Three-Drug Therapies in Psychiatry in the light of the Maximum Ordinality Principle

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Abstract* – The present paper aims at showing the possible adoption in Psychiatry of a *general method* finalized to prescribe the most appropriate therapy based on the knowledge of its correlative effects *in advance*, instead of recognizing them *ex post.

The specific case here considered is the "bipolar disorder", in which the adoption of three different drugs is the most common practice, although with a possible differentiation between the prescription in the morning and in the evening, respectively. Thus the proposed methodology will consider the Ordinal Interactions between the various drugs by evaluating their combined effects, which will result as being not a simple additive "sum", because they are evaluated on the basis of the Maximum Ordinality Principle (MOP).

In this way the Method is able to suggest how to account for the *synergistic effects* of the various drugs, especially when the latter are characterized by different concentrations and also different half-lives.

Three-Drug Therapies, Bipolar Disorder, Psychiatric Therapies, Maximum Ordinality Principle (MOP)

1. Introduction

The Method here proposed is based on the MOP, with specific reference to a three-drug therapy. In this sense it has already been proposed in the case of Immune-targeted therapies [12]. More precisely, when the targeted therapy foresees the adoption of two or more molecules, theoretically designed to interact with the same selected target, according to a pre-defined *time sequence*.

In such a case, the approach based on the MOP is able to show that the most appropriate sequence of the considered entities (molecules or enzyme) can lead to a "*global efficacy*" which can be even higher than the corresponding efficacy when the latter is estimated by considering two or more distinct and separated interactive processes. This is because, as is well known, in Self-Organizing Systems "*The Whole is much more than the sum of its parts*".

In this paper we want to consider another important field of pharmacological therapies: the adoption of three-drug therapies in Psychiatry. More specifically, in the case of a "bipolar disorder", nowadays rather diffused, in which the three adopted drugs are finalized to the inhibition of the Inositol, because the latter is a catalyzer of several undesired reactions in the brain.

Moreover, this field of therapies presents the additional advantage (with respect to oncological therapies) of a *shorter response time* (usually some weeks, with respect to one or two years in the other case). This clearly represents a particular advantage as far as the confirmation of the theoretical evaluations are concerned.

The specific drugs usually adopted in this field are *Carbolithium*, *Depakin* and *Olanzapine*, at different specific doses in the morning with respect to their prescription in the evening of the same day.

2. The Rational of the Method

The Method consists in modeling both the considered drugs, the Inositol and their resulting interaction compounds as *Self-Organizing Systems*, all of them described in the light of *the Maximum Ordinality Principle*, widely illustrated in [10].

In favor of the validity of the Method it is worth recalling that the latter is nothing but the transposition of the same method already adopted in the case of Protein-Protein Interaction (PPI) [1], where the process was analogously modeled in the light of the MOP.

This is because any interaction process, when modeled in mere "functional" terms, is always characterized by an intrinsic insolubility in explicit terms, as a consequence of the famous "Three-body Problem" (H. Poincaré, 1889, more explicitly recalled in [1][2]).

The MOP, vice versa, overcomes the limitations associated to the "Three-body Problem" and, consequently, when both the three drugs and the Inositol are modeled as Self-Organizing Systems in the light of the MOP, the explicit solution to the interaction processes

can be obtained, in a *fast* and *reliable* way, as the *formal solution to an N-body interaction problem*.

In addition, the Method here proposed, with specific reference to the therapy of a "bipolar disorder", presents some special characteristics that facilitate its transposition to other forms of psychiatric therapies or, more in general, to other pharmacological therapies.

3. Ordinal Reconfigurations of the three Drugs and the Inositol

The modeling of the various inter-action processes starts with the Ordinal Reconfigurations of both the three drugs and the Inositol. Where the expression "Ordinal Reconfigurations" means that each component is modeled as a *Self-Organizing System*, and thus characterized by its specific Generativity, which tends to structure the correlative component according to the MOP [10].

This means that the various elements that compose both the three drugs and the Inositol are internally related to each other in terms of Ordinal Relationships, of *Generative Nature*, which, for their specific characteristics, can be termed as "Harmony Relationships" (ib.).

On the basis of such specific properties, the Ordinal Structure of each one of the four considered components can be obtained by simply defining the topology of an arbitrary couple of basic elements, assumed as reference, together with some associated parameters which characterize the entire Structure of each one in the space.

Such a limited number of parameters represent the input to a Simulator, termed as EQS (Emerging Quality Simulator), which is precisely based on the MOP and its associated Harmony Relationships.

