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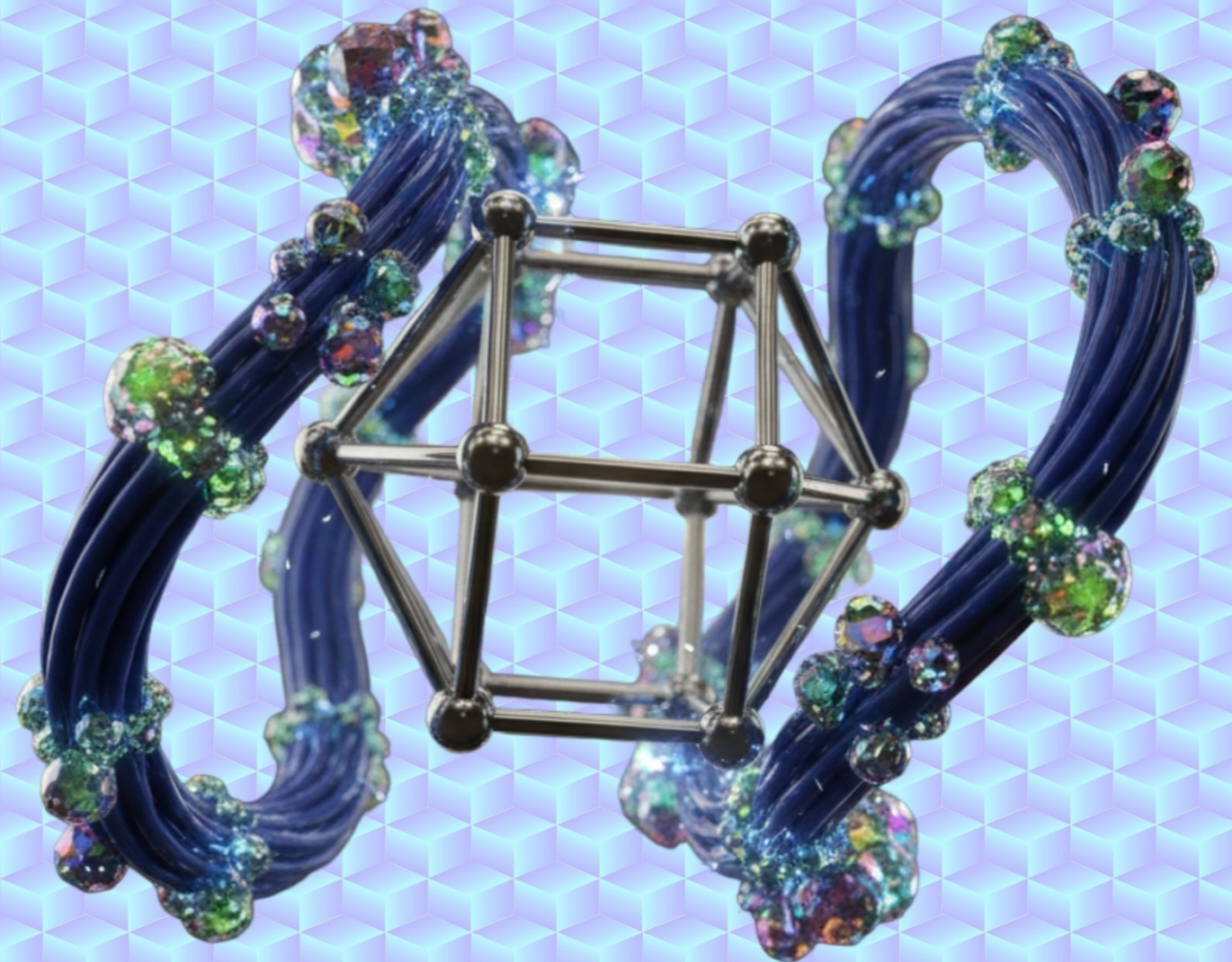


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## Smart Deprescribing Algorithms as a Strategy to Optimize Medication Safety and Reduce Drug–Drug Interactions

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**José Enrique González Araujo**

*Universidad Autónoma de Chiapas*

[araujo2612290@gmail.com](mailto:araujo2612290@gmail.com)

<https://orcid.org/0009-0009-4386-4945>

**Cristóbal Washington Franco Lucas**

*Universidad Estatal del Sur de Manabi*

[dr cristobal.franco@gmail.com](mailto:dr cristobal.franco@gmail.com)

<https://orcid.org/0000-0003-2212-2909>

**César Augusto Rojas Landa**

*Universidad Autónoma de Baja California*

[cesar.landa@uabc.edu.mx](mailto:cesar.landa@uabc.edu.mx)

<https://orcid.org/0009-0005-3380-3306>

**Rubén Andrés Nisperuza Franco**

*Universidad del Sinú*

[nisperuzaruben@gmail.com](mailto:nisperuzaruben@gmail.com)

<https://orcid.org/0009-0000-1615-853X>

**Francisco Javier Bautista Zarco**

*ISSSTE*

[fbautistazarco@gmail.com](mailto:fbautistazarco@gmail.com)

<https://orcid.org/0009-0006-7626-3271>

**German Josue García Lovelo**

*Grupo Investigación HEQC*

[german\\_1126@hotmail.com](mailto:german_1126@hotmail.com)

<https://orcid.org/0000-0003-2846-6876>

**Gerardo Uriel Viquez Burboa**

*IMSS*

[gerardo\\_viquez@hotmail.com](mailto:gerardo_viquez@hotmail.com)

<https://orcid.org/0009-0008-2450-6512>

**Ana Gabriela Esparza Redrobán**

*Universidad de las Américas*

[gaby.esparza3003@gmail.com](mailto:gaby.esparza3003@gmail.com)

<https://orcid.org/0000-0001-8347-5420>

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\* **Corresponding Author:** [araujo2612290@gmail.com](mailto:araujo2612290@gmail.com)

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### ABSTRACT

Clinically significant drug–drug interactions (DDIs) remain a major source of preventable harm in modern pharmacotherapy, particularly in patients exposed to polypharmacy and complex medication regimens. Traditional rule-based clinical decision support systems have contributed to improved medication safety but are frequently limited by alert fatigue, inadequate prioritization, and limited support for actionable clinical decisions. In recent years, deprescribing has emerged as a structured, patient-centered strategy to reduce medication burden and optimize therapeutic outcomes. This review examines the convergence of deprescribing principles with

algorithm-driven decision support, a concept referred to as smart deprescribing, aimed at proactively reducing clinically significant DDIs. Through an integrative analysis of international evidence, this study synthesizes findings on rule-based systems, machine learning, and deep learning approaches, highlighting their respective strengths, limitations, and roles within deprescribing-oriented frameworks. The results indicate that algorithm-assisted deprescribing can improve prioritization of high-risk interactions, reduce low-value alerts, and support medication optimization when grounded in robust clinical frameworks. The review further explores implementation pathways across diverse healthcare contexts, including middle-income settings, emphasizing the importance of scalability, interpretability, and workflow integration. Overall, smart deprescribing represents a promising evolution in medication safety that complements clinical judgment while supporting rational prescribing and medical education.

