WEAVE
CENTRE FOR INTEGRATIVE PSYCHIATRY

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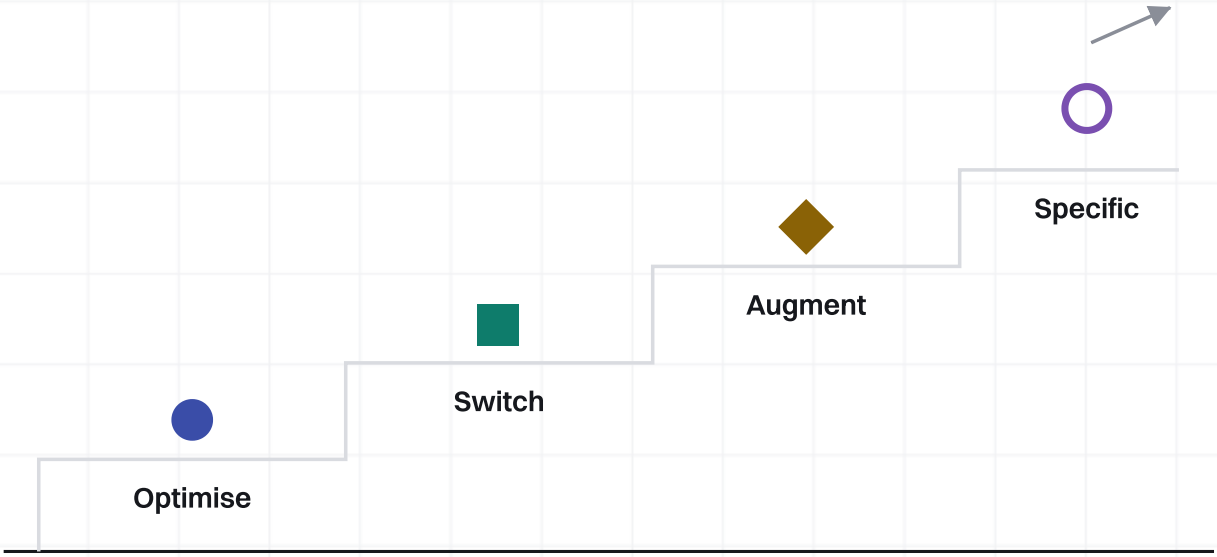


After the First Failure.

When a drug fails, the first question is rarely which one next. It is whether the one already tried was ever given a fair chance. *Resistance is what remains after an adequate trial has truly failed. The rest is pseudoresistance, and it is the commoner thing.*

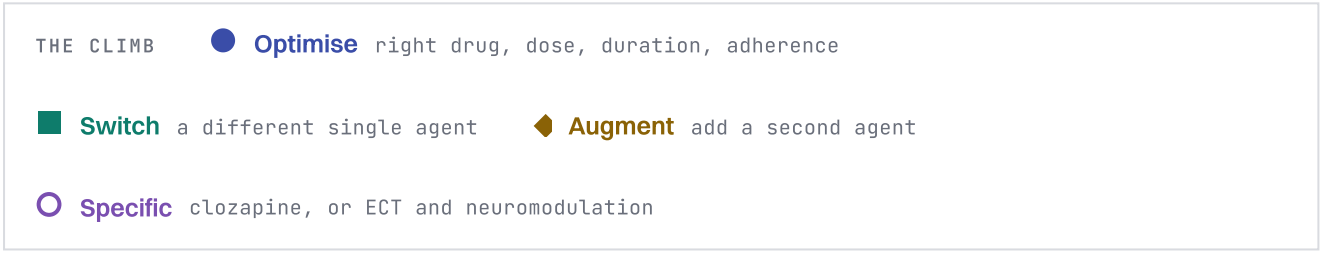
01 What resistance means, and what it hides

DEFINITIONAL

A patient has failed three antidepressants, or three antipsychotics, and the chart now reads treatment-resistant. The word feels like a diagnosis. It is closer to a question. Before asking which drug comes next, ask whether the drugs already tried were ever given a fair chance: the right drug, at the right dose, for long enough, actually taken. Resistance is what is left after an adequate trial has genuinely failed. Everything short of that is pseudoresistance, and it is far more common than the real thing.

This issue follows two illnesses through the same problem. In schizophrenia, treatment-resistant schizophrenia (TRS) is failure of two adequate antipsychotic trials, and it has one specific answer: clozapine.[3,4] In depression, treatment-resistant depression (TRD) is most often failure of two adequate antidepressant trials, classically from different classes, though no single definition is agreed.[1,2,7] Each affects roughly a third of treated patients. Each is approached by the same ordered climb, but the order is not the same, and that difference is itself worth teaching.

THE FOUR TIERS, ONE GRAMMAR OF ESCALATION



TWO REFRAMES WORTH HOLDING

- **A failed trial is not a failed patient.** Resistance describes the match between an illness and its treatment, not willpower or difficulty. A patient who has not improved is owed a better trial before a label, and the first thing to interrogate when a drug has not worked is the prescription, not the person.
- **Most apparent resistance is under-treatment.** The commonest reasons a drug fails are an underdose, too short a trial, and a drug never reliably taken; and even the one specific treatment, clozapine, reaches the patients who need it years too late. The fix is usually ours to make.[5,6]