The input to the Simulator, corresponding to each considered component (i) is thus represented by:

i) the *total number* of elements (N_i);

ii) three topological parameters $(\Sigma_{12}, \Phi_{12}, \Theta_{12})_i$ that define, in polar coordinates, the reciprocal positions of two *arbitrary* elements (conventionally termed as "12"), understood as being *one sole* "*Ordinal" entity*. This is also the reason why the latter is topologically referred to its proper internal reference system;

iii) five additional parameters $(\varepsilon_1, \varepsilon_2, \lambda, \psi_1, \psi_2)_i$ which, together with those previously mentioned, complete the definition of the so-called internal *Relation Space* (RS) of the component analyzed. More specifically: $\varepsilon_{1,i}$ and $\varepsilon_{2,i}$ characterize the spatial orientation of the component *i* (understood as a Whole), with respect to its internal reference axes; while $(\psi_1, \psi_2, \lambda)_i$ define the periodicities (along the three basic axes) of the mathematical solutions which "emerge" from the MOP.

Such solutions are precisely those that give the positions in the space of all the constitutive elements with respect to the internal axes of the considered component. In this way, the afore-mentioned solutions characterize any considered component as a *unique*, *specific* and *irreducible* entity.

This is the reason why any Component, precisely because modeled as a "Self-Organizing" System of *ordinal nature* ([10]), is also characterized by its own specific *self-organizing capacity*, whose *activity* can faithfully be represented by its associated "virtual work", defined (in polar coordinates) as

$$W_i = \sum_{j=2}^{N_i} \{(\rho_{1j}) + (\rho_{1j}\varphi_{1j}) + (\rho_{1j}\vartheta_{1j})\}_i \quad (1),$$

where the subscripts 1j indicate the couples of the constitutive elements successively considered in the sum.

The corresponding Ordinal Ri-Configurations are given in Figures from 1 to 4 respectively, and are characterized by the following corresponding virtual works:

$W_C = 0{,}97$, (2) $W_D = 25{,}05$ (3)

$W_O = 40{,}80$ (4) $W_I = 18.07$ (5).

The mentioned Figures, as already anticipated, are obtained by means of EQS Simulator. Consequently, they do not represent a simple "reproduction" of the Components precisely as available in Literature. This is because their Re-Configurations are obtained in the light of the MOP and its explicit Emerging Solutions, when the latter are structured in the form of *Harmony Relationships*.

This means that the various elements of each Component are not related to each other in terms of "functional relationships". That is, in terms of forces (such as Coulomb forces, Van del Waals forces, Hydrogen bonds, etc.), but are related to each other only in terms of Ordinal Relationships, always of *Generative Nature*.

This consequently means that some differences between the two respective representations of each Component (in Ordinal terms and in Literature) are mainly due to such a different gnoseological perspective.

In addition, it is worth mentioning that each Component, when modeled on the basis of the MOP and its associated Harmony Relationships, is always reconfigured *in its proper space of Relations*. Whereas, on the contrary, the corresponding structures available in Literature are generally represented *in a plane* or, at most, in Cartesian space and, more specifically, they are always interpreted in terms of functional relationships (ib.).

4. Reciprocal Ordinal Interactions between the Three Drugs and the Inositol

The first step consists in evaluating the specific *Affinity* between each one of the three drugs with the Inositol, according to the concept of *Ordinal Inter-Action* (indicated by the symbol ®), where the Affinity is expressed by the following ratio

$$(\delta W)_{r,j} = \{W_{3,j} - (W_{1,j} + W_{2,j})\}/(W_{1,j} + W_{2,j}) \quad (6),$$

that is: the difference between the Virtual Work $(W_{3,j})$ of the final Compound of Interaction *j*, with respect to the sum $(W_{1,j} + W_{2,j})$ of the Virtual Works of Components 1 and 2 of the same interaction j, when the previous difference is referred to the latter sum.

The results of the Interactions between the three considered drugs and the Inositol are indicated here below, where, for the sake of brevity, they are expressed by the following synthetic symbology: Carbolithium = C, Depakin = D, Olanzapine = O, Inositol = I:

Interaction {C ® I} : Affinity = 54,59 % (7)
Interaction {D ® I} : Affinity = 0,27 % (8)
Interaction {O ® I} : Affinity = 0,88 % (9)

Such results show that Carbolithium has a high direct Affinity with the Inositol while the other two Interactions show a negligible Affinity.

However it is also important to evaluate the Affinity between the three drugs among themselves considered, in the perspective of their *subsequent* specific Ordinal Inter-Actions with the Inositol, that is between the latter and the compounds previously obtained. The corresponding results are the following ones:

Interaction {C ® D} : Affinity = 41,94 % (10)
Interaction {C ® O} : Affinity = 17,56 % (11)
Interaction {D ® O} : Affinity = 1,88 % (12)

The successive step consists in evaluating the Affinity of the previous compounds so obtained with the Inositol, which represents the *main target* of the selected drugs. In fact any Interaction with the Inositol, as previously said, is finalized to the "inhibition" of the latter, because it represents a basic catalyzer of undesired reactions in the brain.

The results pertaining to such Ordinal Inter-Actions are shown here below

Interaction {{C ® D} ® I} : Affinity = 1,77 % (13)
Interaction {{C ® O} ® I} : Affinity = 5,76 % (14)
Interaction {{D ® O} ® I} : Affinity = 27,44 % (15).