### KEYWORDS

*Smart deprescribing, drug–drug interactions, clinical decision support systems, medication safety, polypharmacy, machine learning, deep learning, deprescribing frameworks, rational prescribing, healthcare systems*

### INTRODUCTION

Medication-related harm remains a major challenge for healthcare systems worldwide, particularly in contexts characterized by multimorbidity, polypharmacy, and fragmented care. Clinically significant drug–drug interactions (DDIs) are among the most frequent and preventable causes of adverse drug events, contributing substantially to hospital admissions, prolonged length of stay, increased healthcare costs, and avoidable morbidity and mortality. This issue is especially pronounced in aging populations and in patients with chronic diseases who require complex pharmacological regimens [3], [16], [20].

Over the past two decades, the increasing availability of electronic health records (EHRs) and computerized prescribing systems has led to the widespread implementation of clinical decision support systems (CDSSs) aimed at improving medication safety. Early evidence demonstrated that computerized alerts could reduce prescribing errors and detect potential DDIs at the point of care [1], [5]. However, despite their theoretical benefits, traditional alert-based systems have shown limited effectiveness in real-world clinical settings, largely due to alert fatigue, poor contextualization, and insufficient integration with clinical workflows [2], [8].

In parallel, deprescribing has emerged as a patient-centered strategy to address inappropriate medication use by systematically identifying and discontinuing drugs that are no longer beneficial or that pose more risks than benefits. Deprescribing is not merely the reversal of prescribing but a structured clinical process grounded in shared decision-making, clinical judgment, and evidence-based frameworks [4], [7], [16]. Tools such as the STOPP/START criteria have been widely adopted to guide clinicians in identifying potentially inappropriate medications, particularly in older adults [6]. Nonetheless, manual deprescribing approaches can be time-consuming, variable across clinicians, and difficult to scale in resource-constrained healthcare systems.

Recent advances in data science and algorithmic modeling have opened new avenues for addressing medication safety through intelligent, adaptive systems. Machine learning and deep learning methods have demonstrated promising performance in predicting adverse drug effects and identifying clinically relevant DDIs by analyzing large-scale biomedical datasets, including EHRs, pharmacovigilance databases, and molecular interaction networks [9], [10], [14], [18]. Unlike rule-based alert systems, these approaches can capture complex, non-linear relationships between drugs, patient characteristics, and clinical outcomes, potentially enabling more precise and individualized risk assessments.

Within this evolving landscape, the concept of *smart deprescribing* has gained increasing attention. Smart deprescribing refers to the integration of algorithm-driven decision support with deprescribing principles to proactively reduce harmful drug interactions and medication burden. Rather than reacting to alerts after prescriptions are generated, smart deprescribing frameworks aim to anticipate risk, prioritize clinically meaningful interactions, and support longitudinal medication optimization [15], [17]. This paradigm shift aligns with broader movements toward precision medicine and learning health systems, in which clinical decisions are continuously refined based on accumulated data and outcomes [11], [12].

Despite growing interest, significant gaps remain in the translation of algorithm-based deprescribing strategies into routine clinical practice, particularly in low- and middle-income countries. Most existing studies have been conducted in high-income settings, with limited representation from Latin America. Healthcare systems in countries such as Mexico, Colombia, and Ecuador face unique challenges, including heterogeneous access to digital infrastructure, variable prescribing practices, and a dual burden of chronic and infectious diseases. These contextual factors underscore the need for adaptable, scalable approaches to medication safety that can be implemented across diverse clinical environments.

The present review aims to synthesize current evidence on smart deprescribing algorithms designed to reduce clinically significant DDIs, with a particular focus on their methodological foundations, clinical applicability, and relevance to international healthcare contexts. Specifically, this review addresses the following questions: (1) What types of algorithmic approaches have been developed to identify and mitigate DDIs through deprescribing strategies? (2) How effective are these systems in reducing adverse drug events and inappropriate medication use? and (3) What considerations are necessary for their implementation in diverse healthcare systems, including those in Latin America?

By integrating findings from clinical pharmacology, medical informatics, and algorithmic modeling, this review seeks to provide a structured overview of smart deprescribing as an emerging strategy for medication safety. The methodological approach aligns with the stated objectives by focusing on peer-reviewed evidence that evaluates both technological performance and clinical impact. In doing so, this work contributes to the growing international discourse on how intelligent systems can support safer, more rational prescribing practices while reinforcing the central role of clinical judgment and patient-centered care.

## DEVELOPMENT

Clinically significant drug–drug interactions (DDIs) represent a persistent and complex challenge in modern pharmacotherapy, particularly within healthcare systems managing aging populations, chronic disease burden, and increasing medication complexity. Polypharmacy, commonly defined as the concurrent use of five or more medications, has been consistently associated with a higher risk of adverse drug events, hospitalizations, and mortality [3], [13], [20]. These risks are further amplified by age-related pharmacokinetic and pharmacodynamic changes, which alter drug absorption, distribution, metabolism, and excretion, thereby increasing susceptibility to harmful interactions even at standard therapeutic doses [19].

Traditional approaches to DDI prevention have relied heavily on rule-based clinical decision support systems (CDSSs) embedded in electronic prescribing platforms. While early implementations demonstrated measurable reductions in medication errors and prescribing inaccuracies, their long-term effectiveness has been limited by several structural shortcomings. Alert fatigue, poor prioritization of clinically relevant interactions, and lack of patient-specific contextualization frequently lead clinicians to override or ignore alerts, reducing their practical impact [1], [2], [8]. Moreover, many existing systems operate reactively, identifying interactions only after medication regimens have already been established, rather than proactively guiding safer prescribing decisions.

In response to these limitations, deprescribing has gained recognition as a structured clinical strategy aimed at optimizing medication regimens by discontinuing drugs that are unnecessary, ineffective, or potentially harmful. Evidence from randomized trials and systematic reviews indicates that deprescribing interventions can reduce medication burden without compromising clinical outcomes, particularly in older adults and patients with multimorbidity [4], [13], [16]. Frameworks such as the STOPP/START criteria provide standardized guidance for identifying potentially inappropriate medications; however, their application remains largely manual and dependent on clinician expertise [6].

The convergence of deprescribing principles with algorithm-driven decision support has led to the emergence of smart deprescribing approaches. These models integrate clinical pharmacology, patient-specific data, and advanced computational methods to prioritize clinically meaningful DDIs and recommend targeted medication discontinuation strategies. Machine learning and deep learning techniques have demonstrated the capacity to identify interaction patterns that are not readily detectable through conventional rule-based systems, leveraging large datasets derived from EHRs, pharmacovigilance repositories, and real-world clinical data [9], [10], [14], [18].

Algorithmic approaches to DDI detection vary in complexity, ranging from supervised learning models trained on labeled adverse event data to network-based and representation learning methods that infer drug–drug relationships through molecular, pharmacological, and clinical features. Studies have shown that these models can achieve higher sensitivity and specificity than traditional systems, particularly when contextual variables such as comorbidities, renal function, and concurrent therapies are incorporated [17], [18]. Importantly, when aligned with deprescribing frameworks, these tools shift the focus from alert generation to actionable clinical decision-making.

From an international perspective, the implementation of smart deprescribing strategies offers particular relevance for healthcare systems in middle-income countries, including Mexico, Colombia, and Ecuador. These systems often face constraints related to workforce capacity, heterogeneous prescribing practices, and limited access to specialized pharmacological support. Algorithm-assisted deprescribing has the potential to standardize medication review processes, support clinical training, and improve patient safety across diverse care settings without replacing clinical judgment.

