PRE- AND POST-MARKETING PHARMACOVIGILANCE: THE MYTHS OF THE PLACEBO EFFECTS AND OF THE OFF-LABEL USE OF DRUGS.°

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Summary

The rationale for any drug prescription is an enduring myth of modern medicine as the prevalence of the placebo effects and of the off-label use of drugs increases. International pre- and post-marketing pharmacovigilance, begun with our contribution, requires at least an increasingly complex and prompt analysis of experimental and clinical feedback information from individual patients if not an extended, intensive application of "monitored release", which was also initially advocated and implemented. The Reunion of Ancona's hospitals is an appropriate occasion for a demythification and demystification, where the necessary national and locoregional structures can develop beginning from these fundamental aspects of diagnostic, preventive and therapeutic-rehabilitative pharmaco-toxicology.

Keywords: pre-, post-marketing pharmacosurveillance; placebo effects; off-label use.

"A man can give the impression of being very active, he can spread around himself a loud movement and at the same time be totally passive, a prey to forces and passions that have overwhelmed him. ... Man is a creature who is capable of rising above himself, and such elevation, such transcending of himself, such escape from the narrow borders of one's self is indeed, for man, the creative act". Nikolaj Berdjaev in Put', n 50, 1936, 1st Italian ed. in L' Altra Europa, n 3, 1995, and pp 124-125, and in *Pensieri controcorrente*, La casa di Matriona Ed, 2007.

Introduction

Some relevant new contributions, published [1] and in press [2], have been reserved by the author for the presentations of this Academy; for the latter, at least three updates have been proposed in the current year [3]. Here, some new and established issues addressed in the international literature over the last few months will be summarised and discussed in relation to topical, outstanding problems, whose full discussion is available also in Italian, in the proceedings of Turin's Accademia delle Scienze [4] and of Siena's Accademia dei Fisiocritici [5]. The various sectors of Pharmacovigilance (PV), which like all other sectors of the Pharmaco-toxicological Sciences (PTS) are inextricably analytical and explorative [6], have achieved integrated modelling definitions of unprecedented complexity [7] that now go well beyond the apparently deterministic fields [8]. As their myths are accepted [9, 4], this requires at least still some probabilistic demarcation of the applicative mystifications. This is the author's fondest hope.

1. Methodological, analytical and explorative refinements

Although experimental science has as yet failed in defining satisfactorily the irreducible primary transactional general biological relationships, the use of the traditional, invasive, reductionist techniques accepted by the current official pharmacopoeias has nonetheless become clearly indefensible; the less imprecise techniques we are employing (e.g. fluorescent spectroscopy, near infrared and MRI) are capable of increasingly high resolution of spatial and time relations, from subcellular zooming to functional molecular and submolecular imaging [10], with essential contributions from regulatory stabilising definitions for the specific and selective dynamic action of isoreceptors, which is always inextricably structural and functional, and can be optimised in simultaneous mixed kinetics [11]. In PTS the myth of genetic resolution, where it has been explored in detail, has highlighted the need for a systematisation of single nucleotide polymorphisms (STP) as well as of haplotype traits etc [12]. Lacking this, diagnosis at the genome level, whose unwarranted commercial exploitation is unfortunately spreading [13], is even more unreliable, whereas the level of the ever more complex associated epigenetic phenotypes [14] does not guarantee in practice the so-called personalised medicine for basic PTS studies, which precede human clinical investigations. Metabolomics is providing an increasingly significant contribution on the applicative, no longer merely the complementary level, with adoption of the same analytical native holistic methodologies long applied here to the major terminal dysmetabolic syndromes of obesity, diabetes and hypertension, at times associated with the more overtly degenerative syndromes. A longer life expectancy now involves a greater likelihood of their arising, with significant consequences maybe especially for the intermediate levels of the same metabolic networks typical of each stage of development of individual biomedical processes, if the proposed parametrisations (e.g. of the "quasi equilibria" of redox, phosphorylation and nitrosative potentials [15], and of glycosylation, methylation turnover [16], etc) are found to be quantifiable. Clearly, statistical evaluation of the new systems is increasingly central to development and to international standardisation both at the level of basic science and at the clinical and pre- and post marketing (PPM) levels [17]. At the same time, the ethics boards called upon to assess human clinical trials are accepting erroneous practices, it is to be hoped without intentional and systematic ill faith, like separate subgroup analysis [18].

