Metronidazole Extended-Release Formulation in the Management of Multidrug-Resistant Infections: Efficacy, Mechanisms, and Therapeutic Synergy with Current Treatment Options

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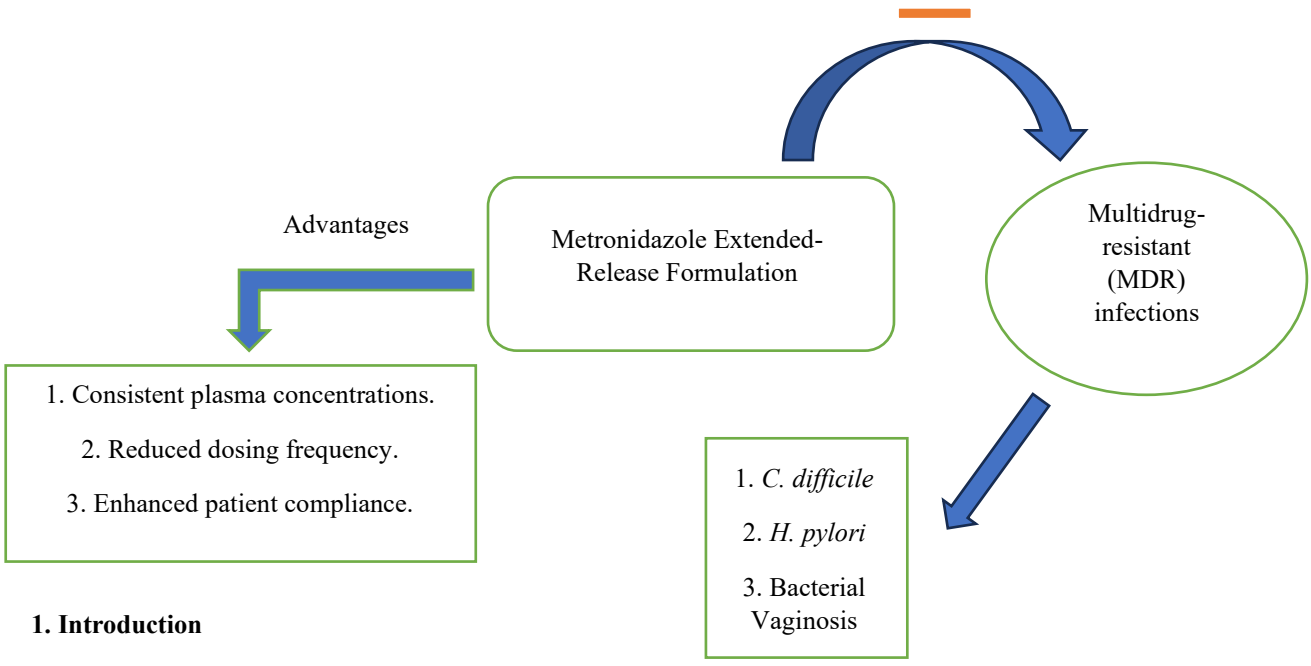
Abstract

Multidrug-resistant (MDR) infections are becoming more prevalent, which presents serious problems for global healthcare and calls for creative approaches to treatment as well as a reassessment of current medications. Because of its strong anaerobic and protozoal action, Metronidazole extended-release formulation has demonstrated promise in treating various MDR illnesses. The function of Metronidazole extended-release formulation in treating MDR infections is examined in various studies, with a focus on anaerobic bacteria that are frequently present in soft-tissue, pelvic, and intra-abdominal infections. The prolonged-release formulation has advantages, such as sustained therapeutic levels and a decreased dosing frequency, which may improve patient adherence and clinical outcomes, even though it is effective in treating diseases like bacterial vaginosis, *Clostridium difficile* infections, etc. This study addresses existing limitations and offers insights into improving treatment for MDR infections by contrasting Metronidazole extended-release formulation with alternative and complementary medicines, including glycopeptides, carbapenems, and combination regimens. Although Metronidazole extended-release formulation is still a useful treatment option for MDR infections, its effectiveness is best complemented by a multidrug strategy that is customized to the complexity and resistance profile of the illness.

