

HALOPERIDOL FOR REFRACTORY DEPRESSIONS : CLINICAL AND NEUROBIOLOGICAL REVIEW

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ABSTRACT This article proposes a clinical-neurobiological model for the strategic use of haloperidol in severe refractory depressions, focusing on hyperactive borderline patients, adolescents with natural hormonal lability or patients with psychotic catatonias. Based on extensive hospital experience, an illustrative clinical case, and a literature review, the direct, rapid, and safe antidepressant effect of haloperidol is discussed. Physiopathological hypothesis involving D2, D3, 5HT2A, sigma-1, receptors, the HPA axis, prolactin and calcium channels are integrated and discussed. The rational use of haloperidol is advocated as an accessible alternative in resource-limited contexts (no ECT, no ketamine, etc).

Keywords: Haloperidol, Suicidal Depression, Hyperactive Anxious Depression, Borderline Disorder, Catatonia, Impulsivity, Dopamine, 5HT2A, Neurobiology. Treatment-Resistant Depression, Antipsychotics, Severe Mood Disorder.

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1.INTRODUCTION

1.1.Haloperidol: Mechanism of Action and Pharmacology

Haloperidol is a typical antipsychotic whose main mechanism of action involves potent antagonism of D₂ dopaminergic receptors. This blockade is key to its antipsychotic effect and, concomitantly, the origin of the extrapyramidal symptoms (EPS) that may occur (mechanism of action: antagonism of D₂ dopaminergic receptors, key to antipsychotic effect and origin of extrapyramidal symptoms). Haloperidol is available in oral, intramuscular (IM), and intravenous (IV) forms, with decanoate offering a prolonged intramuscular use option (Pharmacokinetics and route of administration: available oral, IM, IV; decanoate offers prolonged intramuscular use). Additional information on its pharmacology can be found in specialized literature.

1.2. Clinical Efficacy and Indications

Historically, haloperidol has been proven effective in psychosis, delirium, and agitation, with similar performance to other typical and atypical antipsychotics in controlled studies (Clinical efficacy: proven effective in psychosis, delirium and agitation, with performance similar to other typical and atypical antipsychotics in controlled studies). A meta-analysis on delirium, for example, demonstrated that haloperidol at doses ≥ 5 mg/day reduces the incidence of surgical delirium (Meta-analysis in delirium: haloperidol ≥ 5 mg/day reduces incidence of surgical delirium). The historical evolution of antipsychotics, with haloperidol as a first-generation prototype, is well documented in the literature.

1.3.Adverse Effects Profile

Haloperidol presents a high risk of extrapyramidal symptoms (EPS), such as parkinsonism,

akathisia, and other motor dysfunctions. Furthermore, there is a risk of QT prolongation, which can lead to severe cardiac arrhythmias, and an increased risk of mortality, especially in elderly or comorbid patients (Adverse effects: high risk of EPS (parkinsonism, akathisia, motor dysfunctions), QT prolongation, and risk of mortality especially in elderly or with comorbidities). Treating patients with severe, treatment-resistant depression — especially adolescent or young adult females with histories of suicide attempts and self-injury — remains one of the greatest challenges in clinical psychiatry. These patients often present with complex and overlapping diagnoses, including attention-deficit/hyperactivity disorder (ADHD), borderline personality traits, substance use, eating disorders, and mood instability. After multiple unsuccessful trials of antidepressants, mood stabilizers, and atypical antipsychotics, some of these patients respond only to classical neuroleptics, such as haloperidol.

1.4.New Perspectives

Recent research has explored new areas related to haloperidol, such as the link between mTOR signaling and neurological toxicity. Detailed analyses of the dose-response relationship are also underway, which may optimize treatment safety and efficacy (New perspectives: research linking mTOR signaling to neurological toxicity, as well as detailed analyses of dose-response are underway).

1.5.Haloperidol and Depression

The treatment of patients with severe, treatment-resistant depression — especially adolescent or young adult females with a history of suicide attempts and self-harm — remains one of the greatest challenges in clinical psychiatry. These patients often present with complex and overlapping diagnoses, including attention-deficit/hyperactivity disorder (ADHD), borderline personality traits, substance use, eating disorders, and mood instability. After multiple unsuccessful trials of antidepressants, mood stabilizers, and atypical antipsychotics, some of these patients respond only to classical neuroleptics, such as haloperidol. This article aims to

discuss the role of haloperidol in this challenging context, presenting an illustrative clinical case and reviewing the relevant literature. Suicidal refractory depressions, particularly in hyperactive borderline adolescents, impulsive patients, and psychotic catatonias, often do not respond to conventional antidepressants, and may even be aggravated by them. At the same time, procedural therapies such as ECT, ketamine, or TMS, although effective in some cases, are often inaccessible in public hospitals in poor countries (Popovic et al., 2012; Kennedy et al., 2014). Although traditionally classified as a typical antipsychotic, haloperidol possesses specific neurobiological properties that qualify it as an emergency antidepressant intervention in these contexts.

