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Review

Pharmacological Strategies for Treatment-Resistant Depression: Integrating Novel and Traditional Approaches with Psychopathological Insights

Mario Pinzi, Alessandro Cuomo, Maria Beatrice Rescalli, Caterina Pierini, Luigi Morelli, Andrea Fagiolini

Department of Molecular Medicine, School of Medicine, University of Siena, Siena, Italy

SUMMARY

Background

Treatment-resistant depression (TRD), commonly defined as the failure to achieve adequate response after at least two appropriate antidepressant trials, represents a critical clinical condition in which standard diagnostic categories and stepwise treatment algorithms repeatedly fail; this operational definition itself exposes the limits of uniform models of depression, revealing it as an intrinsically heterogeneous condition composed of distinct depressive configurations rather than a single clinical entity.

Objectives

To propose an integrated framework for TRD that combines classical psychopathology, contemporary neurobiological domains, and established as well as emerging therapeutic strategies, in order to improve treatment matching in resistant cases.

Methods

Narrative and critical synthesis of European phenomenological psychopathology, dimensional neurobiological models, and clinical evidence on traditional, rapid-acting, and experimental treatments for TRD, interpreted through a domain-based approach.

Results

TRD emerges as the variable predominance of distinct symptom domains (e.g., anhedonic, anxious–arousal, cognitive, circadian, inflammatory-like), each associated with specific patterns of treatment response. Apparent resistance often reflects a mismatch between depressive form and therapeutic target, while a subset of patients may show genuine refractoriness. When aligned with the dominant domain, interventions such as ketamine and esketamine, dextromethorphan–bupropion, neuromodulation techniques (TMS, ECT), and emerging plasticity-oriented strategies – including psychedelic compounds and non-hallucinogenic psychoplastogens – acquire clearer clinical meaning.

Conclusions

TRD should be conceptualized as a qualitative configuration rather than a quantitative failure. Integrating psychopathological insight with domain-based neurobiology supports a personalized use of traditional treatments, rapid-acting glutamatergic agents, multimodal interventions, and experimental plasticity-enhancing therapies, offering a coherent framework for managing resistant depression.

Key words: Treatment-resistant depression; Depressive phenotypes; Psychopathology; Domain-based approach; Glutamatergic antidepressants; Personalized psychiatry

Mario Pinzi
E-mail: mario.pinzi@student.unisi.it

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Introduction

Treatment-resistant depression (TRD) represents one of the most complex challenges in contemporary psychiatry [1,2]. The technical–operational definition based on the lack of benefit from two adequate antidepressant treatments – first formulated by Thase and Rush in *Stages of Treatment-*

Resistant Depression (1997) – is useful in both clinical practice and research, yet it remains insufficient to capture the full depth of the clinical phenomenon [3]. Reducing TRD to the failure of successive pharmacological trials risks obscuring a fundamental point already intuited by classical psychopathology: resistance is not merely a pharmacological event but a psychopathological datum, the expression of depressive states with distinct internal structures, trajectories, and logics. Over the past decade, numerous studies have confirmed that depression is not a monolithic entity but a heterogeneous constellation of conditions emerging from the interplay of personality traits, affective patterns, temporal alterations of lived experience, and biological vulnerabilities [4–6]. This heterogeneity explains why some clinical presentations respond readily to standard treatments, while others persist despite multiple therapeutic strategies [1]. Understanding TRD therefore requires acknowledging that resistance arises from distinct depressive phenotypes, many of which were already described in twentieth-century European psychopathology: Jaspers' concept of vital tone (*Vitalgefühl*) (Allgemeine Psychopathologie, 1913), Minkowski's phenomenology of lived time (*Le temps vécu*, 1933), Binswanger's narrowing of the lived world (*Verengung der Welt*) (Melancholie und Manie, 1960), and Tellenbach's rigid *Typus melancholicus* (1961).

The approach proposed in this article builds on this awareness: addressing treatment-resistant depression requires integrating psychopathological insight – capable of grasping modes of lived experience and affective functioning – with both traditional and innovative pharmacological strategies that act on distinct biological systems. Such integration reflects a contemporary tendency in psychiatry, exemplified by dimensional and neurobiological models such as Research Domain Criteria (RDoC), which recognize that disorders do not arise from a single mechanism but from interactions across multiple domains (affective, cognitive, rhythmic, motivational) [7]. TRD thus becomes not only a field of therapeutic intervention but also a meeting point between different schools of thought: Kraepelinian descriptive nosography, European phenomenology, the neuroscience of synaptic plasticity, circadian models, and emerging glutamatergic treatments [8–10].

