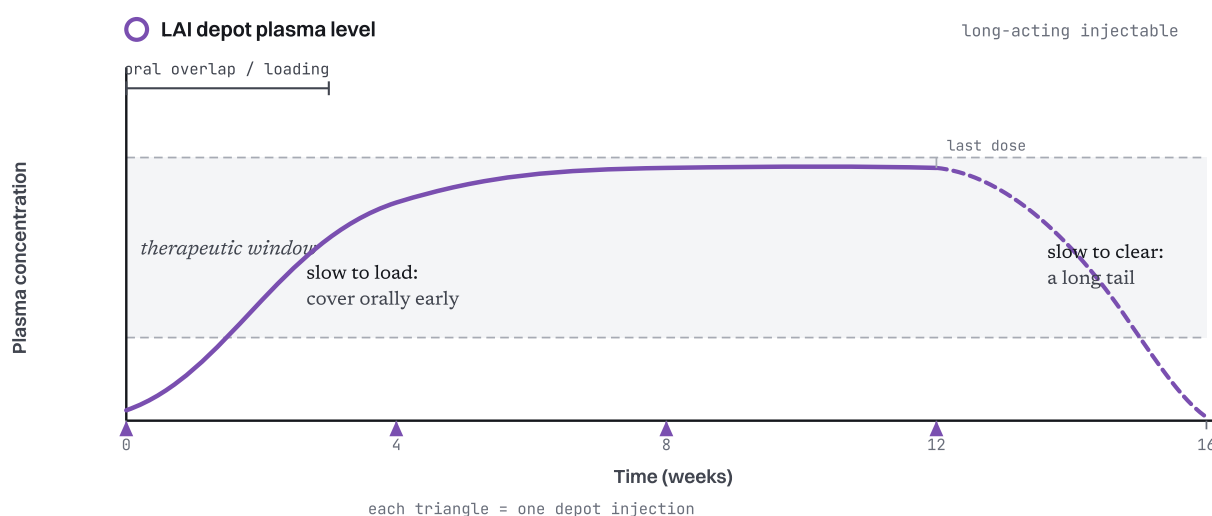
- 1 **Adherence.** If the patient stops taking it, no oral form helps. The long-acting injectable removes the daily decision.
- 2 **Swallowing.** If a tablet cannot go down, or must be taken covertly, an orodispersible, dispersible, or liquid form solves it without changing the drug.
- 3 **Peak tolerability.** If the side effects track the peak, or the patient simply wants once-daily, modified-release flattens the curve.
- 4 **Steadiness and route.** If the patient needs constant levels or cannot use the gut, a transdermal patch delivers steadily and skips the first pass.

The flow below turns those four levers into a single ordered question, ending in one of five forms.



HOW TO READ THIS Start at the top and answer each question in turn. The first YES sends you straight across to its formulation family; a NO drops you to the next question, and the final box catches everyone else as standard immediate-release.

The long-acting injectable is the one formulation that treats a problem the molecule cannot: the patient who stops taking it. Across mirror-image and randomised data, depots reduce hospitalisation and relapse against the same patients' oral treatment, with the clearest signal in real-world use and a genuine, if smaller, effect in trials.^{24,25,26} The benefit is not reserved for chronic non-adherence; it appears in early-phase illness too.²⁷ The cost is paid in pharmacokinetics. Depots show flip-flop kinetics, where the slow release, not elimination, sets the apparent half-life, so they are slow to reach steady state and slow to wash out.^{13,15,16}



HOW TO READ THIS Each triangle on the baseline is one injection. The solid violet line climbs slowly to a steady level over the first weeks, which is why oral cover runs alongside it; the dashed tail after the last dose shows how long the depot keeps releasing once it is stopped.

That slow loading dictates how each depot is started. The rules are molecule-specific, and getting them wrong leaves the patient unprotected for exactly the weeks relapse is most likely.

STARTING A DEPOT, BY MOLECULE

- 1 Risperidone microspheres.** Almost no drug is released for the first three weeks, so oral antipsychotic cover is mandatory through initiation.¹⁷
- 2 Aripiprazole once-monthly.** A fortnight of oral overlap is needed at the classic start; the newer two-injection start removes the overlap entirely.^{19,20}
- 3 Olanzapine pamoate.** Carries the formulation-specific post-injection delirium-sedation syndrome from accidental intravascular spread, which is why every dose needs three hours of observation.²¹
- 4 Paliperidone palmitate.** The interval now stretches to six-monthly, a single injection covering half a year.²³

A formulation you cannot buy is a formulation you cannot prescribe. The table below maps the common psychotropics to the forms actually marketed in India. Brand names are illustrations, not endorsements, and one example is given per form. The forms are coded by family.

