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Title: The Emergence of loss of efficacy during Antidepressant Drug Treatment for Major Depressive Disorder: An Integrative Review of Evidence, Mechanisms, and Clinical Implications

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The Emergence of loss of efficacy during Antidepressant Drug Treatment for Major Depressive Disorder: An Integrative Review of Evidence, Mechanisms, and Clinical Implications

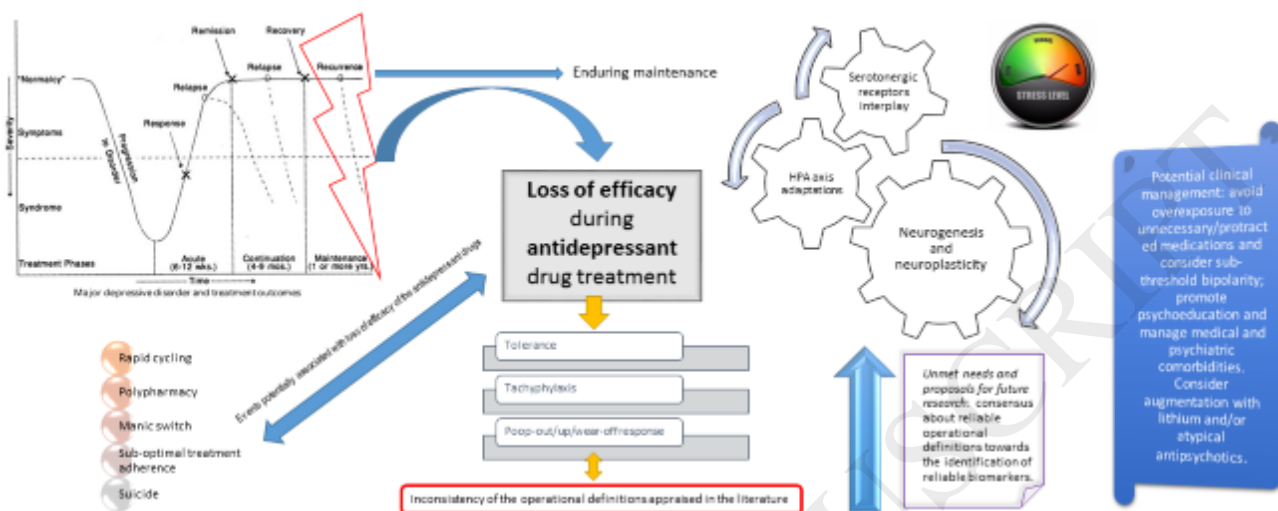
Running Title: *Antidepressant loss of response in MDD*

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Graphical abstract



Abstract

The re-emergence (i.e. ‘breakthrough’) of depressive symptoms despite maintenance treatment of depression with antidepressant drugs is a complex clinical phenomenon referred to as tolerance. Herein we critically appraise evidence from both pre-clinical and clinical studies, focusing on putative mechanisms as well as clinical correlates and implications of the emergence tolerance during antidepressant treatment for major depressive disorder (MDD). It is firstly unclear to what extent this phenotype reflects a pharmacological effect of an antidepressant, is driven by non-adherence, is a marker of latent bipolarity or another comorbidity, a marker of neuroprogression of the underlying disorder or the intrusion of the impact of psychosocial variables into the clinical course. The operational definitions of tolerance and its related phenomena have also been largely inconsistent. Several protective clinical indicators have been proposed, including a rapid-cycling course and comorbid chronic anxiety, whilst poor treatment adherence, proneness to emotional blunting and sub-threshold bipolarity have been identified as possible correlates of tolerance to antidepressant treatment in MDD. Putative neurobiological underpinnings include adaptations in the hypothalamic-pituitary-adrenal (HPA) axis and the serotonergic system. Due to the clinical and diagnostic challenges imposed by the emergence of tolerance to antidepressants, there is an urgent need for upcoming international guidelines to reach a consensus on operational definitions for this complex clinical phenomenon, thus enabling a more precise appreciation of the incidence and correlates of tolerance to antidepressants. Taken together, the present review underscores the need to cautiously weight benefits and risks prior to considering long-term antidepressant treatment for patients with MDD as tolerance may emerge in a subset of patients.

Keywords: Tolerance; tachyphylaxis; loss of response; loss of efficacy; treatment-resistance; antidepressant; withdrawal; relapse; switch.

1. Introduction

The phenotype of tolerance to antidepressant drugs during maintenance treatment of chronic anxiety disorders [1] and major depressive disorder (MDD) may occur in a significant proportion of patients [2], with the return of depressive symptoms of MDD occurring in 9-33% of patients across published trials [3]. The many drivers of this phenomenon and their mechanisms are complex and poorly understood.

Tolerance has been used as a label for a wide range of clinical phenomena characterized by a reduced therapeutic responsiveness to antidepressants following the prolonged and often successful use of these drugs as initial and maintenance treatments for MDD. Increasing the dosage of the antidepressant may re-amplify the drug's effects [4]. However, this widespread clinical approach [5] may exacerbate tolerance and induce chronicity and refractoriness in a substantial subset of patients with MDD [6].

Some patients may also develop tolerance to antidepressant-related side effects, in which case tolerance could be a desirable outcome. In contrast, other patients may develop reverse tolerance (or drug sensitization) thus exhibiting a higher propensity to develop side effects over time even when exposed to low doses of antidepressants [7, 8]. In addition, some of those adverse effects may be due to the so-called nocebo effect [9]. Tolerance may also occur after continuous treatment with an antidepressant drug that may recruit processes that oppose its initial acute effects over time; this phenomenon has been referred to as the oppositional model of tolerance [10].