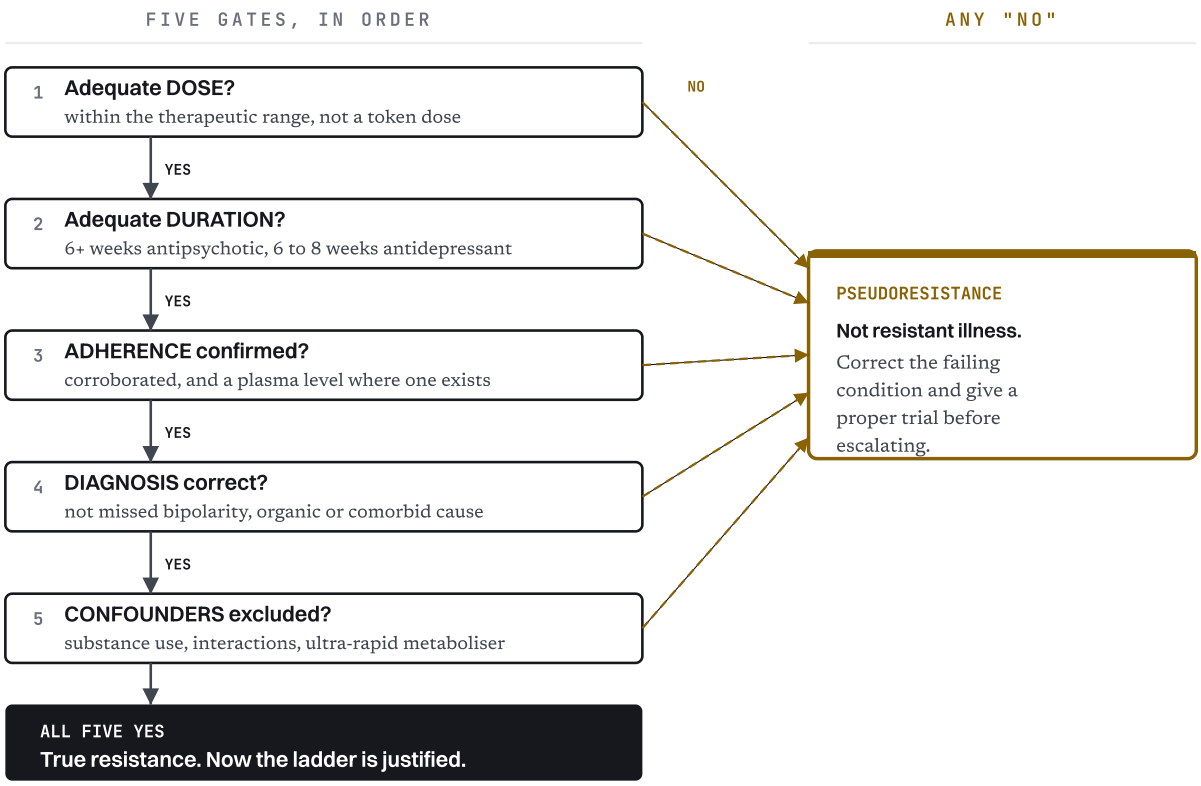
1 in 3 **The shared scale of the problem.** About a third of treated schizophrenia is genuinely resistant,[5,16] and about the same fraction of treated depression,[8,10] once an adequate trial has truly failed. Two different illnesses resist at a broadly similar rate.

The next page sets the gate every patient must pass before the word resistant is earned.

Rule out the impostor first

Apparent resistance has a short list of causes, and each is fixable. Run the patient through five gates before the label is applied. A single No is enough to send you back to a proper trial rather than up the ladder, because escalating against pseudoresistance adds drugs, costs and harm without touching the real problem.[3,5]

FIGURE 1 **The gate before the climb**



HOW TO READ THIS Walk down the five gates in order. A single NO at any gate drops the patient out to the amber pseudoresistance box: correct that failing condition and give a proper trial before the ladder is ever justified.

EXCLUDE FIRST

The four pseudoresistances

01 **Underdose or undertrial.** The drug never reached an effective dose, or was stopped before it could work. The remedy is a proper trial, not a new drug.

02 **Non-adherence.** The most frequent cause, often silent. Corroborate adherence, and where a plasma level exists, measure it before believing the drug failed.

03 **Wrong diagnosis.** Unrecognised bipolarity, an organic cause, or an untreated comorbidity will defeat any first-line drug aimed at the wrong target.

04 **Pharmacokinetic escape.** Substance use, an interacting drug, or an ultra-rapid metaboliser keeps levels subtherapeutic at a normal dose.

02 A short history of a loaded word

Resistance has never had a fixed threshold, only a moving one. In schizophrenia the modern story starts with Kane's 1988 trial, which defined refractory illness by the failure of three antipsychotics and a prospective haloperidol trial, then showed clozapine worked where they had not.[4] The Treatment Response and Resistance in Psychosis (TRRIP) consensus of 2017 modernised the bar: two adequate trials, each at least six weeks at an adequate dose, with adherence confirmed.[3] In depression the same instinct produced staging rather than a single cut. Thase and Rush proposed a five-stage hierarchy in 1997;[11] the Maudsley Staging Method made resistance dimensional, scoring duration, severity and the number of failed treatments rather than a yes or no.[12,13]

The thresholds keep shifting; the principle underneath them does not. A patient is resistant only relative to treatments that were genuinely adequate. So before any definition can be applied, both disorders need the same yardstick: what counts as an adequate trial. Beyond it lies the rarer territory of clozapine-resistant, or ultra-resistant, illness, where even the specific treatment has failed.[14]

HOW THE BAR HAS MOVED

- **Schizophrenia.** From Kane's three failed antipsychotics and a prospective haloperidol trial, to TRRIP's two adequate trials with adherence confirmed. Fewer drugs required, but a harder proof that each was genuinely adequate.
- **Depression.** From Thase and Rush's ordered stages to the Maudsley method's dimensional score. The question shifted from whether the patient is resistant to how resistant, and for how long.