FORMS **IR** immediate-release **ODT** orodispersible **Liq** oral liquid **MR** modified-release **LAI** depot

TABLE 2 India availability by molecule

Molecule	Class	Forms in India	Example brands	Note
Olanzapine	Atypical AP	IR · ODT · Liq · LAI	Oleanz, Oleanz RT, Tolaz LA	LAI = Tolaz LA (Torrent)
Risperidone	Atypical AP	IR · ODT · Liq · LAI	Sizodon, Sizodon MD, Risperdal Consta	Widest range; no oral MR
Quetiapine	Atypical AP	IR · MR	Qutipin, Qutipin SR	SR is India's XR
Aripiprazole	Atypical AP	IR · ODT	Arpizol, Arip MT	Depot not marketed in India
Paliperidone	Atypical AP	MR (oral, only form) · LAI	Palido OD, Invega Sustenna	No IR exists anywhere
Amisulpride	Atypical AP	IR · ODT	Solian, Amazeo OD	No MR, no depot anywhere
FGA depots	Typical AP	LAI (decanoate, IM)	Haloperidol / Fluphenazine / Zuclopenthixol decanoate	Depot only; oral forms historical
Lithium	Mood stabiliser	IR · MR (SR)	Licab, Lithosun SR	No liquid, ODT or depot
Valproate / divalproex	Mood stabiliser	IR · MR (Chrono) · Liq	Encorate, Valparin Chrono, syrup	"Chrono" = controlled-release
Lamotrigine	Mood stabiliser	IR · disp · MR	Lamitor, Lamitor DT, Lamitor OD	MR = Lamitor OD; US Lamictal XR absent
Carbamazepine	Mood stabiliser	IR · MR (CR) · Liq	Tegrital, Tegretol CR, suspension	Plain = Tegrital; CR branded separately
Venlafaxine	SNRI	IR · MR (XR)	Venlor, Venlor XR	XR capsule: do not crush
Bupropion	NDRI	IR · MR (SR + XL)	Bupron, Bupron SR, Bupron XL	India markets all three forms
Fluoxetine	SSRI	IR · Liq	Fludac, Fludac syrup	No weekly form in India
Methylphenidate	Stimulant	IR · MR (SR / OD)	Inspiral, Addwize OD; Concerta	Concerta OROS registered but supply-limited
Atomoxetine	Non-stim ADHD	IR (cap / tab)	Axapta, Attentrol	Inherently once-daily; no separate MR
Clonazepam	Benzodiazepine	IR · ODT	Lonazep, Lonazep MD	Mouth-dissolving widely used
Melatonin	Chronobiotic	IR	Meloset	Prolonged-release (Circadin) not in India

Availability shifts; confirm the current brand and strength on a pharmacy listing or the product insert before prescribing. The clinically loaded gaps are the missing modified-release and depot forms, not the well-stocked plain tablets.

Crushing what must not be crushed. Breaking a modified-release or coated tablet defeats the engineering and can release the whole dose at once. Crushing is a recognised cause of altered pharmacokinetics, lost efficacy, and harm, and it is common: a quarter of solid doses on one psychiatric ward were crushed or opened, many without authorisation.^{29,30} Alcohol makes it worse for some products, dissolving the matrix and dumping the dose.^{32,2} Extended-release stimulants are misused the same way.³¹ When a patient cannot swallow, reach for a form designed for it (orodispersible, liquid, patch), not a crushed modified-release tablet.^{28,33,35}

Switching as if the milligrams matched. Immediate-release and modified-release are not interchangeable dose-for-dose. The same number on the box can mean a different peak, a different duration, and a different dosing frequency. Switch deliberately, against the product information, not by reflex.

Starting a depot without cover. A long-acting injectable is slow to load. Skip the oral overlap where the molecule needs it and the patient is subtherapeutic for weeks, exactly when relapse is most likely. The same slow kinetics mean a depot cannot be taken back once given.

SAFETY

Do not crush or split these

Modified-release and coated forms lose their safety the moment the coating breaks. The common psychiatric offenders:

- 01 Bupropion SR and XL; venlafaxine XR capsules
- 02 Quetiapine SR; lithium SR / CR; divalproex / valproate "Chrono" CR
- 03 Carbamazepine CR; paliperidone oral (an osmotic ER system)
- 04 Methylphenidate OD / extended-release; any tablet marked "do not crush" on the insert
- 05 When in doubt, check the product information before halving a tablet or opening a capsule

TABLE 3 The letters on the box

Abbreviation	What it usually means
IR	Immediate-release: the whole dose is released at once.
SR / CR	Sustained- or controlled-release: drug metered out over hours, usually once or twice daily.
XR / ER / XL	Extended-release: the longest oral profile, typically once daily. The letters are not standardised across makers.
OROS	Osmotic-release oral system: an osmotic pump driving a flat once-daily curve.
MUPS	Multiple-unit pellet system: many coated beads releasing in waves.
ODT / MD / DT	Orodispersible, mouth-dissolving, dispersible: dissolves without water; behaves like IR once absorbed.
LAI	Long-acting injectable, or depot: a slow-release injection lasting weeks to months.

Formulation is usually a convenience and occasionally the treatment; the skill is telling the two apart, then checking the form exists where you practise. Four reminders carry most of the value.