Tachyphylaxis (Ancient Greek *ταχύς*, tachys, "rapid", and *φύλαξις*, phylaxis, "protection") is a type of drug tolerance referring to the sudden, short-term onset of loss of effect following the administration of a drug [11]. Interestingly, the concept of tolerance has implications beyond pharmacodynamic or pharmacokinetic aspects. Specifically, behavioral tolerance and sensitization towards clinical and psychosocial features (e.g. grief or other external life events) may likewise affect

long-term outcomes of the pharmacological treatment for depression. This aspect suggests that “tolerance” could be a more suitable term than “tachyphylaxis” from a clinical standpoint [12].

Apart from the notable exception of the criteria proposed by Rothschild [13] (see Table 1), there are no univocal operational definitions for “tachyphylaxis” or other tolerance-related phenomena. Hence, concepts such as “poop-up/out” (response), “wear-off” (phenomena), “depressive recurrence during maintenance antidepressant treatment” (DRAT), “breakthrough” (depression), and “loss of efficacy” have been used interchangeably and inconsistently in the literature [11, 14]. Supplementary Table S1 (available online) provides a detailed view of the proposed definitions for this complex set of phenomena.

<Please insert Table 1 around here>

This inconsistency is concerning, considering the clinical burden associated with the long-term course of MDD. Moreover, most trials assessing the efficacy, safety, and tolerability of antidepressants are of short duration (i.e., acute trials), while there is a relative paucity of long-term (i.e., maintenance) antidepressant trials. In addition, whenever assessed, maintenance antidepressant drug trials for MDD rarely exceeds 52-week duration [15], and thus uncertainty exists regarding the detrimental role of tolerance in increasing the likelihood of subsequent treatment-resistance to antidepressants despite initial response. Therefore, uncontrolled observational studies provide a significant amount of evidence pertaining to the emergence of tolerance over the course of antidepressant drug treatment for MDD.

During the past decades, several neurobiological and behavioral mechanisms and hypotheses have been implicated in the emergence of tolerance to antidepressant drugs during the treatment of MDD ranging from pharmacokinetics, pharmacodynamics and adaptive models. Nonetheless, additional insights are needed to shed light on such a complex phenomenon.

While this paper focuses on the mechanisms of antidepressant tolerance per se, it is important to note that many causes of perceived loss of treatment efficacy and not pharmacokinetic in origin.

Bipolar disorder, if latent and undiagnosed in the context of a depressive presentation is much more commonly associated with antidepressant “poop out” [16], and that phenotype is regarded by many as suggestive of a latent bipolar phenotype possibly affecting the response to the antidepressant drugs [17]. Stressors and life events can intrude, and cause depression despite previously adequate maintenance efficacy. Neuroprogression of the underlying disorder is associated with treatment resistance. Comorbidities such as substance use disorder can undermine previously effective maintenance therapy [18], although the actual impact of varying potentially contributing factors is yet to be fully appraised. Finally, there is a narrow gap between antidepressants and placebo in acute treatment trials, implying that many people who improve while taking antidepressants are placebo responders. In these people, perceived loss of efficacy may actually be a loss of the placebo effect. But it is equally true that a proportion of people on long-term antidepressants retain robust prophylactic efficacy over time, and the differential neurobiology and clinical phenotype of these groups are not clearly delineated.

The present comprehensive review critically appraises existing evidence about tolerance to drugs for depression. To the best of our knowledge, the present review is the first of its kind to critically appraise the different definitions documented in the literature, attempting to provide a unitary definition for this phenomenon. In order to do so, the present review integrates a critical perspective on the putative mechanisms of tolerance and related phenomena that may emerge over the course of the pharmacological treatment of MDD. In addition, clinical correlates and implications are critically evaluated as an attempt to direct future research and the clinical practice.

2. Search Strategy and Selection criteria

The following keywords or their combination were searched for results indexed in PubMed since inception through July 23rd, 2018: ((((((("antidepressant tolerance"[Title/Abstract]) OR "antidepressant poop out"[Title/Abstract]) OR "antidepressant poop up"[Title/Abstract]) OR "antidepressant tachyphylaxis"[Title/Abstract]) OR "loss of efficacy"[Title/Abstract]) OR "antidepressant withdrawal"[Title/Abstract]) OR "antidepressant wear-off"[Title/Abstract]) OR "breakthrough depression"[Title/Abstract]. The search strategy was then manually augmented to include also the following terms: “withdrawal”, “sensitization”, “switching”, and “treatment-resistant (depression)” upon screening of retrieved cross-references. The following databases were also searched from inception through June 21st, 2018: Scopus, ClinicalTrials.gov (disclosed completed results only), Cochrane Library, PsycINFO, and Web of Science. Eligible studies included both primary and secondary research material providing either qualitative or quantitative information about tolerance to drugs used for depression and related phenomena. We included both pre-clinical and clinical studies, relevant to the present research theme. Detailed search strings are provided in supplementary material 1 (available online).

3. Frequency and clinical correlates of tolerance to antidepressants during the treatment of MDD

The actual rates of tolerance to antidepressant agents and related phenomena remain unclear. This is to a large extent due to the heterogeneity of definitions across the existing literature as well as the co-occurrence of other causes of antidepressant resistance. Moreover, the true rates of tachyphylaxis occurring during continuation treatment with drugs for depression for MDD may be lower than once thought [19], based on the method developed by Quitkin and colleagues in the early 1990s for estimating the proportion of relapse in patients taking medication attributable to the loss of true drug effect versus the loss of the placebo response [19, 20].