The aim of this work is to offer a clinical–phenomenological reading of TRD that clarifies the variety of its phenotypes and, on this basis, provides a reasoned review of the available therapeutic strategies. Integrating psychopathology and pharmacology – far from being a purely theoretical exercise – has become a clinical necessity: only by recognizing differences in the structure of depressive experience can we more precisely guide the use of traditional treatments, novel glutamatergic interventions, circadian therapies, and somatic approaches such as TMS and ECT.

Evolution of depressive models and phenotypes: from early conceptualizations to contemporary complexity

Treatment-resistant depression can only be understood by recognizing that what we call "depression" has never been, in the history of psychopathology, a unitary phenomenon. The various schools of the twentieth century described different ways of *living* depression, each corresponding to specific clinical forms, with distinct courses, meanings, and therapeutic responses. Revisiting these perspectives is not an erudite exercise, but the most direct way to grasp the diversity of depressive phenotypes that today shape treatment outcomes.

In the nineteenth century, European psychiatry laid the foundations for a fundamental distinction between "internal" depressive forms and those more clearly linked to contextual factors. Esquirol conceived depression as a narrowing of affective life, an impoverishment of emotional resonance with the world [11]. Griesinger, by contrast, emphasized the somatic underpinnings of melancholia, proposing a biological model for its most severe manifestations [12]. This tension between psychogenic and organogenic explanations prepared the ground for the major synthesis of the early twentieth century.

With Kraepelin, a central figure of German descriptive psychiatry, depression acquired a clinical architecture capable of distinguishing true forms rather than mere variations of a single condition. Through systematic observation of the course of illness, Kraepelin identified depressions dominated by psychomotor slowing – with inhibition of thought, anergia, and affective impoverishment – and others marked by internal agitation, anxiety, and restlessness [13]. He described severe melancholias characterized by loss of affective resonance, recurrent patterns foreshadowing bipolar disorder, and cyclical variants with pronounced seasonality. These descriptions constitute clinical depressive phenotypes, each with its own trajectory and prognosis. In this sense, Kraepelin anticipated the logic of contemporary diagnostic specifiers: distinguishing between retarded, agitated, melancholic, or mixed depressions means acknowledging the plurality of depressive forms, each already showing markedly different treatment responses – thus prefiguring today's problem of treatment resistance.

During the same period, European phenomenology reframed the understanding of depression, examining it not as a collection of symptoms but as a transformation of lived experience. Jaspers introduced the notion of *vital tone*, showing how depression impoverishes

inner energy and one's orientation toward the world [14]. Minkowski identified the slowing of subjective time as a core feature of suffering: inner temporality becomes heavy, and the future loses substance [15]. Binswanger, through *Daseinsanalyse*, interpreted depression as a constriction of the world and of one's existential possibilities [16]. In these accounts, depression appears as a transformation of the overall form of existence, helping explain the persistence of many clinical pictures.

Anthropological psychopathology, developed primarily in the Heidelberg tradition, added further layers of complexity. Authors such as von Gebsattel, Straus, and above all Tellenbach demonstrated how certain depressions arise from rigid existential styles, inflexible value systems, or temperamentally rooted predispositions [17]. Tellenbach's *Typus melancholicus* – characterized by orderliness, scrupulousness, and hyper-responsibility – constitutes a premorbid model predisposing individuals to recurrent and difficult-to-modify depressions [18].

The second half of the twentieth century witnessed the rise of biological psychiatry, which unified depression under the monoaminergic paradigm. The discovery of antidepressants marked a decisive advance but also revealed profound heterogeneity in response: some forms improved rapidly, while others showed little to no benefit [19]. TRD arises precisely from this discrepancy between a uniform therapeutic model and an intrinsically heterogeneous clinical reality.

The DSM-5-TR represents the categorical outcome of this evolution [20]. Although adopting an atheoretical and symptom-based approach, it introduces specifiers – such as melancholic features, anxious distress, or mixed features – that attempt to capture qualitative dimensions long recognized in the European tradition. Yet what phenomenologists described as entire forms of lived experience is reduced in the DSM to clusters of criteria: a useful and necessary model, but a simplified one.

Biological domains in treatment-resistant depression

While Jaspers spoke of alterations in "vital tone," Minkowski of distortions in lived time, and Kraepelin distinguished between retarded, agitated, and melancholic forms, current research demonstrates that these clinical configurations correspond to distinct biological domains, each with its own trajectories and therapeutic sensitivities.

The first domain to be conceptualized in biological psychiatry was the monoaminergic system, particularly serotonergic and noradrenergic pathways. The classical model of depression as hypofunction of these systems enabled the development of antidepressants that still constitute the cornerstone of treatment [19]. In less structured, more reactive depressive forms – those with preserved affective and cognitive flexibility – serotonergic modulation is often sufficient to restore a balance between mood, anxiety, and impulse regulation. However, the observation that many patients fail to respond to repeated trials of predominantly serotonergic agents has made it evident that, in numerous cases of treatment resistance, the primary issue no longer lies (or not exclusively lies) within this domain [1,21]. Rather, other neurobiological systems – more fundamentally involved in plasticity, reward processing, inflammation, or circadian regulation – appear to play a determining role.