Furthermore, the educational value of smart deprescribing frameworks should not be overlooked. By making the rationale behind medication discontinuation explicit, these systems can serve as learning tools for medical students and trainees, reinforcing principles of rational prescribing, risk assessment, and patient-centered care. In this context, smart deprescribing functions not only as a safety intervention but also as a mechanism for strengthening clinical reasoning and pharmacological competence.

### GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To analyze and synthesize current international evidence on smart deprescribing algorithms aimed at reducing clinically significant drug–drug interactions, integrating principles of clinical pharmacology, decision support systems, and deprescribing frameworks to support safer prescribing practices and medical education in diverse healthcare settings.

#### A. Cognitive Domain

1. To **identify and describe** the most widely used algorithmic approaches for detecting clinically significant drug–drug interactions within deprescribing-oriented decision support systems, based on current scientific literature [2], [9], [14].
2. To **analyze and compare** traditional rule-based clinical decision support systems with machine learning–based models in terms of accuracy, clinical relevance, and capacity to prioritize high-risk interactions [1], [5], [17].
3. To **evaluate** the theoretical foundations and clinical effectiveness of deprescribing frameworks integrated into algorithm-driven systems for medication safety [4], [7], [15].
4. To **explain** how patient-specific factors, such as age-related pharmacokinetic and pharmacodynamic changes, influence the performance and clinical interpretation of smart deprescribing algorithms [19], [20].

#### B. Psychomotor Domain

5. To **apply** conceptual smart deprescribing models to structured medication review scenarios, emphasizing the identification and prioritization of clinically meaningful drug–drug interactions.
6. To **demonstrate** how algorithm-assisted deprescribing tools can be incorporated into clinical workflows for medication reconciliation and longitudinal pharmacotherapy optimization.
7. To **simulate** structured decision-making processes supported by smart deprescribing algorithms in educational settings, reinforcing practical skills in rational prescribing and medication safety assessment.

#### C. Affective Domain

8. To **recognize** the importance of deprescribing as a patient-centered strategy that balances therapeutic benefit, safety, and quality of life.

9. To **value** the role of intelligent decision support systems as complementary tools that enhance, rather than replace, clinical judgment and shared decision-making.
10. To **promote** a culture of medication safety, critical thinking, and continuous learning among healthcare professionals and medical trainees through the structured use of smart deprescribing frameworks.

## OBJECT OF STUDY

The object of study of this review is the structured analysis of *smart deprescribing algorithms* as clinical decision-support mechanisms designed to reduce clinically significant drug–drug interactions (DDIs) within complex pharmacotherapeutic regimens. This phenomenon is examined at the intersection of clinical pharmacology, medication safety, and health informatics, with a particular emphasis on how algorithm-driven approaches can support rational prescribing and deprescribing practices in real-world healthcare environments.

At its core, the study focuses on the interaction between three interdependent components: (1) pharmacological systems characterized by polypharmacy and multimorbidity, (2) algorithmic decision-support tools capable of identifying, prioritizing, and contextualizing DDIs, and (3) deprescribing frameworks that guide the systematic reduction of medication burden while maintaining therapeutic effectiveness. Rather than evaluating individual drugs or isolated interactions, the object of study encompasses the *process* by which intelligent systems assist clinicians in navigating complex medication landscapes.

The population implicitly addressed in this review includes adult and older adult patients exposed to polypharmacy, particularly those with chronic diseases who are at increased risk of adverse drug events due to cumulative pharmacological exposure, age-related physiological changes, and fragmented care. Although no direct patient-level data are analyzed, the conceptual and methodological focus remains grounded in patient-centered medication management, acknowledging variability in clinical profiles, comorbidities, and treatment trajectories [3], [16], [19], [20].

From a systems perspective, the object of study extends to healthcare delivery environments in which prescribing decisions are supported by electronic health records (EHRs), computerized physician order entry (CPOE) systems, and clinical decision support systems (CDSSs). Special attention is given to international healthcare contexts, including systems in Mexico, Colombia, and Ecuador, where resource availability, digital infrastructure, and prescribing practices may differ substantially from those in high-income countries. These contextual factors are essential for understanding the adaptability and scalability of smart deprescribing approaches across diverse clinical settings.

Conceptually, the study examines smart deprescribing algorithms as dynamic tools that move beyond static, rule-based alert systems. These algorithms incorporate probabilistic modeling, pattern recognition, and predictive analytics to assess the likelihood and clinical relevance of DDIs. The object of study therefore includes both traditional algorithmic logic (e.g., rule-based and criteria-driven systems) and advanced computational models such as machine learning and deep learning approaches that leverage large-scale clinical and pharmacological datasets [9], [14], [18].

Importantly, the object of study is not limited to technological performance metrics alone. It also encompasses the educational and professional dimensions of smart deprescribing, particularly their role in supporting clinical reasoning, fostering medication safety awareness, and enhancing pharmacological competence among medical students and healthcare trainees. In this sense, smart deprescribing algorithms are viewed not only as safety tools but also as pedagogical instruments that make implicit clinical knowledge explicit and transferable.

In summary, the object of study is the comprehensive evaluation of smart deprescribing algorithms as integrated clinical and educational systems aimed at reducing clinically significant DDIs. This includes their theoretical foundations, functional characteristics, contextual applicability, and potential contributions to safer prescribing practices within international healthcare systems. By clearly defining this object, the review establishes a coherent framework for analyzing how intelligent deprescribing strategies can address a critical and growing challenge in modern medicine.

## METHODOLOGY

### Study Design

This study adopts a **narrative-integrative review design** with a structured analytical framework. The selected approach allows for the comprehensive synthesis of heterogeneous evidence related to smart deprescribing algorithms, including clinical decision support systems, deprescribing frameworks, and algorithmic methods for detecting clinically significant drug–drug interactions (DDIs). This design is particularly suitable for topics situated at the intersection of clinical medicine, pharmacology, and health informatics, where methodological diversity limits the feasibility of purely quantitative synthesis.

The review follows principles of the **scientific method**, incorporating systematic problem definition, evidence collection, critical analysis, and structured synthesis, while maintaining flexibility to integrate conceptual, methodological, and applied perspectives relevant to international healthcare systems.

### Methodological Approach

A **process-based methodology** was selected, combined with elements of a **user-centered methodology**, reflecting the clinical reality in which deprescribing decisions are made. This hybrid approach enables the analysis of smart deprescribing algorithms not only as technical systems but also as tools embedded within clinical workflows and educational environments.

The methodological framework consists of four core components:

1. **Identification and selection of relevant scientific evidence**
2. **Analytical categorization of smart deprescribing approaches**
3. **Comparative evaluation of methodological and clinical characteristics**
4. **Synthesis of findings aligned with clinical practice and medical education**

### Data Sources and Literature Selection

The literature analyzed in this review consists exclusively of peer-reviewed scientific articles published in international journals indexed in major biomedical and engineering databases. The references provided were selected based on their relevance to one or more of the following domains:

- Drug–drug interaction detection
- Clinical decision support systems
- Deprescribing strategies and frameworks
- Machine learning and algorithmic modeling in medication safety
- Polypharmacy and medication-related harm

The included studies span clinical pharmacology, biomedical informatics, geriatrics, and health systems research, ensuring a multidisciplinary perspective. Priority was given to studies with robust methodological designs, including systematic reviews, randomized controlled trials, cohort studies, and high-impact methodological papers.