Nevertheless, a proportion of depressed patients receiving maintenance treatment with antidepressant drugs appear to develop “genuine” tolerance to antidepressants. It has been estimated that up to 9 to 33% of patients with MDD may develop tolerance to antidepressants [3] as formulated by Fava in 1994 [6]. Similar rates were documented by the National Institute of Mental Health Collaborative Depression Study that reported the development of tolerance in up to 25% (n=43 out of 171 subsequent episodes) among 103 patients with MDD exposed to antidepressants over a 20-year follow-up period [21]. Similarly, Amsterdam and coworkers documented the development of stepwise tachyphylaxis after repeated antidepressant drug exposure among 149 non-refractory patients with MDD, with the odds of response decreasing by 20% after each prior antidepressant treatment exposure. The estimation of the rates of tolerance and related phenomena essentially rely on anecdotal reports or otherwise naturalistic studies, rather than on controlled trials. In addition, the majority of cases reported in the literature set an average duration of remission of approximately 24 weeks [22], so that the actual “maintenance” duration criterion is not consistently met [23]. An important caveat is that many of these studies do not take into account that relapse is driven by a multitude of causes, even in one individual.

Due to a lack of systematic assessment of the occurrence of tolerance in the literature, corresponding clinical features and correlates associated with this phenomenon are likewise poorly characterized. The occurrence of the antidepressant-induced manic switch even among unipolar depressed patients is well documented [24], and sometimes has been referred to as “type-III” bipolar disorder (BD) [25, 26]. In addition, a rapid “poop-out” response to drugs for depression may also portend an underlying bipolar diathesis [11]. This latter occurrence may be perceived as “an apparent” form of tolerance [8]. A closely related phenomenon seems to be “resistance” to antidepressant treatment. As noted, there are many drivers of treatment resistance in depression [27], with a number of clinical factors identified by the studies GSRD (European Group for the Study of Resistant Depression) [28, 29] including, but not limited to, psychiatric and general medicine comorbidities, and a number of clinical-demographic variables affecting the lifetime course and current status of depression, as reviewed by Caraci F. et al., 2018 [30]. In 1984, Lieb and Balter [31] described the emergence of refractoriness in some patients with MDD to drugs for depression that had been previously efficacious. Changing treatment to another antidepressant drug yielded some therapeutic benefits, although time-limited. A similar phenomenon was described and related to long-term low-dose antidepressant treatment by Fava in 1994 [6]. This is compelling taking into consideration that the current concept of treatment-resistance to drugs for depression refers to the acute treatment of depression and may poorly fit the maintenance phase of MDD treatment. Moreover, withdrawal symptoms following antidepressant discontinuation appear to occur during the acute or post-acute phases of treatment of MDD. Yet it has been postulated that some cases of apparent tolerance may actually be due to long-term withdrawal or dependence which may, in turn, be affected by poor compliance to prescribed drugs for depression [2, 6]. Curiously, antidepressant withdrawal phenomena appear to be more antidepressant specific, with venlafaxine and paroxetine much more likely to manifest this

phenomenon than, say, fluoxetine, suggesting a disconnect between mechanisms of possible tolerance and withdrawal [32].

Residual symptoms of depression may endure even during the maintenance treatment of MDD. A potential detrimental manifestation of long-term treatment with antidepressants may be the emotional blunting phenomenon (vide infra) or otherwise “depressogenic” phenomena [33-36].

ACCEPTED MANUSCRIPT

4. Potential mechanisms and models of tolerance to antidepressants

The mechanisms of tolerance to antidepressant drugs are yet to be fully elucidated. Nonetheless, converging evidence suggests a multifactorial and complex origin involving the interplay of both neurobiological and psychosocial mechanisms. Multiple possible neurobiological explanations for the emergence of tolerance to antidepressants and related phenomena have been proposed. For instance, it was postulated that the activation of processes driving tolerance to antidepressant drugs may occur to at varying degrees in every patient receiving antidepressants [3], may only manifest themselves and then be recognized in patients with chronic and recurrent forms of depression who had previously responded to antidepressant therapy at some time [37]. This premise has major implications for the postulated pharmacological models of tolerance, which is regarded as a special form of acquired tolerance over the long-term/chronic course of MDD. Specifically, pharmacokinetic and pharmacodynamic adaptations have been repeatedly advocated as a core mechanism of pharmacological tolerance to antidepressants.

4.1. Pharmacokinetic tolerance

Pharmacokinetic tolerance can result from changes in drug distribution among different bodily compartments, more efficient excretion or metabolic adaptations (e.g. involving cytochrome P450 drug metabolizing enzymes) [8] leading to reduced serum levels of antidepressant drugs over the time [38]. Nonetheless, the dose of the drug may not be a reliable predictor of pharmacokinetic tolerance. Hence some depressed patients who developed tolerance during maintenance treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine 20mg responded to an increased dose of 40mg [39], whilst other patients failed to respond to this strategy [31]. Pharmacokinetic tolerance can also be influenced by exogenous factors such smoking, or drug-drug interactions (i.e. due to induction of

cytochrome P4503A4 isoenzyme due carbamazepine reducing the area under curve of selected antidepressant drugs as milnacipram, mirtazapine, or bupropion) [40].

4.2. Pharmacodynamic tolerance

Pharmacodynamic tolerance is usually assumed when the therapeutic benefits of a drug are lost with repeated or continuous exposure. In this sense, pharmacodynamic tolerance depends only on pharmacological properties of the drug. The dose of the drug and the duration and frequency of administration appear to be the main drivers of pharmacodynamic tolerance [38].