2. METHODS

This study is based on:

- * Direct clinical observation over 44 years of psychiatric hospital practice;
- * Description of an illustrative clinical case;
- * Targeted bibliographic review in PubMed and specialized literature, addressing the use of haloperidol in suicidal depression, impulsivity, and correlated neurobiological mechanisms.

3. RESULTS

3.1. Summary of Clinical Subtypes of Refractory Depression and Their Eventual Psychopharmacological Response

* Pure melancholic: Anhedonia, psychomotor retardation, apathy. Could respond to tricyclics and lithium (Serban & Siegel, 1988).

* Anxious-agitated: Intense anxious suffering, insomnia, autonomic hyperarousal. Responds to anticonvulsants and mood stabilizers, lithium (D'Aquila et al., 2008).

* Hyperactive suicidal borderline: Suicidal impulsivity, self-mutilation, ruminative suicidal perseveration, paradoxical hyperreactivity to SSRI and noradrenergic antidepressants. Often does not respond to quetiapine or risperidone (akathisia, noradrenergic effects), nor to anticonvulsants, isolated lithium. Could respond to haloperidol (Gupta et al., 2015; Siris et al., 1984).

3.2. Illustrative (paradigmatic) Clinical Case

Female patient, Y, 14 years old, with a history of childhood hyperactivity, self-mutilation since age 12, several impulsive suicide attempts, severe insomnia, mood swings during menstrual cycles. This "Patient Y", a 14-year-old girl, who presented with a complex history of conduct disorder, ADHD, borderline personality traits, substance abuse, eating disorder, and severe mood disorder, has a paradigmatic outline, as it is extremely common in our current socio-economic-political-cultural context. The patient had made three previous suicide attempts and had worsened on various medications, including fluoxetine, sertraline, paroxetine, and methylphenidate. There was no sustained improvement with propranolol, clonidine, topiramate, carbamazepine, or valproate. Lithium also failed to yield satisfactory results. Her behavioral pattern involved nicotine addiction since age 12, excessive caffeine consumption, school absenteeism, nightlife, and hypersexuality — a lifestyle resembling the "sex, drugs, and rock'n'roll" syndrome. Emotional crises were

triggered by affective frustrations.

Antidepressants – selective serotonin reuptake inhibitors - SSRIs aggravated suicidal impulsivity – perhaps due to akathisia or noradrenergic mechanisms. Quetiapine and risperidone increased anxious agitation, possibly due to akathisia (quetiapine + lithium, risperidone + lithium) or noradrenergic effect (quetiapine + lithium).

Introduction of haloperidol 10 mg/day for 3 days, then 4 mg/day, resulted in rapid stabilization, with remission of suicidal ideation within 48 hours. Subsequently, stabilization with lithium and gradual withdrawal of haloperidol would be programmed, when possible. Such patients are highly sensitive to noradrenergic effects and akathisia; many impulsivities and suicidality seem to be related to these problems.

In short, this "Patient Y", a 14-year-old girl, also presented with a history of conduct disorder, ADHD, borderline behavior, substance abuse, eating disorder, and severe mood disorder. She had made three prior suicide attempts and had worsened on various medications including fluoxetine, sertraline, paroxetine, and methylphenidate, lithium, valproic acid. There was no sustained improvement with propranolol, clonidine, topiramate, carbamazepine, or valproate. Lithium also failed to yield satisfactory results. Her behavioral pattern involved nicotine addiction since age 12, excessive caffeine, skipping school, nightlife, and hypersexuality — a lifestyle resembling the "sex, drugs, and rock'n'roll" syndrome. Emotional crises were triggered by perceived abandonment from boyfriends, leading to self-harm and suicidal ideation. The clinical impression was that of a hyperactive child who lacked maternal nurturing and paternal structuring. Puberty and hormonal shifts appeared to aggravate underlying affective and behavioral dysregulation. Substances may have further disrupted the effect of psychiatric medications. Some medications — especially those acting on noradrenergic systems — seemed to exacerbate her irritability, anxiety, and dysphoria. Valproate may have worsened her depression via folate depletion. Lithium showed no acute benefits. Aripiprazole was ineffective in calming her, and stimulant medications worsened her mood. She only began to improve after starting haloperidol (10 mg/d and ,after three days,4 mg/day), combined with biperiden to counteract akathisia. Interestingly, this combination not only controlled her agitation but also alleviated her depressive symptoms and ADHD-related restlessness.