One of the most extensively studied domains is inflammation. It is now clear that a subset of patients with treatment-resistant depression exhibit elevated levels of pro-inflammatory markers such as CRP and IL-6, associated with clinical profiles characterized by anergia, psychomotor slowing, and loss of vitality [22–24]. This phenotype closely resembles classical descriptions of "hypometabolic" melancholia, in which the world appears dimmed and the body itself loses reactivity. Unsurprisingly, such forms respond poorly to serotonergic antidepressants and may benefit instead from immunomodulatory strategies or medications that act on more deeply embodied mechanisms.

Alongside this, the glutamatergic domain has opened a radically new therapeutic horizon. The discovery that ketamine can produce rapid improvement even in patients unresponsive to multiple previous treatments demonstrated that treatment-resistant depression cannot be understood solely in monoaminergic terms [25]. Alterations in glutamate signaling and synaptic plasticity, as described by Duman and Aghajanian, appear particularly relevant in depressive presentations marked by cognitive rigidity, ruminative fixation, and a sense of blocked possibility – forms that phenomenological psychopathology had long interpreted as a "closure" of the world and of thought [26,27]. In such cases, resistance is not simply a pharmacological issue but the manifestation of a depressive structure that has lost its capacity for self-remodeling.

Another crucial domain involves circadian rhythms. Genetic and physiological studies have shown that dysregulation of the CLOCK system, BMAL1, or PER genes is associated with depressive states characterized by morning worsening, sleep disturbances, and marked fluctuations in energy throughout the day [8]. This pattern echoes Kraepelinian melancholia, with its pronounced diurnal variation, and suggests that bodily temporality itself can become an obstacle to treatment [28]. Agents such as agomelatine and chronotherapeutic interventions demonstrate that certain resistant depressions respond only when the rhythmic structure of biological

and experiential life is targeted directly.
A distinct domain concerns reward and motivation. Patients who describe emotional emptiness, loss of initiative, and a dissociation between "knowing what I should do" and "feeling it as possible" often exhibit dysfunction within the mesolimbic dopaminergic system [29,30]. This biological dimension resonates with Bleuler's observations on affective impoverishment and Binswanger's accounts of a world that has been lost: these states involve not merely sadness but a weakening of motivational force, one that often renders classical antidepressants ineffective. Molecules such as bupropion are precisely positioned within this clinical space, restoring drive and the capacity to act where serotonin alone is insufficient – by modulating noradrenergic and dopaminergic systems more directly implicated in such psychopathological profiles.
A further level involves neuronal plasticity. Reduced BDNF levels and impaired synaptic remodeling have been observed in patients with more chronic and persistent depressive forms [31]. Once again, biology appears to mirror phenomenology: depressions experienced as a progressive narrowing of the world or a loss of the capacity for change find their neurobiological counterpart in the brain's diminished ability to form new connections. Somatic interventions such as TMS and ECT – and ketamine itself – enhance plasticity and thus respond directly to this biological and experiential need.
Finally, hyperactivation of the stress axis represents a key domain in depressions marked by agitation, somatic anxiety, middle insomnia, and ruminative thinking with a threatening tone. Excess cortisol and dysregulation of the HPA axis - well documented by Pariante and Lightman - clinically correspond to the forms Kraepelin described as "agitated," which are among the most challenging to treat, frequently misdiagnosed as resistant anxiety and often requiring strongly serotonergic antidepressants, and not infrequently adjunctive mood stabilizers or atypical antipsychotics to modulate the anxious–mixed component [32].
Within this interplay of biological domains and psychopathological forms, treatment-resistant depression may reflect both depressive conditions with intrinsic biological rigidity and, in many cases, an incomplete alignment between depressive configuration and therapeutic target – conditions in which biological organization and experiential structure mirror one another. These domains are not isolated components but interacting dimensions that overlap and sometimes reinforce each other, producing clinical configurations that demand targeted, non-interchangeable treatments.
Understanding these domains means recognizing what the history of psychopathology has suggested for more than a century: depression is not a single entity, and not all depressions resist treatment in the same way. It is in the correspondence between lived form and biological domain that the possibility of truly personalized therapy emerges today.