Keywords: Metronidazole, Metronidazole extended-release formulation, Multidrug-Resistant Infections, Alternative therapy, Multidrug Strategy.

Graphical Abstract



1. Introduction

MDR infections are becoming more prevalent worldwide, which poses a serious concern to public health as they affect the effectiveness of conventional treatment regimens and raise morbidity, mortality, and medical expenses

[1]. Both Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), are prone to MDR infections [2], which are defined by resistance to several classes of antibiotics. Due to this difficulty, it is now necessary to investigate new antibiotics and make the most use of established medications that are effective against certain MDR infections [3].

Since Metronidazole extended-release formulation, the extended-release version of metronidazole has shown effective against a variety of anaerobic bacteria and protozoa, it is useful in treating infections that include anaerobes, such as soft tissue, pelvic, and intra-abdominal infections [4]. Clinical results and adherence may be enhanced by the extended-release (ER) formulation's sustained therapeutic levels throughout time, especially in infections that call for protracted treatment. Metronidazole extended-release formulation has been used historically to treat bacterial vaginosis, *Clostridium difficile* infections, and other anaerobic diseases. However, its promise as an adjuvant therapy for MDR infections is rapidly becoming more widespread [5].

Despite its advantages, Metronidazole extended-release formulation has drawbacks, particularly when it comes to treating severe cases that need combination or broader-spectrum treatments and polymicrobial infections. For certain individuals, the long-term use of metronidazole is also restricted by the formation of strains that are resistant to it and side effects include neuropathy and gastrointestinal discomfort [6]. By contrasting Metronidazole extended-release formulation's effectiveness, safety record, and use for a variety of infection types with other medications, this review explores the drug's therapeutic function in the larger context of MDR infection care. In light of growing antibiotic resistance, the review seeks to offer a thorough grasp of how Metronidazole extended-release formulation might be used, either as a primary or supplementary therapy.

2. Background on Metronidazole extended-release formulation

2.1 Mechanism of Action of Metronidazole

Nucleic acid production, which is necessary for microbial development and replication, is eventually inhibited by the drug's method of action, which includes disrupting microbial DNA. Metronidazole's ability to activate in anaerobic settings is what gives it its selective action and sets it apart from other antibiotics. It works especially well against obligate anaerobes [7]. The microbial enzyme ferredoxin or related nitroreductases, which are common in anaerobic organisms, reduce metronidazole inside the target bacteria. Metronidazole is changed into its active form, which is a nitroso radical anion, by this reduction mechanism [8]. Strand breakage and helix instability are the results of direct interactions between these reactive intermediates and the microorganism's DNA. Cell death results from this permanent damage, which inhibits appropriate transcription and DNA replication [9]. Metronidazole preferentially targets anaerobic germs without endangering the cells of hosts or aerobic bacteria since it can only be reduced in anaerobic or oxygen-deprived conditions [10]. Furthermore, cellular structures are further harmed by the oxidative stress brought on by the reactive nitro group [11]. The bactericidal and protozoacidal effects of metronidazole are strengthened by this dual action. Its range of activity includes various anaerobic bacteria and protozoa, as well as therapeutically important pathogens including *Giardia lamblia, Bacteroides fragilis,* and *Clostridium* species [12].

3. Current Treatment Options and Limitations in the Management of Multidrug-Resistant Infections

The development of resistance mechanisms in a variety of pathogens has made managing MDR infections more difficult. This section examines available treatments and their drawbacks, with an emphasis on different antibiotic classes, complementary therapies, and the more general difficulties in managing MDR infections.

3.1. Conventional Antibiotic Groups and Restrictions

a. Inhibitors of beta-lactams and beta-lactamases

Mechanism: The creation of bacterial cell walls is the aim of beta-lactam antibiotics, which include cephalosporins, carbapenems, and penicillins. To get around resistance, beta-lactams are frequently coupled with beta-lactamase inhibitors (such as clavulanic acid and tazobactam).