TABLE 1 **What counts as an adequate trial**

Class	Adequate dose	Minimum duration	Confirm before declaring failure
Antipsychotic (TRS)	Therapeutic dose, around 600 mg/day chlorpromazine-equivalent or above	6 weeks each, 2 trials	Adherence, ideally a plasma level
Antidepressant (TRD)	Within the licensed effective range, pushed to tolerance	6 to 8 weeks	Adherence and an accurate diagnosis
Clozapine	Plasma-level guided, trough at or above 350 ng/mL	Up to 6 months at a therapeutic level	A measured clozapine level, not the dose alone

The TRRIP figure of 600 mg chlorpromazine-equivalent and the 6-week minimum are consensus thresholds, not laws of nature; the point is that the dose was real and the time was given.[3] An adequate clozapine trial is defined by a plasma level, not by the milligrams on the chart.[19]

03 Resistant schizophrenia and depression, side by side

The two resistances rhyme. Each is defined by failed adequate trials, each affects close to a third of treated patients, and each is climbed by optimise, switch, augment, specific. They part company at the specific step, and at one teaching point that decides much of practice: in schizophrenia the specific treatment, clozapine, comes before any combination; in depression, augmentation comes before the specific treatment, ECT. Hold the table below and most of the rest follows.

TABLE 2 **Treatment-resistant schizophrenia against treatment-resistant depression**

Dimension	Treatment-resistant schizophrenia	Treatment-resistant depression
Working definition	Persistent symptoms despite two adequate antipsychotic trials	Inadequate response to two adequate antidepressant trials, classically of different classes
Failed-trial threshold	2 antipsychotics, each 6+ weeks at adequate dose	2 antidepressants, each 6 to 8 weeks at adequate dose
Adequacy proof	Adherence plus, ideally, a plasma level	Adherence plus a confirmed diagnosis
Consensus source	TRRIP 2017 criteria[3]	Staging models; no single agreed definition[1,2]
First specific treatment	Clozapine, before any combination	Augmentation first, then ECT and neuromodulation
Approximate frequency	About a third of schizophrenia[5,16]	About a third of treated depression[8,10]
The commonest trap	Deferring clozapine for more antipsychotics	Calling an inadequate trial a resistant illness

HOW TO READ THIS Read each row straight across the two columns. They agree on every row until First specific treatment, where they cross: clozapine before any combination in schizophrenia, augmentation before ECT in depression.

Both columns begin in the same place: the pseudoresistance gate on the previous page. The dimensions diverge only once true resistance is established.

WHAT THE TABLE IS TELLING YOU

- **Three things rhyme.** Both resistances are defined by failed adequate trials, both affect about a third of patients, and both are climbed by the same four tiers: optimise, switch, augment, specific.
- **One thing differs, and it matters most.** Schizophrenia reaches its specific treatment, clozapine, before any combination; depression augments first and reaches its specific treatment, ECT, only at the top of the climb.
- **Both share one entry condition.** Neither column is entered until pseudoresistance has been excluded. The label is earned, not assumed.