It has been advocated that the regulatory paradigmatic structure—which potentially has a universal scope—should be extended from the general collaborative voluntary databases, initially co-founded for adverse events and reactions, to the preclinical analysis databases prepared for submission applications, to meet an essential requirement of PV exhaustiveness extended PPM since 1982, a decision adopted by the 5th meeting of the Representatives of the national WHO centres and confirmed in 1991, at the 6th Interregional meeting of the Italian Society of Pharmacology, SIF (Cf: [19]). However, the implementation of supranational and national/regional recommendations and regulations remains disappointing. New ideas for healthcare globalisation are anxiously being sought, at times those that are most richly funded [20], which could be reiterated on the 60th anniversary of the foundation of the highest world institution [21].

2. Synergies of allopathic and natural medicine; deficiencies in the definitions of the placebo effects and of classifications aimed at the limited prescription drug products

It is the task of the WHO presidency, now held by China, to explore the limitations of our medicine compared with theirs. However, contaminations have already taken place in several fields of topical interest, beyond Evidence-Based Medicine, dating back to the 1992 paper on JAMA, leading to the founding meeting of Evidence-Based Homeopathy (Ostend, May 2008). It is disarming that not only regions Toscana, Puglia, Liguria, etc, which control the financing, but also Universitities (Bologna, Siena, Chieti, etc) and various professional associations, are promoting the initiatives of the Italian Society of Homeopathy and Integrated Medicine (SIOMI) [Cf: Omeopatia 33, a weekly distributed online since 11 July 2006 (e.news letter@omeopatia33.it)] and participating in the diffusion of complementary and alternative medicines (CAM) –homeopathy, acupuncture, aromatherapy, massotherapy, osteopathy– beginning from the three branches of homeopathy, phytotherapy and acupuncture of integrated medicine.

Our first analysis of the need for a better, more comprehensive qualitative knowledge of the classification spectra of the placebo effects [22] has been followed by an update, "beyond physics", now in press [23], that confirms the critical value of the extensive and joint adoption of the above-mentioned methods - particularly spectrometry and functional MRI – to identify and assess in a quantitative way the cognitive aspects mentioned above that evolve with consensus, as the decisions to continue drug administration, always of a personal character, consequent to ethically inspired prescriptions of professional use and to the potential socially relevant abuse of the same, subject to the regulatory process of registration and monitoring, up to potential withdrawal, in the systematic comparison of natural equivalents (Cf: bioethical, clinical and pharmaceutical analyses applied prior to ethics, below [38] and [34], but also [22, 1]).

Besides the deficiencies of the scientifically inspired convergence of chemical-pharmaceutical pharmaco-toxicological classifications with medico-clinical ones, where the comparison of the validity and completeness of the mixed dynamics and kinetics of the placebo effects to those that result from regulatory approval of the same homeopathic meta-analyses [24] and their quantification can no longer be postponed, we are addressing for the fist time the need for clarifying the problem of the classification of mature drugs, something that is still completely neglected due to arbitrary, increasingly widespread and heavily sponsored off-label practices [25].

This call is presented first of all to the attention of our Academy on a point that is ignored even by the legislator, not only in Italy but also in Europe, in the present context and, worse, in the ongoing evolution of global deregulation. This is something that is no longer even identified or included among the responsibilities of the intelligence of the public authorities, as if we no longer even want to address its risks, overwhelmed by the prevailing confusion.