Limitations: Many bacteria, particularly Gram-negative bacteria, generate beta-lactamase enzymes that break down these antibiotics. The majority of beta-lactams are resistant to carbapenems and extended-spectrum beta-lactamases (ESBLs), which reduces the effectiveness of these combinations against multidrug-resistant bacteria. Examples include meropenem, piperacillin-tazobactam, and amoxicillin-clavulanate [13].

b. Aminoglycosides

Mechanism: By attaching to the 30S ribosomal subunit, aminoglycosides prevent bacteria from synthesizing proteins.

Limitations: Because of their nephrotoxicity and ototoxicity, they are not very effective against anaerobes and need to be well-watched. By altering enzymes or efflux pumps, bacteria can also become resistant, particularly in Pseudomonas and Enterobacter species.

Examples include tobramycin, amikacin, and gentamicin [14].

c. Fluoroquinolones

Mechanism: These drugs block the enzymes topoisomerase IV and bacterial DNA gyrase, which are necessary for DNA replication. Limitations: Fluoroquinolone resistance is common, particularly in *Pseudomonas aeruginosa* and *Escherichia coli*. Some locations have high rates

of resistance, which renders them unreliable for some MDR illnesses. Ciprofloxacin, levofloxacin, and moxifloxacin are a few examples [15].

d. Polymyxin

Mechanism: Particularly effective against Gram-negative species, polymyxins break down the bacterial cell membrane.

Limitations: Because polymyxins are neurotoxic and nephrotoxic, they are frequently used as last resort medications. The effectiveness of this class in treating MDR infections is being diminished by the emergence of resistance in some strains of *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Colistin (polymyxin E) and polymyxin B are two examples

[16].

e. Glycopeptide

Mechanism: Glycopeptides work mainly against Gram-positive organisms by attaching to peptidoglycan precursors and preventing the production of cell walls.

Limitations: Glycopeptides, such as vancomycin, have a nephrotoxic risk and are less efficient against Gram-negative bacteria. VRE is one example of a Gram-positive bacterium that has become resistant.

Teicoplanin and vancomycin are two examples [17].

3.2. More Recent Choices for Antibiotics

a. Oxazolidinones

Mechanism: By attaching itself to the 50S ribosomal subunit, oxazolidinones prevent the production of proteins. Gram-positive bacteria are the main target of their use.

Limitations: Because it suppresses bone marrow and might cause peripheral neuropathy, the major oxazolidinone linezolid has a limited treatment duration. There is an increase in resistance, especially in Enterococcus species.

Examples are tedizolid and linezolid [18].

b. Lipopeptide

Mechanism: Daptomycin, a crucial lipopeptide, works mainly against Gram-positive bacteria by rupturing the cell membrane, which leads to rapid depolarization and bacterial cell death.

Limitations: Needs dosage modification in cases of renal impairment and is ineffective against resistance, especially in Enterococcus species.

Examples are tedizolid and linezolid [18].

c. Lipoglycopeptides

Mechanism: Lipoglycopeptides, like dalbavancin, have the ability to prevent the formation of cell walls and are effective against Gram-positive bacteria.

Limitations: Their use in mixed or Gram-negative infections is restricted by their high cost and restriction to Gram-positive pathogens.

Dalbavancin and Oritavancin are two examples [19].

d. Novel Beta-Lactamase Inhibitors in Cephalosporins

Mechanism: The effectiveness of new cephalosporins against resistant Gram-negative bacteria is increased when they are coupled with beta-lactamase inhibitors (such as ceftolozane-tazobactam). Limitations include limited anaerobic and Gram-positive action, high cost, and the potential for resistance to develop.

Examples are ceftazidime-avibactam and ceftolozane-tazobactam [20].

3.3 Treatments Without Antibiotics

a. Phage Therapy

Mechanism: This alternative kind of treatment makes use of bacteriophages, which are viruses that particularly target and lyse bacteria.