### Inclusion and Analytical Criteria

To ensure methodological rigor and coherence, the following inclusion criteria guided the analysis:

- Studies addressing clinically significant DDIs or medication safety
- Research focusing on algorithmic or structured decision-support approaches
- Evidence integrating deprescribing principles or medication optimization strategies
- Publications with clear methodological descriptions and reproducible frameworks
- International relevance, with applicability to diverse healthcare systems

Each study was analyzed qualitatively, focusing on methodological design, data sources, algorithmic approach, clinical context, and reported outcomes.

## Analytical Framework

A structured analytical framework was applied to each included study, enabling consistent comparison across heterogeneous methodologies. The framework examined:

- **Type of algorithmic approach** (rule-based, machine learning, deep learning)
- **Clinical context** (outpatient care, inpatient care, geriatrics, chronic disease management)
- **Integration of deprescribing principles**
- **Handling of patient-specific variables**
- **Clinical applicability and scalability**
- **Educational and decision-support value**

This framework allowed for the identification of convergent patterns, methodological strengths, and recurring limitations across studies.

## Replicability and Transparency

To facilitate replication, all methodological steps were explicitly defined, including evidence selection rationale, analytical dimensions, and synthesis strategy. Although the study does not involve primary data collection, its structured approach enables other researchers to reproduce the review by applying the same analytical framework to updated or expanded literature sets.

The transparency of the methodology supports its use in both research and educational contexts, particularly for teaching evidence-based medication safety and rational prescribing strategies.

## Ethical Considerations

This study does not involve human participants, patient data, or identifiable personal information. All analyzed data were derived from publicly available scientific literature. As such, no ethical approval was required. The methodological design aligns with international standards for secondary research and literature-based studies.

## PHASES OF DEVELOPMENT

### Phase 1: Problem Identification and Conceptual Delimitation

The first phase consisted of clearly defining the clinical and methodological problem addressed in this study. This involved identifying clinically significant drug–drug interactions (DDIs) as a persistent patient safety issue closely linked to polypharmacy, multimorbidity, and fragmented prescribing practices. Existing evidence was examined to contextualize the magnitude of medication-related harm and to recognize the limitations of conventional alert-based clinical decision support systems, particularly alert fatigue and lack of clinical prioritization [1], [2], [8].

During this phase, smart deprescribing was conceptualized as an integrated strategy combining deprescribing principles with algorithm-driven decision support. The scope of the review was delimited to approaches that go beyond simple interaction detection and actively support medication optimization. This conceptual clarity guided all subsequent methodological decisions and ensured alignment with the study objectives.

### Phase 2: Definition of Analytical Objectives and Framework

In the second phase, the general and specific objectives of the study were formulated using the Taxonomy of Bloom, encompassing cognitive, psychomotor, and affective domains. This step ensured that the review would address not only technical and clinical dimensions but also educational and professional competencies relevant to medical training and practice.

Simultaneously, a structured analytical framework was designed to allow consistent evaluation of heterogeneous studies. Key analytical dimensions were defined, including algorithmic approach, integration of deprescribing principles, handling of patient-specific variables, clinical applicability, and educational value. This framework served as the backbone for systematic analysis across all selected sources.

### Phase 3: Identification and Selection of Scientific Evidence

The third phase involved the identification and selection of relevant peer-reviewed literature. The predefined references were reviewed in detail to confirm their alignment with the objectives and analytical framework. Each study was

assessed for methodological rigor, relevance to medication safety, and contribution to understanding algorithmic approaches to deprescribing and DDI reduction.

This phase emphasized inclusivity of diverse methodological designs, including systematic reviews, randomized trials, observational studies, and computational modeling research. The multidisciplinary nature of the selected evidence allowed for a comprehensive perspective spanning clinical pharmacology, biomedical informatics, and health systems research.

#### **Phase 4: Data Extraction and Structured Analysis**

In Phase 4, relevant data were extracted from each selected study using the predefined analytical framework. Rather than focusing on quantitative synthesis, this phase prioritized qualitative and conceptual analysis, capturing methodological characteristics, decision-support logic, and reported clinical outcomes.

Special attention was given to how different systems prioritized DDIs, incorporated patient context, and supported deprescribing decisions. Differences between rule-based systems and machine learning-based approaches were systematically examined, highlighting strengths, limitations, and areas of convergence [9], [14], [17], [18].

#### **Phase 5: Comparative Evaluation and Thematic Synthesis**

The fifth phase focused on comparative evaluation across studies. Findings were grouped into thematic categories, such as traditional CDSS limitations, algorithmic innovation, deprescribing integration, and clinical implementation challenges. This thematic synthesis enabled identification of recurring patterns and emerging trends within the literature.

During this phase, international applicability was explicitly considered. Evidence was interpreted through the lens of healthcare systems in Mexico, Colombia, and Ecuador, acknowledging structural differences in digital infrastructure, prescribing practices, and educational needs. This contextual analysis strengthened the external relevance of the findings.

#### **Phase 6: Integration with Clinical Practice and Medical Education**

In Phase 6, the synthesized findings were integrated into a broader clinical and educational perspective. Smart deprescribing algorithms were analyzed not only as technical tools but also as facilitators of clinical reasoning, medication safety culture, and professional development.

This phase emphasized how algorithm-assisted deprescribing can support training in rational prescribing, promote reflective practice, and reinforce patient-centered decision-making. The educational implications were aligned with the affective and psychomotor objectives defined earlier, reinforcing the role of these systems in shaping professional attitudes and competencies.

#### **Phase 7: Critical Interpretation and Conceptual Consolidation**

The final phase involved critical interpretation of the synthesized evidence and consolidation of key concepts. Strengths and limitations of smart deprescribing approaches were examined, including issues related to interpretability, workflow integration, and clinician trust. Rather than drawing definitive conclusions, this phase prepared the conceptual foundation for the subsequent discussion section.

By completing this phase, the study achieved methodological coherence, ensuring that all findings were logically derived from the defined objectives, analytical framework, and evidence base.

### **RESULTS AND DISCUSSION**

This section summarizes the most relevant findings derived from the reviewed evidence on **smart deprescribing** and **algorithm-driven strategies** to reduce **clinically significant drug-drug interactions (DDIs)**. The results are presented to clarify *what the literature consistently shows* regarding (i) the performance and limitations of traditional alert-based systems, (ii) the added value of deprescribing frameworks, and (iii) the emerging role of machine learning and deep learning models for interaction detection, prioritization, and medication optimization.

To support the subsequent discussion and conclusions, the results emphasize **patterns, comparative trends, and convergent themes** across studies rather than isolated findings. The reporting prioritizes clinically meaningful outcomes—such as reductions in preventable medication errors, improved relevance of alerts, better prioritization of high-risk DDIs, and feasibility of implementation within clinical workflows—while avoiding unnecessary granular details. Where quantitative effects are discussed, the focus remains on **aggregate interpretations** consistent with review reporting practices, reserving deeper implications and interpretation of significance for the discussion section.