Tolerance to antidepressant drugs involves multiple pharmacological mechanisms at the receptor and signal transduction level, both at pre- and post-synaptic levels. Complex pharmacodynamic and intracellular mechanism adaptations have been proposed for a sustained antidepressant response for treatment-resistant depression, and, potentially, for pharmacodynamic tolerance too, whereas a multi-scale, system biology approach has been likewise suggested [41]. Nonetheless, the simple dissection of each given molecular mechanism potentially linked to antidepressant tolerance would appear excessively simplistic, at best.

In fact, despite the notion that most of the clinically prescribed antidepressant drugs primarily act by modulating the monoamines' transmission, the monoamine transmission itself is modulated by mechanisms other than the essential monoamines and/or regions (e.g. at the midbrain, other subcortical regions, and the cortex). For example, the glutamate is a major tonic/phasic release regulator of serotonin, dopamine, and norepinephrine, meaning that the phenomenon of pharmacodynamic tolerance takes more than a handful of monoamine, and/or multiple sites, timing and regulators [42].

In addition, the loss of efficacy of an antidepressant may be significantly affected by the changes in the maximal binding (B_{max}) or degree of affinity (low vs. high affinity) of multiple receptors after

increase level of neurotransmitter. However, the research on the eventual correlation between B_{max} /affinity changes over the time, loss of antidepressant efficacy, and modifications in the complexity of the receptor-neurotransmitter binding profile is substantially lacking. Notably, in the field of psychopharmacology, a relatively successful model is represented, in the example, by the loss of effect of the antipsychotics linked to dopamine D2 receptor transition from low to high-affinity state [43], although a similar model with potential translational value for antidepressant tolerance is lacking.

Nonetheless, it is worthy to note that pharmacodynamic tolerance may not necessarily develop to all therapeutic or side effects of a given antidepressant drug; it rather occurs that it may develop just towards some effects of the drug (e.g. either side effects or therapeutic effects). A possible explanation for this latter observation is that the function (inhibitory or excitatory) and density of a given receptor may vary depending on the organ system in which it is located. As reviewed in detail elsewhere some receptors are expressed in such high levels in particular brain areas that a large proportion of receptors must be inactivated before a diminishment in efficacy becomes apparent (receptor reserve) [38, 44]. According to the “receptor reserve” hypothesis, tolerance may develop more slowly or not at all when there is a large receptor reserve. This may explain why tolerance to antidepressants is a heterogeneous clinical phenomenon (i.e., tolerance to specific side effects or otherwise the recurrence of specific symptom dimensions may ensue depending on the ‘receptor reserve’ at particular brain networks).

4.2.1 Serotonergic receptors interplay

There is substantial evidence supporting the role of 5-hydroxytryptamine (5-HT) in the pathophysiology of depression and its pharmacological management. Presynaptic 5-HT(1A) and 5-HT(1B) auto-receptors play a major detrimental role in antidepressant treatments [45]. Conversely, stimulation of postsynaptic 5-HT(1A) receptors in corticolimbic networks seem beneficial for antidepressant drug action [46]. The activation of physiological negative feedback mechanisms

operating through auto-receptors (5-HT_{1A}, 5-HT_{1B}, α ₂-adrenoceptors) and postsynaptic receptors (e.g., 5-HT₃) may account for the delayed onset of antidepressant treatment response. While it has been reported that mixed β -adrenoceptor/5-HT_{1A} antagonists as pindolol would accelerate the response of antidepressants [47], especially in the case of selective serotonin reuptake inhibitors (SSRIs) [48], the role of 5HT-1 and 5HT2 receptors in the development of tolerance to drugs for depression has been likewise postulated [2]. It has been hypothesized that some neurobiological mechanisms related to the therapeutic effects of drugs for depression (e.g. a down-regulation of post-synaptic 5HT2 receptors) may, under specific conditions, trigger changes in post-receptor signal transduction pathways, or in neuronal architecture, ultimately leading to an impaired balance and function of serotonin receptors, thus contributing to the emergence of tolerance to antidepressant drug treatment [2].

4.3. The neurotransmitter/hypothalamic-pituitary-adrenal axis interface

There is extensive evidence to suggest that the hypothalamic–pituitary–adrenal axis (HPA) could modulate sensitization and/or tolerance to antidepressants by its reciprocal interactions with serotonin neuroreceptors [49]. Hence a down-regulation of 5HT₂ post-synaptic receptors which has been proposed as one of the final pathways driving therapeutic effects of different antidepressant [50] may facilitate 5HT₁ receptor neurotransmission, which in turn may activate the HPA axis with an increased production of adrenocorticotrophic hormone (ACTH) and cortisol [51]. This over-activation of the HPA axis may unfavorably affect serotonin receptor functioning [52]. Based on these pharmacodynamic effects it was postulated that the long-term treatment with antidepressant drugs may activate the HPA axis which would result in a loss of clinical benefits (i.e. tolerance) at least partly due to effects on serotonergic neurotransmission [2, 8].

4.4. Cross-sensitization

Sensitization to stressors and comorbidities and their neurochemical concomitants may affect the expression of neurotransmitters, receptors and neuropeptides that may thereby alter the responsiveness to antidepressants in a long-lasting way through the modulation of gene expression (e.g. c-fos and related transcription factors) [53]. The consumption of drugs of abuse as well as a wide array of environmental stressors may generate allostasis and deregulate the HPA axis [54]. In this framework, antidepressant drugs may display a protective effect, but long-term antidepressant actions on the HPA axis (*vide supra*) may also increase sensitization of stressors [2], which may affect the likelihood of recurrences, in a clinical scenario that would be attributed to the emergence of tolerance.