Therapeutic strategies for treatment-resistant depression: integrating tradition and innovation

According to current regulatory frameworks and major international clinical guidelines, the management of treatment-resistant depression is organized around a stepwise escalation that distinguishes standard pharmacological strategies from advanced interventions. At present, intranasal esketamine represents the only antidepressant to have received specific regulatory approval for treatment-resistant depression, on the basis of randomized controlled trials demonstrating efficacy in patients who have failed multiple adequately delivered antidepressant treatments [33]. In parallel, neuromodulatory approaches such as electroconvulsive therapy and repetitive transcranial magnetic stimulation – while not 'approved' as pharmacological agents – are formally recognized and recommended by authoritative clinical guidelines. [34].
Alongside these interventions, several augmentation strategies – most notably lithium and atypical antipsychotics – are consistently endorsed within guideline-based algorithms for major depressive disorder with inadequate response, despite the absence of specific regulatory approval for treatment-resistant depression per se [35]. Importantly, such recommendations are largely grounded in operational definitions of resistance based on the number of failed treatment trials, rather than on a qualitative assessment of the internal structure of depressive experience.
As a consequence, progression toward approved or guideline-supported interventions is often driven by treatment sequencing rather than by a systematic evaluation of whether prior pharmacological strategies were adequately aligned with the dominant psychopathological and biological configuration of the depressive episode. Within this perspective, the therapeutic armamentarium for treatment-resistant depression – ranging from optimization and switching to augmentation, neuromodulation, and novel glutamatergic or plasticity-oriented approaches – cannot be understood as a linear algorithm, but rather as a set of tools whose clinical meaning depends on the depressive form to which they are applied.

Optimization and Switching Logics

Studies such as STAR*D have shown how frequently non-response is related to insufficient dosing, treatment durations that are too short, poor adherence, or untreat-

ed comorbidities [1]. Optimization of dosage, duration of exposure to the drug, and management of side effects is therefore the initial step, especially in less structured clinical pictures, where depression still retains a degree of plasticity.

Once optimization has been adequate, the decision to switch should not be purely sequential. Certain clinical phenotypes strongly indicate the need to move from one pharmacodynamic profile to another. In forms with predominant psychomotor slowing, anergia, and ideational flattening – echoing Kraepelinian melancholia and "hypometabolic" profiles – it may be more coherent to replace a "pure" SSRI with agents that exert stronger noradrenergic or dopaminergic effects, such as venlafaxine, duloxetine, or bupropion. Conversely, in depressions with pronounced anxiety, irritability, and somatization – closer to agitated or mixed forms – switching to more sedative agents or compounds with intrinsic anxiolytic properties is often more aligned with the phenomenology of the episode. In this sense, switching is not merely changing molecules, but an attempt to realign the drug profile with the dominant phenomenology: to modulate the most misaligned domain – anxious arousal, anhedonia, psychomotor slowing, or rumination – rather than mechanically reiterating the same monoaminergic logic.

Pharmacogenetic and Pharmacokinetic Pseudo-Resistance in TRD

A significant proportion of patients classified as having treatment-resistant depression do not exhibit genuine neurobiological insensitivity to treatment, but rather pseudo-resistance related to pharmacokinetic factors [36]. Polymorphisms in enzymatic systems such as CYP2D6, CYP2C19, and CYP1A2 crucially influence plasma levels of numerous antidepressants, leading to functional underdosing in ultra-rapid metabolizers or toxic overexposure in poor metabolizers [37]. In such cases, non-response does not reflect failure of the neurobiological target, but inappropriate exposure to the drug.

The same holds for intestinal absorption, often compromised in patients with functional gastrointestinal disorders, chronic inflammation, or microbiota alterations – conditions that can substantially reduce the bioavailability of SSRIs and SNRIs. Observational studies indicate that the introduction of pharmacogenetics into TRD management can allow a "diagnostic reconversion" of a relevant proportion of cases initially labeled as resistant [38]. From this perspective, TRD does not always coincide with a "biologically refractory" depression, but may instead reflect pharmacologically inadequate treatment – once again confirming that resistance is never an abstract entity, but a situated clinical phenomenon.

Classical Augmentation and Somatic Interventions

When response remains partial, augmentation represents the next step. A phenotype-guided approach helps avoid a simple "trial-and-error" escalation. Despite the advent of new compounds, lithium remains one of the augmenting agents with the strongest evidence base, both for its antidepressant effect and for its capacity to reduce suicide risk [39]. From a psychopathological standpoint, it is particularly indicated in recurrent and cyclothymic forms, or in cases suggestive of a bipolar spectrum.