3. Facts that continue to happen

a) Multiplicity of the routes of regulatory trials

The difficulties in accepting the current practice, that can however be improved, of the degree of quality of biological and clinical experiments, which is accepted to be independent of the peer review process (unfortunately rarely conducted in a double-blind fashion), have been discussed repeatedly [26]. The problem of the selection of "normal volunteers" for human studies, "a perfect allegory of our time", is also an object of destructing, suicidal mirth [27]. The question can easily be extended to the experimenters, who are sometimes surreptitiously recruited by the sponsors, specialist practitioners, belonging to the traditional bandwagon of the never too faithful. Here we merely note that the reviews that allow registered drugs to be kept in use, a necessary process, especially in the period immediately following release for sale, which is an increasingly globalised affair (Cf.: PPM-PV in phases IIIa and IVa) – are too often postponed, so much so as to be not systematically performed. The same American regulatory transparency, reduced by back-staging, can be unreliable [28]; in addition, professional observational alarms, ignored unless that are raised by well-established statisticians [29], with data that do not reach the required level of significance, either favourable or adverse, that are not reused to avoid waste, not only of a financial nature [30]; "innovative" products that are proved to be neither new nor useful [31]; general qualities of poor research [32], too often highlighted with great delay or supported with cost motives that belong to the myth of faceless, evanescent "distributed responsibility" [33]. Groups of ethics experimenters are formed that can be modified with changes in the political climate (from neuroethics [34], but also [23, 22, 1] and, below, [38] to neuro marketing it is a short distance), with influences that are far from invisible if sought attentively even if sporadically, with recruitment of well-paid direct and indirect financial promoters, whose independence cannot seriously be sustained (Cf: "inherent counting and accountability"). The free-market system of industrialised countries, a subject of PTS economics, has far from shied away from capitalists, as considered essential by Rajan & Zingales [35], which is shocking when riches can be made from pain and sickness. Here unfortunately the available documentation is shameful, and that facts can still be learnt should not be reassuring [36], because this is already part of the intolerably cynical multiple models of experienced games.

b) Adverse syndromes, including those involving poor effectiveness and direct or indirect damage, can emerge or else remain latent, submerged

It has been stated that a European system is now regulating risk management [37], but horrors related to the use of available drugs are repeatedly reported (for the previous three years, see p 21, Ref [176 of 38]). The thousand patients participating in the Women's Health Initiative (WHI), who received conjugated equine oestrogen and the progestinic medroxyprogesterone acetate to prevent cardiovascular risks and osteoporosis during menopause, and ceased to receive them 5-6 years into the study due to an increased risk of breast cancer, were seen again at 3 years; the data confirmed the preventive value of the drugs, but a continuing greater incidence of breast cancer up to 400% [39].

Aprotinin as a haemostatic agent (inhibitor of excessive plasmin fibrinolysis), approved by the FDA in 1943, has been found to be associated with much higher rates of mortality compared with non-protein analogues (the less expensive aminocaproic and/or tranexamic acids) [40]. This led to further intensive PPM PV investigation and to its extension to the other biological-protein drugs, including the popular darbepoetin and epoetin alpha and etanercept [41], although well after an increment of deaths from anaemia cancerosa had been reported for erythropoietins [42]. The inadequacy of PPM studies was recognised for vascular catheters (associated with an increment of systemic haematological infections [43]), while the same FDA, which has lost none of its technical or analytical, not only epidemiological, authoritativeness, has belatedly concluded that antiepileptics among the oldest, but also the relatively new and innovative varenicicline, developed against nicotine dependence, is associated with psychiatric syndromes and to increased suicide rates [44]. Varenicicline was also proposed for use in alcoholism, where disulfiram, naltrexone, acamprosate, topiramate, ondansetron, baclofen, and the even more recent, still unnamed receptor 1-neurokinin antagonist [45], have met with problems for the lack of numerosity and/or statistical power of patient samples, due to a wide spectrum of sensitivity or resistance (and even refractoriness), ascribed to personal history and to genetic profile: and yet the solution to such state of regulatory paralysis (sustained if not justified by our Giorgio Agamben as an "exception", maybe a case of Husserlian "suspension of judgement") has been proposed long ago and would not involve a high cost! [46].