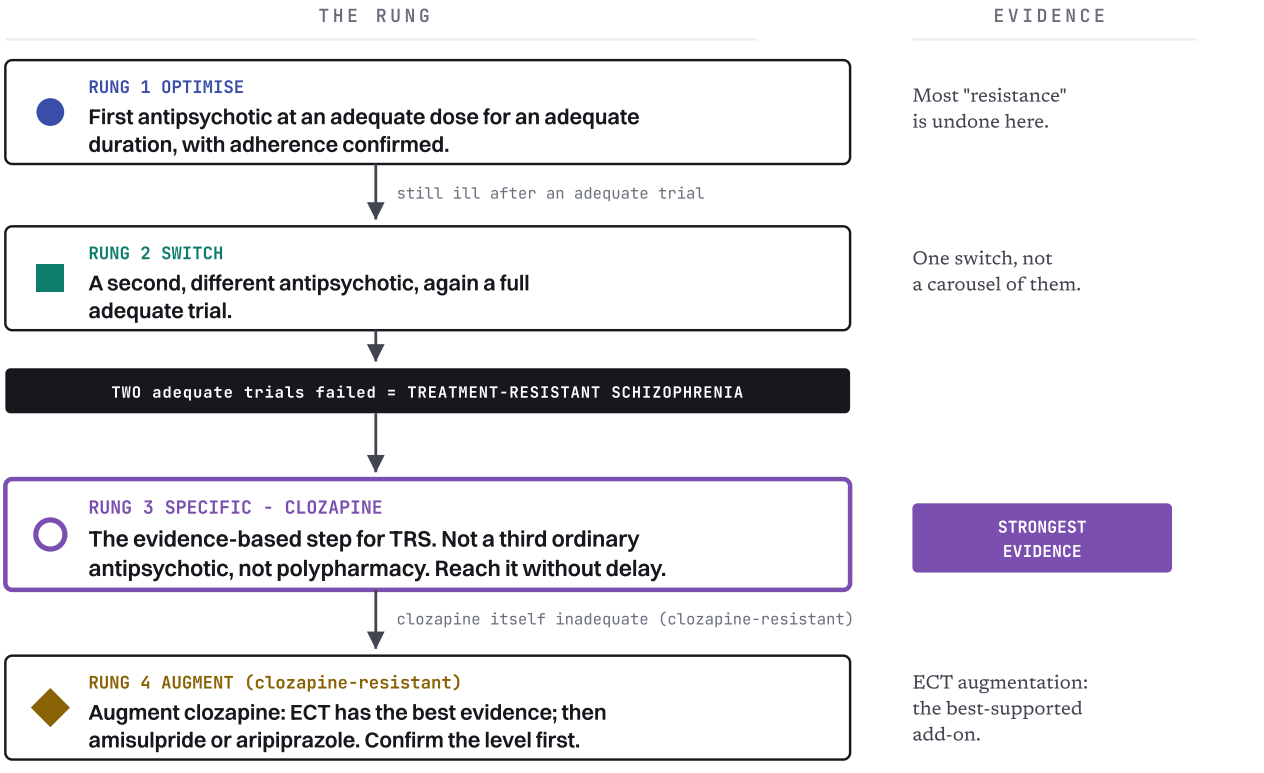
04 The staircase to clozapine

Once two adequate antipsychotic trials have failed, the schizophrenia ladder has a single evidence-based next rung, and it is not a third ordinary antipsychotic. Clozapine is the only antipsychotic with demonstrated superiority in resistant illness. Kane's 1988 trial showed it where chlorpromazine failed;[4] a meta-analysis confirms superiority on positive, total and negative symptoms with a number needed to treat of nine;[15] and in the CATIE comparison it kept patients in treatment for a median of 10.5 months against around three months for a switch to another atypical.[17] Yet it responds in only about 40 percent of those who reach it, which defines the clozapine-resistant minority beyond.[16]

The scandal is the delay. Clozapine is started, on average, almost four years late, after a mean of multiple antipsychotic trials and a stretch of high-dose and combination prescribing that the evidence does not support.[18] The ladder below puts clozapine where it belongs: at rung three, before augmentation, not after a carousel of alternatives.

AT THE BEDSIDE

A man with schizophrenia has failed two antipsychotics, each six weeks at an adequate dose, with adherence confirmed. The next rung is not a third antipsychotic but clozapine: a number needed to treat of nine for response,[15] and in CATIE it held patients in treatment a median of 10.5 months against around three months for a switch to another atypical.[17] Reach it now, not after the average near-four-year delay.[18]



Every rung is gated by an ADEQUATE TRIAL: right dose, right duration, adherence confirmed. Skip the gate and you manufacture false res
Clozapine is reached at rung 3, BEFORE any antipsychotic combination - the order most often got wrong.

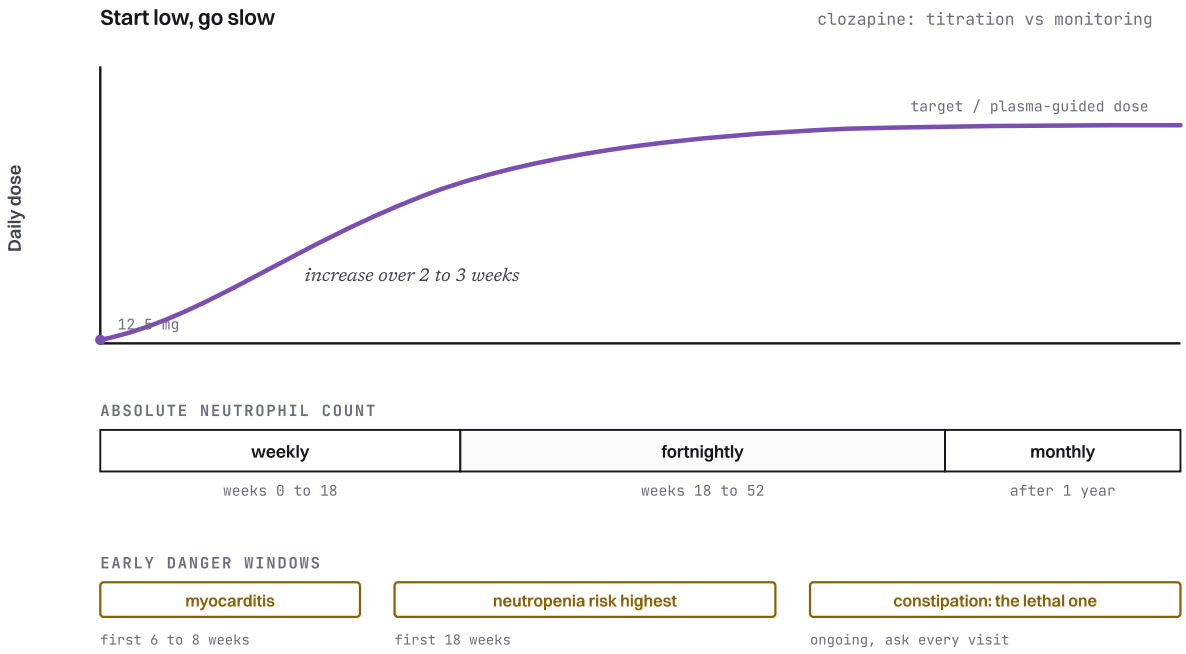
HOW TO READ THIS Climb rung by rung; every rung is gated by an adequate trial (right dose, right duration, adherence confirmed). Two failed adequate trials define resistance and place clozapine at rung three, before any combination, not after a carousel of antipsychotics.

05 Clozapine: the pathway and the monitoring

START LOW, GO SLOW, MEASURE

Clozapine earns its place by working where nothing else does, and it demands a discipline no other antipsychotic asks for. Two numbers govern the start. The titration is slow, from 12.5 mg upward over two to three weeks, because the most dangerous early reactions track a fast rise. And the trial is not adequate until a trough plasma level has reached about 350 ng/mL: Perry's threshold separated responders from non-responders, with 64 percent responding above it against 22 percent below.[19] A patient is not clozapine-resistant until the level, not just the dose, has been pushed and held.[20]

FIGURE 2 **The slow climb against the watch**



Schedule shown is the common pattern; confirm against the product information and local practice. Stop and recheck on any fever or sore throat.

