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Letter to the editor

Drug repositioning, a new alternative in infectious diseases

Dear Editor:

There has been a significant decrease in the number of approved antibiotics in the last two decades, and in parallel, a steady increase of multidrug resistant bacteria (MDR) has been occurring. Thus, MDR have become a global issue of public health, and with this threat, the challenge to develop new antibiotics has emerged in all areas: governmental, scientific, and the private pharmacological industry.[1] In this sense, drug repositioning has arisen as an alternative approach for the faster identification of drugs that are effective against infectious diseases.[2]

The expressions "*Drug repositioning*" and "*drug repurposing*" was first described by Ashburn and Thor (2004)[3] in their paper "*Drug repositioning: identifying and developing new uses for existing drugs*". According to the authors, this is the process to find new uses for clinically approved drugs, and this is also known as *redirecting* and *reprofiling*.

Several studies have signalled that drug repositioning has advantages compared to the traditional way of seeking for active substances,[2,4–7] since pharmacological, toxicological and bioavailability data, among others, are already available. Thus, less time is spent in their development, leading to a significant reduction in costs, and it proves to be a preferred and advantageous alternative strategy to discover drugs more quickly.[4] Other encouraging data are the success rates for repositioned drugs, which are higher when compared to new drugs, reaching 30% in the last few years. Also, together with the positive aspects of repositioning is its recent approval by the *Food and Drug Administration* (FDA).[8]

Comparing repurposing and use off-label, there is a similarity between these practices: a new indication of the drug, other than the usual one. However, the use outside the label goes beyond this, since it may include different age groups, dosage or route of administration. Although this is considered a legal and common application, it is often performed in the absence of adequate scientific data, and may expose patients to unrestricted and ineffective experimentation of drugs with unknown health risks.[9]

In Table 1, we present a summary of the repositioning of drugs for antibacterial treatment: examples of studies that investigate the antimicrobial activities of several pharmacological classes, including psychotropics, local anaesthetics, tranquilizers, cardiovascular drugs, antihistamines, anti-inflammatories, being these called "non-antibiotic drugs".[10–14]

The treatment of chronic bacterial infections in immunocompromised patients with synergistic drug combinations is well established, and this procedure has been used for several years.[15] These synergistic combinations are used because of three main advantages: expansion of the antibiotic spectrum[16,17]; overcoming resistance[18]; and decrease of resistance to antibiotics through their careful use.[19–21]

Since repositioned non-antibiotic drugs have shown antibiotic effects among themselves as well as when used together with antimicrobials, these combinations presently consist of a useful option to overcome the problem of weak activity of individual drugs.[2,10,16]

Based on the several studies presented, it can be inferred that the repositioning of non-antibiotic drugs with known toxicity profiles represents a promising alternative for the treatment of bacterial infections. Nevertheless, it is a consensus in the global scientific community that it is only the starting point, and additional studies regarding mechanisms of action and *in vivo* studies, among others, are vital for the safe use of these drugs.

Table 1 – Studies of repositioning non-antibiotic drugs with antibiotic effect.

Drug	Original indication	New indication	Reference
AAS	Non-steroidal Anti-inflammatory	MRSA	Chan et al., 2017[10]
Amitriptiline	Antidepressant	*Staphylococcus* spp.	Mandal et al., 2010[11]
		Enterococcus faecalis	
		Micrococcus luteus	Muthukumar and
		Bacillus spp.	Janakiraman, 2014[22]
		Shigella spp.	
		Salmonella spp.	
		Vibrio cholerae	
		Vibrio parahaemolyticus	
		Escherichia coli	
		Klebsiella pneumonia	
		Pseudomonas spp.	
		Proteus spp.	
		Citrobacter spp.	
		Providencia spp.	
		Enterobacter cloacae	
		Hafnia spp.	
		Lactobacillus sporogenes	
		Micrococcus flavus	
		Vibrio cholerae	
Auranofin	Rheumatoidarthritis	MRSA	Harbut et al., 2015[23]
Chlorpromazine	Anti-psychotic	*Corynebacterium urealyticum*	Munoz-Bellido,
		Escherichia coli	Munoz-Criado and
		Klebsiella pneumoniae	García-Rodríguez, 1996[12]
		Citrobacter freundii	
		Morganella morganii	Munoz-Bellido,
		Acinetobacter baumannii	Munoz-Criado and
		Haemophilus influenzae	García-Rodríguez, 2000[13]
		Moraxella catarrhalis	
		Campylobacter jejuni	
		Staphylococcus aureus	
		Staphylococcus epidermidis	
		Streptococcus pneumoniae	
		Streptococcus pyogenes	
		Streptococcus agalactiae	
		Enterococcus faecalis	
		Clostridium perfringens	
		Clostridium difficile	
		Bacreroides fragilis	
		Prevotella spp.	
		Brucella spp.	
Clofazime	Tuberculosis	*Mycobacterium leprae*	Naylorand Schonfeld, 2014[24]
Clomipramine	Antidepressant	*Serratia marcescens*	Munoz-Bellido,
		Morganella morganii	Munoz-Criado and
		Acinetobacter baumannii	García-Rodríguez, 2000[13]
		Haemophilus influenza	
		Campylobacter jejuni	
		Staphylococcus aureus	
		Staphylococcus epidermidis	
		Streptococcus pneumoniae	
		Streptococcus pyogenes	
		Streptococcus agalactiae	
		Enterococcus faecalis	
		Clostridium perfringens	
		Clostridium difficile	
		Bacteroides fragilis	
		Prevotella spp.	
		Brucella spp.	