To complete the analysis of all the possible interactions it is worth considering the following one

{{{C ® D}®O}® I} : Affinity = 0,21 % (16)

whose value, as well as the values of all the other interaction processes, are invariant with respect to the order of the considered components represented in parentheses, as it is correspondently shown by the same EQS Simulator.

The previous results show that Carbolithium has a particular Affinity with the Inositol (see Eq. (7)). This is why Carbolithium is considered as being the "elective" drug in the case of "bipolar disorder".

Carbolithium also has an appreciable affinity with Depakin (see Eq. (10)). However, such a resulting compound has not a significant affinity with Inositol.

Depakin, on the contrary, even if it has not a good direct affinity with Inositol (see Eq. 8), after its interaction with Olanzapine, even if at a reduced level of activity (Eq. (12)), shows an inhibition activity on Inositol which is precisely amplified by the form the latter resulting compound (see Eq. (15)).

A similar effect is due to the Interaction between Carbolithium and Olanzapine, which have a significant direct affinity (Eq. (11)), which reflects, although in a reduced form, in the subsequent Ordinal Interaction with the Inositol (Eq. 14)).

Consequently, the inhibition process of Inositol:
- is mainly due to Carbolithium (Affinity 54,59 %)
- then it is due to a previous interaction between Depakin and Olanzapine (affinity 27,44 %)
- finally to a previous interaction between Carbolithium and Olanzapine (Affinity 5,76 %).

These results, however, only represent an ostensive example of the methodological approach adopted, because the analysis refers to one sole structure of Inositol, among its 9 possible isomeric forms.

Analogously, the analysis supposes that Carbolithium interacts in all its specific integrity, that is as Li2CO3, with respect to its possible decomposition in Li2O and CO2.

At this stage, by considering a typical prescription in the morning (C = 150 mg, D = 500 mg, O = 5 mg), together with their respective molecular weight (C = 73,89, D = 144,21, O = 312,44, I = 180,16), and their specific solubility (13 g/l, 1,2 g/l, negligible), it is possible to evaluate the "*global" inhibition effect* on the Inositol.

An analogous evaluation process can be performed in the case of two different prescriptions: one in the morning the other in the evening.

In this case, however, in order to evaluate the "comprehensive" (and not "additive") effects of the two distinct prescriptions, it is fundamental to account for

the specific and different half-life of each drug, especially when the prescription last for some weeks or more, so as to reach the desired stable effects at regime.

In all cases, these evaluations are always subsequent to the fundamental steps of the methodological analysis previously presented, that is precisely those which concern the evaluations of the various Affinities (from (7) to (16)), which can be obtained on the basis of the MOP and its related EQS Simulator.

5. Informatics Advantages

The informatics advantages of the Method proposed are directly referable to the fact, any system modeled on the basis of the MOP, always presents *explicit solutions* in terms of *Incipient Differential Calculus* [3][4].

This means that the Method has the *capacity* of *predicting, in explicit formal terms, the 3D structure of the resulting compound of any Interaction*, essentially because the latter is understood as a Self-Organizing System, whose description is *intrinsically* "*irreducible*" to functional relationships between its parts [8][9].

This correlatively means that the EQS Simulator only requires *a reduced number of computations*, without the adoption of *special numerical methods* in order to get the corresponding solution (ib.).

In addition, the explicit solutions so obtained can be termed as "*emerging solutions*", because *they always show an information content that is much higher than the corresponding content of the initial formulation of the problem* (ib.)[10]. This is because the MOP is specifically finalized to describe "Self-Organizing" Systems according to a *holistic approach*, in which, as already said, "*The Whole is much more than the sum of its parts*".

6. Conclusions

On the bases of the results previously shown, it is possible to assert that the Method here proposed with specific reference to the case of a "polar disorder", it is also applicable to other psychiatric therapies, even if these are based on two or one sole drug, because the latter cases are evidently included in the former case.

This aspect also points out that the Method results as being applicable to the majority of therapies based on pharmacological approaches.

The same method, in fact, can be adopted in the case of Molecular Docking and Drug Design [1][2]. This also shows that the general applicability of the Method specifically manifests when it is considered in its appropriate general context, that is, in the light of *The Maximum Ordinality Principle*.

In fact, by adopting the MOP as the basic reference criterion, together with its associated EQS Simulator, it is possible to models *all the biological Systems*, with very significant related advantages, especially that of knowing the results of any Ordinal Inter-Action *in advance*, instead of *ex post* [9][10], as previously shown in the case of a three-drug therapy in Psychiatry.

More specifically, in such a case the paper shows that, from a theoretical point of view, Carbolithium (or better Lithium), which is considered as being the "elective" drug in psychiatric therapies, manifests its specific positive effects not only when it is by itself considered, but also when it previously "combines" with Depakin and Olanzapine, respectively.

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[13] www.ordinality.org: author's website that presents a general framework about the M.O.P, together with some Ostensive Examples mentioned in this paper.