HOW TO READ THIS The violet curve is the slow dose climb. Below it, on the same weeks axis, sits the neutrophil-count schedule, and beneath that the early danger windows. Read all three against the timeline, not against each other.

QUICK CHECK

What makes a clozapine trial adequate, the dose or the level?

A The trough level. Perry separated responders from non-responders near 350 ng/mL, with 64 percent responding above it against 22 percent below; a patient is not clozapine-resistant until the level, not the dose, has been pushed and held.[19]

The monitoring exists because clozapine can kill quietly. The classic hazard is agranulocytosis, but it is not the commonest fatal one. The next page sets out what to watch, and when.

TABLE 3 **Clozapine: the hazards and their monitoring**

Hazard	When	What to do
Agranulocytosis	Risk highest in the first 3 months	Absolute neutrophil count: weekly to week 18, then fortnightly to a year, then monthly. Stop on severe neutropenia.[21]
Myocarditis	First 6 to 8 weeks	Baseline and serial troponin and C-reactive protein; watch for tachycardia, fever, chest symptoms. Stop and investigate on suspicion.[22]
GI hypomotility	Ongoing; higher case fatality than agranulocytosis	Ask about bowels at every visit; prophylactic laxatives. More lethal once it occurs than agranulocytosis, and far less monitored.[23,24]
Seizures	Dose and rate related	Slow titration; consider valproate cover or a dose reduction at high plasma levels.[25]
Sialorrhoea, sedation	Early and persistent	Common, adherence-limiting; manage by dose timing, then targeted agents.[26]
Metabolic	Months to years	Among the most effective antipsychotics, but with a heavy metabolic and sedative load; monitor weight, glucose, lipids.[27]
Smoking change	Any change in tobacco use	Tobacco induces CYP1A2; stopping smoking, including admission to a smoke-free ward, can raise levels into toxicity. Review the dose and the level.[28]

Bowel

Not the marrow. Clozapine gastrointestinal hypomotility carries a higher case fatality than the agranulocytosis everyone monitors for: more lethal once it occurs, affecting a majority of patients to some degree, yet understated many-fold in the labelling. Ask about the bowels at every visit.[23,24]

SAFETY

The slow gut is the one that kills

The danger clinicians remember is the white cell count; the danger that more often kills is the bowel. Clozapine-induced gastrointestinal hypomotility carries a higher case fatality than agranulocytosis, affects a majority of patients to some degree, and is understated many-fold in prescribing information.[23,24] Ask about constipation at every single visit, prescribe a laxative early, and treat a quiet abdomen as an emergency, not a nuisance. In India, where there is no centralised clozapine registry on the model of the UK or US schemes, the haematological monitoring and the bowel vigilance both fall to the prescriber rather than a system, which makes the discipline more important, not less.[29,30]

When clozapine is not enough

About 40 percent of patients respond to clozapine, which leaves a substantial minority who do not, even at an adequate plasma level held long enough.[16] This is clozapine-resistant, or ultra-resistant, schizophrenia, and the evidence here is thin and the gains modest. Augment, do not abandon, and confirm the level is genuinely adequate before adding anything.

AUGMENTING CLOZAPINE, BY STRENGTH OF EVIDENCE

1. **ECT has the best evidence.** In the one randomised trial, half of clozapine-resistant patients responded to bilateral ECT added to clozapine, against none on clozapine alone, with no meaningful cognitive cost over the course.[31]

2. **Pharmacological add-ons are weaker.** A meta-analysis of clozapine augmentation finds only modest support, with aripiprazole, fluoxetine, sodium valproate and memantine among the better-studied options for particular symptom domains.[32]

3. **Amisulpride and aripiprazole, with realistic expectations.** Amisulpride augmentation gave only a non-significant gain at the cost of more side effects;[33] aripiprazole did not improve total symptoms but reduced negative symptoms and improved the metabolic profile, which is reason enough to use it in the right patient.[34]

BEFORE YOU CONCLUDE

Is the clozapine trial really adequate?

Clozapine-resistant is a high bar, and most apparent clozapine failure is, once again, an inadequate trial. Before augmenting or abandoning, confirm the four things that make the trial real: a measured trough level at or above 350 ng/mL, not the dose alone; adherence corroborated; enough time, up to six months at a therapeutic level; and the dose optimised against tolerability. Only then is the word resistant earned a second time.

QUICK CHECK

Clozapine has been pushed to an adequate trough level and held, and the patient is still ill. What has the best evidence to add?

A ECT. In the one randomised trial, about half of clozapine-resistant patients responded to bilateral ECT added to clozapine, against none on clozapine alone, with no meaningful cognitive cost.[31]

That is the schizophrenia ladder, end to end: optimise, switch, clozapine, then augment clozapine, with the specific treatment reached early rather than late. Depression climbs the same four tiers, but it reorders the top two. There, the patient meets augmentation before they meet the specific treatment, and the staging is dimensional rather than a single line crossed.