Limitations include the requirement for phages unique to each bacterial strain, regulatory obstacles, and a lack of clinical evidence.

Present Use: Mostly experimental and humanitarian usage instances in MDR illnesses that are resistant to therapy [21].

b. Faecal Microbiota Transplantation (FMT)

Mechanism: This technique, which is frequently used to treat *Clostridium difficile* infections that are resistant to antibiotic treatment, involves transferring faeces from a healthy donor to reestablish a balanced gut microbiota.

Limitations: FMT is primarily recommended for recurrent *C. difficile* infections; hazards include the possibility of pathogen spread and legal limitations.

Present Use: Currently approved for recurrent *C. difficile* infections, there is increasing attention in other MDR illnesses connected to the gastrointestinal tract [22].

3.4 Supportive and Adjunctive Therapies

a. Immunotherapy

Mechanism: Boosts the host immune response against infections by using cytokines, antibodies, or immune-modulating medications.

Limitations include low specificity for many MDR infections, high cost, and the possibility of negative immune responses.

Examples include ongoing studies on monoclonal antibodies that target MDR pathogens and bezlotoxumab for recurrent *C. difficile* [23].

3.5 Supplemental Treatments (like Probiotics)

Mechanism: Restoring a balanced microbiota through probiotic use may lessen MDR pathogen invasion [23].

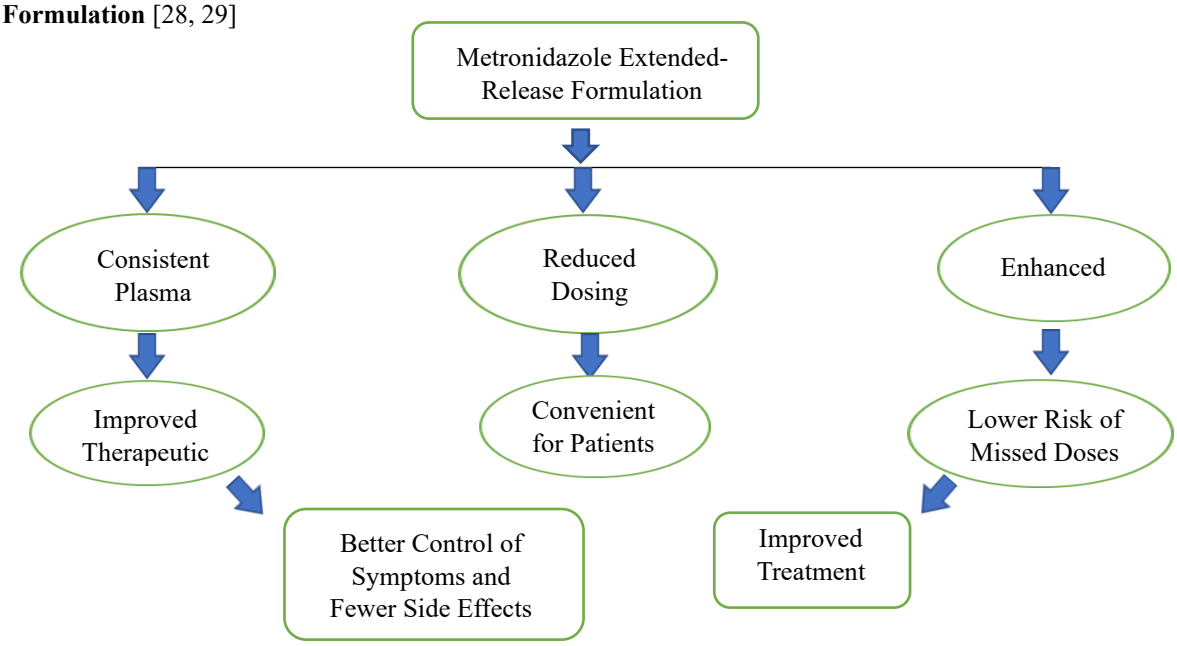
Limitations include possible problems in people with impaired immune systems and a lack of data about effectiveness in treating current MDR infections.