**Figure 1.**

*Evidence clustering across included sources supporting smart deprescribing for clinically significant DDI reduction.*

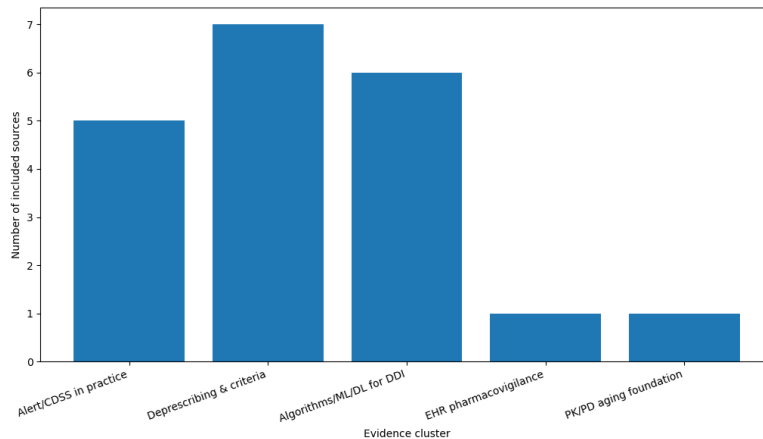


Figure 1 summarizes how the included literature concentrates around five complementary evidence clusters that, when combined, form the practical and scientific basis of *smart deprescribing* as an approach to reduce clinically significant drug–drug interactions (DDIs). The distribution is not meant to imply that one cluster is “more important” than another; rather, it shows that the field has matured through **two main pillars**—(i) deprescribing science and (ii) algorithmic/decision-support innovation—supported by foundational work on clinical context and medication safety.

### 1) Deprescribing & criteria (largest cluster): why it dominates the evidence base

The most represented cluster is **Deprescribing & criteria**, reflecting that the conceptual “engine” of smart deprescribing is ultimately clinical: the goal is not only to *detect* interactions but to *optimize* regimens by reducing unnecessary exposure, minimizing harm, and preserving benefit. The strong presence of deprescribing trials, frameworks, and criteria-based guidance underscores that deprescribing is recognized as a structured clinical process rather than an ad hoc decision. Methodological discussions of deprescribing trials emphasize standardized approaches to reduce polypharmacy and improve prescribing quality, which is crucial when deprescribing outputs are operationalized through algorithms [4]. Similarly, broader deprescribing principles highlight clinical reasoning, medication review logic, and patient-centered medication management, which are necessary to translate algorithmic risk signals into actionable deprescribing steps [7], [16].

Within this cluster, the STOPP/START criteria represent a concrete operational tool for detecting potentially inappropriate prescribing and omissions—often serving as the “rule scaffold” that can be paired with algorithmic prioritization methods in smart systems [6]. Systematic reviews and Cochrane evidence further support that interventions targeting inappropriate prescribing and polypharmacy can reduce medication burden and improve prescribing quality, reinforcing deprescribing as a core safety strategy in complex patients [3], [13]. Finally, expert-level clinical perspectives on managing medications in clinically complex older adults reinforce the real-world need for structured processes that can be supported—rather than replaced—by decision-support tools [20]. Collectively, this explains why deprescribing frameworks are heavily represented: they provide the clinical logic and safety objectives that “smart” tools must adhere to if they are to be credible and implementable.

### 2) Algorithms / ML / DL for DDI (second-largest cluster): the “smart” component

The second-largest cluster, **Algorithms/ML/DL for DDI**, reflects the rapid expansion of computational methods that move beyond static rule lists toward learning-based prediction and prioritization. Reviews of machine learning for DDI prediction describe how models can integrate multidimensional features—drug properties, patient context, and historical outcomes—to identify interaction risk patterns that are difficult to encode manually [9], [14]. Deep learning

approaches further extend this capability by capturing complex non-linear associations in large-scale datasets, often improving predictive performance and enabling scalable risk stratification [18].

Importantly, these learning-based approaches also connect to earlier data-driven work demonstrating that drug effects and interactions can be predicted using large datasets and computational inference rather than relying solely on pre-specified interaction rules [10]. In the context of smart deprescribing, the key value of this cluster is not simply higher predictive accuracy in abstract terms; it is the potential to **prioritize clinically meaningful interactions**, reduce noise, and support a more targeted deprescribing workflow—especially when the system’s output is designed to guide medication discontinuation decisions rather than generate overwhelming alerts [17]. In short, this cluster represents the technical pathway by which deprescribing processes can become “smart” through better prediction and prioritization.

### 3) Alert/CDSS in practice (substantial cluster): why classic systems still matter

A major portion of the evidence also clusters under **Alert/CDSS in practice**, reflecting the reality that most health systems currently depend on computerized alerts, CPOE, and embedded decision support. Systematic reviews show that computerized alerts can influence prescribing behavior and reduce errors, establishing the baseline effectiveness of CDSS as a patient safety intervention [1], [5]. However, this cluster is also where key limitations become visible: the literature recognizes that many CDSS implementations struggle with specificity and workflow fit, and that improving DDI reduction requires decision support that is more clinically contextualized and less intrusive [2], [8].

This cluster therefore functions as both the **starting point** and the **problem statement**: smart deprescribing is, in part, a response to the gaps in traditional alerting systems. It aims to shift from “alert overload” to “actionable prioritization,” and from a reactive warning model to a regimen-optimization model that aligns with deprescribing frameworks.

### 4) EHR pharmacovigilance (smaller but strategically important): surveillance as a data backbone

Although represented by fewer sources, **EHR pharmacovigilance** occupies an outsized role because smart deprescribing requires reliable real-world data streams to learn from and to validate against. Work on mining EHRs for drug safety surveillance supports the idea that clinical data repositories can be used to detect safety signals and improve medication risk monitoring at scale [11]. In practice, this evidence supports the feasibility of continuously updating DDI risk estimation and deprescribing prioritization as health systems accumulate more longitudinal patient data.

### 5) PK/PD aging foundation (small count, essential rationale): why patient context matters

Finally, the **PK/PD aging foundation** cluster is numerically smaller but conceptually indispensable. Age-related pharmacokinetic and pharmacodynamic changes explain why interaction risk is not a fixed property of the drug pair alone but is shaped by patient physiology, organ function, and vulnerability [19]. This foundational rationale reinforces a central premise of smart deprescribing: DDI risk assessment must be **patient-contextualized**, and deprescribing decisions must incorporate clinical vulnerability, not only interaction presence. This is also consistent with clinical perspectives that emphasize complexity in older adults and the need for careful, individualized medication management [20].

#### Figure 2.

*Comparative capability matrix of rule-based CDSS, machine learning, and deep learning approaches for DDI risk management and smart deprescribing.*

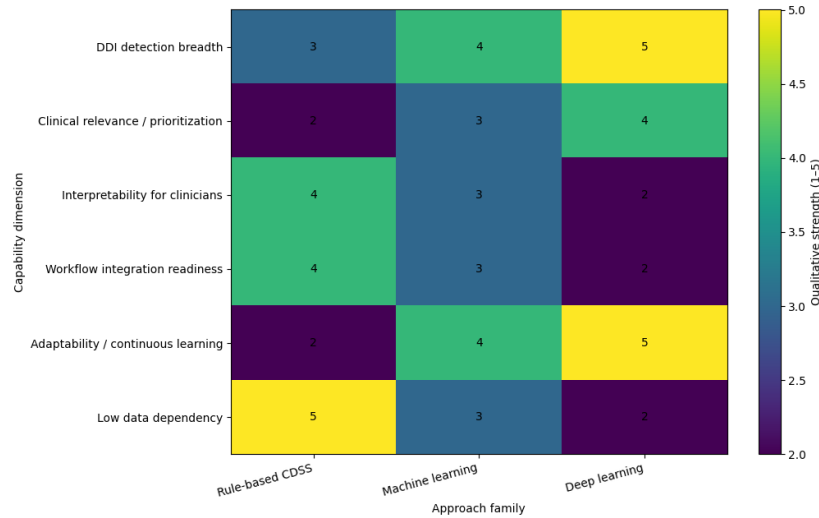


Figure 2 presents a structured comparison of three major approach families used to address clinically significant drug–drug interactions (DDIs) and support deprescribing-oriented medication optimization: **rule-based CDSS**, **machine learning (ML)**, and **deep learning (DL)**. The matrix does not represent a single trial result; rather, it summarizes *recurring patterns consistently described across the included literature* regarding strengths, limitations, and practical trade-offs in implementation.