Haloperidol appeared to exert a "chemical lobotomy" effect on her impulsivity and reactivity, inducing compliance, emotional stability, and reduced novelty-seeking behavior.

3.3. Literature Review

* Haloperidol can produce rapid antidepressant improvement, within a few days (Kennedy et al., 2014).

* Studies indicate D2-High dopaminergic supersensitivity antidepressant effect after slow withdrawal (Seeman, 2002).

* Comparative studies show superiority in psychotic depressive subgroups compared to risperidone (Gupta et al., 2015).

* Efficacy observed in catatonias with food refusal, facilitating recovery (Caixeta, 2024).

3.4. Likely Involved Neurobiological Mechanisms

* Limbic D2: reduction of suicidal emotional salience and rumination (Seeman, 2002).

* α 1-adrenergic: adrenolytic effect - reduction of physical anxiety and hyperarousal (Hudson et al., 2014).

* Sigma-1: modulation of impulsive glutamatergic plasticity (Shirayama & Hashimoto, 2007).

* 5HT2A: reduction of impulsive suicidal agitation (Meltzer & Massey, 2011).

* D3: control of disorganized motivation (Seeman et al., 2014).

* Hypothalamic-pituitary-adrenal axis (HPA): reduction of cortisol and ACTH in hypercortisolemic borderline states (Duval et al., 2000; Sapolsky, 2000).

* Prolactin: blockade of the tuberoinfundibular axis, hormonal stabilization in hyperreactive adolescents (Kvetnansky et al., 2009). Sometimes leading to amenorrhea and anovulatory cycles (prolactin blocking LH, FSH), which can help in the extreme luteal dysphoria – often impulsive, suicidal, “semi-psychotic” – of these patients.

* Calcium channels (L-type): blockade and additional stabilizing effect (Wang et al., 1999).

* Post-withdrawal D2 supersensitivity: prolonged antidepressant potential (Kennedy et al., 2014).

Studies show that patients on haloperidol, in these specific circumstances mentioned in our case,

can benefit from an antidepressant effect with low doses (e.g., 0.5 mg to 2 mg/day), or by using these low doses for a few days and then stopping. When they stop using it, the "denervation" supersensitivity of the postsynaptic button could increase dopaminergic firing, leading to an improvement in depression. This strategy, however, is not indicated by our service, because, in our experience, the depression returns after a few days, and can return very severely and with risk to life.

4.DISCUSSION

Haloperidol, in adequate and cautiously monitored doses, demonstrates relevant direct antidepressant capacity in complex subgroups, especially hyperactive borderlines (like our patient), suicidal mixed states, and psychotic catatonias with food refusal. Its effect is not limited to ataraxia but acts directly as an antidepressant. It acts on limbic-striatal circuits of "suicidal perseveration/obsessiveness" — a mechanism analogous to that observed in motor tics and obsessive-extrapyramidal syndromes (Swerdlow et al., 1990).

Hospital psychiatry in countries with limited resources needs safe, accessible, and effective interventions. Haloperidol, when judiciously indicated, fulfills this role, avoiding more invasive, expensive, or interventionist biological procedures (ECT, Ketamine, TMS, etc.) often unnecessary and impractical in everyday reality (Caixeta, 2024). The excessive "proceduralization" (many procedures, interventionist, invasive, costly, risky, "technological") of modern psychiatry unfortunately disregards this accessible tool.

The complexity of Patient Y's case illustrates the difficulty in treating resistant depression, especially when complex psychiatric and behavioral comorbidities overlap. The failure of multiple classes of conventional psychopharmacological agents highlights the need for alternative therapeutic approaches, such as the use of first-generation antipsychotics like haloperidol.

4.1.Haloperidol for Refractory Depression and Affective Dysregulation

In severe hospital psychiatry, it is common to encounter female patients with childhood ADHD — often inattentive type — who develop anxiety and depressive symptoms during puberty. They frequently worsen during the luteal phase and may evolve into suicidal or self-mutilating behaviors, often with borderline traits, substance use, and mood instability. Antidepressants alone are usually insufficient, and mood stabilizers provide only partial relief. Haloperidol has shown effectiveness in such complex cases. At higher doses, it can control impulsivity and suicidality. Later, maintenance doses can be reduced to minimize side effects such as akathisia, which often requires additional treatment. Mechanistically, haloperidol blocks 5HT_{2A} receptors (as some atypical antipsychotics do) and affects the tuberoinfundibular axis, raising prolactin levels and possibly inducing anovulation. This interference with the hypothalamic-pituitary-gonadal axis may contribute to its efficacy in female patients. Moreover, haloperidol may have indirect effects on glutamate, sigma receptors, NMDA pathways, and cortisol regulation. Clinically, it often improves mood beyond sedation, inducing a "second-order ataraxia" where patients stop complaining about their subdued state and become more compliant and less reactive.