Present Use: Although there is still little proof of its efficacy, it is frequently used as a preventative measure or as an adjuvant to antibiotics to lessen adverse effects [24].

4. Challenges in the Management of MDR Infections

- **New Opposition:** Even more recent antibiotics may not always work since bacteria are still developing resistance mechanisms such as efflux pumps, biofilm development, and enzyme synthesis. To counter these tendencies, antimicrobial management, and resistance surveillance are crucial [25].
- **Limited Pipeline for Development:** Over the past few decades, the development of antibiotics has slowed as fewer pharmaceutical firms have made investments in new antimicrobials because of their high prices and low profitability. Consequently, there are few novel choices available, particularly for Gram-negative MDR pathogens [25].
- **Toxicity and Adverse Effects:** There are serious toxicity hazards associated with several last-resort antibiotics, including polymyxins and aminoglycosides (e.g., nephrotoxicity, neurotoxicity). It can be difficult to weigh the advantages and disadvantages of various treatments, especially for patients who are very sick [26].
- **Expensive Prices and Problems with Access**: Accessibility may be restricted by the exorbitant cost of more recent antibiotics and other treatments (such as faecal microbiota transplantation and monoclonal antibodies), particularly in environments with limited resources. Funding for medical care and insurance coverage may act as obstacles to prompt treatment [26].
- **Treatment Protocol Complexity**: The difficulty of management for MDR infections is increased by the frequent need for combination treatments, extended courses, and specialized monitoring. It can be difficult for both patients and healthcare professionals to ensure adherence to complicated regimens [27].

5. Advantages of Metronidazole extended-release formulation over Conventional Metronidazole Formulation [28, 29]



6. Metronidazole extended-release formulation in the Treatment of MDR Infections

The function of Metronidazole extended-release formulation in treating MDR infections is summarized in the following table, which is arranged according to the main infection types, effectiveness, drawbacks, and comparisons with other therapies.

Infection Type	**Pathogen**	**Metronidazole extended-release formulation Role**	**Efficacy**	**Limitation**	**Ref.**
***Clostridium difficile* Infections (CDI)**	*Clostridium difficile*	Choice for mild-to-moderate CDI, particularly in cases when other therapies are ineffective.	Efficient in mild-to-moderate situations; strong anaerobic action.	Reduced effectiveness for severe CDI; certain strains are becoming more resistant.	[30]
***Helicobacter pylori* Infection**	*Helicobacter pylori*	A part of a combination treatment.	Beneficial in *H. pylori* triple or quadruple treatment regimens.	Some areas have high rates of resistance, and monotherapy has little effectiveness.	[31]
Intra-Abdominal Infections	Anaerobes such as Bacteroides fragilis	Anaerobic component treatment for polymicrobial illnesses	Long-lasting medication levels are provided via extended-release formulation.	Combining medications for aerobic pathogens may be necessary.	[32]
Diabetic Foot Infections	Mixed flora and anaerobes	Used in combination treatment.	Often used alongside broad-spectrum medicines, it is	Limited effectiveness when used alone	[33]

			effective against anaerobes.	to treat mixed infections.	
Bacterial Vaginosis (BV)	*Gardnerella vaginalis* and anaerobes	First-line BV therapy.	Convenient dosage and high effectiveness against causative anaerobes.	Risk of side effects, including gastrointestinal distress; in complex instances, not effective for all infections.	[34]
Periodontal Infections	Anaerobes (Porphyromonas, Prevotella)	Used to treat anaerobic pathogen-induced oral infections.	Focuses on the typical anaerobes seen in periodontal infections.	Dental intervention is necessary as an adjuvant; it is limited to monotherapy.	[35]
Brain Abscesses	Pathogens that are both aerobic and anaerobic	In combination treatment, an adjunct.	Efficient against anaerobic components, particularly when used in formulations with prolonged release.	Sometimes limited penetration; only used in conjunction with other therapies.	[36]
Pelvic Inflammatory Disease (PID)	*C. trachomatis, N. gonorrhoeae*, and anaerobes	A component of anaerobic coverage combination treatment.	Often combined with other antimicrobials, this substance is effective against anaerobes.	Not all causal species are included, such as aerobic bacteria.	[37]

7. Comparative Analysis: Metronidazole extended-release formulation Versus Other Treatments

The therapeutic applications, advantages, and drawbacks of each treatment choice are highlighted in this two-column style that compares Metronidazole extended-release formulation with alternative therapies for MDR infections across a number of characteristics.

