

## The Accepted “Clinical Interaction Model”: A Special Case of Reality

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### Abstract

Pharmacology has focussed on the effects of compounds on tissues and organs with a view to promoting the well-being of a patient. This has been a special case of ‘reality’. With the dual realisation that these compounds can also have effects on microorganisms living in and on the patient and that these microorganisms play a vital role in maintaining the health of the patient it is essential that we modify our perspective to include the host, the microorganisms and compounds that affect either into a general theory for pharmacology.

**Keywords:** Pharmacology; Microorganisms; Psychotherapeutic drugs; Antibiotic

### Opinion

Over a hundred years ago, Poul Ehrlich (1854-1915) proposed a lock and key model for the interaction between drug and target in which a ligand fits into a 3-dimension pocket [1]. For many years, this was a source of inspiration and dovetailed well with the reductionist approach of science. This led to the development of *in vitro* high-throughput screening and the construction of massive combinatorial chemistry libraries. The initial lock and key concept has been modified several times to include ligand and target flexibility (leading to the hand in glove analogy). Theoretically, a highly specific treatment should be better tolerated due to an absence of off-target side effects. Unfortunately, practice has shown that there is a poor correlation between *in vitro* drug effects and *in vivo* efficacy with target-driven approximations [2,3]. Our increasing understanding of the multiple interacting feedback mechanisms operating within the cell has led to the realization that polypharmacology (the interaction of a single drug on multiple targets or the use of multiple drugs on multiple targets) will be necessary to treat the majority of non-monogenic disorders [4-7].

But there is another level of complexity that is equally important and also needs to be considered. Generally speaking, in the development of drugs, the demands are for as high a degree of “medical resolving problems” and as few negative side effects as possible.

For the sake of this discussion, let drugs be divided into two groups: Parasitotropic and organotropic. In this article, we will use the Oxford Dictionary definition of parasite “An organism that lives on, in, or with an organism of another species, obtaining food, shelter, or other benefit”. We naturally attach a negative stigma to the word ‘parasite’ but in the case of the gut microbiota we owe them an apology. An alternative word would be a “mutualist”-an organism which gives a quid pro quo or specific beneficial service to the host which affords it sustenance and domicile (definition adapted from American Naturalist vol. 28, p: 713, 1894).

Parasitotropic-directed drugs, such as antibiotics and chemotherapeutic agents, are developed with aim of exploiting their antimicrobial characteristics, while making every effort to limit their negative side effects on the patient host (human and/or animal). Here, possible positive side effects on the host are neglected.

Organotropic-drugs, on the other hand, are in general developed without any considerations for their possible effects on microorganisms. The focus is on obtaining a beneficial effect on the patient.

The importance of microorganisms for human health is only just beginning to be realised: about half of the cells and only 1% of the genes found in our bodies are human [8]. The gut microbiota has been called the ‘hidden organ’ because it has been overlooked for so long. It is essential for the maintenance of health, behaviour and learning. The microbiota is also involved in metabolising exogenous compounds (e.g. food and medicines), thus significantly affecting drug pharmacokinetics (bioavailability, efficacy and adverse effects) [9]. It is becoming increasingly recognised for its influences on several diseases including obesity, and diabetes [10] and microbial dysbiosis is being linked to autism, depression, Alzheimer’s and Parkinson’s diseases [8,11].

Considering the various roles of microorganisms in our gut, the current approach to drug discovery is thus incomplete. Clinical studies are the first opportunity to ‘observe’ this, and the high rejection rate of candidate drugs may be one of the consequences of this oversight.

Evidence that compounds having both parasitotropic directed and organotropic directed activities have existed in the literature for many years but have been ignored. One of the earliest examples, was methylene blue (a phenothiazine) which has both antimalarial, painkilling and neuroleptic activity [12-15].

In our investigations and in the historical studies we have now been able to confirm that neurotropics (especially psychotherapeutic drugs in general) and their analogues have antimicrobial effects *in vitro* and *in vivo* [16-20].