4.2.Beyond Borderline: When Other Treatments Fail

Attempts to treat these patients with stimulants or non-stimulant ADHD medications are usually ineffective, and valproate may exacerbate depressive symptoms over time. Lithium, often combined with haloperidol, may offer long-term mood stabilization, allowing for a gradual tapering of neuroleptics. Other atypicals, such as quetiapine or aripiprazole, often fail to address the disruptive, impulsive, and borderline symptoms as effectively as haloperidol. These patients frequently have mood profiles that are extremely reactive and frustration-sensitive, which may respond better to carbamazepine or, to a lesser extent, valproate — though the latter's long-term effects on folate metabolism can worsen depressive symptoms. In clinical practice, combining lithium and haloperidol appears to offer both short-term containment and long-term stability in these highly refractory and complex clinical profiles.

Effects of Risperidone and Haloperidol in Treatment-Resistant Depression

Differentiated Indications

Risperidone may also have a beneficial effect in some patients who respond to haloperidol. These are patients with treatment-resistant depression who are not highly disruptive in terms of suicidal risk. They are not in suicidal psychosis. They are not refractory to psychotherapy. They are simply depressed. Thus, they may respond to risperidone.

Suicidal Psychosis and Chemical Lobotomy

For those who are highly psychotic, with suicidal psychosis, when the patient experiences many suicidal raptus, they will need urgent chemical lobotomy. In these cases, a high dose of haloperidol is required. Lower doses are used for maintenance in depression. At this stage of intense suicidal psychosis, it works like electroconvulsive therapy. It remits the patient at higher doses.

Haloperidol Loading Dose

Generally, in a young, treatment-naïve patient without microsomal induction, this dose may reach, for example, 80 to 100 drops of haloperidol, which corresponds to 8 to 10 mg as an initial loading dose. This can rise to 300, 400 mg, depending on the patient's microsomal capacity. The loading dose is administered and then gradually reduced. It acts like electroshock, eliminating the patient's suicidal raptus.

Ataractic Properties of Haloperidol

Risperidone does not have this ataractic power. In fact, the ataractic effect of haloperidol is sui generis. And it applies not only to this suicidal situation, but is also very important in patients who are litigious, querulous, prone to lawsuits, conduct disorders, personality disorders, and

temperament disorders. It is the most ataractic of the neuroleptics without being sedative. Therefore, in the case of chemical lobotomy for depression, it is highly effective. Risperidone lacks this action.

Use of Risperidone in Depression Without Suicidal Psychosis

However, in cases without suicidal raptus or suicidal psychosis, risperidone can be effective, especially at low doses, since it has the advantage of causing little akathisia and few extrapyramidal symptoms, especially below 2 mg.

Possible Worsening of Obsessive Symptoms

The literature also reports that risperidone, due to some serotonin blockade, may worsen certain obsessive symptoms. There are reports of this effect. Thus, some caution is necessary.

Dopaminergic Action at Low Doses

At low doses, it is effective and causes little akathisia. It may have the same effect observed with other neuroleptics — even haloperidol and aripiprazole — of being slightly pro-dopaminergic at very low doses.

It is worth mentioning that there is a significant chemical structural similarity among these neuroleptics — risperidone, aripiprazole — which brings them close in terms of pharmacodynamic action.

Final Considerations

Therefore, it is important to emphasize that risperidone may be used at low doses with an antidepressant effect similar to that of haloperidol, and perhaps other antipsychotics as well, possibly with a pro-dopaminergic effect at low doses. However, caution must be exercised regarding akathisia, which can worsen suicidal raptus. Many suicidal raptus are linked to akathisia.

5. CONCLUSION

Haloperidol represents a rapid and safe indirect antidepressant alternative in refractory suicidal depressions, psychotic catatonias, and suicidal mixed states, offering a practical solution in clinical contexts with economic constraints. Its rational use can save lives in situations of imminent risk.

Patient Y's case highlights that, in scenarios of severe and treatment-resistant depression, especially with complex psychiatric comorbidities and a history of self-harm, classic neuroleptics like haloperidol may emerge as a therapeutic option after the failure of multiple other approaches. Although its use requires caution due to the adverse effects profile, understanding its mechanism of action and careful patient evaluation can justify its application in specific cases where the potential benefit outweighs the risks. Further research is needed to delineate the exact role of haloperidol in resistant depression and to identify patient subpopulations that may benefit most from this intervention.

CONSENT

As per international standards or university standards, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable

DISCLAIMER

We hereby declare that no generative AI technology and text-image generators were used during the writing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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