Infection Type	Comparison: Metronidazole extended-release formulation vs. Other Treatments	Ref.
Infection with CDI	Metronidazole extended-release formulation: Low cost, easy dosage, moderate effectiveness for mild CDI. For moderate-to-severe CDI, vancomycin is more effective, especially in instances that repeat. Fidaxomicin: Costly and difficult to get, yet effective at lowering recurrence.	[38]
Infection with *Helicobacter pylori*	Although resistance is rising in some areas, Metronidazole extended-release formulation is frequently used in combination therapy for *H. pylori*. When resistance rates are low, the standard first-line treatment for H. pylori consists of amoxicillin, clarithromycin, and a proton pump inhibitor. demands a high level of patient compliance.	[39]
Infections Inside the Abdomen	Metronidazole extended-release formulation: Works well against anaerobic substances; for complete coverage, it is frequently used with other medicines.	[40]

	When treating severe infections, piperacillin-tazobactam may work better as a monotherapy due to its broader scope and ability to combat mixed infections.	
Infections of the Diabetic Foot	Metronidazole extended-release formulation: Has little effectiveness when used alone; targets anaerobic components in combination treatment. Carbapenems: Provide broad-spectrum protection against severe polymicrobial infections, but their use is constrained by their high cost and potential for resistance.	[41]
PID	Metronidazole extended-release formulation: Limited by lack of effectiveness against important infections such as N. gonorrhoeae, but effective against anaerobes in combination treatment. Broad-spectrum action of Doxycycline + Ceftriaxone; frequently used in conjunction with Metronidazole extended-release formulation to guarantee anaerobic coverage.	[42]
BV	Metronidazole extended-release formulation: First-line therapy because of its excellent effectiveness and easy dosage. Clindamycin: Used for individuals who are intolerant to metronidazole, it has a similar level of effectiveness but may raise the risk of contracting C. difficile.	[43]
Infections of the Periodontal Region	Metronidazole extended-release formulation: Works well against anaerobic bacteria that are frequently seen in periodontal diseases; it is frequently coupled for maximum effectiveness. For mixed bacterial infections, amoxicillin and clindamycin are frequently administered together; however, long-term treatment may cause resistance.	[44]
Abscesses in the brain	Metronidazole extended-release formulation: Offers minimal CNS penetration when used alone, but anaerobic coverage when used in combination treatment. Third-generation cephalosporins: coupled with Metronidazole extended-release formulation for anaerobic coverage; broad-spectrum efficacious with strong CNS penetration.	[45]

8. Future Perspectives

The increasing problem of antibiotic resistance calls for continuous research into improving current antibiotics, including formulations such as Metronidazole extended-release formulation. This formulation will probably continue to play a significant role in antimicrobial treatment schemes despite the advent of new agents because of its low cost, well-established safety profile, and effectiveness against anaerobes, particularly in settings with limited resources. Future paths consist of:

8.1. Examining the Extended-Release Advantages of Targeted Treatment

The extended-release version of Metronidazole extended-release formulation may be further tested in clinical settings for ailments not currently covered by its indications. To stop recurrences of diseases like bacterial

vaginosis and certain intra-abdominal infections, for example, it may be investigated as a maintenance treatment for persistent infections or as a component of long-term suppressive therapy for high-risk patients [46].