In addition, the ENHANCE study, whose sponsors have been found to be aware not only that the investigation could fail, but actually that it could not but do so, has finally proved something that is not only illuminating but also highly ethically instructive, i.e. the ineffectiveness of ezetimide, which was already on the market, also in association with statin [47]; the resistance to the most widespread (low-dosage) aspirin formulation in preventing the risk of thrombo-embolism entails an adverse prognosis related to the higher pre-existing risk [48]; the "anti marijuana" rimonabant, a selective antagonist of the CB1 cannabinoid receptor, prescribed in Europe but not in the US, caused anxiety and depression, and even an increased suicide rate; in the STRADIVARIUS trial it proved ineffective in reducing the volume of atheromatic plaques [49]. This notwithstanding, and ignoring suspected clinical interactions with the vanilloid system [50], it has become known, possibly not accidentally in the course of the election race, that a study using a synthetic cannabinoid agonist administered rimonabant as an analgesic, without taking into account the spectrum of the possible interactions, with an effectiveness that will necessarily be dependent on individual administration (the association of nabilone and dihydrocodeine is not effective for chronic neuropathic pain [Frank et al., 2008, in 50]. In a lighter tone, it should be noted that soft drinks containing fruit juice increase the risk of developing gout due to their fructose content [51]; atherosclerotic obese subjects are at high risk if glycaemia levels fall too suddenly (interruption of the ACCORD study), and, to mention an issue addressed above, insulin-dependence can be reduced by gastroenteric bypass in obese patients with dysmetabolic syndrome or with type 2 diabetes, but this carries a risk of cardiovascular complications in the consequent hypoglycaemic stage [52]. To go back to osteoporosis, a calcium excess should be avoided [53], and in the elderly action should be taken, although ignoring the established predisposing polymorphisms, to avoid reductions in calcium levels rather than systematically administer bisphosphonates or raloxifene and/or strontium ranelate [54] as advised by drug manufacturers, who magnify their potential benefits and omit to mention the risks. The prevalence of cardiac valvulopathy is a recent confirmation of the effects of the prolonged use of dopaminergic agonists (pergolide, cabergoline, pramipexole) in parkinsonism [55]; the minocycline tetracycline has had terrible effects in patients with amyotrophic lateral sclerosis [56]; the most promising anti-AIDS vaccine developed to date is ineffective or even noxious, where genetic variability is explored in detail [57]; similarly unexpected has been the cardiovascular damage induced by sunitinib, an

advanced drug of the innovative class of selective tyrosine-kinase inhibitors [58]. Finally, to close this painful list of the worst defeats to date, the loss of serendipity in psychopharmacology cannot be doubted [59], as the attack treatment and first-year management of schizophrenia has not been more effective, and has actually been less safe with "second-generation" drugs (sulpiride, olanzapine, quetiapine and ziprasidone) compared with the ancestor haloperidol [60], as has authoritatively been stated [61], while the artefact of editorial selection of data reflecting the apparent ineffectiveness of SSRI [62] antidepressants has been made evident, the uselessness of drug change where treatment monitoring meets with resistance, unless associated with cognitive treatment [63], end of a myth on which the media have not failed to comment [64], together with the extremist confessions of an exemplary toxicologist, oncologist [65], at a time when the ancestor fluoxetine is being overtaken by an innovative experimental rationale [66].

4. Conclusions

Numerous national and international meetings on the latest developments in clinical drug research are heavily financed by sponsors, something that is precluded to those who respect institutional independence and autonomy. The 4th edition, on 28th-29th May 2008, of the meeting that will address the managerial aspects of clinical research in Italy includes sessions on PV quality and the expectations and regulatory problems of off-label drug administration, like orphan diseases, etc [67], while general, "basic" studies, including patents, albeit seldom from Italian researchers, increasingly achieve extraordinary success. Here we report a few others [68]; considering these and those mentioned above, however, it cannot be denied that our own Platonic *daimon*, the Angelus novus, "which appears to be on the verge of departing from something at which it is staring", cannot yet, while having to keep turned, troubled by the “tempest of progress, ...his face turned to the past", but see with bewildered, staring "wide eyes, open-mouthed, ... the rising mounds of ruins ...of the” worsening “catastrophe" of the overall history of humanity, past and present [69], not excluding therefore our passionate PTS operators.