Atypical antipsychotics used in augmentation – particularly quetiapine, olanzapine, aripiprazole, and brexpiprazole – prove especially useful in phenotypes marked by rumination, marked anxiety, inner agitation, and middle insomnia [40]. These correspond to the depressions Eugen Bleuler described as "full" (*gefüllte Depressionen*), rich in mental content, repetitive thoughts, crowded ideation, and somatic hyperactivation, in contrast to "empty" depressions dominated by anergia and affective impoverishment. In such high-density psychomotor and ruminative forms, the capacity of atypicals to modulate dopamine, serotonin, and glutamate within fronto-limbic circuits offers a biological counterpart to the clinical need to dampen mental and bodily "noise".

Augmentation with T3 (liothyronine), though less common, has a well-established tradition, particularly in chronic, hypometabolic depressions and in recurrent forms in individuals – often women – with elements of subclinical thyroid vulnerability [41]. Here the logic is again psychopathological–biological: to intervene in presentations where psychomotor slowing, somatic fatigue, and poor responsiveness to environmental stimuli suggest involvement of energy metabolism. Alongside these major strategies, more targeted modulations can be employed, such as mirtazapine in cases with insomnia and weight loss, buspirone in forms with a strong anxious component, or modafinil in presentations with marked hypersomnia and anergia. Even in these cases, the aim is not to add medications indiscriminately, but to target the central psychopathological node, often corresponding to a specific neurobiological domain.

"Classical" somatic interventions – especially ECT and TMS – acquire a different meaning when viewed through the lens of phenotypes. Electroconvulsive therapy remains indispensable in profound melancholic states with stupor, marked psychomotor inhibition, delusions of guilt or ruin, as well as in situations of high suicide risk or refusal of food and fluids [34]. In such cases, depression appears as a true existential crisis, in which the world closes in and time stops.

Transcranial magnetic stimulation, by contrast, occupies an intermediate position. It is indicated in patients with treatment-resistant depression who retain reasonably

preserved cognitive functioning and present with slowing, anhedonia, and executive deficits, often associated with hypofunction of the dorsolateral prefrontal cortex [42]. In these cases, TMS interacts directly with the domain of synaptic plasticity: it does not act only on symptoms, but on the brain's capacity to reactivate circuits of initiative, attention, and emotional regulation that depression has progressively depleted. In both situations, what guides the choice is not merely the number of failed treatments, but the *type* of resistant depression: severe, psychotic melancholia with immediate life-threatening risk in the case of ECT; resistant but cognitively and executively preserved depression in the case of TMS.

New Strategies: Glutamate, Multimodality, and Specific Domains

Innovative therapies fit naturally into this framework because they act on domains that traditional treatments influence only indirectly. Ketamine has inaugurated a new era in TRD, demonstrating that depression can be rapidly modified through glutamatergic modulation and enhancement of synaptic plasticity [10]. Clinically, glutamatergic interventions appear particularly effective in phenotypes dominated by cognitive rigidity and repetitive ideation, obsessive rumination, a Minkowskian "block of possibilities", profound anhedonia, and loss of initiative. These are the "closed" depressions in which the world appears as a system without openings – experiential configurations phenomenology has described as loss of future or curvature/inflexion of the world.

Intranasal esketamine preserves this mechanism with a more practicable route of administration, allowing repeated interventions in outpatient settings and offering sequential modulation in highly refractory cases. The dextromethorphan–bupropion combination represents a further evolution, as it acts simultaneously on multiple domains: NMDA antagonism, sigma-1 agonism, dopaminergic and noradrenergic enhancement via bupropion, and CYP2D6 inhibition, which prolongs dextromethorphan's effect. Beyond NMDA antagonism, dextromethorphan exerts relevant antidepressant effects through sigma-1 receptor agonism, a mechanism shared with endogenous tryptamines such as N,N-dimethyltryptamine (DMT). Sigma-1 receptors function as intracellular chaperones regulating neuroplasticity, mitochondrial activity, and stress-response signaling, and have been implicated in rapid antidepressant effects independent of classical monoaminergic pathways [43]. Although DMT itself is not developed as a clinical antidepressant, its pharmacological profile has contributed to renewed interest in sigma-1–mediated mechanisms as modulators of plasticity and affective regulation, reinforcing the conceptual framework underlying multimodal agents such as dextromethorphan–bupropion [44].

Emerging and Experimental Pharmacological Strategies in Treatment-Resistant Depression

Recent advances in the pharmacological treatment of treatment-resistant depression (TRD) increasingly focus on compounds capable of rapidly enhancing synaptic plasticity and modulating dysfunctional neural circuits, beyond classical monoaminergic mechanisms [10].