8.2. Possible Contribution to Targeted Treatment Plans and Precision Medicine

The management of infectious diseases is moving toward precision medicine as a result of developments in diagnostic microbiology. Clinicians can more effectively customize treatments when infections and resistance profiles are quickly identified. Rapid diagnostics and Metronidazole extended-release formulation may be used more widely in situations when anaerobic infections are identified early, enabling more focused, efficient treatment that reduces the emergence of resistance [47].

8.3. Mitigation of Resistance by Stewardship and Reasonable Use

Antimicrobial stewardship initiatives are crucial to maintaining Metronidazole extended-release formulation's effectiveness as resistance trends change. Resistance monitoring and evidence-based procedures should direct its continuing usage. By eliminating needless exposure and lowering the chance of resistance, stewardship initiatives can help guarantee that Metronidazole extended-release formulation is saved for illnesses where it is most likely to be beneficial [48].

8.4. Creating New Combinations and Formulations

There is continuous interest in investigating novel medication combinations that might improve Metronidazole extended-release formulation's effectiveness or broaden its range of action. For instance, in complicated infections, combining Metronidazole extended-release formulation with substances that target MDR Gram-negative organisms may assist maximize treatment. Particularly in situations of severe polymicrobial infections, research into synergistic combinations may result in novel treatment methods that enhance patient outcomes [49].

8.5. Adding Metronidazole extended-release formulation to Programs for Outpatient Antimicrobial Therapy (OPAT)

In certain situations, Metronidazole extended-release formulation can be used for OPAT because of its oral bioavailability and extended-release formulation, which lessens the requirement for IV access and hospital care. This can be especially helpful in outpatient settings where it can be difficult to manage anaerobic infections or chronic infections over the long term [50].

9. Conclusion

Modern healthcare has a major difficulty in managing multidrug-resistant infections, which necessitates the development of new therapeutic approaches as well as the efficient use of currently available medications. Extended-release metronidazole, or Metronidazole extended-release formulation, is a well-known antibiotic that has a strong record of success against infections caused by anaerobic bacteria and protozoa. It is a useful treatment for some infections, especially those caused by anaerobic pathogens, like intra-abdominal infections, bacterial vaginosis, and some respiratory and soft-tissue infections. Its extended-release formulation provides benefits in terms of patient adherence and consistent therapeutic levels.

Although Metronidazole extended-release formulation works well in its specific market, it is mostly used as an adjuvant rather than a first-line therapy in the larger management of MDR infections. Metronidazole extended-release formulation's usage as a monotherapy for mixed or severe infections is limited since it is not effective

against several aerobic MDR bacteria. It works best in combination treatments, where it can efficiently target anaerobes as part of a more comprehensive strategy, frequently in conjunction with beta-lactam/beta-lactamase inhibitor combos, carbapenems, or cephalosporins.

Integrating Metronidazole extended-release formulation into precision medicine strategies and stewardship initiatives will enhance its future contribution to MDR infection treatment. Clinicians can optimize its efficacy while lowering the risk of resistance by making sure its usage is focused and supported by evidence. Metronidazole extended-release formulation is still an important element of the antibacterial toolbox even when newer treatments are developed, especially for treating some anaerobic pathogens and complicated polymicrobial illnesses.

Abbreviations

MDR- Multidrug-resistant

MRSA- methicillin-resistant *Staphylococcus aureus*

VRE- vancomycin-resistant *Enterococcus*

ESBLs- extended-spectrum beta-lactamases

FMT- Faecal Microbiota Transplantation

CDI- *Clostridium difficile* Infections

BV- Bacterial Vaginosis

PID- Pelvic Inflammatory Disease

OPAT- Outpatient Antimicrobial Therapy

CRediT authorship contribution statement

Subarnarekha Maitra: Writing – original draft, Resources, Methodology, Investigation, Conceptualization.

Dibya Sinha: Methodology, Investigation, Funding acquisition.

Tathagata Roy: Visualization, Supervision.

Sayani Chaki Roy: Formal analysis, Data curation.

Snehajyoti Ghosh: Formal analysis, Data curation.

Subhankar Das: Formal analysis, Data curation.

Maitreyee Mukherjee: Writing – review & editing, Validation, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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