06 Resistant depression: the staged climb

STAGING

Depression resists by degrees rather than at a single threshold, which is why it is staged rather than simply labelled. STAR*D gave the real-world shape of the problem: remission fell at every step, from about 37 percent at the first treatment to 31, 14 and 13 percent across the next three, and relapse rose with each step required, so that after four sequential treatments roughly a third of patients had still not remitted.[10] The staging models put numbers on that descent. Each failed adequate trial raises the stage, and the higher the stage, the lower the odds the next step will work, which is the empirical core of taking the first failure seriously. The Indian Psychiatric Society guidelines frame the same staged approach for local practice.[45]

TABLE 4 **Three ways to stage resistant depression**

Model	What it counts	Output	Use
Thase & Rush 1997	Failed trials by type, escalating to MAOI then ECT	Five ordered stages	Simple, sequence-based[11]
MGH staging	Number of failed trials, with increments for optimisation and ECT	A continuous score	Dimensional, additive[9]
Maudsley (MSM)	Treatment failures plus episode duration and symptom severity	Score 3 to 15	Predicts longer-term outcome[12,55]

37 / 31 / 14 / 13%

Remission at each STAR*D step. The descent across four sequential treatments is the empirical reason the first failure must be taken seriously: after four steps, about a third of patients have still not remitted.[10]

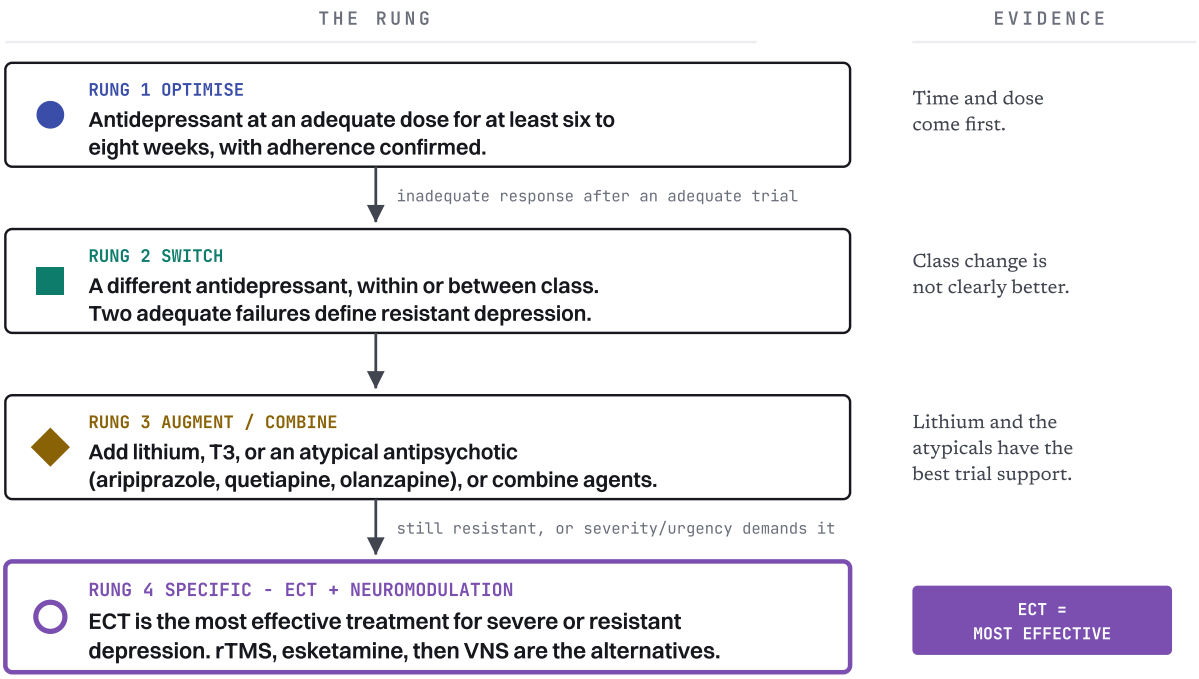
The Thase-Rush model ranks the kind of treatment failed; the Maudsley method scores how ill, how long, and how many failures,[13] and predicts the course better than a binary cut.[55]

WHAT STAGING BUYS YOU

1. **It grades, rather than labels.** Resistance is a slope, not a cliff. A dimensional score separates the patient who has failed two trials from the one who has failed five, where a single resistant or not loses that information.
2. **It predicts the course.** Higher stages carry lower odds of remission and longer episodes, which is why the Maudsley score forecasts outcome better than a yes-or-no cut.
3. **It calibrates intensity.** The further up the stage, the sooner augmentation and the specific treatments earn their place over yet another switch.

The figure overleaf turns the staging into the same four-tier climb, reordered for depression.

Optimise, switch, augment, then ECT



Each failed adequate trial raises the stage (the Maudsley Staging Method scores both the number of failures and the severity). Contrast with schizophrenia: in depression AUGMENTATION precedes the specific step; in schizophrenia CLOZAPINE precedes it.

HOW TO READ THIS The same four rungs as schizophrenia, but the top two swap: augmentation comes at rung three, before the specific step, ECT, at rung four. In schizophrenia clozapine precedes augmentation; in depression augmentation precedes ECT.

TABLE 5 **Switch and augment options in resistant depression**

Strategy	Evidence	In practice
Switch	STAR*D level 2: about 1 in 4 remit, within or between class, with no clear winner[35]	Reasonable after one failure; not clearly better than augmenting
Lithium	Augmentation odds ratio 3.11 over placebo across 10 trials[36,37]	Best-evidenced augmentation; needs level monitoring
T3 (liothyronine)	Comparable to lithium in STAR*D, better tolerated; older meta-analysis supportive[38,39]	Accessible and cheap; a good first augmentation in India
Atypical antipsychotic	Class remission odds ratio 2.00; aripiprazole, quetiapine XR, olanzapine-fluoxetine all positive[40,41,42,43]	Effective; weigh the metabolic and akathisia cost
Esketamine	Added to a new antidepressant, separates from placebo at day 28[44]	Rapid but supervised; limited access in India (see Aporia 07)