4.5. The oppositional model of tolerance

Fava and Offidani proposed an oppositional model of tolerance in which the prolonged exposure to antidepressant drug treatment could induce several neurobiological changes that oppose the initial acute effects of the antidepressant that accounts for its therapeutic benefits. This model may explain the onset of tolerance and also of withdrawal symptoms in a meaningful subset of patients with MDD [2]. However, it is equally true that antidepressant onset is slow to manifest, and is also predicated on sustained exposure and neurotransmitter regulatory changes as well as impacts on processes such as neurogenesis [55] as we will discuss below. All the above-mentioned mechanisms may be part of these oppositional neurobiological processes.

4.6. Neurogenesis and Neuroplasticity

As reviewed by Hayley S. and Litteljohn D (2013), depression is characterized by hampered hippocampal neurogenesis and cortical synaptogenesis, with high recurrence rates and chronicity possibly induced by altered trophic support following stressor-induced reduced activity of growth factors, especially the brain-derived neurotrophic factor (BDNF) [56]. Furthermore, hippocampal

neurogenesis has been mechanistically implicated in the mechanism of action of drugs for depression and that the chronic exposure to drugs for depression may alter this process [57, 58]. In 2011, it was proposed that the emergence of tachyphylaxis might be associated with neuroplastic processes related to dendritic arborization following long-term antidepressant treatment.

Finally, it is worth mentioning that a set of postsynaptic structures implicated in synaptic remodeling are also responsible for changes in dendritic architecture putatively implicated in the action of antidepressants, including the postsynaptic density (PSD) at glutamate synapses, a molecular hub including scaffolding, adaptor and signaling proteins. Multiple lines of evidence both a preclinical and clinical level, suggest that PSD proteins (i.e. Homers, Norbin) may be involved in the response or lack of (sustained) response to canonical antidepressant [59, 60], as well as ketamine and other NMDA-receptor antagonists [61, 62].

4.7. Emotional blunting

A high proportion of patients receiving SSRIs may exhibit a clinical phenomenon referred to as emotional blunting. Those patients often describe their emotions as being “damped-down” or “toned-down”, while some patients refer to a feeling of being in “limbo” and just “not caring” about issues that were they once cared about [34]. Such adverse affective manifestations may persist even after the symptoms of depression have improved and may ensue in patients of all ages [63]. Some authors hypothesized that antidepressant-induced emotional blunting occurs as a result of a down-regulation of dopamine neurotransmission in neural circuits that regulate reward processes, secondary to an activation of 5HT_{2C} receptors in the nucleus accumbens [64]. These changes in emotional processing are not limited to SSRIs and have also been reported in patients treated with mirtazapine, agomelatine, and reboxetine, albeit much less infrequently [65]. In addition, cases of apathy, lack of motivation and frontal lobe syndrome have been described in patients taking SSRIs across different age groups [66].

4.8. Genetic and epigenetic mechanisms

Variations in the sequence, structure, and function of several genes have been shown to influence the acute therapeutic response to antidepressants [14, 67]. Arguably, it is possible that genetic mechanisms could partly contribute to the emergence of tolerance to antidepressants in specific subsets of patients. The genetics of molecules putatively implicated in treatment loss of response or treatment-resistant depression included BDNF, GRIK4, KCNK2, SLC6A4, however, most studies have been based on candidate gene approach, and only for few genes replication supported associations with treatment-resistant depression. Among serotonin receptor, the GG variant for the rs7333412 SNP of the 5HT2A has shown association with less proneness to antidepressant response compared to the AA/AG variant. In the preclinical study, it has been demonstrated that the 5-HT2A receptors may have an inhibitory effect on the neuronal activity of the serotonergic neurons after *acute* administration of SSRIs. GWAS (Genome-Wide Association Studies) did not detect any genome-wide significant association at the variant level, however, signal transduction including genes regulating synaptic plasticity, cytoskeleton architecture, and neurogenesis could be associated with treatment-resistant depression, according to the results by genome-wide association studies of antidepressant response [68]. However, the possible genetic underpinnings related to the onset of tolerance to antidepressants remain unknown.

4.9. Psychosocial stressors and environmental factors

Patients with MDD may be particularly sensitive to interpersonal stressors even after long-term remission of affective symptoms. In this vein, the emerging conceptual framework of “clinical pharmaco-psychology” seems to better fit the complex interactions between pharmacological and individual psychological features [69]. As such, it cannot be ruled out that the “apparent” loss of antidepressant effects may in certain circumstances be due to the detrimental effect of external

stressors. These external stressors promote adaptation (allostasis) and lead over time to “wear and tear” of otherwise compensatory (i.e. adaptive) mechanisms (allostatic load) [54, 70]. The mediators of this adaptation (e.g. cortisol and adrenaline) are released in response to stressors or lifestyle factors, and specific brain regions respond to these repeated stimuli with changes in dendritic branching and in the number of neurons [71]. Hence, it was demonstrated that in MDD the duration of illness predicts a progressive reduction in hippocampal volume [72], such that the process of neuroprogression that leads to treatment resistance in the latter stages of affective disorders may be contributing to the perceived loss of efficacy antidepressants in a subset of patients with MDD. Other factors such as substance abuse may drive treatment non response to treatment, as may non-adherence or partial adherence to medication, which is far more common than many clinicians perceive or patients overtly manifest.

