De Masi S (2020) 01s: 23-24
https://doi.org/10.36118/pharmadvances.01S.2020.06s

COMMENTARY Open Access

Commentary on "The concept of non-pharmacological mechanism of action in medical devices made of substances in practice: what pharmacology can do to promote the scientific implementation of the European medical device regulation"

(Commentary on Racchi M, Govoni S, The concept of non-pharmacological mechanism of action in medical devices made of substances in practice: what pharmacology can do to promote the scientific implementation of the European medical device regulation, Pharmadvances, 2020)

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Introduction

I read with great interest the paper by Racchi and Govoni on the "*Concept of non-pharmacological mechanism of action"*. The authors refer to the new regulation on medical devices (1) especially to the section concerning "medical devices made of substances" (MDMS) and define their mechanism of action as "non-pharmacological", "non-metabolic" and "non-immunological" (in contrast with to the Ph.I.M. rule). This is the starting point for a broad assessment of the pharmacological paradigm that has led, over time, to the perfect coincidence between "mechanism of action" and "therapeutic effect". The key-lock model is the fundamental assumption of the paradigm that aims to infer efficacy from the mechanism of action rather than legitimizing and explaining it through the mechanism of action. MDMS do not respond to the model underlying the pharmacological paradigm and therefore their mechanism of action is defined in negative. This anomaly (2) highlights the complexity of the real interaction between a substance and the human organism and it underlines our substantial lack of knowledge. It is worth noting that the definition of the presumed mechanisms of action is defined by a negative term (non-pharmacological, non-immunological, non-metabolic). The authors explicitly refer to the theory of complexity (3) and its terminology when they mention the new paradigm of system biology and the emerging properties of such systems. Two reflections arise from this interesting work. The first is that in the path of drugs' authorization, the division into phases of the research implies a certain interest for the issue discussed by Racchi. Assessing toxicity of a molecule during Phase I and its activity during Phase II studies certainly implies a great interest in the mechanism of action, reflecting the influence from the pharmacological paradigm (it is not clear how consciously).

However, the authorization process for drugs involves phase III of the clinical study with all its methodological equipment (ITT analysis, blindness, randomization, etc.); this suggests a certain awareness of the existence of a gap between the mechanism of action and the therapeutic effect. This gap should be bridged by phase III studies aiming to collect information on clinical efficacy "as a whole". "As a whole" means the need to confirm clinical efficacy with studies including "environmental" interference (human organism and everything which is outside the key-lock mechanism).

It is probably true that pharmacological research has increasingly neglected the clinical issues in favor of the pharmacokinetic and pharmacodynamic ones, as evidenced by the recent interest dedicated to extrapolation algorithms which should replace phase III studies in the pediatric population (4). The second is that the temptation to reductionism (coincidence between mechanism of action and therapeutic effect) re-emerges in Racchi's purpose of chemical and physical mechanisms (invoked for MDMS), as an alternative to the pharmacological ones, but always referable to a complete predictability of the system. Nothing new in saying that it is necessary to push the reflection on the gap between the mechanism of action and the therapeutic effect beyond the limits imposed by the current pharmacological paradigm. If the phase III studies already include an all-round evaluation of the complex interaction between substance and human organism, these create an experimental setting that excludes interaction with the "external" environment, which is, instead, considered in pragmatic studies

Non-recent documents suggest this interest (5), while more recent initiatives relating to the importance of "patients reported outcome-PRO" reveal an opposite trend compared to the paradigmatic one, imbued with values, social components, etc. that increase the distance between the therapeutic effect and the mechanism of action (6). I believe that we should not to give up at looking for an explanation, i.e. the mechanism of action, for the therapeutic effect, but we should be deeply aware that the adventure of knowledge proceeds with the information it has inside, the order of which is sometime bizarre and irrational.

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