Psychedelic compounds and 5-HT2A receptor agonists

Psychedelic compounds and their modern analogues exert antidepressant effects primarily through agonism of the serotonin 5-HT2A receptor, leading to downstream glutamatergic activation, increased cortical entropy, and activation of plasticity-related signaling pathways, including BDNF and mTOR [45]. Several compounds are currently under clinical development for major depressive disorder, including treatment-resistant populations. Bretisilocin (GM-2505) and luvesilocin (RE104/FT-104) are psilocybin-derived agents in phase 2 clinical trials, designed to preserve antidepressant efficacy while optimizing pharmacokinetic profiles and clinical feasibility [46]. LSD-derived compounds such as MM-120 have received breakthrough therapy designation for affective disorders, further supporting the relevance of this pharmacological class for TRD [47]. Despite promising rapid and sustained effects after limited dosing, these agents remain restricted to controlled clinical settings due to their perceptual and cognitive effects. The pharmacological model of psychedelic treatments implies limited dosing schedules and a temporally defined window of enhanced plasticity, which may facilitate the integration of psychotherapeutic interventions and contribute to the durability of antidepressant effects [48].

Non-hallucinogenic psychoplastogens

Non-hallucinogenic psychoplastogens represent an emerging class of investigational antidepressants designed to enhance synaptic plasticity without inducing psychedelic experiences. Pharmacodynamically, these compounds aim to engage plasticity-related intracellular signaling cascades, including BDNF–TrkB, mTOR, and AMPA-mediated pathways, while avoiding robust or sustained agonism at cortical 5-HT2A receptors, which is primarily responsible for hallucinogenic effects [49]. Preclinical agents such as DLX-159 and TN-001 have been described as serotonergic modulators capable of promoting downstream glutamatergic facilitation and synaptic remodeling, leading to increased dendritic complexity and synaptogenesis in animal models. Importantly, these effects occur without marked perceptual or cognitive alterations, resulting in rapid antidepressant-like responses in preclinical paradigms while preserving a non-psychedelic profile [50]. This pharmacological dissociation between plasticity enhance-

ment and hallucinogenic phenomenology defines the rationale of this class and supports its potential suitability for repeated dosing and outpatient administration in treatment-resistant depression.

Next-generation glutamatergic strategies

In parallel, ongoing research seeks to refine glutamatergic modulation beyond intravenous ketamine and intranasal esketamine. Investigational approaches include oral formulations and prodrugs of esketamine, as well as NMDA receptor modulators with improved pharmacokinetic and tolerability profiles [51]. These agents aim to preserve rapid antidepressant effects while reducing dissociative burden and expanding clinical accessibility. By directly enhancing synaptic plasticity and cortical network reactivity, next-generation glutamatergic compounds target core mechanisms implicated in TRD, particularly in patients who have failed multiple monoaminergic trials [25].

Inflammatory Depression and Immunomodulatory Strategies

Immunomodulatory strategies are increasingly being explored as potential targeted interventions in subsets of patients in whom inflammatory pathways appear particularly dysregulated. Evidence suggests that in depressive presentations characterized by psychomotor slowing, fatigability, anergia, prominent somatic symptoms, hyperphagia, or metacognitive deterioration, elevated inflammatory markers are more frequently observed [22]. In such profiles, adjunctive treatments such as COX-2 inhibitors, minocycline, or high-dose omega-3 fatty acids have shown signals of selective benefit in clinical studies. However, these findings have not yet translated into routine clinical practice and warrant careful patient selection and further investigation. Phenomenologically, these presentations resemble a "low," asthenic form of melancholia, marked by temporal slowing and a contraction of vital energy; within this framework, targeting inflammation may be conceptualized as modulating one of the potential somatic correlates of this depletion of vital tone.

Rational Antidepressant Combinations in TRD

Alongside augmentation strategies, the combination of antidepressants with complementary pharmacodynamic profiles is a widely used clinical practice in TRD, although less formalized in official algorithms. Unlike augmentation with mood stabilizers or antipsychotics, antidepressant combinations aim to broaden several psychopathological domains simultaneously: serotonin for anxiety and rumination; noradrenaline and dopamine for energy, initiative, and executive functioning. Among the most studied combinations are SSRI + bupropion, particularly effective in anhedonic and apathetic presentations, and SNRI + mirtazapine, known as "California Rocket Fuel", indicated in severe depressions with insomnia, weight loss, and marked slowing [52].

Weak Strategies and Therapeutic Impasses in TRD

Alongside validated strategies, real-world management of TRD includes numerous off-label attempts supported by fragile theoretical rationales. Memantine, despite being grounded in a glutamatergic hypothesis, has yielded heterogeneous and often disappointing results in trials on resistant depression, with effects that are more cognitive than genuinely antidepressant [9]. Prolonged use of benzodiazepines – frequently adopted in anxious TRD – is associated with worsening anergia, reduced attention, and diminished antidepressant response in the long term, in addition to dependence and tolerance [53]. Likewise, the non-selective use of sedative antipsychotics may stabilize a "switched-off" depression without truly modifying its internal structure. A genuinely personalized reading of TRD therefore requires not only choosing the right treatment, but also recognizing those strategies which, although theoretically seductive, risk crystallizing resistance rather than resolving it.