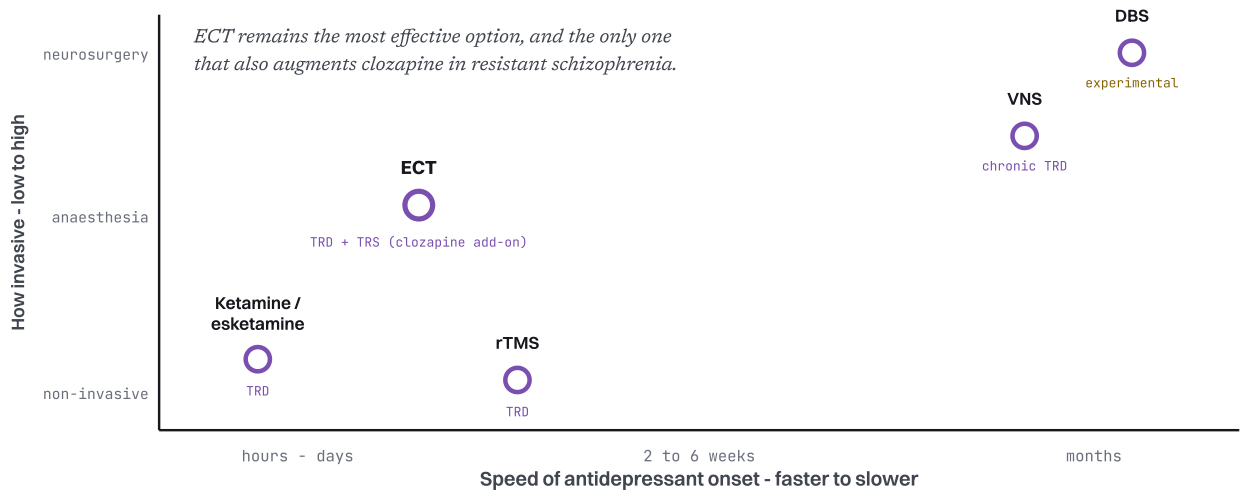
07 When drugs are not enough

Beyond the drugs sit the physical treatments, and they share the top of both ladders. ECT is the workhorse and the strongest of all: more effective than simulated ECT and than pharmacotherapy in the landmark meta-analysis, and the one neuromodulation that also augments clozapine in resistant schizophrenia.[46,31] The rest are options for depression. They differ less in whether they work than in how fast, and how invasive they are, which is what the map below plots.

THE OPTIONS, HONESTLY GRADED

- **rTMS.** An established, guideline-endorsed option for resistant depression: in the pivotal trial roughly twice the remission of sham with few dropouts, and a meta-analysis of 29 trials puts response at 29 against 10 percent for sham.[47,48]
- **Ketamine.** A single infusion lifts mood within hours: up to 71 percent responding by the next day in the early placebo-controlled trial, and 64 percent against an active midazolam control. The effect is real but short, and maintenance is the open question.[49,50]
- **VNS.** A long game, not an acute one. The acute trial was negative on its primary outcome; the case rests on five-year registry data showing higher cumulative response than treatment as usual.[51,52]
- **DBS.** Still experimental. Early open-label work was promising, but the controlled subcallosal-cingulate trial was stopped for futility, so it remains a research treatment, not a clinical one.[53,54]

FIGURE 3 **Onset against invasiveness**



HOW TO READ THIS Left to right is speed of onset (ketamine fastest, VNS slowest); bottom to top is how invasive each is (non-invasive rTMS low, neurosurgical DBS high). ECT sits mid-onset and mid-invasive, and is the only node that also augments clozapine in resistant schizophrenia.

In Indian practice ECT is the accessible workhorse for both resistant depression and as a clozapine add-on; rTMS is increasingly available in urban centres; ketamine is used off-label in some academic settings; VNS and DBS for depression remain effectively research-only.

08 Three ways to get it wrong

PITFALLS

Calling pseudoresistance resistance. The first and commonest error is to escalate against a trial that was never adequate. An underdose, a six-day course mistaken for a six-week one, a drug the patient quietly stopped: each looks like resistance and is not. Every rung of either ladder is gated by the same five checks, and skipping them does not just waste a step, it manufactures a resistant patient out of an undertreated one. The cost is real: more drugs, more harm, and a label that follows the patient.

Deferring clozapine for more antipsychotics. In schizophrenia the specific treatment is reached too late, on average by almost four years, after high-dose and combination prescribing the evidence does not support.[18] Clozapine is rung three, before augmentation, not a last resort after every other atypical has been tried in turn. A second ordinary antipsychotic that fails its adequate trial is the signal to move to clozapine, not to add a third.

Stopping the specific treatment short. A clozapine trial is not adequate until the plasma level has reached about 350 ng/mL and held; stopping on the dose alone, without a level, declares a failure that may not exist.[19] The mirror error in depression is to abandon a strategy before an adequate trial, or to read the steep fall in remission at higher stages as a reason to stop climbing rather than as the reason to reach for ECT.

AT THE BEDSIDE

A patient is referred as clozapine-resistant. They have been on 400 mg for four weeks; no trough level was ever drawn, and two ordinary antipsychotics were run together before clozapine was reached. Two of the three errors are already in play: the specific treatment came late, after combination prescribing,[18] and failure is being declared on the dose, not on a level held long enough.[19] The next step is not a new drug. Draw the level, optimise to a trough at or above 350 ng/mL, and give it time before the word resistant is earned a second time.

QUICK CHECK

Two adequate antipsychotic trials have failed. Is the next step a third antipsychotic, or clozapine?

A Clozapine, at rung three, before any combination. Deferring it for more antipsychotics is the commonest error in schizophrenia, and the average delay to clozapine is almost four years.[18]

HOLD THIS

The order is the lesson

Both disorders climb optimise, switch, augment, specific. Schizophrenia reaches its specific treatment, clozapine, at the third rung, before any combination. Depression augments at the third rung and reaches its specific treatment, ECT, at the fourth. Get the order right, gate every rung with an adequate trial, and most of resistance management is already done.