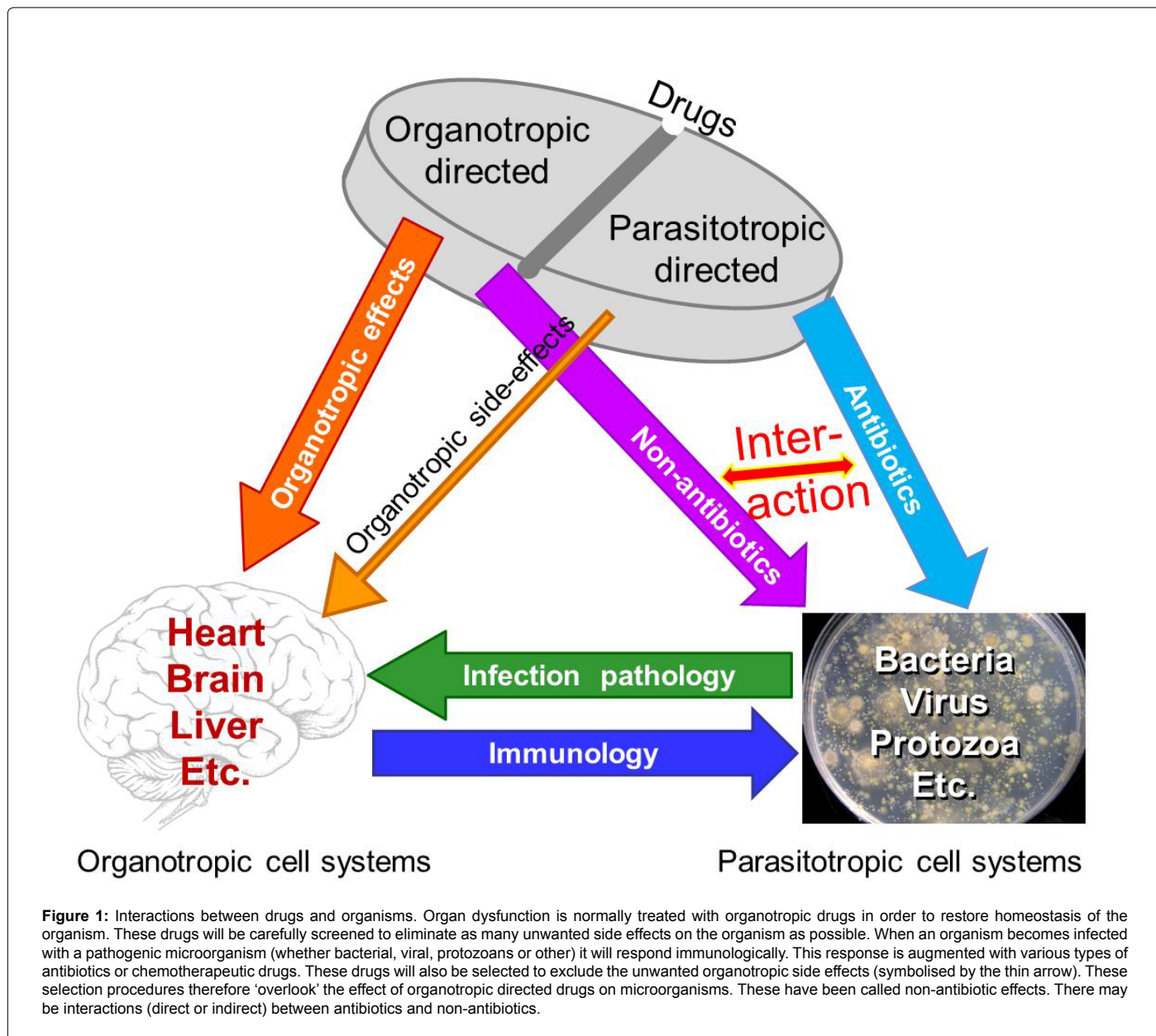
These drugs and other compounds having both organotropic directed and parasitotropic directed activities are called ‘non-antibiotics’ [21]. Clinically, the parasitotropic effect of the organotropic drugs is generally ignored, and, for all intents and purposes, the possibility for both negative and positive side effects have been neglected. This biologically ‘symmetric’ model was proposed many years ago in 1979 (Figure 1) [22,23].

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When an organism becomes infected with a pathogenic microorganism (whether bacterial, viral, protozoan or other) it will respond immunologically. This response is augmented with various types of antibiotics or chemotherapeutic drugs. These drugs will also be selected to exclude the unwanted organotropic side effects (symbolised by the thin arrow). These selection procedures therefore 'overlook' the effect of organotropic directed drugs on microorganisms. These have been called non-antibiotic effects. There may be interactions (direct or indirect) between antibiotics and non-antibiotics.

### Consequences of the Two-sided Effect of Psychotherapeutic Drugs and Other Non-Antibiotics

The observation, which was initially made relating psychotherapeutics (and their stereo-isomeric analogues) with an antimicrobial effect, opens up a new paradigm in clinical microbiology

and in clinical pharmacology. Exploring this paradigm raises a number of questions which can only partially be answered currently:

1) What is the significance of the two-sided effect, and the theoretical and clinical consequences of the organotropic drugs having an impact simultaneously on the organs (the host) and the microorganisms (the good and the bad bugs on/in the patient)? In other words, what is the significance, generally speaking of these non-antibiotics on the host and the microorganisms and their interaction e.g. in the infected patient? Such an activity of the non-antibiotic might be negative side effect (killing the good bugs) or positive side effects (killing the bad bugs). A few examples are known. Microorganisms have been known to be a target for phenothiazine's for many years [24].