TRD and Suicide Risk: A Specific Therapeutic Domain

The presence of persistent suicidal ideation in TRD defines a distinct clinical subgroup, in which the goal of treatment is not only antidepressant but explicitly *vital-protective*. Lithium remains the only drug with consistent evidence for reducing long-term suicide risk in both bipolar and unipolar mood disorders [54].

Ketamine and esketamine, in turn, show a rapid effect on suicidal ideation independent of overall mood improvement, and thus can be considered urgent neurobiological interventions. ECT, finally, maintains the most powerful global anti-suicidal effect in profound melancholias with psychomotor blockage, delusions of guilt, and immediate life-threatening risk [55,56]. In this domain, TRD cannot be managed according to gradual algorithms: therapeutic choice is guided by the need to preserve life even before improving symptoms and therefore assumes an ethical as well as a clinical significance.

Closing Synthesis: Resistance as Refractoriness and Misalignment

Within this framework, it becomes crucial to distinguish between genuinely treatment-resistant depressions and forms of apparent resistance arising from inadequate alignment between depressive configuration and therapeutic target. In cases of true treatment resistance, currently available interventions converge on a limited set of strategies, including glutamatergic modulation with ketamine or esketamine and electroconvulsive therapy, which remain among the most robustly supported op-

tions for patients who have failed multiple adequately delivered treatments [25 34].

By contrast, a substantial proportion of depressive presentations labelled as 'treatment-resistant' reflect a pseudo-resistance driven by failure to recognize the dominant psychopathological dimension and the neurobiological system most critically involved. In these cases, non-response does not indicate true refractoriness, but rather insufficient matching between depressive form, pharmacodynamic target, and treatment intensity [6].

From this perspective, effective pharmacological intervention requires identifying prevailing clinical domain. Serotonergic dysregulation is primarily associated with impaired emotional modulation, heightened anxiety, reduced inner relaxation, and diminished subjective well-being; noradrenergic dysfunction more closely relates to anergia, psychomotor slowing, impaired initiative, and reduced capacity to mobilize effort; while dopaminergic deficits underlie disturbances of motivation, reward processing, and goal-directed behavior [57]. Antidepressants are therefore not interchangeable, and both pharmacodynamic profile and dosage represent critical clinical variables influencing response [58].

Careful alignment between psychopathological configuration and monoaminergic target allows domain-informed pharmacological matching. Within this framework, serotonergic–noradrenergic agents such as duloxetine are particularly suited to depressive presentations dominated by anergia, psychomotor slowing, and prominent somatic or painful components [59]. Multimodal agents such as vortioxetine, through complex serotonergic receptor modulation, may be particularly relevant in depressive presentations with prominent neurocognitive involvement [60]. Agomelatine and chronotherapeutic interventions align with depressive states marked by circadian dysregulation and diurnal variation [8]. Mirtazapine, partly through its antihistaminergic properties, is especially indicated in depressions accompanied by insomnia, weight loss, and appetite reduction [61], while trazodone – through combined serotonergic antagonism and prominent antihistaminergic and α1-adrenergic blockade – finds its place in depressive states with prominent anxiety, hyperarousal, and sleep fragmentation [62].

From this standpoint, much of what is currently classified as treatment-resistant depression does not reflect true biological refractoriness, but a clinically remediable mismatch between depressive form, monoaminergic target, and treatment intensity. Resistance thus appears not only as a quantitative threshold – defined by two or more failed treatments – but, in a substantial proportion of cases, as a qualitative configuration: the expression of a misalignment between depressive phenotype and the chosen therapeutic target. Classical psychopathology provides the lenses to recognize these forms; biological models indicate the underlying domains; and pharmacology, both traditional and innovative, offers a range of tools that – when used in accordance with this map – can transform what may appear as treatment resistance into a genuinely personalized course of care."

Discussion

The difficulty in treating TRD arises largely from the fact that contemporary clinical practice continues to employ diagnostic tools and therapeutic algorithms built upon an overly uniform representation of depression. Classical psychopathology, by contrast, had already recognized since the early twentieth century that depressive states differ profoundly in their internal structure.

What neuroscience has produced over the last two decades is not a refutation of these insights but a biological confirmation of them. The differentiation between inflammatory, glutamatergic, circadian, dopaminergic, neurotrophic, and HPA-axis domains reflects the same heterogeneity described at the experiential level.