4.10. Preclinical models of tolerance to antidepressants

A recent review by Bernalov, Müller, Relo and Hudzik [38] provides a critique of preclinical models of tolerance to different neuro-psychopharmacological agents with major translational and clinical applications. Most antidepressant drug efficacy studies are conducted over a minimum of several weeks. On the other hand, it is worthy to note that most preclinical efficacy studies are limited to the acute or subacute administration of drugs, while the risk of losing efficacy during long-term treatment is not fully assessed and modelled [38]. Taking into account the plausible predictive value of preclinical models for depression in determining mechanisms related to the emergence of tolerance to antidepressants, the inclusion of studies using repeated drug exposure early during drug discovery could be of relevance [38].

Please refer to Figure n.1 for a pictorial synthesis of the main mechanisms accounted for loss of response to antidepressants.

<Please insert Figure 1 around here>

5. Critical appraisal of the evidence

In 2001, Nassir Ghaemi and colleagues adopted the label of “antidepressant view of the world”, referring to an increase in research interest and a sharp increase in the prescription of antidepressant drugs worldwide [73] as being the (by)product of what Ross Baldessarini conceptualized as the “pharmaco-centric view of the world” in the year 2000 [74], based on the historical contributions of Gerald Klerman [75, 76]. According to their claims, these latter prominent researchers prompted-out for the risk of over-prescribing antidepressant drugs, especially since the early 1980s, often with poor attention to subsequent outcomes, especially iatrogenic switch into mania and also a potentially deleterious impact on the course of mood disorders in general. Parker [77] more recently argued that the perceived efficacy limitations of antidepressants is an artifact of the fact that depression is not one illness, but an umbrella term under which a range of different illness with different causes, some being biological, some psychological and some social co-locate. These have different trajectories and treatment responses and that bundling them together leads to efficacy signals of antidepressant medications being swamped and effectively lost.

While at that time no specific mention to the phenomenon of tolerance to antidepressant drugs during maintenance treatment for MDD, concerns were also raised about the true efficacy of antidepressant drugs, beyond tolerability concerns [78], and “antidepressant loss of response (acute but not prophylactic response) was proposed as a potential marker for an underlying bipolar diathesis [79]. Yet, such controversial appraisals of the evidence almost invariably focused on the acute treatment of milder, non-treatment resistant forms of depression [80], thus neglecting the ostensible emergence of tolerance in some patients with MDD exposed to enduring treatment with antidepressant drugs.

Several aspects may contribute to this scenario. Among others, the inconsistency of the operational definitions appraised in the literature hinders a rigorous assessment of the phenomenon of tolerance to antidepressants. For instance, the timeframe of “maintenance”, which is often much shorter

(i.e., 16-weeks [81]) than 52-weeks, and the lack of stratification across varying mood, cognitive, and psychosocial functioning symptoms of depression also limits a proper appraisal of tolerance to antidepressants during treatment for MDD. Whilst the Rothschild scale for tachyphylaxis assesses different domains (Table 1), other reports often merge those dimensions in a single category undermining the investigation of core symptoms that may either define tolerance to antidepressants or could otherwise precede the onset of tolerance. In addition, terms such as “relapse” and “recurrence” are often used interchangeably in the handful literature reporting about tolerance/tachyphylaxis to antidepressants.

Similarly, most of the evidence fails to take into account the heterogeneity of depression including rapid-cycling, (sub-threshold) mixed features, atypical, psychotic, suicidal, resistant, seasonal depression, or thyroid axis dysfunctional depression, while appraising the emergence of tolerance to antidepressant agents [82]. Furthermore, antidepressants comprise heterogeneous compounds. While the interplay among different serotonergic receptors and long-term adaptive mechanisms have been implicated in the emergence of tolerance to SSRIs, no head-to-head comparisons are available for alternative classes, especially for newer generation antidepressant drugs [66, 83]. While the present review could not stratify the findings based on the pharmacological class of antidepressants, due to the lack of corresponding information in the appraised evidence, we rather strived at presenting the results owing to the plausible neurobiological effect, consistent with the recent neuroscience-based nomenclature (NbN) approach, aiming at overcome the boundary of the previous class-based nomenclature of the “drugs used in the treatment of depression” [84]. From this perspective, it is recommended that future studies would follow the NbN approach to encompass drugs possibly used (also) for depression, but not currently enlisted among the classical monoamine modulator drugs formerly known as “antidepressants” (e.g. the second-generation antipsychotic quetiapine). In fact, at writing time there is just a quite outdated literature on tranylcypromine, which has amphetamine-like

effects, that may have a particular propensity to tolerance [85], urging for a critical update on the matter owing to the much recommended NbN approach.

In particular, rapid cycling, which is a bipolar *forme fruste*, was already noted as a potential concern related to the prescription of antidepressants since the 1980s [86]. However, reverse causality cannot be ruled out [87]. For example, MDD patients exposed to antidepressants for a long period of time may be more prone to develop a rapid cycling course over time. Although this phenomenon may be due to the presence of a bipolar diathesis [88], it may also result from the development of tolerance to antidepressants as previously discussed. Therefore, further research is needed to elucidate the temporal relationships between rapid cycling and tolerance to antidepressants.