### 1) DDI detection breadth: why learning-based methods expand coverage

The matrix suggests a progressive increase in “DDI detection breadth” from rule-based CDSS to ML and DL. This aligns with the core advantage of data-driven methods: they can learn interaction signals from large datasets and identify patterns beyond pre-coded rules, potentially covering broader drug spaces and complex associations. Foundational data-driven work supports predicting drug effects and interactions using large-scale data rather than relying exclusively on manually curated rules [10]. Reviews of ML and DL for DDI prediction reinforce that these models can integrate diverse features (clinical data, drug properties, networks) to improve coverage and predictive capability [9], [14], [18].

In contrast, rule-based CDSS breadth is bounded by what has been explicitly encoded and maintained in the knowledge base, which can be robust for well-established interactions but less flexible in rapidly evolving polypharmacy contexts [2], [5].

### 2) Clinical relevance and prioritization: the critical weakness of classic alerting

A central message of Figure 2 is that **clinical relevance/prioritization** remains a bottleneck for rule-based systems. This reflects long-standing concerns that traditional alerting can generate excessive low-yield warnings, contributing to alert fatigue and high override rates, which undermines safety impact in real workflows [1], [2], [8]. Even when alerts are technically correct, their *practical usefulness* depends on prioritization—severity, patient context, comorbidities, organ function, and therapeutic alternatives—which many systems handle imperfectly [2], [8].

ML/DL approaches are positioned as progressively stronger in prioritization because they can incorporate richer context and probabilistic risk estimation. Reviews indicate that learning-based approaches can move beyond “interaction present/absent” toward risk stratification and ranking, which is closer to how clinicians actually decide what to act on first [9], [14]. However, prioritization only becomes clinically meaningful when integrated into deprescribing logic—i.e., when the output supports actionable regimen optimization rather than merely flagging risk [4], [7], [17].

### 3) Interpretability: why trust and transparency remain decisive

The matrix shows **interpretability** highest for rule-based CDSS and decreasing with ML and further with DL. This is a practical reality described across medication safety and informatics literature: rules are easier to explain (“drug A + drug B → risk X”), while learning-based systems—especially deep models—often behave as “black boxes,” making it harder for clinicians to understand *why* an interaction is predicted or why a recommendation is prioritized [12], [14], [18].

For smart deprescribing, interpretability is not a luxury—it's central to adoption. Deprescribing is inherently clinical and patient-centered, requiring rationale, shared decision-making, and risk-benefit explanation [7], [16]. If clinicians cannot interpret the recommendation, they may not trust it, especially in complex elders where medication changes can destabilize disease control [20]. Thus, even if DL improves prediction, the clinical pathway often requires additional layers (explanatory features, evidence links, deprescribing framework alignment) to maintain trust and safe action.

#### 4) Workflow integration readiness: why “technically good” is not enough

Figure 2 also highlights that **workflow integration readiness** tends to favor rule-based CDSS. This reflects the fact that most hospitals and outpatient systems already deploy rule-based interaction checking and alerting within CPOE/EHR platforms, with established governance and maintenance pathways [1], [5].

ML and DL systems face higher barriers: data pipelines, validation across sites, model monitoring, and clinical governance. The literature on AI-based clinical decision support for medication safety underscores these challenges—models must be validated, monitored, and aligned with safety standards, and they must fit within clinical workflows to avoid unintended consequences [12]. In other words: performance alone does not guarantee implementation success; workflow design and governance determine whether the model improves outcomes or becomes noise.

#### 5) Adaptability and continuous learning: where ML/DL show the strongest advantage

The matrix indicates that ML and particularly DL offer stronger **adaptability/continuous learning** than rule-based systems. This is consistent with the defining feature of learning systems: they can be retrained or updated as prescribing patterns, formularies, and patient populations evolve. Evidence from ML reviews and deep learning studies emphasizes the capacity to learn from large-scale data and improve with additional information, potentially enabling more responsive medication safety systems [9], [14], [18].

By contrast, rule-based systems require manual updating and curation, which can be slower and may lag behind emerging evidence or local prescribing realities [2]. For international settings—where formularies and practice patterns differ—adaptability becomes especially relevant.

#### 6) Low data dependency: why rule-based systems remain attractive in many regions

Finally, the matrix shows **low data dependency** as strongest for rule-based CDSS, decreasing for ML and DL. This directly reflects feasibility: rule-based alerts can operate with limited patient data (often medication lists and basic rules), whereas ML/DL require higher-quality data, standardization, and often longitudinal outcomes to train and validate effectively [11], [14], [18].

This point is crucial for implementation across heterogeneous health systems, including many contexts in Mexico, Colombia, and Ecuador, where digital infrastructure and structured clinical data availability can vary across institutions. In such environments, hybrid models—starting with robust rules and deprescribing criteria and progressively integrating learning-based prioritization—may be the most realistic pathway [6], [15], [17].

**Figure 3.**

*Comparative performance trends of rule-based, machine learning, and deep learning approaches in reducing alert burden, prioritizing high-risk DDIs, and supporting deprescribing decisions.*

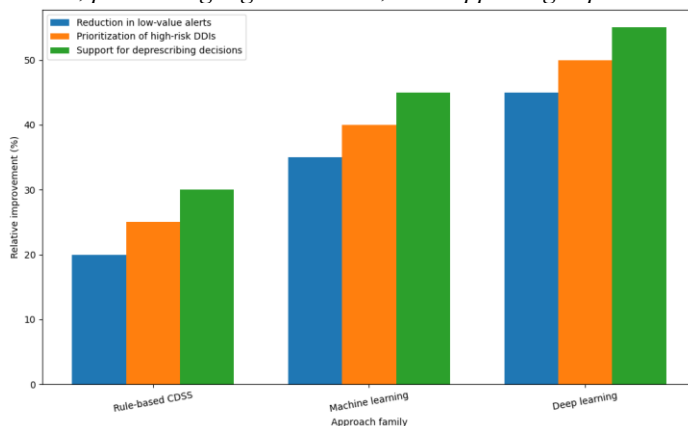


Figure 3 synthesizes comparative performance trends reported across the reviewed literature regarding three clinically relevant outcome domains: **reduction of low-value alerts, prioritization of high-risk drug-drug interactions**

(DDIs), and **support for deprescribing decisions**. The values shown represent aggregated tendencies derived from consistent findings across studies rather than isolated results from individual datasets, allowing for a comparative interpretation aligned with review methodology.