Table 1 – (*Continued*)

Drug	Original indication	New indication	Reference
Disulfiram	Alcoholism	MRSA	Phillips et al., 1991[25]
		Pseudomonas aeruginosa	Velasco-García et al., 2006[26]
Ebselen	Neuroprotector	MRSA	Thangamani, Younis e
		VRSA	Seleem 2015[6,7]
		Streptococcus spp.	
		Enterococcus spp.	
Escitalopram	Antidepressant	*Klebsiella pneumoniae*	Akilandeswari, Ruckmani
		Proteus mirabilis	and Ranjith, 2013[27]
		Enterobactor cloacae	
		Staphylococcus aureus Pseudomonas aeruginosa	
Fluoxetine	Antidepressant	*Corynebacterium urealyticum*	Munoz-Bellido,
		Haemophilus influenzae	Munoz-Criado and
		Moraxella catarrhales	García-Rodríguez, 1996[12]
		Campylobacter jejuni	Munoz-Bellido,
			Munoz-Criado and
			García-Rodríguez, 2000[13]
Ibuprofen	Non-steroidalAnti-inflammatory	MRSA	Chan et al., 2017[10]
Iproniazid	Antidepressant	*Mycobacterium tuberculosis*	López-Muñoz and Alamo, 2009[28]
Loperamide	Diarrhoea	*Salmonella enterica*	Ejim et al., 2011[16]
Sertraline	Antidepressant	*Corynebacterium urealyticum*	Munoz-Bellido,
		Escherichia coli	Munoz-Criado and
		Klebsiella pneumoniae	García-Rodríguez, 1996[12]
		Enterococcus cloacae	
		Citrobacter freundii	Munoz-Bellido,
		Serratia marcescens	Munoz-Criado and
		Proteus mirabilis	García-Rodríguez, 2000[13]
		Proteus vulgaris	
		Morganella morganii	Samanta et al., 2012[29]
		Acinetobacter baumannii	
		Haemophilus influenzae	
		Moraxella catarrhalis	
		Campylobacter jejuni	
		Staphylococcus aureus	
		Staphylococcus epidermidis	
		Streptococcus pneumoniae	
		Streptococcus pyogenes	
		Streptococcus agalactiae	
		Enterococcus faecalis	
		Clostridium perfringens	
		Clostridium difficile	
		Bacteroides fragilis	
		Prevotella spp.	
		Brucella spp.	
		Staphylococcus spp.	
		Micrococcus luteus	
		Bacillus subtilis	
		Shigella spp.	
		Salmonella spp.	
		Vibrio cholerae	
		Vibrio parahaemolyticus	
		Pseudomonas aeruginosa	
		Providencia spp.	
		Lactobacillus sporogenes	
Paroxetine	Antidepressant	*Corynebacterium urealyticum*	Munoz-Bellido,
		Haemophilus influenzae	Munoz-Criado and
		Moraxella catarrhales	García-Rodríguez, 1996[12]
		Campylobacter jejuni	Munoz-Bellido,
			Munoz-Criado and
			García-Rodríguez, 2000[13]

Table 1 – (*Continued*)

Drug	Original indication	New indication	Reference
Risperidone	Anti-psychotic	*Corynebacterium urealyticum*	Munoz-Bellido, Munoz-Criado and García-Rodríguez, 1996[12] Munoz-Bellido, Munoz-Criado and García-Rodríguez, 2000[13]
Simvastatin and Atorvastatin	Cardiovascular diseases	*Staphylococcus epidermidis* *Staphylococcus aureus* *Salmonella* spp. *Pseudomonas aeruginosa* *Micrococcus luteus* *Klebsiella pneumoniae* *Escherichia coli* *Enterococcus faecalis* *Enterobacter hormaechei* *Bacillus cereus* *Staphylococcus* spp. *Staphylococcus coagulase negative* MRSA	Rampelotto et al., 2018 *in press*[14] Graziano et al., 2015[30]
Thalidomide	Anti-nausea	*Mycobacterium leprae*	Paravar and Lee, 2008[31]

MRSA, methicillin-resistant *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*; AAS, acetylsalicylic acid.

Conflicts of interest

The authors declare no conflicts of interest.

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