Co-occurring chronic anxiety disorders and obsessive-compulsive disorder (OCD) may often account for the prescription of higher doses of antidepressant drugs, especially serotonergic compounds compared to MDD cases without such comorbidities. Higher doses are not uncommonly a prescription strategy to deal with non-response rather than an indication of pharmacokinetic need. Comorbid anxiety disorders in patients with MDD may however further propel the development of tolerance to antidepressants. In addition, tolerance to an antidepressant may occur even among patients without a primary diagnosis of MDD [2]. Similarly, comorbid medical conditions as hypothyroidism, and/or the concomitant use of beta-blockers, corticosteroids, or other agents with potential depressogenic activity should be likewise been taken into consideration before considering the hypothesis of “true” tolerance to antidepressants. Table 2 summarizes possible warning signs that should raise clinical suspicion for the possibility of tolerance to antidepressants.

<Please insert Table 2 around here>

It should be noted that outcomes from the largest antidepressant trial conducted to date, the Sequenced Treatment Alternatives to Relieve Depression Study (STAR*D) can be interpreted under the perspective of the oppositional model of tolerance [2, 89]. As pointed out by Nelson [90] when

sustained recovery (taking into account relapse rates while on treatment) was considered, the cumulative rate was only 43%. Furthermore, in steps 3 and 4 of the trial, in addition to low remission rates, nearly half of those remitting ended up experiencing a relapse [89]. This highlights that long-lasting remission following antidepressant drug treatment for MDD is challenging. Moreover, it is possible that once tolerance to antidepressants is established, further augmentation and combination therapies may work acutely but not necessarily in the long-term, but the same caveat about the multiplicity of drivers of persistent depression still applies. A recent Cochrane review further indicates that the therapeutic benefits of maintenance and continuation treatments with antidepressants in preventing relapses and recurrences in late-life depression remain inconclusive [91].

An additional critical issue undermining the appraisal of tolerance to antidepressants derives from the non-controlled nature of the reports on the matter, which are almost invariably naturalistic, and based on anecdotal retrospective data. Moreover, critical clinical outcomes such as chronic depression and even the emergence of suicidality during long-term maintenance treatment with antidepressants deserve further investigation within the context of tolerance to antidepressant agents.

A notable clinical scenario refers to behavioral toxicity, a clinical situation in which the pharmacological actions of a drug that within therapeutic dose range has been found to possess clinical utility, may produce alterations in mood, perceptual, cognitive and psychomotor functions that limit the capacity of the individual or constitute a hazard to one's well-being [92]. This concept encompasses adverse events that may be limited to the period of drug administration and/or persist long after its discontinuation. This latter phenomenon is accounted as iatrogenic comorbidity [93]. Tolerance may in certain clinical circumstances comprise an iatrogenic comorbidity [93], and further research on this area is needed, especially its relationship with the onset of emotional blunting phenomena (possibly due to prolonged post-synaptic 5-HT_{2A} stimulation resulting in reduced dopaminergic activity in the striatum). At least hypothetically, the prolonged exposure to the SSRIs may promote tolerance to newer

antidepressants, including the multimodal agent vortioxetine, since it has been recently reported that the acute efficacy of this latter drug may vary across countries according to the extent of antidepressant use [94]. Lastly, the phenomenon of tolerance may contribute to poorer outcomes in people with depression exposed to long-term antidepressant treatment, although as noted earlier, there are many confounds of this association [95, 96].

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6. Conclusion and outlook

This review provides evidence that the emergence of tolerance during long-term antidepressant drug treatment may contribute to worse outcomes in a subset of patients with depression. At the same time, it outlines a lack of consensus in the literature regarding the operational definition for this complex clinical phenomenon and its confounds. This aspect hinders a more precise appreciation of the frequency and correlates of tolerance to antidepressants. Particularly, well-designed maintenance randomized controlled trials of antidepressant agents should account for the development of tolerance to antidepressants.

Furthermore, treatment adherence to prescribed antidepressants should be assessed before establishing the possibility of “true” tolerance. The possibility of exposure to environmental stressors and also the proper attention to other variables towards to the optimal practice of clinical pharmacopsychology [69] should also be considered. Moreover, a proper weighing of benefits and risks should be warranted prior to considering long-term treatment with antidepressant agents in MDD [97] and bipolar disorder [98]. In fact, tolerance may more likely develop in bipolar disorder simply because depression is more recurrent in that condition than in MDD although tolerance may be a potential marker of latent bipolarity. Hence, an open question is whether, irrespective of depression subtype, tolerance is more common in patients who are highly recurrent.

Finally, available international guidelines for the management of depression do not give proper consideration to the phenomenon of tolerance to and its various potential deleterious consequences, and while some guidance exists about the “optimal” duration of pharmacological trials for depression, even upon achievement of successful maintenance treatment, no clear indication exists about the eventual need to discontinue antidepressant drug treatment after a specific timeframe. This is compelling considering that the continuation and maintenance treatment with antidepressants carries no therapeutic benefit for a sizable proportion of patients with MDD [99], and as discussed above may even be

harmful for a subgroup of patients. Ultimately that the main principle behind a clinical prescription should be “primum non nocere”, which is the Latin translation of the Hippocratic concept of “first do not harm” [100]. This precept that should be followed in the absence of conclusive evidence in support of the long-term safety of antidepressant agents, at least among patients with MDD potentially at risk of developing clinically-manifest, “genuine” tolerance to antidepressant drugs with its various detrimental consequences.

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Conflict of interest and disclosure statement

Disclosure Statement

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Table 1. The operational definition of antidepressant tachyphylaxis proposed by Rothschild [13].