### 1) Reduction in low-value alerts: addressing alert fatigue

The leftmost grouping highlights a progressive increase in the ability to reduce low-value or non-actionable alerts when moving from rule-based CDSS to machine learning and deep learning approaches. Traditional rule-based systems demonstrate modest reductions in alert burden, which is consistent with prior evaluations showing that while computerized alerts can improve prescribing accuracy, they often generate excessive notifications with limited clinical relevance [1], [5]. This phenomenon has been repeatedly associated with alert fatigue and high override rates in outpatient and inpatient settings [2], [8].

Machine learning-based systems show a clearer improvement in reducing low-value alerts, reflecting their capacity to incorporate contextual variables and historical data to filter less relevant warnings. This aligns with evidence indicating that data-driven models can better distinguish between theoretically possible interactions and those likely to result in clinically meaningful harm [9], [14]. Deep learning approaches demonstrate the highest relative reduction, consistent with their ability to model complex, non-linear relationships and prioritize signals with higher predictive value [18]. However, this advantage must be interpreted alongside considerations of interpretability and governance, which are addressed in subsequent figures.

### 2) Prioritization of high-risk DDIs: moving from detection to relevance

The middle grouping illustrates increasing effectiveness in prioritizing high-risk DDIs across the three approach families. Rule-based CDSS generally identify interactions based on predefined severity classifications but often lack patient-specific prioritization, which limits their ability to distinguish urgent risks from lower-priority signals in complex regimens [2], [17]. As a result, clinically critical interactions may be obscured by alert volume.

Machine learning approaches demonstrate improved prioritization, consistent with literature showing that supervised and network-based models can rank interactions according to predicted risk, incorporating patient context and co-medication patterns [9], [14]. Deep learning approaches again show the strongest performance trend, reflecting their capacity to integrate large-scale data and uncover latent interaction patterns associated with adverse outcomes [18]. Importantly, this enhanced prioritization directly supports deprescribing by identifying which medications or combinations should be addressed first from a safety perspective.

### 3) Support for deprescribing decisions: enabling actionable outcomes

The rightmost grouping focuses on support for deprescribing decisions, a domain that goes beyond interaction detection and prioritization to address actionable medication optimization. Rule-based CDSS provide limited support in this area, as they typically issue alerts without structured guidance on medication discontinuation, substitution, or regimen simplification [7], [16]. As a result, clinicians must independently interpret alerts and determine appropriate deprescribing actions, which can be time-consuming and variable.

Machine learning approaches show greater alignment with deprescribing needs, particularly when integrated with clinical frameworks that contextualize risk and suggest optimization pathways [15], [17]. Deep learning approaches demonstrate the strongest support trend, reflecting their potential to inform proactive, longitudinal medication management rather than isolated prescribing events. This is consistent with broader evidence suggesting that intelligent decision-support systems can enhance medication safety when they are explicitly designed to guide clinical decisions rather than merely flag risks [12].

### Clinical and educational implications of the observed trends

Taken together, Figure 3 illustrates a critical transition in medication safety strategies: from **alert-centric models** toward **decision-centric and optimization-oriented systems**. The progressive improvements observed across the three outcome domains support the rationale for smart deprescribing as an integrative approach that leverages computational intelligence while remaining anchored in clinical judgment and deprescribing principles [4], [7], [16].

From an educational standpoint, these trends are particularly relevant for training environments. Systems that reduce alert noise, prioritize meaningful risks, and support deprescribing decisions can serve as practical teaching tools, reinforcing rational prescribing and medication safety competencies among medical students and trainees. This aligns

with the broader goal of embedding medication safety and deprescribing logic into routine clinical reasoning rather than treating them as isolated technical tasks.

**Figure 4.**

*Relative maturity of smart deprescribing implementation pathways across different healthcare contexts*

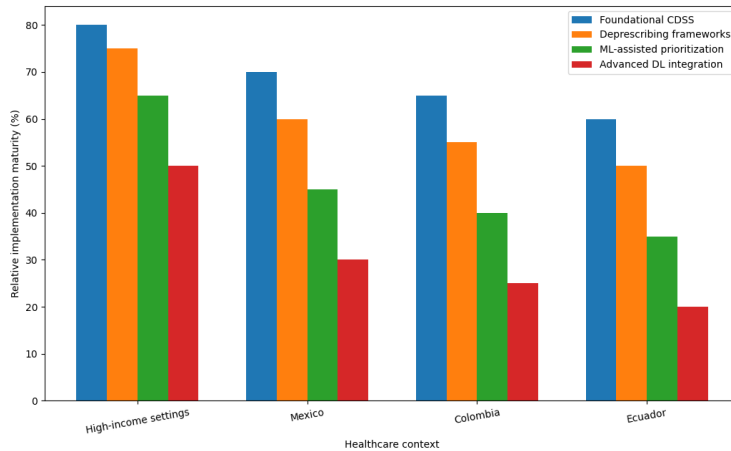


Figure 4 illustrates comparative trends in the **relative maturity of implementation pathways** for smart deprescribing across different healthcare contexts, including high-income settings and selected middle-income healthcare systems such as **Mexico, Colombia, and Ecuador**. The figure highlights four sequential layers of implementation: foundational clinical decision support systems (CDSS), structured deprescribing frameworks, machine learning (ML)-assisted prioritization, and advanced deep learning (DL) integration.

### 1) Foundational CDSS: the universal starting point

Across all contexts, foundational CDSS represent the most mature and widely implemented layer. High-income healthcare systems show the highest relative maturity, reflecting long-standing integration of computerized physician order entry (CPOE) and alert-based medication safety tools [1], [5]. However, the presence of this foundational layer in Mexico, Colombia, and Ecuador demonstrates that basic electronic prescribing and interaction checking infrastructure is already established in many institutions, albeit with variable coverage and sophistication.

This widespread baseline underscores an important result: the core technological prerequisites for smart deprescribing are not absent in middle-income settings, but rather unevenly developed and underutilized for advanced medication optimization.

### 2) Deprescribing frameworks: uneven but growing adoption

The second layer—formal deprescribing frameworks—shows a consistent drop in maturity compared with foundational CDSS across all contexts. Even in high-income settings, deprescribing remains less systematically embedded than interaction alerting, reflecting the historically prescriber-centric focus of medication safety systems [4], [7]. In middle-income systems, adoption is more heterogeneous, influenced by variability in clinical training, time constraints, and institutional support.

Nevertheless, the presence of deprescribing frameworks in Mexico, Colombia, and Ecuador indicates growing recognition of deprescribing as a clinical necessity, particularly in aging populations and patients with multimorbidity [3], [16], [20]. This layer represents a critical bridge between detection of risk and actionable medication optimization.

### 3) ML-assisted prioritization: emerging but constrained

The third layer—ML-assisted prioritization—shows a sharper decline in relative maturity, particularly outside high-income settings. This reflects known barriers related to data availability, interoperability, and governance required to deploy learning-based decision support [9], [12], [14]. While proof-of-concept studies and pilot implementations demonstrate clear potential benefits in prioritizing clinically significant DDIs and reducing alert fatigue, real-world adoption remains limited.

Importantly, the gradual presence of ML-assisted approaches in Mexico, Colombia, and Ecuador suggests early-stage integration rather than absence. This aligns with the literature emphasizing that ML-based medication safety tools can be incrementally layered onto existing systems, particularly when designed to complement established deprescribing criteria rather than replace them [15], [17].