Nevertheless, the available literature presents significant limitations. Biological studies often isolate single mechanisms, losing the complexity of real-world clinical configurations. Pharmacological research, even the most recent, tends to enroll highly heterogeneous populations under the label of "treatment-resistant depression," making it difficult to identify subgroups that are genuinely responsive. Evidence regarding psychedelics and glutamatergic agents, although promising, still requires a clearer definition of the phenotypes most likely to benefit; not all generalized depressions will respond to the same neurobiological modulation. Finally, categorical models such as the DSM, despite their utility in communication, flatten distinctions that everyday practice shows to be fundamental.

Future perspectives require studies that integrate phenomenological assessment, biological measures, and longitudinal monitoring, overcoming the artificial separation between subjective and objective dimensions. Within this perspective, the increasing interest in biological markers should not be interpreted as a search for reductive diagnostic shortcuts, but as an attempt to reduce heterogeneity within treatment-resistant depression and to support domain-informed therapeutic decisions. Several biological markers are currently under investigation to refine stratification within TRD populations and to improve therapeutic matching. These include inflammatory markers such as high-sensitivity C-reactive protein and interleukin-6, which identify subgroups of patients with poorer response to serotonergic antidepressants and differential response to glutamatergic or immunomodulatory [63 64]. Dysregulation of the hypothalamic–pituitary–adrenal axis, reflected by altered

cortisol dynamics or dexamethasone suppression, has been associated with anxious and agitated TRD phenotypes and reduced antidepressant responsiveness [32]. Circadian biomarkers, including actigraphy-based rhythm disruption and melatonin onset abnormalities, further characterize depressive subtypes with prominent sleep–wake [8]. Finally, pharmacogenetic variability in CYP450 enzymes – discussed earlier as a source of pseudo-resistance – also contributes to interindividual differences in treatment exposure and response, reinforcing the need for biologically informed personalization without replacing clinical and psychopathological judgment [38].

Trials should select patients based on phenotype – ruminative, anhedonic, agitated, retarded, circadian – rather than solely by the number of failed treatments. We need instruments capable of capturing depressive experience with greater subtlety and biomarkers capable of engaging with this complexity rather than ignoring it. Ultimately, TRD represents the point at which psychiatry confronts both its limits and its potential for evolution. Resistance is not an obstacle to bypass but an invitation to recognize that depression is a plural phenomenon requiring a plural form of care. Psychopathology, pharmacology, and neuroscience are not three different languages but three ways of describing, with different emphases, the same fabric of human suffering. Only when these languages enter into dialogue can treatment aspire to become truly personalized.

Conclusion

Treatment-resistant depression represents one of the clearest points at which psychiatry encounters the limits of its theoretical models and therapeutic instruments. What is termed "resistance" reflects not merely pharmacological failure, but a mismatch between heterogeneous forms of depressive suffering and diagnostic–therapeutic systems that, for operational reasons, tend to oversimplify them. In this sense, TRD exposes the intrinsically plural nature of depression.

This plurality was already articulated within classical psychopathology and has been increasingly corroborated by contemporary neuroscience, which conceptualizes depression as the variable predominance of distinct symptom domains rather than as a unitary disorder. When viewed through this lens, both established and novel treatments acquire clearer clinical meaning, as each preferentially acts on specific domains and depressive configurations.

Psychopathology provides the necessary orientation within this therapeutic diversity, enabling the clinician to identify the prevailing depressive form, the dominant domain of dysregulation, and the internal logic underlying apparent resistance. Modern biological interventions do not oppose phenomenological understanding; rather, they extend it by acting on the structures that organize depressive experience, including plasticity, rhythm, reward, and cognitive flexibility.

Reconceptualizing TRD in this way does not entail abandoning scientific rigor, but rejecting uniform models of depression in favor of a differentiated, person-centered approach. No single framework – biological, phenomenological, or nosographic – is sufficient in isolation. Only their integration allows for a comprehensive understanding of treatment resistance and supports a form of psychiatry that is both methodologically robust and responsive to the singular configuration of each patient's suffering.

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Conflict of Interest statement

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Authors' Contributions

Conceptualization: Mario Pinzi, Alessandro Cuomo, Maria Beatrice Rescalli, Caterina Pierini, Luigi Morelli, Andrea Fagiolini.

Literature review and synthesis: Mario Pinzi, Alessandro Cuomo, Maria Beatrice Rescalli, Caterina Pierini, Luigi Morelli, Andrea Fagiolini.

Writing – original draft: Mario Pinzi, Alessandro Cuomo, Maria Beatrice Rescalli, Caterina Pierini, Luigi Morelli, Andrea Fagiolini.

Writing – review and editing: Mario Pinzi, Alessandro Cuomo, Maria Beatrice Rescalli, Caterina Pierini, Luigi Morelli, Andrea Fagiolini. Supervision: Andrea Fagiolini.

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