For what has been felt by our sensibility as a permanent responsibility of the sector (and group), our generational contribution in this university has benefited from possibilities of maybe a unique nature ever since the foundation of the university, enabling unequalled teaching performance, still as exceptional as necessary, stated and documented as excellent by the highest international bodies [70], although less appreciated locally.

It cannot be denied that the Service of Clinical Pharmacology and Toxicology, associated to the WHO-ITA, has developed here research lines, as documented in previous publications [Cf: 1, 2], that have continued to grow spontaneously, meeting all requirements from the regional territory [71]; they have later been contrasted by alternative national and regional regulations that might have been interpreted in a very different way and though continuously been modified have remained inadequate. The results, distributed through a centralised interactive WHO network that began here and now encompasses 79 Countries, have been able to be applied in Italy only in the participating interuniversity Centres affiliated to Siena’s IMO, through the first and single Ancona section of "Human Pharmaco-toxicology". The section has evolved on the operative, analytical and research levels, where the survival of its scientific and operational activity, including permanent PV (certified) [72], has been sustained solely by personal resources.

The expensive and complex analytical equipment, the first to be authorised as also interdisciplinary, some of it still unique in the University, justified by the specific, adequate pharmaco-toxico-kinetic modelling of the curriculum of our teaching, is the fruit of the

investment of exclusively public funds and property acquired for the same technical skill achieved by the group; it is continuously subjected to verifications and internal quality assurance checks – certified laboratories for biomedical isotopes and mass spectrometric units and finally the often mentioned MR spectroscopy, accredited for more than 25 years for region-wide experimental and clinical analyses of more than 79 drugs, toxic agents and metabolites. The centre has official collaborations with national bodies, MINSAN, MIUR-MURST, CNR and ISS, as well as with NRC-Canada [73]. It was initially cofinanced by the regional government of Marche for programmes whose obligations have always been discharged by the university side [74]; then suddenly, unexpectedly, unacceptably and incredibly the equipment has ceased to be usable due to unmotivated unilateral interventions, never effectively countered by the internal bodies. The destructive effects of this state of things have now lasted for more than a decade, with no one demonstrating the slightest interest or competence in resuming a useful activity, at least by maintaining the existing equipment in working order.

Not even the achievement in the tasks assigned and consistently discharged of a vast consensus at the highest European technical levels has been of any value [75].

Hence a bewilderment that cannot be tolerated where, for example, the ethics board advising on drug experimentation, also at the clinical level, does not include at least the support of the PV-PPM programme, which since 1979 has been the first instance of temporary monitored registration in Italy [76] (for naloxone). It is comforting that this has been considered useful, if not necessary, by the international critical views mentioned herein, not only for products whose patents have expired, which have become available as generics, but also (an with the qualifications that are now considered as indispensable by the reported literature) for those undergoing standardised trials and anyway in view of effectiveness optimisation and minimisation of the risks related to the prescription for approved use, use authorised on compassionate grounds for orphan diseases, as well as in the off-label cases included among those that have finally been formally established [Cf: 25].

The difficulties met with by the national coordination centre of clinical trials, AIFA, investigated for corruption by the judges and the interim Health minister are quite understandable; at the same time legislative measures are being prepared, possibly to provide other guarantees, regarding "safety interventions", which may be among the earliest applications of "central deregulation". These envisage a peripheral healthcare organisation that may lack components extrapolated from the reference Ministry, maybe with multiple generalisations that may become increasingly widespread and are claimed as sustainable, of constitutionally protected exceptions, without even a recognition of, and thus a respect for what has been developed and pursued at the peripheral seats—and may still exist—if only in relation to personal initiatives.

At a time when the institution of the Ospedali Riuniti of Ancona has finally become operational, it is hoped that it will not be unfairly limited or isolated, and that it can resume its activity under the new organisation, to become an increasingly prestigious reference structure both regionally and at the international level.

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