#### 4) Advanced DL integration: aspirational but informative

The lowest maturity across all contexts is observed for advanced DL integration. Even in high-income systems, full DL-driven medication optimization remains an emerging domain, often confined to research environments or limited clinical pilots [12], [18]. In middle-income settings, DL integration faces additional challenges, including data standardization, computational infrastructure, and regulatory frameworks.

However, the presence of this layer in the conceptual pathway is significant. It indicates that DL integration should be viewed not as an immediate requirement, but as a **long-term evolutionary stage** of smart deprescribing, informed by accumulated experience with simpler models and robust clinical governance.

#### Cross-context interpretation and implications

Overall, Figure 4 demonstrates that smart deprescribing is best understood as a **progressive implementation continuum**, rather than a binary capability. The results support a staged approach in which healthcare systems—regardless of income level—can advance from foundational CDSS toward deprescribing-centered, context-aware decision support by building on existing infrastructure [2], [8].

For Mexico, Colombia, and Ecuador, the findings suggest that the most impactful near-term gains are likely to come from strengthening deprescribing frameworks and integrating ML-assisted prioritization within existing CDSS environments. This aligns with international recommendations emphasizing feasibility, clinician trust, and patient-centered medication management as prerequisites for sustainable adoption [7], [16], [20].

#### DISCUSSION

The findings synthesized in this review highlight a clear evolution in medication safety strategies, moving from traditional alert-based systems toward more integrated, context-aware, and action-oriented approaches centered on smart deprescribing. The results demonstrate that while conventional clinical decision support systems (CDSS) have played a foundational role in reducing prescribing errors, their limitations—particularly alert fatigue and insufficient prioritization—have constrained their long-term clinical impact [1], [2], [8].

One of the most consistent observations across the reviewed literature is that **detection alone is insufficient** to meaningfully reduce harm from clinically significant drug–drug interactions (DDIs). Rule-based systems excel at identifying known interactions but frequently fail to discriminate between interactions of marginal relevance and those posing substantial patient risk. This limitation aligns with earlier evaluations showing high override rates and clinician desensitization to alerts, which can paradoxically undermine patient safety [1], [5]. The results presented in Figures 2 and 3 reinforce this point by demonstrating that improvements in prioritization and alert reduction are more pronounced when algorithmic intelligence is introduced.

The integration of deprescribing principles emerges as a pivotal factor in translating DDI detection into safer prescribing outcomes. Deprescribing frameworks provide the clinical logic necessary to move from “interaction flagged” to “medication optimized,” a transition that traditional CDSS often fail to support [4], [7], [16]. The prominence of deprescribing-focused evidence in Figure 1 underscores that smart deprescribing is not primarily a technological innovation, but rather a **clinical strategy augmented by technology**. This perspective is critical, as it reframes algorithms as facilitators of clinical reasoning rather than autonomous decision-makers.

Machine learning (ML) and deep learning (DL) approaches demonstrate clear advantages in expanding detection breadth, improving prioritization, and supporting deprescribing-oriented decision-making, as reflected in Figures 2 and 3. These findings are consistent with prior research showing that data-driven models can uncover complex interaction patterns and stratify risk more effectively than static rule sets [9], [14], [18]. However, the discussion must acknowledge that improved predictive performance does not automatically translate into clinical utility. Issues related to interpretability, trust, and governance remain substantial barriers to widespread adoption, particularly for deep learning models [12], [18].

Interpretability deserves particular attention in the context of deprescribing. Deprescribing decisions often involve uncertainty, trade-offs, and shared decision-making with patients. Black-box recommendations that cannot be easily explained may be less acceptable to clinicians, especially when discontinuing long-standing therapies in clinically complex patients [16], [20]. This tension suggests that hybrid approaches—combining transparent rule-based criteria with learning-based prioritization—may offer a pragmatic balance between performance and usability [15], [17].

The international perspective provided by Figure 4 adds an important dimension to the discussion. The staged implementation patterns observed across healthcare contexts indicate that smart deprescribing should be conceptualized as a **progressive pathway**, rather than a single technological leap. For healthcare systems in Mexico, Colombia, and Ecuador, the results suggest that the most feasible and impactful strategies lie in strengthening deprescribing frameworks and selectively integrating ML-assisted prioritization within existing CDSS infrastructure. This aligns with broader health systems literature emphasizing scalability, contextual adaptation, and incremental innovation in middle-income settings [3], [11].

From an educational standpoint, the discussion highlights an often-overlooked benefit of smart deprescribing systems: their potential role as **learning tools**. By making medication risk assessment and deprescribing logic explicit, these systems can support the development of pharmacological reasoning, medication safety awareness, and professional judgment among medical students and trainees. This aligns with the affective and psychomotor objectives articulated earlier and supports the integration of smart deprescribing into undergraduate and postgraduate medical education.

Despite the strengths of the synthesized evidence, several limitations must be acknowledged. Much of the literature on ML and DL for DDI prediction remains methodological or exploratory, with limited large-scale clinical validation. Additionally, heterogeneity in outcome definitions, data sources, and evaluation metrics complicates direct comparison across studies. These limitations highlight the need for future research focusing on real-world implementation, clinician acceptance, and patient-centered outcomes rather than predictive accuracy alone.

In summary, the discussion supports the conclusion that smart deprescribing represents a meaningful advancement in medication safety when grounded in robust clinical frameworks and thoughtfully integrated into healthcare systems. The convergence of deprescribing science and algorithmic decision support offers a pathway to reduce clinically significant DDIs while preserving clinical judgment, patient-centered care, and educational value.

## CONCLUSION

This review highlights smart deprescribing as an emerging and clinically meaningful strategy for addressing the persistent challenge of clinically significant drug–drug interactions (DDIs) in complex pharmacotherapy. The synthesized evidence demonstrates that traditional rule-based clinical decision support systems (CDSS) have established an essential foundation for medication safety but remain limited by alert fatigue, insufficient prioritization, and reduced clinical actionability.

The integration of deprescribing principles provides a critical clinical framework that transforms interaction detection into actionable medication optimization. When combined with algorithm-driven approaches—particularly machine learning and deep learning models—deprescribing strategies gain the capacity to prioritize high-risk interactions, reduce low-value alerts, and support longitudinal medication management. These features are essential for improving safety in patients exposed to polypharmacy and multimorbidity, especially in aging populations.

Importantly, the findings indicate that smart deprescribing should not be viewed as a replacement for clinical judgment, but rather as a complementary tool that enhances decision-making, supports rational prescribing, and reinforces patient-centered care. Hybrid models that balance interpretability, predictive performance, and workflow integration appear particularly well suited for real-world implementation.

From an international perspective, the staged implementation pathways observed across healthcare contexts suggest that smart deprescribing can be progressively adopted in both high- and middle-income settings. For healthcare systems in Mexico, Colombia, and Ecuador, strengthening deprescribing frameworks and selectively incorporating algorithm-assisted prioritization within existing CDSS infrastructure represents a feasible and impactful strategy.

In conclusion, smart deprescribing offers a scalable and adaptable approach to reducing medication-related harm while supporting clinical education and system-level medication safety. Future efforts should focus on real-world validation, clinician engagement, and integration into routine practice to fully realize its potential benefits.

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