09 Before you escalate

THE TAKEAWAYS

Treatment resistance is, before anything else, a claim that needs checking. Most of the value in managing it lies in two moves: proving the resistance is real, and then climbing in the right order for the disorder in front of you.

WHAT THIS ISSUE COMES DOWN TO

1. **Resistance is what remains after an adequate trial.** Exclude pseudoresistance first: dose, duration, adherence, diagnosis, confounders. A failed trial is more often a failure of the trial than of the patient.
2. **About a third of each illness is genuinely resistant.** The frequency is similar in schizophrenia and depression, and so is the four-tier climb: optimise, switch, augment, specific.
3. **In schizophrenia, clozapine comes before combination.** After two adequate antipsychotic trials, clozapine is the evidence-based step, reached at rung three, not deferred for polypharmacy. Its adequacy is a plasma level, not a dose.
4. **In depression, augment before the specific step.** Lithium, T3 and the atypicals carry the augmentation evidence; ECT is the most effective treatment and the top rung. The order is the opposite of schizophrenia, and that is the point to remember.

REMEMBER

DOSE · DURATION · ADHERENCE · DIAGNOSIS · CONFOUNDERS

Clear all five gates before the word resistant is earned. Most apparent resistance is one of these five, not a resistant illness, and the commonest is a trial that was never adequate.

BEDSIDE CHECK

When a treatment has not worked

01 Was the trial adequate: right dose, right duration, actually taken? If not, this is pseudoresistance, not resistance.

02 Is the diagnosis still right, and are substances, interactions or rapid metabolism keeping levels low?

03 In schizophrenia, after two adequate trials, have I moved to clozapine rather than a third antipsychotic, and checked a level before calling it a failure?

04 In depression, have I climbed optimise to switch to augment, and considered ECT for the severe or the resistant rather than another drug?

05 If I am about to add a third agent, would the evidence not point instead to the specific treatment for this disorder?

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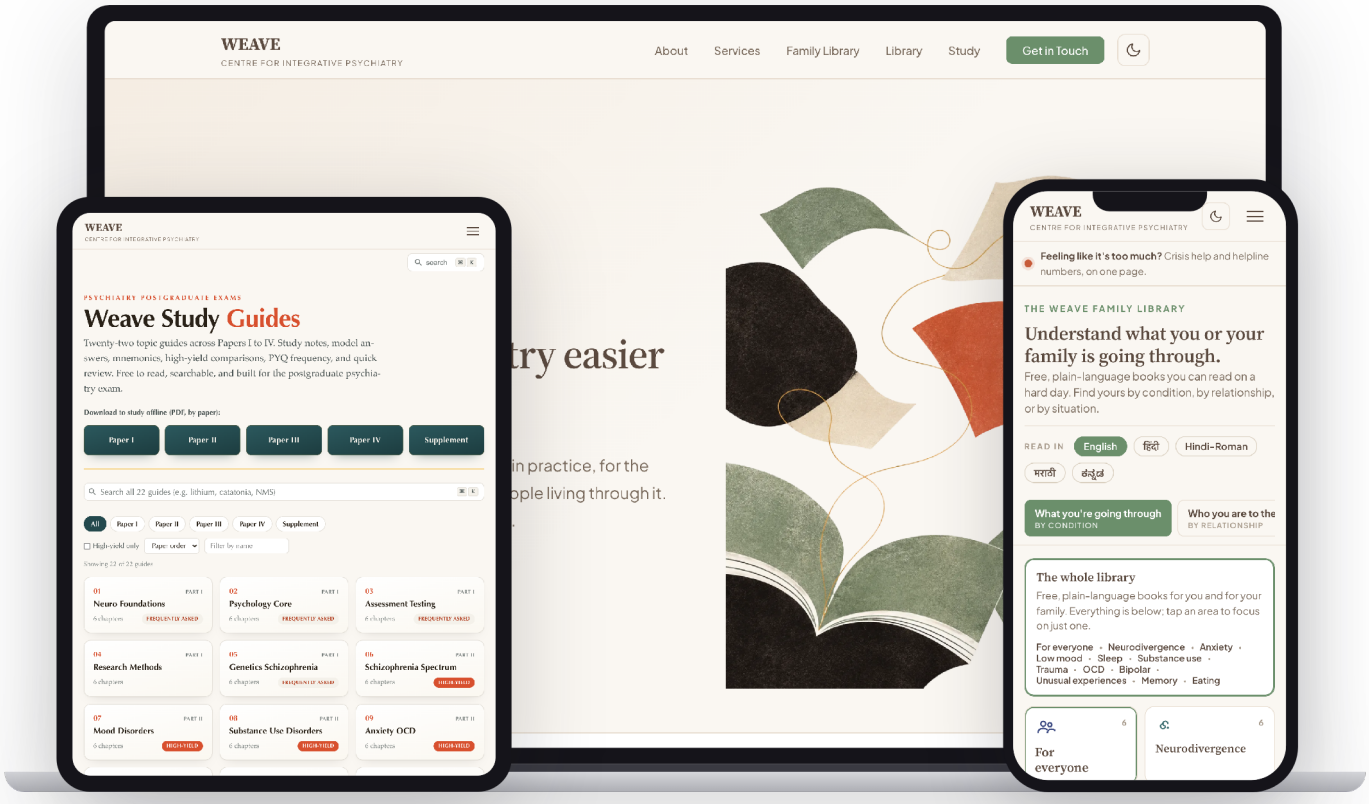

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