Patients having ulcus ventriculi were treated-with trimipramine (a phenothiazine). This was used in Norway even before it was known that ulcus ventriculi was caused by a *Helicobacter pylori* infection [25,26].

The same two-sided activity has been seen in patients treated with chlorpromazine (a phenothiazine) for mental diseases in the beginning of the 1950's, where 'by accident' they were also cured for TB [27-29].

Also, modern new drugs (e.g. diclophenac) used for rheumatic diseases have an unexpected antimicrobial activity and are able to cure urinary tract infections [30-32].

Diclofenac and ibuprofen have also shown distinct antibacterial activity against *Enterococcus faecalis* and diclofenac has shown synergistic effects with the antipsychotic trifluoperazine [33].

2) Is the non-antibiotic activity of organotropic drugs limited to the field of the psychotherapeutic group or can it be found in other classes of pharmaceutical compounds?

Intrinsically, there is no obvious reason why there should be a limitation to psychotherapeutic compounds. Thus, we should be vigilant with all compounds, irrespective if they are drugs, food additives or even normal molecules in our food or environment if they can affect either our organism or our parasites [34-36].

Antimicrobial activity has been found in many other compounds including flavanones, isoflavones and prenylflavanones [37,38]; antihistamines [39,40], antihypertensive agent methyl-L-DOPA [41]; cardiovascular drugs oxyfedrine and dobutamine [42]; local and general anaesthetics [17,43,44] and barbiturates [45].

A comprehensive search for antimicrobial activity of non-antibiotic drugs, (selected from 90 different pharmaceutical products) against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans* identified numerous active compounds including paroxetine, buflomedile, bencyclane, hydroxyzine, risedronate, atomoxetine, oseltamivir, valproate, niclozamide and oxybendazol [35,46]. This study alone underlines the fact that the antimicrobial activity of compounds that were not developed for that purpose are not common and that this urgently needs to be taken into consideration-whether it is for treatment, as a food additive or in the environment around us. This is probably only the tip of the iceberg: many more compounds need to be investigated in future to obtain a more representative picture.

3) All organotropic drugs have, a *priori*, the possibility to interact with both the organs in the host and on the microorganisms in and outside the host (the patient). Therefore, each eukaryotic-directed compound in the clinic has to be considered to be a non-antibiotic until the opposite has been demonstrated [35,46].

This is currently generally not investigated during drug development but should be.

4) Non-antibiotics have the potential to interfere with natural microbial flora of the host. What is the effect on the healthy host?

While we are only just beginning to understand the importance of

this microbiome, we can still only guess at the consequences of changes to it. In the light of their antimicrobial effect, these non-antibiotics would be expected to disturb the "ecological" balance. This topic has already attracted attention in the antibiotic research in 1980 [47,48]. Even food needs to be evaluated: grapefruit oil contains components which act as potential novel efflux pump modulators in methicillin-resistant *S. aureus* bacterial strains [49].

5) Antibiotics and non-antibiotics can have a significant impact on the microbiota in the gut (and elsewhere in or on the organism). This will alter the nutritional content of the gut and which in turn may lead to the expansion of pathogenic (antibiotic resistant) populations [50] and lead to the development of disease [51].

Even though current studies of the correlation of antibiotic use with the development of diabetes are inconclusive [52], it becomes necessary to consider the additional influence of non-antibiotics in order to obtain a clearer picture both of the positive and negative side effects of the very different classes of non-antibiotics: pharmaceutical compounds, foods, food additives, chemicals in our environment, etc. and their possible interactions with each other or with the classical "antibiotics".

6) One of the clinically relevant consequences of inadequate regard for the prokaryotic effect of eukaryote-directed drugs might be that the beneficial effects obtained may be incorrectly ascribed. In other words, the understanding of the disease and its diagnosis and treatment may be based on a scientific or clinical fallacy.

There are reports of specially-sensitive patients who were treated with the antihistamine (and neuroleptic) trimipramine for their irritable bowel syndrome. Their cure was not, as believed for the disease, but in reality, for their *Helicobacter* infection in the stomach (see discussion above [25,26]). This raises the questions of how many unknown (mental) diseases are infections and how many patients are "treated lifelong with neuroleptics" for unknown zoonosis and infections?

7) Often organotropic compounds are prescribed together with classical antibiotics/ chemotherapeutics. In the patient, the pharmacological response might be synergistic/ antagonistic or no interaction on the natural/pathogen microorganisms and the immune-system.