Rothschild Scale for Antidepressant Tachyphylaxis (RSAT)							
Items	Energy Level	Motivation and Interest	Cognitive Functioning	Weight Gain	Sleep	Sexual functioning	Affect
Range Score	0-4	0-4	0-4	0-4	0-5	0-4	0-4

Note: The conceptualization of antidepressant tachyphylaxis proposed by Rothschild A.J. (2008) stresses out the notion that a patient who develops tachyphylaxis does not experience a full-threshold major depressive episode. This is in contrast with most of the alternative definitions proposed by other authors (please refer to table S1, available online, for details). A score ≥ 7 in the RSAT is considered indicative of the presence of antidepressant tachyphylaxis.

Table 2. Clinical “warning signs” indicative of possible tolerance to antidepressant drugs.

Warning sign	Possible management
Non-adherence	Enhancement of the physician-patient relationship; psychoeducational interventions; avoid polypharmacy.
Worsening (severity) of the index depressive episodes or rapid “poop-out” response to the antidepressant	Consider sub-threshold bipolarity, increased risk for suicidality, treatment-emergent manic switch, mixed states, rapid cycling, lack of adherence to treatment, unrecognized psychiatric (e.g. chronic anxiety disorders or obsessive-compulsive disorder) and/or medical comorbidities.
Loss of an associated placebo response	Clinicians should suspect a self-limited placebo response among patients receiving subthreshold doses of antidepressants. Switching to antidepressant doses within the therapeutic range should be considered.
Plausible tolerance regardless of the suspected cause	Among other attempts, drug holiday increasing or decreasing the antidepressant dose, change of the antidepressant class, combination or augmentation strategies should be pursued. Declining plasma concentrations of the drugs due to drug-to-drug interactions, detrimental metabolites, or other physiological or physiopathological adaptations need to be ruled out.

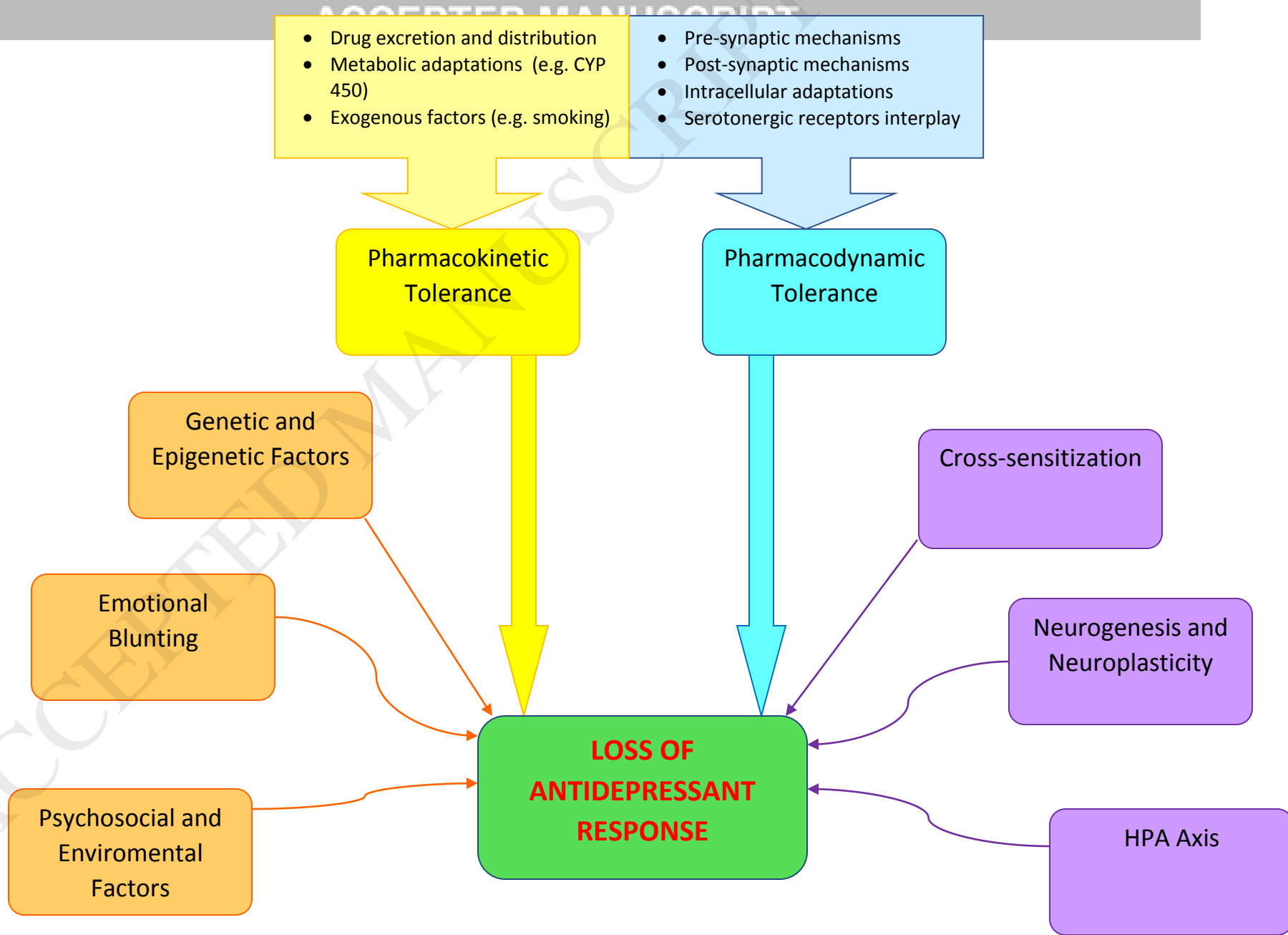


Figure 1: Pictorial representation of the main mechanisms potentially concurring to loss of antidepressant response.