WHAT THIS ISSUE COMES DOWN TO

- 1 **Name the problem first.** A peak, a trough, a swallow, or adherence. The answer points to a family: modified-release for peaks and once-daily, an orodispersible or liquid for swallowing, the long-acting injectable for adherence.
- 2 **Same shape, not the same drug.** Immediate-release and modified-release are not interchangeable milligram-for-milligram. Switch against the product information, never by reflex.
- 3 **Never crush modified-release.** Breaking the coating can dump the whole dose at once. When a patient cannot swallow, choose a form built for it, not a crushed tablet.
- 4 **Cover the depot while it loads.** A long-acting injectable is slow to reach steady state and cannot be taken back. Plan the oral overlap the molecule needs.

REMEMBER

PROBLEM • SHELF • COATING • COVER

Name the **problem** (peak, trough, swallow, or adherence); confirm the form sits on the Indian **shelf**; if it is modified-release, never break the **coating**; if it is a depot, give the oral **cover** the molecule needs while it loads.

BEDSIDE CHECK

Before you sign the prescription

For any psychotropic, in order:

- 01 Which problem am I solving: a peak, a trough, a swallow, or adherence? The answer names the family.
- 02 Does the form I want exist in India, and as what brand and strength?
- 03 If it is modified-release, have I told the patient never to crush or split it?
- 04 If I am switching IR to MR or back, have I checked the product information instead of matching the milligrams?
- 05 If it is a depot, does this molecule need oral overlap, and have I planned it?

Get those four right and the rest is detail. The clinician who can name the right form for the patient in front of them, and knows whether it exists on the Indian shelf, has done the harder half of prescribing well.

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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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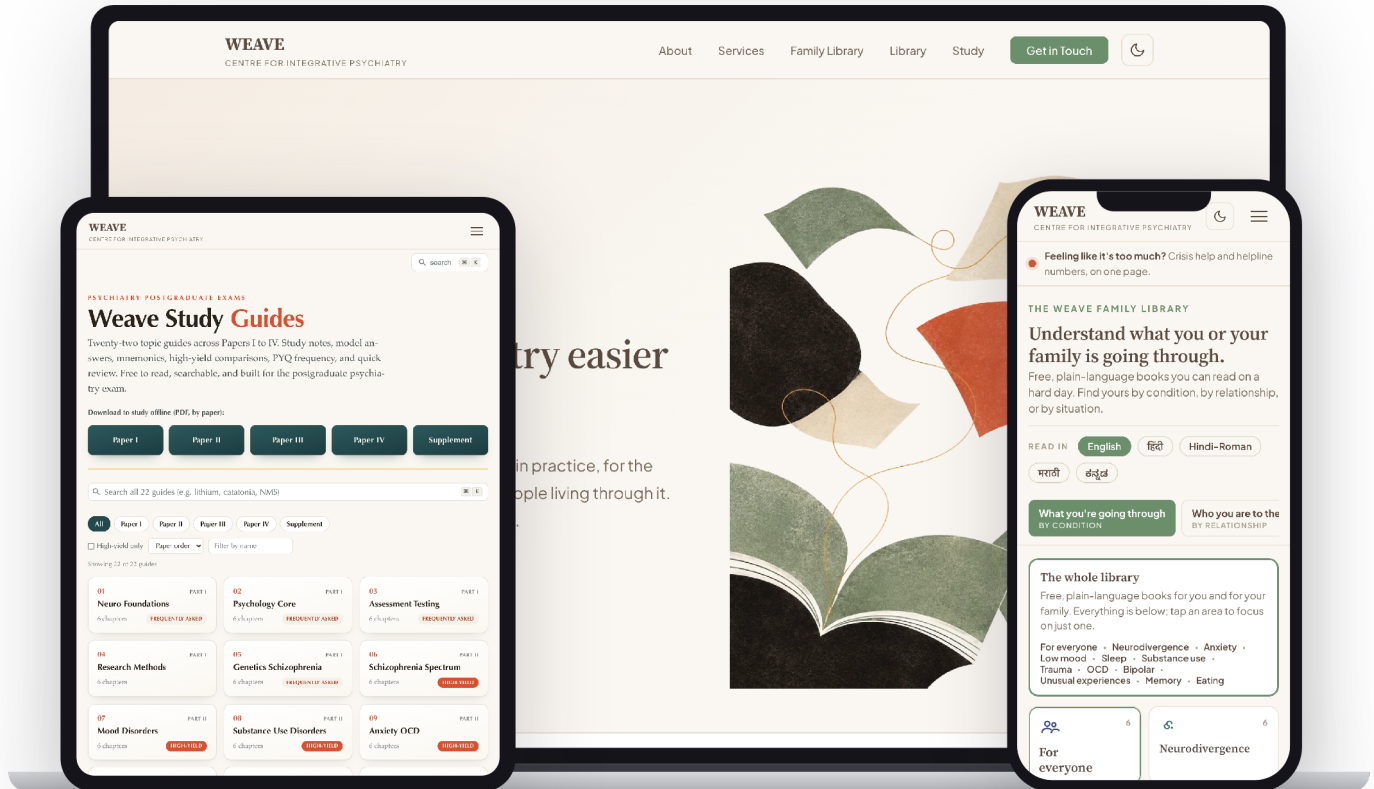
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