In a recent study, the combined action of dicloxacillin (DCX) in combination with thioridazine (TDZ) was found to be toxic in a normal porcine model for catheter-carried *Staphylococcus aureus* infections. Reduction of the dose of both revealed a synergistic activity between the antibiotic and the non-antibiotic [53]. Similar synergistic effects have been observed between thioridazine in combination with antibiotics for treating extensively drug-resistant infections of pulmonary tuberculosis [54,55].

These possibilities for active utilization of the antimicrobial potency of non-antibiotic have opened a new pharmacological world and several new possibilities for treating especially infections that we,

Perspective	Expectation	References
Can antibiotic resistance be reversed?	Yes	[39,40,55-61]
Can pathogenicity and virulence be reduced by means of psychotherapeutics and/or other non-antibiotics and their analogues?	Yes	[62-66]
Can the synergy between psychotherapeutics and "classical" antibiotics/chemotherapeutics be exploited (for example to reduce the dose)?	Yes	[53, 56,67-69]
Can new antibiotics be developed from the already known non-antibiotics	Yes	[19,54,55,64,70-74]
Can "purer" drugs be developed by utilizing stereo-specificity? Up until 1985, 85% of all drugs were mixtures	Yes	[71,72,75,76-78]
Will this polypharmacy have any influence on the pharmacokinetics or pharmacodynamics of clinical treatment for the patient/host	Yes	[60,75,79-86]

Table 1: Possibilities for active utilization of the antimicrobial activity of non-antibiotics are listed below.



up until now, have not been able to treat. The demonstration of the antimicrobial activity of non-antibiotics raises a number of exciting perspectives. These are illustrated in Table 1.

Poul Ehrlich was the first to note that methylene blue stained not only bacteria but also nervous tissue preferentially to other tissues, presumably because of their increased lipid content. There are considerable differences in the composition of membranes both between prokaryotes and eukaryotes and between different membranes in the eukaryotic cell. For example, cardiolipin is a major component in membrane domains in bacteria and mitochondria [87]. Other phospholipids are distributed in the various eukaryotic membranes in a decidedly non-random manner [88]. Since most of the non-antibiotics are lipophilic, they will naturally accumulate in membranes. Furthermore, the solubility of for example phenothiazine is different in different phospholipids [20] and therefore the effects of the non-antibiotic will be exerted locally even at the sub-cellular level. Interestingly, organism-wide proteomic studies have shown that the brain is the tissue with the second largest number of enriched proteins (318) (second only to the testis) and of these, many are low expression and membrane bound (and therefore potentially drug targets) [89]. Since it is calculated that 50% of drug targets are membrane proteins [90] (class I GPCRs (45%), nuclear receptors (2%), ligand-gated and voltage gated ion channels (5%) [91] while soluble proteins like enzymes constitute 29-50% [92-94] it is perhaps not so surprising that non-antibiotics can also influence neurological signalling and cell communication.

It would therefore be relevant to carry out a comparative scientific study of the frequency of infections, the bacterial flora and their resistance characteristics in patients. Perhaps this could be effectively carried out using psychiatric patients under long-term treatment with psychopharmacological drugs (especially those treated with phenothiazines, thioxanthenes or phenylpiperidines which have been shown to have non-antibiotic activities) [23].

In this discussion, we hope that we have illustrated that the clinical interaction is much more complex than generally taken into account. For the same reasons, the development of antibiotic resistance is equally complex and the simple cessation of the use of antibiotics would not lead to the recovery of antibiotic sensitive microorganisms. In order to understand the complexity of resistance it will be necessary to investigate and include the many different parameters important also for the general resistance development-as illustrated in this biologically 'symmetric' model [95].

## Conclusion

There is a need for a general theory which describes interactions between the host organism, microorganisms and compounds (including drugs, pharmacological compounds and compounds which are chemically foreign or hostile to a biological system).

Thus, we are now able to fill more and more compounds into the gap described in the general model were the parasitotropic activity of organotropic drugs (non-antibiotics) earlier was totally neglected.

Previously, its importance was estimated to be zero in a mathematical model. A revision of the mathematical model to describe the influence of non-antibiotics in real life will result in a general theory of the interplay between host organism, microorganisms and drugs. These interactions may be either synergistic (positive e.g. inhibit resistance development even up to reversal of resistance by boosting antimicrobial activities of classical antibiotic/chemotherapeutics), indifference, or antagonistic

(negative: support pathogen growth, resistance development or interfere negative with the classical antibiotics/chemotherapeutics) as suggested already in 1979 [21-23,96]. The mathematical model will also have to include revisions to the ADME and to PK/PD considerations, resulting from the modified nutritional status in the gut.

Thus, the zero activity of non-antibiotics is a special case of the reality in the clinical pharmacology.

The instatement of non-antibiotics allows us to develop pharmacology into a general description of reality which encompasses both the 'overlooked organ' (the 'parasites' in and on us) and the compounds which affect them.

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